Kidney Medicine

Cystatin C as a GFR Estimation Marker in Acute and Chronic Illness: A Systematic Review

Ogechi M. Adingwupu, Ernesto Rodolpho Barbosa, Paul M. Palevsky, Joseph A. Vassalotti, Andrew S. Levey, and Lesley A. Inker

Rationale & Objective: Creatinine-based GFR estimating (eGFRcr) equations may be inaccurate in populations with acute or chronic illness. The accuracy of GFR equations that use cystatin C (eGFRcys) or creatinine-cystatin C (eGFRcr-cys) is not well studied in these populations.

Study Design: A systematic review of original articles identified from PubMed and expert sources. Two reviewers screened articles independently and identified those meeting inclusion criteria.

Setting & Study Populations: Adults and children with acute or chronic illness.

Selection Criteria for Studies: Studies published since 2011 that compared performance of eGFRcr, eGFRcys, and eGFRcr-cys relative to measured GFR (mGFR), used standardized assays for creatinine or cystatin C, and used eGFR equations developed using such assays. Studies of ambulatory clinical populations or research studies in populations with only CKD, kidney transplant recipients, only diabetes, kidney donor candidates, and community-based cohorts were excluded.

Data Extraction: Data extracted from full text.

Analytical Approach: Bias and percentages of estimates within 30% of mGFR (P_{30}) of eGFR compared with mGFR were evaluated.

Results: Of the 179 citations, 26 studies met the inclusion criteria: 24 in adults and 2 in children in clinical populations with cancer (n=5), HIV (n=5), cirrhosis (n=3), liver transplant (n=3), heart failure (n=2), neuromuscular diseases (n=1) critical illness (n=5), and obesity (n=2). In general, eGFRcr-cys had greater accuracy than eGFRcr or eGFRcys equations among study populations with cancer, HIV, and obesity, but did not perform consistently better in cirrhosis, liver transplant, heart failure, neuromuscular disease, and critical illness.

Limitations: Participants were selected because of concern for inaccurate eGFRcr, which may bias results. Most studies had small sample sizes, limiting generalizability.

Conclusions: eGFRcr-cys improves GFR estimation in populations with a variety of acute and chronic illnesses, providing indications for cystatin C measurement. Performance was poor in many studies, suggesting the need for more frequent mGFR.

Complete author and article information provided before references.

Correspondence to L.A. Inker (Lesley.Inker@tuftsmedicine.org)

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Chronic kidney disease (CKD) is common, especially in people with acute and chronic illness. Estimating GFR using serum creatinine (eGFRcr) is the initial test for glomerular filtration rate (GFR) evaluation, but eGFRcr is less accurate relative to measured GFR (mGFR) in such populations.[1] Systematic differences in the non-GFR determinants of creatinine between these populations and those used to develop the equations are likely the critical cause of error in eGFRcr. Non-GFR determinants of creatinine include generation by diet and muscle mass, tubular secretion, and extra-renal elimination.[2,3] Common examples of error in eGFRcr because of presence of non-GFR determinants of serum creatinine include overestimation of mGFR owing to decreased creatinine generation (muscle wasting), underestimation of mGFR owing to drug-induced inhibition of tubular creatinine secretion (trimethoprim and dolutegravir) or decreased extra-renal creatinine elimination (antibiotics in patients with gastrointestinal bacterial overgrowth).

Cystatin C is an alternative filtration marker that is receiving increased attention. After adjustment for mGFR, compared with creatinine, cystatin C is less affected by age, sex, and race and alterations in diet, muscle mass, tubular handling, and extra-renal elimination.[2-5] Recent recommendations by US nephrology societies encourage increased use of cystatin C to improve the accuracy of race-free GFR estimates.[6] Estimated GFR from cystatin C (eGFRcys) is generally not more accurate than eGFRcr in populations without comorbid illness, indicating the presence of the non-GFR determinants of cystatin C. Higher levels of cystatin C have been associated with greater adiposity, smoking, hyperthyroidism, glucocorticoid excess, and chronic inflammation, as indicated by insulin resistance, higher levels of C-reactive protein and tumor necrosis factor, or lower levels of serum albumin.[3,5,7-15]

Studies in ambulatory clinical populations with CKD or diabetes, kidney donor candidates, and community-based populations in adults and children have demonstrated that estimated GFR using both creatinine and cystatin C (eGFRcr-cys) provides more accurate estimates of mGFR than either eGFRcr or eGFRcys.[6,16-19] We have previously hypothesized that the greater accuracy of eGFRcr-cys is because of the fact that the non-GFR determinants of creatinine and cystatin C are partially independent of each other and therefore the use of both markers reduces the error owing to non-GFR determinants.[16,20] In populations with acute or chronic illness, in which eGFRcr may be inaccurate, it is not known whether eGFRcr-cys continues to provide more accurate estimates than both eGFRcr and eGFRcys.

PLAIN-LANGUAGE SUMMARY

Kidney function, specifically glomerular filtration rate (GFR), estimated using creatinine (eGFRcr) is often inaccurate in people with acute and chronic illness. The accuracy of estimates using cystatin C alone (eGFRcys) or together with creatinine (eGFRcr-cys) is not well studied in these populations. We conducted a systematic review to address the knowledge gap. Of the 179 papers reviewed, we identified 26 studies in clinical populations with cancer (n=5); HIV (n=5); cirrhosis (n=3); liver transplant (n=3); heart failure (n=2); neuromuscular disease (n=1); critical illness (n=5); and obesity (n=2). In general, eGFRcr-cys improved the GFR estimation in HIV, cancer, and obesity, providing indications for cystatin C measurement. Performance was poor in many studies, suggesting the need for more frequent measured GFR.

A decade ago, we performed a systematic review to summarize available data to compare the performance of eGFRcys, eGFRcr, and eGFRcr-cys relative to mGFR in general and clinical populations. At the time, we reviewed 8 studies in all; 2 were in healthy volunteers and 6 were in patients with CKD (n=1), diabetes (n=1), cystic fibrosis (n=1), Fabry disease (n=1), HIV (n=1), and liver transplant patients (n=1). We found mixed results as to whether eGFRcys performed better than eGFRcr in general and CKD populations, and in populations with chronic illness. Of importance, comparisons were limited by use of assays for creatinine and cystatin C that were not traceable to reference materials, small sample sizes, and variation in metrics to evaluate equation performance. We thought it timely to reassess this question given that growing interest in the use of cystatin C has sparked national efforts to facilitate its increased, routine, and timely use in clinical practice.[6] The goal of our study was to update our assessment of the comparative performance of eGFRcr, eGFRcys, and eGFRcr-cys equations relative to mGFR in populations with acute or chronic illness in which eGFRcr may be inaccurate. We then use these results to make some suggestions for the use of cystatin C and measured GFR in clinical practice.

METHODS

The methods and reporting in this review follow Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study was registered on PROSPERO (ID CRD42023414735).

Data Sources and Searches

We used the PubMed or MEDLINE database to conduct a comprehensive search of literature published from 2011 to date that evaluated the performance of eGFRcr, eGFRcys, and eGFRcr-cys using equations developed by multiple research groups. A broad preliminary database search of key words was performed, followed by a refined search using the MesH Advanced Search Builder (Table S1). We included additional studies received from experts.

