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Diagnostic standard: assessing glomerular filtration rate

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ABSTRACT

Creatinine-based estimated glomerular filtration rate (eGFR) is imprecise at individual level, due to non-GFR-related serum creatinine determinants, including atypical muscle mass. Cystatin C has the advantage of being independent of muscle mass, a feature that led to the development of race- and sex-free equations. Yet, cystatin C–based equations do not perform better than creatinine-based equations for estimating GFR unless both variables are included together. The new race-free Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation had slight opposite biases between Black and non-Black subjects in the USA, but has poorer performance than that the previous version in European populations. The European Kidney Function Consortium (EKFC) equation developed in 2021 can be used in both children and adults, is more accurate in young and old adults, and is applicable to non-white European populations, by rescaling the Q factor, i.e. population median creatinine, in a potentially universal way. A sex- and race-free cystatin C–based EKFC, with the same mathematical design, has also be defined. New developments in the field of GFR estimation would be standardization of cystatin C assays, development of creatinine-based eGFR equations that incorporate muscle mass data, implementation of new endogenous biomarkers and the use of artificial intelligence. Standardization of different GFR measurement methods would also be a future challenge, as well as new technologies for measuring GFR. Future research is also needed into discrepancies between cystatin C and creatinine, which is associated with high risk of adverse events: we need to standardize the definition of discrepancy and understand its determinants.

Keywords: creatinine, cystatin C, glomerular filtration rate, iohexol

Box : In a nutshell

1. The non–glomerular filtration rate (GFR) determinants of creatinine make creatinine-based GFR estimation equations imprecise at the individual level.
2. Because of other non-GFR determinants of cystatin C, estimated GFR equations based on this biomarker are not more accurate than those based on creatinine in the general population; however, the use of both biomarkers slightly improves the performance of GFR estimation.
3. Equations based on cystatin C could nonetheless be more accurate than those based on creatinine in situations where creatinine performs poorly, including cases of abnormal muscle mass.
4. When the degree of precision required for a clinical situation is high, a GFR measurement using a reference method is required.

INTRODUCTION

The renal function of a patient can be evaluated with various parameters, but the glomerular filtration rate (GFR) is certainly the most important one for an organ with the important role of filtration and excretion [1]. Estimated GFR (eGFR) is used in daily practice by every nephrologist for (almost) every patient. Estimating GFR is crucial to adapt drug dosage and to correctly classify patients allowing adequate clinical decision and follow-up. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines published landmark recommendations for the evaluation and management of Chronic Kidney Disease (CKD) [2]. These guidelines made important proposals for the diagnosis of CKD. Among other recommendations, the KDIGO recommended to use the creatinine-based (eGFRcr) Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to estimate GFR, to use cystatin C–based eGFR (eGFRcys) equations when eGFRcr is less accurate or to confirm CKD diagnosis when eGFRcr is between 45 and 60 mL/min/1.73 m^2 (in patients without any other kidney damage), and to consider the CKD diagnosis in all subjects with eGFR <60 mL/min/1.73 m^2 [2]. These recommendations have sometimes been criticized [3–5], and since 2012, the research in the field of CKD diagnosis, and more specifically in the field of GFR

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estimation and measurement, has evolved greatly. These KDIGO guidelines are currently being revised. Writing an article on the 'standard diagnostic' squeezed between these two publications is therefore not easy! We made the choice to focus the current article on the clinical and individual level. Indeed, not a criticism but just a fact, many recommendations by the KDIGO are based on and/or justified by population and/or epidemiological data [2]: the eGFRcr CKD-EPI equation is preferred over the Modified Diet in Renal Disease study (MDRD) equation, not only because its accuracy to estimate GFR is better but also because the CKD-EPI equation is better associated with adverse outcomes than the MDRD [6]. In the same view, eGFRcys can be preferred over eGFRcr, not because this biomarker is better at estimating GFR (indeed, cystatin C is not better in the general population [7, 8]) but because cystatin C is better associated with cardiovascular mortality [9]. The target audience of the KDIGO guidelines is by nature very large, and absolutely not restricted to nephrologists. In this article, we will try to emphasize the role of the nephrologist and to focus on the individual (more than on populations and epidemiology) and on the clinical aspects of GFR estimation, trying to answer a simple question: How can I, as a nephrologist, best estimate the GFR for the patient in front of me?

