Time to Rethink the Current Paradigm for Assessing Kidney Function in Drug Development and Beyond

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Chronic kidney disease (CKD) is an important health issue that affects ~ 9.1% of the world adult population. Serum creatinine is the most commonly used biomarker for assessing kidney function and is utilized in different equations for estimating creatinine clearance or glomerular filtration rate (GFR). The Cockcroft–Gault formula for adults and "original" Schwartz formula for children have been the most commonly used equations for estimating kidney function during the last 3–4 decades. Introduction of standardized serum creatinine bioanalytical methodology has reduced interlaboratory variability but is not intended to be used with Cockcroft–Gault or original Schwartz equations. More accurate equations (for instance, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) for adults and bedside Schwartz or Chronic Kidney Disease in Children Schwartz equation for children) based on standardized serum creatinine values (and another biomarker—cystatin C) have been introduced and validated in recent years. Recently, the CKD-EPI equation refitted without a race variable was introduced. Clinical practice guidance in nephrology advocates a shift to these equations for managing health care of patients with CKD. The guidance also recommends use of albuminuria in addition to GFR for CKD diagnosis and management. Significant research with large data sets would be necessary to evaluate whether this paradigm would also be valuable in drug dose adjustments. This article attempts to highlight some important advancements in the field from a clinical pharmacology perspective and is a call to action to industry, regulators, and academia to rethink the current paradigm for assessing kidney function to enable dose recommendation in patients with CKD.

Chronic kidney disease (CKD) is a global health problem that is defined by the presence of abnormalities in kidney structure or function for at least 3 months, irrespective of the cause.[1] Kidney Disease Improving Global Outcome (KDIGO) guidelines recommend classifying CKD as well as its prognosis based on cause, glomerular filtration rate (GFR), and albuminuria.[2] It is estimated that 15% (~ 37 million) of the US adult population has CKD.[3] In 2017, it was estimated that ~ 9.1% of the global adult population has CKD.[4]

GFR is widely accepted as the best surrogate for kidney function.[5,6] The measurement of GFR involves assessing the urinary or plasma clearance of the exogenous filtration marker inulin, which is a gold standard[7] Other exogenous markers such as iothalamate, iohexol, and chromium-51-ethylenediamine tetraacetic acid (^{51}Cr EDTA) are also utilized.[8] However, this process is complex and cumbersome and generally not routinely performed in drug development or clinical practice. Therefore, GFR is estimated using mathematical models that rely on measurement of endogenous markers such as creatinine and cystatin C in serum. Over the years, multiple equations for GFR estimation have been proposed in the literature. There also exists a great degree of variability in the assays utilized for measurement of endogenous serum biomarkers and how they are applied for estimation of GFR. Errors in biomarker measurement or inappropriate choice of equation can lead to inaccurate GFR estimation and consequently to misclassification of the level of kidney impairment which may be deleterious to patients in terms of dose adjustments and potentially health outcomes.[9]

Considered from a clinical pharmacology perspective, reduction in kidney function can lead to changes in drug exposure due to reduced excretion of the drug and its metabolites via the kidneys, and inhibition of drug metabolizing enzymes and transporters.[10] The absorption, plasma protein binding, and tissue distribution of the drug can also be affected. Therefore, it is important to establish the relationship between kidney function and drug's pharmacokinetics during drug development in order to recommend the appropriate dose that ensures safe and effective use of drugs in patients with impaired kidney function. Drug regulatory agencies provide guidance on this topic for industry.[11] Accurate determination of kidney function is important for robust characterization of the relationship between kidney function and drug pharmacokinetics.

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In this manuscript, we describe the context for development and utilization of different equations for estimation of GFR in adults as well as in children (**Figure 1**). Common factors encountered in clinical trials or real-world settings that impact serum creatinine measurement and thus the ability to accurately estimate GFR are also described. Ultimately, we propose that the paradigm for the assessment of kidney function and for deriving dosing recommendations in subjects with kidney disease should be aligned with KDIGO guidelines for diagnosing and prognosticating kidney disease severity[2]

MEASUREMENT OF GFR

GFR cannot be directly measured but can be indirectly measured by the clearance of exogenous filtration markers that are eliminated by filtration only and neither secreted nor reabsorbed by the kidney.[7] The gold standard method for measuring GFR is classic inulin clearance.[12] In clinical research and practice, other clearance markers and methods are used such as iohexol, iothalamate, diethylenetriamine pentaacetic acid (DTPA), and ^{51}Cr-EDTA[13,14](**Figure 1**). These methods are rigorous and include intravenous bolus administration of the exogenous filtration marker (continuous infusion in the case of inulin), and timed blood sampling and urine collection. These methods are associated with errors in measuring true GFR.[12] Soveri *et al*. reported sufficient accuracy of renal clearance of ^{51}Cr-EDTA and iothalamate and plasma clearance of ^{51}Cr-EDTA and iohexol for measuring GFR when compared with inulin clearance.[7]

GFR can be approximated by creatinine clearance which can be measured using 6 to 24 hours' urine collection and a blood sample to quantify serum creatinine. It is generally only employed for hospitalized patients due to the inconvenience of the long urine collection period. The following equation can be used to obtain measured GFR:

$$\text{creatinine clearance}\left(\frac{\text{mL}}{\text{min}}\right) = \frac{\text{creatinine}_{\text{urine}}\left(\frac{\text{mg}}{\text{dL}}\right) \times \text{urine volume (mL)}}{\text{creatinine}_{\text{serum}}\left(\frac{\text{mg}}{\text{dL}}\right) \times \text{time}\,(h) \times 60}$$

[Correction added on 11 March 2022, after first online publication: The units for urine volume used in the above equation for the measurement of GFR should be in mL and it has been corrected in this version].

ESTIMATION OF GFR

In typical clinical practice as well as in clinical trials, GFR is frequently estimated using one of several equations described later in this manuscript (**Table S1**) that were empirically developed based on data from a large number of subjects. These equations have helped to overcome the practical problems encountered with the use of exogenous markers for measuring