Study Selection

The target population included both adults and children with acute or chronic illness other than CKD. Studies were eligible if they (1) included mGFR using plasma or urinary clearance of an exogenous filtration marker (iothalamate, iohexol, dextran, ^{51}Cr-ethylenediaminetetraacetic acid [EDTA], ^{99m}Tc-diethylenetriamine pentaacetate [DTPA]) as the reference standard; (2) used estimating equations that were developed using assays for serum creatinine and cystatin C that were standardized to international reference materials; (3) used assays for standardized serum creatinine and cystatin C assays in the study population; (4) reported at least 1 performance metric relative to mGFR (ie, bias or P_{30}); and (5) were original research articles published in English. Of eligible studies, we excluded those in populations outside the scope of this review. Because our goal was to focus on populations with acute and chronic illness, we excluded studies of ambulatory clinical populations or research studies in populations with CKD (including kidney transplant recipients) or diabetes, kidney donor candidates, and community-based cohorts (Fig S1). For papers that reported on key subgroups, we report each subgroup as a separate study (here on in referred to as studies). Within some studies, results for 1 or more equations are reported; thus performance of each equation is a unit of analysis (here on in referred to as reports).

Data Extraction and Quality Assessment

Two authors (OMA and ERB) reviewed the titles and abstracts for initial study selection. The final list of selected studies was discussed with the corresponding author (LAI) to rule out discrepancies and for additional validation. Full-text papers were reviewed to assess risk of bias using the national institute of health quality assessment tool for observational cohort and cross-sectional studies (Item S1).[21] Data was extracted from eligible studies and inputted into a spreadsheet created to capture pertinent information. For each study, we collected data on the study details (eg, study design, sample size, population, and location), patient characteristics (eg, age, sex, and ethnicity), laboratory methods (eg, creatinine, cystatin C, and GFR measurement methods), eGFR equations, and the measured outcomes.

Metrics for Performance Relative to Measured GFR

Many metrics are used to assess performance of eGFR equations relative to mGFR. We used bias and P_{30} because they were reported most consistently. Bias was defined as the median or mean difference of eGFR − mGFR. Where

bias was defined otherwise (ie, mGFR − eGFR), we converted to former for consistency. Thus, a positive bias denotes an overestimate of mGFR and negative bias an underestimate. To facilitate comparisons, bias was further categorized by its magnitude into small (less than +/− 5 mL/min/1.73 m^2), medium (+/− 5 to +/− 10 mL/min/1.73 m^2), and large (greater than +/− 10 mL/min/1.73 m^2). For comparison among the equations, we use small bias (regardless of over or underestimate), medium overestimate, medium underestimate, large overestimate, or large underestimate. P_{30} was defined as the proportion of eGFR within 30% of mGFR. P_{30} was further categorized by magnitude into high (90%), moderate (80%-89%), and low (< 80%). P_{30} from 75%-80% to 90% has been considered to be adequate for decision-making in many clinical circumstances; P_{30} >90% is considered optimal.[22]

RESULTS

We reviewed 179 titles and abstracts, 44 of which qualified for full-text review (Fig S1). After full-text review, 24 papers matched the eligibility criteria. Table S2 shows the reasons for exclusion. Of the 14 studies excluded for use of unstandardized cystatin C measures, 4 were performed after the availability of cystatin C assays traceable to reference materials.[23] Two of the 24 papers evaluated 2 subgroups, respectively; hence, we reported these 2 papers as 4 studies. Thus, we included 26 studies in our final evaluation (Table 1).[24-47] The bias of included papers is shown in Table S3.

The 26 studies were conducted between 1988 and 2020 and include the following comorbid illnesses: cancer (n=5); HIV (n=5); cirrhosis (n=3); liver transplant (n=3); heart failure (n=2); critical illness (n=5); neuromuscular disease (n=1); and obesity (n=2). Most were adult only studies; however, some were in children or both children and adults. Of note, only 13 studies had a sample size of more than 100.

GFR Estimating Equations Evaluated

A total of 17 eGFR equations developed by 8 research groups were evaluated across the 26 studies (Fig S1; Table 2).[48-58] This included 5 adult, 3 pediatric, and 1 full age spectrum eGFRcr equation; 2 adult, 2 pediatric, and 1 full age spectrum eGFRcys equation, and 2 adult and 1 pediatric eGFRcr-cys equation. Furthermore, 9 of the equations evaluated were developed in North American populations, 4 in Japanese populations, and 4 in European populations. Of note, a few studies used equations that were not developed specifically for their geographic population, even though geographic-specific equations existed. For instance, a study of Japanese cancer patients used the CKD-EPI equations, when known Japanese modifications of these equations exist. Because the MDRD study equation was not reported by itself and was not recommended over the era in which these studies were conducted, we report on its performance only in supplementary information (Figs S2 and S3).

Performance of GFR Estimating Equations

The bias and P_{30} of eGFRcr, eGFRcys, and eGFRcr-cys varied across the 26 studies in acute and chronic illness populations (Figs 1 and 2). Overall, there were 30 reports of bias for eGFRcr, 27 for eGFRcys, and 22 for eGFRcr-cys. 21 (69%) of the 30 eGFRcr reports showed moderate or large bias, with the majority (81%) showing an overestimate of mGFR. Fifteen of the 27 (54%) eGFRcys reports demonstrated moderate or large bias with majority (73%) showing an underestimate of mGFR. Fourteen of the 22 (61%) eGFRcr-cys reports showed moderate-to-large bias, with the majority (64%) showing an underestimate of mGFR. There was a similar number of reports of P_{30} overall, as with bias for eGFRcr and eGFRcys. eGFRcr-cys had one additional report of P_{30}.[23] None of the eGFRcr reports had high P_{30}, but 2 of the 26 (7%) reports for eGFRcys and 5 of the 23 (21%) reports for eGFRcr-cys reported a high P_{30}.

Cancer

There were 5 publications of cancer populations.[24-27] Two studies were in hematopoietic stem cell transplant recipients, and 4 were in blood and solid organ cancer patients. Four were conducted in Japan and 1 in Brazil, and 4 were in adults and 1 in children. Of the 5 reports in Japan, only 2 used modifications of equations recommended for Japan.

Among the 4 reports in adults, the direction and magnitude of bias varied. For eGFRcr, 1 report showed small bias and the others showed moderate to large over or- underestimate of mGFR. For eGFRcys, 3 reports showed small bias and 1 report showed moderate underestimate. For eGFRcr-cys, there were 3 reports, with 1 showing small bias and the other 2 showing moderate underestimates. The P_{30} for eGFRcr-cys was moderate to high (81%-92%).

