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CKJ REVIEW

New and old GFR equations: a European perspective

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ABSTRACT

Glomerular filtration rate (GFR) is estimated in clinical practice from equations based on the serum concentration of endogenous biomarkers and demographic data. The 2009 creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI$_{2009}$) was recommended worldwide until 2021, when it was recalibrated to remove the African-American race factor. The CKD-EPI$_{2009}$ and CKD-EPI$_{cr2021}$ equations overestimate GFR of adults aged 18–30 years, with a strong overestimation in estimated GFR (eGFR) at age 18 years. CKD-EPI$_{Cr2021}$ does not perform better than CKD-EPI$_{2009}$ in US population, overestimating GFR in non-Black subjects, and underestimating it in Black subjects with the same magnitude. CKD-EPI$_{Cr2021}$ performed worse than the CKD-EPI$_{2009}$ in White Europeans, and provides no or limited performance gains in Black European and Black African populations. The European Kidney Function Consortium (EKFC) equation, which incorporates median normal value of serum creatinine in healthy population, overcomes the limitations of the CKD-EPI equations: it provides a continuity of eGFR at the transition between pediatric and adult care, and performs reasonably well in diverse populations, assuming dedicated scaling of serum creatinine (Q) values is used. The new EKFC equation based on cystatin C (EKFC$_{CC}$) shares the same mathematical construction, namely, it incorporates the median cystatin C value in the general population, which is independent of sex and ethnicity. EKFC$_{CC}$ is therefore a sex-free and race-free equation, which performs better than the CKD-EPI equation based on cystatin C. Despite advances in the field of GFR estimation, no equation is perfectly accurate, and GFR measurement by exogenous tracer clearance is still required in specific populations and/or specific clinical situations.

Keywords: creatinine, cystatin C, European Kidney Function Consortium, glomerular filtration rate, iohexol

INTRODUCTION

Chronic kidney disease (CKD) is, in the vast majority of cases, a pauci-symptomatic disease. The role of the clinical laboratory to screen, detect, manage and follow CKD is thus of fundamental importance. Two variables are of particular interest in this context: glomerular filtration rate (GFR) and albuminuria (or proteinuria). According to these two parameters, a diagnosis of

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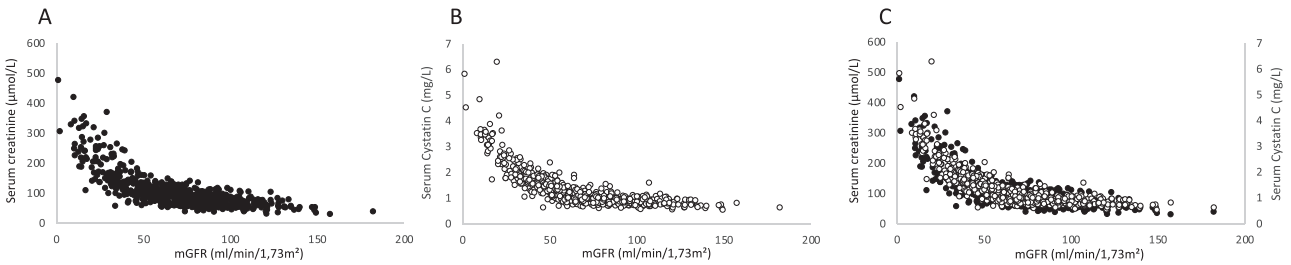

Figure 1: Inverse association between measured GFR and serum creatinine (**A**) and cystatin C (**B**). The inverse relationship with measured GFR is similar for both biomarkers (**C**).