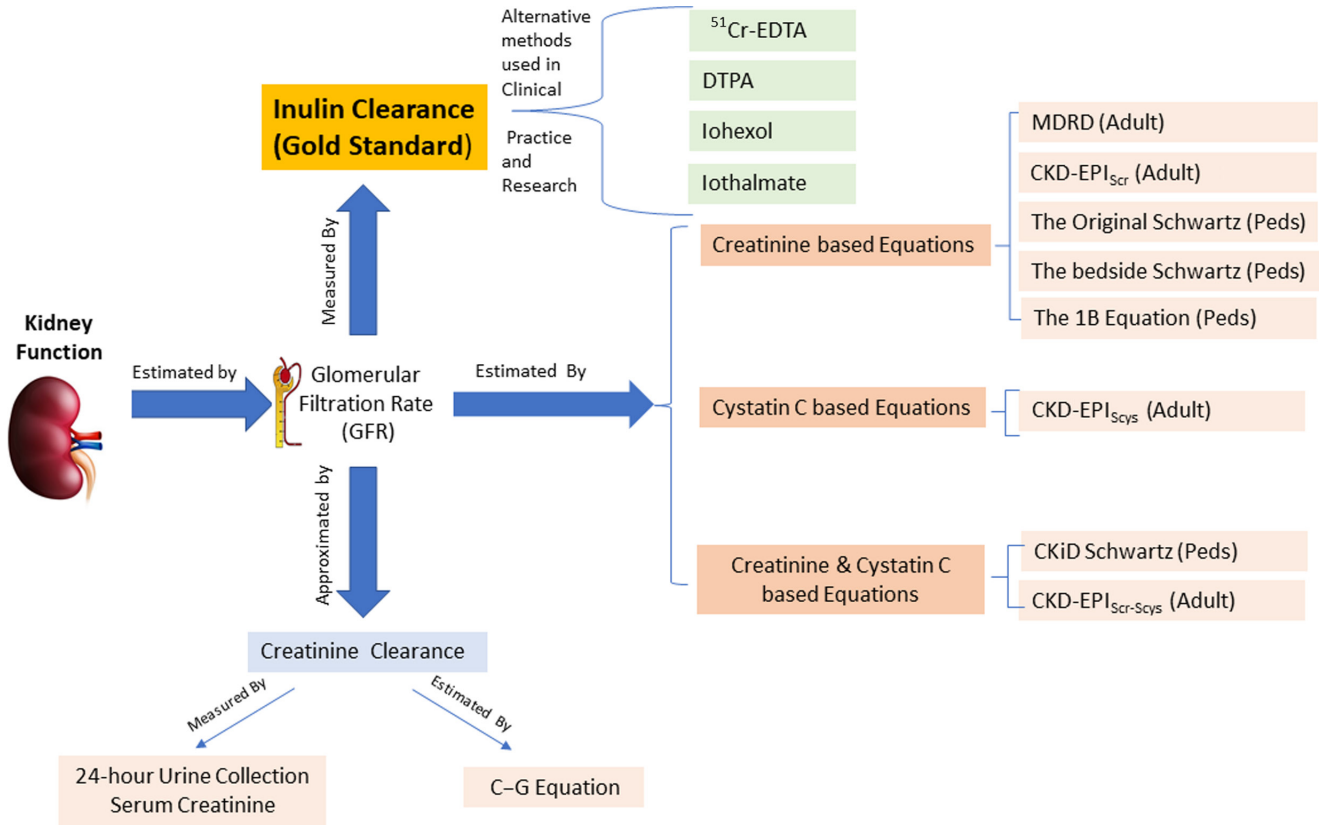

Figure 1 Common markers and equations used in kidney function assessment. C–G, Cockcroft–Gault; CKD-EPI$_{Scr}$, Chronic Kidney Disease Epidemiology Collaboration serum creatinine–based equation; CKD-EPI$_{Scr\text{-}Scys}$, Chronic Kidney Disease Epidemiology Collaboration serum creatinine–cystatin C–based equation; CKD-EPI$_{Scys}$, Chronic Kidney Disease Epidemiology Collaboration cystatin C–based equation; CKiD, Chronic Kidney Disease in Children; DTPA, diethylenetriamine pentaacetic acid; EDTA, ethylenediamine tetraacetic acid; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; 1B equation, includes BUN (blood urea nitrogen) along with serum creatinine but not cystatin; ^{51}Cr-EDTA, chromium-51-ethylenediamine tetraacetic acid.

GFR as well as the collection of timed urine and serum samples for approximating GFR. The equations depend on measuring serum markers and account for additional factors such as age, sex, and race. The most commonly used markers are serum creatinine and cystatin. Creatinine, a low-molecular-weight cation (113 daltons), is not metabolized, not bound to plasma proteins, and freely filtered by the glomerulus in the kidneys. However, creatinine is also actively secreted by tubular cells in the kidneys, accounting for 10–40% of excreted creatinine in normal individuals.[15,16] Active secretion of creatinine has been shown to be mediated via OAT2,[17,18] as well as OCT2,[19] MATE1, and MATE2K transporters.[20] Cystatin C is a cationic nonglycosylated 13 kilodalton cysteine protease that is constitutively expressed by all nucleated cells in the body. In healthy individuals, tubular reabsorption and catabolism is complete with very minor urinary excretion.[21,22] Increased urinary elimination happens in kidney disorders. Glomerular filtration is the primary mechanism for cystatin C removal and has been incorporated in the GFR estimation equations in the recent years to overcome some of the limitations associated with equations based on serum creatinine alone. Important aspects for quantifying creatinine and cystatin C are outlined in **Box 1**.

Equations for adults

Several equations for assessing kidney function in adults have been developed over the years.

Serum creatinine–based equations. While several serum creatinine equations are available to estimate kidney function, the appropriate choice of equation depends on the bioanalytical methodology (IDMS traceable or not) used for quantifying creatinine. The most noteworthy serum creatinine–based equations that have been developed are the Cockcroft–Gault (C–G) equation, Modification of Diet in Renal Disease (MDRD) equation, and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

The C–G equation estimates clearance of creatinine,[37] whereas the MDRD and CKD-EPI equations estimate GFR.[38,39] This is important to keep in mind as creatinine (as discussed earlier) has some active secretion into the urine in addition to filtration.

Cockcroft—Gault equation. This equation was developed in 1973 using data from 249 White men whose creatinine clearance ranged between 30 and 130 mL/min.[40] An empirical correction factor for women based on lesser muscle mass in women compared

Box 1 Important consideration associated with the Bioanalysis of creatinine and cystatin-C

CREATININE (SERUM OR URINE)

1. Photometric Methods
   a The Original Jaffe Method
      - ✓ The most commonly used method for reporting creatinine levels in clinical laboratory reports.
      - ✓ Named after Max Jaffe who discovered that adding picric acid to creatinine in alkaline medium produced a yellow-orange color.[23] The intensity of the color is measured photometrically to quantify creatinine concentrations based on the method developed by Otto Folin in 1900.[24]
      - ✓ **Pros:** Highly cost effective
      - ✓ **Cons:**
        1. Lack of specificity: Interference from other chromogens (such as protein, glucose, and bilirubin) can lead to incorrect creatinine measurement in certain populations such as patients with diabetes or cirrhosis.[25,26] Compensated Jaffe methods that were developed to account for nonspecificity did not resolve the issue.
        2. Interlaboratory variability: A major concern with creatinine measurement using the Jaffe method has been the interlaboratory variability due to differences in internal standard. Therefore, the National Institute for Standards and Technology (NIST) released a standard reference material (SRM 967a-Creatinine in Frozen Human Serum), which is traceable to an isotope dilution mass spectrometry (IDMS) reference measurement procedure, for use in establishing calibrations for routine creatinine measurement procedures to reduce interlaboratory variability. It is important to understand that IDMS standardization does not address the issue of assay nonspecificity.[27] The Jaffe method following these recommendations is referred to as the IDMS traceable Jaffe method. An understanding for the type of assays employed in measuring creatinine is important since the output between IDMS-traceable and IDMS-non traceable methodology can vary from 10% to 20% depending on the reference material used by individual laboratories using a non–IDMS-standardized reference material[28] and not all laboratories worldwide offer the IDMS-traceable Jaffe method.

