National Institute for Health and Care Excellence

Draft

Chronic kidney disease

[M] Evidence reviews for cystatin C based equations to estimate GFR in adults, children and young people

NICE guideline <number>

Evidence reviews underpinning research recommendation on the diagnostic accuracy of cystatin C equations in the NICE guideline

January 2021

Draft for Consultation

These evidence reviews were developed by NICE Guideline Updates Team

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ISBN:

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Cystatin C based equations to estimated GFR

1.1 Review question

What is the accuracy of cystatin C-based equations to estimate GFR as a measurement of kidney function in adults, children and young people?

1.1.1 Introduction

The glomerular filtration rate (GFR) is equal to the sum of the filtration rates in all of the functioning nephrons and is the best index of overall kidney function. Knowledge of GFR is essential for the diagnosis and management of CKD, with a normal GFR being approximately 100 ml/min/1.73 m2.

The gold standard methods of assessing GFR require measurement of an ideal filtration marker, typically using markers such inulin, 51Cr-EDTA, 99mTc-DTPA, 125I-iothalamate and iohexol. However, gold standard methods of assessing GFR are technically demanding, expensive, time-consuming and unsuitable for widespread identification of CKD in the 'at risk' population. Estimates of GFR can be obtained using serum creatinine, which is a universally available endogenous test of kidney function. Various equations have been constructed that allow conversion of serum creatinine levels (sometimes along with demographic information such as age and sex) to GFR.

More recently, plasma cystatin-C has been introduced as an alternative endogenous marker. Cystatin C is a 13 kDa cationic protein produced by all nucleated cells and plasma cystatin C concentrations are chiefly determined by GFR. Previous NICE guidance reviewed the evidence for cystatin C equations for adults and recommended that an eGFR measurement using cystatin C should be considered to confirm or rule out CKD in people with an eGFR (according to a creatinine-based equation) of 45-59 ml/min/1.73 m^2, sustained for at least 90 days, without proteinuria or other markers of kidney disease. Additionally, NICE recommended that whenever a request for serum cystatin C measurement is made, clinical laboratories should report an estimate of GFR using the CKD-EPI equation. However, this guideline did not look at evidence for children and young people and new cystatin-based eGFR equations have been evaluated in adults, children and young people since this guideline was published and therefore that was the main aim of this review.

1.1.2 Summary of the protocol

Table 1: PICO table for the accuracy of cystatin C-based equations to estimate GFR

Population	Adults, children and young people with suspected or diagnosed chronic kidney disease (GFR categories G1-G5).
Index test	Different Cystatin-C equations to estimate GFR
Reference standard	Measured GFR (urinary or plasma clearance of inulin, iohexol, iothalamate, para aminohippurate [PAH], diethylenetriaminepentaacetic acid [DTPA] or ethylenediaminetetraacetic acid [EDTA]).
Outcomes	• Likelihood ratios • Specificity • Sensitivity • PPV • NPV • AUC

	• Percentage of participants with index tests values within 10, 15 or 30% (P10, P15, P30) of the reference standard.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods section in Appendix B.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Protocol deviation

Due to limited data for the outcomes specified in the review protocol, the committee agreed that the included outcomes should be expanded to include P values. P values refer to the percentage of participants with an index test value (eGFR score) sufficiently close to their score on the reference standard (mGFR). P values below P50 were deemed useful for decision making and data were found for P10, P15 and P30 (referring to the percentage of the total sample who had an index test score within 10%, 15% and 30% of their reference standard score, respectively).

Studies have demonstrated that eGFR equations have different levels of accuracy when applied to different ethnic groups. In the previous NICE guideline, studies were excluded if they contained a population of participants considerably different from the UK (for example, studies conducted in China only including Chinese participants). The committee agreed that these studies should also be excluded from the present review.

GRADE was not used in this review because imprecision could not be evaluated using P10, P15, P30 and AUC as minimal clinically important differences could not be used for these accuracy values.

1.1.4 Diagnostic evidence

1.1.4.1 Included studies

A systematic literature search for diagnostic cross-sectional studies and systematic reviews of diagnostic cross-sectional studies was conducted for this review. This returned 2,694 references (see Appendix C for literature search strategy). Based on title and abstract screening against the review protocol, 2,610 references were excluded, and 84 references were ordered for screening based on their full texts.

Of the 84 references screened as full texts, only 5 cross sectional studies met the inclusion criteria specified in the review protocol for this question (Appendix A) and therefore a decision was made to include cohort studies. Nine cohort studies were found (7 retrospective and 2 prospective) bringing the total number of included papers to 14. The clinical evidence study selection is presented as a diagram in 0.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. This search returned 238 references for this review question, these were screened on title and abstract. Four references were ordered for full text screening. None of these references were included based on their relevance to the review protocol (Appendix A).

See section 1.1.12 References – included studies for a list of references of included studies.

1.1.4.2 Excluded studies

See Appendix K for a list of excluded studies with the primary reason for exclusion.

1.1.5 Summary of studies included in the diagnostic evidence

A summary of the studies included in this review can be found in Table 2 and a summary of the different cystatin c-equations can be found in Table 3.

Table 2: Summary of studies included in this review

Study	Design	Sample	Equation name (s)	Reference standard	Risk of bias Indirectness[1]
Bevc 2011	Retrospective cohort study	317 Suspected or established renal dysfunction ≥ 65 years old	Simple cystatin-c	EDTA	Moderate Partially applicable
Bevc 2012	Retrospective cohort study	255 GFR 30-89 ml/min/1.73m^2 ≥18 years old *patients were referred for EDTA due to suspected or established renal dysfunction, only those in the above GFR range were included.	Simple cystatin-c	EDTA	Moderate Directly applicable
Bevc 2017	Retrospective cohort study	106 ≥18 years old Suspected or established renal dysfunction	CKD-EPI 1	EDTA	Moderate Partially applicable
Deng 2015	Retrospective cohort study	81 Possible renal dysfunction <18 years of age	Modified Schwartz (using CysC instead of SCr – see **Error! Reference source not found.**)	Iohexol	Moderate Partially applicable
Hari 2014	Cross-sectional study	42 Diagnosed CKD <18 years of age	Hari	DTPA	Moderate Directly applicable
Hojs 2010	Retrospective cohort study	592 ≥18 years old *patients were referred for EDTA due to suspected or established renal dysfunction,	Grubb Hojs Hoek Larsson	EDTA	Moderate Directly applicable

Study	Design	Sample	Equation name (s)	Reference standard	Risk of bias Indirectness[1]
		only those with CKD were included for analysis.	Simple cystatin-c		
Hojs 2011	Retrospective cohort study	764 ≥18 years old *patients were referred for EDTA due to suspected or established renal dysfunction, only those with CKD were included for analysis.	Hojs	EDTA	Moderate Directly applicable
Inker 2018	Retrospective cohort study	294 Adults *GFR was measured in an ancillary study within the Multi-Ethnic Study of Atherosclerosis (MESA), a community-based cohort of older black and white adults (MESA-Kidney)	CKD-EPI 4	Clearance of iohexol	Moderate Directly applicable
Lemoine 2016	Cross-sectional study	166 Suspected or established renal dysfunction Obesity (BMI ≥ 30 kg/m^2)	CKD-EPI 4	Insulin or iohexol clearance	Moderate Partially applicable
Ng 2018	Prospective cohort study	187 >18 years Young adults with CKD	CKD-EPI 4	Clearance of iohexol	Moderate Directly applicable
Salvador 2019	Cross-sectional study	96 <18 years of age CKD	Modified Schwartz (using CysC instead of SCr – see Table 3) CAPA FAS	Iohexol	Low Directly applicable
Teo 2012	Cross-sectional study	232 >21 years of age Stable CKD, with a GFR of 10-90 ml/min.	CKD-EPI 2 CKD-EPI 3	DTPA	Low Directly applicable
Werner 2017	Prospective cohort study	126 ≥70 years of age	CKD-EPI 4 FAS	Insulin or iohexol clearance	Low Partially applicable

Study	Design	Sample	Equation name (s)	Reference standard	Risk of bias Indirectness[1]
			CAPA		
White 2019	Cross-sectional study	86 ≥18 years of age Stable CKD	CKD-EPI 4	Insulin or iohexol clearance	Low Directly applicable

[1] *see Appendix E for full details of risk of bias and indirectness*

See Appendix E for full evidence tables.

Table 3: Summary of cystatin-c equations

Equation name	Equation formula	Number of studies assessed in	Populations assessed in
CAPA	$130 \times (ScysC^{-1.069}) \times (age^{-0.117}) - 7$	2	Children Adults (70+ only)
CKD-EPI 1	$133 \times (ScysC/0.8)^{-1.328} \times 0.996^{Age}$ (× 0.932 if female) *One studies also applied the following adjustment in people with serum cystatin levels of 0.8 or less: $133 \times (ScysC/0.8)^{-1.328} \times 0.996^{Age}$ (× 0.932 if female)	1	Adults (70+ only)
CKD-EPI 2	$76.7 \times (-0.105 + 1.13 \times ScysC)^{-1.19}$	1	Adults
CKD-EPI 3	$127.7 \times (-0.105 + 1.13 \times ScysC)^{-1.17} \times age^{-0.13}$ (x0.91 if female) (x1.06 if African-American)	1	Adults
CKD-EPI 4	$133 \times \min(Scys/0.8, 1)^{-0.499} \times \max(Scys/0.8, 1)^{-0.328} \times 0.996^{Age}$ (×0932 if female). min indicates the minimum of cys/0.8 or 1, and max the maximum of cys/0.8 or 1. Two studies applied the following adjustment for the maximum of cys/0.8 or 1: $\max(Scys/0.8, 1)^{-1.328}$	5	Adults (all) Adults (70+ only)
FAS	$107.3/(ScysC/0.82)$ If over 40: $107.3/(ScysC/0.82) \times 0.988^{(age-40)}$ If over 70: $107.3/(ScysC/0.95) \times 0.988^{(age-40)}$	2	Children Adults (70+ only)
Grubb	$89.12 \times ScysC^{-1.1675}$ (x 1.384 if <14)	1	Adults (all) Children
Hari	96.9 – 30.4 x ScysC	1	Children

Equation name	Equation formula	Number of studies assessed in	Populations assessed in
Hoek	-4.32 + (80.35 x 1/ScysC)	1	Adults (all)
Hojs	90.63 x $ScysC^{-1.192}$	2	Adults (all)
Larsson	77.24 x $ScysC^{-1.2623}$	1	Adults (all)
Schwartz	$(70.69 \times ScysC)^{-0.931}$	2	Children
Simple Cys-C equation	100/ScysC	5	Adults (all) Adults (65+) Adults (70+) Children

1.1.6 Summary of the diagnostic evidence

Table 4 was considered to be the most appropriate way to summarise the evidence and as a result, evidence statements have not been written for this evidence. None of the included studies could be combined to produce a pooled effect estimate. Therefore, results are presented per study.

Table 4: Summary of the diagnostic evidence by equation, population and outcomes

Equation	Population	Sample size	Likelihood ratio (95% CI)S	AUC	P10	P15	P30	Quality of evidence (Risk of bias)
CAPA	Children with CKD	96			21%		55%	Low
	Elderly adults with suspected or confirmed CKD	126					94.4%	Low
	Elderly adults with a GFR <45	41					90.2%	Low
CKD-EPI 1	Elderly adults with suspected or confirmed CKD	106		0.94				Moderate

Equation	Population	Sample size	Likelihood ratio (95% CI)S	AUC	P10	P15	P30	Quality of evidence (Risk of bias)
CKD-EPI 2	Adults with CKD	232				50.4%	86.6%	Low
CKD-EPI 3	Adults with CKD	232				51.7%	87.1%	Low
CKD-EPI 4	Black and white adults	294					88.8%	Moderate
	Black and white female adults	140					86.4%	Moderate
	Black and white male adults	154					90.9%	Moderate
	Black adults	139					89.2%	Moderate
	Black female adults	Not reported					88.6%	Moderate
	Black male adults	Not reported					89.9%	Moderate
	White adults	155					88.4%	Moderate
	White female adults	Not reported					84.3%	Moderate
	White male adults	Not reported					91.8%	Moderate
	Young adults with CKD	187					74%	Moderate
	Adults With CKD	86			37%		77%	Low
	Adults with a GFR of <30	44			30%		64%	Moderate
	Adults with a GFR of 30-59	23			35%		87%	Moderate

Equation	Population	Sample size	Likelihood ratio (95% CI)S	AUC	P10	P15	P30	Quality of evidence (Risk of bias)
	Adults with a GFR of ≥60	15			60%		100%	Moderate
	Adults with suspected or confirmed CKD	166					76%	Moderate
	Elderly adults with suspected or confirmed CKD	126					92.1%	Low
	Elderly adults with a GFR <45	41					95.1%	Moderate
FAS	Children with CKD	96			24%		67%	Moderate
	Elderly adults with suspected or confirmed CKD	126					88.9%	Low
	Elderly adults with a GFR <45	41					87.1%	Moderate
Grubb	Adults with suspected or confirmed CKD	592		0.98			52.4%	Moderate
	Elderly adults with suspected or confirmed CKD	234					41.6%	Moderate
Hari	Children with GFR category G2	42			60.5%		92.1%	Moderate

Equation	Population	Sample size	Likelihood ratio (95% CI)S	AUC	P10	P15	P30	Quality of evidence (Risk of bias)
Hoek	Adults with suspected or confirmed CKD	592		0.98			72.6%	Moderate
	Elderly adults with suspected or confirmed CKD	234					72.6%	Moderate
Hojs	Adults with suspected or confirmed CKD	592		0.98			74.4%	Moderate
	Adults with suspected or confirmed CKD	764		0.98				Moderate
	Elderly adults with suspected or confirmed CKD	234					74.4%	Moderate
	Adults with GFR category G1	116					75.9%	Moderate
	Adults with GFR category G2	131					82.4%	Moderate
	Adults with GFR category G3	191					78.0%	Moderate
	Adults with GFR category G4	211					69.7%	Moderate
	Adults with GFR category G5	115					53.0%	Moderate

Equation	Population	Sample size	Likelihood ratio (95% CI)S	AUC	P10	P15	P30	Quality of evidence (Risk of bias)
Larsson	Adults with suspected or confirmed CKD	592		0.98			5.9%	Moderate
	Elderly adults with suspected or confirmed CKD	234					6.0%	Moderate
Schwartz	Children with CKD	96			44%		90.0%	Moderate
	Children with suspected renal dysfunction	81				53.1%	79.0%	Moderate
Simple cystatin C equation	Adults with suspected or confirmed CKD	592		0.98			35.3%	Moderate
		255	LR+: 7.00 (4.09, 11.99) Large increase probability of GFR ≤60 mL/min/1.73 m^2 LR-: 0.22 (0.16, 0.30) Moderate decrease probability of GFR ≤60 mL/min/1.73 m^2	0.91				Moderate
		764		0.98				Moderate
		234					44.0%	Moderate

Equation	Population	Sample size	Likelihood ratio (95% CI)S	AUC	P10	P15	P30	Quality of evidence (Risk of bias)
	Elderly adults with suspected or confirmed CKD	317	LR+: LR+: 21.76 (5.59, 84.73) Very large increase probability of GFR ≤60 mL/min/1.73 m^2 LR-: 0.15 (0.11, 0.21) Large decrease probability of GFR ≤60 mL/min/1.73 m^2	0.98				Moderate
		106		0.94				Moderate
	Adults with GFR category G1	116					86.2%	Moderate
	Elderly adults with GFR category G1 1	6					50.0%	Moderate
	Adults with GFR category G2	104					83.7%	Moderate
		131					77.9%	Moderate
	Elderly adults with GFR category G2	45					86.7%	Moderate
		151					53.6%	Moderate

Equation	Population	Sample size	Likelihood ratio (95% CI)S	AUC	P10	P15	P30	Quality of evidence (Risk of bias)
	Adults with GFR category G3	191					51.3%	Moderate
	Elderly adults with GFR category G3	95					47.4%	Moderate
	Adults with GFR category G4	211					32.7%	Moderate
	Elderly adults with GFR category G4	113					28.3%	Moderate
	Adults with GFR category G5	115					7.0%	Moderate
	Elderly adults with GFR category G5	58					6.9%	Moderate

LR+: positive likelihood ratio; LR-: negative likelihood ratio

See Appendix G for full GRADE tables for likelihood ratio outcomes.

1.1.7 Economic evidence

A systematic review was conducted to identify economic evaluations for this review question. The search returned 338 records which were sifted against the review protocol and 337 records were excluded based on title and abstract. One record was included after the full text review. Additionally, modelling was undertaken for this review question in the 2014 update of the NICE CKD guideline. This review question was not prioritised for modelling in the 2020 update of the guideline, so this analysis has not been updated. The results of this 2014 model have therefore been included in the guideline in the same way as those from a published journal article.

1.1.7.1 Included studies

A summary of the studies included in the cost-effective review is given below. Detailed information on the studies from the review can be found in **Error! Reference source not found.**, and the study selection is described in **Error! Reference source not found.**.

In the 2014 update of the NICE CKD guideline it was decided that this review question was important to model. However, in the current update it was decided that the model would not be updated. This is due to the difficulty of modelling the consequences of inaccurate eGFR measurements, and the fact this question was regarded as being of lower priority than the questions on phosphate binders and referral to secondary care. The model in 2014 showed that using $eGFR_{cystatin\ C}$ was cost saving as it reduces the number of false positives identified compared to using creatinine alone, and this was part of the justification for why the committee decided to introduce the test to the recommendations at that time. However, the 2014 recommendations were tested in a 2017 publication which found that they were not cost saving. The 2014 model also included sensitivity and specificity data that was excluded in the current review, (either due to the population not fitting the current protocol, or it not being clear that the population had CKD). This reduces the confidence in the results of the 2014 analysis, as there is less confidence in the inputs into the model, since we no longer believe the clinical data used are fully applicable. The full model is in **Error! Reference source not found.**.

One subsequently published study by Shardlow et al (2017). compared different testing and monitoring approaches. Even though it was a cost consequence (rather than cost-utility) analysis it was included due to it being similar to the analysis done for the 2014 update, and was specifically conducted to estimate the impact of implementing the 2014 NICE recommendations. This study disagreed with the model from the 2014 guideline and found that the cost of monitoring would increase by £23 per person (£25.39 in 2020 prices) if cystatin C-based equations were used. It also found that in an elderly population $eGFR_{cystatin\ C}$ resulted in a greater number of patients being reclassified to a more severe CKD category.

The 2017 model was conducted to assess the effect of the introduction of the 2014 recommendations. The two models have different populations with the 2014 study using suspected CKD and CKD-EPI_{creat} eGFR 45-59 mL/min/1.73 m^2 and ACR <3; the 2017 study required two results of CKD-EPI_{creat} eGFR 30-59 mL/min/1.73 m^2 90 days apart. The two studies also had different sources for the diagnostics accuracy data, with 2014 from multiple sources including unpublished data for the over 75-year olds, 2017 used cohort data from 32 Derbyshire GP practices. The 2017 study found that using $eGFR_{cystatin\ C}$ is not cost saving and therefore should not be recommended for use in general practice. The 2017 study found that the cost saving from the reduced numbers diagnosed with CKD was outweighed by the increase costs in monitoring.

1.1.7.2 Excluded studies

There were no excluded studies for this review question.