HIV

Five publications of adults with HIV were included. Three were conducted in North America, one in Europe, and one in Japan.[28-32] Among the 4 reports from North America and Europe, the direction and magnitude of bias for eGFRcr, eGFRcys, and eGFRcr-cys varied. The P_{30} was moderate to high in all reports for eGFRcr-cys (81%-91%) and 4 of 5 reports for eGFRcys (80%-93%).[28-32]

Cirrhosis and Liver Transplant Recipients

Six publications of populations with liver disease were included (3 with cirrhosis and 3 with liver transplants). For adults with cirrhosis and liver transplant,[33-37] the direction and magnitude of bias of eGFRcr, eGFRcys, and eGFRcr-cys varied. The range for P_{30} was low for eGFRcr (41%-76%), and low to moderate for eGFRcr-cys, and eGFRcys (60%-86%, and 42%-83%, respectively). For children with transplants, eGFRcr had a small bias or large overestimation, whereas all eGFRcys showed small bias. P_{30} for eGFRcys was moderate (86%-88%), whereas P_{30}

Table 1. Characteristics of Studies Reviewed by Population

Author, year	Study Period	N	Age, y	Male, n (%)	GFR Measurement Method Filtration Marker (Clearance Method)	Measured GFR, mL/min/1.73m^2
Cancer						
Shibata et al[24] (2015)	2007-2010	41	66 (7.3)	26 (63)	Inulin (U)	76.3 (26.4)
Hingorani et al[25] (2015)	2009-2013	50	55 (23-72)[a]	38 (76)	Iohexol (P)	99.9 (24.6)
Hingorani et al[25] (2015)[b]	2009-2013	35	55 (23-69)[a]	28 (80)	Iohexol (P)	86.1 (28.9)
Matsuoka et al[26] (2020)[b]	2016-2019	17	11 (5-17)[a]	9 (53)	Inulin (U)	105.8 (22.8)
Costa et al[27] (2021)	2015-2017	1200	59 (13)	611 (51)	^{51}Cr-EDTA (P)	78.5 (21.7)
HIV						
Inker et al[28] (2012)	2009-2011	200	48 (8)	145 (73)	Iohexol (P)	87 (26)
Bhasin et al[29] (2013)	Nr	187	49 (45-53)[a]	121 (65)	Iohexol (P)	101 (85-116)[a]
Gagneux-Brunon et al[30] (2013)	2011-2012	203	49 (10)	166 (82)	Iohexol (P)	95 (24)
Yukawa et al[31] (2018)	2014	15	46 (42-46.5)[a]	15 (100)	Inulin (U)	84.6 (77.3-97.6)[a]
Lucas et al[32] (2020)	2010-2019	222	50 (45-54)[a]	145 (65)	Iohexol (P)	88 (74-100)8
Cirrhosis						
De Souza et al[33] (2014)	2010-2012	202	56 (19-72)[a]	145 (72)	Inulin, U	83 (6-167)[a]
Torre et al[34] (2016)	2013-2014	91	51 (12)	43 (47)	^{99m}Tc-DTPA (U)	71.7 (28.1)
Stämmler et al[35] (2023)	2012-2019	203	59 (13)	90 (63)	Iothal (U)/ Inulin (U)	62.5 (26.5)
Liver Transplant						
Wagner et al[36] (2012)	2008-2010	49	men: 54 (30-64); women: 54 (41-69)[a]	33(67)	Inulin (P)	60.1 (10.9-97.8)[a]
Allen et al[37] (2015)	1988-2010	401	56 (11)	229 (57)	Iothal (U)	49 (34-65)
Bluhme et al[38] (2021)	2007-2015	91	13.9 (8.3)	48 (53)	Iohexol (P)	96 (40.5)
Heart Failure						
Kervella et al[39] (2017)	2012-2016	66	67 (14)	48 (73)	Inulin (U)	26 (11)
Swolinsky et al[40] (2021)	2019	38	72 (14)	29 (76)	Dextran (P)	35 (12)
Neuromuscular Disease						
Aldenbratt et al[41] (2021)	2010-2014	145	46 (14)	68 (47)	Iohexol (P)	81 (19)
Critical Illness						
Delanaye et al[42] (2014)	Nr	47	62 (17)	25 (53)	Iohexol (U)	96 (54)
Carlier et al[43] (2015)	2005; 2008-2009	68	58 (39-68)[a]	46 (68)	Inulin (U)	80 (31-114)[a]
Ravn et al[44] (2019)	2013-2014	30	67 (54-72)[a]	14 (47)	Iohexol (P)	84.5 (64-104)[a]
Sangla et al[45] (2020)	2018-2019	63	66 (54-75)[a]	43 (68)	Iohexol (P)	51.5 (19.3-85.6)[a]
Haines et al[46] (2023)	2019-2020	27	51 (38-63)[a]	25 (66)[a]	Iohexol (P)	58 (39-70)[a]
Obesity						
Chang et al[47] (2020) (prebariatric)	Nr	27	46.2 (10.8)	9 (33)	Iohexol (P)	84.1 (22.0)
Chang et al[47] (2020) (postbariatric)	Nr	27	47.1 (10.8)	9 (33.3)	Iohexol (P)	89.2 (19.9)

Note: Age and measured GFR are expressed as mean (SD) or median (IQR or range). Male is expressed as N (percent). Creatinine and cystatin C assays used in all studies were calibrated to certified reference materials such as IDMS for creatinine and ERM4-DA471/IFCC for cystatin C.

Abbreviations: NR, not reported; P, plasma clearance; U, urine clearance; GFR, glomerular filtration rate; DTPA, diethylenetriamine penta-acetate; EDTA, ethylenediamine tetra-acetic acid; Iothal, iothalamate.

[a]Presented as median values.

[b]Presented as hematopoietic stem cell transplant studies.

Table 2. Characteristics of Estimating GFR Equations Evaluated

	Development Dataset						
Equation, Y	**Population**	**n**	**Age, y**	**mGFR mL/min/1.7m²**	**GFR Measurement Method Filtration Marker (Clearance Method)**	**Validation Dataset n**	**Variables**
Creatinine							
MDRD,[48,49] 2006	CKD (adults)	1,070	50.6 ± 12.7	39.8 ± 21.2	Iothal (U)	558 (I)	Cr, age, sex, and race
CKD-EPI,[49] 2009	CKD and non-CKD (adults)	8,254	47 ± 15	68 ± 40	Iothal (U)	3771 (E)	Cr, age, sex, and race
Matsuo,[50,c] 2009	CKD or healthy kidney donors (adults)	413	51.4 ± 16.5	59.1 ± 35.4	Inulin (U)	350	Cr, age, and sex
CkiD,[51] 2009	CKD (children)	349	10.8 (7.7-14.3)[a]	41.3 (32.0-51.7)[a]	Iohexol (P)	168(I)	Cr and height
Lund-Malmo Revised,[52] 2011	Referred for GFR evaluation (adults)	850	60 (26-85)	55 (9-121)[b]	Iohexol (P)	850 (I)	Cr, age, and sex
Lyon,[53] 2012	CKD or referred for GFR evaluation (children)	360	12.7 (9.5-15.3)[a]	86 (65-109)[a]	Inulin (U)	109 (E)	Cr, sex, age, and height
Uemura,[54,c] 2014	CKD (children)	131	10.8 (7.5-13.9)[a]	66.6 (46.5-93.5)[a]	Inulin (U)	131(I)	Cr
FAS,[55] 2016	CKD or general population (adults and children)	NA	1- ≥70	53-95[b]	Inulin (U), Iothal (P/U), and Iohexol (P)	6,870	Cr and Q
CKD-EPI,[17] 2021	CKD and non-CKD (adults)	8,254	47 ± 15	68 ± 40	Iothal (U)	4,050 (E)	Cr, age, and sex
Cystatin C							
CKiD,[18] 2012	CKD (children)	643	1-16[b]	43.3 (32.6-55.6)[a]	Iohexol (P)	322 (I)	Cys
CKD-EPI,[16] 2012	CKD (adults)	5,352	47 ± 15	68 ± 39	Iothal (U)	1,119 (E)	Cys, age, and sex
Horio,[56,c] 2013	CKD (adults)	413	51 ± 17	59 ± 35	Inulin (U)	350 (E)	Cys, age, and sex
Uemura,[57,c] 2014	CKD (children)	135	10.6 (7.0-13.7)[a]	66.3 (46.1-93.3)[a]	Inulin (U)	135 (I)	Cys
CAPA,[58] 2014	CKD or referred for GFR evaluation (adults and children)	3,164	2-86[b]	9-200[b]	Iohexol (P) Inulin (P/U)	1,796 (E)	Cys and age
Creatinine-Cystatin C							
CKiD,[18] 2012	CKD (children)	643	1-16[b]	43.3 (32.6-55.6)[a]	Iohexol (P)	322 (I)	Cr, Cys, BUN, height, and sex
CKD-EPI,[16] 2012	CKD (adults)	5,352	47 ± 15	68 ± 39	Iothal (U)	1,119 (E)	Cr, Cys, age, sex, and race
CKD-EPI,[17] 2021	CKD and non-CKD (adults)	5,352	47 ± 15	68 ± 39	Iothal (U)	4,050 (E)	Cr, Cys, age, and sex