   b Enzymatic Method
      - ✓ Introduced in the 1970s[29] and involves an enzymatic reaction with creatinine producing a red dye that is photometrically measured. Several different kinds of liquid and dry enzymatic methods are available.
      - ✓ **Pros**: IDMS-traceable method with analytical sensitivity and specificity[30] superior to that of the Jaffe method because it reduces interference by other compounds such as glucose, ketone bodies, and ascorbic acid.[27] Therefore, enzymatic methods are more suitable than the original Jaffe method, for instance, in patients with diabetes.[30]

2. Chromatograph-Based Methods
   - ✓ **Isotope dilution gas chromatography**–based analysis is the **gold standard** for quantifying creatinine concentration since these assays measure absolute creatinine concentration.
   - ✓ Various liquid chromatography-mass spectrometry techniques have been developed.[31,32]
   - ✓ They are not commonly applied due to the complexity of the methodology and high costs.

CYSTATIN C (SERUM)

- ✓ A human serum certified reference material for cystatin C (DA471/IFCC (International Federation of Clinical Chemistry and Laboratory Medicine)) was developed.[33]
- ✓ The accuracy of the routinely used methods (nephelometry, turbidimetry, or ligand binding) to quantify cystatin C needs further improvement.[34,35]
- ✓ A peptide-based isotope dilution mass spectrometry method for cystatin C has also been developed that allows the measurement of the exact concentration using the reference standard material; however, such assays are not used in routine clinical practice.[36]

with men was added later and expressed as shown in the formula below:

$$\text{Creatinine Clearance}\left(\frac{\text{mL}}{\text{min}}\right) = \frac{\left(140-\text{age (years)}\right)\times\text{Body weight (kg)}\times(0.85\text{ if female})}{72\times\text{serum creatinine}\left(\frac{\text{mg}}{\text{dL}}\right)}$$

This equation has several shortcomings. One important potential source of imprecision in this equation is the inclusion of body weight. Higher body weight is neither necessarily linked with greater muscle mass nor with higher kidney volume/number of functioning nephrons.[41] Accordingly, this equation is biased in the case of individuals with abnormal body mass index (BMI > 25 kg/m^2).[42] Furthermore, this equation was developed without data from non-White individuals and therefore its accuracy for the non-White population is unknown.

Prior to widespread adoption of IDMS standardization, the C–G equation had been used for several decades in clinical studies to relate drug exposure changes associated with changes in kidney function. The main intention of the equation was to predict creatinine clearance rather than estimate GFR, and hence, it was validated against measured creatinine clearance. However, since creatinine clearance (CrCL) overestimates GFR due to creatinine tubular secretion component, the C–G equation also overestimates GFR, especially at lower creatinine concentrations.

The C–G equation was empirically developed using data from a IDMS-nontraceable creatinine assay. However, in the United States, a majority of the laboratories have switched to IDMS-traceable creatinine measurements.[43] Since IDMS traceable creatinine assays generally report lower values of creatinine than IDMS nontraceable assays, the C–G equation based on IDMS-traceable creatinine assay overestimates GFR by 10% to 20%, which may lead to misclassification of subjects into different kidney disease groups.[28] There is no revised version of the equation for use with standardized creatinine assays. Additionally, the range of bias for IDMS nontraceable assays is even greater based on assay and instrument, and therefore, a correction factor cannot be easily applied to studies performed prior to the introduction of IDMS standardization. While some empirical corrections for IDMS standardization have been suggested, they have not been validated to date and therefore not widely accepted. The US National Kidney Foundation and the KDIGO guidelines[2] recommend against using the C–G equation for evaluating GFR for purposes such as drug dosing recommendations and recommend using an equation that estimates GFR from creatinine methods with calibration traceable to an IDMS reference measurement procedure.[44]

The MDRD and the CKD-EPI are the most widely used IDMS-traceable equations for estimating GFR in adults.[45]

MDRD equation. This equation was introduced by Levey and colleagues in 1999[38] and was established based on measured GFR using data from 1,628 patients of which 1,070 were selected randomly as the training sample and the remaining 558 patients formed the validation sample. The patients included in establishing this equation had a GFR ranging from 5 to 90 mL/min/1.73 m^2. The equation (using non–IDMS-traceable serum creatinine values) was expressed as follows:

$$\text{GFR} = 186\times\text{serum creatinine}^{-1.154}\times\text{age}^{-0.203}\times(0.742\text{ if female})\times(1.210\text{ if African American})$$

where GFR is in mL/min/1.73 m^2, age is in years, and serum creatinine in mg/dL.

Following the introduction of IDMS standardization, the equation was re-expressed in 2007 as follows:[46]

$$\text{GFR} = 175\times\text{serum creatinine}^{(-1.154)}\times\text{Age}^{(-0.203)}\times(0.742\text{ if female})\times(1.212\text{ if African American}).$$

This equation has several advantages over the C–G equation, with one obvious advantage being the inclusion of women as well as African American individuals in the development of the equation. This equation has been validated extensively in White and African American patients and has shown good performance for patients with all common causes of CKD. This equation is considered more accurate than the C–G equation and does not require weight or height variables because the results are reported normalized to a body surface area of 1.73 m^2, which is an accepted average adult surface area. Furthermore, the MDRD equation provides an estimate of GFR rather than creatinine clearance, and the estimated GFR (eGFR) correlates well with measured GFR in the patients with CKD in the lower eGFR < 60 mL/min/1.73 m^2 range. However, the MDRD equation also has some limitations, including that it is less accurate at GFR values ≥ 60 mL/min/1.73 m^2, whereby the reported values are underestimated.[39] Using the MDRD equation, if the GFR estimate is found to be higher than 60 mL/min/1.73 m^2, it is suggested not to report the actual value but to only indicate GFR ≥60 mL/min/1.73 m^2.[47]

CKD-EPI equation. This equation was introduced by Levey *et al.* in 2009, the same group that developed MDRD a decade earlier.[39] It was developed based on data from 5,504 patients, of which 63% were White individuals and 43% were women. This equation can only be implemented with IDMS-traceable serum creatinine measurements.