1.1.8 Summary of included economic evidence

National Clinical Guideline Centre 2014

Study	Comparators	Costs[1]	Percentage correct	Uncertainty	Applicability	Limitations
National Clinical Guideline Centre 2014 Cost effectiveness analysis NHS perspective Decision Tree One-year time horizon	$CKD\text{-}EPI_{Creat}$:no further testing, diagnosed as CKD stage 3a $CKD\text{-}EPI_{Cys}$: eGFR is re-calculated using serum cystatin C and the CKD-EPIcys equation $CKD\text{-}EPI_{Create\text{-}cys}$: eGFR is re-calculated using serum cystatin C and serum creatinine and the combined CKD-EPI equation	Age 75+ $CKD\text{-}EPI_{Creat}$: £57.39 $CKD\text{-}EPI_{Cys}$: £47.27 $CKD\text{-}EPI_{Creat\text{-}cys}$: £51.40 Age<75 No hypertension $CKD\text{-}EPI_{Creat}$: £57.39 $CKD\text{-}EPI_{Cys}$: £42.26 $CKD\text{-}EPI_{Creat\text{-}cys}$: £49.13 Age<75 hypertension $CKD\text{-}EPI_{Creat}$: £65.15 $CKD\text{-}EPI_{Cys}$: £44.14 $CKD\text{-}EPI_{Creat\text{-}cys}$: £48.76	Age 75+ $CKD\text{-}EPI_{Creat}$: 79.8 $CKD\text{-}EPI_{Cys}$: 76.6 $CKD\text{-}EPI_{Creat\text{-}cys}$: 80.5 Age<75 No hypertension $CKD\text{-}EPI_{Creat}$: 67 $CKD\text{-}EPI_{Cys}$: 75 $CKD\text{-}EPI_{Creat\text{-}cys}$: 81 Age<75 hypertension $CKD\text{-}EPI_{Creat}$: 70 $CKD\text{-}EPI_{Cys}$: 79 $CKD\text{-}EPI_{Creat\text{-}cys}$: 79	Probabilistic sensitivity analysis was done around the input parameter point estimates. Prices were kept deterministic. When changing drug and management costs to 5 years rather than 1 year, it increased the costs but $CKD\text{-}EPI_{cys}$ was still the most cost-effective result. Other sensitivity analyses did not have a large effect. .	Partially applicable	Potentially serious limitations

[1]Costs inflated from sterling 2014 to sterling 2020 using the EPPI Centre cost converter accessed 22/10/2020, inflation factor 1.11.

1 ***Shardlow 2017***

Study	Comparators	Costs differences[1]	Total increase per patient	Uncertainty	Applicability	Limitations
Shardlow 2017 Cost consequence analysis NHS perspective 5-year time horizon	Implementing cystatin C testing and 12 months of monitoring using $eGFR_{cystatin\ C}$	£14,180.11	£25.39	No sensitivity analysis was done	Partially Applicable	Potentially serious limitations
	Implementing cystatin C testing and 12 months of monitoring using $eGFR_{creatinine\ and\ cystatin\ C}$	£3,561.87	£8.83			

2 *[1]Costs inflated from sterling 2015 to sterling 2020 using the EPPI Centre cost converter accessed 22/10/2020, inflation factor 1.10.*

1.1.9 Economic model

No original health economic modelling was done for this review question in the 2020 update of the guideline.

1.1.10 The committee's discussion and interpretation of the evidence

1.1.10.1. The outcomes that matter most

Cystatin-C equations to estimate GFR (eGFR) have the potential to be used to diagnose people with CKD without those people having to undergo more rigorous and invasive methods of measuring GFR. It is important that any measurement of GFR is accurate and does not produce too many false negative or false positive results.

False positive results would result in a person without CKD receiving a diagnosis and undergoing unnecessary treatment. False negative results would result in a person being incorrectly told that they do not have CKD, which would result in them not receiving needed treatment.

It is also important that the estimate of GFR obtained using cystatin-c equations is sufficiently close to the measured GFR value to ensure that people with CKD receive accurate staging. This is particularly important when cystatin-c measures are combined with creatinine-based measures to stratify the stage of CKD. For example, the equation may correctly identify someone with CKD but may give a value indicative of having early stage disease when their measured GFR suggests later stage disease.

The committee valued sensitivity (and negative likelihood ratios which are most affected by sensitivity) over specificity (and positive likelihood ratios) as it is more important that people with CKD do not go underdiagnosed. However, sensitivity and specificity were only reported by 2 studies. P30 was reported by almost all studies, fewer studies reported P15, P10 and AUC. Minimal clinically important differences could not be used for these accuracy values which made harder to use them for decision making.

1.1.10.2 The quality of the evidence

The committee agreed that there were serious limitations with the quality of the evidence available and this was a primary driver in their decision to no longer recommend that cystatin-c equations be considered during diagnosis of CKD. Previous recommendations were also based on very limited evidence. See the section of 'benefits and harms' for a discussion about the committee decision for no longer recommending cystatin-c equations.

The risk of bias associated with the studies was mainly moderate due to being retrospective studies, having an important time difference between cystatin-c and reference standard measurements, and having selection bias.

Selection bias was seen in several retrospective studies in which all people with cystatin-c on record were included in the analysis, this has the potential for selection bias if cystatin-c is not routinely measured during diagnosis of CKD in the participating centre(s) as the included participants would have had certain clinical features which warranted measurement of cystatin-c. Studies with any issues were downgraded.

Most studies rely on the use of P30 values to measure the diagnostic accuracy of the cystatin-c equations. A P30 values informs how the percentage of the participants with an eGFR within 30% of their mGFR value. This measure is of limited usefulness as a 30% deviation from the mGFR is still a potentially large difference. Additionally, it does not inform as to whether the actual estimated value is above or below the measured value and does not inform of the risk of false negative and false positive results.

Relatively few studies reported P10 and P15 values. These measures are more suitable for assessing eGFR as they allow for a smaller margin of error. Several equations were identified as having P10-15 values of over 50%. However, there was remaining uncertainty surrounding these equations due to evidence coming from single studies, with small to moderate sample sizes. Additionally, it is unclear how much variance there was for those participants with eGFR that was more than 10-15% different from their mGFR, it is therefore possible that using these equations in practice would result in a large number of participants receiving inaccurate estimates.

Some studies assessed the sensitivity and specificity of cystatin-c equations. As GFR is continuous, the estimates had to be dichotomised, with GFR estimates of 60 or less being positive and those over 60 being negative. These data were reported for the simple cystatin-c equation however evidence from P30 values for this equation suggested that it was not sufficiently accurate.

Finally, meta-analysis of the data was not possible. There were 12 different cystatin-c equations evaluated across 12 different studies. There were only a limited number of equations with data from multiple studies and among these, differences in study design (retrospective or prospective cohort studies, or cross-sectional studies) or population (children/young people, adults or the elderly) meant that it was unsuitable to combine the data in meta-analysis.

1.1.10.3 Benefits and harms

The committee noted that the recommendations in the previous guideline were based on very limited evidence and agreed that these recommendations have seen little implementation in everyday practice, noting the uncertainty surrounding their evidence and the costs associated with these tests and added complexity of laboratory processes as potential reasons for this.

The evidence used in the previous guideline was from studies with limitations on populations (CKD population could not be separated from overall cohort; suspected or confirmed CKD was not a requirement for inclusion into the study) and study design (derivation study without external validation). These studies were not included in the update of the evidence because of these limitations (see Appendix L for more details on reasons for excluding these studies: Inker 2012; Kilbride 2013; Schaeffner 2012).

The committee agreed that the quality of the evidence meant that they could not be confident in the accuracy of cystatin-c based estimates of GFR. In particular, most studies relied on P30 values to measure diagnostic accuracy, which allows to an unacceptable degree of variation between the estimated and measured values, particularly in the lower stages of disease. Results showed that P30 values ranged from 6 to 100%, P15 values were around 50% and P10 values were from 21 to 60%. P values also do not inform whether the eGFR was an overestimate or an underestimate. This is important clinically as it means that there is uncertainty as to the risk posed by these equations for producing false positive and false negative results, particularly when used in people with lower stage kidney disease. Results showed that AUC values were 0.9 and higher which is considered to be outstanding. However, having only AUC values lacks clinical interpretability because AUC represents the performance of cystatin-c across all GFR thresholds and there was very limited evidence on sensitivity and specificity which reports on specific clinical thresholds (for example, GFR ≤60 mL/min/1.73 m^2). The committee also highlighted that cystatin-c has not been widely used in clinical practice and that not longer recommending its use would not have an impact on daily practice where creatinine is used to estimate GFR.

The lack of meta-analysis meant that each equation typically relied on evidence from a single study, many of which had small sample sizes. There are now numerous different cystatin-c based equations, for which there is uncertain diagnostic accuracy.

The committee agreed that the issues in the evidence meant that there is remaining uncertainty surrounding the risks associated with using these equations in the diagnostic pathway and they should not be recommended as a result. Further research is needed to determine whether or not these equations are useful and so the committee made a research recommendation (see Appendix M).

1.1.10.4 Cost effectiveness and resource use

The committee noted that the evidence was contradictory (with the modelling from the 2014 guideline suggesting using cystatin equations would be cost-effective, whilst the Shardlow study suggested it would increase costs) and therefore it was difficult to feel confident in making a recommendation. Both studies were rated as being of a similar quality, with different limitations. The committee agreed it was not appropriate to regard false negatives as having no adverse consequences, as was done in the 2014 modelling. In contrast, the committee agreed that the population in Shardlow 2017 did not fully fit the review question as it contained patients with an eGFR of less than 45 mL/min/1.73 m^2, whilst the recommendations were only for it to be used in people with an eGFR between 45 and 60 mL/min/1.73 m2. The committee also agreed that evaluating cystatin equations using a single data point is not fully relevant, as many patients in the real world get more than one test. The committee noted that the majority of laboratories do not measure GFR using cystatin-c at present, and therefore keeping the recommendation would still represent a change in practice, as it has not been widely adopted. Stopping measuring GFR using cystatin-c may reduce resource use from the few laboratories that do measure GFR using cystatin-c. The committee agreed that it was not possible to make any recommendations in this area and that it was appropriate to remove the recommendation made in 2014.

1.1.11 Recommendations supported by this evidence review

This evidence review supports the research recommendation on the diagnostic accuracy of cystatin C equations. No recommendations were made from this evidence review.

1.1.12 References – included studies

1.1.12.1 Diagnostic

Bevc, Sebastjan, Hojs, Nina, Hojs, Radovan et al. (2017) Estimation of Glomerular Filtration Rate in Elderly Chronic Kidney Disease Patients: Comparison of Three Novel Sophisticated Equations and Simple Cystatin C Equation. Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy 21(2): 126-132

Bevc, Sebastjan, Hojs, Radovan, Ekart, Robert et al. (2012) Simple cystatin C formula compared to serum creatinine-based formulas for estimation of glomerular filtration rate in patients with mildly to moderately impaired kidney function. Kidney & blood pressure research 35(6): 649-54

Bevc, Sebastjan, Hojs, Radovan, Ekart, Robert et al. (2011) Simple cystatin C formula compared to sophisticated CKD-EPI formulas for estimation of glomerular filtration rate in the elderly. Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy 15(3): 261-8

Deng, F., Finer, G., Haymond, S. et al. (2015) Applicability of estimating glomerular filtration rate equations in pediatric patients: Comparison with a measured glomerular filtration rate by iohexol clearance. Translational Research 165(3): 437-445

Du, Yue, Sun, Ting-Ting, Hou, Ling et al. (2015) Applicability of various estimation formulas to assess renal function in Chinese children. World journal of pediatrics : WJP 11(4): 346-51

Fan, Li, Inker, Lesley A, Rossert, Jerome et al. (2014) Glomerular filtration rate estimation using cystatin C alone or combined with creatinine as a confirmatory test. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 29(6): 1195-203

Hari, Pankaj, Ramakrishnan, Lakshmy, Gupta, Ruby et al. (2014) Cystatin C-based glomerular filtration rate estimating equations in early chronic kidney disease. Indian pediatrics 51(4): 273-7

Hojs, R, Bevc, S, Ekart, R et al. (2011) Kidney function estimating equations in patients with chronic kidney disease. International journal of clinical practice 65(4): 458-64

Hojs, Radovan, Bevc, Sebastjan, Ekart, Robert et al. (2010) Serum cystatin C-based formulas for prediction of glomerular filtration rate in patients with chronic kidney disease. Nephron. Clinical practice 114(2): c118-26

Inker, Lesley A, Levey, Andrew S, Tighiouart, Hocine et al. (2018) Performance of glomerular filtration rate estimating equations in a community-based sample of Blacks and Whites: the multiethnic study of atherosclerosis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 33(3): 417-425

Lemoine, Sandrine, Panaye, Marine, Pelletier, Caroline et al. (2016) Cystatin C-Creatinine Based Glomerular Filtration Rate Equation in Obese Chronic Kidney Disease Patients: Impact of Deindexation and Gender. American journal of nephrology 44(1): 63-70

Ng, Derek K, Schwartz, George J, Schneider, Michael F et al. (2018) Combination of pediatric and adult formulas yield valid glomerular filtration rate estimates in young adults with a history of pediatric chronic kidney disease. Kidney international 94(1): 170-177

Salvador, C.L., Tondel, C., Rowe, A.D. et al. (2019) Estimating glomerular filtration rate in children: evaluation of creatinine- and cystatin C-based equations. Pediatric Nephrology 34(2): 301-311

Teo, Boon Wee, Xu, Hui, Wang, Danhua et al. (2012) Estimating glomerular filtration rates by use of both cystatin C and standardized serum creatinine avoids ethnicity coefficients in Asian patients with chronic kidney disease. Clinical chemistry 58(2): 450-7

Werner, Karin, Pihlsgard, Mats, Elmstahl, Solve et al. (2017) Combining Cystatin C and Creatinine Yields a Reliable Glomerular Filtration Rate Estimation in Older Adults in Contrast to beta-Trace Protein and beta2-Microglobulin. Nephron 137(1): 29-37

White, Christine A, Allen, Celine M, Akbari, Ayub et al. (2019) Comparison of the new and traditional CKD-EPI GFR estimation equations with urinary inulin clearance: A study of equation performance. Clinica chimica acta; international journal of clinical chemistry 488: 189-195

1.1.12.2 Economic

Shardlow, Adam, McIntyre, Natasha J, Fraser, Simon D. S et al. (2017) The clinical utility and cost impact of cystatin C measurement in the diagnosis and management of chronic kidney disease: A primary care cohort study. PLoS Med 14(10): e1002400.

Appendices

Appendix A – Review protocols

Review protocol for the accuracy of cystatin C-based equations to estimate GFR as a measurement of kidney function in adults, children and young people?

ID	Field	Content
0.	PROSPERO registration number	153331
1.	Review title	What is the accuracy of cystatin C-based equations to estimate GFR as a measurement of kidney function in adults, children and young people?
2.	Review question	What is the accuracy of cystatin C-based equations to estimate GFR as a measurement of kidney function in adults, children and young people?
3.	Objective	To determine the accuracy of cystatin C-based equations to estimate GFR as a measurement of kidney function.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase Searches will be restricted by:

		• From 25 November 2013 for adults • No limit for children and young people • English language • Human studies The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	The risk of progression and adverse outcomes in a person with, or at risk of, CKD is currently determined through monitoring creatinine-based estimates of GFR (eGFRcreatinine) and urine albumin:creatinine ratio. Estimates of GFR based on serum cystatin C (eGFRcystatinC) have a higher specificity for significant disease outcomes than those based on serum creatinine. For people with a borderline diagnosis, eGFRcystatinC is an additional diagnostic tool that may reduce over diagnosis. New evidence suggests the use of risk equations in predicting end stage renal disease in CKD patients.
6.	Population	Inclusion: Adults, children and young people with suspected or diagnosed chronic kidney disease (GFR categories G1-G5). Exclusion: • people receiving renal replacement therapy (RRT)

		• people with acute kidney injury combined with rapidly progressive glomerulonephritis • pregnant women • people receiving palliative care
7.	Test	Different Cystatin-C equations to estimate GFR
8.	Reference standard	Measured GFR (urinary or plasma clearance of inulin, iohexol, iothalamate, para aminohippurate [PAH], diethylenetriaminepentaacetic acid [DTPA] or ethylenediaminetetraacetic acid [EDTA]).
9.	Types of study to be included	• Diagnostic cross-sectional studies • Systematic reviews of diagnostic cross-sectional studies[1]
10.	Other exclusion criteria	• Abstracts and conference proceedings • Theses • Non-human studies • Studies that do not use international standardisation for cystatin C tests (CE marked or FDA approved)
11.	Context	NICE guideline CG182 chronic kidney disease in adults: assessment and management will be updated by this question. This guideline will be combined with guidelines CG157 chronic kidney disease (stage 4 or 5): management of hyperphosphataemia and NG 8

[1] Cohort studies were also included as a protocol deviation

		chronic kidney disease: managing anaemia. The guideline will be extended to cover the assessment and management of chronic kidney disease in children and young people.
12.	Primary outcomes (critical outcomes)	• Likelihood ratios[2]
13.	Secondary outcomes (important outcomes)	• Area Under Curve calculations If necessary we will calculate likelihood ratios from: o Specificity o Sensitivity o PPV o NPV
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

[2] P measures were also used as primary outcomes as a protocol deviation

		The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. Data will be extracted from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the test and reference standard used; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the QUADAS 2 checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Meta-analysis of diagnostic test accuracy data will be conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010). Where five or more studies are available for all included strata, a bivariate model will be fitted using the mada package in R v3.4.0, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data are not available (2-4 studies), separate independent pooling was performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using Microsoft Excel.

		Random-effects models (der Simonian and Laird) will be fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).
17.	Analysis of sub-groups	If there is heterogeneity within pooled data for an outcome, and if the data can be disambiguated, specific consideration will be given to the following subgroups: • Age band (older people [>70] and children and young people [<18]). • Family background (ethnic group). • Risk (people at high risk of developing progressive CKD (for example, people with diabetes, hypertension or cardiovascular disease, or people recovering from acute kidney injury, HIV)). • Family history of renal disease • BMI (low/normal/high as defined by author) • Gender.
18.	Type and method of review	☐ Intervention ☒ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)

19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	7th October 2019		
22.	Anticipated completion date	December 2020		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results	☐	☐

		against eligibility criteria		
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** Guideline Updates Team **5b Named contact e-mail** TBA@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	Review team members	From the Guideline Updates Team: • Mr Chris Carmona		

		• Mr Thomas Jarratt • Dr Yolanda Martinez • Mr Gabriel Rogers • Ms Hannah Nicholas • Ms Lynda Ayiku
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team which is part of NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].

29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Chronic Kidney Disease, eGFR measures, Cystatin C-based equations
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☒ Completed but not published

		☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

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Appendix B – Methods

Diagnostic test accuracy evidence

In this guideline, diagnostic test accuracy (DTA) data are classified as any data in which a feature – be it a symptom, a risk factor, a test result or the output of some algorithm that combines many such features – is observed in some people who have the condition of interest at the time of the test and some people who do not.. Diagnostic accuracy data can be summarised in a number of ways. Those that were used for decision making in this guideline are as follows:

- **Positive likelihood ratios** describe how many times more likely positive features are in people with the condition compared to people without the condition. Values greater than 1 indicate that a positive result makes the condition more likely.
  - LR^+ = (TP/[TP+FN])/(FP/[FP+TN])
- **Negative likelihood ratios** describe how many times less likely negative features are in people with the condition compared to people without the condition. Values less than 1 indicate that a negative result makes the condition less likely.
  - LR^- = (FN/[TP+FN])/(TN/[FP+TN])
- **Sensitivity** is the probability that the feature will be positive in a person with the condition.
  - sensitivity = TP/(TP+FN)
- **Specificity** is the probability that the feature will be negative in a person without the condition.
  - specificity = TN/(FP+TN)
- P values refer to the percentage of participants with a continuous index test value sufficiently close to their score on the reference standard. In this review P values below P50 were deemed useful for decision making and data were found for P10, P15 and P30 (referring to the percentage of the total sample who had an index test score within 10%, 15% and 30% of their reference standard score, respectively).

Interpretation of diagnostic accuracy measures

Clinical decision thresholds were chosen by the committee to correspond to the likelihood ratio above (for positive likelihood ratios) or below (for negative likelihood ratios) which a diagnostic test was accurate enough to be recommended. The following schema, adapted from the suggestions of Jaeschke et al. (1994), was used inform these discussions.

Table 5: Interpretation of likelihood ratios

Value of the likelihood ratios	Interpretation
LR ≤ 0.1	**Very large** decrease in probability of disease
0.1 < LR ≤ 0.2	**Large** decrease in probability of disease
0.2 < LR ≤ 0.5	**Moderate** decrease in probability of disease
0.5 < LR ≤ 1.0	**Slight** decrease in probability of disease
1.0 < LR < 2.0	**Slight** increase in probability of disease
2.0 ≤ LR < 5.0	**Moderate** increase in probability of disease
5.0 ≤ LR < 10.0	**Large** increase in probability of disease
LR ≥ 10.0	**Very large** increase in probability of disease

The schema above has the effect of setting a minimal important difference for positive likelihoods ratio at 2, and a corresponding minimal important difference for negative

likelihood ratios at 0.5. Likelihood ratios (whether positive or negative) falling between these thresholds were judged to indicate no meaningful change in the probability of disease.

