

# Which is the best glomerular filtration marker: Creatinine, cystatin C or both?

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## Abstract

**Background:** The glomerular filtration rate (GFR) is estimated by the serum or plasma concentration of creatinine and/or cystatin C using equations that include demographic data. The equations worldwide most widely used are those of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) consortium and updated in 2021 to remove the Afro-American racial correction factor. In 2021 and then in 2023, the European Kidney Function Consortium also developed equations based on creatinine and cystatin C, usable across the full age spectrum, and constructed by including the *Q* value (i.e. the median creatinine or cystatin C in healthy men and women, which is customizable for specific populations).

**Methods:** The aim of this narrative review is to examine the strengths and weaknesses of each biomarker.

**Results:** Both biomarkers have non-GFR determinants, namely muscle mass, protein intake and tubular secretion for creatinine; dysthyroidism and systemic corticosteroids for cystatin C, as well as other more debated determinants (diabetes, obesity, proteinuria, inflammatory syndrome). These non-GFR determinants are the reason why no equation based on a single endogenous biomarker has an accuracy within 30% greater than 90% over the entire age spectrum (in at least one patient in 10, estimated GFR is at least 30% higher or at least 30% lower than the measured GFR).

**Conclusion:** Equations combining the two biomarkers provide a better estimate of GFR, particularly in the subgroup of patients whose estimates based on each of the biomarkers are highly discordant. These patients must also be identified as being at increased risk of morbidity, particularly cardiovascular, and mortality.

## KEYWORDS

biomarkers, glomerular filtration rate, kidney function

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## 1 | INTRODUCTION

The glomerular filtration rate (GFR), which is used as the kidney function indicator, is estimated in current clinical practice by the serum or plasma concentration of endogenous markers. A few years after blood urea nitrogen,<sup>1</sup> creatinine was one of the first endogenous biomarker used to estimate GFR. Creatinine is a small molecule of .113 kilodalton (kDa), and the terminal catabolite of creatine and phosphocreatine. Its generation is therefore mainly dependent on muscle mass.<sup>2</sup> Most creatinine is eliminated by glomerular filtration, but some is also excreted via tubular secretion, with the relative proportion of tubular secretion varying from one individual to another.<sup>3,4</sup> Creatinine was first employed to assess kidney function, by measuring its clearance, in the 1930s and 1940s.<sup>5-7</sup> The Cockcroft–Gault equation, which was originally developed to estimate creatinine clearance, was historically the first widely used method for assessing renal function.<sup>8</sup> But this equation performs poorly in estimating GFR,<sup>9,10</sup> notably because it was not designed for this purpose (it models creatinine clearance which is greater than GFR), and because it was developed from a small population, and with creatinine bioassays which were not standardized as they are at present. The first ‘modern’ creatinine-based equation used worldwide to truly estimate GFR was the Modification of Diet in Renal Disease (MDRD) equation.<sup>11</sup> In addition to being more precise than the Cockcroft–Gault equation, this equation had the advantage of being automatically generated by laboratories on the basis of serum creatinine concentration, age and sex (weight was not required). The creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation published in 2009 (CKD-EPI<sub>creat2009</sub>) aimed to correct weaknesses in the MDRD equation, in particular its underestimation of GFR at high GFR ranges.<sup>12</sup> This equation has been adopted worldwide, notably following the publication of the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines.<sup>13</sup> In 2021, the CKD-EPI equation was revised with the aim of estimating GFR from serum creatinine without racial consideration.<sup>14</sup> In the United States, this new equation was adopted immediately, at the instigation of the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN).<sup>15</sup> A few months earlier, the European Kidney Function Consortium (EKFC) had developed a creatinine-based estimated GFR (eGFR) equation (EKFC<sub>creat</sub>) that had the advantages of being usable across the full age spectrum.<sup>16</sup> In this review, we will limit analyses and discussions about creatinine-based eGFR equations to CKD-EPI<sub>creat2009</sub>, CKD-EPI<sub>creat2021</sub> and EKFC<sub>creat</sub> equations (Table 1).

Cystatin C, an extracellular inhibitor of cysteine proteases, is a small protein of around 13 kDa, discovered in

1979<sup>17</sup> and soon afterwards considered a marker of glomerular filtration.<sup>18,19</sup> Cystatin C is produced by all nucleated cells and is eliminated by glomerular filtration before being metabolized in the proximal kidney tubules.<sup>20,21</sup> Cystatin C is therefore only present in very small concentrations in the urine, and its clearance cannot be directly measured. The emergence in the 1990s of immunonephelometric<sup>22</sup> and immunoturbidimetric<sup>23</sup> methods for measuring serum cystatin C enabled this assay to be used routinely, and subsequently led to the development of GFR estimation equations based on cystatin C in the 2000s.<sup>24-26</sup> Another major advance for the use of cystatin C in clinical practice has been the publication of a certified reference material for the calibration of laboratory tests.<sup>27</sup> In 2012, the CKD EPI group published the cystatin C-based CKD-EPI equation (CKD-EPI<sub>Cys</sub>), as well as a combined equation using creatinine and cystatin C (CKD-EPI<sub>creat-Cys</sub>),<sup>28</sup> updated in 2021 to remove the race correction factor.<sup>14</sup> In 2023, the EKFC consortium published the cystatin C-based EKFC equation (EKFC<sub>cys</sub>), which had the same mathematical structure as the EKFC<sub>creat</sub> equation, and which was independent not only of race, but also of gender.<sup>29</sup> The EKFC equation based on both creatinine and cystatin C (EKFC<sub>creat-cys</sub>) was the mean of EKFC<sub>creat</sub> and EKFC<sub>cys</sub>.<sup>29</sup> In this review, we will limit analyses and discussions about cystatin C-based eGFR equations to CKD-EPI<sub>cys</sub>, CKD-EPI<sub>creat-cys</sub>, EKFC<sub>cys</sub> and EKFC<sub>creat-cys</sub> equations (Table 2).

Creatinine is currently the most widely used biomarker worldwide for estimating GFR. However, guidelines from the American Society of Nephrology and the National Kidney Foundation in 2021 recommend the wider use of cystatin C, whose serum concentration is not affected by the race of patients and which, when combined with creatinine, would provide a better estimate of GFR.<sup>15</sup> This US recommendation to use cystatin C more widely has also just been endorsed by the new 2024 KDIGO.<sup>30</sup> The implementation of these guidelines raises a number of questions, including the additional cost of a large-scale cystatin C assay in addition to that for creatinine, the reliability of biological assays for the two biomarkers, and the performance of GFR estimation equations based on one or other or both of the biomarkers.