DIAGNOSTIC STANDARD

Circulating biomarkers of renal function

In 2023, the most used biomarker to estimate GFR is still serum creatinine. From a pragmatic point of view, serum creatinine measurement is easy and cheap, and its measurement is analytically robust and standardized. However, as nephrologists, we know all the limitations of serum creatinine as a renal biomarker: non-GFR determinants (mainly dependence on muscular mass, tubular secretion, extrarenal excretion, effect of diet), lack of sensitivity (low GFR whereas 'normal' creatinine concentration) and lack of specificity of the dosage (especially with the Jaffe methods). It is beyond the scope of the current article to remind the reader how difficult the interpretation of a serum creatinine result can be [10, 11]. However, one frequently forgotten difficulty in serum creatinine interpretation is the non-linear, but inverse (hyperbolic) relation between this biomarker and GFR. This makes the interpretation of serum creatinine, and still more of changes in creatinine values (in the same patient), sometimes difficult to apprehend. An increase of 0.5 mg/dL in the same patients will represent two different GFR changes if baseline serum creatinine is 1.0 or 3.0 mg/dL. This is one of the major advantages of all eGFRcr equations: making the association between 'true' and eGFRcr more linear [10, 12, 13]. The inverse relationship is also found between cystatin C and GFR, making the interpretation of eGFRcys equations also popular. Cystatin C, described for the first time as a potential GFR biomarker by Anders Grubb *et al.* in 1985 [14], is presented as a renal biomarker with the advantage of being non-dependent (or at least much less so than creatinine) on muscular mass [15]. This observation makes cystatin C less dependent on population characteristics and leads to the possibility of developing eGFR equations without including the race or even sex variables, those variables being tightly correlated with muscular mass [7]. Interestingly, in the two largest studies developing and validating eGFRcys equations [the CKD-EPI consortium and the European Kidney Function Consortium (EKFC)], the eGFRcys equation was not performing better than eGFRcr equations. This suggests non-GFR determinants of plasma cystatin C that are not included in the eGFRcys equations—among them, thyroid function is the best known (the other determinants are more debated in the literature) [15–17]. Only using the two biomarkers (eGFRcr-cys) in the same equation can lead eventually to better accuracy and precision in estimating GFR [7, 18]. Having said that, several studies in specific populations also suggest that cystatin C could be more accurate, especially in a situation where creatinine performance is particularly poor (subjects with abnormal muscular mass) [19–22].

Equations to estimate GFR

It is beyond the scope of the current article to review in detail the strengths and limitations of the multiple eGFRcr and eGFRcys equations published up to now [13]. Main equations developed in general population are shown in Table 1. To make a long story short, the first widely used eGFRcr equation was the Cockcroft and Gault study equation, published in 1976 [23]. However, this equation had several methodological limitations, and its accuracy for estimating GFR has been proven to be poor in comparison with 'modern' equations [24–26]. One important limitation is the fact that this equation is an estimation of creatinine clearance (expressed in mL/min), which cannot be considered itself as a reference method, according to the large imprecision of creatinine clearance at the individual level. In 1999, the MDRD study equation was the first eGFRcr equation developed from a large cohort, using serum creatinine, race, age and sex as variables [26]. This equation had the big advantage of being easy to implement by clinical laboratories, allowing them to easily report eGFRcr results automatically [27]. The MDRD equation has been updated in 2009 by the CKD-EPI eGFRcr equation proposed by the consortium [8]. Compared with the MDRD, this equation had better performance in 'normal' GFR levels (MDRD was underestimating GFR at this level). The added value of the CKD-EPI equation was especially relevant at the population level (the prevalence of CKD in the population was more correctly assessed with the CKD-EPI equation, and CKD-EPI was better associated with mortality than the MDRD study equation). However, the increased performance of the CKD-EPI over the MDRD equation at the individual level is probably more limited [5]. Recently, the 2009 version has been largely criticized as a source of discrimination for Black populations in USA [28]. This has lead the authors of the CKD-EPI equation to propose a new CKD-EPI eGFRcr equation, 'version 2021', without any reference to race [18]. Because the association between serum creatinine and GFR is factually different in Black and non-Black populations (more in men than in women), this new equation is less accurate in non-Black populations (and not better in Black populations) [7, 18, 29–31]. However, the goal of the authors was met, as the (absolute) bias was now similar for this equation in the two populations [18]. This equation has been rapidly adopted in USA [32]. In Europe (but also in Africa), the enthusiasm for this equation was less marked. Indeed, in these continents, it has been shown that the CKD-EPI$_{2009}$ equation should be used without the racial correction in Black people [33–37]. As the CKD-EPI$_{2021}$ does not perform better than the CKD-EPI$_{2009}$ in Black African and Black European populations, and given that the CKD-EPI$_{2009}$ without any race correction performs better than with correction, and as, eventually, the CKD-EPI$_{2021}$ performs worse than the CKD-EPI$_{2009}$ in white Europeans, it follows logically that this new equation not be used in Europe and Africa [13, 38]. The European Renal Association (ERA) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) do currently not recommend using the CKD-EPI$_{2021}$ eGFRcr equation [39, 40]. In 2021, a new eGFRcr equation, the EKFC equation, has been developed from a large (mainly European) collaboration [41] (a calculator is