CKD will be made and/or confirmed and important decisions will be taken regarding therapy, inscription on the waiting list for kidney transplantation or, at least in part, starting renal replacement therapy [1]. In the current review, we will focus on GFR, which is also very important for drug dosage adaptation in CKD patients. In an ideal world, every CKD patient should know his/her exact GFR value with a "true" measurement. However, measuring GFR is currently not available in every center. Moreover, it remains relatively costly and cumbersome. Here, the word "relatively" is important. Certainly, measuring GFR is more complex than estimating GFR using endogenous biomarkers like creatinine or cystatin C. However, this complexity should not be over-exaggerated. Nowadays, we are far from the complexity of original inulin urinary clearances [2]. Simplified and relatively inexpensive methods (for a reference method) like iohexol plasma clearances are available and more and more used in Europe [3, 4]. In Sweden, iohexol plasma clearance is performed as part of the normal care [5]. However, the fact is that, in clinical practice, GFR is most of the time estimated from equations using biological biomarkers and demographic variables like sex, age and, for some, weight, height and/or ethnicity. For more than a century, the biomarker used to estimate GFR has been serum creatinine, which is available worldwide and for which assays are standardized and inexpensive [6]. However, for several reasons, serum creatinine is not a perfect biomarker of renal function [7–9]. Among these reasons, two are especially important and can justify the use of equations. First, the relationship between serum creatinine (and it is also true for other renal biomarkers, like cystatin C) and GFR is unfortunately not direct, but inverse and hyperbolic (see Fig. 1). For this reason, in a given subject, a small change in serum creatinine (sometimes only due to analytical variations) will result in a large change in GFR in the normal or high GFR range. At the opposite side, in the low GFR range, a big change in serum creatinine concentration will only result in a minor change in GFR [10]. Integrating serum creatinine in an equation with different exponents (e.g. for low versus high serum creatinine) will help the clinician to better integrate this inverse relationship. The second major disadvantage is the effect of so-called non-GFR determinants of serum creatinine. Among others, the major non-GFR determinant for serum creatinine concentration is the muscular mass. In other words, serum creatinine concentration will depend not only on GFR, but also on muscular mass, as serum creatinine is the catabolite of creatine, a muscular molecule [9, 11]. The best illustration is the difference of serum creatinine between healthy women (0.7 mg/dL) and men (0.9 mg/dL), whereas measured indexed GFR is not different according to sex [12]. This means that the same serum creatinine level is basically associated with a different GFR value (expressed in mL/min/1.73 m²) in men and women. Using an equation integrating the sex variable (correction applied on the creatinine result) will help the physician to better interpret these differences in terms of GFR values. In such equations, at the same age, a woman with a creatinine at 0.7 mg/dL and a man with a creatinine at 0.9 mg/dL will eventually have the same estimated GFR.

The same argument has been often advanced to justify the difference of serum creatinine according to race or ethnicity [13, 14], but we will see further in the current article that is probably not so simple [15].

A SHORT HISTORY OF CREATININE-BASED EQUATIONS

Cockcroft and Gault equation

To date, more than 50 different creatinine-based equations have been proposed in the literature. To the best of our knowledge, the first equation was published by Effersoe in 1957 [16]. It is beyond the current article to review all these equations, and we will focus only on the most popular ones (Table 1). The first equation that has been widely used is the Cockcroft and Gault equation [17]. This equation was published in 1976 and included serum creatinine, age, gender and weight. The equation was relatively easy to use and to calculate and, before the computer era, this simplicity probably explains part of its popularity. The Cockcroft and Gault equation had, however, many limitations: the development cohort included very few women, the equation is supposed to estimate creatinine clearance expressed in mL/min (not measured GFR, expressed in mL/min/1.73 m²), and serum creatinine was measured with an old, nowadays unavailable, assay. Even though the Cockcroft–Gault equation is still (sometimes) considered in pharmacology [18], several studies have clearly shown that the Cockcroft and Gault equation was less accurate than "modern" equations to estimate GFR [19–21]. Moreover, clinical decisions are based on the more recent equations in clinical practice [22].

Modification of Diet in Renal Disease study (MDRD) equation

The year 1999 was an important milestone in the story of estimating equations. Indeed, Levey *et al*., who would later lead the Chronic Kidney Disease Epidemiology (CKD-EPI) consortium, proposed a new equation, the Modification of Diet in Renal Disease study (MDRD) equation. The novelty was that this equation, which is mathematically much more complex than the Cockcroft–Gault equation, did not include the weight variable, but only serum creatinine, age, sex and race [19]. This is of importance because age and sex variables were available in clinical laboratory allowing automatic and systematic reporting of an

Table 1: Main creatinine-based equations.