Note: Data are presented as mean (standard deviation or range), median (IQR), and N (percent).
Abbreviations: Cys, Cystatin C; Cr, creatinine; E, external validation; I, internal validation; P, plasma clearance; U, urine clearance; Iothal, iothalamate; NA, not applicable; CKD, chronic kidney disease; GFR, glomerular filtration rate; mGFR, measured GFR.
[a]Indicates median (IQR).
[b]Indicates range.
[c]Indicates Japanese equations.

Study, year	Country	GFR measurement method	N	Age	Creatinine Equations	Creatinine Bias	Cystatin C Equations	Cystatin C Bias	Creatinine-Cystatin C Equations	Creatinine-Cystatin C Bias
Cancer										
Shibata, 2015[24] hematological cancer	Japan	Inulin (U)	41	A	*Japanese eGFR (Matsuo)*	0.01	*Japanese eGFR (Horio)*	0.1	_	_
Hingorani, 2015[25] hematological cancer	Japan	Iohexol (P)	50	A	*CKD-EPI 2009*	-15.6 (-21.4, -9.8)	*CKD-EPI 2012*	-1.1 (-7.9, 5.8)	*CKD-EPI 2012*	-7.9 (-13.1,-2.7)
Hingorani, 2015[25] HSC	Japan	Iohexol (P)	35	A	*CKD-EPI 2009*	-8 (-15.1, -0.9)	*CKD-EPI 2012*	-7.1 (-15.4, 1.2)	*CKD-EPI 2012*	-8.2 (-15.1, -1.3)
Matsuoka, 2020[26] *HSC*	Japan	Inulin (U)	17	C	*Bedside CKiD*	50.4 (38.6, 62.1)	*CKiD*	−16.7 (−24.1, −9.2)	*CKiD*	9.1 (1.9, 16.3)
					Uemura	27.7 (16.1, 39.2)	*Uemura*	20.2 (10.8, 29.5)	_	_
Costa e Silva, 2021[27] solid organ cancer	Brazil	EDTA (P)	1200	A	*CKD-EPI 2009*	8.1 (7.1, 8.9)	*CKD-EPI 2012*	-4.6 (-5.5, -3.7)	*CKD-EPI 2012*	2 (1.1, 2.6)
HIV										
Inker, 2012[28]	USA	Iohexol (P)	200	A	*CKD-EPI 2009*	-5.4 (-7.9, -2.9)	*CKD-EPI 2012*	-4.3 (-7.7, -1.2)	*CKD-EPI 2012*	-6.4 (-9.3, -3.1)
Bhasin, 2013[29]	USA	Iohexol (P)	187	A	*CKD-EPI 2009*	-1.1 (-12.4, - 10.4)	*CKD-EPI 2012*	-16.3 (-27.8, -1.8)	*CKD-EPI 2012*	-7.2 (-19.8, - 2.2)
Gagneuax-Brunon, 2013[30]	France	Iohexol (P)	203	A	*CKD-EPI 2009*	2.6	*CKD-EPI 2012*	1.2	*CKD-EPI 2012*	2.5
Yukawa, 2018[31]	Japan	Inulin (U)	15	A	*Japanese eGFR (Matsuo)*	-23.6 (-34.1, -16.1)	*Japanese eGFRcys (Horio)*	-0.6 (-8.3, 1.3)	_	_
Lucas, 2020[32]	USA	Iohexol (P)	222	A	*CKD-EPI 2009*	8.7 (6.8, 10.6)	*CKD-EPI 2012*	-3.8 (-5.8, -1.7)	*CKD-EPI 2012*	2.2 (0.6,3.8)
Cirrhosis										
De Souza, 2014[33]	France	Inulin (U)	202	A	CKD-EPI 2009	-	*CKD-EPI 2012*	-	*CKD-EPI 2012*	-
Torre, 2016[34]	Mexico	DTPA (U)	91	A	CKD-EPI 2009	29.6 (24.6, 34.6)	*CKD-EPI 2012*	-1.4 (-6.4, 3.5)	CKD-EPI2012	11.7 (7.4, 16.1)
Stammler, 2023[35]	USA & France	Iothal (U)	203	A	CKD-EPI2009	1 (-1, 3)	_	_	CKD-EPI2012	-6 (-8, -5)
					CKD-EPI2021	4 (2, 7)	_	_	CKD-EPI2021	-4 (-6, -3)
Liver Transplant										
Wagner, 2012[36]	Austria	Inulin (U)	49	A	*CKD-EPI 2009*	13.9	*CKD-EPI 2012*	-12.2	_	_
Allen, 2015[37]*	USA	Iothalamate (U)	401	A	*CKD-EPI 2009*	8.2 (6.2, 10.2)	*CKD-EPI 2012*	-27.9 (-25.9, -29.8)	*CKD-EPI 2012*	-12.3 (-10.6, -14.0)
Bluhme, 2021[38]	Sweden	Iohexol (P)	91	C	*CKiD/MDRD*	18.5 (14.6, 22.3)	*CKD-EPI2012*	0.2 (-3.0, 3.3)	_	_
					Lyon	4 (0.5, 7.6)	*CAPA*	3.1 (-0.4, 6.6)	_	_
					FAS	13.5 (9.1, 18.0)	_	_	_	_
Heart Failure										
Kervella, 2017[39]	France	Inulin (U)	66	A	*CKD-EPI 2009*	15.2 (11.5, 19.0)	*CKD-EPI 2012*	4.1 (1.6, 6.5)	*CKD-EPI 2012*	7.8 (5.6, 10.1)
Swolinsky, 2021[40]	Germany	Dextran (P)	38	A	*CKD-EPI2009*	5.4	*CKD-EPI 2012*	-4	*CKD-EPI 2012*	-0.4
Neuromuscular Disease										
Aldenbratt, 2022[41]	Sweden	Iohexol (P)	145	A	*CKD-EPI2009*	27 (24, 35)	*CAPA*	22.2 (19.1, 25.2)	*CAPA+CKD-EPI2009*	26.1 (23.6, 29.1)
Critical Illness										
Delanaye, 2014[42]	Belgium & France	Iohexol (U)	47	A	*CKD-EPI 2009*	1	*CKD-EPI 2012*	-26	*CKD-EPI 2012*	-12
Carlier, 2015[43]	Belgium	Inulin (U)	68	A	*CKD-EPI 2009*	23.4 (10.5, 29.7)	*CKD-EPI 2012*	-9.3 (-17.2, -3.7)	*CKD-EPI 2012*	3.9 (-1.3, 9.5)
Ravn, 2019[44]	Sweden	Iohexol (P)	30	A	*LM-REV*	8 (-4.2, 16.2)	*CAPA*	-26 (-30.4, -19.7)	*CKD-EPI2012*	-10 (-17.1, -0.6)
					CKD-EPI2009	14 (2.2, 24.1)	*CKD-EPI2012*	-25 (-32.3, -20.3)	*CAPA+LM-REV*	-11.5 (-19.6, -0.1)
Sangla, 2020[45]	Switzerland	Iohexol (P)	63	A	*CKD-EPI 2009*	24 (-37, 84)	*CKD-EPI 2012*	11 (-40, 63)	*CKD-EPI 2012*	17 (-30, 64)
Haines, 2023[46]	United Kingdom	Iohexol (P)	27	A	*CKD-EPI 2021*	59 (49, 69)	*CKD-EPI 2012*	22 (13, 31)		
Obesity										
Chang, 2020[47] Pre-bariatric	USA	Iohexol (P)	27	A	*CKD-EPI 2009*	3.6 (−3.2, 8.9)	*CKD-EPI 2012*	−8.1 (−16.1, −0.9)	*CKD-EPI 2012*	-4 (-8.0, 0.7)
Chang, 2020[47] Post-bariatric	USA	Iohexol (P)	27	A	*CKD-EPI 2009*	8.4 (1.5, 12.3)	*CKD-EPI 2012*	-10.7 (-16.2, -5.5)	*CKD-EPI 2012*	-1.9 (-7.6, 3.8)

