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

Section	Question	Answer
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

Section	Question	Answer
	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 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 (Reference standard was conducted at the same time as serum creatinine and cystatin were measured.)

Section	Question	Answer
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

Section	Question	Answer
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 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?	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 (Reference standard was conducted at the same time as serum creatinine and cystatin were measured.)
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 millilitres per min per 1.73m2. Before 51CrEDTA was injected, blood was withdrawn for measuring serum creatinine and serum cystatin C.

Quality assessment

Section	Question	Answer
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.)

Section	Question	Answer
	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 iohexol 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 $84.69Sycs^{-1.68} \times 1.384$ (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)	Iohexol 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 post-iohexol 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

Section	Question	Answer
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

Section	Question	Answer
	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?	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 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

Section	Question	Answer
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 derivation 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 oedema 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

Section	Question	Answer
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 an 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

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?	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

Section	Question	Answer
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. 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

Section	Question	Answer
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 details	Study location Slovenia Study setting Single centre Sources of funding Supported 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

Section	Question	Answer
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. 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

Section	Question	Answer
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 Centre 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) $133 \times \min(cysC/0.8,1)^{-0.499} \times \max(cysC/0.8,1)^{-1.328} \times 0.996^{Age} \times 0.932$ (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 (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

Section	Question	Answer
	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)
	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 iohexol 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

Section	Question	Answer
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

Section	Question	Answer
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 iohexol 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

Section	Question	Answer
		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
	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)

Section	Question	Answer
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 $70.69 \times (cystC^{-0.931})$

	CAPA FAS
Reference standard (s)	Iohexol 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

Section	Question	Answer
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 (Unclear whether the index tests were interpreted with knowledge of the results of the reference standard. However, as these are objectively measured this is not a major problem.)
	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

Section	Question	Answer
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 creatinine 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, oedema, 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) $76.7 \times (-0.105+1.13 \times CystC)^{-1.19}$ eGFR5 China collaborative group formula $eGFR5 = 86 \times CysC^{-1:132}$ CKD-EPI (cyst - race modified) equation 1 $127.7 \times (-0.105+1.13 \times CystC)^{-1.17} \times age^{-0.13}$ (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

Section	Question	Answer
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

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?	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 iohexol clearance Plasma clearance of iohexol was performed by a single sample method

Quality assessment

Section	Question	Answer
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

Section	Question	Answer
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 Centre 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 iohexol clearance Urinary insulin clearance:

Quality assessment

Section	Question	Answer
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.)

Section	Question	Answer
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