Quality assessment

Individual studies were quality assessed using the QUADAS-2 tool, which contains four domains: patient selection, index test, reference standard, and flow and timing. Each individual study was classified into one of the following two groups:

- Low risk of bias – Evidence of non-serious bias in zero or one domain.
- Moderate risk of bias – Evidence of non-serious bias in two domains only, or serious bias in one domain only.
- High risk of bias – Evidence of bias in at least three domains, or of serious bias in at least two domains.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, index features and/or reference standard in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, index feature and/or reference standard.
- Partially indirect – Important deviations from the protocol in one of the population, index feature and/or reference standard.
- Indirect – Important deviations from the protocol in at least two of the population, index feature and/or reference standard.

Methods for combining diagnostic test accuracy evidence

Meta-analysis of diagnostic test accuracy data was conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

Where applicable, diagnostic syntheses were stratified by:

- Presenting symptomatology (features shared by all participants in the study, but not all people who could be considered for a diagnosis in clinical practice).
- The reference standard used for true diagnosis.

Where five or more studies were available for all included strata, a bivariate model was fitted using the mada package in R v3.4.0, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data were not available (2-4 studies), separate independent pooling was performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using Microsoft Excel. This approach is conservative as it is likely to somewhat underestimate test accuracy, due to failing to account for the correlation and trade-off between sensitivity and specificity (see Deeks 2010).

Random-effects models (der Simonian and Laird) were fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results

from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Modified GRADE for diagnostic test accuracy evidence

GRADE has not been developed for use with diagnostic studies; therefore a modified approach was applied using the GRADE framework. GRADE assessments were only undertaken for positive and negative likelihood ratios, as the MIDs used to assess imprecision were based on these outcomes, but results for sensitivity and specificity are also presented alongside those data.

Cross-sectional and cohort studies (retrospective and prospective cohort studies) were initially rated as high-quality evidence if well conducted, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness) as detailed in Table X below. All retrospective cohort studies were judged to be at moderate or high risk of bias.

Table 6: Rationale for downgrading quality of evidence for diagnostic questions

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.

GRADE criteria	Reasons for downgrading quality
Imprecision	If the 95% confidence interval for positive or negative likelihood ratios crossed the decision threshold for recommending a test the outcome was downgraded 1 level. If the 95% confidence interval crossed 1 (the likelihood ratio corresponding to no diagnostic utility), the outcome was downgraded 1 level. If the 95% confidence interval crossed 1 and the decision threshold for recommending a test the outcome was downgraded 2 levels as suffering from very serious imprecision. For information on how decision thresholds were determined, see the section on interpretation of diagnostic accuracy measures. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 7.

Table 7 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 8.

Table 8 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Protocol deviation

One published study by Shardlow et al (2017). compared different testing and monitoring approaches. Even though it was a cost consequence (rather than cost-utility) analysis it was included due to it being similar to the analysis done for the 2014 update, and was specifically conducted to estimate the impact of implementing the 2014 NICE recommendations

Appendix C – Literature search strategies

Background to the search

A NICE information specialist conducted the literature searches for the evidence review. The searches were originally run between the 27th to the 30th of September 2019 and updated on the 2nd of September 2020. This search report is compliant with the requirements of PRISMA-S.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

The MEDLINE strategy below was quality assured (QA) by trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude conferences in Embase were applied in adherence to standard NICE practice and the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Clinical searches

Databases	Date searched	Version/files	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	27th Sept 2019	Issue 9 of 12, September 2019	263
Cochrane Database of Systematic Reviews (CDSR)	27th Sept 2019	Issue 9 of 12, September 2019	0
Database of Abstracts of Reviews of Effect (DARE)	27th Sept 2019	Up to 2015	4

Embase (Ovid)	27th Sept 2019	Embase <1974 to 2019 Week 38>	2199
MEDLINE (Ovid)	27th Sept 2019	Ovid MEDLINE(R) <1946 to September 25, 2019>	1,753
MEDLINE In-Process (Ovid)	27th Sept 2019	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to September 25, 2019>	145
MEDLINE Epub Ahead of Print[c]	27th Sept 2019	Ovid MEDLINE(R) Epub Ahead of Print <September 25, 2019>	24

The following search filters were applied in MEDLINE and Embase to identify RCTs and systematic reviews:

- RCT filters:
  - McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.
    Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

  - McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

    Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association, 94(1), 41-47.

- Systematic reviews filters:
  - Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

    In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

    In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

Search strategies
Database: Ovid MEDLINE(R) <1946 to September 25, 2019> Search Strategy: ----------

[c] Please search for both development and re-run searches

1 exp Kidney Diseases/ (497391)

2 exp Kidney Function Tests/ (76828)

3 exp Kidney/ (343115)

4 (renal* or kidney* or ckd*).tw. (761085)

5 or/1-4 (1017739)

6 Cystatin C/ (3831)

7 cystatin*.tw. (6866)

8 6 or 7 (7238)

9 Glomerular Filtration Rate/ (42224)

10 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (153913)

11 9 or 10 (167119)

12 5 and 8 and 11 (2668)

13 (MEDLINE or pubmed).tw. (146077)

14 systematic review.tw. (105059)

15 systematic review.pt. (112263)

16 meta-analysis.pt. (104847)

17 intervention$.ti. (115118)

18 or/13-17 (345036)

19 randomized controlled trial.pt. (489804)

20 randomi?ed.mp. (757539)

21 placebo.mp. (187874)

22 or/19-21 (807948)

23 exp "Sensitivity and Specificity"/ (561765)

24 (sensitivity or specificity).tw. (868249)

25 ((pre-test or pretest or post-test) adj probability).tw. (2161)

26 (predictive value* or PPV or NPV).tw. (95689)

27 likelihood*.tw. (113908)

28 exp likelihood functions/ (21380)

29 (ROC curve* or AUC).tw. (70620)

30 (diagnos* adj2 (performance* or accurac* or utilit* or value* or valid* or efficien* or effectiveness)).tw. (92754)

31 (reference or gold standard).tw. (379541)

32 (sensitiv: or diagnos:).mp. or di.fs. (5523763)

33 validation studies/ (96716)

34 validation studies as topic/ (2065)

35 or/23-34 (6166632)

36 Cross sectional.tw. (260423)

37 Cross-sectional studies/ (304354)

38 36 or 37 (374957)

39 18 or 22 or 35 or 38 (7152846)

40 12 and 39 (1912)

41 limit 40 to english language (1784)

42 animals/ not humans/ (4586194)

43 41 not 42 (1753)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to September 25, 2019>

Search Strategy:

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1 exp Kidney Diseases/ (0)

2 exp Kidney Function Tests/ (0)

3 exp Kidney/ (0)

4 (renal* or kidney* or ckd*).tw. (64254)

5 or/1-4 (64254)

6 Cystatin C/ (0)

7 cystatin*.tw. (775)

8 6 or 7 (775)

9 Glomerular Filtration Rate/ (0)

10 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (15219)

11 9 or 10 (15219)

12 5 and 8 and 11 (288)

13 (MEDLINE or pubmed).tw. (31025)

14 systematic review.tw. (25571)

15 systematic review.pt. (401)

16 meta-analysis.pt. (36)

17 intervention$.ti. (18977)

18 or/13-17 (60048)

19 randomized controlled trial.pt. (276)

20 randomi?ed.mp. (67506)

21 placebo.mp. (16469)

22 or/19-21 (73359)

23 exp "Sensitivity and Specificity"/ (0)

24 (sensitivity or specificity).tw. (104550)

25 ((pre-test or pretest or post-test) adj probability).tw. (243)

26 (predictive value* or PPV or NPV).tw. (11406)

27 likelihood*.tw. (16994)

28 exp likelihood functions/ (0)

29 (ROC curve* or AUC).tw. (10885)

30 (diagnos* adj2 (performance* or accurac* or utilit* or value* or valid* or efficien* or effectiveness)).tw. (11989)

31 (reference or gold standard).tw. (61575)

32 (sensitiv: or diagnos:).mp. or di.fs. (387294)

33 validation studies/ (0)

34 validation studies as topic/ (0)

35 or/23-34 (468019)

36 Cross sectional.tw. (53118)

37 Cross-sectional studies/ (0)

38 36 or 37 (53118)

39 18 or 22 or 35 or 38 (603730)

40 12 and 39 (146)

41 limit 40 to english language (145)

42 animals/ not humans/ (0)

43 41 not 42 (145)

Database: Ovid MEDLINE(R) Epub Ahead of Print <September 25, 2019>

Search Strategy:

---

1 exp Kidney Diseases/ (0)

2 exp Kidney Function Tests/ (0)

3 exp Kidney/ (0)

4 (renal* or kidney* or ckd*).tw. (9792)

5 or/1-4 (9792)

6 Cystatin C/ (0)

7 cystatin*.tw. (117)

8 6 or 7 (117)

9 Glomerular Filtration Rate/ (0)

10 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (2354)

11 9 or 10 (2354)

12 5 and 8 and 11 (46)

13 (MEDLINE or pubmed).tw. (6532)

14 systematic review.tw. (6137)

15 systematic review.pt. (24)

16 meta-analysis.pt. (13)

17 intervention$.ti. (3820)

18 or/13-17 (12802)

19 randomized controlled trial.pt. (1)

20 randomi?ed.mp. (12712)

21 placebo.mp. (3060)

22 or/19-21 (13785)

23 exp "Sensitivity and Specificity"/ (0)

24 (sensitivity or specificity).tw. (14024)

25 ((pre-test or pretest or post-test) adj probability).tw. (41)

26 (predictive value* or PPV or NPV).tw. (2107)

27 likelihood*.tw. (3706)

28 exp likelihood functions/ (0)

29 (ROC curve* or AUC).tw. (2319)

30 (diagnos* adj2 (performance* or accurac* or utilit* or value* or valid* or efficien* or effectiveness)).tw. (2337)

31 (reference or gold standard).tw. (7633)

32 (sensitiv: or diagnos:).mp. or di.fs. (53029)

33 validation studies/ (0)

34 validation studies as topic/ (0)

35 or/23-34 (64669)

36 Cross sectional.tw. (8415)

37 Cross-sectional studies/ (0)

38 36 or 37 (8415)

39 18 or 22 or 35 or 38 (89662)

40 12 and 39 (25)

41 limit 40 to english language (24)

42 animals/ not humans/ (0)

43 41 not 42 (24)

Database: Embase <1974 to 2019 Week 38>

Search Strategy:

---

1 exp kidney disease/ (872924)

2 exp kidney function/ (183502)

3 kidney function test/ (11181)

4 exp kidney function test kit/ (7)

5 exp kidney/ (381785)

6 (kidney* or renal or ckd).tw. (1102681)

7 or/1-6 (1496749)

8 cystatin C/ (11138)

9 cystatin*.tw. (11437)

10 8 or 9 (14083)

11 exp glomerulus filtration rate/ (94500)

12 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (256511)

13 11 or 12 (284375)

14 7 and 10 and 13 (5651)

15 (MEDLINE or pubmed).tw. (233306)

16 exp systematic review/ or systematic review.tw. (265213)

17 meta-analysis/ (172003)

18 intervention$.ti. (186280)

19 or/15-18 (600864)

20 random:.tw. (1460784)

21 placebo:.mp. (442607)

22 double-blind:.tw. (203247)

23 or/20-22 (1711800)

24 "sensitivity and specificity"/ (337998)

25 (sensitivity or specificity).tw. (1243966)

26 ((pre-test or pretest or post-test) adj probability).tw. (4231)

27 (predictive value* or PPV or NPV).tw. (166819)

28 likelihood*.tw. (176665)

29 (ROC curve* or AUC).tw. (143373)

30 (diagnos* adj2 (performance* or accurac* or utilit* or value* or valid* or efficien* or effectiveness)).tw. (151844)

31 (reference or gold standard).tw. (583275)

32 (sensitiv: or diagnos:).mp. or di.fs. (7496339)

33 diagnostic accuracy/ (243580)

34 diagnostic test accuracy study/ (112675)

35 validation study/ (79767)

36 or/24-35 (8327840)

37 (cross sectional adj (study or studies)).tw. (197988)

38 cross-sectional study/ (318267)

39 37 or 38 (360931)

40 19 or 23 or 36 or 39 (10141696)

41 14 and 40 (3483)

42 limit 41 to english language (3295)

43 nonhuman/ not human/ (4488204)

44 42 not 43 (3225)

45 limit 44 to (conference abstract or conference paper or "conference review" or letter) (1026)

46 44 not 45 (2199)

Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Kidney Diseases] explode all trees	14667
#2	MeSH descriptor: [Kidney Function Tests] explode all trees	4009
#3	MeSH descriptor: [Kidney] explode all trees	3824
#4	(renal* or kidney* or ckd*):ti,ab,kw	74049
#5	#1 or #2 or #3 or #4	75637
#6	MeSH descriptor: [Cystatin C] this term only	164
#7	(cystatin*):ti,ab,kw	1018
#8	#6 or #7	1018
#9	MeSH descriptor: [Glomerular Filtration Rate] this term only	2571
#10	(glomerul* or GFR* or eGFR* or e-GFR*):ti,ab,kw	17293
#11	#9 or #10	17293
#12	#5 and #8 and #11	501
#13	"conference":pt or (clinicaltrials or trialsearch):so	424276
#14	#12 not #13	263 (Central only)

CRD databases

1	MeSH DESCRIPTOR Kidney Diseases EXPLODE ALL TREES	1433	Delete
2	MeSH DESCRIPTOR Kidney Function Tests EXPLODE ALL TREES	141	Delete
3	MeSH DESCRIPTOR Kidney EXPLODE ALL TREES	176	Delete
4	(renal* or kidney* or ckd*)	3317	Delete

5	(#1 or #2 or #3 or #4)	3447	Delete
6	MeSH DESCRIPTOR Cystatin C	8	Delete
7	(cystatin*)	12	Delete
8	#6 OR #7	12	Delete
9	MeSH DESCRIPTOR Glomerular Filtration Rate	92	Delete
10	(glomerul* or GFR* or eGFR* or e-GFR*)	416	Delete
11	(#9 or #10)	416	Delete
12	(#5 and #8 and #11)	6	Delete

Cost-effectiveness searches

Databases	Date searched	Version/files	No. retrieved
MEDLINE (Ovid)	30th Sept 2019	Ovid MEDLINE(R) <1946 to September 27, 2019>	152
MEDLINE in Process (Ovid)	30th Sept 2019	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to September 27, 2019>	20
MEDLINE epub (Ovid)	30th Sept 2019	Ovid MEDLINE(R) Epub Ahead of Print <September 27, 2019>	2
Embase (Ovid)	30th Sept 2019	Embase <1974 to 2019 Week 39>	289
EconLit (Ovid)	30th Sept 2019	Econlit <1886 to September 12, 2019>	0
NHS Economic Evaluation Database (NHS EED) (legacy database)	27th Sept 2019	Up to 2015	1
CRD HTA	27th Sept 2019	Up to 2018	1

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

  Several modifications have been made to these filters over the years that are standard NICE practice.

Search strategies

Database: Ovid MEDLINE(R) <1946 to September 27, 2019>

Search Strategy:

---

1 exp Kidney Diseases/ (497482)

2 exp Kidney Function Tests/ (76838)

3 exp Kidney/ (343141)

4 (renal* or kidney* or ckd*).tw. (761239)

5 or/1-4 (1017912)

6 Cystatin C/ (3831)

7 cystatin*.tw. (6868)

8 6 or 7 (7240)

9 Glomerular Filtration Rate/ (42229)

10 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (153947)

11 9 or 10 (167155)

12 5 and 8 and 11 (2670)

13 Economics/ (27076)

14 exp "Costs and Cost Analysis"/ (228437)

15 Economics, Dental/ (1907)

16 exp Economics, Hospital/ (23895)

17 exp Economics, Medical/ (14123)

18 Economics, Nursing/ (3994)

19 Economics, Pharmaceutical/ (2890)

20 Budgets/ (11170)

21 exp Models, Economic/ (14398)

22 Markov Chains/ (13660)

23 Monte Carlo Method/ (27171)

24 Decision Trees/ (10696)

25 econom$.tw. (224357)

26 cba.tw. (9611)

27 cea.tw. (19862)

28 cua.tw. (951)

29 markov$.tw. (16972)

30 (monte adj carlo).tw. (28569)

31 (decision adj3 (tree$ or analys$)).tw. (12375)

32 (cost or costs or costing$ or costly or costed).tw. (434602)

33 (price$ or pricing$).tw. (31743)

34 budget$.tw. (22682)

35 expenditure$.tw. (46882)

36 (value adj3 (money or monetary)).tw. (1972)

37 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3391)

38 or/13-37 (880530)

39 "Quality of Life"/ (181707)

40 quality of life.tw. (213914)

41 "Value of Life"/ (5659)

42 Quality-Adjusted Life Years/ (11411)

43 quality adjusted life.tw. (9988)

44 (qaly$ or qald$ or qale$ or qtime$).tw. (8206)

45 disability adjusted life.tw. (2434)

46 daly$.tw. (2232)

47 Health Status Indicators/ (23007)

48 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (21385)

49 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1272)

50 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4536)

51 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (28)

52 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (373)

53 (euroqol or euro qol or eq5d or eq 5d).tw. (8002)

54 (qol or hql or hqol or hrqol).tw. (40727)

55 (hye or hyes).tw. (58)

56 health$ year$ equivalent$.tw. (38)

57 utilit$.tw. (161238)

58 (hui or hui1 or hui2 or hui3).tw. (1221)

59 disutili$.tw. (359)

60 rosser.tw. (86)

61 quality of wellbeing.tw. (12)

62 quality of well-being.tw. (368)

63 qwb.tw. (186)

64 willingness to pay.tw. (4051)

65 standard gamble$.tw. (768)

66 time trade off.tw. (995)

67 time tradeoff.tw. (224)

68 tto.tw. (862)

69 or/39-68 (463135)

70 38 or 69 (1279518)

71 12 and 70 (164)

72 limit 71 to english language (156)

73 animals/ not humans/ (4586713)

74 72 not 73 (152)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to September 27, 2019>

Search Strategy:

---

1 exp Kidney Diseases/ (0)

2 exp Kidney Function Tests/ (0)

3 exp Kidney/ (0)

4 (renal* or kidney* or ckd*).tw. (64458)

5 or/1-4 (64458)

6 Cystatin C/ (0)

7 cystatin*.tw. (778)

8 6 or 7 (778)

9 Glomerular Filtration Rate/ (0)

10 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (15280)

11 9 or 10 (15280)

12 5 and 8 and 11 (289)

13 Economics/ (0)

14 exp "Costs and Cost Analysis"/ (0)

15 Economics, Dental/ (0)

16 exp Economics, Hospital/ (0)

17 exp Economics, Medical/ (0)

18 Economics, Nursing/ (0)

19 Economics, Pharmaceutical/ (0)

20 Budgets/ (0)

21 exp Models, Economic/ (0)

22 Markov Chains/ (0)

23 Monte Carlo Method/ (0)

24 Decision Trees/ (0)

25 econom$.tw. (40748)

26 cba.tw. (391)

27 cea.tw. (1714)

28 cua.tw. (185)

29 markov$.tw. (5237)

30 (monte adj carlo).tw. (16070)

31 (decision adj3 (tree$ or analys$)).tw. (2126)

32 (cost or costs or costing$ or costly or costed).tw. (87679)

33 (price$ or pricing$).tw. (5392)

34 budget$.tw. (4642)

35 expenditure$.tw. (6014)

36 (value adj3 (money or monetary)).tw. (342)

37 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (510)

38 or/13-37 (152249)

39 "Quality of Life"/ (0)

40 quality of life.tw. (35458)

41 "Value of Life"/ (0)

42 Quality-Adjusted Life Years/ (0)

43 quality adjusted life.tw. (1527)

44 (qaly$ or qald$ or qale$ or qtime$).tw. (1292)

45 disability adjusted life.tw. (467)

46 daly$.tw. (426)

47 Health Status Indicators/ (0)

48 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (2502)

49 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (704)

50 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (703)

51 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (4)

52 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (17)

53 (euroqol or euro qol or eq5d or eq 5d).tw. (1549)

54 (qol or hql or hqol or hrqol).tw. (6782)

55 (hye or hyes).tw. (7)

56 health$ year$ equivalent$.tw. (2)

57 utilit$.tw. (28443)

58 (hui or hui1 or hui2 or hui3).tw. (167)

59 disutili$.tw. (65)

60 rosser.tw. (9)

61 quality of wellbeing.tw. (7)

62 quality of well-being.tw. (28)

63 qwb.tw. (9)

64 willingness to pay.tw. (849)

65 standard gamble$.tw. (55)

66 time trade off.tw. (115)

67 time tradeoff.tw. (16)

