Measurement and Estimation of GFR for Use in Clinical Practice: Core Curriculum 2021

Introduction

Glomerular filtration rate (GFR) is used to diagnose, stage, and manage chronic kidney disease (CKD); ascertain the prognosis for CKD-related events and mortality; and determine drug dosages. Assessment of GFR is thus central to medical practice, research, and public health (Table 1). Methods tomeasureGFR are laborious, expensive, and not broadly available, and are therefore not appropriate as first-line diagnostic tools. Estimated GFR (eGFR), based on the concentration of endogenous substances, particularly creatinine, is widely available and appropriate for use as a firstline tool, but has limitations that should be considered in its interpretation. Current clinical practice guidelines recommend eGFR rather than blood concentrations of creatinine or serum cystatin C and recommend eGFR based on creatinine (eGFRcr) in most circumstances and eGFR based on cystatin C (eGFRcys) or measured GFR (mGFR) when greater accuracy is required. In this installment of AJKD's Core Curriculum in Nephrology, we provide nephrologists, other health care professionals, researchers, and others with the physiologic rationale and evidence base for GFR assessment, as well as its limitations, to allow rational and judicious use of the tools available.

Table 1. Key Examples for the Importance of GFR to Clinical Practice, Research, and Health Policy

Clinical Decision	Current level of GFR	Change in level of GFR
Diagnosis	• Detection of CKD • Evaluation for kidney donation	• Detection of AKI and AKD • Detection of CKD progression
Prognosis	• Risk of CKD complications and CVD • Risk for CKD progression • Risk for medical errors • Risk for perioperative complications • Risk for mortality	• Risk for kidney failure
Treatment	• Referral to nephrologists • Referral for kidney transplantation • Placement of dialysis access • Dosage and monitoring for medications cleared by the kidney • Determine safety of diagnostic tests or procedures • Eligibility for clinical trials	• Treatment of AKI • Monitoring drug toxicity

Measurement of GFR

The kidneys play several roles in the body, including metabolism and excretion of substances, volume and blood pressure regulation, erythropoietin production, and regulation of acid-base and bone and mineral homeostasis. Assessment of the overall function of the kidney is a complex task. Glomerular filtration is one of many functions of the kidney. GFR is considered the best overall assessment of these functions, and, in general, loss of these other functions correlates with decreased GFR (Box 1).

The normal value for GFR in healthy young adults varies by study, with reported ranges from approximately 100 to 125 mL/min per 1.73 m2 of body surface area (BSA). GFR is known to vary according to hemodynamics, sympathetic tone, diet, time of the day, exercise, body size, pregnancy, and drugs. Even in stable conditions, within-person variability of mGFR is common and likely to contribute to random measurement error in GFR assessment. GFR is indexed by BSA because kidney size is proportional to body size and allows for comparisons of an individual's GFR versus normative values.

GFR is the rate at which the glomerulus filters plasma to produce an ultrafiltrate. Because GFR cannot be measured directly in humans, it is not possible to know "true" GFR with certainty. GFR is measured using clearance of an ideal exogenous substance and is defined as the volume cleared of that substance per time. An ideal filtration marker should be excreted by the kidneys , not be protein-bound, and not be secreted or reabsorbed in the tubules.

Urinary clearance of inulin was described by Homer Smith in 1935, and it is still the gold standard for GFR measurement. It requires a continuous infusion of inulin, bladder catheterization, and timed serum and urine collections. Inulin is considered the only true ideal filtration marker but is hard to maintain in solution, and complex assays are required. Because of the complexity of the inulin-based protocol, it is not widely used.

In the United States, the 2 most common alternative methods used are urinary clearance of iothalamate and plasma clearance of iohexol, as both markers satisfy the criteria of exogenous filtration markers, have reliable assays and high correlations with inulin clearance, and are available. Urinary clearance is performed by subcutaneous injection of the exogenous marker and waiting 45-60 minutes to obtain equilibrium, followed by blood sample collection surrounding each urinary clearance period (Fig 1). In clinical practice, 1 or 2 urinary clearance

Box 1. Use of GFR as the Overall Assessment of Kidney Function

• GFR is the best overall index of kidney function in health and disease

> Direct measure of kidney function

> GFR decrease is correlated with decrease in other kidney functions, such as tubular reabsorption and secretion and endocrine and metabolic functions, and therefore associated with many physiologic and clinical consequences, including biochemical complications and uremic symptoms

> In CKD, reduced GFR correlates with extent of pathologic findings

> Reduced before onset of symptoms > Low GFR is defined as kidney failure

• Pitfalls

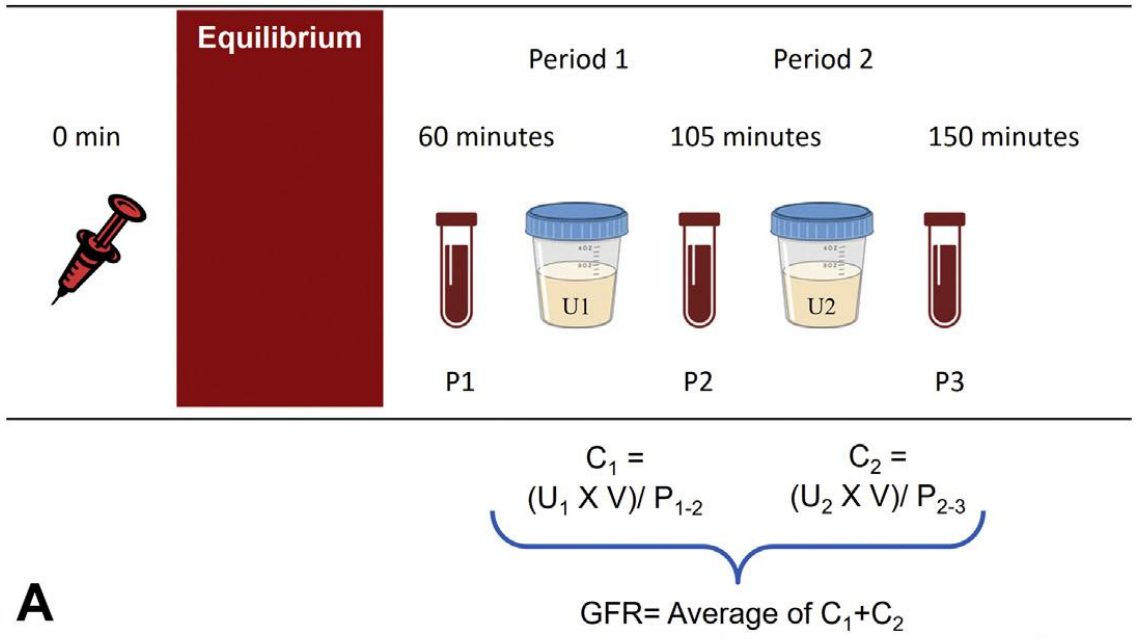
> GFR is not the only kidney function > Measurements are difficult to perform