In this narrative review, we will examine the strengths and weaknesses of both creatinine and cystatin C, by firstly studying the non-GFR determinants of the serum concentration of each biomarker, then the analytical problems of the assays for each of them, the accuracy of the equations for estimating the GFR based on creatinine and/or cystatin C, and lastly by focusing on situations where creatinine and cystatin C are discordant. Finally, we will propose how creatinine and cystatin C may be used in clinical practice, in the light of the issues discussed, in the area of the new KDIGO 2024.

TABLE 1 Description and characteristics of CKD-EPI and EKFC GFR estimation equations based on creatinine.

Equation name	Equation description	Equation variables	Race or population adjustment factors	Age spectrum of application
CKD-EPI <sub>Creat 2009</sub>	$141 \times \min(S_{cr}/\kappa, 1)^\alpha \times \max(S_{cr}/\kappa, 1)^{-1.209} \times .9929^{Age} \times 1.018$ [female gender] $S_{cr}$ = Serum creatinine in mg/dL (for serum creatinine in $\mu\text{mol/L}$ , divide by 88.4) Age: in years $\kappa$ : .7 for females, and .9 for males. $\min(S_{cr}/\kappa, 1)$ is the minimum of $S_{cr}/\kappa$ or 1, and $\max(S_{cr}/\kappa, 1)$ is the maximum of $S_{cr}/\kappa$ or 1. $\alpha = -.329$ for females, or $-.411$ for males	Serum creatinine Age Gender	Multiply the calculated GFR by 1.159 if African American (not applicable to non-African American Black individuals)	$\geq 18$ years
CKD-EPI <sub>Creat 2021</sub>	$142 \times \min(S_{cr}/\kappa, 1)^\alpha \times \max(S_{cr}/\kappa, 1)^{-1.200} \times .9938^{Age} \times 1.012$ [female gender] $S_{cr}$ = Serum creatinine in mg/dL (for serum creatinine in $\mu\text{mol/L}$ , divide by 88.4) Age: in years $\kappa$ : .7 for females, and .9 for males. $\min(S_{cr}/\kappa, 1)$ is the minimum of $S_{cr}/\kappa$ or 1, and $\max(S_{cr}/\kappa, 1)$ is the maximum of $S_{cr}/\kappa$ or 1. $\alpha = -.241$ for females, or $-.302$ for males	Serum creatinine Age Gender	No adjustment factor	$\geq 18$ years
EKFC <sub>Creat</sub>	If age $\leq 40$ years: if $S_{Cr}/Q < 1$ : $107.3 \times (S_{Cr}/Q)^{-.322}$ if $S_{Cr}/Q \geq 1$ : $107.3 \times (S_{Cr}/Q)^{-1.132}$ If age $> 40$ years: if $S_{Cr}/Q < 1$ : $107.3 \times (S_{Cr}/Q)^{-.322} \times .990^{(Age - 40)}$ if $S_{Cr}/Q \geq 1$ : $107.3 \times (S_{Cr}/Q)^{-1.132} \times .990^{(Age - 40)}$ $S_{Cr}$ = Serum creatinine expressed in the same unit as Q factor (mg/dL or $\mu\text{mol/L}$ ) Q values for ages 2–25: Males: $Q = 3.200 + .259 \times Age - .543 \times \ln(Age) - .00763 \times Age^2 + .0000790 \times Age^3$ Females $Q = 3.080 + .177 \times Age - .223 \times \ln(Age) - .00596 \times Age^2 + .0000686 \times Age^3$ Q values for ages $> 25$ years in White Europeans: Males: $Q = 80 \mu\text{mol/L}$ (.90 mg/dL) Females: $Q = 62 \mu\text{mol/L}$ (.70 mg/dL) Q values (in $\mu\text{mol/L}$ or mg/dL) correspond to median serum creatinine for specific age and sex populations.	Serum creatinine Age Gender	Population-specific Q values: Q values for ages $> 25$ years: White Europeans: Males: $Q = 80 \mu\text{mol/L}$ (.90 mg/dL) Females: $Q = 62 \mu\text{mol/L}$ (.70 mg/dL) Black Europeans: Males: $Q = 90 \mu\text{mol/L}$ (1.02 mg/dL) Females: $Q = 65 \mu\text{mol/L}$ (.74 mg/dL) Black Africans: Males: $Q = 85 \mu\text{mol/L}$ (.96 mg/dL) Females: $Q = 65 \mu\text{mol/L}$ (.74 mg/dL) White US population: Males: $Q = 82 \mu\text{mol/L}$ (.93 mg/dL) Females: $Q = 65 \mu\text{mol/L}$ (.73 mg/dL) Black US population: Males: $Q = 88 \mu\text{mol/L}$ (1.00 mg/dL) Females: $Q = 65 \mu\text{mol/L}$ (.73 mg/dL) US race-free Q values: Males: $Q = 86 \mu\text{mol/L}$ (1.00 mg/dL) Females: $Q = 65 \mu\text{mol/L}$ (.73 mg/dL)	$\geq 2$ years

TABLE 2 Description and characteristics of CKD-EPI and EKFC GFR estimation equations based on cystatin C or creatinine C combined with creatinine.

