



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

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Assessment of glomerular filtration rate (GFR) is fundamental to clinical practice, public health, and research. The kidney has several critical functions; GFR is used as an overall assessment of these kidney functions. GFR is used to diagnose, stage, and manage chronic kidney disease (CKD); ascertain the prognosis for chronic kidney disease–related events and mortality; and determine drug dosages. GFR is the rate at which the glomerulus filters plasma to produce an ultrafiltrate and can be assessed from clearance or serum levels of filtration markers. Clearance measurements using exogenous filtration markers are difficult to perform in routine clinical practice, so GFR is more commonly estimated through equations based on serum concentrations of endogenous filtration markers, most commonly creatinine. These GFR estimates are reasonably accurate, but optimal care for patients may require a confirmatory test for a more accurate GFR assessment. Confirmatory tests currently available include cystatin C–based equations, urinary or plasma clearance of exogenous filtration markers, or urinary clearance of creatinine. Appreciation of the concept of GFR and methods for optimal assessment in routine practice or special circumstances, and their strengths and limitations, are critical in making judicious use of the available tools.

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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 to measure GFR 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 first-line 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 (eGFR_{cr}) in most circumstances and eGFR based on cystatin C (eGFR_{cys}) 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.

What Is GFR and How Is it Measured and Estimated?

Case 1: A 45-year-old man with immunoglobulin A nephropathy presents for regular

consultation. He is otherwise healthy, has no history of hypertension, and is currently taking losartan 100 mg/d. Findings of the physical examination are unremarkable, blood pressure is 120/84 mm Hg, and body mass index (BMI) is 24 kg/m². His serum creatinine level (Scr) is 1.21 mg/dL which translates to an eGFR_{cr} of 72 mL/min/1.73 m², in addition to microscopic hematuria with dysmorphic red blood cells and a urinary albumin-creatinine ratio (UACR) of 300 mg/g.

Case 2: A 60-year-old woman with a 20-year history of diabetes and hypertension is referred to you. She has diabetic retinopathy, previous myocardial infarction, and a right transtibial amputation. Her BMI is 27 kg/m², Scr is 1.38 mg/dL, eGFR_{cr} is 41 mL/min/1.73 m², and UACR is 780 mg/g. She is currently using ramipril, furosemide, carvedilol, aspirin, a statin agent, metformin, and multiple injections of short- and long-acting insulin. Her doctor is considering prescribing an SGLT2 (sodium/glucose cotransporter 2) inhibitor.

Question 1: In your opinion, for each case, which method(s) should be used for initial GFR assessment?

- Iohexol plasma clearance
- eGFR_{cys}
- 24-Hour urine for creatinine clearance (CL_{cr})
- eGFR_{cr}
- eGFR using a combination of creatinine and cystatin C (eGFR_{cr-cys})

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

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	<ul style="list-style-type: none"> • Detection of CKD • Evaluation for kidney donation 	<ul style="list-style-type: none"> • Detection of AKI and AKD • Detection of CKD progression
Prognosis	<ul style="list-style-type: none"> • Risk of CKD complications and CVD • Risk for CKD progression • Risk for medical errors • Risk for perioperative complications • Risk for mortality 	<ul style="list-style-type: none"> • Risk for kidney failure
Treatment	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Treatment of AKI • Monitoring drug toxicity

Abbreviations: AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate. Adapted with permission from Stevens and Levey, 2009 (*J Am Soc Nephrol*. <https://doi.org/10.1681/asn.2009020171>). Original content ©2009 American Society of Nephrology.

Question 2: In each case, would a confirmatory test for the level of GFR be helpful in your clinical decision-making (yes or no)?

For the answers to these questions, see the following text.

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

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

periods are used, in contrast to the 3 or 4 periods used in research studies. 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. We have posted the forms we use for measurement of plasma clearance of iohexol on the CKD Epidemiology Collaboration (CKD-EPI) website. Several newer methods might soon become available, facilitating more widespread use of GFR. For example, 2 novel markers currently being evaluated are conjugated to fluorescein, allowing transdermal measurement of the exogenous marker administered intravenously.

