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Cystatin C as a biomarker of chronic kidney disease: latest developments

Stefanie Benoit¹, Eileen A. Ciccio^{1,2}, Prasad Devarajan^{1,*}

¹Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH 45229, USA

²Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, USA

Abstract

Introduction: Chronic kidney disease (CKD) is common, occurring in over 10% of individuals globally, and is increasing in prevalence. The limitations of traditional biomarkers of renal dysfunction, such as serum creatinine, have been well-demonstrated in the literature. Therefore, augmenting clinical assessment with newer biomarkers, such as serum cystatin C, has the potential to improve disease monitoring and patient care.

Areas covered: The present paper assesses the utility and limitations of serum cystatin C as a biomarker for CKD in light of the current literature.

Expert opinion: Serum cystatin C has been well established as an early and accurate biomarker of CKD that is particularly helpful in patients for whom creatinine is an inadequate marker or for whom more cumbersome methods of glomerular filtration rate (GFR) measurement are impractical. Current research questions are no longer focused on if, but rather when and how often cystatin C should be used in the evaluation of CKD patients. However, transition of all reagents and estimated GFR equations to the newly established International Standard is critical for developing generalizable data.

Keywords

biomarkers; chronic kidney disease; cystatin C; estimated glomerular filtration rate

1. Introduction

Chronic kidney disease (CKD) is common and increasing worldwide[1], particularly in the setting of increasing obesity, diabetes mellitus, and hypertension[2]. In a recent systemic review and meta-analysis, the prevalence was found to be consistently 11–13% globally,

*Corresponding author: Prasad Devarajan, prasad.devarajan@cchmc.org.
Drs. Benoit and Ciccio contributed equally to this work

Declaration of Interest

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with higher rates in women than men and in high-income countries compared to low-income countries[3]. In the United States, although CKD prevalence in the past 20 years has stabilized at about 15% of the overall adult population, the number of younger individuals (less than 60 years of age) living with CKD is still increasing[2]. Unfortunately, patient awareness of impaired renal function is strikingly low, even among those patients with advanced stage 4 CKD[2]. Early diagnosis and treatment are significant in reducing the known morbidity and mortality associated with chronic kidney disease[2]. Thus, it is important that the field continue to optimize methods to accurately diagnose patients with impaired renal function.

The most commonly used method of estimating glomerular filtration rate (GFR) is measurement of serum creatinine. Creatinine is a breakdown product of creatine phosphate in skeletal muscle and is derived from a patient's native muscle metabolism as well as consumption of dietary creatine (e.g. meat and creatine supplements). While it is freely filtered by the renal glomeruli, with no reabsorption or renal metabolism, it is actively secreted by the proximal tubule. Due to the substantial amount of urinary creatinine derived from tubular secretion, GFR calculated by 24-creatinine clearance can exceed the measured GFR by the gold standard inulin clearance by 10 to 40%[4]. In addition, given the endogenous source of creatinine is skeletal muscle, there are a variety of demographic factors that affect serum creatinine, including age, gender, and race/ethnicity[5]. Multiple GFR estimating equations have been developed in an attempt to account for these variations. The equations recommended in 2012 by Kidney Disease Outcomes Quality Initiative are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for adults and the Updated "Bedside" Schwartz equation for children[5]. However, only approximately 85% and 79% of estimated GFRs using these two equations, respectively, are within 30% of simultaneously accurately measured GFR values[5].

Cystatin C, a 13-kDa cysteine proteinase inhibitor protein, is produced by all nucleated cells at a steady rate[6] and is freely filtered by the kidney with near-complete reabsorption and catabolism in the proximal tubule and no significant urinary excretion[7]. Thus, serum cystatin C levels are much less affected by such patient characteristics such as gender, age, body size and composition, and nutritional status. It was first proposed as a glomerular filtration biomarker in 1985, and its clinical utility in comparison to creatinine has been argued and vetted now for more than 30 years, as summarized in Table 1[8]. In this review, we will address the most recent developments in the clinical application of serum cystatin C measurements and assess its value as a biomarker in CKD patients.