Equation name	Equation description	Equation variables	Race or population adjustment factors	Age spectrum of application
CKD-EPI <sub>Cys</sub>	$135 \times \min(S_{\text{cys}}/.8, 1)^{-.499} \times \max(S_{\text{cys}}/.8, 1)^{-1.328} \times .996^{\text{Age}} \times .832$ [female gender] $S_{\text{cys}}$ = serum Cystatin C in mg/dL Age: in years min ( $S_{\text{cys}}/.8, 1$ ) is the minimum of $S_{\text{cys}}/.8$ or 1, and max ( $S_{\text{cys}}/.8, 1$ ) is the maximum of $S_{\text{cys}}/.8$ or 1.	Serum cystatin C Age Gender	No adjustment factor	≥18 years
CKD-EPI <sub>Cr-Cys</sub> 2012	$135 \times \min(S_{\text{cr}}/\kappa, 1)^{\alpha} \times \max(S_{\text{cr}}/\kappa, 1)^{-.601} \times \min(S_{\text{cys}}/.8, 1)^{-.375} \times \max(S_{\text{cys}}/.8, 1)^{-.711}$ $.9952^{\text{Age}} \times .932$ [female gender] $S_{\text{cr}}$ = Serum creatinine in mg/dL (If creatinine is in $\mu\text{mol/L}$ , divide by 88.4) $S_{\text{cys}}$ = serum cystatin C in mg/dL Age: in years $\kappa$ : .7 for females, and .9 for males. min ( $S_{\text{cr}}/\kappa, 1$ ) is the minimum of $S_{\text{cr}}/\kappa$ or 1, and max ( $S_{\text{cr}}/\kappa, 1$ ) is the maximum of $S_{\text{cr}}/\kappa$ or 1. min ( $S_{\text{cys}}/.8, 1$ ) is the minimum of $S_{\text{cys}}/.8$ or 1, and max ( $S_{\text{cys}}/.8, 1$ ) is the maximum of $S_{\text{cys}}/.8$ or 1. $\alpha = -.248$ for females, or $-.207$ for males	Serum creatinine Serum cystatin C Age Gender	Multiply the calculated GFR by 1.08 if African American.	≥18 years
CKD-EPI <sub>Cr-Cys</sub> 2021	$135 \times \min(S_{\text{cr}}/\kappa, 1)^{\alpha} \times \max(S_{\text{cr}}/\kappa, 1)^{-.544} \times \min(S_{\text{cys}}/.8, 1)^{-.323} \times \max(S_{\text{cys}}/.8, 1)^{-.778}$ $.9961^{\text{Age}} \times .963$ [female gender] $S_{\text{cr}}$ = Serum creatinine in mg/dL (If creatinine is in $\mu\text{mol/L}$ , divide by 88.4) $S_{\text{cys}}$ = Serum cystatin C in mg/dL Age: in years $\kappa$ : .7 for females, and .9 for males. min ( $S_{\text{cr}}/\kappa, 1$ ) is the minimum of $S_{\text{cr}}/\kappa$ or 1, and max ( $S_{\text{cr}}/\kappa, 1$ ) is the maximum of $S_{\text{cr}}/\kappa$ or 1. min ( $S_{\text{cys}}/.8, 1$ ) is the minimum of $S_{\text{cys}}/.8$ or 1, and max ( $S_{\text{cys}}/.8, 1$ ) is the maximum of $S_{\text{cys}}/.8$ or 1. $\alpha = -.219$ for females, or $-.144$ for males.	Serum creatinine Serum cystatin C Age Gender	No adjustment factor	≥18 years
EKFC <sub>Cys</sub>	if age ≤ 40 years: if $S_{\text{cys}}/Q < 1$ : $107.3 \times (S_{\text{Cr}}/Q)^{-.322}$ if $S_{\text{Cr}}/Q \geq 1$ : $107.3 \times (S_{\text{Cr}}/Q)^{-1.132}$ If age > 40 years: if $S_{\text{Cr}}/Q < 1$ : $107.3 \times (S_{\text{Cr}}/Q)^{-.322} \times .990^{(\text{Age} - 40)}$ if $S_{\text{Cr}}/Q \geq 1$ : $107.3 \times (S_{\text{Cr}}/Q)^{-1.132} \times .990^{(\text{Age} - 40)}$ $S_{\text{cys}}$ = Serum cystatin C expressed as the Q factor in mg/dL. Adult gender-free Q values: If age < 50 years: $Q = .83$ mg/dL If age ≥ 50 years: $Q = .005 \times (\text{age} - 50)$ Q values (mg/dL) correspond to median serum cystatin C for general population.	Serum cystatin C Age	No adjustment factor	≥2 years
EKFC creat cys	Mean values for EKFC <sub>creat</sub> and EKFC <sub>cystatin C</sub>	Serum cystatin C Age Gender	Population-specific Q values: Cf <a href="#">Table 1</a> .	≥2 years

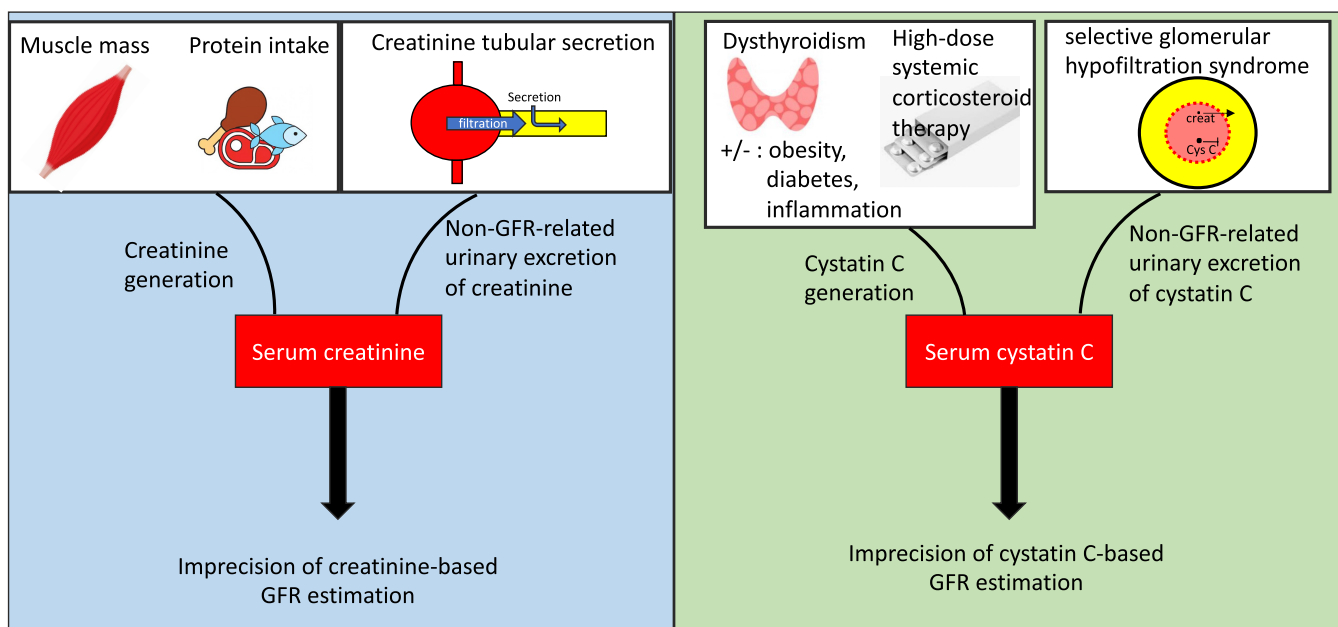
## 2 | NON-GFR DETERMINANTS OF SERUM CREATININE AND CYSTATIN C

Creatinine and cystatin C are both used as biomarkers in GFR estimation equations, as they have an inverse, hyperbolic relationship with GFR. But for both of them, GFR is not the only determinant of their serum concentrations (Figure 1).