The IDMS-traceable serum creatinine based CKD-EPI (CKD-EPI$_{Scr}$) equation is expressed as follows:

$$\text{GFR} = 141\times\min\left(\frac{\text{SCr}}{k},1\right)^{\alpha}\times\max\left(\frac{\text{SCr}}{k},1\right)^{-1.209}\times0.993^{\text{Age}}\times1.018\ [\text{if female}]\times1.159\ [\text{if African American}]$$

where κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.

The eGFR results based on this CKD-EPI equation were as accurate as MDRD-derived eGFR results in patients with eGFR < 60 mL/min/1.73 m^2 but more accurate in patients with eGFR > 60 mL/

min/1.73 m^2.[39] The authors of the CKD-EPI equation suggest that the equation is useful for reporting eGFR up to 120 mL/min.

Serum cystatin C–based equations. Unlike creatinine, cystatin is not as influenced by muscle mass and diet (described later) and thus presents an opportunity to reduce interindividual variability in estimating GFR.

CKD-EPI cystatin C equation. Cystatin-based GFR equations have been developed and improved over the years.[48] The CKD-EPI cystatin C ($CKD\text{-}EPI_{Scys}$) equation (2012) is expressed as follows:[49]

$$GFR = 133 \times \min\left(\frac{Scys}{0.8}, 1\right)^{-0.499} \times \max\left(\frac{Scys}{0.8}, 1\right)^{-1.328} \times (0.996)^{Age} \times [0.932 \text{ if female}]$$

where Scys is serum cystatin C, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scys/κ or 1. [Correction added on 11 March 2022, after first online publication: In the above equation, "max" term was included with age component in error. This has been corrected in this version.]

This equation is as accurate as the 2009 CKD-EPI creatinine equation in estimating GFR but has the advantage that it does not require specification of race and may be more accurate in patients with decreased muscle mass. This could be a reasonable equation to consider during drug development if the drug candidate is known to inhibit MATE1, MATE2-K, OCT2/OCT3, or OAT2-mediated, tubular secretion of creatinine in the kidney. This would be equally important if the subjects in a trial (or in clinical practice) are consuming drugs that inhibit transporter-mediated tubular secretion of creatinine in the kidney.[19] In these situations, serum creatinine is higher when the patients are on these transporter inhibitors due to reduction in creatinine excretion, and as a result serum creatinine–based formulas could underestimate true GFR.

Serum creatinine–cystatin C–based equation

$CKD\text{-}EPI_{Scr\text{-}Scys}$ (combined formula). This formula was developed using data from 5,352 individuals (including data from 3,522 individuals for development and 1,830 individuals for internal validation). An additional data set from 1,119 individuals (five cohorts) was utilized for external validation.[49] This equation can be expressed as follows:

$$GFR = 135 \times \min\left(\frac{Scr}{k}, 1\right)^{\alpha} \times \max\left(\frac{Scr}{k}, 1\right)^{-0.601} \times \min\left(\frac{Scys}{0.8}, 1\right)^{-0.375} \times \max\left(\frac{Scys}{0.8}, 1\right)^{-0.711} \times (0.995)^{Age} \times [0.969 \text{ if female}] \; [\times 1.08 \text{ if black}]$$

where Scr is serum creatinine, Scys is serum cystatin C, κ is 0.7 for females and 0.9 for males, α is −0.248 for females and −0.207 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

This equation improved precision and was found to result in a better classification of patients to stages of CKD severity. Clinically, it is recommended in situations when creatinine-based GFR is thought to be less accurate (for instance muscle wasting or chronic illnesses) or to reconfirm CKD in case the estimates are < 60 mL/min/1.73 m^2 without albuminuria.[49]

Further validation of this equation and acceptance in clinic is a matter of current research and will be addressed in the future.

Comparison of performance of various equations

Michels and colleagues compared kidney function estimations based on C–G, MDRD, and CKD-EPI equations with a gold standard GFR measurement using ^{125}I-iothalamate, within strata of GFR, gender, age, body weight, and BMI.[42] Overall, the CKD-EPI equation had highest accuracy ($P < 0.01$ compared with C–G) and did not differ significantly from MDRD ($P = 0.14$). Notably, despite the correction factor for weight, the C–G equation overestimated GFR for obese and overweight individuals compared with individuals with normal body weight while MDRD and CKD-EPI equations demonstrated no bias in GFR estimation for the entire range (≤ 18.5 to ≥ 30 kg/m^2) of BMI tested. Similarly, the C–G equation overestimated GFR for individuals under the age of 59 and for women as compared with the MDRD and CKD-EPI equations. It should be noted that neither the MDRD nor the CKD-EPI equations have been validated in children, pregnant women, or in some racial or ethnic subgroups. Equations that combine both serum creatinine and cystatin have been proposed to improve accuracy.

Recent updates

Considering that race is a social and not a biologic factor, and that including race in equations ignores the diversity within and across racial groups, the National Kidney Foundation (NKF) and American Society of Nephrology (ASN) created a task force to reassess the inclusion of race in eGFR equations.[50,51] They tested the performance of several equations by race and recommended a refit of the $CKD\text{-}EPI_{Scr}$ and $CKD\text{-}EPI_{Scr\text{-}Scys}$ equation without the race variable (see **Table S1** for the actual equations). Both the equations consider racial diversity in the US population and yet don't have a race variable. The $CKD\text{-}EPI_{Scr}$ Refit equation appears to minimize bias as a function of race without compromising accuracy. Given that the high throughput method for analysis of creatinine is standardized and available across the United States, the NFK and ASN task force recommends immediate incorporation of this equation in all labs across the United States. The $CKD\ EPI_{Scr\text{-}Scys\_}$ Refit ($CKD\text{-}EPI_{Scr\text{-}Scys\_R}$) equation appears to have a higher accuracy, but the standardized cystatin assay is currently only available in some laboratories in the United States. If accumulating data supports its performance, $CKD\text{-}EPI_{Scr\text{-}Scys\_R}$ could become the preferred or the confirmatory equation in the United States in the future. It is unclear at this time the uptake of these two refitted equations in other parts of the world. Validation of these equations in other countries should be expected in the future. In any case, it could be prudent in some situations to confirm

creatinine-based GFR estimations with cystatin C in some individuals in clinical trials.

Equations for children

Similar to adults, GFR is the most common parameter utilized to estimate kidney function in children. The original Schwartz equation could be used to estimate GFR in infants and children as well as adolescents and was based on creatinine measurements in 77 children using the non–IDMS-traceable Jaffe method. In this equation, GFR is expressed as a function of height and serum creatinine[52] concentration along with a proportionality constant which varies as a function of age and sex. The original Schwartz equation can be expressed as follows:

$$\text{GFR} = \frac{k \times \text{height (cm)}}{\text{serum creatinine}\left(\frac{\text{mg}}{\text{dL}}\right)}$$

where GFR is in mL/min/1.73 m^2. k is varied as follows: 0.33 for infants (low birth weight < 1 year); 0.45 for term infants throughout the first year of life; 0.55 for children and adolescent girls; 0.7 for adolescent boys.