Urinary clearance of the endogenous filtration marker creatinine can be measured as a confirmatory test. It systematically overestimates GFR, with greater overestimation at lower GFR values. Tubular secretion of creatinine can account for a substantial portion of excretion relative to GFR. The amount of creatinine secretion can be estimated in humans only by computing the difference between CL_{Cr} and measured GFR. In the MDRD (Modification of Diet in Renal Disease) Study, creatinine secretion was estimated to be 5-10 mL/min/1.73 m². Urea is reabsorbed by the tubules, and use of the average of the creatinine and urea clearances for people with GFR <40 mL/min/1.73 m² may yield a more precise estimate 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

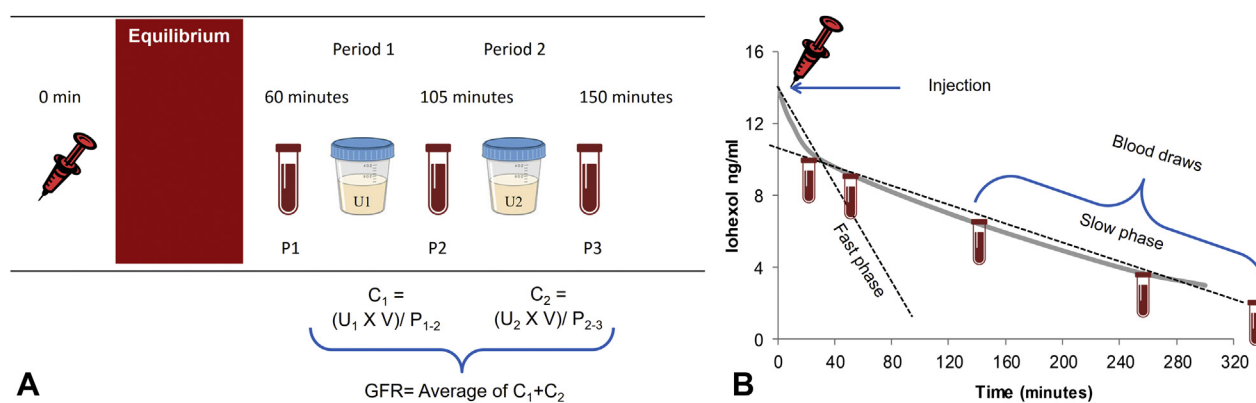


Figure 1. Scheme for urinary and plasma clearance. (A) Urinary clearance is usually performed using subcutaneous injection of an exogenous filtration marker to allow for slow release of the marker into the circulation, providing more constant plasma levels than with an intravenous bolus. In clinical 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 marker 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 marker 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.

anticipate GFR being measured in greater frequency given the increased emphasis on confirmatory tests for the first-line $eGFR_{Cr}$.

Additional Readings

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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

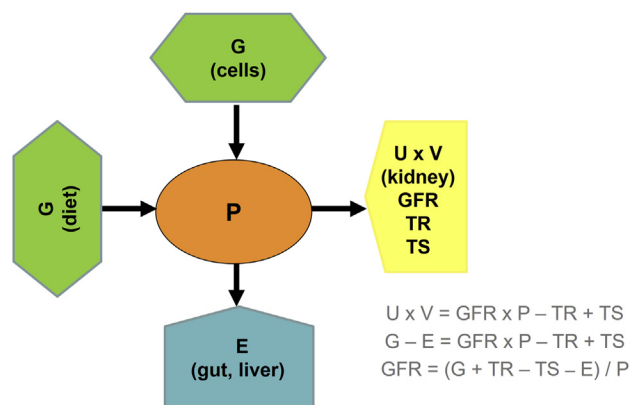


Figure 2. Relationship of plasma levels of endogenous filtration markers with glomerular filtration rate (GFR). In the steady state, a constant plasma concentration (P , in mg/min) of the filtration marker is maintained because generation (G , in mg/min) is equal to the sum of urinary excretion (UV , 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 illustration 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.

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). The recommendation was made for the CKD-EPI

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.

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 eGFR_{cr} 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 eGFR_{cr}.

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, eGFR_{cys}) and creatinine and cystatin C (ie, eGFR_{cr-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 eGFR_{cys} is not more accurate than eGFR_{cr}, but eGFR_{cr-cys} is more accurate than either alone (Fig 3).