Name	Age (years)	Sex		eGFR equation
Cockcroft and Gault	≥18			((140 – age) × weight/SCr)*0.85 if female
MDRD study equation	≥18			$GFR = 175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female)
CKD-EPI$_{crea}$ (ASR)	≥18	Female	SCr ≤ 0.70	$144 \times (SCr/0.70)^{-0.329} \times 0.9929^{Age} \times 1.159$ (if Black)
			SCr > 0.70	$144 \times (SCr/0.70)^{-1.209} \times 0.9929^{Age} \times 1.159$ (if Black)
		Male	SCr ≤ 0.90	$141 \times (SCr/0.90)^{-0.411} \times 0.9929^{Age} \times 1.159$ (if Black)
			SCr > 0.90	$141 \times (SCr/0.90)^{-1.209} \times 0.9929^{Age} \times 1.159$ (if Black)
CKD-EPI$_{crea}$ (AS)	≥18	Female	SCr ≤ 0.70	$143 \times (SCr/0.70)^{-0.241} \times 0.9938^{Age}$
			SCr > 0.70	$143 \times (SCr/0.70)^{-1.200} \times 0.9938^{Age}$
		Male	SCr ≤ 0.90	$142 \times (SCr/0.90)^{-0.302} \times 0.9938^{Age}$
			SCr > 0.90	$142 \times (SCr/0.90)^{-1.200} \times 0.9938^{Age}$
EKFC$_{Crea}$	18–40	Female	SCr/Q < 1.0	$107.3 \times (SCr/Q)^{-0.322}$
			SCr/Q ≥ 1.0	$107.3 \times (SCr/Q)^{-1.132}$
		Male	SCr/Q < 1.0	$107.3 \times (SCr/Q)^{-0.322}$
			SCr/Q ≥ 1.0	$107.3 \times (SCr/Q)^{-1.132}$
	>40	Female	SCr/Q < 1.0	$107.3 \times (SCr/Q)^{-0.322} \times 0.990^{(Age-40)}$
			SCr/Q ≥ 1.0	$107.3 \times (SCr/Q)^{-1.132} \times 0.990^{(Age-40)}$
		Male	SCr/Q < 1.0	$107.3 \times (SCr/Q)^{-0.322} \times 0.990^{(Age-40)}$
			SCr/Q ≥ 1.0	$107.3 \times (SCr/Q)^{-1.132} \times 0.990^{(Age-40)}$
LMREV	≥18	Female	<150 (in µmol/L)	$X = 2.5 + 0.0121 \times (150 - SCr)$ (SCr in µmol/L)
			≥150	$X = 2.5 - 0.926 \times \log(SCr/150)$
		Male	<180	$X = 2.56 + 0.00968 \times (180 - SCr)$
			≥180	$X = 2.56 - 0.926 \times \log(SCr/180)$
				$GFR = \exp(X - 0.0158 \times age + 0.438 \times \log(age))$
BIS	≥70			BIS1: $3736 \times SCr^{-0.87} \times age^{-0.95} \times 0.82$ (if female)

ASR: age, sex and race factors; AS: age and sex but no race factor; BIS: Berline initiative study; LMREV: Revised Lund Malmo; SCr: serum creatinine (for Q values see Table 2).

estimating GFR result along with serum creatinine [23]. This equation has rapidly replaced the Cockcroft and Gault equation in Nephrology. The MDRD equation has been developed from the MDRD cohort in which GFR was measured by iothalamate urinary clearances. Serum creatinine was measured by a Jaffe assay that was not standardized to the gold standard in the seminal publication [19], but the equation was later recalibrated to be used with standardized, isotope dilution mass spectrometry (IDMS) traceable assays [24] (the calibration was thus "indirect", which is a serious limitation) [7, 10, 25]. However, the MDRD study cohort was a CKD cohort with a vast majority of patients with GFR <60 mL/min/1.73 m², and it is well known that the relationship between GFR and serum creatinine is different in CKD and healthy subjects. The results of the MDRD study equation tended to systematically underestimate GFR, and consequently to overestimate the CKD prevalence in any population.