> Estimates can be biased and imprecise compared to measured GFR

> GFR can be relatively insensitive for detection of early kidney disease and monitoring progression

Urinary retention limits urinary clearance. This can be overcome to some extent by bladder ultrasound or additional clearance periods to ensure all urine is excreted. Plasma clearance is assessed by intravenous injection of the exogenous marker, followed by repeated blood sampling. The clearance is computed from the ratio of the injected amount of iohexol to the area under the disappearance curve (Fig 1). An advantage of the measurement of plasma clearances is that it does not require urinary collection, which is critical in populations in which bladder emptying may be impaired, such as elderly persons or children with urinary tract abnormalities. The main limitation is the need for late samples in patients with low levels of GFR.

All methods are associated with systematic or random error. Sources of error include the clearance method itself, the nonideal behavior of the exogenous filtration marker used, and the assays themselves. The overall magnitude of errors is less than the error in currently available eGFR, as we will discuss below, and mGFR remains a key component of assessment of GFR. Nevertheless, these considerations have implications as we anticipate GFR being measured in greater frequency given the increased emphasis on confirmatory tests for the firstline eGFR cr


Equilibrium
Period 1
Period 2
0 min
60 minutes
105 minutes
150 minutes
U1
U2
P1
P2
P3
C_1 = $(U_1 X V)/ P_{1-2}$
C_2 = $(U_2 X V)/ P_{2-3}$
GFR= Average of C_1+C_2
A

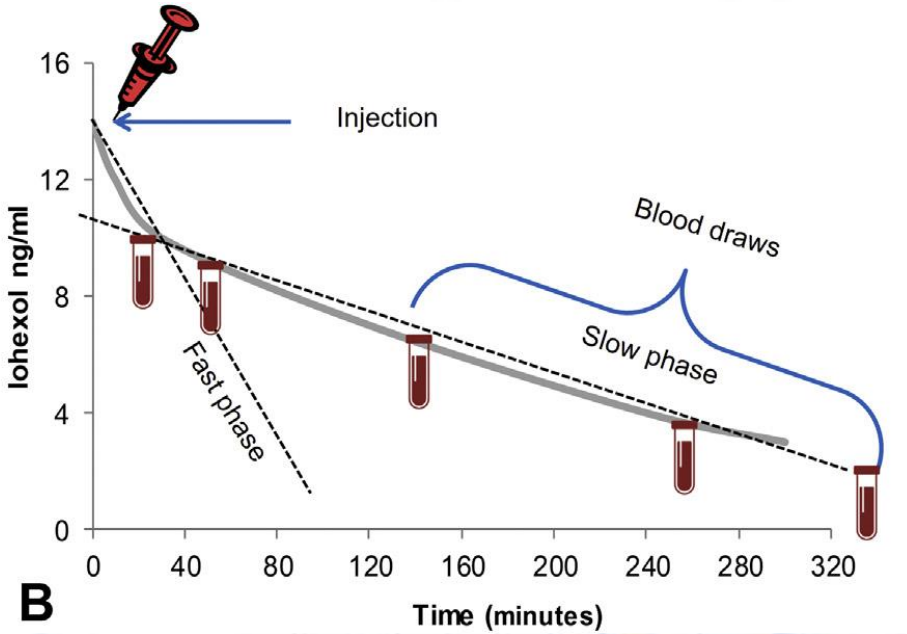
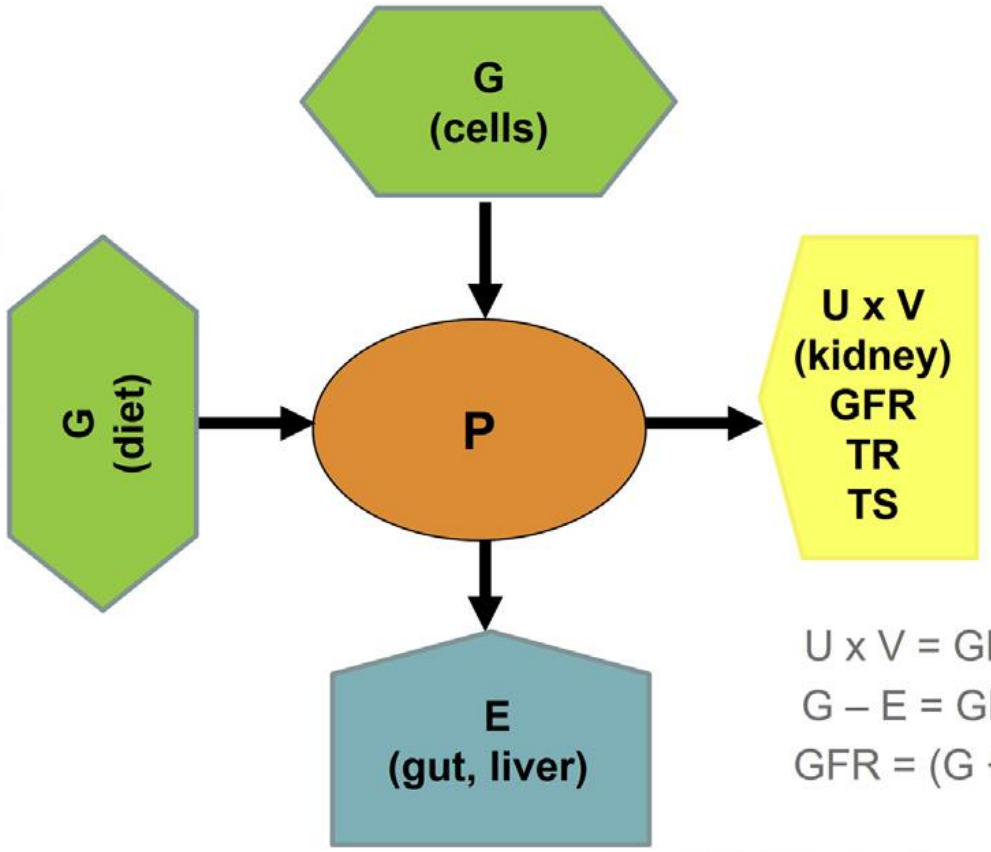