Despite the increased precision of eGFR_{cr-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 eGFR_{cr}. Because there are only 2 markers, it not always obvious how to interpret discrepancies between eGFR_{cr} and eGFR_{cys}. Although the interpretation is sometimes straightforward (eg, for otherwise healthy amputees, eGFR_{cr} but not eGFR_{cys} 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 eGFR_{cr} versus eGFR_{cys}. Indeed, in patients with severe HIV or heart or liver failure, both eGFR_{cr} 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 eGFR_{cr-cys} (Fig 4).

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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)	$(140 - \text{age} \times \text{weight}) / (72 \times \text{Scr}) \times 0.85$ 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	$175 \times \text{Scr}^{-1.154} \times \text{age}^{-0.203} \times 0.745$ if female $\times 1.212$ 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	$141 \times \min(\text{Scr}/\kappa, 1)^\alpha \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018$ if female $\times 1.159$ if Black $\alpha = -0.329$ (female); -0.411 (male); $\kappa = 0.7$ (female); $\kappa = 0.9$ (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	$0.413 \times (\text{height in cm}/\text{Scr})$	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	$K \times \text{height}/\text{Scr}$ K for males 1-11 y, $39 \times 1.008^{(\text{age}-12)}$; 12-17 y, $39 \times 1.045^{(\text{age}-12)}$; 18-25 y, 50.8; K for females: 1-11 y, $36.1 \times 1.008^{(\text{age}-12)}$; 12-17 y, $39 \times 1.023^{(\text{age}-12)}$; 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	$133 \times \min(\text{Scys}/0.8, 1)^{-0.499} \times \max(\text{Scys}/0.8, 1)^{-1.328} \times 0.996^{\text{age}} \times 0.932$ 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	$70.69 \times \text{Scys}^{0.931}$	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	$K \times 1/\text{Scys}$ K for males 1-14 y, $87.2 \times 1.011^{(\text{age}-15)}$; 15-17 y, $87.2 \times 0.960^{(\text{age}-15)}$; 18-25 y, 77.1; K for females: 1-11 y, 79.9 $\times 1.004^{(\text{age}-12)}$; 12-17 y, 79.9 $\times 0.974^{(\text{age}-12)}$; 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-cys})						
Adult	CKD-EPI eGFR _{cr-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	$135 \times \min(\text{Scr}/k, 1)^a \times \max(\text{Scr}/k, 1)^{-0.601} \times \min(\text{Scys}/0.8, 1)^{-0.375} \times \max(\text{Scys}/0.8, 1)^{-0.711} \times 0.995^{\text{age}} \times 0.969$ if female $\times 1.08$ if Black $\alpha = -0.248$ (female); -0.207 (male); $k = 0.7$ (female); $k = 0.9$ (male)	Improved precision and accuracy vs CKD-EPI eGFR _{cr} and eGFR _{cys} ; recommended in adults as confirmatory test
Pediatric	CKID eGFR _{cr-cys} (2012) ^h	Plasma clearance of iothexol	No	389 boys/254 girls; mGFR 43 mL/min/1.73 m ²	$39.8 \times (\text{height}/\text{Scr})^{0.456} \times (1.8/\text{Scys})^{0.418} \times (30/\text{SUN})^{0.079} \times (1.076^{\text{male}}) \times (\text{height in m}/1.4)^{0.179}$	Iohexol measurements have since been recalibrated; cystatin C assay not standardized

Table S1 displays equations developed by other research groups. Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CKID, Chronic Kidney Disease in Children; eGFR, estimated glomerular filtration rate; eGFR_{cr}, eGFR from creatinine; eGFR_{cr-cys}, eGFR from a combination of creatinine and cystatin C; eGFR_{cys}, eGFR from cystatin C; mCl_{cr}, measured creatinine clearance; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate; Scr, serum creatinine (in mg/dL); Scys, serum cystatin C (in mg/L); SUN, serum urea nitrogen.

^aCockcroft and Gault, 1976 (*Nephron*. <https://doi.org/10.1159/000180580>).