Chronic Kidney Disease Epidemiology (CKD-EPI) equation

A new equation was thus proposed by the CKD-EPI consortium in 2009, here called the CKD-EPI$_{2009}$ equation [26]. This equation was developed from several different cohorts, including cohorts with healthy subjects. The sample size of the development and validation datasets was much larger than for the Cockcroft–Gault and MDRD equations. Most (but not all) measured GFR were urine iothalamate clearances, and all serum creatinine concentrations were supposed to be IDMS traceable (even if, once again, the way the calibration was performed in some of the cohorts is questionable [27]). To overcome the problem of the underestimation in healthy subjects, the authors proposed to apply a different exponent to serum creatinine if serum creatinine was higher or lower than 0.7 mg/dL for women and 0.9 mg/dL for men [26]. This American equation has been largely adopted worldwide and is currently the equation recommended for adults by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [1]. It is important to mention here that European experts in the field of GFR have also proposed different equations to estimate GFR. Among them, the Revised Lund Malmö (RLM) equation [28] and the Berlin Iniative Study (BIS) equation [29] deserve to be mentioned. Both are methodologically very solid. GFR was measured by iohexol plasma clearances, serum creatinine was measured with enzymatic and IDMS-traceable assays, and the sample size was large. The LMR equation performs very well in White European populations (and can be used in other populations with some adjustments) and is currently used in Sweden [28, 30]. The creatinine-based BIS equation is limited to subjects older than 70 years, but its performance is good [29]. Compared with the CKD-EPI$_{2009}$ equation, the success of the LMR and the BIS equations was much more limited, in part because these equations have been little tested outside Europe. The CKD-EPI$_{2009}$ equation is thus the recommended and most used equation worldwide, but this equation is not without limitations, notably in the way it models two important variables, i.e. age and race.

Limitations of the CKD-EPI$_{2009}$ equation

Age

The CKD-EPI$_{2009}$ equation is recommended for adults, i.e. subjects older than 18 years [1]. The variable age in the CKD-EPI$_{2009}$ equation is considered as a continuous variable, meaning that the relationship between serum creatinine and GFR did not

Table 2: Q values for creatinine and cystatin C in different populations.

	Q creatinine (mg/dL)		
Populations	Male	Female	Q cystatin C (mg/L)
White Europeans [37]	0.90	0.70	0.83 until 50 years Q = 0.83 + 0.005x(Age – 50) thereafter
Black Europeans [48]	1.02	0.74	0.83 until 50 years Q = 0.83 + 0.005x(Age – 50) thereafter
White US [49]	0.94	0.70	0.83 until 50 years Q = 0.83 + 0.005x(Age – 50) thereafter
Black US [49]	1.03	0.72	NA
Black Africans [46]	0.96	0.72	0.83 until 50 years Q = 0.83 + 0.005x(Age – 50) thereafter

NA: not available.

change from 18 years to old ages in this equation [26]. It is true that, at the population level, median serum creatinine values only slightly increase with aging [31]. However, GFR is stable until 40 years of age and only physiologically declines with aging beyond 40 years, and thus, age in the CKD-EPI$_{2009}$ equation does not adequately reflect the way GFR evolves with age [12, 32]. So, this method of modeling the association between creatinine, GFR and age in the CKD-EPI equation is an over-simplification [33–36]. Indeed, the way age is mathematically considered in the CKD-EPI$_{2009}$ equation does not fit with reality, as the mathematical form of CKD-EPI$_{2009}$ equation assumes a monotonic continuously decreasing function with age, from 18 years to old ages. As a consequence, this equation strongly overestimates GFR in subjects between 18 and 30 years old [37, 38]. Moreover, the KDIGO currently recommend two equations: the CKD-EPI$_{2009}$ equation in adults and the bedside Schwartz equation in children and adolescents [1, 39]. However, there is no continuum between the two equations. This leads to implausible jumps in estimated GFR (eGFR) at 18 years when GFR estimation switches from the Schwartz to the CKD-EPI$_{2009}$ equation [40].