Figure 1. Bias creatinine and cystatin c estimating GFR equations by clinical population. Bias was defined as the median or mean difference between eGFR and mGFR (ie, eGFR − mGFR medium underestimate). Positive bias denotes overestimate and negative bias underestimate.* Bias in study given as %Bias (ln). Units are mL/min/1.73m^2 for bias. (Green box) indicates small bias with magnitude of median difference of between −5 and +5 mL/min/1.73 m^2; (yellow box) indicates medium underestimate as median difference of −5 to −10 mL/min/1.732m^2. (spotted yellow box) indicates medium overestimate as median difference of

Study, year	Country	N	Age	Creatinine		Cystatin C		Creatinine-Cystatin C	
				Equations	Accuracy, P_{30}	Equations	Accuracy, P_{30}	Equations	Accuracy, P_{30}
Cancer									
Shibata, 2015[24] hematological cancer	Japan	41	A	*Matsuo*	_	*Horio*	_	_	_
Hingorani, 2015[25] hematological cancer	Japan	50	A	*CKD-EPI 2009*	79	*CKD-EPI 2012*	76	*CKD-EPI 2012*	89
Hingorani, 2015[25] HSC	Japan	50	A	*CKD-EPI 2009*	82	*CKD-EPI 2012*	72	*CKD-EPI 2012*	84
Matsuoka, 2020[26] HSC	Japan	17	P	*Bedside CKiD*	23	*CKiD*	81	*CKiD*	81
				Uemura	55	*Uemura*	61	_	_
Costa e Silva, 2021[27] solid organ cancer	Brazil	1200	A	*CKD-EPI 2009*	81 (79, 83)	*CKD-EPI 2012*	88 (86, 90)	*CKD-EPI 2012*	92 (91, 94)
HIV									
Inker, 2012[28]	USA	200	A	*CKD-EPI 2009*	85 (80, 90)	*CKD-EPI 2012*	83 (77, 88)	*CKD-EPI 2012*	90 (86, 94)
Bhasin, 2013[29]	USA	187	A	*CKD-EPI 2009*	89 (83, 93)	*CKD-EPI 2012*	79 (72, 85)	*CKD-EPI 2012*	91 (85, 94)
Gagneuax-Brunon, 2013[30]	France	203	A	*CKD-EPI 2009*	82	*CKD-EPI 2012*	80	*CKD-EPI 2012*	81
Yukawa, 2018[31]	Japan	15	A	*Matsuo*	40 (12, 68)	*Horio*	93 (79, 100)	_	_
Lucas, 2020[32]	USA	222	A	*CKD-EPI 2009*	79 (76, 82)	*CKD-EPI 2012*	83 (80, 85)	*CKD-EPI 2012*	88 (86, 91)
Cirrhosis									
De Souza, 2014[33]	France	202	A	*CKD-EPI 2009*	56	*CKD-EPI 2012*	83	*CKD-EPI 2012*	78
Torre, 2016[34]	Mexico	91	A	*CKD-EPI 2009*	41 (30, 51)	*CKD-EPI 2012*	63 (52, 73)	CKD-EPI 2012	60 (50, 71)
Stammler, 2023[35]	USA & France	203	A	*CKD-EPI 2009*	75 (69, 81)	_	_	*CKD-EPI 2012*	86 (81, 91)
				CKD-EPI 2021	74 (68, 80)	_	_	*CKD-EPI 2021*	86 (81, 90)
Liver Transplant									
Wagner, 2012[36]	Austria	49	A	*CKD-EPI 2009*	52	*CKD-EPI 2012*	42	_	_
Allen, 2015[37]	USA	401	A	*CKD-EPI 2009*	76 (72, 79)	*CKD-EPI 2012*	60 (56, 64)	*CKD-EPI 2012*	84 (82, 87)
Bluhme, 2021[38]	Sweden	91	P	*CKiD/MDRD*	68 (61, 75)	*CKD-EPI 2012*	86 (82, 91)	_	_
				Lyon	84 (79, 89)	*CAPA*	88 (83, 92)	_	_
				FAS	68 (60, 77)	_	_	_	_
Heart Failure									
Kervella, 2017[39]	France	66	A	*CKD-EPI 2009*	33 (23, 45)	*CKD-EPI 2012*	65 (53, 76)	*CKD-EPI 2012*	52 (40, 63)
Swolinsky, 2021[40]	Germany	38	A	*CKD-EPI 2009*	66	*CKD-EPI 2012*	56	*CKD-EPI 2012*	74
Neuromuscular Disease									
Aldenbratt, 2022[41]	Sweden	145	A	*CKD-EPI2009*	37 (30, 46)	*CAPA*	49 (41, 57)	*CAPA+ CKD-EPI2009*	44 (35, 51)
Critical Illness									
Delanaye, 2014[42]	Belgium& France	47	A	*CKD-EPI 2009*	60	*CKD-EPI 2012*	53	*CKD-EPI 2012*	62
Carlier, 2015[43]	Belgium	68	A	*CKD-EPI 2009*	40 (29, 52)	*CKD-EPI 2012*	45 (33, 57)	*CKD-EPI 2012*	54 (11, 65)
Ravn, 2019[44]	Sweden	30	A	*LM-REV*	67 (49, 81)	*CAPA*	47 (30, 64)	*CKD-EPI2012*	80 (63, 91)
				CKD-EPI2009	63 (46, 78)	*CKD-EPI2012*	43 (27, 61)	*CAPA+LM-REV*	87 (70, 95)
Sangla, 2020[45]	Switzerland	63	A	*CKD-EPI 2009*	44	*CKD-EPI 2012*	46	*CKD-EPI 2012*	56
Haines, 2023[46]	United Kingdom	27	A	*CKD-EPI 2021*	_	*CKD-EPI 2012*	_	_	_
Obesity									
Chang, 2020[47] Pre-bariatric	USA	27	A	*CKD-EPI 2009*	85 (70, 96)	*CKD-EPI 2012*	78 (59, 93)	*CKD-EPI 2012*	93 (81, 100)
Chang, 2020[47] Post-bariatric	USA	27	A	*CKD-EPI 2009*	85 (70, 96)	*CKD-EPI 2012*	93 (81, 100)	*CKD-EPI 2012*	93 (81, 100)