In the case of creatinine, its excretion by the kidneys is due not only to glomerular filtration, but also to tubular secretion. Creatinine clearance, which includes clearance from tubular secretion in addition to clearance from glomerular filtration, is therefore greater than GFR.<sup>31</sup> On average, approximately 20% of creatinine clearance comes from tubular secretion, but there is wide inter-individual variability, with some individuals having physiologically no tubular creatinine secretion, and others in whom over 40% of creatinine clearance comes from tubular creatinine secretion.<sup>3,4</sup> In the case of high tubular secretion, creatinine-based eGFR (eGFR<sub>creat</sub>) equations will tend to overestimate GFR. Conversely, if tubular creatinine secretion is abolished, these equations will tend to underestimate GFR.<sup>32</sup> The other non-GFR determinants of serum creatinine are those related to its generation. Since creatinine results from the nonenzymatic conversion of creatine and phosphocreatine in muscle, its urinary excretion (except in circumstances of acute kidney failure or recovery from acute kidney failure) is proportional to muscle mass,<sup>2</sup> and its serum concentration is thus largely

influenced by muscle mass. In a patient with low muscle mass, eGFR<sub>creat</sub> will overestimate the true GFR,<sup>33,34</sup> while conversely a patient with high muscle mass will have a creatinine-based eGFR that may be lower.<sup>35</sup> A minority of creatinine generation also comes from the diet. Creatine in meat is converted to creatinine during cooking, which is then absorbed in the intestinal tract leading to an increase in serum creatinine.<sup>36,37</sup> The same phenomenon also occurs after eating cooked fish.<sup>38</sup> These physiological data explain why vegetarian individuals have lower serum creatinine concentrations than nonvegetarians (which may lead to an overestimation of eGFR<sub>creat</sub>).<sup>39</sup> It is challenging to determine for a given patient whether he or she falls within the abnormal range for tubular creatinine secretion, muscle mass and protein intake, and therefore whether the creatinine-based GFR estimate may be inaccurate. Apart from the cases of drugs that block tubular secretion of creatinine,<sup>40–45</sup> it is not possible to predict on clinical or biological criteria whether tubular creatinine secretion is important for a given individual. The diagnosis of myopenia or of above-normal muscle mass can be obvious in a number of extreme situations, but it is important to keep in mind that body mass index is only weakly correlated with muscle mass,<sup>46</sup> and that physicians may significantly underdiagnose patients with low muscle mass.<sup>47</sup> In the same way, for protein intake, apart from extreme cases, it is often difficult to accurately assess the quantity of protein intake.<sup>48</sup>

The non-GFR determinants of cystatin C are likely to be more diverse, and possibly not yet all identified (Figure 1).



**FIGURE 1** Non-GFR determinants of creatinine and cystatin C. Serum concentrations of these two endogenous GFR biomarkers depend not only on the GFR, but also on factors that affect their generation, and on other factors that have an impact on their non-glomerular urinary excretion.

Uncontrolled hypothyroidism and hyperthyroidism have a major impact on cystatin C concentration. More than 20 years ago, Fricker et al. observed that cystatin C levels in nine patients with hypothyroidism rose from .84 to 1.1 mg/L before and after hormone replacement therapy.<sup>49</sup> These variations were clinically significant: for a 60-year-old man, the GFR estimated by CKD-EPI<sub>cys</sub> would decrease from 98 to 69 mL/min/1.73 m<sup>2</sup>, whereas the true GFR should potentially increase when moving from hypothyroidism to normal thyroid function. Conversely, in 13 other patients, treatment of hyperthyroidism was accompanied by a decrease in cystatin C from 1.32 to .95 mg/L. Here again, if we consider the example of a 60-year-old man, this corresponds to an increase in GFR from 54 to 83 mL/min/1.73 m<sup>2</sup>, whereas, once again, mGFR should decrease when the patients moves from hyper- to normothyroidism.<sup>49</sup> Systemic corticosteroid therapy has also long been identified as a source of increased serum cystatin C concentrations, and hence of underestimation of true GFR by the cystatin C-based eGFR (eGFR<sub>cys</sub>).<sup>50</sup> This is a dose-dependent effect, with an increase in cystatin C of up to 30% after three daily doses of 500 mg methylprednisolone, which disappears within a few days.<sup>50</sup> Pöge et al. found an effect of prednisone on serum cystatin C concentration only for doses of 10 mg or more per day.<sup>51</sup> Tsushita et al. found a significant effect for prednisolone doses higher than .17 mg/kg/day.<sup>52</sup> In a cross-sectional analysis of 3418 patients who underwent GFR measurement using exogenous tracer clearance and measurement of cystatin C, Stevens et al found that diabetes, proteinuria, body mass index, C-reactive protein, white blood cell count and lower serum albumin were non-GFR-related determinants of serum cystatin C.<sup>53</sup> The association between visceral and subcutaneous adiposity with higher serum levels of cystatin C had already been demonstrated previously.<sup>54</sup> It should be noted, however, that the influence of inflammation and diabetes on serum cystatin C is still debated.<sup>55–57</sup>

While the non-GFR determinants of serum creatinine are limited to muscle mass, protein intake and tubular creatinine secretion, those of serum cystatin C are more diverse, and some are probably still unknown. Except in very specific situations, such as dysthyroidism or high-dose corticosteroid therapy, it seems impossible today to try to predict for a given patient whether cystatin C will be abnormally high or low in relation to actual GFR.

### 3 | BIOMARKER ASSAYS: STANDARDIZATION AND COST

The two main methods for measuring creatinine are the colorimetric Jaffe method and enzymatic assays. The

Jaffe method consists in measuring the rate of formation of the orange-yellow coloration linked to the formation of a complex between creatinine and picrate in alkaline medium.<sup>58</sup> Many endogenous and exogenous substances can interfere with the reaction and therefore the measurement. Enzymatic methods appeared in clinical practice in the 1980s and were less prone to interference.<sup>59–61</sup> Major efforts to standardize creatinine assays were initiated in the 2000s.<sup>62</sup> An essential prerequisite was the establishment of creatinine determination by isotope dilution and mass spectrometry (IDMS), a highly accurate, reproducible and interference-free method.<sup>63,64</sup> With the development of a human serum creatinine reference material designated National Institute of Standards and Technology—Standard Reference Material 967 (NIST SRM 967), a calibration program using this material has been followed by all manufacturers. Today, most creatinine assays (and this is especially true for enzymatic assays) are traceable to the reference assay IDMS. The enzymatic creatinine assays are more reliable than colorimetric assays, notably due to better precision for low creatinine levels,<sup>65–67</sup> and the absence of interference from noncreatinine chromogens.<sup>68</sup> However, there are also interferences with enzymatic creatinine assays, the most widely recognized being the erroneous elevation of creatinine levels in the presence of a significant IgM paraprotein.<sup>69–71</sup>

Cystatin C is determined by immunonephelometric and immunoturbidimetric methods.<sup>22,23</sup> Despite the existence of a reference material, ERM-DA471/IFCC for cystatin C, since 2010,<sup>27</sup> there are still discrepancies between cystatin C assays from one manufacturer to another.<sup>72,73</sup> Although these discrepancies tend to become less apparent over time,<sup>74,75</sup> they may persist, with differences from one manufacturer to another potentially having clinical implications.<sup>76</sup>

In terms of the analytical aspect of biomarker assays, it should be noted that the cost of an enzymatic creatinine assay is higher than that of a colorimetric assay using the compensated Jaffe method, and that the cost of a cystatin C assay can be as much as 10 times higher than that of an enzymatic creatinine assay. The cost of the cystatin C assay remains an obstacle to its widespread use worldwide, even if a worldwide adoption would probably result in a reduction in the cost of the test.