Race

A semantic comment is here required. The word "race" is not considered in the same way in Europe and in the USA. In the USA, the word race is used as its social meaning, whereas in Europe, it remains as its biological meaning, and therefore, European nephrologists are reluctant to use it, as race has obviously no biological justification. In Europe, using the word race is yet considered as racist [41]. In the current article, we will use the word race when it is related to American practices. Because the MDRD and the CKD-EPI$_{2009}$ equations were developed in the USA, the authors applied a race coefficient. Indeed, it is very clear, strictly speaking from a scientific point of view, that the relationship between serum creatinine and GFR is not the same in Black and non-Black Americans [42, 43]. To briefly summarize, the same concentration of creatinine will correspond to a different GFR value in the Black and non-Black US population (with higher GFR value in Black people). This is a scientific fact. However, and it is a pity, we must admit that, in 2023, we still do not know why such a difference is observed between White and Black US populations [41, 43]. Some European data support a role of muscular mass to explain slight differences in creatinine concentrations between Black and White Europeans [44, 45]. However, the supposed much higher muscular mass in American Black people is actually not supported by strong data [15, 43]. Also, creatinine tubular secretion does not seem to be very different [43, 45]. The effect of diet is potentially important, but difficult to study, and other hypotheses, like a different conversion rate of creatine into creatinine, are not well studied. Going back to semantics, one issue is that the race coefficient in the CKD-EPI$_{2009}$ equation was considered for all Black people. However, *sensu stricto*, this Black coefficient should have been named a Black US coefficient. Indeed, several studies outside USA have shown that this coefficient was not applicable to other Black populations in Europe, Brazil and Africa. On the other hand, all these studies have shown that the performance of the CKD-EPI equation in these populations was better without any correction [45–48]. This observation can be illustrated simply by the distribution of normal GFR and normal serum creatinine in these populations. There are good reasons to believe that measured GFRs in healthy populations are not different in White and Black populations in Europe, USA and Africa [33, 35, 36]. However, serum creatinine in these same populations is not similar, especially in men. Serum creatinine in healthy White men and women is very similar in US and European populations. Compared with White populations, the difference in creatinine is much more important with Black European and Black African, and still more with Black American populations [48, 49]. A point frequently forgotten is that the differences in women, are much less marked (Table 2) [41]. These observations lead to two important conclusions. First, difference in serum creatinine has nothing to do with race or ethnicity (and of course, nothing to do with skin color), but with population differences [48]. Here, the term "population" is quite vague on purpose, and can include global items like ancestry and lifestyle. Second, the correction applied by the CKD-EPI$_{2009}$ or MDRD study equation at the GFR level (as it was the case with their coefficient), although mathematically efficient was misleading. Indeed, if a correction should be applied, it should be at the creatinine level (as is the case for the sex variable), not at the GFR level [41, 49–51].

Recent developments in equations and biomarkers

A societal force has driven a recent development in the CKD-EPI$_{2009}$ equation. Indeed, since 2019, many arguments have been addressed in USA to omit the racial factor that was judged as discriminatory. Among other arguments, authors illustrated the fact that at the same creatinine level, estimated GFR was higher in Black American people than in non-Black, which would lead to a delay in the eligibility for kidney transplant waiting list [15, 52]. This led the CKD-EPI group to propose a new creatinine-based equation (the CKD-EPI$_{creat2021}$ equation). This equation, published in the *New England Journal of Medicine* [53], was immediately endorsed by the American Society of Nephrology, the National Kidney Foundation and the American Association of Clinical Chemistry [54, 55]. The new race-free CKD-EPI$_{creat2021}$ equation ended the polemic in USA.

Yet, from a European perspective, some points need to be discussed. First, the new equation has been developed with the intention to have the same performance in Black and non-Black populations. The scientific approach was not the classical

Table 3: CKD-EPI and EKFC equations with cystatin C.