68 tto.tw. (114)

69 or/39-68 (66145)

70 38 or 69 (209742)

71 12 and 70 (20)

72 limit 71 to english language (20)

73 animals/ not humans/ (0)

74 72 not 73 (20)

Database: Ovid MEDLINE(R) Epub Ahead of Print <September 27, 2019>

Search Strategy:

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1 exp Kidney Diseases/ (0)

2 exp Kidney Function Tests/ (0)

3 exp Kidney/ (0)

4 (renal* or kidney* or ckd*).tw. (9779)

5 or/1-4 (9779)

6 Cystatin C/ (0)

7 cystatin*.tw. (117)

8 6 or 7 (117)

9 Glomerular Filtration Rate/ (0)

10 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (2347)

11 9 or 10 (2347)

12 5 and 8 and 11 (45)

13 Economics/ (0)

14 exp "Costs and Cost Analysis"/ (0)

15 Economics, Dental/ (0)

16 exp Economics, Hospital/ (0)

17 exp Economics, Medical/ (0)

18 Economics, Nursing/ (0)

19 Economics, Pharmaceutical/ (0)

20 Budgets/ (0)

21 exp Models, Economic/ (0)

22 Markov Chains/ (0)

23 Monte Carlo Method/ (0)

24 Decision Trees/ (0)

25 econom$.tw. (6053)

26 cba.tw. (60)

27 cea.tw. (315)

28 cua.tw. (23)

29 markov$.tw. (693)

30 (monte adj carlo).tw. (1191)

31 (decision adj3 (tree$ or analys$)).tw. (394)

32 (cost or costs or costing$ or costly or costed).tw. (12288)

33 (price$ or pricing$).tw. (866)

34 budget$.tw. (548)

35 expenditure$.tw. (1180)

36 (value adj3 (money or monetary)).tw. (63)

37 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (50)

38 or/13-37 (20309)

39 "Quality of Life"/ (0)

40 quality of life.tw. (6637)

41 "Value of Life"/ (0)

42 Quality-Adjusted Life Years/ (0)

43 quality adjusted life.tw. (361)

44 (qaly$ or qald$ or qale$ or qtime$).tw. (317)

45 disability adjusted life.tw. (89)

46 daly$.tw. (79)

47 Health Status Indicators/ (0)

48 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (446)

49 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (49)

50 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (150)

51 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (1)

52 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (5)

53 (euroqol or euro qol or eq5d or eq 5d).tw. (346)

54 (qol or hql or hqol or hrqol).tw. (1297)

55 (hye or hyes).tw. (2)

56 health$ year$ equivalent$.tw. (0)

57 utilit$.tw. (4762)

58 (hui or hui1 or hui2 or hui3).tw. (25)

59 disutili$.tw. (16)

60 rosser.tw. (0)

61 quality of wellbeing.tw. (1)

62 quality of well-being.tw. (5)

63 qwb.tw. (3)

64 willingness to pay.tw. (154)

65 standard gamble$.tw. (9)

66 time trade off.tw. (21)

67 time tradeoff.tw. (5)

68 tto.tw. (19)

69 or/39-68 (11684)

70 38 or 69 (30270)

71 12 and 70 (2)

72 limit 71 to english language (2)

73 animals/ not humans/ (0)

74 72 not 73 (2)

Database: Embase <1974 to 2019 Week 39>

Search Strategy:

---

1 exp kidney disease/ (873979)

2 exp kidney function/ (183670)

3 kidney function test/ (11191)

4 exp kidney function test kit/ (7)

5 exp kidney/ (382032)

6 (kidney* or renal or ckd).tw. (1103875)

7 or/1-6 (1498304)

8 cystatin C/ (11157)

9 cystatin*.tw. (11453)

10 8 or 9 (14106)

11 exp glomerulus filtration rate/ (94658)

12 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (256965)

13 11 or 12 (284880)

14 7 and 10 and 13 (5660)

15 exp Health Economics/ (816504)

16 exp "Health Care Cost"/ (282505)

17 exp Pharmacoeconomics/ (196933)

18 Monte Carlo Method/ (37461)

19 Decision Tree/ (11670)

20 econom$.tw. (344332)

21 cba.tw. (12473)

22 cea.tw. (33162)

23 cua.tw. (1406)

24 markov$.tw. (28118)

25 (monte adj carlo).tw. (44772)

26 (decision adj3 (tree$ or analys$)).tw. (21500)

27 (cost or costs or costing$ or costly or costed).tw. (720674)

28 (price$ or pricing$).tw. (53865)

29 budget$.tw. (36463)

30 expenditure$.tw. (71042)

31 (value adj3 (money or monetary)).tw. (3263)

32 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (8370)

33 or/15-32 (1664436)

34 "Quality of Life"/ (442640)

35 Quality Adjusted Life Year/ (24794)

36 Quality of Life Index/ (2693)

37 Short Form 36/ (27102)

38 Health Status/ (122581)

39 quality of life.tw. (409078)

40 quality adjusted life.tw. (18230)

41 (qaly$ or qald$ or qale$ or qtime$).tw. (18616)

42 disability adjusted life.tw. (3690)

43 daly$.tw. (3656)

44 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (39774)

45 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2248)

46 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (8910)

47 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (55)

48 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (438)

49 (euroqol or euro qol or eq5d or eq 5d).tw. (18765)

50 (qol or hql or hqol or hrqol).tw. (90017)

51 (hye or hyes).tw. (127)

52 health$ year$ equivalent$.tw. (41)

53 utilit$.tw. (271106)

54 (hui or hui1 or hui2 or hui3).tw. (2140)

55 disutili$.tw. (861)

56 rosser.tw. (121)

57 quality of wellbeing.tw. (41)

58 quality of well-being.tw. (474)

59 qwb.tw. (239)

60 willingness to pay.tw. (7966)

61 standard gamble$.tw. (1075)

62 time trade off.tw. (1644)

63 time tradeoff.tw. (283)

64 tto.tw. (1580)

65 or/34-64 (930241)

66 33 or 65 (2447056)

67 14 and 66 (424)

68 limit 67 to (conference abstract or conference paper or "conference review") (116)

69 67 not 68 (308)

70 limit 69 to english language (294)

71 nonhuman/ not human/ (4494386)

72 70 not 71 (289)

Database: Econlit <1886 to September 12, 2019>

Search Strategy:

---

1 [exp Kidney Diseases/] (0)

2 [exp Kidney Function Tests/] (0)

3 [exp Kidney/] (0)

4 (renal* or kidney* or ckd*).tw. (316)

5 or/1-4 (316)

6 [Cystatin C/] (0)

7 cystatin*.tw. (0)

8 6 or 7 (0)

9 [Glomerular Filtration Rate/] (0)

10 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (12)

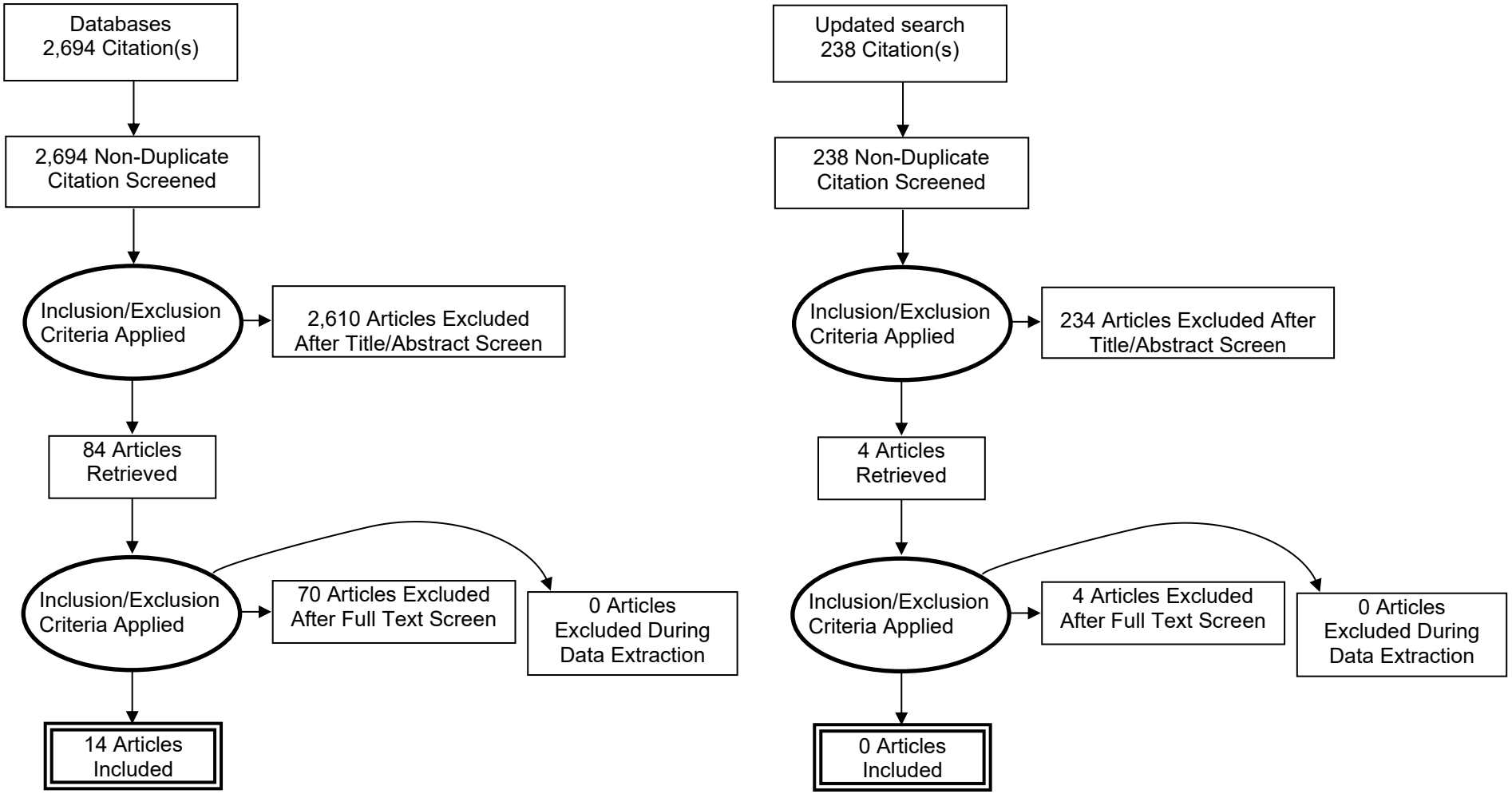
11 9 or 10 (12)

12 5 and 8 and 11 (0)

CRD databases

1	MeSH DESCRIPTOR Kidney Diseases EXPLODE ALL TREES	1433	Delete
2	MeSH DESCRIPTOR Kidney Function Tests EXPLODE ALL TREES	141	Delete
3	MeSH DESCRIPTOR Kidney EXPLODE ALL TREES	176	Delete
4	(renal* or kidney* or ckd*)	3317	Delete
5	(#1 or #2 or #3 or #4)	3447	Delete
6	MeSH DESCRIPTOR Cystatin C	8	Delete
7	(cystatin*)	12	Delete
8	#6 OR #7	12	Delete
9	MeSH DESCRIPTOR Glomerular Filtration Rate	92	Delete
10	(glomerul* or GFR* or eGFR* or e-GFR*)	416	Delete
11	(#9 or #10)	416	Delete
12	(#5 and #8 and #11)	6	Delete (4 DARE, 1 NHS EED, 1 HTA)

Appendix D –Diagnostic evidence study selection



Appendix E –Diagnostic evidence tables

Bevc, 2011

Bibliographic Reference	Bevc, Sebastjan; Hojs, Radovan; Ekart, Robert; Gorenjak, Maksimiljan; Puklavec, Ludvik; Simple cystatin C formula compared to sophisticated CKD-EPI formulas for estimation of glomerular filtration rate in the elderly.; Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy; 2011; vol. 15 (no. 3); 261-8

Study Characteristics

Study type	Retrospective cohort study unclear, likely retrospective
Study details	Study location Slovenia Study setting referrals for 51Cr-EDTA clearance Sources of funding supported by a grant (L3-0328) from the Slovenian Research Agency (ARRS).
Inclusion criteria	Age >65 years old Suspected or established kidney dysfunction referred for 51Cr-EDTA clearance by nephrologists, diabetologists, cardiologists, or general internists because of suspected or established renal dysfunction.
Exclusion criteria	None reported.
Sample characteristics	Sample size 317 Female 53.6% Mean age (SD) 72.7 (SD 5.1) mGFR (SD) ml/min/1.73m2 34.5 (SD 22.6)
Index test(s)	Simple Cystatin C equation 100/ScysC
Reference standard (s)	EDTA estimated from a single 51Cr-EDTA injection and three blood samples (120, 180, and 240 min after parenteral application of the marker) according to the Committee on Renal Clearance recommendations

Quality assessment

Patient selection: risk of bias
Was a consecutive or random sample of patients enrolled? Unclear *(Sampling method is unclear. It is likely a retrospective study in which all patients who underwent EDTA measurement were included.)* *Was a case-control design avoided?* Yes *Did the study avoid inappropriate exclusions?*

Yes

Could the selection of patients have introduced bias?

Low

(Study likely included all patients who underwent both the reference standard and index tests (or measurements needed to calculate the index tests). However, there is limited reported on study design and on the period of time data collection took place.)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Unclear

(Participants were referred due to suspected or established renal dysfunction. However, this includes a wide range of potential conditions and it is unclear how many have CKD)

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Low

(Index tests are determined objectively and are unlikely to have allowed for bias.)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low

(reference standard is determined objectively and is unlikely to have allowed for bias.)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

(reference standard was conducted at the same time as serum creatinine and cystatin were measured.)

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Study included all participants with cystatin-c measurements on record. If the participating centres do not routinely measure cystatin-c then this represents a risk of selection bias)

Directness

Partially applicable

(Participants were referred due to suspected or established renal dysfunction. However, this includes a wide range of potential conditions and it is unclear how many have CKD.)

Bevc, 2012

Bibliographic Reference	Bevc, Sebastjan; Hojs, Radovan; Ekart, Robert; Gorenjak, Maksimiljan; Puklavec, Ludvik; Simple cystatin C formula compared to serum creatinine-based formulas for estimation of glomerular filtration rate in patients with mildly to moderately impaired kidney function.; Kidney & blood pressure research; 2012; vol. 35 (no. 6); 649-54

Study Characteristics

Study type	Retrospective cohort study Unclear, likely retrospective.
Study details	Study location Slovenia Study setting

	referrals for 51Cr-EDTA clearance Study dates Unclear Sources of funding supported by grant L3-0328 from the Slovenian Research Agency (ARRS).
Inclusion criteria	GFR GFR of 30-89 ml/min/1.73m2 Suspected or established kidney dysfunction included patients who were referred for 51 Cr-EDTA clearance by nephrologists, diabetologists, cardiologists or general internists because of suspected or established renal dysfunction.
Exclusion criteria	None reported
Sample characteristics	Sample size 255 Female 46.3% Mean age (SD) 59.7 (SD 14.1) mGFR (SD) ml/min/1.73m2 55.5
Index test(s)	Simple Cystatin C equation 100/ScysC
Reference standard (s)	EDTA The GFR was estimated from a single 51 Cr-EDTA injection and three blood samples (120, 180 and 240 min after parenteral application of the marker) according to the Committee on Renal Clearance Recommendations

Quality assessment

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

No

(Study retrospectively assessed people with suspected or established renal dysfunction but only analysed people with a GFR between 30 and 89, with more extreme values therefore being excluded. This poses a risk of bias a there is more variability with very low and high values and may affect diagnostic accuracy)

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

High

(Study likely only included people who recorded a GFR of between 30 and 89 ml/min/1.73m2 and therefore more extreme values on the reference standard would have been excluded from analysis).

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Unclear

(Participants were referred due to suspected or established renal dysfunction. Participants were subsequently excluded if their GFR was outside of the range 30-89 ml/min/1.73m2. Therefore, the study contained participants with mildly to moderately impaired renal function but not necessarily CKD. However, as these participants all had a GFR <90 it is likely that these participants either had CKD were reasonably suspected of CKD.)

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Low

(Index tests are determined objectively and is unlikely to have allowed for bias.)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low

(reference standard is determined objectively and is unlikely to have allowed for bias.)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

(reference standard was conducted at the same time as serum creatinine and cystatin were measured.)

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Study retrospectively assessed people with suspected or established renal dysfunction but only analysed people with a GFR between 30 and 89, with more extreme values therefore being excluded. This poses a risk of bias a there is more variability with very low and high values and may affect diagnostic accuracy. Additionally, the study retrospectively included all participants with cystatin-c measurements on record. If the participating centres do not routinely measure cystatin-c then this represents a risk of selection bias)

Directness

Directly applicable

Bevc, 2017

Bibliographic Reference	Bevc, Sebastjan; Hojs, Nina; Hojs, Radovan; Ekart, Robert; Gorenjak, Maksimiljan; Puklavec, Ludvik; Estimation of Glomerular Filtration Rate in Elderly Chronic Kidney Disease Patients: Comparison of Three Novel Sophisticated Equations and Simple Cystatin C Equation.; Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy; 2017; vol. 21 (no. 2); 126-132

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location Slovenia
Inclusion criteria	suspected or established kidney dysfunction "referred for measuring 51CrEDTA clearance by nephrologists, diabetologists, cardiologists or general internists because of suspected or established renal dysfunction."
Exclusion criteria	None reported

Sample characteristics	Sample size 106 Female 54.7% Cystatin (mg/L) mean 1.79 (SD 0.6) Mean eGFR (SD) ml/min/1.73m2 simple CysC equation: 60.2 (16.2); CKD-EPI CysC equation: 65.7 (9.5) mGFR (SD) ml/min/1.73m2 52.2 (15.9)
Index test(s)	CKD-EPI (CysC only equation) 0.8 or less serum CysC (mg/L): 133 x (CysC/0.8)^-0.499 x 0.996^age [x0.932 if female]; >0.8: 133 x (CysC/0.8)^-1.328 x 0.996^age [x0.932 if female] Simple Cystatin C equation 100/Scys(mg/L)
Reference standard (s)	EDTA 51CrEDTA was injected intravenously; blood samples were obtained 120, 180 and 240 min after the injection. GFR was measured from 51CrEDTA clearance according to the Committee on Renal Clearance recommendations (22). 51CrEDTA clearance was calculated in mililiters per min per 1.73m2. Before 51CrEDTA was injected, blood was withdrawn for measuring serum creatinine and serum cystatin C.

Quality assessment

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Unclear

(Sampling method is unclear. It is likely a retrospective study in which all patients who underwent EDTA measurement were included.)

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Unclear

(Participants were included based on the results of the reference standard.)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

(Participants were referred due to suspected or established renal dysfunction. However, this includes a wide range of potential conditions and it is unclear how many have CKD)

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(likely that tests were conducted with knowledge of other tests already conducted.)

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Low

(index tests were determined objectively and are unlikely to have allowed for bias.)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low

(reference standard is determined objectively and is unlikely to have allowed for bias.)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

(reference standard was measured at the same time as the serum creatinine and cystatin.)

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Study included all participants with cystatin-c measurements on record. If the participating centres do not routinely measure cystatin-c then this represents a risk of selection bias)

Directness

Partially applicable

(Participants were referred due to suspected or established renal dysfunction. However, this includes a wide range of potential conditions and it is unclear how many have CKD)

Deng, 2015

Bibliographic Reference	Deng, F.; Finer, G.; Haymond, S.; Brooks, E.; Langman, C.B.; Applicability of estimating glomerular filtration rate equations in pediatric patients: Comparison with a measured glomerular filtration rate by iohexol clearance; Translational Research; 2015; vol. 165 (no. 3); 437-445

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location USA Study setting Children's hospital, Chicago Study dates November 2012 - January 2014 Sources of funding supported in part by grants from the National Institutes of Health, HD 074596-02, DK666174, and DK083908-01 and by a grant, National Science Foundation of China, NSFC 81302447 from Dr Deng's hospital, First Affiliated Hospital of Anhui Medical University, Hefei, Anhui Province, China.
Inclusion criteria	Underwent iohexel reference standard Possible kidney dysfunction Under 18 years of age
Exclusion criteria	None reported
Sample characteristics	Sample size 81 Female 45.7% Mean age (SD) 12.60 (5.14) years Transplant recipient 8.6%
Index test(s)	Filler equation 91.62 (1/Scys)^1.123 Grubb equation 84.69Sycs^-1.68 x 1.384 (for ages < 14 years) Bokenkamp equation (162/Scys) - 30

	Schwartz equation 2009 41.9(1.8/Scys)^0.777 Schwartz equation 2012 70.69Scys^-0.931
Reference standard (s)	Iohexel We measured iohexol in serum by a validated liquid chromatography tandem mass spectroscopy method from 4 serial blood samples collected at 10, 30, 120, and 300 minutes postiohexol injection with the clearance calculated using the concentration of iohexol as a function of time in 2 curves (fast and slow plasma disappearance)

Quality assessment

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

High

(Study included people aged up to 20 years (children plus adults aged between 18 and 20 years). Participants were included if they were referred for GFR measurement due to possible kidney dysfunction, which may include people without suspected or confirmed CKD).