In 2006, Schwartz *et al*. sought to determine the accuracy of the original equation by comparing it with the gold standard plasma disappearance of iohexol.[53] The authors demonstrated that the equation correlated well with the gold standard ($r^2 > 0.9$) but overestimated GFR by 12.2 mL/min/1.73 m^2. Partly, the overestimation was attributed to the change in creatinine measurement methods. Therefore, multiple new equations were tested with IDMS-traceable creatinine measurements using the enzymatic assay. The bedside Schwartz equation was developed as an alternative and utilized the same parameters as the original Schwartz equation. It was developed using samples from 349 children (age: 1 to 16 years old).[54] The bedside Schwartz equation is expressed as follows:

$$\text{GFR} = \frac{0.413 \times \text{height (cm)}}{\text{serum creatinine}\left(\frac{\text{mg}}{\text{dL}}\right)}$$

In an accuracy comparison, it was found to have a P30 of 79%, where P30 denotes percentage of estimates within 30% of the gold standard measured value.

However, serum creatinine alone was not sufficient to accurately estimate GFR. Therefore, multiple new equations based on additional measurement of cystatin and/or blood urea nitrogen (BUN) were proposed. The most comprehensive equation was based on ~ 600 samples and proposed estimating GFR as a function of height, serum creatinine, cystatin C (measured using nephelometric method), BUN, and sex and is referred to as CKiD (Chronic Kidney Disease in Children) Schwartz.[55,56] This equation demonstrates improvement over creatinine-based equations with a P30 of 91% and a P10 of 45%.[56] Note that these equations were based on non–IFCC-standardized cystatin C measurements. In the future, additional correction factors may be required for IFCC-standardized cystatin C measurement.[57] CKiD Schwartz can be expressed as follows:

$$\text{GFR} = 39.8 \times \left[\frac{\text{ht}}{\text{Scr}}\right]^{0.456} \times \left[\frac{1.8}{\text{CysC}}\right]^{0.418} \times \left[\frac{30}{\text{BUN}}\right]^{0.079} \times [1.076]^{\text{Male}} \times [1.00]^{\text{Female}} \times \left[\frac{\text{ht}}{1.4}\right]^{0.179}$$

where GFR is in mL/min/1.73 m^2, BUN is blood urea nitrogen in mg/dL, CysC is cystatin in mg/L, ht is height in meters, and Scr is serum creatinine in mg/dL.

Another equation recommended for use in clinical practice is the "1B" equation,[2] which includes BUN along with serum creatinine but not cystatin and is presented below.

$$\text{eGFR} = 40.7 \times \left(\frac{\text{height}}{\text{Scr}}\right)^{0.64} \times \left(\frac{30}{\text{BUN}}\right)^{0.202}$$

Where eGFR is in mL/min/1.73 m^2, height is in meters, and SCr and BUN are in mg/dL.

Multiple studies with unique data sets for measured GFR in children have been conducted that compare the accuracy of different equations. The challenge with combining information from these individual studies is that not all equations are utilized in each study, thus providing pieces to the puzzle but leaving some gaps in the overall understanding. However, some general trends have been observed consistently. Equations that combine both serum creatinine and cystatin C typically outperform the equations based on creatinine alone or cystatin C alone. For example, Salvador *et al*. demonstrated that the CKiD Schwartz equation performed the best with a P10 of 48% and a P30 of 90% as compared with others.[58] Similarly, based on a data set of 81 children and measured GFR determination by iohexol clearance, Deng *et al*. demonstrated that the CKiD Schwartz equation performed best with a P15 of 62% and a P30 of 83%.[59] Ng *et al*. demonstrated based on a data set of 730 participants that the CKiD Schwartz equation not only estimates measured GFR with good accuracy but also demonstrates as strong or stronger association with CKD-related biomarkers than even measured GFR.[60]

In contrast, using iohexol and inulin clearance as a gold standard in 702 children, Leion *et al*. studied the diagnostic performance of 10 creatinine-based, 5 cystatin C–based, and 3 combined cystatin C–creatinine–based eGFR equations and compared them with the result of the average of 9 pairs of eGFR_cystatin C and eGFR_creatinine estimates.[61] The average of a suitable creatinine-based and a cystatin C–based equation generally displayed a better diagnostic performance than estimates obtained by equations using only one of these analytes or by complex equations using both analytes.

Formulas for evaluating GFR in adults and children are summarized in Supplementary Materials (**Table S1**).

FACTORS AND HEALTH CONDITIONS THAT INFLUENCE SERUM MARKERS FOR GFR ESTIMATION

Serum creatinine

There are several common factors such as diet, exercise, medications, race, etc. that may have a temporary but large impact on serum creatinine levels which can result in misleading GFR estimates. Also, there are some health conditions where the biomarker

or GFR equation used needs to be considered carefully. Many of these factors are not commonly known and accounted for in an appropriate manner:

Meat consumption. Consumption of a cooked meat meal (54 g protein, but not a nonmeat-based meal containing the same amount of protein) has been shown to cause a temporary increase in serum creatinine value and a drop in estimated GFR values to the extent of resulting misclassification of the kidney function stages of some study participants.[62,63] Different studies reported an increase in serum creatinine ranging from 10% to 30%. The impact was greater in individuals with higher degrees of kidney impairment. The serum creatinine increase with diet depends on the amount of meat consumed as cooking meat converts the creatine in meat into creatinine. For instance, a large cooked meat meal (225 g protein) was shown to cause an average of 52% increase in serum creatinine.[64] In various studies, the time to observing the maximum serum creatinine increase can vary up to 4 hours postprandial and probably varies due to the different gastrointestinal transit times of the participants. The effects of meat consumption on serum creatinine disappeared after 12 hours of fasting by the study participants.[62]

Physical exercise. Heavy exercise such as running a marathon can cause a temporary increase in serum creatinine and cystatin levels.[65,66] Around 40% increase in serum creatinine and 20% increase in cystatin levels were documented in recreational male marathon runners. Skeletal muscle breakdown as well as reduced blood flow to the kidneys could be the contributing factors. The impact of sports is more pronounced in amateur and untrained individuals.