Figure 2. Accuracy of creatinine and cystatin C estimating GFR equations by clinical population. Accuracy was defined as the proportion of eGFR within 30% of mGFR (P_{30}). Where defined as 1-P_{30}, we converted it to P_{30} for consistency. Units are percent for P_{30}. Green box indicates high accuracy with P_{30} of magnitude > 90%. Yellow box indicates moderate accuracy with P_{30} of magnitude 80%-90 %; (red box) indicates low accuracy with P_{30} of magnitude less than 80%. GFR, glomerular filtration rate; mGFR, measured GFR; eGFR, estimated GFR.

was low to moderate for eGFRcr (68%-84%). The eGFRcr-cys was not reported.[38]

Heart Failure

Two studies of adults with heart failure in Europe were included. For eGFRcr and eGFRcr-cys, the 2 reports showed small bias or moderate-to-large overestimates. The bias was small for both reports of eGFRcys. P_{30} was low for all 3 equations (33%-66%, 52%-74%, and 56%-65%, respectively).[39,40]

Neuromuscular Disease

One publication of adults with primary neuromuscular disease in Europe was included. A large overestimation with low P_{30} (all < 50%) was observed for eGFRcr, eGFRcys, and eGFRcr-cys.[41]

5-10 mL/min/1.732m^2. Red box indicates large underestimate as median difference of less than −10 mL/min/1.732m^2 (ie, greater magnitude than less than −10). Spotted red box indicates large overestimate as median difference of greater than 10 mL/min/1.73 m^2. HSC, hematopoietic stem cell transplant; A, adult; C, children.

Table 3. Indications for Measurement of Cystatin C

Domain	Specific Clinical Condition	Cause of Decreased Accuracy	Comments on GFR Evaluation for Individual Patients[a]
Body habitus and changes in muscle mass	Anorexia nervosa[68]	non-GFR determinants of Scr	eGFRcys may be appropriate if no comorbid illness other than reduction in muscle mass
	Extreme sport/exercise/ body builder	non-GFR determinants of Scr	eGFRcys may be appropriate if no comorbid illness other than increase in muscle mass
	Above knee amputation[67]	non-GFR determinants of Scr	eGFRcys may be appropriate in those without other comorbid conditions Suggest eGFRcr-cys in those with comorbid illness
	Spinal cord injury with paraplegia/paraparesis or quadriplegia/ quadriparesis	non-GFR determinants of Scr	eGFRcys may be appropriate in those without other comorbid illness Suggest eGFRcr-cys in those with comorbid illness
	Class III obesity[47]	non-GFR determinants of Scr and Scys	eGFRcr-cys demonstrated to be most accurate
Lifestyle	Smoking[3,8,69]	non-GFR determinants of Scys	eGFRcr may be appropriate if no changes to non-GFR determinants of Scr or comorbid illness
Diet	Low protein diet[70,71]	non-GFR determinants of Scr	eGFRcys may be appropriate if no changes to non-GFR determinants of Scr or comorbid illness
	Keto-diets	non-GFR determinants of Scr	
	Vegetarian	non-GFR determinants of Scr	
	High protein diets and creatine supplements	non-GFR determinants of Scr	
Illness other than CKD	Malnutrition	Chronic illness, presumed effect on non-GFR determinants of Scr and Scys	eGFRcr-cys may be appopriate because of coexistence of malnutrition and inflammation Suggest using mGFR for treatment decisions based on level of GFR
	Cancer[24-27]	Chronic illness, presumed effect on non-GFR determinants of Scr and Scys	eGFRcr-cys demonstrated to be most accurate in populations studied but likelihood of lesser accuracy in more frail patients. Suggest using mGFR for critical treatment decisions based on level of GFR
	Heart failure[39,40]	Chronic illness, presumed impact on non-GFR determinants of Scr and Scys	eGFRcys less biased but all eGFR have low inaccuracy. Suggest using eGFRcr-cys or eGFRcys for routine GFR evaluation. Suggest using mGFR for critical treatment decisions based on level of GFR
	Cirrhosis or liver transplant[33-38]	Chronic illness, presumed effect on non-GFR determinants of Scr and Scys	eGFRcys less biased but all eGFR have low inaccuracy. Suggest using eGFRcr-cys or eGFRcys for routine GFR evaluation. Suggest using mGFR for critical treatment decisions based on level of GFR
	Critical illness[42-46]	Chronic illness, presumed effect on non-GFR determinants of Scr and Scys	eGFRcr and eGFRcys have bias and low accuracy. Suggest using eGFRcr-cys for routine GFR evaluation Suggest using mGFR for treatment decisions based on level of GFR
	HIV[28,29,30-32]	Chronic illness, presumed effect on non-GFR determinants of Scr and Scys	eGFRcr-cys demonstrated to be most accurate in populations studied but likelihood of lesser accuracy in more frail patients. Suggest using mGFR for critical treatment decisions based on level of GFR
	Catabolic consuming diseases (eg, TB, hematologic,	Chronic illness, presumed impact on	eGFRcr and eGFRcys have bias. Suggest using eGFRcr-cys for routine GFR evaluation.

(Continued)

Table 3 (Cont'd). Indications for Measurement of Cystatin C

Domain	Specific Clinical Condition	Cause of Decreased Accuracy	Comments on GFR Evaluation for Individual Patients[a]
	malignancies, and severe skin diseases)[25,26]	non-GFR determinants of Scr and Scys	Suggest using mGFR for treatment decisions based on level of GFR
	Muscle wasting diseases[41]	Chronic illness, presumed impact on non-GFR determinants of Scr and Scys	eGFRcr and eGFRcys have bias Suggest using eGFRcr-cys for routine GFR evaluation. Suggest using mGFR for treatment decisions based on level of GFR
Drug effects	Steroids (anabolic and hormone)	non-GFR determinants of Scr. Effect on Scys not known	Physiological effect on Scys unknown, suggest eGFRcr-cys
	Decreases in tubular secretion[72]	non-GFR determinants of Scr	eGFRcys may be appropriate if drug affects only creatinine and no comorbid illness
	Broad spectrum antibiotics that decrease extra-renal elimination	non-GFR determinants of Scr	eGFRcys may be appropriate if drug affects only creatinine and no comorbid illness

Abbreviations: GFR, glomerular filtration rate; mGFR, measured GFR obtained from plasma or urinary clearance of exogamous filtration markers; eGFR, estimated GFR; Scr or cr, creatinine; Scys or cys, cystatin C; TB, tuberculous; BMI, body mass index; CKD, chronic kidney disease.
[a]For all domains, data minimal or not exisitant. Suggestions based on best available evidence.