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Low

(index tests are determined objectively and are unlikely to have allowed for bias.)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

(reference standard is determined objectively and is unlikely to have allowed for bias.)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

(reference standard was assessed at the same time serum creatinine and cystatin were measured.)

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Study included all participants with cystatin-c measurements on record. If the participating centres do not routinely measure cystatin-c then this represents a risk of selection bias)

Directness

Partially applicable

(Study included people aged up to 20 years (children and adults aged between 18 and 20 years). Reasons for referral for GFR being measured is unclear. It is unclear whether participant had (or were suspected of) CKD.)

Hari, 2014

Bibliographic Reference	Hari, Pankaj; Ramakrishnan, Lakshmy; Gupta, Ruby; Kumar, Rakesh; Bagga, Arvind; Cystatin C-based glomerular filtration rate estimating equations in early chronic kidney disease.; Indian pediatrics; 2014; vol. 51 (no. 4); 273-7

Study Characteristics

Study type	Cross-sectional study both a derivaton and external* validation study (only the validation cohort was extracted for this review. *Equations were tested on a separate cohort of recruited participants to the derivation cohort.
Study details	Study location India Study setting All India Institute of Medical Sciences, New Delhi, India Sources of funding Intramural research grant of AIIMS
Inclusion criteria	Age 2-18 years of age CKD Underwent 99TCm-DTPA reference standard with an mGFR between 60-90 ml/min/1.73m2
Exclusion criteria	Receiving dialysis other jaundice or severe edema medications receiving cotrimoxazole, corticosteroids or cephalosporins in the previous week
Sample characteristics	Sample size 42 Female 19% Mean age (SD) median (IQR): 9 (5-12) years Cystatin (mg/L) median (IQR)*: 0.7 (0.45-0.85) mGFR (SD) ml/min/1.73m2 median (IQR)*: 79 (72, 84)
Index test(s)	Hari equation 96.9 - 30.4 x ScysC
Reference standard (s)	DTPA

Quality assessment

Patient selection: risk of bias
Was a consecutive or random sample of patients enrolled?
Yes
Was a case-control design avoided?
Yes
Did the study avoid inappropriate exclusions?
Yes
Could the selection of patients have introduced bias?

High

(Participants in the validation dataset were different to those used in the derivation set. However, as both groups were recruited from a common sample these people are likely to have similar characteristics than a random external sample.)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

(all participants were 18 years or younger and referred due to CKD, caused primarily (83.1%) by GU tract anomalies. All participants had a GFR of between 60 and 90 ml/min/1.73m2)

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Low

(index tests are determined objectively and are unlikely to have allowed for bias.)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low

(reference standard is determined objectively and is unlikely to have allowed for bias.)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

No

("Cystatin C concentration was measured by particle enhanced immunoturbidimetry using the Cystatin PET kit (DAKO, Hamburg, Germany) within 3 months of collection")

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

High

(Cystatin C concentration was measured by particle enhanced immunoturbidimetry using the Cystatin PET kit (DAKO, Hamburg, Germany) within 3 months of collection)

Overall risk of bias and directness

Risk of Bias

Moderate

(Participants in the validation dataset were different to those used in the derivation set. However, as both groups were recruited from a common sample these people are likely to have similar characteristics than an external sample. Additionally, Cystatin C could have been measured for a period of up to 3 months after DTPA)

Directness

Directly applicable

Hojs, 2011

Bibliographic Reference	Hojs, R; Bevc, S; Ekart, R; Gorenjak, M; Puklavec, L; Kidney function estimating equations in patients with chronic kidney disease.; International journal of clinical practice; 2011; vol. 65 (no. 4); 458-64

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location Slovenia Study setting referrals for 51Cr-EDTA

	Sources of funding supported by a grant (L3-0328) from the Slovenian Research Agency (ARRS).
Inclusion criteria	suspected or established kidney dysfunction referred for 51CrEDTA clearance because of suspected or established renal dysfunction.
Exclusion criteria	None reported
Sample characteristics	Sample size 764 Female 42.0% Mean age (SD) 57.7 (SD 13.1) mGFR (SD) ml/min/1.73m2 47.5 (SD 34)
Index test(s)	Simple Cystatin C equation 100/ScysC Hojs equation 90.63 x ScysC^-1.192
Reference standard (s)	EDTA GFR was estimated from a single 51CrEDTA injection and three blood samples (120, 180 and 240 min after parenteral application of the marker) according to Committee on renal clearance recommendations

Quality assessment

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Unclear

(Likely that the study was retrospective and that all participants who had CKD diagnosed were included.)

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

High

(Study included all participants with cystatin-c measurements on record. If the participating centres do not routinely measure cystatin-c then this represents a risk of selection bias)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

(all participants were referred for testing due to suspected or established renal dysfunction. However, only those with CKD were retained for analysis.)

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Low

(index tests are determined objectively and is unlikely to have allowed for bias.)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low

(reference standard is determined objectively and is unlikely to have allowed for bias.)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

No

(Reference standard was conducted at the same time serum cystatin was measured.)

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Study included all participants with cystatin-c measurements on record. If the participating centres do not routinely measure cystatin-c then this represents a risk of selection bias)

Directness

Directly applicable

Hojs, 2010

Bibliographic Reference	Hojs, Radovan; Bevc, Sebastjan; Ekart, Robert; Gorenjak, Maksimiljan; Puklavec, Ludvik; Serum cystatin C-based formulas for prediction of glomerular filtration rate in patients with chronic kidney disease.; Nephron. Clinical practice; 2010; vol. 114 (no. 2); c118-26

Study Characteristics

Study type	Retrospective cohort study study
Study details	Study location Slovenia Study setting Single centre Sources of funding upported by a grant (L3-0328) from the Slovenia Research agency
Inclusion criteria	Age Caucasians aged at least 18 years old CKD were referred by nephrologists, diabetologists, cardiologists or general internists for measurement of EDTA clearance due to suspected or established renal dysfunction. (all participants had CKD, this was likely established after referral although this is not clear).
Sample characteristics	Sample size 592 Female 57.6 Mean age (SD) 57.8 years mGFR (SD) ml/min/1.73m2 47 (34)
Index test(s)	Hoek equation -4.32+[80.35 x 1/cystatin C] Grubb equation 89.12 x CystC^-1.1675 Larsson equation 77.24 x CystC^-1.2623 Simple Cystatin C equation 100/CystC Hojs equation 90.63 x CystC^-1.192

Reference standard (s)	EDTA 51CrEDTA clearance measured by a single injection of EDTA and 3 blood samples (120, 180 and 240 min after parenteral application of the marker)

Quality assessment

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Unclear

(Likely that the study was retrospective and that all participants who had CKD diagnosed were included.)

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

(all participants were referred for testing due to suspected or established renal dysfunction. However, only those with CKD were retained for analysis.)

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Low

(index tests are determined objectively and are unlikely to have allowed for bias.)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low

(reference standard is determined objectively and is unlikely to have allowed for bias.)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

No

(Reference standard was conducted at the same time serum cystatin was measured.)

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Study included all participants with cystatin-c measurements on record. If the participating centres do not routinely measure cystatin-c then this represents a risk of selection bias)

Directness

Directly applicable

Inker, 2018

Bibliographic Reference	Inker, Lesley A; Levey, Andrew S; Tighiouart, Hocine; Shafi, Tariq; Eckfeldt, John H; Johnson, Craig; Okparavero, Aghogho; Post, Wendy S; Coresh, Josef; Shlipak, Michael G; Performance of glomerular filtration rate estimating equations in a community-based sample of Blacks and Whites: the multiethnic study of atherosclerosis.; Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association; 2018; vol. 33 (no. 3); 417-425

Study Characteristics

Study type	Retrospective cohort study Ancillary study of the Multi-Ethnic Study of Atherosclerosis (MESA)
Study details	Study location US Study setting University MESA field centre Study dates Participants were recruited between May 2012 and April 2014 Sources of funding This research was supported by a grant from the National Institutes of Health; the National Heart, Lung, and Blood Institute and National Center for Research Resources.
Inclusion criteria	Participants completing third, fourth or fifth visit to the MESA study
Exclusion criteria	None reported
Sample characteristics	Sample size 294 Female 52.7% Mean age (SD) 70.7 (SD 8.6) % Diabetes 25% mGFR (SD) ml/min/1.73m2 72.6 (SD 18.8)
Index test(s)	CKD-EPI (CysC only equation) 133 x min(cysC/0.8,1)^-0.499 x max(cysC/0.8,1)^-1.328×0.996^Age x 0.932 (if female)
Reference standard (s)	Clearance of iohexol

Quality assessment

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Unclear

Section	Question	Answer
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Unclear
	Could the selection of patients have introduced bias?	Unclear *(Exclusion criteria were not reported)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low *(Measured GFR was within CKD categories 1 and 2)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
	If a threshold was used, was it pre-specified?	Yes
	Could the conduct or interpretation of the index test have introduced bias?	Low *(Index tests are determined objectively and is unlikely to have allowed for bias)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(Reference standard is determined objectively and is unlikely to have allowed for bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear *(Length of time between tests is unclear)*

Section	Question	Answer
	Did all patients receive a reference standard?	Yes
	Did patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	Unclear *(Length of time between tests is unclear)*
Overall risk of bias and directness	Risk of Bias	Moderate
	Directness	Directly applicable

Lemoine, 2016

Bibliographic Reference	Lemoine, Sandrine; Panaye, Marine; Pelletier, Caroline; Bon, Chantal; Juillard, Laurent; Dubourg, Laurence; Guebre-Egziabher, Fitsum; Cystatin C-Creatinine Based Glomerular Filtration Rate Equation in Obese Chronic Kidney Disease Patients: Impact of Deindexation and Gender.; American journal of nephrology; 2016; vol. 44 (no. 1); 63-70

Study Characteristics

Study type	Cross-sectional study prospectively collected data
Study details	Study location France Study setting Single centre in Lyon, France Study dates February 2013 - 2015 Sources of funding none reported
Inclusion criteria	suspected or established kidney dysfunction referred in our unit for various nephropathies due to suspected or established renal function Obesity BMI ≥ 30 kg/m 2
Sample characteristics	Sample size 166 Female 56% Mean age (SD) 58 (SD 14) years Cystatin (mg/L) 1.44 (SD 0.62) BMI (kg/m2) mean 36.7 (SD 5.5) Transplant recipient 9%

	kidney donor 2.3%
Index test(s)	CKD-EPI (CysC only equation) values also given for a De-indexed version of the formula (output in ml/min)
Reference standard (s)	Insulin or iohexel clearance "Inulin clearance (INUTEST 25%; Fresenius, Kabi, Austria) was performed in 46% of patients with a loading dose of 30 mg/kg that was injected in 10 min, with a maintenance dose infusion of a solution of inulin of 40 mg/kg. The urine was collected every 30 min, and we performed blood tests in the middle of each period of urine collection (3–4 collection periods of 30 min). Inulin clearance was calculated in each period (UV/P) to obtain the average (where U is urinary inulin, V is urine volume and P is plasmatic inulin). Measurements of plasma and urine polyfructosan concentrations were performed using an enzymatic method [16] . We injected 8 ml iohexol (300 mg; Omnipaque; GE Healthcare SAS, Vélizy-Villacoublay, France). The dose injected was determined by the weight of the syringe before and after injection. Blood collection was performed at 120, 180 and 240 min. The serum iohexol concentration was measured by HPLC [17] . The GFR was calculated as GFR = slope × dose/concentration at time 0 corrected with the Bröchner– Mortensen equation"

Quality assessment

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

High

(participants were referred due to various nephropathies because of suspected or confirmed renal function. It is not clear how many participants had suspected or confirmed CKD specifically)

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Low

(index tests are determined objectively and are unlikely to have allowed for bias.)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low

(reference standard is determined objectively and is unlikely to have allowed for bias.)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Unclear

(length of time between tests is unclear)

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

No

(46% of patients underwent inulin clearance reference standard and 54% underwent iohexel clearance. It is unclear how comparable these reference standards are.)

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

High

(Differences in reference standard and lack of clarity over timing in relation to index tests poses a potential bias.)

Overall risk of bias and directness

Risk of Bias

Moderate

(Participants received different reference standard. It is not clear whether these tests have similar accuracy. It is not clear whether serum cystatin was measured at the same time as the reference standard was conducted.)

Directness

Partially applicable.

(Participants were referred due to suspected or confirmed kidney dysfunction and had "various nephropathies". It is unclear how many of these participants were suspected of or a had a diagnosis of CKD.)

Ng, 2018

Bibliographic Reference	Ng, Derek K; Schwartz, George J; Schneider, Michael F; Furth, Susan L; Warady, Bradley A; Combination of pediatric and adult formulas yield valid glomerular filtration rate estimates in young adults with a history of pediatric chronic kidney disease.; Kidney international; 2018; vol. 94 (no. 1); 170-177

Study Characteristics

Study type	Prospective cohort study
Study details	Study location US and Canada Study setting Multicentre Study dates Recruitment began in 2005 Sources of funding The children prospective cohort study (CKiD) was supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases, with additional funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute
Inclusion criteria	CKD GFR <90 ml/min/1.73m² Participants who contributed data after the age of 18 years
Exclusion criteria	None reported
Sample characteristics	Sample size 187 Female 42% Median age (interquartile range) 18.7 (18.3 to 19.3) Cystatin (mg/L) Median 1.6 (interquartile range 1.2 to 2.2) BMI (kg/m2) Median 23 (interquartile range 20 to 29) Mean eGFR (SD) ml/min/1.73m2 51.8 (SD 29.4)

	mGFR (SD) ml/min/1.73m2 49.2 (SD 22.5)
Index test(s)	CKD-EPI (CysC only equation) 133 x min(cysC/0.8,1)^-0.499 x max(cysC/0.8,1)^-1.328×0.996^Age x 0.932 (if female)
Reference standard (s)	Clearance of iohexol

Quality assessment

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Unclear
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Unclear
	Could the selection of patients have introduced bias?	Unclear *(Unclear how participants were enrolled; exclusions were not reported)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low *(All participants had CKD)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
	If a threshold was used, was it pre-specified?	Yes
	Could the conduct or interpretation of the index test have introduced bias?	Low *(Index tests are determined objectively and are unlikely to have allowed for bias)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear

Section	Question	Answer
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(Reference standard is determined objectively and is unlikely to have allowed for bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear *(Length of time between tests is unclear)*
	Did all patients receive a reference standard?	Yes
	Did patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	Unclear *(Length of time between tests is unclear)*
Overall risk of bias and directness	Risk of Bias	Moderate
	Directness	Directly applicable

Salvador, 2019

Bibliographic Reference	Salvador, C.L.; Tondel, C.; Rowe, A.D.; Bjerre, A.; Brun, A.; Brackman, D.; Morkrid, L.; Estimating glomerular filtration rate in children: evaluation of creatinine- and cystatin C-based equations; Pediatric Nephrology; 2019; vol. 34 (no. 2); 301-311

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Norway Study setting Haukeland University Hospital and Oslo University Hospital Sources of funding The study was supported by grants from the Health Trust of Western Norway, The Norwegian Society of Nephrology, Haukeland University Hospital, and Oslo University Hospital.
Inclusion criteria	Age Under 18 years old

	CKD
Sample characteristics	Sample size 96 Female 42.7% Mean age (SD) median (range)*: 9.2 (0.25-17.5) Cystatin (mg/L) 1.11 (0.44, 5.47) mGFR (SD) ml/min/1.73m2 median range*: 65.9 (6.3,153); 42.7% <60, 57.3% 60+
Index test(s)	Schwartz equation 2009 70.69 x (cystC^-0.931) CAPA FAS
Reference standard (s)	Iohexel Iohexol was administrated via an intravenous cannula as Omnipaque® 300 mg I/mL (647 mg iohexol/mL, GE Healthcare, Oslo, Norway) in doses according to the patient's weight; < 10 kg, 1 mL; 10–20 kg, 2 mL; 20–30 kg, 3 mL; 30– 40 kg, 4 mL; ≥ 40 kg, 5 mL. Serum samples were collected from a vein of the contralateral arm of the iohexol injection at seven time points 10–300 min after injection for calculation of the seven-point reference mGFR (GFR7p), using the method of Sapirstein. GFR was normalized to body surface area calculated by the method of Haycock.

Quality assessment

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

(all participants had CKD and were aged under 18 years)

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Low

(index tests are determined objectively and are unlikely to have allowed for bias.)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low

(reference standard is determined objectively and is unlikely to have allowed for bias.)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

(serum samples for index tests were taken up to 300 minutes after the reference standard.)

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Low

Directness

Directly applicable

Teo, 2012

Bibliographic Reference	Teo, Boon Wee; Xu, Hui; Wang, Danhua; Li, Jialiang; Sinha, Arvind Kumar; Shuter, Borys; Sethi, Sunil; Lee, Evan J C; Estimating glomerular filtration rates by use of both cystatin C and standardized serum creatinine avoids ethnicity coefficients in Asian patients with chronic kidney disease.; Clinical chemistry; 2012; vol. 58 (no. 2); 450-7

Study Characteristics

Study type	Cross-sectional study a parallel substudy of the Asian Kidney Disease Study.
Study details	Study location Singapore Study setting outpatient nephrology clinics in the National University Hospital, Singapore
Inclusion criteria	Age over 21 years old CKD stable CKD defined as 2 serum creatinines measured 60 days apart of <20% difference and following practice guidelines. GFR serum creatinine with an estimated or measured GFR (mGFR) (MDRD, Cockcroft–Gault (10), or creatinine clearance) of 10 –90 mL/min.
Exclusion criteria	other acute kidney function deterioration, amputation, edema, pleural effusion or ascites, skeletal muscle atrophy, or any condition that potentially interferes with the accuracy of the measurement of GFR. Inability to consent physical conditions that render phlebotomy for blood samples difficult inability to collect urine samples successfully
Sample characteristics	Sample size 232 Female 48.3% Mean age (SD) 58.4 (12.8) Cystatin (mg/L) 1.66 (0.78) Mean eGFR (SD) ml/min/1.73m2 CKD-EPI: 52.8 (27.5) for overall population, 52.5 (30.2) for Chinese population; CKD-EPI (cyst - race modified): 50.3 (30.1) for overall population, 53.3 (32.4) for Chinese population; China collaborative group formula; 74.5 (39.1) for Chinese population mGFR (SD) ml/min/1.73m2 51.7 (27.5)
Index test(s)	CKD-EPI (CysC only equation) 76.7 x (-0.105+1.13 x CystC)^-1.19 eGFR5 China collaborative group formula eGFR5=86 x CysC^-1:132 CKD-EPI (cyst - race modified) equation 1 127.7 x (-0.105+1.13 x CystC)^-1.17 x age^-0.13 (x 0.91 if female)(x 1.06 if african-american)
Reference standard (s)	DTPA 3-sample plasma clearance of 99mTc-DTPA by use of an intravenous bolus of Technescan diethylene triamine pentaacetic acid

Quality assessment

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

(All participants presented with CKD)

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Low

(index tests are determined objectively and are unlikely to have allowed for bias.)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

No

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low

(reference standard is determined objectively and is unlikely to have allowed for bias.)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

(Serum samples were taken at the same time as GFR measurement)

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Low

Directness

Indirectly applicable

>50% of participants were of ethnicities for whom the cystatin-c equations to estimate GFR are known to have different accuracies.