Injection
Blood draws
Slow phase
Fast phase
Iohexol ng/ml
16
12
8
4
0
0
40
80
120
160
200
240
280
320
Time (minutes)
B

Figure 1. Scheme for urinary and plasma clearance. (A) Urinary clearance is usually performed using subcutaneous injection of an exogenous filtration marker to allow for slow release of the marker into the circulation, providing more constant plasma levels than with an intravenous bolus. In clinical practice, 1 or 2 urinary clearance periods are used, and, in research, 3 clearance periods are most commonly used. Each period can range from 30 to 60 minutes depending on urine flow. In research studies, we aim for urine flow of 3 mL/min. Water intake is encouraged to allow for urine flow. Plasma blood samples are ideally collected within 5 minutes of void. The plasma levels are log transformed and then averaged. The syringe represents the injection of the exogenous filtration marker. The red tube represents the blood draw, and the container represents the urine collection. (B) Plasma clearance is computed as the ratio of the injected amount of exogenous filtration maker to the area under the disappearance curve. The total area is the sum of the fast decay due to distribution from the blood space, and the slow decay is related to renal clearance from filtration or tubular secretion. Early blood samples, usually taken at 10 and 30 minutes, are required to compute the fast phase. At least 2 blood samples taken at 120 minutes or later, most commonly at 120 and 240 minutes, are required to compute the slow phase. In patients with a moderate glomerular filtration rate (GFR), we obtain a sample at 300 minutes. In patients with a very low GFR, we obtain a sample at 24 hours. Blood samples can be drawn at other times as long as accurate times are recorded and used in calculation. The ideal method uses both phases for computation of plasma clearance using the 2-compartment model. The 1-compartment model requires samples from only the slow phase. With the use of a mathematical correction for the fast phase, the 1-compartment model has been shown to be an accurate estimate of the 2-compartment models and is used in clinical practice and research studies. The solid gray line represents the exogenous filtration maker plasma concentration levels over time, and the dashed black lines represent the fast and slow decay curves. The Chronic Kidney Disease Epidemiology Collaboration website (https://www.tuftsmedicalcenter.org/Research-Clinical-Trials/Institutes-Centers-Labs/Chronic-Kidney-Disease-Epidemiology-Collaboration/Overview) details the protocol used in our practice.

Estimating GFR From the Serum Concentration of Endogenous Markers

GFR is most commonly estimated based on blood concentration of an endogenous filtration marker. The level of any endogenous filtration marker is determined by GFR and physiologic processes other than GFR, referred to as non-GFR determinants, which include generation, tubular secretion or reabsorption, and extrarenal elimination (Fig 2). These physiological processes cannot be easily measured. Estimating equations include demographic and clinical variables as surrogates of the combined impact of all of the non-GFR determinants. Incorporation of clinical and demographic factors to explain the variation of endogenous filtration markers that is unrelated to GFR leads to GFR estimates that are more accurate than the blood concentrations of endogenous filtration markers alone. GFR estimates are also more useful because they are expressed on the GFR scale. For these reasons, clinical laboratories have automatically reported eGFR whenever the filtration marker is ordered. However, GFR estimating equations are not without limitations. In capturing the relationship between a marker and its non-GFR determinants, surrogates can reflect only average values; this relationship varies among individual people even when they have the same characteristics. Appreciation of these limitations and how to proceed with identification of the appropriate confirmatory test is central for optimal assessment of GFR

The most common endogenous filtration marker is creatinine. Freely filtered by the glomerulus, creatinine is subject to extrarenal elimination by the gastrointestinal tract, is secreted by the renal tubules, and is generated from muscle mass or diet, primarily from animal protein intake (Table 2). The 2012 KDIGO (Kidney Disease: Improving Global Outcomes) CKD guideline recommends eGFR cr to be the initial form of assessment in adults because it is inexpensive and the simplest, most widely available method worldwide, allowing prediction of GFR with satisfactory bias and accuracy in “normal” conditions (ie, conditions in which the non-GFR determinants of creatinine are not expected to be particularly relevant). The KDIGO work group reviewed the evidence for available creatinine-based GFR estimating equations and recommended the 2009 CKD-EPI creatinine equation for adults and the CKiD (CKD in Children) equation for children (Table 3).



$$U \times V = GFR \times P - TR + TS$$

$$G - E = GFR \times P - TR + TS$$

$$GFR = (G + TR - TS - E) / P$$

Figure 2. Relationship of plasma levels of endogenous filtration markers with glomerular filtration rate (GFR). In the steady state, a constant plasma concentration (P, in mg/min) of the filtration marker is maintained because generation (G, in mg/min) is equal to the sum of urinary excretion (UV, in mg/min) and extrarenal elimination (E, in mg/min). Thus, GFR is related to the reciprocal of the plasma concentration of the marker (P), but it is also influenced by its non-GFR determinants (generation [G], tubular secretion [TS], tubular reabsorption [TR], and extrarenal elimination [E]). If the non-GFR determinants are known, the GFR can be estimated from the plasma concentration. In the nonsteady state, the rate and direction of change in the level of the filtration marker and estimated GFR (eGFR) are also affected by the magnitude of change in GFR and the volume of distribution of the filtration marker. Hence, the eGFR reflects the magnitude and direction of the change in GFR but does not accurately reflect the level of GFR. After a decrease in GFR, the decrease in eGFR is less than the decrease in GFR, and eGFR thus exceeds GFR. Conversely, after an increase in GFR, the increase in eGFR is less than the increase in GFR, and eGFR is thus lower than GFR. As the plasma level approaches the new steady state, the eGFR approaches the GFR, allowing more accurate estimation of GFR.