Name	Age (years)	Sex			eGFR equation
$CKD\text{-}EPI_{ScysC}$	≥18	Female		ScysC ≤ 0.80	$133 \times (SCysC/0.80)^{-0.499} \times 0.9962^{Age} \times 0.932$
				ScysC > 0.80	$133 \times (SCysC/0.80)^{-1.328} \times 0.9962^{Age} \times 0.932$
		Male		ScysC ≤ 0.80	$133 \times (SCysC/0.80)^{-0.499} \times 0.9962^{Age}$
				ScysC > 0.80	$133 \times (SCysC/0.80)^{-1.328} \times 0.9962^{Age}$
$CKD\text{-}EPI_{SCr+ScysC}$ (ASR)	≥18	Female	SCr ≤ 0.70	ScysC ≤ 0.80	$130 \times (SCr/0.70)^{-0.248} \times (ScysC/0.80)^{-0.375} \times 0.9952^{Age}$
			SCr ≤ 0.70	ScysC > 0.80	$130 \times (SCr/0.70)^{-0.248} \times (ScysC/0.80)^{-0.711} \times 0.9952^{Age}$
			SCr > 0.70	ScysC ≤ 0.80	$130 \times (SCr/0.70)^{-0.601} \times (ScysC/0.80)^{-0.375} \times 0.9952^{Age}$
			SCr > 0.70	ScysC > 0.80	$130 \times (SCr/0.70)^{-0.601} \times (ScysC/0.80)^{-0.711} \times 0.9952^{Age}$
	≥18	Male	SCr ≤ 0.90	ScysC ≤ 0.80	$135 \times (SCr/0.90)^{-0.207} \times (ScysC/0.80)^{-0.375} \times 0.9952^{Age}$
			SCr ≤ 0.90	ScysC > 0.80	$135 \times (SCr/0.90)^{-0.207} \times (ScysC/0.80)^{-0.711} \times 0.9952^{Age}$
			SCr > 0.90	ScysC ≤ 0.80	$135 \times (SCr/0.90)^{-0.601} \times (ScysC/0.80)^{-0.375} \times 0.9952^{Age}$
			SCr > 0.90	ScysC > 0.80	$135 \times (SCr/0.90)^{-0.601} \times (ScysC/0.80)^{-0.711} \times 0.9952^{Age}$
$CKD\text{-}EPI_{SCr+ScysC}$ (AS)	≥18	Female	SCr ≤ 0.70	ScysC ≤ 0.80	$130 \times (SCr/0.70)^{-0.219} \times (ScysC/0.80)^{-0.323} \times 0.9961^{Age}$
			SCr ≤ 0.70	ScysC > 0.80	$130 \times (SCr/0.70)^{-0.219} \times (ScysC/0.80)^{-0.778} \times 0.9961^{Age}$
			SCr > 0.70	ScysC ≤ 0.80	$130 \times (SCr/0.70)^{-0.544} \times (ScysC/0.80)^{-0.323} \times 0.9961^{Age}$
			SCr > 0.70	ScysC > 0.80	$130 \times (SCr/0.70)^{-0.544} \times (ScysC/0.80)^{-0.778} \times 0.9961^{Age}$
	≥18	Male	SCr ≤ 0.90	ScysC ≤ 0.80	$135 \times (SCr/0.90)^{-0.144} \times (ScysC/0.80)^{-0.323} \times 0.9961^{Age}$
			SCr ≤ 0.90	ScysC > 0.80	$135 \times (SCr/0.90)^{-0.144} \times (ScysC/0.80)^{-0.778} \times 0.9961^{Age}$
			SCr > 0.90	ScysC ≤ 0.80	$135 \times (SCr/0.90)^{-0.544} \times (ScysC/0.80)^{-0.323} \times 0.9961^{Age}$
			SCr > 0.90	ScysC > 0.80	$135 \times (SCr/0.90)^{-0.544} \times (ScysC/0.80)^{-0.778} \times 0.9961^{Age}$
$EKFC_{ScysC}$	18–40			ScysC/Q < 1.0	$107.3 \times (SCysC/Q)^{-0.322}$
				ScysC/Q ≥ 1.0	$107.3 \times (SCysC/Q)^{-1.132}$
	>40			ScysC/Q < 1.0	$107.3 \times (SCysC/Q)^{-0.322} \times 0.990^{(Age-40)}$
				ScysC/Q ≥ 1.0	$107.3 \times (SCysC/Q)^{-1.132} \times 0.990^{(Age-40)}$
$EKFC_{SCr+ScysC}$	≤18				Median of $EKFC_{SCr}$ and $EKFC_{Cys}$

ASR: age, sex and race factors; AS: age and sex but no race factor; ScycC: serum cystatin C; SCr: serum creatinine Q value for creatinine: see Table 2 Q value for cystatin C: Q = 0.83 until 50 years and Q = 0.83 + 0.005x(Age−50) after 50 years.