Table 1: Main eGFR equations.

Name	Age (years)	Sex			eGFR equation
CKD-EPI$_{Crea}$ (ASR) [8]	≥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]	≥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		$142 \times (SCr/0.90)^{-1.200} \times 0.9938^{Age}$
CKD-EPI$_{CysC}$ [86]	≥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-EPI$_{Crea+CysC}$ (ASR) [86]	≥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-EPI$_{Crea+CysC}$ (AS) [18]	≥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$_{Crea}$ [41]	25–40	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		$107.3 \times (SCr/Q)^{-1.132} \times 0.990^{(Age-40)}$
EKFC$_{CysC}$ [7]	18–40		ScysC/0.83 < 1.0		$107.3 \times (SCysC/0.83)^{-0.322}$
			ScysC/0.83 ≥ 1.0		$107.3 \times (SCysC/0.83)^{-1.132}$
	>40		ScysC/0.83 < 1.0		$107.3 \times (SCysC/0.83)^{-0.322} \times 0.990^{(Age-40)}$
			ScysC/0.83 ≥ 1.0		$107.3 \times (SCysC/0.83)^{-1.132} \times 0.990^{(Age-40)}$
	>50		ScysC/Q < 1.0		$107.3 \times (SCysC/Q)^{-0.322} \times 0.990^{(Age-40)}$
			Q = 0.83 + 0.005 × (Age–50)		
			ScysC/Q ≥ 1.0		$107.3 \times (SCysC/Q)^{-1.132} \times 0.990^{(Age-40)}$
			Q = 0.83 + 0.005 × (Age-50)		
LMREV [50]		Female	<150 (in µmol/L)		X = 2.5 + 0.0121 × (150–SCr) (SCr in µmol/L)
			≥150		X = 2.5–0.926 × log(SCr/150)
		Male	<180		X = 2.56 + 0.00968 × (180–SCr)
			≥180		X = 2.56–0.926 × log(SCr/180)
					GFR = e × p(X–0.0158 × age + 0.438 × log(age))
CAPA [49]					$130 \times ScysC^{-1.069} \times age^{-0.117} - 7$

ASR, age, sex and race factors; AS, age and sex but no race factor; Q, rescaling factor for the biomarker; LMREV, Revised Lund–Malmö; SCr, serum creatinine; ScysC, serum cystatin C.
To make a more continuous transition from the pediatric EKFC$_{Crea}$ equation to the adult EKFC$_{Crea}$ equation, the Q-values for children, adolescents and young adults (up to 25 years old) can be calculated from (note that the Q-value obtained from these equations is expressed in µmol/L):
- Men, age ≤25 years: $\ln(Q) = 3.200 + 0.259 \times age - 0.543 \times \log(age) - 0.00763 \times age^2 + 0.0000790 \times age^3$
- Women, age ≤25 years: $\ln(Q) = 3.080 + 0.177 \times age - 0.223 \times \log(age) - 0.00596 \times age^2 + 0.0000686 \times age^3$