2.0 International standardization of reagent

There were considerable differences between the multiple cystatin C reagents and assays that have been developed over time. As a result, there are numerous cystatin C estimated GFR (eGFR) equations with different power functions to account for the variation in concentrations measured. Pottel et al demonstrated that these equations have more or less the same mathematical form, and $eGFR = 79.7 CysC^{-1.12}$ explains 96% of the variation in predicted eGFR of those equations[9]. The lack of uniformity made it difficult to reproduce or share data across institutions[10].

In June 2010 the International Federation of Clinical Chemistry (IFCC) and Laboratory Medicine Working Group on Standardization of Cystatin C released an international certified cystatin C reference material (ERM-DA471/IFCC)[11]. The reference material was made available to clinical laboratories in late 2010, and the College of American Pathologists launched a cystatin C surveillance survey, CYS-Survey, in 2011. Despite availability of the international standard, the 2014 CYS-Survey of 141 laboratories showed substantial method based bias between different manufacturers[**12]. For example, the cystatin C values in mg/L for the normal sample was 0.780 for Siemens, 0.870 for Gentian, 0.967 for Roche, 1.061 for Diazyme, and 0.970 for other/not specified reagents. The mean cystatin C values reported for the chronic kidney disease sample was 2.052 for Siemens, 2.312 for Gentian, 2.247 for Roche, 2.909 for Diazyme, and 2.413 for other/not specified reagents, again illustrating the wide variability. A separate study conducted between 7 clinical laboratories located in France and Belgium in 2015 showed persistence of unacceptably high biases in 7 of the 8 automated assays tested[13]. Thus, further work still needs to be done to improve manufacturers' calibration traceability to the ERM-DA471/IFCC reference material in order to minimize manufacturer-to-manufacturer error. Quantification and minimization of error from variation in the processes of calibration, such as use of a one-point calibration procedure, which can be subject to the bias and drift of a single reference point, will also be required before cystatin C can be fully actualized as a clinical biomarker[10].

2.1. Longitudinal calibrations

Beyond standardizing the results between different clinical labs and assay manufacturers, there were also issues with calibrating results from the same manufacturer across time. There was a downward drift in Siemens' particle-enhanced nephelometric immunoassay (PENIA) results over time. In 2011, Larsson et al reported an unexpected improvement in PENIA-derived cystatin C concentrations within a longitudinal cohort, which prompted the group to reanalyze the cystatin C levels of banked serum specimens using Gentian's particle-enhanced turbidimetric immunoassay (PETIA)[14]. While the methods were found to have good correlation ($r^2=0.994-0.995$) in the 2005 and 2006 samples, samples from 2008 through 2012 showed a 15% decrease in the results obtained with the Siemens method. This drift was clinically significant, as a cystatin C concentration corresponding to a GFR of 60 mL/min/1.73 m² in 2005 increased to approximately 80 mL/min/1.73 m² in 2010[14]. This drift was recognized by other laboratories as well[15].

It was not until early 2018 that Siemens announced it was going to discontinue the non-standardized cystatin C reagent kits and replace them with IFCC-calibrated kits in the United States market[16]. The company reported that the calibrated values would be 17.4% higher than the pre-IFC values[16]. This change was particularly important for the results of landmark longitudinal CKD studies, such as the chronic kidney disease in children (CKiD) study, which has collected over 3,000 cystatin C values across this time period of changes. Schwartz et al found that the cystatin C values of previously measured IFCC standards were consistently 17% higher with the newer IFCC-calibrated reagent[16]. Thus, they suggest it is possible to convert pre-IFCC cystatin C values to the new IFCC-calibrated values by multiplying the concentration by 1.17.

We use the Siemens PENIA assay in our hospital, and with the change to the new IFC-calibrated reference material, we conducted our own quality improvement work to assess the mean change in cystatin C value between the two reagents in our lab and to determine which GFR estimation equation would produce the most accurate eGFR. Using reagent from the non-standardized and IFCC-standardized kits, we measured the cystatin C in 105 consecutive patients at the time of a measured GFR by nuclear medicine DTPA. We found that the standardized assay resulted in a mean increase in the serum cystatin C value of 24%, with a more pronounced increase at higher measured GFRs. This again demonstrates the need for further standardization across manufacturers and clinical laboratories.