Werner, 2017

Bibliographic Reference	Werner, Karin; Pihlsgard, Mats; Elmstahl, Solve; Legrand, Helen; Nyman, Ulf; Christensson, Anders; Combining Cystatin C and Creatinine Yields a Reliable Glomerular Filtration Rate Estimation in Older Adults in Contrast to beta-Trace Protein and beta2-Microglobulin.; Nephron; 2017; vol. 137 (no. 1); 29-37

Study Characteristics

Study type	Prospective cohort study
Study details	Study location Sweden Study setting

	Study recruited for an ongoing population-based study of older adults in southern Sweden randomized from the general population. Sources of funding None reported
Inclusion criteria	Age At least 70 years of age. GFR Participants were recruited to obtain balanced groups for each of the following GFR categories: <30, 30-60, and >60.
Exclusion criteria	None reported
Sample characteristics	Sample size 126 Female 49% Mean age (SD) 82.7 (SD 6.4) years mGFR (SD) ml/min/1.73m2 54 (SD 20)
Index test(s)	CKD-EPI (CysC only equation) 133×min (cys/0.8, 1)^-0.499×max(cys/0.8, 1)^-0.328 0.996^Age×0932 [if female] min indicates the minimum of cys/0.8 or 1, and max the maximum of cys/0.8 or 1. FAS equation 107.3/(cysC/0.82) x (0.988^(age-40) if age >40 years) if aged 70 years plus: 107.3/(cysC/0.95) x (0.988^(age-40) if age >40 years) CAPA equation 130 x (ScysC^-1.069) x (age^-0.117) -7
Reference standard (s)	Insulin or iohexel clearance Plasma clearance of iohexol was performed by a single sample method

Quality assessment

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

No

(Participants were recruited from a separate study conducted in the general population. Participants were recruited on the basis of their GFR as estimated in this study.)

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

High

(Participants were included from a general population study based on their GFR. It is not clear whether participants with a GFR in the > 60 grouping have CKD.)

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Low

(although the study notes for some participants used the first generation of Roche 1 as the reagent for cystatin measurement whereas others used the second generation)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low

(reference standard is determined objectively and is unlikely to have allowed for bias.)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Unclear

(unclear length of time between GFR measurements and measurement of cystatin C. As this study was prospective any delay in measurement is not expected to be very long.)

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Low

Directness

Partially applicable

(participants in the GFR >60 grouping may not have had CKD)

White, 2019

Bibliographic Reference	White, Christine A; Allen, Celine M; Akbari, Ayub; Collier, Christine P; Holland, David C; Day, Andrew G; Knoll, Greg A; Comparison of the new and traditional CKD-EPI GFR estimation equations with urinary inulin clearance: A study of equation performance.; Clinica chimica acta; international journal of clinical chemistry; 2019; vol. 488; 189-195

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Canada Study setting outpatient general nephrology, CKD, and transplant clinics at Kingston Health Sciences Center Sources of funding supported by the Canadian Institutes for Health Research (grant number 106510)
Inclusion criteria	Age at least 18 years of age CKD stable CKD
Exclusion criteria	Pregnant or breastfeeding; A negative plasma beta-HCG test was required for women of childbearing age prior to testing. Receiving dialysis likely need for dialysis or repeat transplant within 3 months allergy known allergy to iodine, inulin, shellfish or contrast dye other known impaired bladder emptying; likely death from co-morbid disease within 3 months
Sample characteristics	Sample size 86 Female 40% Mean age (SD) 60.2 (14.5) Mean eGFR (SD) ml/min/1.73m2 median (IQR)* CKD-EPI (CysC): 31.4 (19.8 - 54.0) mGFR (SD) ml/min/1.73m2 median (IQR)*: 28.9 (18.5 - 47.8)

Index test(s)	CKD-EPI (CysC only equation) 133 x min(cysC/0.8,1)^-0.499 x max(cysC/0.8,1)^-1.328×0.996^Age x 0.932 (if female)
Reference standard (s)	Insulin or iohexel clearance Urinary insulin clearance:

Quality assessment

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

(All people had CKD and were prospectively recruited.)

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Low

(index tests are determined objectively and are unlikely to have allowed for bias.)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low

(reference standard is determined objectively and is unlikely to have allowed for bias.)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

(Serum cystatin-C samples were measured immediately before reference standard was conducted.)

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Low

Directness

Directly applicable

Appendix F – Forest plots

None of the included studies could be combined to produce a pooled effect estimate.

Appendix G – GRADE tables

GRADE tables were not used for P values and AUC.

Likelihood ratio outcomes

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Elderly adults (>65 years old) with suspected or confirmed renal dysfunction Index test: Simple CysC equation Reference standard: GFR ≤60 mL/min/1.73 m^2 with 51Cr-EDTA										
Bevc 2011	Retrospective cohort study	317	0.85 (0.81, 0.89)	0.96 (0.87, 1.00)	LR+: 21.76 (5.59, 84.73)	Serious[1]	Serious[2]	N/A	Not serious	Low
					LR-: 0.15 (0.11, 0.21)	Serious[1]	Serious[2]	N/A	Not serious	Low
Adults with suspected or confirmed renal dysfunction (>18-year olds only) Index test: Simple CysC equation Reference standard: GFR ≤60 mL/min/1.73 m^2 with 51Cr-EDTA										
Bevc 2012	Retrospective cohort study	255	0.81 (0.74, 0.87)	0.88 (0.81, 0.94)	LR+: 7.00 (4.09, 11.99)	Serious[1]	Not serious	N/A	Not serious	Moderate
					LR-: 0.22 (0.16, 0.30)	Serious[1]	Not serious	N/A	Not serious	Moderate

1. Study was at moderate risk of bias
2. Study was only partially applicable to the review question.

Appendix H – Economic evidence study selection

1 Appendix I – Economic evidence tables

2 National Clinical Guideline Centre 2014

Study	National Clinical Guideline Centre. Chronic kidney disease (partial update). Assessed at: https://www.nice.org.uk/guidance/cg182/evidence/appendices-a-r-pdf-191905166			
Study details	**Population & interventions**	**Costs**	**Outcome (percentage)**	**Percentage correct**
Economic analysis: Cost consequence analysis **Study design:** Decision tree **Approach to analysis:** Simple decision tree according to diagnostic outcomes (True positive, False positive, True negative, False negative **Perspective:** NHS perspective **Time horizon:** 1 year **Intervention effect duration:** 1 year **Discounting:** No discounting as time horizon is 1 year	**Population:** People with suspected CKD categorised into • Adults 75+ • Adults under 75 with hypertension • Adults under 75 without hypertension **Interventions** CKD-EPI$_{Cys}$: eGFR is re-calculated using serum cystatin C and the CKD-EPI$_{cys}$ equation CKD-EPI$_{Create-cys}$: eGFR is re-calculated using serum cystatin C and serum creatinine and the combined CKD-EPI equation **Comparitor**	Age 75+ CKD-EPI$_{Create}$: £51.75 CKD-EPI$_{Cys}$: £42.63 CKD-EPI$_{Create-cys}$: £46.35 Age<75 No hypertension CKD-EPI$_{Create}$: £51.75 CKD-EPI$_{Cys}$: £38.11 CKD-EPI$_{Create-cys}$: £44.30 Age<75 hypertension CKD-EPI$_{Create}$: £58.75 CKD-EPI$_{Cys}$: £39.80 CKD-EPI$_{Create-cys}$: £43.97	**False Positive** Age 75+ CKD-EPI$_{Create}$: 20.2 CKD-EPI$_{Cys}$: 10.6 CKD-EPI$_{Create-cys}$: 12.2 Age<75 No hypertension CKD-EPI$_{Create}$: 33 CKD-EPI$_{Cys}$: 13 CKD-EPI$_{Create-cys}$: 17 Age<75 hypertension CKD-EPI$_{Create}$: 30 CKD-EPI$_{Cys}$: 7 CKD-EPI$_{Create-cys}$: 11 **False Negative** Age 75+ CKD-EPI$_{Create}$: 0 CKD-EPI$_{Cys}$: 12.9 CKD-EPI$_{Create-cys}$: 7.3	Age 75+ CKD-EPI$_{Create}$: 79.8 CKD-EPI$_{Cys}$: 76.6 CKD-EPI$_{Create-cys}$: 80.5 Age<75 No hypertension CKD-EPI$_{Create}$: 67 CKD-EPI$_{Cys}$: 75 CKD-EPI$_{Create-cys}$: 81 Age<75 hypertension CKD-EPI$_{Create}$: 70 CKD-EPI$_{Cys}$: 79 CKD-EPI$_{Create-cys}$: 79

	CKD-EPI$_{create}$: no further testing, the person is diagnosed as having CKD stage 3a		Age<75 No hypertension CKD-EPI$_{Create}$: 0 CKD-EPI$_{Cys}$: 12 CKD-EPI$_{Create-cys}$: 3 Age<75 hypertension CKD-EPI$_{Create}$: 0 CKD-EPI$_{Cys}$: 14 CKD-EPI$_{Create-cys}$: 11	
Data sources				
Outcomes: Proportion of patients falsely diagnosed as having CKD (False positive - FP), Proportion of patients falsely diagnosed as not having CKD (False Negative - FN), NHS cost at 1 year **Costs:** All costs were obtained from standard UK sources. The cost of drugs used data the National Drug Tariff and Prescription Cost Analysis England. The cost of CKD management were from PSSRU and NHS Reference costs. Costs included in the model were visits to the GP and nurse, biochemistry, haematology tests. Drug costs included were angiotensin-converting enzyme inhibitor, diuretic, calcium channel blocker, beta blocker, alpha blocker and angiotensin receptor blocker. A weighted drug use was used in the model.				
Comments				
Model from 2014 NICE guideline. This review question was not prioritised for modelling in the 2020 update of the guideline, so this analysis has not been updated.				
Overall applicability: Partially applicable				
Conducted from an NHS perspective but no health-related outcomes as it is a cost consequence analysis				
Overall quality: Minor limitations				
Data from the best available sources and time horizon sufficient *[1] Costs as reported, costs were inflated in the evidence profiles to 2020 prices*				

1 **Shardlow 2017**

Study	Shardlow A, McIntyre NJ, Fraser SDS, Roderick P, Raftery J, Fluck RJ, et al. (2017) The clinical utility and cost impact of cystatin C measurement in the diagnosis and management of chronic kidney disease: A primary care cohort study. PLoS Med 14(10): e1002400. https://doi. org/10.1371/journal.pmed.1002400

Study details	Population & interventions	Costs[1]	Outcomes	Total increase per patient
Economic analysis: Cost consequence analysis **Study design:** Cohort study **Perspective:** NHS perspective **Time horizon:** 5 years **Discounting:** None	**Population:** Adults over 18 years with eGFR result consistent with two CKD stage 3 values at least 90 days apart. People were excluded if they were judged to have less than a year to live, unable to visit their primary care surgery or previously received a solid organ transplant. 1,741 people were included in the study, 653 had CKD G3a using $eGFR_{creat}$ **Interventions** Implementing cystatin C testing and 12 months of monitoring using $eGFR_{cystatin\ C}$ Implementing cystatin C testing and 12 months of monitoring using $eGFR_{creatinine\ and\ cystatin\ C}$ **Comparator** $eGFR_{creat}$: standard care	**Cost differences:** Implementing cystatin C testing and 12 months of monitoring using $eGFR_{cystatin\ C}$ compared with $eGFR_{creat}$: £12,843 Implementing cystatin C testing and 12 months of monitoring using $eGFR_{creatinine\ and\ ystatin\ C}$ compared with $eGFR_{creat}$: £3,226 **Currency & cost year:** Sterling 2015 **Cost components incorporated:** Monitoring, removing eGFR and uACR (urine albumin to creatinine ratio) from annual review, biannual assessment of eGFR and uACR, nephrology	**N/A**	Implementing cystatin C testing and 12 months of monitoring using $eGFR_{cystatin\ C}$: £23 Implementing cystatin C testing and 12 months of monitoring using $eGFR_{creatinine\ and\ ystatin\ C}$: £8 **Analysis of uncertainty:** None
Data sources				
Quality of life weights: None				

Costs: All costs were obtained from standard UK sources and used due to patients being reclassified with different tests. The cost of drugs used data from Prescription Cost Analysis 2010. The price and unit costs for screening and appointments were sourced from the Unit Costs of Health and Social Care 2010 (Curtis 2010) and from the CKD Costing Report 2008 (NICE 2008).
Comments
Source of funding: Research Project Grant from the Dunhill Medical Trust. Previous funding from British Renal Society and Kidney Research UK. Unrestricted educational grant from Roche Products Ltd
Overall applicability: Partially applicable
Conducted from an NHS perspective but no health-related outcomes as it is a cost consequence analysis
Overall quality: Minor limitations
Data from the best available sources with sufficient time horizon

1 [1] *Costs as reported, costs were inflated in the evidence profiles to 2020 prices*

2 **Economic evaluation checklist [National Clinical Guideline Centre 2014]**

National Clinical Guideline Centre. Chronic kidney disease (partial update). Assessed at: https://www.nice.org.uk/guidance/cg182/evidence/appendices-a-r-pdf-191905166		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	
1.5 Is the perspective for outcomes appropriate for the review question?	No	No QALYs are included in the analysis
1.6 Are all future costs and outcomes discounted appropriately?	NA	Only 1 year time horizon
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe	No	No QALYs are included in the analysis, cost consequence analysis

National Clinical Guideline Centre. Chronic kidney disease (partial update). Assessed at: https://www.nice.org.uk/guidance/cg182/evidence/appendices-a-r-pdf-191905166		
Category	**Rating**	**Comments**
rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).		
1.8 OVERALL JUDGEMENT	**PARTIALLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Partly	Quality of life not included
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	No	The input studies were excluded in this evidence review
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	No	QALYs not included in the analysis
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

1 Economic evaluation checklist [Shardlow 2017]

Shardlow A, McIntyre NJ, Fraser SDS, Roderick P, Raftery J, Fluck RJ, et al. (2017) The clinical utility and cost impact of cystatin C measurement in the diagnosis and management of chronic kidney disease: A primary care cohort study. PLoS Med 14(10): e1002400. https://doi.org/10.1371/journal.pmed.1002400		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	
1.5 Is the perspective for outcomes appropriate for the review question?	No	No QALYs were included in the analysis
1.6 Are all future costs and outcomes discounted appropriately?	No	No discounting done
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	No	No QALYs included in this analysis, cost consequence analysis
1.8 OVERALL JUDGEMENT	**PARTIALLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Partly	Quality of life not included
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	

Shardlow A, McIntyre NJ, Fraser SDS, Roderick P, Raftery J, Fluck RJ, et al. (2017) The clinical utility and cost impact of cystatin C measurement in the diagnosis and management of chronic kidney disease: A primary care cohort study. PLoS Med 14(10): e1002400. https://doi.org/10.1371/journal.pmed.1002400		
Category	**Rating**	**Comments**
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	No	QALYs not included in the analysis
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	No sensitivity analysis done
2.11 Has no potential financial conflict of interest been declared?	Yes	Other conflicts of interest have been declared
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

1

Appendix J – Health economic model

No health economic modelling was undertaken for this review question.

Appendix K – 2014 Health economic model

The model described below was developed in 2014 for the update of the CKD guideline conducted then. This review question was not prioritised for modelling in the 2020 update of the guideline, so this analysis has not been updated. The results of this 2014 model have therefore been included in the guideline in the same way as those from a published journal article. (see Appendix I).

Cost-effectiveness analysis: cystatin C testing in the diagnosis of CKD

Methods

Model overview

Estimated glomerular filtration rate (eGFR) is an estimate of kidney function routinely used in clinical practice because measuring GFR (mGFR) is impractical and costly. An eGFR of less than 60 mL/min/1.73m^2 on at least 2 occasions separated by >90 days defines Chronic Kidney Disease (CKD) stage 3 and below. Current practice in the UK is to estimate GFR from serum creatinine (SCr) using the isotope dilution mass spectrometry (IDMS) related MDRD (Modification of Diet in Renal Disease) equation.

The use of a marker of kidney damage (urinary albumin:creatinine Ratio, ACR) is also routinely used in clinical practice. The finding of an elevated urinary ACR (≥3 mg/mmol) defines CKD when the eGFR is ≥60 mL/min/1.73m^2 and refines the classification of CKD regardless of kidney function, providing prognostic information at any level of eGFR.

The use of a universal threshold eGFR of 60 mL/min/1.73m^2 for the diagnosis of CKD in the absence of markers of significant kidney damage has been a source of controversy since the international 5 stage classification of CKD was first introduced. This is partly driven by the increasing inaccuracy of the estimating equations at higher GFR levels. Derivation of a newer estimating equation based on the CKD Epidemiology Consortium creatinine equation (CKD-EPI$_{creat}$) equation, has improved the accuracy of estimated GFR. Measurement of an additional marker of kidney function, cystatin C, has also been suggested to better define CKD using the CKD-EPI cystatin C equation (CKD-EPI $_{cys}$), or a combined equation using creatinine and cystatin, the CKD-EPI $_{creat-cys}$. It is proposed that use of these equations, particularly in the GFR range 45-59 mL/min/1.73 m^2, leads to more accurate diagnosis of CKD. Therefore the trade-offs are represented by the cost of the additional cystatin C measurements versus the cost of misdiagnosed patients (false positives) who are unnecessarily labelled as CKD and placed in a CKD management programme.

A significant number of patients will be affected by the choice of equation (~7% prevalence of CKD stages 3-5 in the general population using QICKD data). The guideline update literature review found no new evidence since the publication of CG73 on the cost-effectiveness of eGFR equations for this topic. As a consequence, the GDG has identified this topic as a high priority for an original economic analysis.

Comparators

Three diagnostic strategies for patients with suspected CKD (CKD-EPI$_{creat}$ 45-59 and ACR <3) were devised to allow for differential use of diagnostic tests.

The strategies compared are:

- CKD-EPI$_{creat}$: In this strategy, no further testing is conducted and the person is diagnosed as having CKD stage 3a.
- CKD-EPI $_{cys}$: In this strategy, eGFR is re-calculated using serum cystatin C and the CKD-EPI$_{cys}$ equation.
- CKD-EPI$_{creat-cys}$: In this strategy, eGFR is re-calculated using serum cystatin C and serum creatinine and the combined CKD-EPI equation.

After reviewing the clinical evidence it was decided unnecessary to consider the MDRD equation since CKD-EPI$_{creat}$ has both greater precision and less bias and is no more costly to administer.

Population

People with suspected CKD (CKD-EPI$_{creat}$ eGFR 45-59 mL/min/1.73 m^2 and ACR <3), categorised into the following subgroups.

- Adults 75+ years of age
- Adults under 75 years of age
  - With and without hypertension

Time horizon, perspective, discount rates used

The time horizon was one year in the base case. The perspective was that of the UK NHS.

Outcomes

The main outcomes of the model are:

- Proportion of patients falsely diagnosed as having CKD (False positive - FP)
- Proportion of patients falsely diagnosed as not having CKD (False Negative - FN)
- NHS cost at 1 year

Deviations from NICE reference case

QALYs were not calculated. The GDG decided that the key outcome would be false positives avoided (not QALYs). This is because:

- Most people, especially older people, who are eGFR 45-59 mL/min/1.73 m^2 will not progress to later stages of CKD
- Although we use a GFR cut-off to diagnose CKD, kidney function is a continuum and therefore (before disease has progressed) the FP, TP, FN, FP will have (almost) identical quality of life.
- It was agreed that a substantial proportion of FNs would be picked up by re-screening before significant disease progression.

Given the main outcome selected by the GDG was the number of FPs avoided, it was agreed that cost savings should be estimated over a short time horizon 12 months. This means that the cost savings associated with cystatin C are conservatively estimated. This was subjected to sensitivity analysis.

Approach to modelling

The model is a simple decision tree that categorises patients according to diagnostic outcomes (false positive (FP), true negative (TN), false negative (FN), and true positive (TP) results) – the model structure is presented in Figure 1.

Model inputs

Diagnostic accuracy data

The GDG requested data from studies in the guideline review for patients with CKD-EPI$_{creat}$ 45-59 mL/min/1.73 m^2 and ACR<3mg/mmol. Data was sought from studies that contained both CKD-EPI$_{creat}$ and CKD-EPI$_{creat}$. Data was received from the following studies:

- CKD-EPI derivation and validation cohorts (Inker 2012).
  - Age<75 Hypertension, No diabetes (n=142)
  - Age>75 No hypertension, No diabetes (n=150)
- Kilbride et al (2013)
  - Age 75+ (n=81)

Since there was little data for older patients, this was supplemented with unpublished data from the AGES-Reykjavik study (Inker 2013), provided by the authors of the CKD-EPI study.

- Age 75+ (n=156)

As indicated for the younger cohort we were able to sub-divide between those with and without hypertension and the few patients with diabetes were excluded. For the older cohort few patients did not have hypertension and a substantial proportion did have diabetes but the numbers were too small to allow further disaggregation.