Critical Illness

Five publications of adults admitted to intensive care units in Europe were included (Fig 1). For both eGFRcr and eGFRcr-cys, 1 reported small bias and the rest showed moderate-to-large overestimate. All reports for eGFRcys showed moderate-to-large underestimate or overestimate. P_{30} was low for all reports of eGFRcr (40%-67%) and eGFRcys (43%-53%), and moderate for 2 of the 5 reports of eGFRcr-cys (80%-87%).[42-46]

Obesity

One publication reported on adults with baseline body mass index ≥ 35 kg/m^2 from a single center in North America before and 6 months after bariatric surgery. Before surgery, there was small bias for eGFRcr and eGFRcr-cys and moderate underestimate for eGFRcys. P_{30} was low to high, and higher for eGFRcr-cys than eGFRcr or eGFRcys (93% vs 85% and 78%, respectively). After surgery, the magnitude of bias increased for both eGFRcr and eGFRcys but decreased for eGFRcr-cys. P_{30} for eGFRcr-cys remained consistent and high (93%).[47]

DISCUSSION

The greater accuracy of eGFRcr-cys compared with either eGFRcr or eGFRcys was recognized over a decade ago, but uptake of cystatin C measurement has been slow.[59,60] With the more widespread use of standardized assays,[61] the confirmation of greater accuracy of eGFRcr-cys than eGFRcr or eGFRcys from independent research groups,[16,62,63] and the greater importance of use of eGFRcr-cys compared with race-free eGFRcr in the United States, and the recommendation for its use in the most recent KDIGO 2023 guidelines, we anticipate substantial future growth in utilization of cystatin C. However, there are not explicit indications for when cystatin C should be measured, preventing widespread implementation of these recommendations. To provide evidence to support such indications, we performed a systematic review of papers evaluating the performance of eGFR equations using cystatin C, creatinine, or both in 26 studies in populations with acute and chronic illness, including cancer, HIV, cirrhosis, liver transplant, heart failure, neuromuscular disease, critical illness, and obesity. The key observations were the following: First, common use of non-standardized assays for cystatin C and use of equations developed with nonstandardized assays more than a decade following standardization of the cystatin C assay. Second, insufficient data for all populations studies, both in terms of the number of studies for any 1 population as well as large inconsistencies in the relative performance of eGFRcr versus eGFRcys even among populations with the same comorbid illness. Third, more reports of moderate-to-large bias for eGFRcr than for eGFRcys and eGFRcr-cys, consistent with selection of study populations for known variation in non-GFR determinants of serum creatinine, and more reports of eGFRcr overestimating mGFR than underestimating mGFR, consistent with decreased creatinine generation. Fourth, possible support for better performance of eGFRcr-cys than eGFRcr or eGFRcys among study populations with cancer, HIV, and obesity is consistent with findings in the general and populations with CKD, but not for populations with cirrhosis, liver transplant, heart failure, neuromuscular disease, and critical illness populations. Fifth, no apparent variation in findings across estimating equations developed by different research groups, indicating the main explanation for our findings relates to the endogenous filtration markers rather than the specific equations used. Our study adds to the previous literature by summarizing available data to support indications for use of cystatin C in clinical practice; performance was poor in many

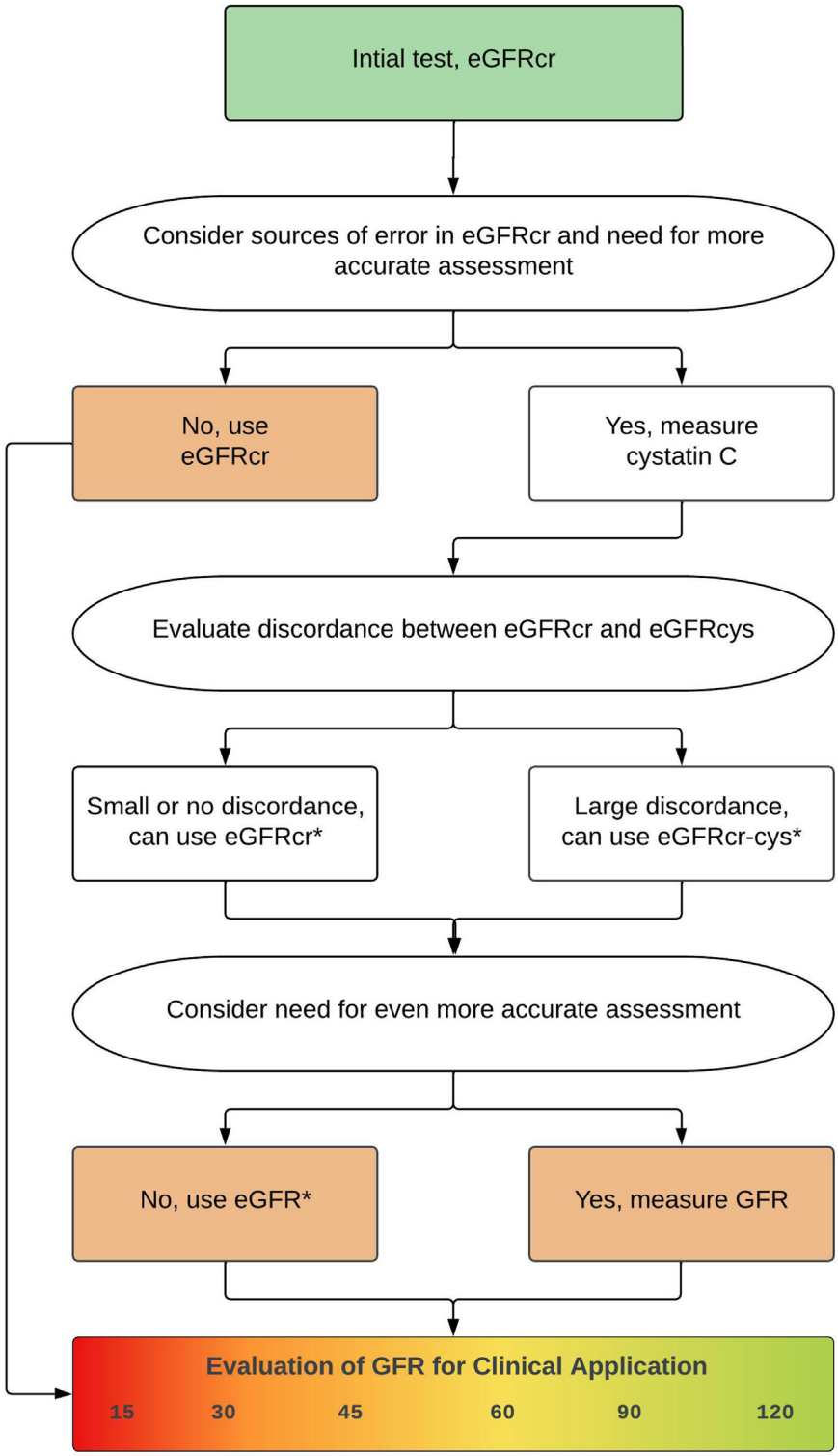

Figure 3. GFR evaluation using initial and supportive tests. The algorithm describes the approach to the evaluation of GFR. Our approach is to use initial and supportive testing to develop a final assessment of true glomerular filtration rate (GFR) and to apply it in individual decision-making at each point in time.[1] The initial test for evaluation of GFR is often eGFRcr, which will be available in most patients because creatinine is measured routinely as part of the basic metabolic panel. If the eGFRcr is expected to be inaccurate, or if a more accurate assessment of GFR is needed for clinical decision-making, such as diagnosis or staging of CKD or drug dosing, then cystatin C should be measured and the discordance between eGFRcr and eGFRcys should be assessed.[69,73] If eGFRcr and eGFRcys are not discordant (within 15 mL/min/1.73 m^2 or 20%-30% of each other), then accuracy of eGFRcr, eGFRcys, and eGFRcr-cys is similar. If eGFRcr and eGFRcys are discordant (not within 15 mL/min/1.73 m^2 or 20%-30% of each other), then eGFRcr-cys is generally more accurate than either eGFRcr or eGFRcys, with some exceptions, such as otherwise healthy

studies, suggesting the need for more frequent mGFR in these settings.