2.2 Universal cystatin C eGFR equation

A final opportunity presented by the introduction of an international standard was the ability to create a new, universal GFR estimation equation. New CKD-EPI equations for cystatin C alone and combined with creatinine were the first to be published in 2012[17]. The 2012 CKD-EPI cystatin C equation showed comparable performance to the 2009 equation, while it no longer required a race coefficient, and the age and sex coefficients were smaller. They found that combining creatinine and cystatin C resulted in the best GFR estimation, and the 2012 CKD-EPI equations swiftly became the preferred method for estimating GFR in the adult population[18].

It was notable that the CKD-EPI equation was developed in a population of Caucasians and African Americans with a mean age of 47[17]. In 2014, Grubb et al published a novel GFR estimation equation developed using Caucasian, Asian, pediatric, and adult (CAPA) cohorts. In addition to introducing diversity of race and age and using the new IFCC-calibrated reference material, they developed calibration equations to account for the differences between assays of the different manufacturers[19]. The resulting CAPA equation had similar bias, precision, and accuracy when compared to the CKD-EPI equation, but with the advantage of requiring only cystatin C and age as variables. The percent of estimated GFR results within 30% of measured GFR for both equations across all ages and demographics was consistently greater than 70%, although they both performed least well in children and older adults.

The third and most recent set of equations to be developed since the IFCC-calibrated standard became available is the Full Age Spectrum (FAS) equations published in 2017 by Pottel et al[20]. These equations were developed using the assumptions that the average GFR of children, adolescents, and young adults is 107.3 mL/min/1.73m², age related GFR decline begins at 40 years of age, and that the deviation in a patient's creatinine and/or cystatin C from their age specific population norm can then be used to calculate their estimated GFR. While creatinine requires multiple normalization factors for different ages due to changes in muscle mass over time, the value of 0.82 mg/L was determined to be the cystatin C normalization factor for children, adolescents, and adults up to 70 years of age; 0.95 mg/L was the mode of distribution for cystatin C in healthy adults greater than 70 years of age, and thus was selected as the normalization factor for that age group. In general, the FAS cystatin C based equations performed as well as or better than the CKD-EPI and CAPA equations.

Although they were designed to encompass all age ranges, an important shortfall of both the CAPA and FAS equations is in children with CKD. The Schwartz Cystatin C equation, published in 2012, was developed in the CKiD cohort, which is made up of children between 1 and 16 years of age with eGFRs of 30 to 90 mL/min/1.73 m², using Seaman's non-calibrated reagents. As a result, the Schwartz equations has an excellent P30 (a measure of accuracy, defined as the percent of estimates within 30% of measured GFR or mGFR) specifically for children with mGFR < 60 mL/min/1.73 m² of 91% in the original study[21], 86% in the FAS development paper[**20], and 98% in a 2019 paper by Salvator et al comparing eGFR equations in a pediatric CKD cohort[22]. In stark contrast, the P30 in children with CKD for the CAPA cystatin C equation in the FAS and Salvator papers were 66.7% and 46%, respectively; for the FAS cystatin C equation, the P30 were 68.4% and 46%, respectively. Since the Schwartz cystatin C equation does not require additional variables, such as height, automated reporting of eGFR for pediatric patients with eGFR < 60 mL/min/1.73 m² using this equation may be feasible. The clinical value and utility of this strategy would need to be carefully weighed against the complication of a multi-equation system and what transition from child to adult equations would look like.

3.0 Cystatin C for Estimation of GFR in CKD

Once an accurate value for serum cystatin C is obtained, the next questions are when and how to use them. The most basic application of cystatin C is for GFR estimation. The 2012 Kidney Disease Improving Global Outcomes (KDIGO) suggested measuring cystatin C in adults with a creatinine eGFR between 45 – 60 mL/min/1.73 m² but who lack other markers of kidney damage in order to confirm the diagnosis of CKD[23]. Recent publications examining the practical application of this recommendation have examined whether this has added to diagnostic accuracy. In addition, because Cystatin C is more expensive to run than creatinine, with the reagent costing approximately 10 times as much, the implications for public health expenditure have also been examined[24].