Note creatinine can be measured in serum or plasma (depicted here as plasma for illustratrion purposes only). Adapted with permission from Levey et al, 2014 (Am J Kidney Dis. https://doi.org/10.1053/j.ajkd.2013.12.006). Original graphic ©2014 National Kidney Foundation.

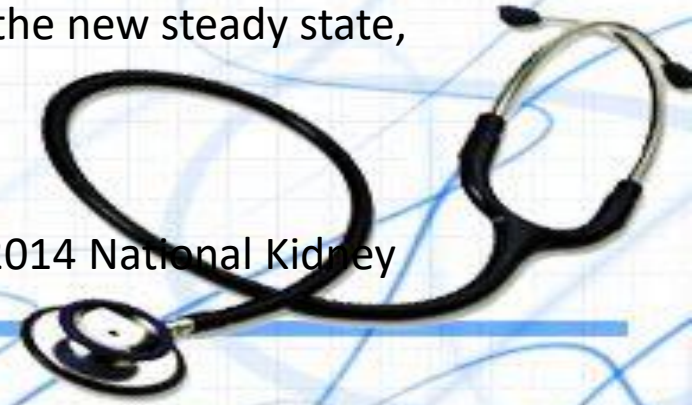


Table 2. Clinical Conditions in Which the Non-GFR Determinants of Selected Filtration Markers May Be Influential on the Reported eGFR

Non-GFR determinant	Creatinine	Cystatin C
Generation		
Body composition	Extremes of muscle mass (amputation, muscle wasting disease, body builders)	Obesity
Health state	Chronic severe illness; frailty	Inflammation; thyroid; smoking
Diet	High protein or creatine supplements; vegetarian diet	Not known, but thought to be minimal
Tubular handling		
Drugs	Cimetidine, trimethoprim, fenofibrate, dolutegravir, tyrosine kinase inhibitors	Steroids; others, not well understood
Other	Low GFR	–
Increased extrakidney elimination	Antibiotics, low eGFR	Not known
Nonsteady state	AKI, dialysis, edematous state	AKI, dialysis, edematous state

Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate.

The recommendation was made for the CKD-EPI equation to replace the commonly used MDRD Study equation based on evidence that the former is more accurate across the range of GFR and in key subgroups and better predicted adverse events. The work group recognized that other more accurate equations might be developed in the future and therefore recommended consideration of those when available.

Since the publication of the CKD-EPI equation, several new equations have been published (Table S1). For example, a recent equation was developed by the European Kidney Function Consortium (EKFC) that allows accurate estimation of GFR in adults and children using a single equation, which is a worthy goal. The EKFC equation was developed for use only in White individuals and therefore lacks representation of the diversity of the US population, in particular individuals of races/ethnicities that are associated with high risk for CKD. Regardless of the specific equation, the accuracy of eGFRcr is limited by variation in GFR determinants of serum creatinine that are not captured by the demographic and clinical variables. Table 2 lists selected clinical scenarios that might lead to bias or imprecision in eGFRcr.

Cystatin C is an alternative endogenous filtration marker that appears to be less influenced by non-GFR determinants than creatinine in ambulatory patients. It is freely filtered at the glomerulus, is catabolized in the tubules with reabsorption of its metabolites, and undergoes extrarenal elimination to some extent. Cystatin C is not excreted in the urine, and it is therefore hard to assess its non-GFR determinants, but less direct evidence shows that non-GFR determinants of cystatin C include inflammation, smoking, thyroid abnormalities, and fat mass (Table 2). Table 3 shows the KDIGO-recommended CKD-EPI GFR estimating equations based on cystatin C (ie, eGFRcys) and creatinine and cystatin C (ie, eGFRcr-cys), and Table S1 shows equations developed by other research groups. Regardless of the specific cystatin C or creatinine/cystatin C equation, studies show that eGFRcys is not more accurate than eGFR cr, but eGFRcr-cys is more accurate than either alone (Fig 3).

Despite the increased precision of eGFRcr-cys, it is not without limitations. eGFR cr-cys does not meet the requirement for a true confirmatory test because it is not independent from eGFRcr. Because there are only 2 markers, it not always obvious how to interpret discrepancies between eGFR cr and eGFRcys. Although the interpretation is sometimes straightforward (eg, for otherwise healthy amputees, eGFRcr but not eGFRcys overestimates mGFR), because factors associated with non-GFR determinants of cystatin C are less well known, the interpretation is less clear in many other circumstances. Data show that, for children and patients with cystic fibrosis or muscle-wasting diseases, there is variation in the relative performance of eGFRcr versus eGFRcys. Indeed, in patients with severe HIV or heart or liver failure, both eGFRcr and eGFR cys lead to large errors compared with mGFR. There is ongoing research on other novel endogenous markers, which are not yet integrated into practice and not further discussed in this article, but that might address these limitations as well as present the path forward for GFR across the age spectrum.

Wise users of eGFR cr know when to rely on it alone or when to incorporate other sources of information. For clinical circumstances in which there is a concern that eGFR cr may be less accurate, it is recommended to perform a second-line or confirmatory test, either the clearance tests discussed above or eGFR cys or eGFRcr-cys (Fig 4).