### 4 | ACCURACY OF GFR ESTIMATION WITH THE TWO DIFFERENT BIOMARKERS

In the original study, the CKD-EPI<sub>creat2009</sub> equation was developed from 8254 participants from 10 studies in

which GFR was measured by urinary iothalamate clearance. The equation was externally validated in 2896 participants from 16 other studies, in which it had a bias (median difference between measured and estimated GFR) of 2.5 mL/min/1.73 m<sup>2</sup> (95% CI: 2.1–2.9), and an accuracy within 30% (AW30: percentage of patients with estimated GFR between –30% and +30% of measured GFR) of 84.1% (95% CI: 83.0–85.3).<sup>12</sup> AW30 was lower in patients with an eGFR below 60 mL/min/1.73 m<sup>2</sup>, at 79.9% (95% CI 78.1–81.7) versus 88.3% (95% CI 86.9–89.7) in those with an eGFR >60 mL/min/1.73 m<sup>2</sup>. Because of a different relationship between serum creatinine concentration and GFR in Black versus non-Black individuals, this equation included a race correction factor: for two patients of the same gender, age and serum creatinine, eGFR was 16% higher in Black patients. The reliability of this correction using a race factor was questionable, since the external validation population included only 10% Black participants. This race correction factor was also rapidly shown to be too high for Black European and African patients.<sup>77,78</sup> In the United States, this race correction factor has been a source of controversy in recent years for societal reasons, including the fact that race is a social construct and not a biological reality, that the Black American population is not homogeneous since there is an ethnic diversity and miscegenation not taken into account by a simple multiplicative factor, and also because it has been hypothesized that the later registration of Black patients on the kidney transplant waiting list could be at least partly due to this correction factor (leading to higher eGFR results).<sup>79,80</sup> This serum creatinine–GFR relationship, which has been clearly shown to differ according to race,<sup>81</sup> can be considered a limit or weakness of the creatinine-based eGFR. It should also be noted that while it is well established that body composition, including muscle mass, differs according to race,<sup>82</sup> there are conflicting data concerning this muscular explanation for differences in serum creatinine–GFR relationships according to race.<sup>83–85</sup>

In the United States, it was decided to resolve this issue by adopting a race-free equation.<sup>15</sup> This CKD-EPI<sub>creat2021</sub> equation was assessed in an external validation dataset including 4050 individuals from 12 studies, with GFR measured mainly by iothalamate plasma clearance, and including 579 Black individuals.<sup>14</sup> This choice not to include a race factor in the equation resulted in the introduction of opposite biases for Black and non-Black individuals, which were equivalent in absolute values: overestimation of 3.9 mL/min/1.73 m<sup>2</sup> (95% CI: 3.4; 4.4) in non-Blacks and underestimation of 3.6 mL/min/1.73 m<sup>2</sup> (95% CI: 1.8; 5.5) in Blacks (the CKD-EPI<sub>creat2009</sub> equation was otherwise unbiased in non-Blacks, and overestimated GFR by 3.7 mL/min/1.73 m<sup>2</sup>

[95% CI: 1.8; 5.4] in Blacks). AW30% was equivalent in Blacks and non-Blacks individuals, at 87.2% (95% CI: 81.7; 87.6) and 86.5% (95% CI: 85.4; 87.6), and was lower than that of CKD-EPI<sub>creat2009</sub> for non-Black individuals (AW30%: 89.5% (95% CI: 88.5, 90.4)).<sup>14</sup> This once again indicated, as with the CKD-EPI<sub>creat2009</sub> equation, that in at least one on 10 cases, the eGFR was wrong by more than 30%.

Another way of resolving the dilemma of whether to adjust the eGFR equation to populations or not (thereby losing accuracy) would be to use cystatin C as a biomarker, since race is not one of the non-GFR determinants of its serum concentration. However, because of the other determinants of serum cystatin C that are not related to the GFR, the CKD-EPI<sub>cys</sub> equation did not perform better than the eGFR<sub>creat</sub>. In the original article, which included 5352 patients for development and internal validation, and 1119 patients for external validation, AW30% was 85.9% (95% CI: 83.8; 87.8) for CKD-EPI<sub>cys</sub> versus 87.2% (95% CI: 85.3; 89.1) for CKD-EPI<sub>creat2009</sub>.<sup>28</sup> Among the 4050 individuals in the external validation of CKD-EPI<sub>creat2021</sub> study, AW30 for CKD-EPI<sub>cys</sub> was 84.6% (95% CI: 81.7; 87.6) in Black participants and 88.9% (95% CI: 87.9; 89.9%) in non-Black participants. The AW30 target of over 90% was therefore not achieved.<sup>14</sup>

The composite CKD-EPI equation using the two biomarkers from 2012 (CKD-EPI<sub>creat-cys2012</sub>) almost achieved this objective, with an AW30 of 91.5% (95% CI: 89.8; 93).<sup>28</sup> The same was true for the race-free version updated in 2021 (CKD-EPI<sub>creat-cys2021</sub>).<sup>14</sup> Note that the AW30 of CKD-EPI<sub>creat-cys2021</sub> was slightly worse than that of CKD-EPI<sub>creat-cys2012</sub> in non-Black participants, due to an overestimation of mGFR by almost 3 mL/min/1.73 m<sup>2</sup>, whereas the initial equation was unbiased.