The Renal Risk in Derby study looked for a change in CKD classification with cystatin C measurement for 1,741 older adult primary care patients with a mean age of 73 years, who had either CKD G3a or G3b defined by 2 eGFR values more than 90 days apart[**25]. They used the CKD-EPI cystatin C and combined equations to calculate eGFR. They found use of cystatin C to confirm diagnosis resulted in 7.7% of patients being reclassified as not having CKD, while 59% were reclassified as having more advanced CKD. Using the combined equation, 5.5% and 42.9% of patients were reclassified as not having CKD and having more advanced CKD, respectively. The additional testing in all CKD 3aA1 patients in England would increase the cost of monitoring CKD patients by £31 million per year[**25].

A prior meta-analysis had produced opposite results, with a larger proportion of CKD G3a patients being reclassified to no CKD (35–47%) than to more advanced CKD (21–27%) [**26]. Notably, the mean age of patients was 55 – 60 years, significantly younger. Variability in cystatin C with age was also noted in the Irish Longitudinal Study on Ageing[27]. Using a cross-sectional analysis of 5,386 participants, they found that cystatin C rose sharply after the age of 65 years such that the probability a patient would be reclassified as having more advanced CKD increased from 15% at age 50 years to 80% at age 80 years. These studies

raise the question of whether there are age-related determinants that confound its role as a filtration marker. The addition of cystatin C to creatinine was shown to improve the accuracy of GFR estimation in patients over 70 years of age[28], although conflicting results were found in patients over 80 years old[29].

While the general application of cystatin C to CKD screening requires more study, there are subsets of patients for whom cystatin C has been shown to be a superior biomarker and it should be utilized to accurately assess GFR. These include patients with abnormal creatinine excretion, including sickle cell disease[30], and patients with low muscle mass, including Duchenne muscular dystrophy[31], spina bifida[32,33] and perhaps preterm infants[34], congenital heart patients[35], and those undergoing chemotherapy[36].

3.1 Still imperfect at best

While we have continued to strive toward an accurate and precise endogenous biomarker of GFR, the reality is that our biomarkers and equations remain imperfect[37]. Using data from 882 adult patients who had a measured GFR, Luis-Lima et al evaluated the reliability of their simultaneously obtained creatinine and cystatin C values in the correct classification of their CKD[37]. They used the IFCC-calibrated reagent for cystatin C measurements. The mean age of the patients was 57.4 years. They found that error in classification of CKD by eGFR was very common, occurring about 50% of the time using creatinine based formulas and 30% of the time using cystatin C based formulas. Combined formulas did not perform better than cystatin C only equations. They also found that some cystatin C based formulas developed prior to reagent standardization performed as well as the newer equations discussed earlier.

Even more basic to our question of how to determine the GFR is a new realization from a paper by Roe et al examining the variation of measured GFR in 20 adult patients with moderate CKD[38]. Measuring Iohexol clearance, creatinine, and cystatin C weekly for four consecutive weeks, they found that within-subject biological variation of the measured GFR was 6.7% (95%CI: 5.6–8.2), which was higher than that of any of the estimated GFRs, which ranged from 5 – 5.3%. Using this data, they could then derive reference change values, which are the calculated eGFRs at which there is a 95% probability that the GFR actually changed from baseline. The positive and negative RCVs for estimated GFRs from the MDRD equation were 15.1% and 13.1%, respectively. Thus, if a baseline MDRD GFR was 59 mL/min/1.73m², a significant increase or decrease would be values of >68 or <51 mL/min/1.73m², respectively [38].

3.2 New methods on the horizons

Due to the known and unknown confounders of both creatinine and cystatin C in determining eGFR, there are efforts to identify other biomarkers of GFR. Freed et al recently developed a liquid chromatography – tandem mass spectrometry test that quantitatively measures 4 serum metabolites: N-acetylthreonine, pseudouridine, phenyl-L-cetylglutamine, and tryptophan[39]. They developed an equation based on these 4 metabolites (eGFR_{met}) that is independent of creatinine, cystatin C, and demographic factors. When combined with

creatinine and cystatin C, their equation was more accurate than any other current approach (P30 of 93%).