Compared with our previous systematic review published in 2011, we found improved consistency in reporting of performance metrics, with most studies reporting measures of bias and P_{30}, and most, but not all, reporting 95% confidence intervals around the estimated value. Use of uniform metrics facilitates comparisons across the studies. We noted greater use of standardized assays, although 14 studies were excluded for not using standardized cystatin C. However, several limitations in the available data persisted. For many of the included studies, the cystatin C and GFR measurements were performed because of concern that eGFRcr is not accurate, likely biasing the results against the eGFRcr. Furthermore, few studies had a large sample size, with only a few studies per comorbid illness, which limits the generalizability of the reported findings. A further limitation is that only 2 studies evaluated the newest of GFR estimating equations, such as EKFC or 2021 CKD-EPI equations.[17,64] Few studies in children with comorbid illnesses were found during our literature search indicating a gap in knowledge for this age group.

Observed differences between eGFR and mGFR are related to biological or analytical variation in either mGFR or eGFR (Table S4). Error in eGFR because of biological variation in non-GFR determinants of the endogenous filtration marker is the most likely explanation for our findings. We had expected to see poor performance of eGFRcr as the effect of comorbid illness on muscle mass leading to decreased creatinine generation is well-known. The poor performance of eGFRcys and eGFRcr-cys in many studies suggests that these illnesses are also associated with variation in non-GFR determinants of cystatin C, which if present could reduce the accuracy of eGFRcys and of eGFRcr-cys. Possibility of analytical variability for both exogenous and endogenous filtration markers should also be considered. Although we restricted the studies to those which used standardized assays for both creatinine and cystatin C, there are not traceability programs for exogenous filtration markers, and thus we could not impose a similar restriction for mGFR. In addition, we included all methods for mGFR, despite recognition of variability to each other and the importance of tailoring the protocol for the population.[65] One study in a critical illness population used plasma clearance of iohexol, known to lead to higher values in mGFR relative to the true GFR. In this study, large differences between eGFR and mGFR were observed, which may be potentially due in part to error in mGFR.[44,66]

In Table 3,[67-72] we list indications for measurement of cystatin C. The greater accuracy of eGFRcr-cys in cancer, HIV, and obesity supports possible use of eGFRcr-cys in these clinical setting. However, the very ill or frail were not represented in these cohorts, and it is possible that eGFRcr-cys may not be as accurate as observed in the included studies. We suggest more investigations. In the meantime, we suggest increased use of mGFR for GFR-based decisions, as for example, in the decisions to use of carboplatin versus cis-platinum to avoid kidney toxicity at low GFR. The lack of studies and low accuracy of eGFR in populations with liver disease, heart failure, neuromuscular disease, or critical illness suggests consideration of mGFR in these settings, too, as for example in clinical decisions surrounding combined heart and kidney or liver and kidney transplantation versus heart or liver transplantation alone. By contrast, in otherwise healthy populations with decreased creatinine generation owing to reduced muscle mass, or decreased creatinine secretion because of use of specific medications, we would hypothesize that eGFRcys may be more accurate than eGFRcr.[67,68]

With more frequent cystatin C measurement, an algorithmic approach will be helpful to encourage appropriate measurement of cystatin C or mGFR based on accuracy of eGFR, as suggested in Table 3, and the clinical need (Fig 3). The algorithm also provides guidance to physicians if large discordance between eGFRcr and eGFRcys is observed.[69,73] In such settings, eGFRcr-cys is generally more accurate than either eGFRcr or eGFRcys, with some exceptions. For example, in otherwise healthy populations with increased creatinine generation owing to increased muscle mass, or decreased creatinine secretion or extra-renal elimination because of use of specific medications, eGFRcys may be the most accurate. In addition, one study of an older adult population showed that the lower eGFR, regardless of the marker, may be more likely be to be correct, presumably due to higher prevalence of CKD.[69,73-75] If an even more accurate assessment of GFR is needed for clinical decision-making, then GFR should be measured using plasma or urinary clearance of exogenous filtration markers, if available. This approach would need to be taken for each time GFR is being used to make important clinical decisions.

populations with increased creatinine generation owing to increased muscle mass, or decreased creatinine secretion or extra-renal elimination because of use of specific medications, when eGFRcys may be more accurate. If an even more accurate assessment of GFR is needed for a clinical decision, then GFR should be measured using plasma or urinary clearance of exogenous filtration markers, if available. This consideration should be applied to anytime GFR is required for a clinical decision. It is important to determine how accurate an assessment of GFR needs to be for a clinical decision. P_{30} for eGFR does not generally exceed 90% (90% of eGFR within 30% of mGFR). P_{15} for mGFR does not generally exceed 90% (90% of mGFR within 15% of true mGFR). At a GFR of 60 mL/min/1.73 m^2, 30% accuracy for eGFR corresponds to 42-78 mL/min/1.73 m^2 and 15% accuracy for mGFR corresponds to 51-69 mL/min/1.73 m^2. At a GFR of 30 mL/min/1.73 m^2, 30% accuracy for eGFR corresponds to 21-39 mL/min/1.73 m^2 and 15% accuracy for mGFR corresponds to 26-35 mL/min/1.73 m^2. *Use eGFRcr or eGFRcr-cys depending on discordance between eGFRcr and eGFRcys.

Our data support current recommendations for incorporation of cystatin C measurements into routine clinical testing. In the United States, the National Kidney Foundation Laboratory Engagement Group has several initiatives for widespread education and policy changes.[76] Our data also reinforce the message that measuring GFR using clearance of exogenous filtration markers is an important part of GFR evaluation and would also require increased efforts for widespread implementation. The sparsity of data and well-conducted studies in these clinical populations highlights the need for more high-quality research on estimated and measured GFR in populations with acute or chronic comorbid illness.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Flow chart of systematic review.

Figure S2. Bias creatinine and cystatin c estimating GFR equations (including MDRD) by clinical population.

Figure S3. Accuracy of creatinine and cystatin c estimating GFR equations (including MDRD) by clinical population.

Item S1. Risk of bias assessment tool.

Table S1. Search Strategy.

Table S2. Studies Excluded at Full-Text Review.

Table S3. Quality Assessment of Included Papers.

Table S4. Factors Affecting Errors in GFR Estimates.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Ogechi M. Adingwupu, MD, MPH, Ernesto Rodolpho Barbosa, MS, Paul M. Palevsky, MD, Joseph A. Vassalotti, MD, Andrew S. Levey, MD, Lesley A. Inker, MD MS

Authors' Affiliations: Department of Medicine, Division of Nephrology, Tufts Medical Center, Boston, MA (OMA, ASL, LAI); Tufts University School of Medicine, Boston, MA (ERB); Renal Section, Medical Service, Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, PA (PMP); Icahn School of Medicine at Mount Sinai, New York, NY; National Kidney Foundation, Inc, New York, NY (JAV).

Address for Correspondence: Lesley A Inker, MD, MS, Division of Nephrology, Tufts Medical Center, 800 Washington Street, Box #391, Boston, MA 02111. Email: Lesley.Inker@tuftsmedicine.org

Authors' Contributions: Research idea and study design: OMA, LAI; data acquisition: ERB, OMA, LAI; data analysis/interpretation: LAI, ASL, OMA, JAV, PMP; supervision or mentorship: LAI, ASL. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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