The EKFC<sub>creat</sub> equation, published in 2021, has the advantage compared to creatinine-based CKD-EPI equations of being usable across the full age spectrum from the age of 2.<sup>16</sup> Indeed, it had been shown that using paediatric eGFR equations up to the age of 18, and then the CKD-EPI<sub>creat2009</sub> equation thereafter, led to a sudden rise in eGFR that was not physiologically plausible.<sup>86</sup> In addition, the CKD-EPI equations all share the common weakness of significantly overestimating GFR up to the age of 30.<sup>81</sup> The EKFC equation is constructed mathematically by including the Q value, which is the median creatinine in healthy males and females. Q value can be seen as a surrogate for non-GFR determinants of serum creatinine, including muscle mass and diet. We will see that this feature has made it possible to adapt this equation to populations other than White European individuals, in whom it was initially developed, without the need to re-develop it. In the seminal study, in which the EKFC<sub>creat</sub> equation was developed on 11,251

participants from 7 studies and validated on 8378 participants from 6 other studies (Whites European only, mGFR consisting largely of iohexol plasma clearance), EKFC<sub>creat</sub> showed lower biases than CKD-EPI<sub>creat2009</sub> in all age categories, and particularly in young adults under 40. AW30 was superior to CKD-EPI<sub>creat2009</sub> in individuals under 40 and in those aged 65 and over, with no significant difference in accuracy at intermediate ages. But like the CKD-EPI equations based on one biomarker, the AW30 of EKFC<sub>creat</sub> remained slightly below 90%.<sup>16</sup> It was shown that the EKFC<sub>creat</sub> equation outperformed the CKD-EPI<sub>creat2021</sub> equation in Black Europeans and Black Africans, especially when the Q value was rescaled in these populations.<sup>81</sup> More recently, the EKFC<sub>creat</sub> equation with population-specific Q values in the United States has also been shown to be superior to the CKD-EPI<sub>creat2021</sub> equation.<sup>87</sup> By using a Q factor that would be the mean of those of African Americans and non-Black Americans, a race-free EKFC equation can be used, with limited loss of performance compared to the population-specific EKFC equation.<sup>87</sup> In the adult Chinese population, the EKFC<sub>creat</sub> equation using rescaled Q value was also superior to CKD-EPI<sub>creat2009</sub>.<sup>88</sup>

The EKFC consortium has also developed an equation based on cystatin C, using the same mathematical construction as the EKFC<sub>creat</sub> equation. This race-free (as is the CKD-EPI<sub>cys</sub> equation) and gender-free equation performed better than the CKD-EPI<sub>cys</sub> equation in various cohorts from Europe, the United States and Africa. The critical threshold of an AW30 above 90% was still not reached<sup>29</sup>; however, such a goal was reached for the combined equation.<sup>29</sup>

To conclude by summarizing the issue of the performance of eGFR equations based on creatinine or cystatin C or both: (1) eGFR<sub>cys</sub> has the advantage of being race-independent, but is not more accurate than eGFR<sub>creat</sub>; (2) equations including the two biomarkers perform better than those based on a single biomarker; (3) EKFC equations have demonstrated superiority over CKD-EPI equations, because of a greater stability across age groups, and the use of flexible Q values for creatinine.

## 5 | PERFORMANCE OF eGFR EQUATIONS WHEN CREATININE AND CYSTATIN C ARE DISCORDANT

The increasing use of cystatin C in addition to creatinine results in the identification of a growing proportion of patients with discrepancies between creatinine- and cystatin C-based eGFR. In these situations, there is a crucial issue to know the appropriate biomarker to be used. Fu

et al provided important insights into these issues in a cross-sectional study of 6185 Swedish adults referred for measuring GFR for clinical indications (9404 GFR measurements by iohexol plasma clearance) with creatinine and cystatin C available.<sup>56</sup> They found that CKD-EPI<sub>cys</sub> was within a range of more or less 20% of CKD-EPI<sub>creat2021</sub> in 45% of patients, that CKD-EPI<sub>cys</sub> was lower by more than 20% of CKD-EPI<sub>creat2021</sub> in 47% of cases, while finding CKD-EPI<sub>cys</sub> higher by more than 20% of CKD-EPI<sub>creat2021</sub> was rare, affecting only 8% of patients. Note that the high proportion of creatinine-based GFRs higher than cystatin C-based GFRs may be explained, among other factors, by the choice to study CKD-EPI<sub>creat2021</sub>, which is known to overestimate GFR in White European patients,<sup>81</sup> and by the medical indications for which GFR measurements were performed (we can hypothesize that some patients were selected because of myopenia, for example). The most important result of this study was to show that when CKD-EPI<sub>creat2021</sub> and CKD-EPI<sub>cys</sub> were concordant, these two equations, like the CKD-EPI<sub>creatcys2021</sub> equation, had no significant bias, and accuracies close to 90% in all three cases. But in the case of discordance between CKD-EPI<sub>creat2021</sub> and CKD-EPI<sub>cys</sub>, the equations based on a single biomarker were biased in opposite directions, with poor AW30%, whereas CKD-EPI<sub>creatcys2021</sub> had no significant bias in these two groups, and AW30% close to 90%.<sup>56</sup> The authors suggest the plausible explanation that errors in the opposite direction of biomarkers, linked to non-GFR determinants, compensate when the two biomarkers are included in the same equation. However, we must not forget that both biomarkers can also be wrong in the same direction: in the group where CKD-EPI<sub>creat2021</sub> and CKD-EPI<sub>cys</sub> are concordant, this was the case for the almost 12% of patients for whom CKD-EPI<sub>creatcys2021</sub> was incorrect by more than 30%.<sup>56</sup> Interestingly, in the study by Fu et al., subgroup analyses showed that these conclusions were valid for patients with severe obesity, a history of cardiovascular disease, diabetes, heart failure, liver disease or cancer.<sup>56</sup>

Similar analyses were conducted on the external validation data set of the 2021 CKD-EPI study.<sup>89</sup> The proportion of patients with discordant eGFR was lower, probably due to the patient selection criteria (GFRs were not measured for clinical indication), but the authors also found that in the case of concordant eGFR<sub>creat</sub> and eGFR<sub>cys</sub>, the three equations (CKD-EPI<sub>creat2021</sub>, CKD-EPI<sub>cys</sub> and CKD-EPI<sub>creat-cys2021</sub>) had equivalent accuracies and were unbiased, whereas when eGFR<sub>creat</sub> and eGFR<sub>cys</sub> were discordant, CKD-EPI<sub>creat-cys2021</sub> performed best.

In summary, these data suggest that the combined use of creatinine and cystatin C biomarkers is valuable, as it is generally either more accurate than GFR estimation based on a single biomarker (when creatinine and cystatin

C are discordant), or as accurate as estimation based on a single biomarker (when creatinine and cystatin C are concordant). Further studies seem however necessary to strengthen this conclusion. Notably, these statements seem validated only with CKD-EPI equations. It would be interesting to assess whether similar results are obtained with EKFC equations.