Q can be obtained in mg/dL using exp(Q)/88.4.
For white European subjects, age > 25 years, use:
- Men: Q = 0.90 mg/dL
- Women: Q = 0.70 mg/dL (see [34, 47] for Q-values in other populations).

available from https://ekfccalculator.pages.dev/). The goal of the EKFC equation was to better model the association between GFR, serum creatinine and the usual variables included in equations, like age and sex. First, the equation was designed to take into consideration the fact that GFR is constant from 2 years to 40 years and then declines with aging (renal senescence) [41, 42], whereas serum creatinine evolves in a totally different way (serum creatinine increases during childhood and adolescence and remains relatively constant with aging thereafter) [43]. The EKFC equation thus integrates these different associations between age on one side and serum creatinine and GFR on the other side [with an equation evolving after 40 years and Q-value specific according to age (see below)]. Consequently, the same equation can be used in both children and adults (guaranteeing continuity across the adolescence/adulthood transition) [44]. The EKFC eGFRcr equation seems also more accurate in young and old adults then the CKD-EPI eGFRcr equation [13, 41]. Moreover, serum creatinine is clearly different between men and women, whereas measured GFR does not seem to be different. Similar to sex, race (we prefer the term 'population') is also important, as it has been shown that serum creatinine can be different between people living in the USA, Africa or Europe [34, 38], whereas, once again, the measured GFR does not seem to be very different between these populations [45, 46]. The EKFC equation adjusts or rescales serum creatinine with a Q-value, defined as the median normal concentration of serum creatinine in a given population (for example, in European non-Black population the Q-value is 0.9 mg/dL for men and 0.7 mg/dL for women) [41]. A specific Q-value can easily be defined for different populations, as has been shown in Black European, Black African or Chinese populations [34, 47]. In case of mixed populations, and/or if a totally race-free equation is required, and/or if race is not available, a race-free Q-value can be proposed, as we have recently proposed for the USA [48]. A population can be difficult to define in a world where social diversity is hopefully increasing. When defining a Q-value that applies to a population, the term 'population' is deliberately vague because the aim is to make the Q-value very flexible. Indeed, the 'population' can be as large or small as required. The 'population' can be a continent, a country (the EKFC equation would deserve a validation with dedicated Q-values notably in Asian countries), a region or the population attending a laboratory. Each laboratory equipped with a computerized system can easily calculate its own Q-value in adults by computing the median value of serum creatinine of the population obtained in the previous years in men or women, excluding hospitalized patients and patients followed by nephrologists. A population can also be more limited as a societal entity (notably in minorities) where Q-values can be defined from healthy people of the group. A self-defined population can easily develop its own Q-value (and check whether these Q-values are really different from those that already exist), the rest of the equation remains unchanged. Finally, the eGFRcr EKFC equation has exactly the same shape as the eGFRcys equation (only a Q-value specific to cystatin C is required) [7, 41].

Both the CKD-EPI and the EKFC consortia have proposed eGFRcys equations (the EKFC equation using a Q-value independent of sex) and eGFRcr-cys equations [7, 18]. Again, in these two large trials, only the equation combining both biomarkers really improves the ability of the equation to better estimate GFR. To end this section about equations, we would like to mention the equations developed, and currently used in daily practice, in Sweden: the Revised Lund–Malmö equation (eGFRcr) and the Caucasian, Asian, Pediatric, and Adult equation (CAPA, eGFRcys). These equations have a pretty good performance in non-Black European people (and can probably be adapted to other populations as well) [49, 50].