Medications. In addition to passive filtration, creatinine is also actively secreted (estimate: 10–40%) from the proximal tubular cells of the kidney.[17,67] A consideration of the active secretion is important as some medications are known to inhibit the tubular secretion of creatinine, causing an increase in serum creatinine levels, and influence GFR estimation without actually influencing the GFR:[68] cephalosporins, aminoglycosides, flucytosine, cisplatin, cimetidine,[69,70] and trimethoprim.[69,70] A similar increase in serum creatinine due to an inhibition of kidney transporters such as MATE, OCT2/OCT3, and OAT2 has also been recently reported for some drugs indicated in the fields of oncology, for instance, abemaciclib and tyrosine kinase inhibitors imatinib, crizotinib, gefitinib, pazopanib, sorafenib, and sunitinib,[71] and HIV/AIDS.[17]

Race. Before the race-refitted equation proposals came out, some of the adult equations for estimating kidney function used a race variable.[72] The binary coding of Black or not Black was considered error-prone when using race as a coefficient for estimation of GFR. Further, the applicability of the coefficient for African American individuals to Black individuals in other parts of the world has been questioned. In fact, the use of the African American factor was found to result in GFR overestimation in European African individuals.[73] In the context of Africa, it has been discussed as to whether Black would refer to individuals from sub-Saharan Africa as much as those from North Africa.[72] Some studies showed that the use of the race coefficient for the sub-Saharan population did not improve the performance of creatinine-based GFR equations.[74] In fact, both the MDRD and CKD-EPI equations performed better without the race coefficient in participants with GFR ≥ 60 mL/min/1.73 m^2.[75] Another study from Democratic Repulic of the Congo showed that MDRD and CKD-EPI equations performed better without race correction and cystatin C–based equations improved performance.[76] A large collaborative work to improve estimation of GFR in sub-Saharan Africa is ongoing.[77] For patients with mixed ancestry (e.g., Latinx individuals), classification of race can also be very challenging.

Besides White and African American races, other races are not represented in some of the original GFR equations. However, different modifications have been suggested for the GFR equations in work done in different Asian countries.[78–82] Modifications exist for original MDRD, modified MDRD, and CKD-EPI equations. The Japanese Society of nephrology recommends a three-variable equation for assessing GFR (see **Table S1** for the actual equation).[83] It has some resemblance to the MDRD equation and uses the IDMS-standardized serum creatinine values.

The evaluation of the recently proposed race-refitted equations for adults in other parts of the world and also other races in the United States would help to better appreciate the wider applicability of the equations in clinical pharmacology.[50,51]

Cystic fibrosis. Accurate assessment of kidney function in patients with cystic fibrosis is vital for determining the appropriate dose of medications and for early detection of kidney disease. Cystatin C–based eGFR may be preferable due to reduced muscle mass and hence serum creatinine in patients with cystic fibrosis.[84]

Kidney transplantation. A reliable assessment of allograft function is crucial in kidney transplant management and for predicting clinical outcomes. Therefore, GFR measurement is critical for the follow-up of patients post kidney transplantation. The Nankivell equation is the only equation that is derived from 146 patients with kidney transplant and with repeat measurements.[85] However, as some of the transplant patients in this study were in an early post-transplant phase or with acute dysfunction, which may impact the prediction of GFR, this equation is not commonly used globally in the follow-up of kidney transplant patients. The MDRD, CKD-EPI, and C–G equations are commonly used for assessing kidney function in kidney transplant recipients.[2] A recent evaluation of the performance of all published creatinine-based GFR-estimating equations in a large and diverse population of solid-organ transplant recipients suggested that the CKD-EPI and MDRD equations were more accurate than other GFR-estimating equations in this population.[86]

Pregnancy. Kidney function is altered during pregnancy due to the dramatic hormonal and hemodynamic changes, and these changes must be accounted for when evaluating kidney function. The physiologic increase in GFR during pregnancy normally results

in a decrease in concentration of serum creatinine, which falls by an average of 0.4 mg/dL to a pregnancy range of 0.4 to 0.8 mg/dL.[87] Hence, a serum creatinine of 1.0 mg/dL, although normal in a nonpregnant individual, reflects kidney impairment in a pregnant woman. Consistent with its tendency to underestimate GFR when GFR is greater than 60 mL/min, the MDRD equation underestimates GFR in pregnant women with and without preeclampsia.[88,89] The CKD-EPI equation also appears to underestimate GFR to a similar degree as the MDRD equation in a study comparing both equations with 24-hour urine collections in preeclamptic patients. Additionally, no correlation was found in a prospective study comparing cystatin-C–based GFR calculations to inulin clearances at three timepoints in 12 pregnant patients.[90] Thus, 24-hour urine collection for calculation of creatinine clearance remains the preferred standard for estimating GFR in pregnant women.

Serum cystatin

Cystatin C levels are influenced by, besides kidney function, factors such as obesity, thyroid disorders, viral load in HIV patients, cancer, high dose steroid therapy, inflammation, and smoking.[91] Unlike serum creatinine, serum cystatin C level is less impacted by age,[92,93] sex,[93,94] muscle mass,[95] or dietary protein intake,[96] so serum cystatin C level is considered to be superior to serum creatinine for the diagnosis of early chronic kidney disease[21,49,97,98] when other factors that may influence serum cystatin C level are accounted for. Smoking status is one of these factors. In a meta-analysis with 8,592 individuals, it was found that cigarette smoking was associated with higher serum cystatin C levels after adjusting for creatinine clearance, indicating that smoking may impact cystatin C levels independent of its effect on kidney function.[99] Time-dependent change in serum cystatin C after smoking cessation was also observed in a study with 86 smokers.[100] Serum cystatin C decreased significantly at 3 months after smoking cessation and remained unchanged compared with the baseline serum cystatin C from 3 months to 1 year after smoking cessation, probably due to improvement of vascular function and increase in blood flow. Another factor that influences serum cystatin C level is obesity. In numerous clinical trials, it has been demonstrated that obesity either determined by BMI[101–103] or waist circumference[104] was independently associated with a high serum cystatin C level. A study with 2,583 subjects from the National Health and Nutrition Examination Survey 1999 to 2002 in the United States[102] indicated that high cystatin C level in subjects with high BMI is probably due to secretion of cystatin by enlarged adipose tissue.

POTENTIAL ALTERNATIVE KIDNEY FUNCTION CATEGORIZATION FOR DOSE RECOMMENDATION IN KIDNEY IMPAIRMENT

No matter which equation is utilized, a certain level of discordance exists between measured GFR (the gold standard) and eGFR. This discordance is the least for equations that utilize both serum creatinine and cystatin C to estimate GFR. However, despite using multiparametric models, less than 50% of eGFR values are within 10% of the measured GFR while 90% of eGFR values are within 30% of measured GFR. Given that the value of eGFR ranges from 15 mL/min/1.73 m^2 in subjects with severe kidney impairment to 89 mL/min/1.73 m^2 in subjects with mild kidney impairment, a variance of 30% is quite significant and can lead to mis-categorization of a significant number of subjects between mild vs. moderate or moderate vs. severe kidney impairment and specifically for values that are close to borderlines of a category. This can be a challenge during drug development as well as in adjusting doses of a drug for a patient with kidney impairment in clinics. For a long time, clinical pharmacologists have struggled with the question whether, for instance, a subject with an eGFR value of 59 mL/min/1.73 m^2 (upper limit of moderate renal impairment) should receive the same dose as a subject with an eGFR value of 31 mL/min/1.73 m^2 (lower limit of moderate renal impairment), but no good alternative frameworks exist.