Table 3. Equations Estimating mGFR from Endogenous Filtration Markers With Large Representation of North Americans

Age	Marker	Reference Method	Standardized Assay	Derivation Study Characteristics	Equation	Comment
Creatinine ($eGFR_{cr}$)						
Adult	Cockcroft-Gault (1976)[a]	mCL_{cr}	No	249 men; 0% Black participants (presumed)	(140 − age × weight)/(72 × Scr) × 0.85 if female	Underestimates mCL_{cr} in older age, obesity, and edematous states
Adult	MDRD Study (2006)[b]	Urinary iothalamate	Yes	983 men/645 women; mGFR 40 mL/min/1.73 m^2; age 50.6 y; 12% Black participants	$175 \times Scr^{-1.154} \times age^{-0.203} \times 0.745$ if female × 1.212 if Black	Underestimates mGFR in high-normal GFR values
Adult	CKD-EPI $eGFR_{cr}$ (2009)[c]	Urinary iothalamate, other mGFR	Yes	4,648 men/3,606 women; mGFR 68 mL/min/1.73 m^2; age 47 y; 30% Black participants	$141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{age}$ × 1.018 if female × 1.159 if Black | α = −0.329 (female); −0.411 (male); κ = 0.7 (female); κ = 0.9 (male)	Unbiased across range of GFR; recommended in adults
Pediatric	CKiD Schwartz "bedside" (2009)[d]	Plasma clearance of iohexol	Yes	213 boys/136 girls; mGFR 41 mL/min/1.73 m^2; age 10.8 y; 15% Black participants	0.413 × (height in cm/Scr)	Iohexol measurements have since been recalibrated
Pediatric and young adult (age 18-26 y)	Average of CKiD (2009) and CKD-EPI (2009)[e]	Per CKiD 2009 and CKD-EPI 2009 equations			–	Improves eGFR accuracy in young adults; iohexol measurements have since been recalibrated
Pediatric and young adult	CKiD $eGFR_{cr}$ U25 (2021)[f]	Plasma clearance of iohexol	Yes	387 boys/231 girls; mGFR 48 mL/min/1.73 m^2; age 13 y; 7% Black participants	K × height/Scr | K for males 1-11 y, $39 \times 1.008^{(age-12)}$; 12-17 y, $39 \times 1.045^{(age-12)}$; 18-25 y, 50.8; K for females: 1-11 y, $36.1 \times 1.008^{(age-12)}$; 12-17 y, $39 \times 1.023^{(age-12)}$; 18-25 y, 41.4	Improves performance vs CKiD "bedside," especially for age <5 and >18 y
Cystatin C ($eGFR_{cys}$)						
Adult	CKD-EPI $eGFR_{cys}$ (2012)[g]	Urinary iothalamate	Yes	3,107 men/2,245 women; mGFR 68 mL/min/1.73 m^2; age 47 y; 33% Black participants	$133 \times \min(Scys/0.8, 1)^{-0.499} \times \max(Scys/0.8, 1)^{-1.328} \times 0.996^{age}$ × 0.932 if female	Similar performance to CKD-EPI $eGFR_{cr}$ but decreased impact of age, sex, and race
Pediatric	CKiD Cys (Schwartz "bedside" cystatin C; 2012)[h]	Plasma clearance of iohexol	No	389 boys/254 girls; mGFR 43 mL/min/1.73 m^2	$70.69 \times S_{cys}^{0.931}$	Iohexol measurements have since been recalibrated; cystatin C assay not standardized
Pediatric and young adult	CKiD $eGFR_{cys}$ U25 (2021)[f]	Plasma clearance of iohexol	Yes	387 boys/231 girls; mGFR 48 mL/min/1.73 m^2; age 13 y; 7% Black participants	K × 1/Scys | K for males 1-14 y, $87.2 \times 1.011^{(age-15)}$; 15-17 y, $87.2 \times 0.960^{(age-15)}$; 18-25 y, 77.1; K for females: 1-11 y, $79.9 \times 1.004^{(age-12)}$; 12-17 y, $79.9 \times 0.974^{(age-12)}$; 18-25 y, 68.3	Improves performance vs CKiD "bedside," especially for age <5 and >18 y

(Continued)

Table 3 (Cont'd). Equations Estimating mGFR from Endogenous Filtration Markers With Large Representation of North Americans

Age	Marker	Reference Method	Standardized Assay	Derivation Study Characteristics	Equation	Comment
Creatinine and cystatin C ($eGFR_{cr\text{-}cys}$)						
Adult	CKD-EPI $eGFR_{cr\text{-}cys}$ (2012)[g]	Urinary iothalamate	Yes	3,107 men/2,245 women; mGFR 68 mL/min/1.73 m^2; age 47 y; 33% Black participants	$135 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-0.601} \times \min(Scys/0.8, 1)^{-0.375} \times \max(Scys/0.8, 1)^{-0.711} \times 0.995^{age} \times 0.969$ if female $\times 1.08$ if Black | $\alpha = -0.248$ (female); -0.207 (male); $\kappa = 0.7$ (female); $\kappa = 0.9$ (male)	Improved precision and accuracy vs CKD-EPI $eGFR_{cr}$ and $eGFR_{cys}$; recommended in adults as confirmatory test
Pediatric	CKiD $eGFR_{cr\text{-}cys}$ (2012)[h]	Plasma clearance of iohexol	No	389 boys/254 girls; mGFR 43 mL/min/1.73 m^2	$39.8 \times (height/Scr)^{0.456} \times (1.8/Scys)^{0.418} \times (30/SUN)^{0.079} \times (1.076^{male}) \times (height\ in\ m/1.4)^{0.179}$	Iohexol measurements have since been recalibrated; cystatin C assay not standardized

Race and Ethnicity and GFR Estimation

The MDRD Study and the CKD-EPI creatinine and creatinine/cystatin C equations require specification of race group as defined by Black versus non-Black individuals. The inclusion of the term is based on the empirical observation that Black participants in the MDRD Study had higher levels of serum creatinine for the same level of GFR compared with non-Black participants. The resulting association was confirmed in the African American Study of Kidney Disease and in other populations. This finding was thought to reflect biological differences related to non-GFR determinants of serum creatinine, such as tubular secretion or creatinine generation. In addition, empirical support for differences in non-GFR determinants of serum creatinine, one study in hemodialysis patients showed that Black patients had higher levels of serum creatinine even after adjustment for nutritional variables (albumin, phosphorus, glucose, predialysis urea, transferrin), weight, and reactance and resistance by bioelectrical impedance. More recent studies have demonstrated increased levels of serum creatinine with greater proportion of genetic African ancestry. However, the cause of the higher serum creatinine in the Black individuals for the same level of measured GFR remains not well understood.