Limitations of equations: they remain an estimation

The debate about the better equation to use could be an endless discussion. Every new equation is supposed to improve the performance of the previous ones (except the eGFRcr CKD-EPI$_{2021}$ for which the objective was a societal one of eliminating the racial correction factor). Among eGFRcr, only the EKFC equation has the ambition of being used universally, even if, currently, it is especially well validated in Europe, and in West and Central Africa [41, 51]. In the USA, the eGFRcr CKD-EPI equations, published in 2009, have been the most studied, but the performance of the eGFRcr EKFC equation in US cohorts seems very similar to eGFR CKD-EPI equation [48]. eGFRcr CKD-EPI equations have been studied in Asian countries, often with a correction factor, and the first results of the EKFC equations (with dedicated Q-values) are promising but further studies seem necessary [52]. However, all equations (even the best including both biomarkers) have the same limitation, which is a lack of precision at the individual level [53–55]. This fact is reflected by the metrics used in trials studying and comparing the equations. The best equations reach an accuracy within 30% of 90%. That means that we are accepting and expecting that an eGFR result is within 30% of a measured GFR result, which is a quite large range. Moreover, in the best case, the difference between eGFR and measured GFR will be more than 30% in 1 case in 10. In the same vein, the ability of any equation to classify a subject in the same staging as measured GFR is, at best, around 70%. With eGFR, a nephrologist will misclassify 30% of patients (at the best) [18, 41]. We do not know exactly how relevant this misclassification is in clinical practice, as studies comparing the impact of such misclassifications between eGFR and measured GFR on clinical care are lacking. Nevertheless, nephrologists must keep these limitations in mind, and in some specific situations and/or some specific patients, a measured GFR remains justified [56, 57].

Box: Strategies how to personalize the diagnostic approach.

1. All equations, eGFRcr, eGFRcys and eGFRcr-cys, remain an estimation. At the individual level, this estimation can be insufficient. If a high degree of precision is required for a given patient and/or a given clinical situation, measuring GFR with a reference method should be considered. Simplified methods, like iohexol plasma clearance, are available. In other cases, one can measure biomarkers and estimate GFR. The first biomarker to be used in clinical practice is serum creatinine. We suggest considering the equation that has been best validated regarding the characteristics of the patient. If there is doubt regarding the ability of serum creatinine to correctly estimate GFR, cystatin C can be measured. Cystatin C is not influenced by characteristics of populations and equations can be used without the sex or race variables. If cystatin C can be measured, it is recommended to use both creatinine and cystatin C in an equation, in most cases.