^bLevey et al, 2006 (*Ann Intern Med*. <https://doi.org/10.7326/0003-4819-145-4-200608150-00004>).

^cLevey et al, 2009 (*Ann Intern Med*. <https://doi.org/10.7326/0003-4819-150-9-200905050-00008>); published correction appears at <https://doi.org/10.7326/0003-4819-155-6-201109200-00024>.

^dSchwartz et al, 2009 (*J Am Soc Nephrol*. <https://doi.org/10.1681/asn.2008030287>).

^eNg et al, 2018 (*Kidney Int*. <https://doi.org/10.1016/j.kint.2018.01.034>).

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Review of Cases 1 and 2

The first patient has a high GFR and has a favorable prognosis, and, at present, there are no indicated treatments for his disease. A more accurate estimate of GFR would not change his management plan, and a confirmatory test is not required; thus, the answers to questions 1 and 2 are (a) and no, respectively. In contrast, for the second patient, the precise value for GFR would affect management, especially in consideration of whether to continue metformin and start SGLT2 inhibitors. Her amputation is the major concern with the use of creatinine. However, her presumed high fat mass and ongoing smoking raise concerns about eGFR_{cys} or eGFR_{cr-cys}. As such, a clearance measurement is indicated; therefore, the answers to questions 1 and 2 for case 2 are (a) or (c) and yes, respectively.

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 $eGFR_{cr}$ or $eGFR_{cr-cys}$. 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 GFR_{cr} 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.

The American Society of Nephrology and National Kidney Foundation have jointly set up a task force to thoroughly and carefully consider all possible methods by which GFR can be estimated without specification of race, as well as the social and clinical implications, with final recommendations to be “based on rigorous science, and be part of a national conversation about uniform reporting of $eGFR$ across health care systems.” In advance of these updated recommendations, 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.

There are also outstanding questions whether coefficients for $eGFR_{cr}$ for race or ethnic groups other than Black people are required. In some Asian countries, studies demonstrated that calibration factors increased the accuracy of the CKD-EPI creatinine or MDRD Study equations. For example, in Japan, a modified CKD-EPI creatinine equation is used that