Recently, important concerns have been raised with the use of a term for Black race in GFR estimation. First, race is not a reliable proxy for genetic or biological differences, and, as such, its definition lacks precision and is dynamic over time and across geography. Second, some are concerned that its use may lead to disparities in medical care. Given these concerns, there is an increasing call for the elimination of the term for Black race when using eGFRcr or eGFRcr-cys. Its removal would lead to lower eGFR in some patients who self-identify as Black, especially at higher levels of GFR. For example, if a 60-year-old man had a creatinine level of 1.0 mg/dL, he would have a GFRcr of 94 mL/min/1.73 m2 if he self-identified as Black and a GFR cr of 81 mL/min/ 1.73 m2 if he self-identified as White. Those who have called for its elimination cite the possible benefit that a lower eGFR leads to improved care, as, for example, earlier care for CKD and earlier kidney transplant evaluations. However, others are concerned that lower eGFR could decrease the use of medications such as metformin, SGLT2 inhibitors, and chemotherapy drugs, could have an impact on life or disability
insurance, and decrease acceptance of kidney donor candidates.

we recommend continued use of CKD-EPI $eGFR_{cr}$ as the first-line test with full disclosure of the use of race in GFR estimation and the use of $eGFR_{cys}$ as an alternative first-line test for patients who wish not to disclose race or in whom race is mixed or not known. We anticipate the task force's recommendations to be available in 2021.

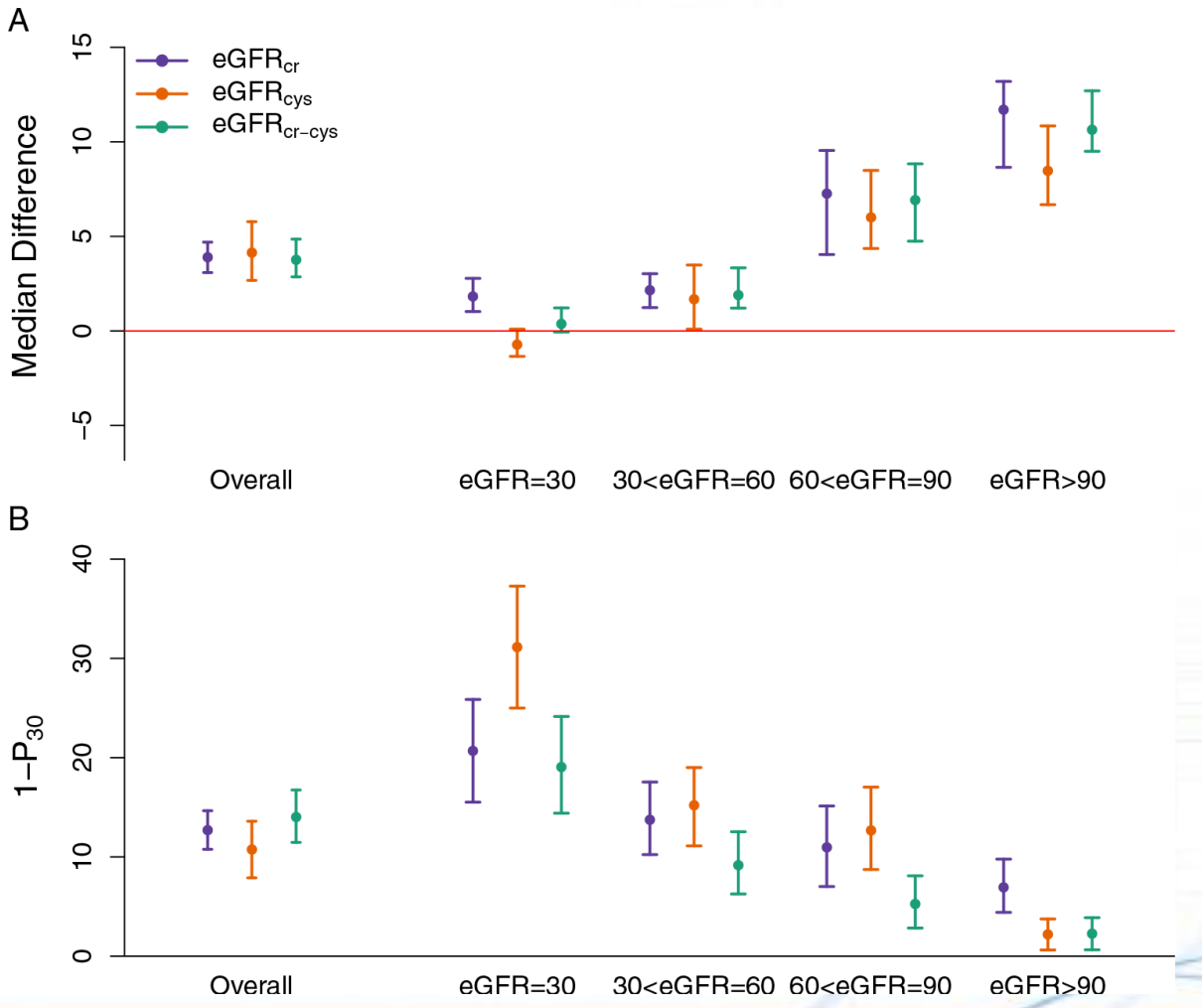
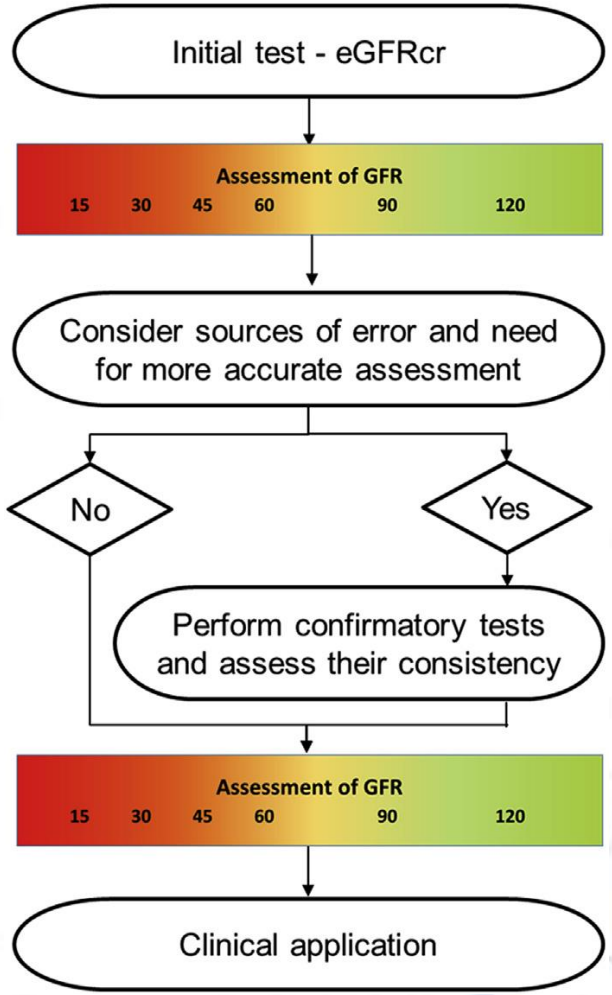