## 6 | PROGNOSTIC IMPACT OF CREATININE AND CYSTATIN C DISCREPANCIES

Another advantage of using the two biomarkers together is to identify patients at risk of adverse clinical events. It has been established for many years that  $eGFR_{cys}$  predicts mortality, cardiovascular risk and end-stage kidney disease better than  $eGFR_{creat}$ .<sup>90,91</sup> This has recently been re-demonstrated in over 80,000 Swedish individuals aged over 65 in the general population.<sup>92</sup> More recently, several studies have focused on the clinical impact of a discrepancy between creatinine and cystatin C. Among the 9092 participants in the Systolic Blood Pressure Intervention Trial (SPRINT) study, the greater the difference between  $CKD-EPI_{creat2009}$  and  $CKD-EPI_{cys}$ , the higher the frailty index, and the greater the incidence of falls with injury, hospitalizations, cardiovascular events and mortality.<sup>93</sup> In a multicentre South Korean cohort of 2096 CKD patients, patients with the greatest difference between  $CKD-EPI_{creat2009}$  and  $CKD-EPI_{cys}$  had increased risks of major cardiovascular events, and of accelerated coronary artery calcification progression.<sup>94</sup> Chen et al confirmed in the US multicentre Chronic Renal Insufficiency Cohort (CRIC) cohort, in almost 5000 CKD patients, that a significant difference between  $CKD-EPI_{creat2021}$  and  $CKD-EPI_{cys}$  was associated with mortality and end-stage kidney disease, and they also showed longitudinal changes over time of this difference between the two  $eGFR$  equations were associated with mortality.<sup>95</sup> The authors made the same demonstration, in the same population, using baseline differences and time course of creatinine-based and cystatin C-based  $eGFR$ s for risk of heart failure hospitalization.<sup>96</sup>

Recently, these results have been confirmed in the general population: among 160,000 Swedish adults, patients with the highest  $CKD-EPI_{cys}/CKD-EPI_{creat2021}$  ratios had increased risks of acute kidney injury, end-stage kidney disease, cardiovascular disease, heart failure and death.<sup>97</sup>

There are many potential explanations for the deleterious prognostic impact of a low  $eGFR_{cys}/eGFR_{creat}$  ratio. Such an abnormal ratio may be explained by creatinine that would be abnormally low in relation to GFR, due to myopenia, or severely reduced protein intake. The other cause (either isolated or associated with the abnormal

serum creatinine) of such an abnormal ratio may be due to abnormally high cystatin C in relation to GFR. This abnormal elevation of cystatin C could be due to non-GFR-related determinants of cystatin C, such as inflammation obesity or diabetes, but we have seen that the impact of these factors on serum cystatin C concentration, unlike dysthyroidism and corticosteroid therapy, is controversial.

Another explanation for an abnormally high serum cystatin C concentration would be the selective glomerular hypofiltration syndrome (also called 'the shrunken pore syndrome'). In some pathological conditions, the glomerular filtration of cystatin C, whose molecular weight is 13 kDa would be impaired compared to that of creatinine, whose molecular weight is much lower (.113 kDa). The shrinking or elongation of endothelial cell pores in glomerular capillaries may be responsible for this impaired filtration of cystatin C.<sup>98</sup> This shrunken-pore syndrome (SPS) hypothesis is supported by ultrastructural data: in a study of 17 patients with diabetic nephropathy and 12 patients with minimal change disease, the  $eGFR_{cys}/eGFR_{creat}$  ratio was 74% in the former group versus 98% in the latter, and glomerular membrane thickness was strongly inversely correlated with the  $eGFR_{cys}/eGFR_{creat}$  ratio.<sup>99</sup> This hypothesis of SPS would also explain the cardiovascular and mortality risk associated with a lower  $eGFR_{cys}/eGFR_{creat}$  ratio: cystatin C would not be the only molecule imperfectly filtered in SPS. Other molecules with a molecular weight of between 5 and 30 kDa would also be affected, significantly modifying the proteome.<sup>100</sup> Proteome analysis in 156 patients divided into four groups of 39 patients defined as having normal mGFR with SPS, normal mGFR without SPS, decreased mGFR with SPS and decreased mGFR without SPS, led to the identification of 30 SPS-specific proteins, including 18 proteins reported to promote atherosclerosis.<sup>101</sup> Selective glomerular hypofiltration syndrome could therefore be another non-GFR determinant of cystatin C and may explain, at least in part, the higher morbidity and mortality risk associated with the finding of a lowered  $eGFR_{cys}/eGFR_{creat}$  ratio.

## 7 | ASSESSMENT OF GFR FROM CREATININE AND/OR CYSTATIN C IN THE KDIGO 2024 CLINICAL PRACTICE GUIDELINES FOR THE EVALUATION AND MANAGEMENT OF CHRONIC KIDNEY DISEASE

The new 2024 KDIGO have adopted guidelines on the use of biomarkers and equations to assess GFR.<sup>30</sup> While previous KDIGOs called for the primary use of the  $CKD-EPI_{creat2009}$  equation, this update recognizes the possibility of using

other equations validated in given geographical areas, including the CKD-EPI equations, but also the EKFC equations and their respective modifications in given regions.

These new guidelines also underscore that when the cystatin C assay is available, the GFR category should be determined on the basis of the  $eGFR_{\text{creat-cys}}$ , and that when  $eGFR_{\text{creat}}$  is prone to be less accurate,  $eGFR_{\text{creat-cys}}$  should be used if GFR will affect clinical decision-making. These new KDIGO guidelines also remind us that when more precise GFR determination will have an impact on therapeutic decisions, GFR measurement by plasma or urinary clearance of an exogenous filtration marker is required.

## 8 | PRACTICAL RECOMMENDATIONS FOR ASSESSING GFR IN CLINICAL PRACTICE

Based on the evidence provided by this review, especially the advantages and disadvantages of each of the two biomarkers, which are summarized in Table 3, we propose an algorithm for assessing GFR at the individual level, according to the level of precision required (Figure 2). One of the main features of the approach we are proposing is not to include a step to assess the usefulness of dosing cystatin C in addition to or instead of creatinine. Indeed, it may be hazardous to attempt to predict in a patient whether the creatinine-based eGFR will be erroneous or not. In addition, equations combining creatinine and cystatin C are more accurate than those based on a single biomarker, and measuring both markers makes it possible to identify patients at risk of adverse clinical events if biomarkers are discordant. Finally, we are convinced that the cystatin C assay will become increasingly accessible and more standardized in the near future.