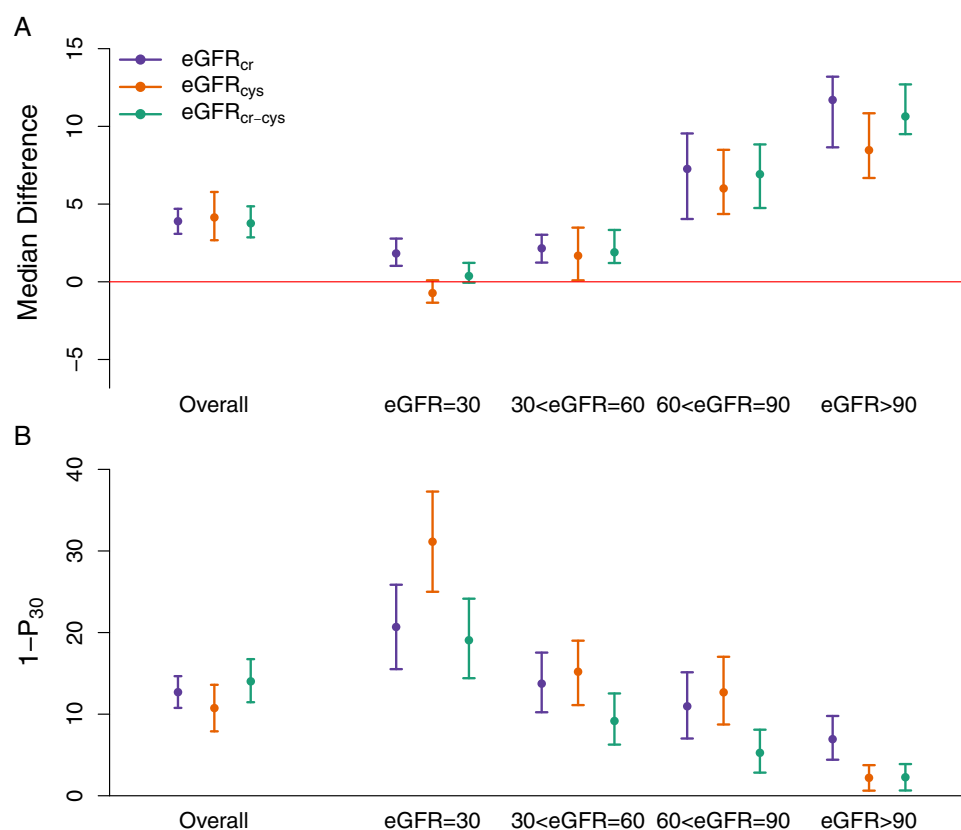


Figure 3. Estimated glomerular filtration rate ($eGFR$) from creatinine ($eGFR_{cr}$), from cystatin C ($eGFR_{cys}$), and from a combination of creatinine and cystatin C ($eGFR_{cr-cys}$) compared with measured GFR ($mGFR$). (A) Median difference between $mGFR$ and $eGFR$. The bias is similar with the 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 $mGFR$ ($1 - P_{30}$). 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.

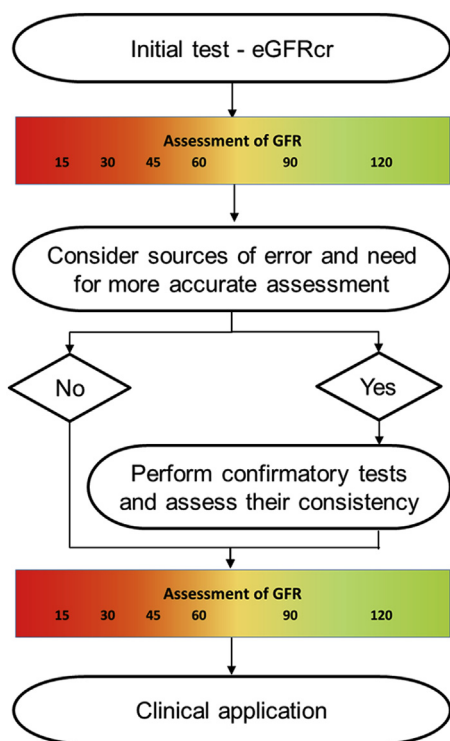


Figure 4. Approach to glomerular filtration rate (GFR) evaluation using initial and confirmatory testing. Our approach is to use initial and confirmatory testing to develop a final assessment of true GFR and to apply it in individual decision-making. Estimated GFR from creatinine (eGFR_{cr}) is the appropriate initial test, which must be interpreted in light of its limitations. Estimated GFR from cystatin C, estimated GFR from a combination of creatinine and cystatin C, and measured creatinine clearance are useful confirmatory tests in some circumstances, and measured GFR is an appropriate confirmatory test if available and performed using an accurate procedure. We recommend the most convenient confirmatory test that will enable clinical decision-making, recognizing that more than one confirmatory test may be required. Clinical application requires additional clinical information for appropriate use, such as a clinical action plan for KDIGO (Kidney Disease: Improving Global Outcomes) GFR categories, drug dosing, or use in predictive instruments. Adapted with permission from Levey et al, 2020 (*Nature Reviews Nephrology*. <https://doi.org/10.1038/s41581-019-0191-y>). Original content ©2019 Springer Nature Limited.

applies a correction factor of 0.813, thereby decreasing the eGFR_{cr}. This and other calibration factors have not been shown to be generalizable across countries, which may also reflect population differences in the non-GFR determinants or differences in methods to measure GFR or assay creatinine. eGFR_{cys} appeared more accurate than eGFR_{cr} across all Asian countries and does not require a calibration factor. However, one study in Australian Aboriginals and in Pakistan suggests that this might not be universal. In our practice, we do not use these correction factors for people from Asia currently living in the United States given the variation seen and the absence of data to inform us of the

accuracy of eGFR in Asian individuals in the United States. As such, we readily use confirmatory tests should the GFR value impact diagnosis, management, or prognostic decisions.

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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 eGFR_{cr} could be considered. For some, this would be an indication for referral to a nephrologist. Above, we discussed this in the context of cases 1 and 2. Here we discuss 3 examples to further expand on how GFR confirmatory tests may affect critical decisions.