A
Median Difference
15
10
5
0
−5
eGFR$_{cr}$
eGFR$_{cys}$
eGFR$_{cr-cys}$
Overall
eGFR=30
30<eGFR=60
60<eGFR=90
eGFR>90
B
1−P$_{30}$
40
30
20
10
0
Overall
eGFR=30
30<eGFR=60
60<eGFR=90
eGFR>90

Figure 3. Estimated glomerular filtration rate (eGFR) from creatinine (eGFRcr), from cystatin C (eGFRcys), and from a combination of creatinine and cystatin C (eGFRcr-cys) compared with measured GFR (mGFR). (A) Median difference between mGFR and eGFR. The bias is similar with the equation using creatinine alone, the equation using cystatin C alone, and the combined creatinine–cystatin C equation. (B) Accuracy of the 3 equations with respect to the percentage of estimates that were >30% of the mGFR (1 – P30). I-bars indicate 95% CIs. Adapted with permission from Inker et al, 2012 (N Engl J Med. https://doi.org/10.1056/nejmoa1114248). Original graphic ©2011 Massachusetts Medical Society


Initial test - eGFRcr
Assessment of GFR
15 30 45 60 90 120
Consider sources of error and need for more accurate assessment
No
Yes
Perform confirmatory tests and assess their consistency
Assessment of GFR
15 30 45 60 90 120
Clinical application

Clinical Applications of Confirmatory Tests for GFR Evaluation

The challenge is to identify which patients require a confirmatory test. In Fig 4, we present an algorithm to assist in determining when a confirmatory test for eGFRcr could be considered. For some, this would be an indication for referral to a nephrologist.

When cystatin C was first discussed as a possible alternative to creatinine almost 2 decades ago, many thought it could be used to replace creatinine in settings in which muscle mass was known to be significantly reduced, such as in critically ill patients. As discussed earlier in this article, it is now known that cystatin C too has non-GFR determinants that might vary across health and disease. Indeed, data show that children, those with cystic fibrosis or muscle-wasting diseases, and liver transplant recipients show variation in the relative performance of eGFRcr versus eGFR cys, suggesting that eGFRcys cannot be used automatically in these settings.

In hospitalized patients, we recommend 24-hour urine collection for measurement of creatinine, urea, and albuminuria, as an observed 24-hour urine collection is less prone to error than collections performed in ambulatory patients. Thus, the best answer to question 5 is (d).

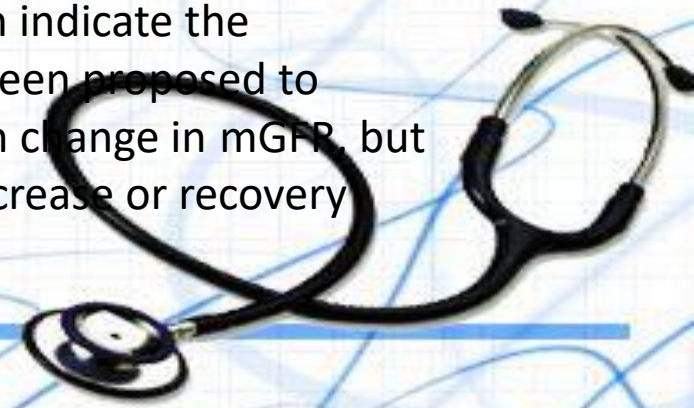
Changes in Body Composition Over Time

Extremes of body composition are conditions associated with lower accuracy of eGFR as a result of differential volume distribution and creatinine and cystatin C generation and because the equations were not developed in populations representative of the extremes of body composition. Few studies have evaluated the performance of eGFR cr and eGFRcys in persons with obesity, with conflicting results. In some, the Cockcroft-Gault equation overestimated GFR (because the formula includes weight) and the MDRD Study and CKD-EPI eGFRcr underestimated GFR. However, 2 studies that evaluated patients with morbid obesity or class III obesity (BMI >40 kg/m2) demonstrated that CKD-EPI eGFR cr overestimated GFR. Conversely, eGFRcys generally underestimates GFR in people with morbid obesity, an observation compatible with the positive association between cystatin C and greater fat mass. Based on these data, some suggest that eGFR cr-cys is the most accurate eGFR in cases of morbid obesity, similar to what is recommended in the general population.