"hypothesis–thesis–demonstration," as the conclusion of the study was known and the equation has been developed to fit with this conclusion. Second, for the first time in the history of GFR estimation, the new equation was not better than the previous ones. Indeed, the $CKD\text{-}EPI_{creat2021}$ equation does not perform better in Black populations (eGFR is now underestimating GFR in Black populations, but the absolute bias was similar to the bias of the $CKD\text{-}EPI_{2009}$ equation) and is performing worse in non-Black populations (eGFR is now overestimating GFR in non-Black populations whereas the bias of the $CKD\text{-}EPI_{2009}$ equation was close to zero), but the absolute bias of eGFR is the same in both populations [53]. As always with estimating GFR, the impact of such a change is relatively limited at the individual level but the impact is huge at the population level [56, 57]. Third, once again, the vast majority of the Black populations included in the development of the $CKD\text{-}EPI_{creat2021}$ equation were from the USA. However, as already mentioned, it was advised in Europe and Africa to use the $CKD\text{-}EPI_{2009}$ equation without the race coefficient [35, 47, 48]. Recent data have shown that the new $CKD\text{-}EPI_{creat2021}$ equation performed worse than the $CKD\text{-}EPI_{2009}$ equation in White European populations, without any or only few gains of performance in Black European and Black African populations [48]. The impact of the new equation on the prediction of outcomes was also minimal [58]. These results led the European Renal Association and the European Federation of Laboratory Medicine to make the recommendation not to use the $CKD\text{-}EPI_{creat2021}$ equation in Europe [59, 60].

In 2021, a new equation was also published in *Annals of Internal Medicine* by the European Kidney Function Consortium (EKFC) [37]. The EKFC includes data mainly from Europe with measured GFR available in 19 629 subjects. Serum creatinine was measured with IDMS traceable assays and GFR was measured with different recognized reference methods (mostly iohexol plasma clearances) [61]. The equation is an evolution of the previous Full Age Spectrum equation [62]. The goal of this equation was to overcome the limitations of the bedside Schwartz and CKD-EPI equations, regarding age and race modeling. The age variable is modeled in a fully different way to guarantee continuity at the transition between pediatric and adult nephrology care and to better fit with the well-known decline in GFR starting at 40 years. In the EKFC equation the Q_{creat} variable is key. Q_{creat} is the median normal value of serum creatinine in a given population [31, 63]. The different variables influencing serum creatinine in a population, i.e. non-GFR determinants of creatinine, will be integrated in this Q_{creat} value. Accordingly, Q_{creat} values will be different between children and adults, and in adults will be logically different between female and male adults. Q_{creat} values will be influenced by age in children and adolescents, but not in adults [64]. Q_{creat} will also be different in different populations (once again, differences are between populations, not between race) [48, 49]. Populations are self-defined and as large or small as necessary. One can even imagine an individual Q_{creat} value which would be the Q value of a given individual in a healthy state at 20 years. If we consider the population, the Q_{creat} can easily be determined either by using big data from laboratories (integrating, as an example, all results from non-hospitalized subjects and excluding patients followed in Nephrology departments) or using more limited data in a very well phenotyped healthy population (like kidney donors) [48]. Once the Q_{creat} is established (see some examples for some populations

in Table 2), the EKFC equation is easy to use and eGFR can be automatically and systematically given by the laboratories, without requiring development of a new equation.

Several studies have shown that EKFC overcomes the limitations of the CKD-EPI equations: there is now a continuum between adults and children or adolescents as the same equation is now used in all populations [40]; the EKFC equation performs much better in a young adult population (especially before 30 years) and slightly better in old people [37]; and the EKFC equation performs reasonably well in diverse populations, especially when dedicated Q values are used [48, 65]. The EKFC equation needs, however, to be studied in Asia and USA, once again with dedicated Q values. In the USA, one can easily imagine using a mean Q value for Black and non-Black populations to obtain a race-free creatinine-based EKFC equation (which is quite similar to the approach used in the development of the CKD-EPI$_{creat2021}$ equation).