The data is shown in Table 9. The individual results of the two 75+ cohorts are not presented because some of the data is academic in confidence. However, we can confirm that the prevalence, sensitivity and specificity across those two cohorts were very similar, suggesting that aggregation is not unreasonable.

Figure 1: Decision Tree

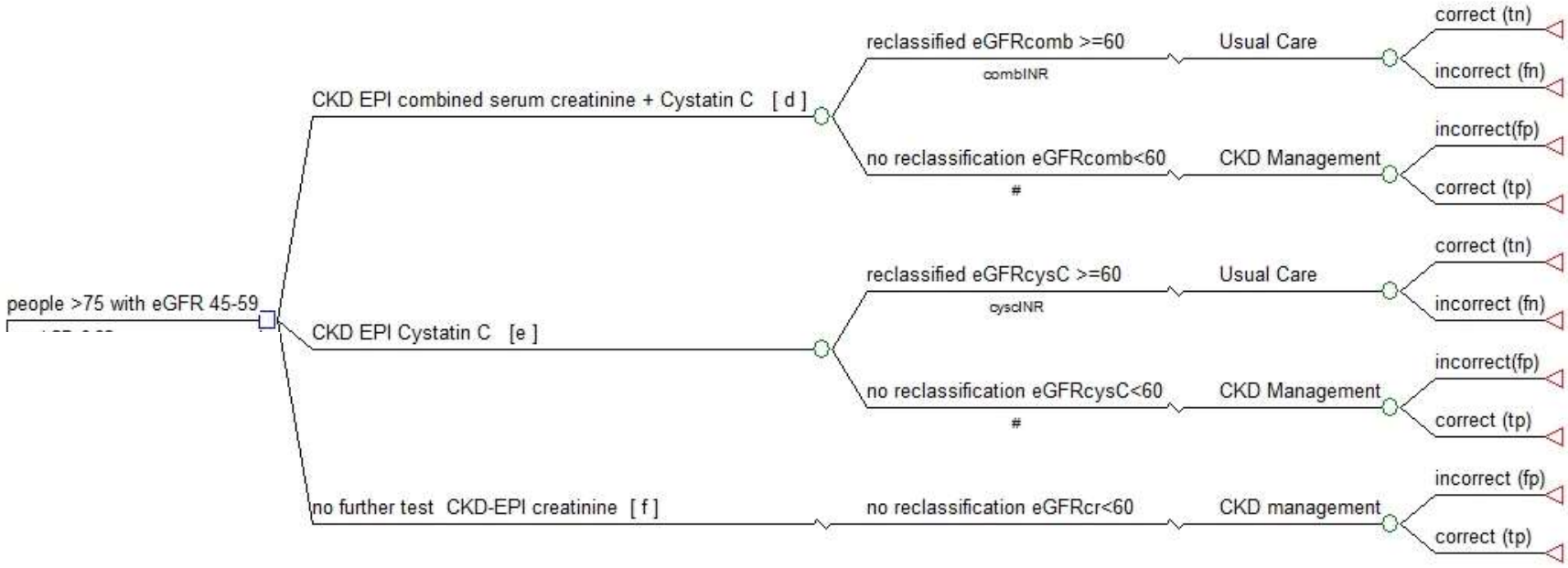


Table 9 Diagnostic data

Age 75+

CKD-EPI$_{cys}$				NO. of CD
	mGFR<60	mGFR>60		183
TP	160	25	FP	
FN	29	23	TN	
Total	189	48	237	

CKD-EPI $_{creat-cys}$				NO. of CD
	mGFR<60	mGFR>60		192
TP	173	29	FP	
FN	16	19	TN	
Total	189	48	237	

Age<75 No hypertension

CKD-EPI $_{cysC}$				NO. of CD
	mGFR<60	mGFR>60		113
TP	83	20	FP	
FN	17	30	TN	
Total	100	50	150	

CKD-EPI $_{creat-cys}$				NO. of CD
	mGFR<60	mGFR>60		121
TP	96	25	FP	
FN	4	25	TN	
Total	100	50	150	

CD=correct diagnoses, FN=false negative, FP=false positive, TN=true negative, TP=true positive.All mGFR values are measured in mL/min/1.73 m^2

Resource use and cost

Diagnosis

In the base case it was assumed that the cystatin C test is requested at the same time as the confirmatory creatinine test, 3 months after the first abnormal eGFR reading. Manpower, equipment and storage costs for the different strategies were considered equal and excluded from this analysis. In terms of resources required, the only difference between GFR estimation methods is the chemical reagent required for the laboratory analysis. Due to the lack of published information on the costs of diagnostic tests, the GDG estimated that the cost of a serum creatinine reagent was £0.25 and serum cystatin C reagent was £2.50.

In sensitivity analysis we looked at alternative scenario where the cystatin C test was ordered after the results of the confirmatory creatinine test are known. In this scenario there are no costs associated with the CKD-EPI$_{creat}$ strategy and for the other strategies we allocated the full cost of a serum creatine test assumed to be £3 plus another £3 for phlebotomy (SA3 and SA4).

Since there will be a number of false negative results from both cystatin C strategies, in a sensitivity analyses we added a re-test at 12 months including a test (£6) plus a 10 minute GP visit (£37) for patients who were classified as not having CKD (SA1 and SA4).

CKD management

The components of CKD management are described in Table 10. The unit costs of these components were taken from standard sources. Patients categorised as CKD-EPI$_{cys}$ eGFR >60 mL/min/1.73 m^2 or CKD-EPI$_{creat-cys}$ eGFR >60 mL/min/1.73 m^2 do not incur these CKD management costs. They only accrue diagnostic test costs. No additional costs were assumed for false negative patients.

Drugs

It was hypothesised that people with CKD and hypertension might receive more intensive anti-hypertensive therapy. We conducted a comparison of antihypertensive costs for patients with (eGFR 45-59 mL/min/1.73 m^2) and without CKD (eGFR 60-89 mL/min/1.73 m^2) using data from general practice[329]- Table 11. The Drug and CKD management costs were estimated only for one year in the base case. However, in a sensitivity analysis, they were assumed to continue for 5 years (SA2). The annual cost of antihypertensive medication was lower by 15% (£7.00) in the group with eGFR 60-89 ml/min/1.73 m^2, which is probably an under-estimate since CKD patients might also be on higher doses of individual drugs.

Table 10: Annual Incremental cost of CKD management

Component	Unit Cost	Annual frequency	Source
GP visit 10 mins	£37.00	1	PSSRU 2012
GP nurse visit 10 mins	£7.50	1	PSSRU 2012
Biochemistry test	£3.00	1	NHS Reference Costs 2011-2012
Haematology test	£1.00	1	NHS Reference Costs 2011-2012
Phlebotomy	£3.00	1	NHS Reference Costs 2011-2012
Total cost	£51.50		

Table 11: Cost of antihypertensive medication

	Unit cost*	Patients with eGFR 45-59 ml/min/1.73 m^2 (n=7,993)		Patients with eGFR 60-89 ml/min/1.73 m^2 (n=25,001)		Assumption*	
Angiotensin-converting-enzyme inhibitor	£ 16.57	4884	61%	14263	57%	Weighted average of ramipril 10mg/day, lisinopril 20mg/day, perindopril erbumine 4mg/day	
Diuretic	£ 11.47	5056	63%	12374	49%	bendroflumethiazide	2.5 mg daily
Calcium channel blocker	£ 12.78	4271	53%	12410	50%	amlodipine	5 mg once daily
Beta blocker	£ 15.38	4032	50%	9787	39%	bisoprolol	10mg daily
Angiotensin receptor blocker	£ 40.71	2322	29%	6083	24%	Weighted average of irbesartan 150mg/day, candesartan 4mg/day, losartan 50mg/day	
Alpha blocker	£ 11.99	1391	17%	3551	14%	doxazosin	1 mg daily
Drugs per patient			2.15		2.34		
Weighted average cost			£ 46.10		£ 39.10		

** Source : National Drug Tariff 2012, Prescription Cost Analysis England 2012.*

Computations

Diagnostic Outcomes

For each equation patients were subdivided according to their estimated

	mGFR<60	mGFR>60
eGFR<60	True positive (TP)	False positive (FP)
eGFR>60	False negative (FN)	True negative (TN)

All GFR values units are ml/min/1.73 m²

Using this data, we calculated the following:

Prevalence=$^{TP + FN}/_{(FN + FP + TN + TP)}$ [*Same for all equations]*

Specificity= $^{TN}/_{(TN + FP)}$

Sensitvity= $^{TP}/_{(FN + TP)}$

Diagnostic odds ratio (DOR)= $\frac{^{TP}/_{FN}}{^{FP}/_{TN}}$

For the probabilistic analysis we calculate

TP=Sensitvity x prevalence

FN=(1-sensitvity) x prevalence

TN=Specificity x (1-prevalence)

FN=(1-specificity) x (1-prevalence)

Where the specificity, prevalence and DOR are each defined by a distribution (see Uncertainty, below) and the sensitivity is defined as:

Sensitvity= $^{1}\Big/\left(1 + \frac{1}{DOR\left(\frac{1-specificity}{specificity}\right)}\right)$.

Costs

TP, FP=Test cost+drug cost+CKD management cost

TN, FN=Test cost only (+Re-test cost in sensitivity analysis)

Uncertainty

The base case model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input

parameter which was varied. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution. The model was run 10,000 times for the base case analyses and results were summarised.

We checked for convergence by plotting incremental cost on a graph for the probabilistic base case analysis. The incremental costs had converged by the 500th iteration.

The way in which distributions are defined reflects the nature of the data, so for example probabilities were given a beta distribution, which is bounded by zero and one, reflecting that a probability cannot be outside of this range. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 12: Description of the type and properties of distributions used in the probabilistic analysis

Parameter	Type of distribution	Properties of distribution
Prevalence of 'true' CKD Specificty Probability of being on a drug	Beta	Bounded between 0 and 1. Alpha=pN Beta=(1-p)N Where p=sample probability and N=sample size (For specificity N=the number of true neatives plus false positives in the sample)
Natural log of the diagnostic odds ratio (DOR)	normal	The DOR is bounded at zero. The mean of the distribution=ln(DOR). The standard error is defined as: $SEln(DOR) = \sqrt{\frac{1}{TP} + \frac{1}{FN} + \frac{1}{TN} + \frac{1}{FP}}$

Prices were left deterministic (that is, they were not varied in the probabilistic analysis). The sensitivity is calculated as a function of the DOR and the specificity, which captures the inverse relationship between sensitivity and specificity.

In addition sensitivity analyses were undertaken to test the robustness of model assumptions. These sensitivity analyses were conducted deterministically (that is, based on the parameter point estimates rather than their distributions). In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results.

Table 13: Prevalence and accuracy by cohort

	Prevalence	Sensitivity of eGFR CKD-EPI$_{cys}$	Specificity of eGFR CKD-EPI$_{cys}$	Sensitivity of eGFR CKD-EPI$_{creat-cys}$	Specificity of eGFR CKD-EPI$_{creat-cys}$
Age 75+	80%	85%	48%	92%	40%
Age<75 No hypertension	67%	83%	60%	96%	50%
Age<75 Hypertension	70%	80%	76%	85%	64%

Table 14: Base case results (probabilistic)

	Diagnostic outcomes			Mean costs (£)			
	Correct	FP	FN	Diagnosis	Additional drugs	CKD Care	Total
Age75+							
CKD-EPI$_{creat}$	79.8%	20.2%	0%	0.25		51.50	51.75
CKD-EPI$_{cys}$	76.6%	10.6%	12.9%	2.75		39.88	42.63
CKD-EPI$_{creat-cys}$	80.5%	12.2%	7.3%	2.75		43.60	46.35
Age<75 No hypertension							
CKD-EPI$_{creat}$	67%	33%	0%	0.25	0	51.50	51.75
CKD-EPI$_{cys}$	75%	13%	12%	2.75	0	35.36	38.11
CKD-EPI$_{creat-cys}$	81%	17%	3%	2.75	0	41.55	44.30
Age<75 Hypertension							

	Diagnostic outcomes			Mean costs (£)			
	Correct	**FP**	**FN**	**Diagnosis**	**Additional drugs**	**CKD Care**	**Total**
CKD-EPI$_{creat}$	70%	30%	0%	0.25	7.00	51.50	58.75
CKD-EPI$_{cys}$	79%	7%	14%	2.75	4.43	32.62	39.80
CKD-EPI$_{creat-cys}$	79%	11%	11%	2.75	4.93	36.29	43.97

FP=false positive, FN=false negative

Table 15: Base case results - incremental results (probabilistic)

	False Positives				False negatives				Cost (£)			
		Incremental vs CKD-EPIcreat				Incremental vs CKD-EPIcreat				Incremental vs CKD-EPIcreat		
	%		lower 95%	upper 95%	%		lower 95%	upper 95%	Mean		lower 95%	upper 95%
Age75+												
CKD-EPI$_{creat}$	20.2%				0.0%				51.75			
CKD-EPI$_{cys}$	10.6%	-9.7%	-13.8%	-6.3%	12.9%	12.9%	5.4%	24.4%	42.63	-9.12	-16.10	-4.05
CKD-EPI$_{creat-cys}$	12.2%	-8.0%	-11.8%	-4.9%	7.3%	7.3%	2.7%	15.7%	46.35	-5.40	-10.65	-1.80
Age<75 No hypertension												
CKD-EPI$_{creat}$	33.3%				0.0%				51.75			
CKD-EPI$_{cys}$	13.3%	-20.0%	-26.9%	-14.0%	12.1%	12.1%	4.9%	23.5%	38.11	-13.64	-17.60	-9.88
CKD-EPI$_{creat-cys}$	16.7%	-16.6%	-23.2%	-11.1%	2.7%	2.7%	0.7%	5.7%	44.30	-7.45	-10.99	-4.41
Age<75 Hypertension												
CKD-EPI$_{creat}$	29.6%				0.0%				58.75			
CKD-EPI$_{cys}$	7.0%	-22.5%	-29.6%	-16.1%	14.1%	14.1%	9.0%	20.2%	39.80	-18.94	-23.60	-14.39
CKD-EPI$_{creat-cys}$	10.6%	-19.0%	-25.7%	-13.0%	10.5%	10.5%	6.0%	16.0%	43.97	-14.77	-19.16	-10.56

Table 16: Sensitivity analysis (deterministic)

	Base case (probabilistic)	Base case (deterministic)	SA1	SA2	SA3	SA4
Age75+						
CKD-EPI$_{creat}$	51.75	51.75	51.75	257.75	51.50	51.50
CKD-EPI$_{cys}$	42.63	42.95	52.39	203.75	46.20	55.64
CKD-EPI$_{creat-cys}$	46.35	46.64	52.99	222.22	49.89	56.24
Age<75 No hypertension						
CKD-EPI$_{creat}$	51.75	51.75	51.75	257.75	51.50	51.50
CKD-EPI$_{cys}$	38.11	38.11	51.59	179.57	41.36	54.84
CKD-EPI$_{creat-cys}$	44.30	44.29	52.61	210.47	47.54	55.86
Age<75 Hypertension						
CKD-EPI$_{creat}$	58.75	58.75	58.75	292.74	58.50	58.50
CKD-EPI$_{cys}$	39.80	39.83	55.57	188.13	43.08	58.82
CKD-EPI$_{creat-cys}$	43.97	43.95	56.66	208.73	47.20	59.91

SA1=Sensitivity Analysis 1=The same as base case except that people that are CKD-EPI$_{cys}$>60 or CKD-EPI$_{creat-cys}$>60 are re-tested after 12 months incurring another test and a GP visit. SA2=Sensitivity Analysis 2= The same as base case except that CKD drug and management costs are for 5 years (not 1 year)
SA3=Sensitivity analysis 3=The same as base case except that cystatin C test is ordered after the result of the follow-up creatinine test
SA4=Sensitivity analysis 4=The same as SA1 except that cystatin C test is ordered after the result of the follow-up creatinine test

Results

The prevalence of 'true CKD' (mGFR<60 ml/min/1.73 m^2) was lower in the younger cohorts suggesting that the CKD-EPI creatinine equation is over-predicting CKD in these patients (Table 13). Sensitivity of the test was similar across the 3 cohorts but specificity was greater in the younger cohorts particularly in the hypertensive cohort, suggesting that the CKD-EPI creatinine equation is over-predicting in younger people much more so than the two cystatin-based equations. Across all 3 cohorts the combined equation was more sensitive but the cystatin C equation was more specific.

In all 3 cohorts, the cystatin c equation produced the fewest false positive results, which led to it being the lowest cost strategy – the cost of the test being more than offset by the subsequent reduction in drug and management costs (Table 14 and Table 15). In the cohort of older patients and the cohort of non-hypertensive patients, it was actually the combined equation that had the most accurate diagnoses since it had fewer false negative results due to its greater sensitivity.

If we consider CKD management costs over 5 years then the cost savings per patient tested compared with the creatinine test alone increase (Table 16) – for example, for younger patients without hypertension they increased from £14 to £78 per patient.

If we add the cost of a follow-up test (Table 16) to try and pick up false negatives after a year then CKD-EPI_{cys} is the least cost strategy for younger patients but not for older patients. However, if we increase the timeframe of CKD management costs to 2 or more years then CKD-EPI_{cys} is the lowest cost strategy for older patients as well.

If the cystatin C test is ordered after the results of the follow-up test are known (Table 16) then the CKD-EPI_{cys} is the least cost strategy but not if there is a follow-up test to try and pick up false negatives after a year. However, again, if we increase the timeframe of CKD management costs to 2 or more years then CKD-EPI_{cys} is the lowest cost strategy again.

Interpreting Results

Summary of results

Additional eGFR measurement for people with CKD-EPI_{creat} eGFR 45-59 ml/min/1.73 m^2 is cost saving and reduces the number of false positives compared to eGFR measurement with serum creatinine alone for all subgroups investigated. However, additional GFR estimation using cystatin C or cystatin C + creatinine for people with CKD-EPI_{creat} eGFR 45-59 ml/min/1.73 m^2 will also increase the number of false negatives identified.

Limitations and Interpretation

The GDG considered False Positives as the outcome of greatest concern because of the risks of medication and the unnecessary anxiety caused by over-diagnosis, which may have broader impacts on patients including life insurance premiums. The GDG assumed that False Negatives would not experience significant adverse effects as they would mostly be identified in the future according to other symptoms.

It would be difficult to estimate the longer-term cost and health impact of the different strategies, since this would depend on the progression of disease in the CKD negative patients (CKD-EPi_{creat} 45-59 and CKD-$EPI_{creat\ cys}$=60+ and ACR,3) and how that progression is affected by CKD management, which we believe is not known with any precision. But it is acknowledged that this is a limitation of the analysis. However, it is perhaps not a serious one since most false negatives would be subsequently identified before significant progression especially if there is re-testing of CKD-negative patients after 12 months, as in

the sensitivity analysis. The analysis was assessed as partially applicable since it did not estimate quality-adjusted life-years.

The cost savings attributable to cystatin c testing were sensitive to some of the assumptions made. For example the addition of the cost of a re-test after 12 months to pick up patients previously given a false negative result meant that there were not net savings. But even in this scenario, when the conservative time horizon of 1 year was increased to 2 years then savings were apparent again. This means that re-testing at 1 year might be the optimal strategy. In the absence of re-testing at 1 year, the use of the CKD-EPI$_{creat-cys}$ equation could be considered a reasonable option being the most accurate test and with much of the cost savings of the CKD-EPI$_{cys}$ equation strategy. The analysis cannot definitively conclude which is more cost-effective CKD-EPI$_{creat-cys}$ or CKD-EPI$_{cys}$ since there is a trade-off between accuracy and cost.

The guideline's clinical review did not reveal strong evidence for differences in the relative accuracy of the different equations according to ethnicity or the presence of cardiovascular disease or diabetes or a history of acute kidney injury and therefore the findings of this analysis are likely to apply to all these subgroups. The cost savings we observed are only for people without diabetes. For those with diabetes, unless stage of CKD has significantly progressed, CKD management is unlikely to add to their NHS costs, since they will already be having regular contact with primary care and regular testing of kidney function. However, the GDG agreed that a separate diagnostic testing strategy for patients with diabetes would be confusing and therefore a single recommendation was made for all the comorbidity subgroups.