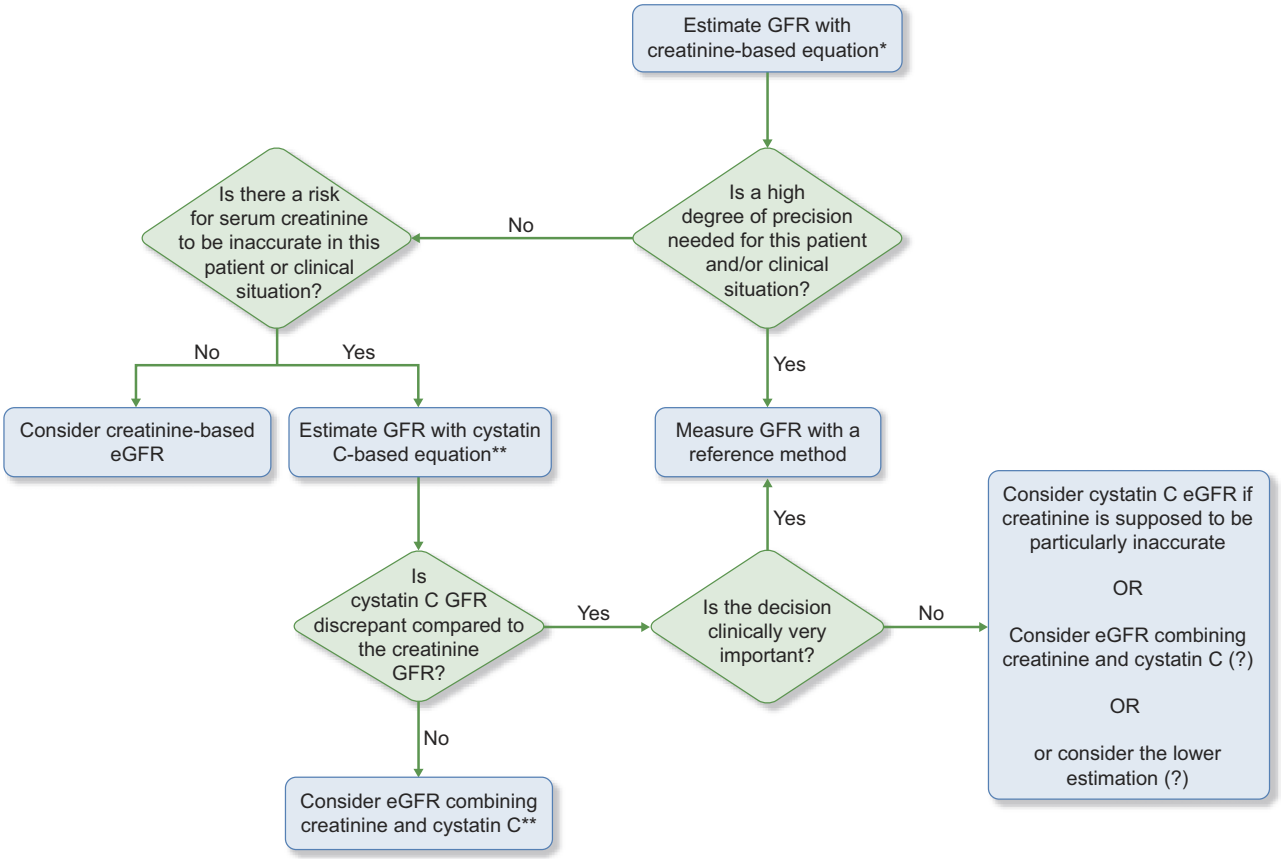

Figure 1: Estimation of GFR in Nephrology, in clinical practice and at the individual level. *Using the best validated equation in your region and/or population. **Using the cystatin C or combined equation corresponding to the creatinine-based equation used at the first step.

NEW DEVELOPMENTS FOR ESTIMATING AND MEASURING GFR

Standardization

In the field of estimating and measuring GFR, standardization is critically important. As has been illustrated in the past with serum creatinine, a standardized measurement of the biomarkers is required as the impact of a non-standardization can be huge [10, 58, 59]. In 2023, the standardization of the creatinine assays can be considered to have been achieved, but, in reality, such a standardization is definitively proven only for (most) commercially available enzymatic assays [60], whereas some doubt is persisting for Jaffe assays [61]. Standardization of cystatin C assays is more challenging for different reasons. Today, the standardization of cystatin C is less implemented than for creatinine assays, but improvements have been made in recent years [62]. The standardization of measuring GFR is still more complex, as various markers (iohexol, iothalamate, DTPA, inulin, etc.) and several different methodologies (urinary versus plasma clearance, single-sample versus multiple-sample, etc.) have been described in the literature [63]. Without excluding other recognized reference methods and for pragmatic reasons, iohexol plasma clearance is currently the method that seems the easiest to implement with (possible) common methodologies [64]. A work on this topic is in progress by the EKFC.

Technology

A possible future development would be the use of eGFRcr equations that incorporate muscle mass data, using for example CT segmentation software that is now becoming more widely available. Such an approach could make it feasible to provide a race- and sex-free eGFR, and to obtain a more accurate eGFR in the case of aberrant muscle mass [65]. New biomarkers to estimate GFR have been proposed such as proenkephalin [66], or myo-inositol and valine [67]. Further research is however required before these become clinically usable. Recent research in metabolomics showed also some promising results, but the real added value for clinical practice is yet to be proven [68, 69]. Moreover, the challenge is difficult for all these new biomarkers, as they have to prove their superiority, their analytical robustness and, still more challenging, their cost-effectiveness in comparison with creatinine and cystatin C. Recently, the first publications on the role of machine learning algorithms have been released [70, 71]. If the first results are not totally convincing [72], this avenue needs to be explored in the near future.

Briefly, new technologies are also being developed in the field of measured GFR with the goal of making measured GFR more easily available to nephrologists [64, 73].