Other researchers are moving away from endogenous biomarkers altogether. Fluorescent molecules have been developed that act as ideal filtration markers[40]. Rather than depending on a steady state concentration, the plasma disappearance rate of these exogenous markers can be measured using transdermal sensors. This technique would permit continuous monitoring of GFR, thus it is being called the “Real-time GFR”. In 2018, the MediBeacon, Inc Transdermal GFR Measurement System (TGFR) was granted Breakthrough Device designation, which expedites FDA review. While currently available for pre-clinical research, the device is not yet cleared for use in humans.

4.0 Cystatin C for risk prediction in CKD

Over the past 15 years it has been well established that cystatin C is an independent predictor of morbidity and mortality in a variety of populations. It has been associated with progression to end stage renal disease and mortality in patients with diabetes[41,42], acute kidney injury[43,44], CKD[45–47], and on dialysis[48]. It can detect renal dysfunction and predict mortality in liver patients, including those with liver cirrhosis[49–54], acute-on-chronic liver failure[55,56], and liver transplant recipients[57–59]. Cystatin C has also been associated with mortality in patients with COPD[60], stroke[61–63], and HIV[64]. The largest body of work, however, has been examining the association between cystatin C and cardiovascular disease. Rising cystatin C values are associated with the development and progression of cardiovascular disease (CVD), independent of renal function and other cardiovascular risk factors[65–71]. Cystatin C also has been found to hold prognostic value for procedure related outcomes[72–76], critical illness[44,77], and CVD and all cause mortality in both CVD patients[78–81] and the general population[82]. There is physiologic plausibility of this relationship, as cystatin C is an inhibitor of cysteine proteases and has been found to be directly involved in the atherosclerotic process[83–85].

Whether the relationship between cystatin C and CVD is truly causal or is a consequence of confounding or reverse causality is hard to determine. In an effort to tease out the relationship between cystatin C and CVD, researchers have utilized the epidemiologic technique of Mendelian randomization. This analytical method uses known genetic variants to support causal relationships between modifiable risk factors and disease[86]. Using data from 59 studies encompassing over 300,000 people, van der Laan et al again demonstrated the strong observational associations between circulating concentrations of cystatin C and risk of CVD, but also showed that cystatin C was associated with many potential confounders[87]. They then applied the genetic variant rs911119 in the gene CST3 to the analysis, which associates with CST3 gene expression and directly encodes cystatin C. This genetic variant is ideal in that it has a very strong association with circulating cystatin C concentrations and is not associated with potential confounders. In Mendelian randomization analysis, no evidence for a causal association with CVD was identified, and thus they could provide no evidence of a causal role for circulating cystatin C in the etiology of atherosclerotic vascular disease[87].

Although causality was not established in this study, Cystatin C remains a novel biomarker of CVD and mortality in patients with CKD. This was demonstrated in a study of nearly 12,000 patients with CKD identified by creatinine eGFR using the CKD-EPI equation, in which the adverse outcomes of mortality, CVD, heart failure, and kidney failure were limited to the patient who also had CKD by cystatin C as well[46]. It is well known that there must be >50% reduction in GFR before the eGFR becomes abnormal by creatinine[88]. Thus, waiting on a significant change in creatinine prior to use of cystatin C may lead to missed opportunities.

Finally, Cystatin C has emerged as an interesting marker of early hypertensive nephropathy. In pregnant women with normal creatinine eGFR, elevated cystatin C at the end of the first trimester is associated with the development of pre-eclampsia[89]. Cystatin C levels were significantly increased in young, healthy pre-hypertensive patients compared to normotensive patients[36]. Cystatin C was also higher in patients with white coat hypertension compared to normotensive counterparts, and was positively associated with the left ventricular mass index, indicating it may be a marker of subclinical organ damage[90]. As the 2012 KDIGO recommendations currently stand, these patients would not have cystatin C levels measured.