KDIGO guidelines recommend that nephrologists approach kidney disease classification as well as prognosis with a composite of cause, GFR categories (index of kidney function in health and disease), and albuminuria categories (marker of kidney damage).[2,105] Independent of eGFR, albuminuria has been shown to be associated with cardiovascular and kidney events as well as cognitive decline in addition to overall mortality.[106–108] In line with the eGFR-based estimates, KDIGO guidelines agree that eGFR values < 30 mL/min/1.73 m^2 correspond with severe kidney impairment irrespective of the degree of albuminuria. However, they deviate from eGFR-based categorization for eGFR values ≥ 30 mL/min/1.73 m^2 as demonstrated in **Table 1**.

This eGFR and albuminuria-based categorization was developed by KDIGO based on correlation of these parameters with diagnosis and progression of CKD in subjects with various forms of kidney diseases and has been applied successfully by nephrologists for almost a decade. It is worthwhile testing whether this algorithm may serve as a better predictor of drug pharmacokinetics as well and thus provide a more nuanced and accurate framework for dose modifications of drugs whose exposure is impacted by kidney impairment.

DISCUSSION

Drug labeling guides adjustments of dosages for patients with impaired kidney function. Despite the availability of various endogenous and exogenous markers for evaluating kidney function, serum creatinine is the most convenient and commonly utilized marker. While there are several methods available for measuring serum creatinine, the Jaffe method and its modifications are by far the most commonly employed methodology due to low cost and fast turnaround despite having the potential of bias by the various chromogens in the sample. If a clinical study includes patients where chromogens such as glucose or bilirubin are expected to be elevated and variable due to the disease state, an enzymatic method can be utilized instead to provide a more accurate assessment of serum creatinine. However, the higher cost of utilizing an enzymatic approach during trials and in the clinic post approval would need to be justified on a case-by-case basis.

Introduction of IDMS traceable serum creatinine bioanalytical methodologies has immensely helped to reduce interlaboratory variability in measurement of serum creatinine. The advancements

Table 1 CKD classification

Definition of kidney function recommended by drug regulators during new drug development (range and description)	CKD classification and prognosis based on GFR and albuminuria categories groupings with similar relative risk from KDIGO guidance[2] (range and description)
eGFR ≥ 90 (Normal)	eGFR ≥ 60 & UA < 3 (Low risk)
90 > eGFR ≥ 60 (Mild impairment)	eGFR ≥ 60 & 3 ≤ UA ≤ 30 60 > eGFR ≥ 45 & UA < 3 (moderately increased risk)
60 > eGFR ≥ 30 (Moderate impairment)	eGFR ≥ 60 & UA ≥ 30 60 > eGFR ≥ 45 & 3 ≤ UA ≤ 30 45 > eGFR ≥ 30 & UA < 3 (high risk)
eGFR 30 > eGFR ≥ 15 (Severe impairment)	60 > eGFR ≥ 45 & UA ≥ 30 45 > eGFR ≥ 30 & UA ≥ 3 15 ≥ eGFR < 30 & any UA level (very high risk)
eGFR < 15 Kidney failure	eGFR < 15 & any UA level (very high risk)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate in mL/min/1.73 m^2; KDIGO, Kidney Disease Improving Global Outcome; UA, albuminuria in mg/mmol.

over the last several years in standardization and the availability of various bioanalytical methods for measuring serum creatinine are important to consider during clinical drug development. Although the IDMS-traceable serum creatinine measurement is the norm in most laboratories in the United States, that may not be true all over the world. A knowledge of the methodology would ensure that the most appropriate estimating equations are applied. For instance, use of the CKD-EPI formula with the non–IDMS-traceable serum creatinine concentrations would result in an underestimation of GFR.[28] On the other hand, use of IDMS-standardized serum creatinine values with the C–G formula or the original version of MDRD would overestimate GFR.

Besides not being designed for the IDMS-traceable serum creatinine methods that are commonly used today, the C–G formula is biased for common factors such as age, BMI, and sex as described previously. Therefore, we propose that this formula be retired entirely in new drug development. While this change cannot be addressed in the label of the drugs that were approved in the past, we propose that it should be an important consideration for drugs currently under development.

Currently, the CKD-EPI formula presents several advantages over other formulas for adults with impaired kidney function. While the MDRD equation demonstrates similar bias as the CKD-EPI formula, it is only recommended by the inventors of the equation to be used for eGFR < 60 mL/min/1.73 m^2. Therefore, CKD-EPI_{Scr} emerges as the formula with least bias, well suited for IDMS-traceable creatinine measurement and can be applied for the entire range of eGFR values (up to 120 mL/min/1.73 m^2). This is in line with KDIGO guidance recommending usage of CKD-EPI_{Scr} for estimation of kidney function in patients with any form of chronic kidney disease and should therefore be utilized both during clinical trials and post approval for consistent categorization and dose recommendations. However, if the lab measuring serum creatinine uses a non–IDMS-traceable methodology, it is important to use an alternate formula (for instance, original MDRD equation). There are other situations where CKD-EPI based on creatinine is not appropriate. For instance, if the drug under development or coadministered drug inhibits tubular secretion of creatinine (based on transporter interaction), an alternate formula based on another marker such as cystatin C would be appropriate in these circumstances. Also, in case of ailments with reduced muscle mass (for instance, cystic fibrosis), a cystatin C–based formula may be more appropriate. Hence, in line with the KDIGO guidance, in some instances it may be worthwhile to follow up the initial GFR estimation using CKD-EPI_{Scr} with estimation using CKD-EPI_{Scys} or CKD-$EPI_{Scr\text{-}Scys}$ or even measured GFR based on creatinine or an exogenous marker.

While formulas containing weight (e.g., C–G) were found to severely bias GFR estimation in obese/overweight patients, formulas indexed for body surface area (BSA) (CKD-EPI and MDRD) were also found to underestimate GFR.[41] Similarly, for patients with cancer, the most accurate GFR output was obtained with the CKD-EPI formula not indexed to BSA.[109] This is understandable as neither GFR nor the number of glomeruli change as a linear function of BSA. Given that the clearance of a drug via the kidneys is thought to be proportional to individual GFR (in mL/min), US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance recommends removing the BSA indexing from GFR estimates by multiplying the standardized GFR by the individual's BSA and dividing by 1.73.