Case 3: You are now evaluating a 45-year-old woman who presents to your clinic with an Scr of 1 mg/d, which computes to an eGFR of 68 mL/min/1.73 m² using the CKD-EPI equation. She reports a history of migraines that have increased in frequency in the past 2 years, for which she takes nonsteroidal anti-inflammatory agents (NSAIDs). Her primary-care doctor is concerned that she should avoid NSAIDs with this level of GFR. Prior GFR estimates are not available.

Question 3: What next step(s) regarding GFR assessment should you take?

- Tell her that she can never take any NSAIDs because she has CKD and is at high risk for progression
- Tell her she can take NSAIDs because she has no evidence of CKD
- Measure GFR using plasma or urinary clearance of iothexol
- Measure cystatin C to compute $eGFR_{cys}$ and $eGFR_{cr-cys}$

For the answer to the question, see the following text.

GFR is used for diagnosis, staging, and management of CKD. CKD is defined by a $GFR < 60 \text{ mL/min/1.73 m}^2$ or evidence of kidney damage that is present for ≥ 3 months. In the United States, the most common presentation of kidney damage is albuminuria. Other markers include other urine findings or radiologic abnormalities. GFR and albuminuria are also used to stage the severity of CKD, with decreasing GFR and increasing albuminuria indicating patients with more severe disease and at higher risk for progression to kidney failure and other complications of CKD, particularly cardiovascular disease and mortality. The Kidney Failure Risk Equation uses age, sex, GFR, and UACR to predict the risk for onset of kidney failure with replacement therapy within 2 or 5 years.

For case 3, the patient's $eGFR$ is substantially lower than normal levels but is above the threshold for the definition of CKD. Examination of urine sediment showed bland urine, and albuminuria is quantified at 15 mg/g. The patient reported frequent urinary tract infections as a teenager, and you arrange for an ultrasound examination to be performed. No abnormalities are noted. She also reported a high-protein diet, so you confirm the $eGFR_{cr}$ with a cystatin measurement; thus, the best answer for question 3 is (d). $eGFR_{cys}$ is $77 \text{ mL/min/1.73 m}^2$ and $eGFR_{cr-cys}$ is $73 \text{ mL/min/1.73 m}^2$. Given the consistency of $eGFR_{cr}$ and $eGFR_{cys}$, you do not think further confirmatory tests are required. Based on these data, you determine that she does not have any evidence of CKD. You are unable to ascertain whether the reduced $eGFR$ is related to long-term NSAID use or GFR in the lower part of the normal range. You recommend alternative migraine medications to enable reduction of NSAID use and follow up in 3-6 months to help determine if a reduced NSAID dose leads to an improved GFR.

Case 4. You are evaluating a 58-year-old woman who is willing to donate her kidney to her son, who has immunoglobulin A nephropathy and CKD G5A2 (ie, GFR of 15-29 mL/min/1.73 m^2 and $UACR$ of 30-300 mg/g). She is otherwise healthy and has no history of previous conditions or comorbid conditions. She had 2 uneventful full-term pregnancies in her twenties. Her blood pressure is 110/74 mm Hg, her weight is 130 lb (59 kg), and her BMI is 24 kg/m^2 . She brings recent laboratory tests showing an Scr of 0.9 mg/dL (which computes to an $eGFR$ of 70 mL/min/1.73 m^2 using the CKD-EPI equation), and exhibits no hematuria or proteinuria based on a spot urine sample.

1.73 m^2 using the CKD-EPI equation), and exhibits no hematuria or proteinuria based on a spot urine sample.

Question 4: What next step(s) regarding GFR assessment should you take?

- Tell her she is not a candidate because her GFR is lower than the threshold at your institution
- Tell her she is a candidate because the risk of kidney failure with replacement therapy is 0.08% based on the End-Stage Renal Disease Risk Tool for Kidney Donor Candidates (<http://www.transplantmodels.com/esrdrisk/>)
- Obtain an $mGFR$
- Perform a 24-hour CL_{cr} measurement

For the answer to the question, see the following text.