GFR Assessment in AKI

KDIGO defines AKI based on serum creatinine level and urinary output. This practice has some limitations because the absolute and proportionate increases in serum creatinine levels are influenced by the baseline GFR as well as the magnitude of the decrease in GFR. Thus, we recommend computing the change in GFR as an additional tool to assess the severity of AKI. For example, for a patient with a creatinine level of 2.0 mg/dL and baseline eGFR of 24 mL/min/1.73 m2, the definition of AKI could be met by an increase in creatinine level to 2.3 mg/dL, but this would represent only a small change in GFR (to 20 mL/ min/1.73 m2). In contrast, a change in creatinine level from 1.0 to 1.3 mg/dL would be equivalent to a change in GFR from 55 to 40 mL/min/1.73 m2.

An acute change in GFR would cause any serum levels of endogenous filtration markers to be in nonsteady state, with a lag until the serum levels increase to match the change in GFR. The converse is true for recovery from AKI. During the nonsteady state, neither the serum level nor the eGFR would be an accurate estimate of the GFR. The change in serum level and a change in eGFR can indicate the magnitude and direction of the change in true GFR. A kinetic eGFR equation has been proposed to account for the magnitude of change. It has not yet been validated compared with change in mGFR, but we recommend it as one tool to better estimate the true GFR in cases of acute decrease or recovery.



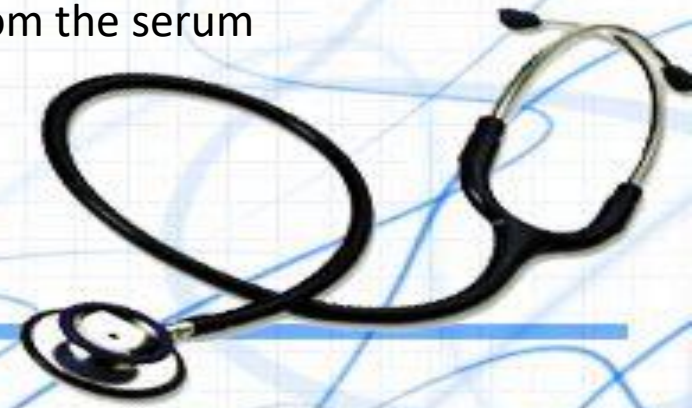
GFR Assessment in Transplant

Posttransplant, patients commonly have changes in the non-GFR determinants of endogenous biomarkers related to drug effects or systemic diseases. In one meta-analysis, the CKD-EPI and MDRD Study equations were more accurate than the other creatinine-based equations, consistent with what has been described in other nontransplant populations. Transplant recipients were not included in the CKD-EPI cystatin C development and validation studies. Subsequent studies assessing the performance of the cystatin C–based equations have yielded conflicting results. It is reasonable to continue to use the creatinine-based equation as part of routine assessment in transplant recipients, with further use of confirmatory tests in clinical situations suspected to lead to an increase in the non-GFR determinants of serum creatinine, similar to the approach in the nontransplant population

GFR Assessment in Patients Undergoing Dialysis

Residual kidney function is defined as the function of the native kidneys in patients undergoing kidney replacement therapy. It is regularly monitored in patients undergoing peritoneal dialysis as a component of total dialysis adequacy. eGFR should not be used to assess residual kidney function because many factors in dialysis may compromise its accuracy, such as dynamic changes in the volume distribution and removal during dialysis. Residual kidney function is most commonly measured as the average of urea and creatinine urinary clearances measured between sessions for patients undergoing hemodialysis, or as 24- or 48-hour urine collections in patients undergoing
peritoneal dialysis, although it has not been well validated. Urinary clearance of exogenous filtration markers can be used. Plasma clearance of exogenous filtration markers may have reduced accuracy in patients undergoing dialysis, with a trend toward overestimation, as a result of the delayed decay curve due to lower GFR. As discussed above, a later measurement, usually after 24 hours, can be added to improve accuracy. Small studies have tried to develop equations to predict GFR from the serum concentration of endogenous markers; none are ready for practice at this time.

Despite their roles as additional tools for clinical practice, all these methods need more robust validation.



Drug Dosing

Box 2. 2010 KDIGO Drug Dosing Conference Recommendations for Kidney Function Assessment in Clinical Practice

1. GFR should be the standard measure to evaluate kidney function for staging of CKD and drug dosing purposes.
2. Clinicians should use the most accurate method/tool to assess kidney function for the individual patient (ie, eCLcr or eGFR or mGFR).
3. Timed clearances of creatinine and urea may be particularly of value for patients with AKI.
4. Metrics to determine the most accurate eGFR methodology include rigor of development process, comparison vs gold standard, and measures of bias, precision, and accuracy in multiple patient populations.
5. Clinical laboratories should report eGFR in mL/min as well as mL/min/1.73 m2.

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; eCLcr, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; mGFR, measured glomerular filtration rate. Adapted with permission from Matzke et al, 2011 (Kidney Int. https://doi.org/10.1038/ki.2011.322). Original content ©2011 International Society of Nephrology.

An accurate assessment of GFR is important for guiding decisions related to the choice and dosing of drugs. Certain drugs are contraindicated or have not been tested below certain thresholds of GFR, as is the case for metformin, alendronate, and SGLT2 inhibitors. In addition, several drugs require dose adjustments according to kidney clearance, as occurs with many chemotherapy drugs and antibiotic agents.

In the 1998 US Food and Drug Administration (FDA) Guidance for Pharmacokinetic Assessment of Drugs in Renal Patients, the Cockcroft-Gault equation was mentioned for possible use (Table 3). This equation continues to be used despite the fact that it has now been shown to be substantially inaccurate in many patients

recommends that a “creatinine-based equation is usually sufficient for pharmacokinetic studies,” including the use of the CKD-EPI equations (which should be nonindexed for BSA and expressed in milliliters per minute) or the Cockcroft-Gault equation. If the latter is used, the FDA recommends the use of

alternative body metrics (ideal body weight or adjusted body weight) in those with overweight or obesity. Converting indexed eGFR to nonindexed eGFR can be performed by multiplying the indexed eGFR value by the patient’s BSA divided by 1.73. We recently showed that there are no relevant differences in the performances of indexed and nonindexed CKD-EPI eGFRs compared with indexed and nonindexed mGFRs, respectively.