5.0 Conclusion

The creation of a calibrated reagent has opened the door to standardization of cystatin C values across clinical laboratories and development of universal GFR estimation equations. Now 10 years out from IFCC reagent standardization, there is still significant variability in results reported between laboratories[12]. And our best cystatin C based GFR estimates are over 30% off more than 20% of the time[37]. This puts significant limitations on the universality of research data and the utility of cystatin C as a clinical test. That being said, the list of laboratory and clinical imprecisions of creatinine, which remains the most common standard for estimation of GFR, is longer (Table 1). Cystatin C has been found to be more accurate than serum creatinine in many different patient populations[7]. It captures earlier, more subtle changes in kidney function, the cost-effectiveness and clinical relevance of which has yet to be parsed out. Cystatin C has been well established as an independent predictor of morbidity, mortality, and progression to ESRD in a variety of populations, which has opened up many veins of research beyond that of accurate GFR estimation.

6.0 Expert opinion

Cystatin C is a useful clinical biomarker with significant potential. The key area for improvement at this time is ensuring manufacturer calibration traceability to the IFCC reference material. Accountability through continued publication of College of American Pathologists surveys could help inform clinical laboratories as to which manufacturer provides high quality calibration. Clinical laboratories should also strive to utilize the highest quality manufacturers and standardize their approach to cystatin C testing across institutions. Consistent measurements across institutions will improve the quality of our data, facilitate multicenter data analysis, and better inform the incorporation of cystatin C into diagnostic criteria and treatment guidelines for CKD.

It is worth stating that even in its current state of imperfection, cystatin C has still been found to provide a more accurate estimate of GFR than creatinine in certain patient populations. In these groups of patients, particularly those with abnormal muscle mass or creatinine excretion, such as patients with sickle cell disease, Duchenne muscular dystrophy, and spina bifida, cystatin C should be incorporated into CKD screening now.

Assuming calibration traceability improves and laboratory measurements become more uniform over the coming years, the cost and long term benefits of cystatin C monitoring are also worth thoughtful investigation. The cost-effectiveness of routine testing and clinical utility of reclassifying large swaths of patients into higher stages of CKD has been raised. In cases of hypertensive or diabetic nephropathy, in which interventions could retard progression, earlier identification of more mild renal impairment may arguably be of value. Early intervention trials based on cystatin C could inform future cost analyses. These analyses should take into account the costs of early intervention, benefits of prevention of progression to end stage renal disease and loss of quality adjusted life-years.

While cystatin C continues to define its place in the clinical estimation of GFR, the future of accurate, easily accessible GFR assessment may very well lie in the discovery of novel endogenous biomarkers or the design of optimal exogenous biomarkers with real-time GFR tracing technologies, as were discussed above. Even with calibration and laboratory technique at their optimum, GFR estimation with cystatin C will still fall victim to its non-GFR determinants, such as thyroid function and steroid use. What will continue to set Cystatin C apart from other biomarkers, however, is its independent association with cardiovascular disease, end stage renal disease, and all-cause mortality. Although no causal relationship has been established, these relationships offer exciting avenues of research to understand common pathways of morbidity and mortality in cardiovascular and renal disease. And unlike serum creatinine, this prognostic value will preserve its utility even after alternative means of estimating GFR have superseded both of these biomarkers.

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Article highlights:

- Serum cystatin C is an earlier and more accurate biomarker of GFR than creatinine in many patient populations.
- Cystatin C is independently associated with cardiovascular disease, end stage renal disease, and all-cause mortality.
- The new IFCC-calibrated reagent has made standardization of cystatin C values across clinical laboratories and the creation of universal GFR estimation equations possible.
- Clinical laboratories should strive to standardize their approach and broaden availability of this assay.
- The cost and long term benefits of routine cystatin C monitoring and earlier diagnosis of renal impairment and cardiovascular risk with cystatin C is worth thoughtful prospective investigation.