The goal of evaluation of living kidney donor candidates is to assess risk for perioperative and long-term adverse outcomes after donation, particularly the risk for kidney failure. The 2016 KDIGO guideline on evaluating and caring for living kidney donors recommends making an assessment of risk by synthesizing multiple sources of information. GFR assessment is a crucial part of that evaluation. In the United States, the Organ Procurement and Transplantation Network requires urine collection to measure the urine albumin or urine protein level, as well as clearance measurements for assessment of GFR using measured CL_{cr} or measured GFR using exogenous markers and plasma or CL_{cr} ; thus, the best answers to question 4 are (c) and (d). Although a urine collection is often used to perform a confirmatory test for GFR using measured CL_{cr} , urine collections are fraught with error, and we recommend using information from $eGFR$ in addition to the CL_{cr} to provide greater confidence in the value of the GFR. In our practice, we use $eGFR_{cr}$ followed by $eGFR_{cys}$ and $eGFR_{cr-cys}$ and assign a posttest probability of $mGFR > 80 \text{ mL/min/1.73 m}^2$ (or $90 \text{ mL/min/1.73 m}^2$, depending on the applicable institution's threshold for donor eligibility).

For case 4, the candidate donor's cystatin C level was 0.7 mg/L , corresponding to $eGFR_{cys}$ and $eGFR_{cr-cys}$ values of 88 and 105 mL/min/1.73 m^2 , respectively. Posttest probabilities of $mGFR > 80 \text{ mL/min/1.73 m}^2$ were 78% using $eGFR_{cr}$ alone and 93% using $eGFR_{cys}$. Measured CL_{cr} was 75 mL/min/1.73 m^2 . Albumin excretion was 20 mg/d , and renal imaging was normal. On questioning, the patient states that, over the past year, she has substantially increased her exercise regimen to be fit for donating her kidney. Indeed, she had collected her 24-hour urine sample during an exercise session and suspects that she might have missed a urine collection. Thus, all together, we evaluate that she has a high probability for $GFR > 80 \text{ mL/min/1.73 m}^2$ and therefore meets GFR

criteria for donation. Assessment of her overall candidacy will depend on other criteria.

Case 5: You are the attending physician on the consultation service and have been asked to provide guidance to the heart failure team whether a 56-year-old man with stage D heart failure who is being evaluated for a heart transplant should have a simultaneous kidney transplant. He has heart failure due to ischemic cardiomyopathy but no other comorbid conditions. He has been hospitalized and essentially bedbound for >1 month. Before admission, $eGFR_{cr}$ was approximately 50 mL/min/1.73 m². He had an episode of acute kidney injury (AKI) with $eGFR_{cr}$ decreasing to 15 mL/min/1.73 m², but it has increased to 40 mL/min/1.73 m² and has been stable at this level for the past 2 weeks. Your hospital's threshold is 30 mL/min/1.73 m² for consideration of simultaneous kidney transplant.

Question 5: What next step(s) regarding GFR assessment should you take?

- Tell the heart failure team that the patient should not receive a kidney transplant because his GFR is higher than the threshold
- Measure cystatin C and compute $eGFR_{cys}$
- Perform an mGFR
- Perform a 24-hour urine collection for albuminuria, urea, and CL_{cr}

For the answer to the question, see the following text.

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 $eGFR_{cr}$ versus $eGFR_{cys}$, suggesting that $eGFR_{cys}$ 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). Moreover, the urine collection provides information on albuminuria that is also important for transplant evaluation. We use our calculator for 24-hour urine (<https://www.tuftsmedicalcenter.org/Research-Clinical-Trials/Institutes-Centers-Labs/Chronic-Kidney-Disease-Epidemiology-Collaboration/Calculators>) to compute and record all relevant information. For hospitals in which mGFR using exogenous markers is available, that is also an option (thus, answer [c] may also be appropriate), but it is important to

remember that plasma clearance may overestimate true GFR in edematous patients.

For the patient described in case 4, in the 1,000 mL of urine collected over a period of 24 hours, urine creatinine excretion was 600 mg and urine urea excretion was 10 g. Given the serum concentrations of creatinine and serum urea nitrogen of 1.45 mg/dL and 70 mg/dL, respectively, the creatinine and urea clearance were 29 and 10 mL/min/1.73 m², respectively, leading to an average of 18 mL/min/1.73 m². You recommend simultaneous heart and kidney transplant.