Evidence statement

One original comparative cost analysis found that CKD-EPI$_{cys}$ was less costly than CKD-EPI$_{creat}$ and CKD-EPI$_{creat-cys}$ for diagnosing CKD in people with CKD-EPI$_{creat}$45-59, ACR<3mg/mmol and without diabetes (magnitude of cost savings varied according to age group, comorbidity, time horizon and re-testing strategy). This analysis was assessed as partially applicable with minor limitations.

References

Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. New England Journal of Medicine. 2012; 367(1):20-29

Kilbride HS, Stevens PE, Eaglestone G, Knight S, Carter JL, Delaney MP et al. Accuracy of the MDRD (Modification of Diet in Renal Disease) Study and CKD-EPI (CKD Epidemiology Collaboration) Equations for Estimation of GFR in the Elderly. American Journal of Kidney Diseases. 2013; 61(1):57-66

Inker LA, Fan L, Okparavero AA, Gudnason V, Eriksdottir G, Andresdottir MB et al. Comparing cystatin C and creatinine for estimating measured GFR and CKD prevalence in a community based sample of the elderly. Journal of the American Society of Nephrology. 2013; 24:164A

Appendix L – Excluded studies

Diagnostic studies

Study	Reason for exclusion
Andersen, Trine Borup, Jodal, Lars, Boegsted, Martin et al. (2012) GFR prediction from cystatin C and creatinine in children: effect of including body cell mass. American journal of kidney diseases : the official journal of the National Kidney Foundation 59(1): 50-7	- Could not separate CKD population from overall cohort
Andersen, Trine Borup, Jodal, Lars, Erlandsen, Erland J et al. (2013) Detecting reduced renal function in children: comparison of GFR-models and serum markers. Pediatric nephrology (Berlin, Germany) 28(1): 83-92	- Derivation study without external validation results are only available for the models derived in this study. Although this study did test existing equations, these were only used to inform their model and results were not presented
Aydin, Funda, Budak, Evrim Surer, Demirelli, Serkan et al. (2015) Comparison of Cystatin C and beta-Trace Protein Versus 99mTc-DTPA Plasma Sampling in Determining Glomerular Filtration Rate in Chronic Renal Disease. Journal of nuclear medicine technology 43(3): 206-13	- Outcomes are not reported in a format meeting the protocol
Bacchetta, Justine, Cochat, Pierre, Rognant, Nicolas et al. (2011) Which creatinine and cystatin C equations can be reliably used in children?. Clinical journal of the American Society of Nephrology : CJASN 6(3): 552-60	- Could not separate CKD population from overall cohort population consisted of >10% renal transplant patients.
Berg, Ulla B, Nyman, Ulf, Back, Rune et al. (2015) New standardized cystatin C and creatinine GFR equations in children validated with inulin clearance. Pediatric nephrology (Berlin, Germany) 30(8): 1317-26	- Could not separate CKD population from overall cohort
Bevc, Sebastjan, Hojs, Nina, Knehtl, Masa et al. (2019) Cystatin C as a predictor of mortality in elderly patients with chronic kidney disease. The aging male : the official journal of the International Society for the Study of the Aging Male 22(1): 62-67	- Outcome to be predicted do not match that specified in the protocol
Bjork, Jonas, Back, Sten Erik, Ebert, Natalie et al. (2018) GFR estimation based on standardized creatinine and cystatin C: a European multicenter analysis in older adults. Clinical chemistry and laboratory medicine 56(3): 422-435	- Participants were not required to have suspected or confirmed CKD
Bjork, Jonas, Grubb, Anders, Larsson, Anders et al. (2015) Accuracy of GFR estimating equations combining standardized cystatin C and creatinine assays: a cross-sectional study in Sweden. Clinical chemistry and laboratory medicine 53(3): 403-14	- Internal validation study
Bukabau, J.B., Yayo, E., Gnionsahe, A. et al. (2019) Performance of creatinine- or cystatin C-based equations to estimate glomerular filtration rate in sub-Saharan African populations. Kidney International 95(5): 1181-1189	- Could not separate CKD population from overall cohort

Study	Reason for exclusion
Corrao, A M, Lisi, G, Di Pasqua, G et al. (2006) Serum cystatin C as a reliable marker of changes in glomerular filtration rate in children with urinary tract malformations. The Journal of urology 175(1): 303-9	- Study does not contain any relevant index tests
Dart, A B, McGavock, J, Sharma, A et al. (2019) Estimating glomerular filtration rate in youth with obesity and type 2 diabetes: the iCARE study equation. Pediatric nephrology (Berlin, Germany) 34(9): 1565-1574	- Unclear whether participants were suspected of CKD Validation cohort were 26 youth with BMI >85th percentile without diabetes
den Bakker, Emil, Gemke, Reinoud, van Wijk, Joanna A E et al. (2018) Combining GFR estimates from cystatin C and creatinine-what is the optimal mix?. Pediatric nephrology (Berlin, Germany) 33(9): 1553-1563	- Could not separate CKD population from overall cohort
Donmez, Osman, Korkmaz, Huseyin Anil, Yildiz, Nalan et al. (2015) Comparison of serum cystatin C and creatinine levels in determining glomerular filtration rate in children with stage I to III chronic renal disease. Renal failure 37(5): 784-90	- 2x2 not reported / calculable P15/30 also not available
Filler, G., Foster, J., Acker, A. et al. (2005) The Cockcroft-Gault formula should not be used in children. Kidney International 67(6): 2321-2324	- Could not separate CKD population from overall cohort
Filler, G, Priem, F, Vollmer, I et al. (1999) Diagnostic sensitivity of serum cystatin for impaired glomerular filtration rate. Pediatric nephrology (Berlin, Germany) 13(6): 501-5	- Study does not contain any relevant index tests
Filler, Guido and Lepage, Nathalie (2003) Should the Schwartz formula for estimation of GFR be replaced by cystatin C formula?. Pediatric nephrology (Berlin, Germany) 18(10): 981-5	- 2x2 not reported / calculable p30 also not reported
Gabutti, Luca, Ferrari, Nicola, Mombelli, Giorgio et al. (2004) Does cystatin C improve the precision of Cockcroft and Gault's creatinine clearance estimation?. Journal of nephrology 17(5): 673-8	- Reference standard in study does not match that specified in protocol
Grubb, A, Bjork, J, Lindstrom, V et al. (2005) A cystatin C-based formula without anthropometric variables estimates glomerular filtration rate better than creatinine clearance using the Cockcroft-Gault formula. Scandinavian journal of clinical and laboratory investigation 65(2): 153-62	- Derivation study without external validation
Guan, Changjie, Liang, Ming, Liu, Riguang et al. (2018) Assessment of creatinine and cystatin C-based eGFR equations in Chinese older adults with chronic kidney disease. International urology and nephrology 50(12): 2229-2238	- Assessment tool do not match that specified in the protocol only compared Cystatin and creatinine combined equations
Hojs, R, Bevc, S, Ekart, R et al. (2008) Serum cystatin C-based equation compared to serum creatinine-based equations for estimation of glomerular filtration rate in patients with chronic kidney disease. Clinical nephrology 70(1): 10-7	- Derivation study without external validation

Study	Reason for exclusion
Huang, Shih-Han S, Macnab, Jennifer J, Sontrop, Jessica M et al. (2011) Performance of the creatinine-based and the cystatin C-based glomerular filtration rate (GFR) estimating equations in a heterogenous sample of patients referred for nuclear GFR testing. Translational research : the journal of laboratory and clinical medicine 157(6): 357-67	- Participants were not required to have suspected or confirmed CKD
Inker, Lesley A, Schmid, Christopher H, Tighiouart, Hocine et al. (2012) Estimating glomerular filtration rate from serum creatinine and cystatin C. The New England journal of medicine 367(1): 20-9	- 2x2 not reported / calculable P30 available - Could not separate CKD population from overall cohort
Jeong, Tae-Dong, Lee, Woochang, Yun, Yeo-Min et al. (2016) Development and validation of the Korean version of CKD-EPI equation to estimate glomerular filtration rate. Clinical biochemistry 49(9): 713-719	- Could not separate CKD population from overall cohort
Kilbride, Hannah S, Stevens, Paul E, Eaglestone, Gillian et al. (2013) Accuracy of the MDRD (Modification of Diet in Renal Disease) study and CKD-EPI (CKD Epidemiology Collaboration) equations for estimation of GFR in the elderly. American journal of kidney diseases : the official journal of the National Kidney Foundation 61(1): 57-66	- Unclear whether participants had CKD although subgroup analyses included people with GFR <60, suspected or confirmed CKD was not a requirement for inclusion into the study
Kumaresan, R. and Giri, P. (2012) A comparison between serum Creatinine and cystatin C-based formulae: Estimating glomerular filtration rate in chronic kidney disease patients. Asian Journal of Pharmaceutical and Clinical Research 5(suppl1): 42-44	- 2x2 not reported / calculable P30 not available
Lamb, Edmund J, Brettell, Elizabeth A, Cockwell, Paul et al. (2014) The eGFR-C study: accuracy of glomerular filtration rate (GFR) estimation using creatinine and cystatin C and albuminuria for monitoring disease progression in patients with stage 3 chronic kidney disease--prospective longitudinal study in a multiethnic population. BMC nephrology 15: 13	- methods/rationale only
Levey AS, Coresh J, Greene T et al. (2006) Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Annals of internal medicine 145(4): 247-254	- Study does not contain any relevant index tests
Liu, Xun, Ma, Huijuan, Huang, Hui et al. (2013) Is the Chronic Kidney Disease Epidemiology Collaboration creatinine-cystatin C equation useful for glomerular filtration rate estimation in the elderly?. Clinical interventions in aging 8: 1387-91	- Population does not meet the protocol
Luis-Lima, S., Escamilla-Cabrera, B., Negrin-Mena, N. et al. (2019) Chronic kidney disease staging with cystatin C or creatinine-based formulas: Flipping the coin. Nephrology Dialysis Transplantation 34(2): 287-294	- Could not separate CKD population from overall cohort most of the participants were not recruited due to suspected or confirmed CKD. Additionally, the

Study	Reason for exclusion
	study include renal transplant and pre-dialysis patients
Major, R.W.; Shepherd, D.; Brunskill, N.J. (2018) Reclassification of chronic kidney disease stage, eligibility for cystatin-c and its associated costs in a UK primary care cohort. Nephron 139(1): 39-46	- Assessment tool do not match that specified in the protocol Cystatin-C equation not evaluated
Masaebi, F., Looha, M.A., Wang, Z. et al. (2020) Evaluation of neutrophil gelatinase-associated lipocalin and cystatin C in early diagnosis of chronic kidney disease in the absence of the Gold Standard. Galen Medical Journal 9: e1698	- Study does not contain any relevant index tests
Mohammed, R.A.-A., El-Shazely, A., Haridy, M.A.M.A. et al. (2019) Diagnostic values of serum cystatin C and urinary fetuin-A as early biochemical markers in predicting diabetic nephropathy among patients with type 2 diabetes mellitus. Research Journal of Pharmaceutical, Biological and Chemical Sciences 10(6): 237-244	- Study does not contain any relevant index tests
Mousavinasab, N. and Jalalzadeh, M. (2017) A comparison of estimated GFRs based on formulas of serum cystatin C and serum creatinine. Nephro-Urology Monthly 9(3): e46569	- 2x2 not reported / calculable P30 also not reported
Narvaez-Sanchez, Raul, Gonzalez, Luz, Salamanca, Alba et al. (2008) Cystatin C could be a replacement to serum creatinine for diagnosing and monitoring kidney function in children. Clinical biochemistry 41(78): 498-503	- Assessment tool do not match that specified in the protocol serum cystatin only (no equation used)
Neirynck, Nathalie, Eloot, Sunny, Glorieux, Griet et al. (2012) Estimated glomerular filtration rate is a poor predictor of the concentration of middle molecular weight uremic solutes in chronic kidney disease. PloS one 7(8): e44201	- Reference standard in study does not match that specified in protocol reference standard was based on eGFR
Ng, Derek K, Schwartz, George J, Warady, Bradley A et al. (2017) Relationships of Measured Iohexol GFR and Estimated GFR With CKD-Related Biomarkers in Children and Adolescents. American journal of kidney diseases : the official journal of the National Kidney Foundation 70(3): 397-405	- Assessment tool do not match that specified in the protocol only looked at an equation which contained both Creatinine and Cystatin C
Padala S, Tighiouart H, Inker LA et al. (2012) Accuracy of a GFR estimating equation over time in people with a wide range of kidney function. American journal of kidney diseases : the official journal of the National Kidney Foundation 60(2): 217-224	- Derivation study without external validation the study used data from derivation studies
Pei, Xiao-Hua, He, Juan, Liu, Qiao et al. (2012) Evaluation of serum creatinine- and cystatin C-based equations for the estimation of glomerular filtration rate in a Chinese population. Scandinavian journal of urology and nephrology 46(3): 223-31	- Participants were not required to have suspected or confirmed CKD

Study	Reason for exclusion
Rowe, C., Sitch, A.J., Barratt, J. et al. (2019) Biological variation of measured and estimated glomerular filtration rate in patients with chronic kidney disease. Kidney International 96(2): 429-435	- 2x2 not reported / calculable P30 calculation also not possible.
Salek, T. and Palicka, V. (2014) Comparison of creatinine clearance and estimated glomerular filtration rate in patients with chronic kidney disease. Klinicka Biochemie a Metabolismus 22(3): 123-126	- Reference standard in study does not match that specified in protocol
Scarr, D., Bjornstad, P., Lovblom, L.E. et al. (2019) Estimating GFR by Serum Creatinine, Cystatin C, and beta2-Microglobulin in Older Adults: Results From the Canadian Study of Longevity in Type 1 Diabetes. Kidney International Reports 4(6): 786-796	- Participants were not required to have suspected or confirmed CKD
Schaeffner, Elke S, Ebert, Natalie, Delanaye, Pierre et al. (2012) Two novel equations to estimate kidney function in persons aged 70 years or older. Annals of internal medicine 157(7): 471-81	- Derivation study without external validation
Serezlija, Elma; Serdarevic, Nafija; Begic, Lejla (2017) The Estimation of Glomerular Filtration Rate Based on the Serum Cystatin C and Creatinine Values. Clinical laboratory 63(7): 1099-1106	- Unclear whether participants had CKD participants were recruited based on GFR but subgroup analysis according to level of GFR is not available.
Shardlow, Adam, McIntyre, Natasha J, Fraser, Simon D S et al. (2017) The clinical utility and cost impact of cystatin C measurement in the diagnosis and management of chronic kidney disease: A primary care cohort study. PLoS medicine 14(10): e1002400	- Reference standard in study does not match that specified in protocol
Stevens LA, Claybon MA, Schmid CH et al. (2011) Evaluation of the Chronic Kidney Disease Epidemiology Collaboration equation for estimating the glomerular filtration rate in multiple ethnicities. Kidney international 79(5): 555-562	- Participants were not required to have suspected or confirmed CKD Datasets included around 15% of participants who were kidney donors (without CKD), additionally, of the participants with CKD in the external validation set, 29% were transplant recipients.
Trimarchi, Hernan, Muryan, Alexis, Toscano, Agostina et al. (2014) Proteinuria, (99m) Tc-DTPA Scintigraphy, Creatinine-, Cystatin- and Combined-Based Equations in the Assessment of Chronic Kidney Disease. ISRN nephrology 2014: 430247	- Outcomes are not reported in a format meeting the protocol
Uemura, Osamu, Nagai, Takuhito, Ishikura, Kenji et al. (2014) Cystatin C-based equation for estimating glomerular filtration rate in Japanese children and adolescents. Clinical and experimental nephrology 18(5): 718-25	- Outcomes are not reported in a format meeting the protocol p30 / 2x2 table are only available for the derived tool (which did not undergo any validation in this study).
van Deventer, Hendrick E, Paiker, Janice E, Katz, Ivor J et al. (2011) A comparison of cystatin C- and creatinine-based prediction equations for the estimation of glomerular filtration rate in black South Africans.	- Population does not meet the protocol

Study	Reason for exclusion
Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 26(5): 1553-8	
Vega, Almudena, Garcia de Vinuesa, Soledad, Goicoechea, Marian et al. (2014) Evaluation of methods based on creatinine and cystatin C to estimate glomerular filtration rate in chronic kidney disease. International urology and nephrology 46(6): 1161-7	- 2x2 not reported / calculable not all participants underwent the index tests so 2x2 table is not possible. P50 value is available but no P30.
Xun L, Cheng W, Hua T et al. (2010) Assessing glomerular filtration rate (GFR) in elderly Chinese patients with chronic kidney disease (CKD): a comparison of various predictive equations. Archives of gerontology and geriatrics 51(1): 13-20	- Study does not contain any relevant index tests
Yang, S.-K., Liu, J., Zhang, X.-M. et al. (2016) Diagnostic Accuracy of Serum Cystatin C for the Evaluation of Renal Dysfunction in Diabetic Patients: A Meta-Analysis. Therapeutic Apheresis and Dialysis 20(6): 579-587	- Study does not contain any relevant index tests
Ye, Xiaoshuang, Liu, Xun, Song, Dan et al. (2016) Estimating glomerular filtration rate by serum creatinine or/and cystatin C equations: An analysis of multi-centre Chinese subjects. Nephrology (Carlton, Vic.) 21(5): 372-8	- Participants were not required to have suspected or confirmed CKD
Ye, Xiaoshuang, Wei, Lu, Pei, Xiaohua et al. (2014) Application of creatinine- and/or cystatin C-based glomerular filtration rate estimation equations in elderly Chinese. Clinical interventions in aging 9: 1539-49	- Could not separate CKD population from overall cohort
Yong, Zhenzhu, Li, Fen, Pei, Xiaohua et al. (2019) A comparison between 2017 FAS and 2012 CKD-EPI equations: a multi-center validation study in Chinese adult population. International urology and nephrology 51(1): 139-146	- Participants were not required to have suspected or confirmed CKD
Zappitelli, Michael, Parvex, Paloma, Joseph, Lawrence et al. (2006) Derivation and validation of cystatin C-based prediction equations for GFR in children. American journal of kidney diseases : the official journal of the National Kidney Foundation 48(2): 221-30	- Could not separate CKD population from overall cohort contained all children undergoing iothalamate GFR testing, unclear how many had CKD or reason for testing (so suspected CKD cannot be confirmed either)
Zou, L.-X., Sun, L., Nicholas, S.B. et al. (2020) Comparison of bias and accuracy using cystatin C and creatinine in CKD-EPI equations for GFR estimation. European Journal of Internal Medicine	- Population does not meet the protocol

Appendix M– Research recommendations – full details

M.1.1 Research recommendation

What is the accuracy of cystatin C-based equations to estimate GFR as a measurement of kidney function in adults, children and young people?

M.1.2 Why this is important

The committee agreed that there were serious limitations with the quality of the available evidence and that previous recommendations were also based on very limited evidence. Therefore, the committee decided to no longer recommend that cystatin-c equations be considered during diagnosis of CKD. This meant that there was remaining uncertainty surrounding the risks associated with using these equations in the diagnostic pathway. Further research is needed to determine whether or not these equations are useful.

M.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Cystatin C based equations have the potential to be used to rule-out CKD. However, there is currently insufficient evidence to recommend the use of cystatin C equations.
Relevance to NICE guidance	The research may inform future updates of key recommendations in the guidance.
Relevance to the NHS	The outcome would affect the type of equations used to estimate GFR to be used to rule-out CKD and avoid costly and time-consuming further tests.
National priorities	Moderate
Current evidence base	Low quality evidence (the committee agreed that because of the lack of high-quality evidence they could not make positive recommendations for the use of cystatin C equations to estimate GFR).
Equality considerations	The equations are known to work differently in people of different ethnicities. This difference is most established in people of Chinese descent compared to white Europeans. It is important that the effect of ethnicity on diagnostic accuracy is studied. It is unclear whether the diagnostic accuracy of eGFR equations differs between age groups however this possibility should also be explored.

M.1.4 Modified PICO table

Population	Adults, children and young people with suspected or confirmed CKD
Index tests	Equations to estimate GFR using cystatin C

Reference standards	Measured GFR (urinary or plasma clearance of inulin, iohexol, iothalamate, para aminohippurate [PAH], diethylenetriaminepentaacetic acid [DTPA] or ethylenediaminetetraacetic acid [EDTA]).
Outcome measures	• Likelihood ratios • Specificity • Sensitivity • PPV • NPV • AUC • Percentage of participants with index tests values within 10 or 15% (P10, P15) of the reference standard.
Study design	Cross-sectional study design
Timeframe	Not applicable
Additional information	Subgroups of interest: • Ethnicity • Age • CKD stage