Table 1:

Non-GFR determinants of serum creatinine and cystatin C[23,87]

	Creatinine	Cystatin C
Biomarker Generation	<ul style="list-style-type: none"> • Race/ethnicity other than US and European black and white • Gender • Age • Extremes of muscle mass • Extremes of body size • High protein diet • Ingesting cooked meat • Creatine supplements • Muscle wasting diseases • Limb amputation 	<ul style="list-style-type: none"> • Race/ethnicity other than US and European black and white • Gender • Age • Disorders of thyroid function • Administration of corticosteroids • Inflammation and high cell turnover states • Common genetic variants
Tubular Secretion	<ul style="list-style-type: none"> • Drug-induced inhibition by trimethoprim, cimetidine, fenofibrate • Tubular secretion increased in CKD 	<ul style="list-style-type: none"> • None identified
Assay Interference	<ul style="list-style-type: none"> • Spectral interferences (bilirubin, some drugs) • Chemical interferences (glucose, ketones, bilirubin, some drugs) 	<ul style="list-style-type: none"> • Heterophilic antibodies

GFR, glomerular filtration rate; CKD, chronic kidney disease

Table 2:

Post IFCC-calibrated cystatin C reagent GFR estimate equations

Cystatin C-based equations					
CKD-EPI[17] (2012)	Male	cysC 0.8	133*(cysC/0.8) ^{-0.499} *0.996 ^{Age}		
		cysC>0.8	133*(cysC/0.8) ^{-1.328} *0.996 ^{Age}		
	Female	cysC 0.8	133*(cysC/0.8) ^{-0.499} *0.996 ^{Age} *0.932		
		cysC>0.8	133*(cysC/0.8) ^{-1.328} *0.996 ^{Age} *0.932		
CAPA[19] (2014)	130 × (cys C) ^{-1.069} × Age ^{-0.117} − 7				
FAS[**20] (2017)	<70 yo	QcysC=0.95	$\frac{107.3}{\frac{ScysC}{QcysC}} \times \left[0.988^{(Age - 40)} \text{when Age} > 40 \text{years} \right]$		
	70 yo	QcysC=0.82			
Combined equations					
CKD-EPI[17] (2012)	Male	Cr 0.9	cysC 0.8	135*(Cr/0.9) ^{-0.207} *(cysC/0.8) ^{-0.375} *0.995 ^{Age} (*1.08 if black)	
			cysC>0.8	135*(Cr/0.9) ^{-0.207} *(cysC/0.8) ^{-0.711} *0.995 ^{Age} (*1.08 if black)	
		Cr >0.9	cysC 0.8	135*(Cr/0.9) ^{-0.601} *(cysC/0.8) ^{-0.375} *0.995 ^{Age} (*1.08 if black)	
			cysC>0.8	135*(Cr/0.9) ^{-0.601} *(cysC/0.8) ^{-0.711} *0.995 ^{Age} (*1.08 if black)	
	Female	Cr 0.7	cysC 0.8	130*(Cr/0.7) ^{-0.248} *(cysC/0.8) ^{-0.375} *0.995 ^{Age} (*1.08 if black)	
			cysC>0.8	130*(Cr/0.7) ^{-0.248} *(cysC/0.8) ^{-0.711} *0.995 ^{Age} (*1.08 if black)	
		Cr >0.7	cysC 0.8	130*(Cr/0.7) ^{-0.601} *(cysC/0.8) ^{-0.375} *0.995 ^{Age} (*1.08 if black)	
			cysC>0.8	130*(Cr/0.7) ^{-0.601} *(cysC/0.8) ^{-0.711} *0.995 ^{Age} (*1.08 if black)	
FAS[**20] (2017)	<70 yo	QcysC=0.95	Male	Qcrea=0.9	$\frac{107.3}{\alpha \times \frac{SCr}{Qcrea} + (1 - \alpha) \times \frac{CysC}{Qcysc}} \times \left[0.988^{(Age - 40)} \text{when Age} > 40 \text{years} \right]$
			Female	Qcrea=0.7	
	70 yo	QcysC=0.82	Male	Qcrea=0.9	
			Female	Qcrea=0.7	

All eGFR are in ml/min/1.73m². CysC=cystatin C (mg/L), Cr=creatinine (mg/dL), yo=years old