As for adults, there are several formulas available for children. The original Schwartz equation is appropriate if the lab uses non–IDMS-traceable creatinine concentration measurement. For IDMS-traceable measurements, modified/bedside Schwartz is appropriate and has been one of the most commonly used formulas in recent years. There are other more recent options available such as the CKiD Schwartz equation incorporating creatinine, cystatin, and BUN or the 1B equation with creatinine and BUN. It should be noted that the GFR thresholds applied in adults would also apply in children above the age of 2 years.[2] Normal GFR in newborns is less than 60 mL/min/1.73 m^2. GFR keeps increasing during the first months of life. Hence, criteria of GFR < 60 mL/min/1.73 m^2 or duration > 3 months to define kidney disease doesn't quite apply. Age-appropriate values for GFR along with albuminuria ≥ 30 mg/24 hours and age-appropriate normal electrolyte values need to be considered.

Overall, it would be important to stay consistent within a drug development program but, importantly, to use a formula that is the most appropriate based on the bioanalytical method used by the lab. Presumably, that will be the IDMS-traceable methodology in central labs. However, if a local lab uses the non–IDMS-traceable method, appropriate formulas such as the original MDRD for adults or original Schwartz formula for children could be employed instead.

The current draft FDA guidance (2020) and final EMA guideline (2016) are quite similar in describing how pharmaceutical companies should develop dosing recommendations for patients with kidney impairment. There are no agency-specific requirements

for methodology of GFR assessment. The most recent draft FDA guidance considers the use of measured GFR (using an exogenous marker), measured CrCL, or any contemporary, widely accepted, and clinically applicable estimating equation for the population being studied as reasonable to assess kidney function in pharmacokinetics studies. The EMA guideline recommends the use of a method accurately measuring GFR using an exogenous marker to determine kidney function particularly for drugs with a narrow therapeutic index, and the use of estimation methods for other drugs. Given the lack of a regulatory recommendation for assessment of GFR, it is likely that pharmaceutical companies will continue to use their own preferred method for estimation of kidney function based on historical precedent at the organization. As described above, many of these methods have limitations and are inaccurate over the entire range of kidney function. Therefore, it is desired that future regulatory guidelines address the use of an updated GFR equation such as CKD-EPI.

Additionally, when dosing recommendation for patients with impairment of the kidneys is provided in the drug prescribing information, it is important to clearly identify the method used for assessing kidney function during the evaluation of the effect of kidney impairment on the drug. A review of 122 US prescription labels for drugs that were approved from 2018 to April 2021, and for which evaluation of the impact of kidney impairment was relevant, revealed that ~ 40% of the labels did not include the method of estimation of kidney function. Among those drugs where the method of assessing kidney function was listed, ~ 60% used the estimated CrCL derived from the C–G equation to assess kidney function. However, it is unclear whether non–IDMS-traceable creatinine measurements were utilized for the development of those drugs. Given the timing of their approval, it is reasonable to expect that many of them would have utilized IDMS-traceable creatinine measurement and therefore utilization of MDRD or CKD-EPI equations would be more appropriate. Since utilization of different equations during drug development vs. real-world experience can lead to mis-categorization of patients and consequently incorrect dose adjustments, we highly recommend that the regulators require description of the eGFR equation in the label.

Irrespective of the equation used in clinical trials, clinical pharmacologists and practitioners involved in clinical studies should pay attention to the potential artificial increase in serum creatinine levels that is caused by factors other than kidney disease such as diet and exercise (by amateurs and untrained individuals) or effect of administered medication(s) on kidney transporters. The effect of diet and exercise can be controlled by requesting study participants to abstain from cooked meat in the 12 hours prior and heavy exercise in the 24 hours prior to planned testing for serum creatinine. The equations without a race variable recently recommended by the NFK and ASN task force (CKD-EPI$_{Scr}$ Refit and CKD-EPI$_{Scr\text{-}Scys}$ Refit) can be expected to become the norm in clinical practice in the United States very shortly. An evaluation of their performance in other regions of the world can be expected in the future and would help to understand the choice of equation to be used during drug development in global clinical trials. However, knowledge gaps exist for special populations such as patients with kidney transplant or pregnancies that need to be addressed in future studies. It should be noted that this manuscript does not address compensating for changes in liver function due to kidney disease. The potential harm to patients with CKD for whom doses of prescription or over-the-counter drugs are not adequately adjusted due to incorrect classification to kidney impairment categories is beyond the scope of this manuscript but is an important associated topic. A summary of recommendations for GFR assessment during drug development is provided in **Table 2**.

Overall, given all the advancements and knowledge build-up described in this manuscript, there is a need to unify the approach toward characterizing kidney function and dosing recommendations in subjects with kidney impairment. One approach can be through recommending equations appropriate to the method of serum creatinine measurement to characterize kidney function in regulatory guidance and update all currently available labeling to indicate which equation should be used by the healthcare provider to inform dosing recommendation in patients with impairment of the kidneys. KDIGO guidelines propose chronic kidney disease prognosis utilizing GFR as well as albuminuria.[2] We propose to test whether utilizing GFR along with albuminuria could help reduce the variability in the

Table 2 Summary of recommendations for GFR assessment during drug development

Choose clinical labs that use IDMS-traceable assay to measure creatinine. If a lab is chosen that uses non–IDMS-traceable creatinine assay, capture this information in the database.
If IDMS-traceable creatinine assay is utilized, use CKD-EPI equation for adults and one of the appropriate equations for children (bedside Schwartz or Schwartz-CKiD or 1B). If non–IDMS-traceable creatinine assay is utilized, use appropriate equation (original MDRD equation for adults or original Schwartz equation for children).
If dealing with patients where level of non-creatinine chromogen in serum can interfere with creatinine assay (e.g., diabetes or cirrhosis), consider using enzymatic creatinine assay.
Ensure that the final drug label clearly states which equation was used for assessing kidney functioning during drug development.
Remove BSA indexing from the GFR equations.
In phase I trials, study participants should be requested to abstain from cooked meat in the 12 hours prior and heavy exercise in the 24 hours prior to planned testing.
Be aware of comedication usage by study participants that can block the active secretion of creatinine via the kidneys and bias GFR assessment.

BSA, body surface area; CKD-EPI, Chronic Kidney Disease Epidemiology collaboration; CKiD, Chronic Kidney Disease in Children; GFR, glomerular filtration rate; IDMS, isotope dilution mass spectrometry; MDRD, Modification of Diet in Renal Disease; 1B equation, includes BUN (blood urea nitrogen) along with serum creatinine but not cystatin C.

relationship between drug pharmacokinetics and kidney function in comparison with the current paradigm of utilizing GFR alone for kidney function categorization. Note that KDIGO-based categorization was designed to predict CKD classification and prognosis which overlaps with but is distinct from kidney function assessment and its impact on drug pharmacokinetics to aid dose recommendations. Therefore, significant research with large data sets is required to evaluate whether the paradigm recommended by KDIGO for predicting CKD prognosis can also be applied toward creating a better prediction of drug pharmacokinetics than the current GFR-based approach. If successful, this can help minimize mis-categorization of patients with impairment of the kidneys and thus provide a better risk–benefit profile for this underserved special population.

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