There is another interesting property of the EKFC equation. Indeed, the equation is applicable to other renal biomarkers, as long as appropriate biomarker specific Q values are available. Recently, the EKFC studied the performance of a cystatin C–based equation in a large cohort of diverse populations, mainly from Europe (n = 11 231) but also with data from the USA (White population, n = 1093) and Africa (n = 508) [65]. In this article published in the *New England Journal of Medicine*, a Q value for cystatin C (Q_{CC}) was first established for adults from a large database (n = 227 643) from Sweden, the only country where cystatin C is currently measured in daily practice. Then, we showed in a matched analysis that cystatin C concentration was not different between Black and non-Black European individuals, confirming that cystatin C concentration was not discordant between populations, contrary to serum creatinine. We also observed that the cystatin C concentration was only slightly different between males and females. In other words, the Q_{CC} is the same (or very similar) in all populations (0.83 mg/L) (whatever the continent), but is also independent of sex. The EKFC equation based on cystatin C (once again, the same mathematical equation as the EKFC based on creatinine, but with Q_{CC}) can be used independently of sex (or gender) and independently of race. This EKFC$_{CC}$ globally performs better than the corresponding CKD-EPI$_{CC}$ (the main cystatin C–based equations are listed in Table 3). EKFC$_{CC}$ had the same accuracy and precision as the EKFC$_{creat}$, keeping in mind that only "age" is needed to calculate EKFC$_{CC}$. As it is also the case for the CKD-EPI equations, the EKFC equation combining cystatin C and creatinine (actually the mean value of EKFC$_{creat}$ and EKFC$_{CC}$) showed significantly better performance to estimate GFR, with close to 90% of eGFR results being within ±30% of measured GFR. EKFC equations are available (as an Excel sheet) on https://www.chuliege.be/nephrologie-EKFC.

CONCLUSIONS: THERE ARE NO MAGIC FORMULAE

Advantages of cystatin C, from both a scientific and societal point of view, should promote its use in daily practice (as it is yet the case in Sweden) in the near future. Current limitations are the standardization of the assays and the cost [66]. In Belgium, for the moment, the reagent cost for a cystatin C test is, at best, around 5 euros depending on the number of tests performed by the laboratory and the price per kit, whereas Jaffe and enzymatic creatinine costs are around 5 cents and 20 cents, respectively. A wider use should logically decrease the cost of the assays even if, by nature (the measurement of cystatin C is currently done using antibodies), the cost would remain higher than the cost of creatinine assays [67]. Improvements are constantly observed in the standardization of assays [68]. The place of cystatin C in the screening and management of CKD needs to be specified in light of recent publications, and keeping in mind that it has long been known that cystatin C is much better than creatinine for predicting outcomes, especially cardiovascular outcomes [69]. The explanation of the better predictive role of cystatin C over creatinine is currently still debated: is it due to the better estimation of GFR? Or is it due to non-GFR determinants of cystatin C, such as inflammation? Discrepant results between creatinine- and cystatin C–based equations are frequent and further studies should help us to understand how to interpret such discrepancies [70].

Every step towards improving the estimation of GFR is valuable. However, we must keep in mind that all equations are a relatively rough estimation [56]. A precise measurement of GFR in specific populations and/or specific clinical situations might be required [71, 72]. As an example, the potential of equations to estimate measured GFR in ±10% remains very low [73]. In the same vein, in all equations, the mathematical weight of the biomarker is by far the most important. In a given context or patient (like a patient hospitalized for a long time in the intensive care unit), serum creatinine is known to be an imperfect marker of renal function (because of muscular mass). In this context, there is no reason to think that integrating creatinine in an equation will give an accurate result: equations are not magic!

Therefore, development of new equations should not hamper either the use of measured GFR or clinical research in the field of measured GFR. We can hope for improvements in the future with a better implementation of existing methods (like iohexol plasma methods) and/or the development of new techniques allowing rapid, bedside GFR measurement [74]. Research and clinical use of measured and estimated GFR are fully complementary, not exclusive.

CONFLICT OF INTEREST STATEMENT

P.D. and E.C. are consultants for Nephrolyx. P.D. is Associate Editor for *CKJ*.

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