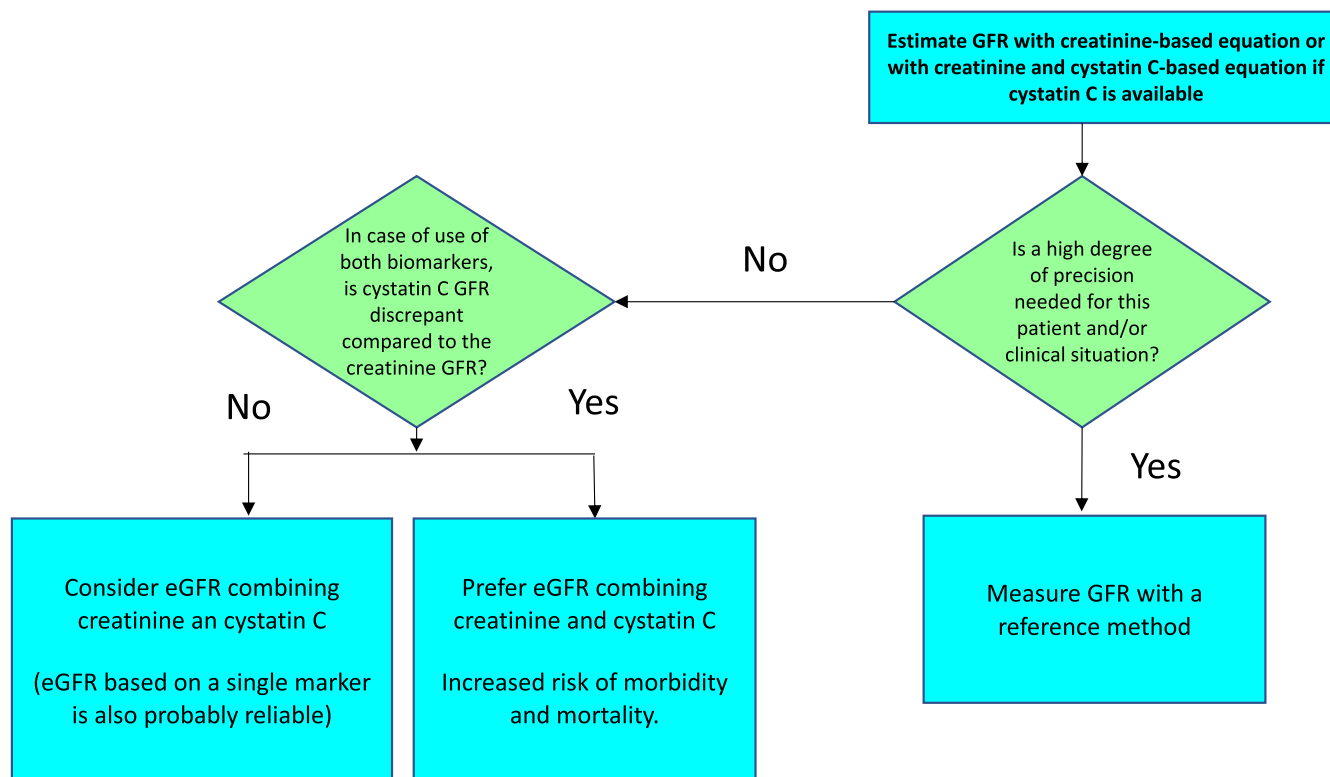
We would also like to point out that GFR estimations, whether based on creatinine, cystatin C, or both, remain estimations, with risks of error. If a high degree of precision is required for a given patient in order to make a clinical decision, the GFR should be measured by the clearance of an exogenous tracer. Such situations may include, among others, assessing eligibility for living kidney donation, adapting the dosage of drugs with narrow therapeutic margins, providing support for the decision to start dialysis when a patient has clinical symptoms compatible with a uremic syndrome but an eGFR that is still relatively preserved.

## 9 | CONCLUSION

In conclusion, creatinine and cystatin C are two endogenous GFR biomarkers, which each have non-GFR

TABLE 3 Advantages and limitations of creatinine and cystatin C.

	Creatinine	Cystatin C	Creatinine + cystatin C
Non-GFR determinants of biomarkers	Well known, few in number, and assessable in certain situations (muscle mass, protein intake, tubular secretion of creatinine)	More diverse, possibly not all identified (dysthyroidism and systemic corticosteroid therapy are well demonstrated. Diabetes mellitus, obesity and inflammation are probably among the factors causing abnormally high levels of cystatin C)	Non-GFR determinants of creatinine and cystatin C may counterbalance each other if they have an opposite impact on each biomarker (e.g. sarcopenia and obesity)
Impact of race or population characteristics on estimated GFR accuracy	It is overcome either by using a correction factor on the eGFR result (e.g. CKD-EPI <sub>creat-2019</sub> ), or a correction factor on creatinine (specific Q value in the EKFC equation), or by developing so-called race-free equations, which are a compromise in terms of bias between several populations (CKD-EPI <sub>creat2021</sub> )	Cystatin C concentration is not affected by race	The impact of race or population characteristics on serum creatinine is less apparent than with equations based on this biomarker alone
Cost of assay	Very affordable and available worldwide	More expensive than creatinine assay	The costs of the two dosages add up
Standardization	The goal of standardization has been achieved The vast majority of creatinine assays are traceable to the IDMS reference assay	The cost should decrease in the future with the large-scale deployment of the assay Despite the existence of a reference material, ERM-DA471/IFCC for cystatin C, there are still discrepancies between cystatin C assays from one manufacturer to another These discrepancies tend to become less apparent over time	This means standardizing the assays for each biomarker



**FIGURE 2** Approach to assessing GFR at individual level. This algorithm is inspired by the one published in the article entitled ‘Diagnostic standard: assessing glomerular filtration rate’ (Nephrol Dial Transplant. 2023 Nov 9;gfd241. doi: [10.1093/ndt/gfad241](https://doi.org/10.1093/ndt/gfad241)). In this new algorithm, we have removed the steps for deciding if measuring cystatin C in addition to creatinine is useful or not. Indeed, predicting at an individual level whether the creatinine-based eGFR will be incorrect or not can be uncertain. In addition, the new 2024 KDIGO states that when the cystatin C assay is available, the GFR category should be determined on the basis of an estimate based on the combination of the 2 biomarkers.

determinants accounting for the inaccuracies of single-biomarker GFR estimation equations. Cystatin C-based equations do not perform better than those based on creatinine. The advantages of creatinine over cystatin C are the low cost of the assay, and the almost perfect standardization of assays worldwide. Furthermore, the fact that non-GFR-related determinants of serum creatinine concentration are well identified (muscle mass, protein intake, pharmacological inhibition of tubular creatinine secretion) means that the clinician can predict in some circumstances that the creatinine-based eGFR will be aberrant or not, whereas with cystatin C this prediction is impossible, except in rare cases of high-dose corticosteroid therapy or uncontrolled dysthyroidism. The combined use of both biomarkers is the most advantageous approach, as GFR estimates based on both creatinine and cystatin C are generally more accurate than those based on a single biomarker, notably when creatinine and cystatin C are discordant. Moreover, the identification of such a discrepancy between cystatin C-based eGFR and creatinine-based eGFR is a well-established risk factor for frailty, morbidity and mortality, especially of cardiovascular origin.

## CONFLICT OF INTEREST STATEMENT

Both authors are members of the European Kidney Function Consortium.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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