Special patient groups

We must keep in mind that for all eGFRcr equations, serum creatinine is and remains the most important variable (also from a mathematical point of view). If for any reason serum creatinine is not a good biomarker for a given patient, there is no reason to think that the equation will be accurate. Both eGFRcr and eGFRcys equations are mathematical constructions, they are not 'magic formulae'. The performance of biomarkers and estimating equations is particularly poor in some populations [74]. We

can cite (without being exhaustive): elderly and frail patients, patients with cirrhosis, patients with amputation, patients with neuromuscular diseases and patients with anorexia nervosa. In all these examples, eGFRcr will tend to overestimate GFR and the discrepancy between eGFRcr and eGFRcys will be large. It is therefore tempting to develop specific equations for specific patients. Accordingly, eGFRcr and/or eGFRcys equations have been proposed specifically for the elderly population [75], patients with cancer [76] or obesity [77], or, very recently, for kidney transplant patients [78]. The risk is obviously a proliferation of formulae. Such a specific equation could be considered if the added value in comparison with the more 'general' equations (like EKFC or CKD-EPI) is significant and clinically relevant, which is not currently the case for most of these equations.

Open debates and future research

The debate regarding the choice of the biomarker, cystatin C versus creatinine, for estimating GFR is not over yet. If cystatin C has a clear added value in terms of prognosis, its real added value, and still more its cost-effectiveness, for estimating GFR is less obvious and require further studies.

Much research is currently focusing on patients with discrepant results between creatinine and cystatin C. Such discrepant results are not rare in the general population, or still more in most specific populations (like those with abnormal muscle mass), but in the majority of the cases eGFRcys results give lower eGFR results than eGFRcr results [79–83]. The definition of a 'discrepant' result needs still to be standardized: absolute versus relative difference? Which threshold? Of interest, it seems that these patients with discrepant eGFRs have a higher risk of adverse events, including renal events [79, 80, 82, 83]. Different interesting hypotheses regarding such discrepancies have been elaborated, like the shrunken pore syndrome or a surrogate marker of frailty [15, 84]. Coming back to the estimation of GFR *sensu stricto*, it remains to be determined which result is most accurate when eGFRcys and eGFRcr equations are discrepant [81]. Some argue for the use of equations combining both biomarkers, whereas others think the lower eGFR results should be considered [85]. Finally, we underline that research is also currently being conducted in the field of 'measuring GFR' [73].

SUMMARY

In Fig. 1, we proposed a pragmatic approach for 'how to estimate GFR in clinical practice' which is supposed to be 'patient-centred'. We suggest how to consider creatinine, cystatin C and measured GFR (most are and remain, however, 'suggestions'). We must recognize that, pragmatically speaking, cystatin C and measured GFR are still not available in many centres and countries. In many developing countries or isolated regions, obtaining an accurate serum creatinine is already a challenge. We must keep in mind that measuring GFR and cystatin C are a privilege for rich countries. As suggested in the flow chart, we emphasize that estimating GFR by cystatin C and measuring GFR by a reference method cannot be considered at the same hierarchical level, especially at the individual level. Like every measure, measuring GFR by a reference method has its own variability. However, measuring GFR remains the most precise way to apprehend GFR, whereas cystatin C–based eGFR remains an estimation. Measuring GFR remains indicated when a high level of precision is needed (the best example being in the context of kidney donation) and/or when estimating GFR accuracy is too low. Measuring GFR is neither cumbersome nor complex (from a clinical or an analytical point of view). Of course, the cost of measuring GFR is higher than using biomarkers alone, but this cost is much lower than many reference methods in medicine and indications are also more restrictive (only required when a high degree of precision in GFR is needed).

Implementation of cystatin C and measured GFR is a real challenge for the future in Nephrology. This is not impossible as both are part of daily clinical nephrological practice in Sweden. There is no doubt that more studies are still required to facilitate and justify a wider implementation of these parameters in clinical Nephrology.

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AUTHORS' CONTRIBUTIONS

P.D. wrote the first draft. All other authors critically reviewed the manuscript.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

P.D. and E.C. are consultants for Nephrolyx.

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