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Changes in Body Composition Over Time

Case 6: You are seeing a 45-year-old man who had bariatric surgery 6 months earlier. He has hypertension, hyperuricemia, and sleep apnea. He used to smoke but quit 2 weeks before the procedure. His medical records show that, at 2 months before surgery, he had a weight of 304 pounds (138 kg), height of 6 feet, BMI of 41.2 kg/m², BSA of 2.55 m², and $eGFR_{cr}$, $eGFR_{cys}$, and $eGFR_{cr-cys}$ of 93, 65, and 77 mL/min/1.73 m², respectively. At this current visit, his weight is 224 lb (102 kg), BMI is 30.4 kg/m², BSA is 2.24 m², and $eGFR_{cr}$, $eGFR_{cys}$, and $eGFR_{cr-cys}$ are 119, 83, and 99 mL/min/1.73 m², respectively.

Question 6: Based on these data, how do you evaluate the impact of the procedure on his GFR?

- GFR is improved because all $eGFR$ values show an increase since the procedure
- GFR is improved because the $eGFR_{cr-cys}$ value shows an increase in $eGFR$ since the procedure
- GFR is improved because all nonindexed $eGFR$ values show an increase since the procedure

- d) GFR is improved because the nonindexed $eGFR_{cr-cys}$ value shows an increase in eGFR since the procedure
- e) You should assess mGFR because creatinine and cystatin C are affected by non-GFR determinants and will change as a result of weight loss

For the answer to the question, see the following text.

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 $eGFR_{cys}$ 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 $eGFR_{cr}$ underestimated GFR. However, 2 studies that evaluated patients with morbid obesity or class III obesity ($BMI > 40 \text{ kg/m}^2$) demonstrated that CKD-EPI $eGFR_{cr}$ overestimated GFR. Conversely, $eGFR_{cys}$ 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.

Additional problems emerge when body composition changes suddenly, as non-GFR determinants of filtration markers are different before and after the change in body composition. Clearance measurements will give a more precise assessment of the changes that have occurred and should be considered if the exact measurement of GFR will affect clinical decision-making.

For the patient in case 6, before surgery, mGFR was 98 mL/min/1.73 m² and 144 mL/min. After surgery, mGFR was 95 mL/min/1.73 m² and 133 mL/min. Before surgery, $eGFR_{cr}$ (93 mL/min/1.73 m² and 137 mL/min), $eGFR_{cys}$ (65 mL/min/1.73 m² and 95 mL/min), and $eGFR_{cr-cys}$ (77 mL/min/1.73 m² and 113 mL/min) all underestimated mGFR, although this effect was most prominent for $eGFR_{cys}$. After surgery, $eGFR_{cr}$ (119 mL/min/1.73 m² and 154 mL/min) and $eGFR_{cr-cys}$ (99 mL/min/1.73 m² and 145 mL/min) overestimated mGFR, whereas $eGFR_{cys}$ (83 mL/min/1.73 m² and 122 mL/min) underestimated it. These results illustrate the problems with accuracy of eGFR in obesity and also after bariatric surgery. There is a paucity of evidence of the accuracy of GFR estimates in situations in which significant changes in body composition have occurred. One important note is that, in conditions in which BSA significantly changes, such as seen in this case (BSA decreased from 2.55 to 2.24 kg/m²), it is preferable to use nonindexed mGFR and eGFR for comparisons before and after the change. Therefore, the patient's GFR decreased after bariatric surgery, which was

clear only after an mGFR was obtained. Thus, the best answer to question 6 is (e).

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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 of GFR.

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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.

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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.

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Drug Dosing

Case 2, continued: You are reviewing the medications taken by this 60-year-old woman with diabetes and hypertension. She is currently using ramipril, furosemide,

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, eCL_{cr} 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; eCL_{cr}, 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.

carvedilol, aspirin, a statin agent, metformin, multiple injections of short- and long-acting insulin, and alendronate (started 1 y ago after a femoral fracture event). Her glycated hemoglobin level is 7.5%, and she brings a capillary glycemia diary with no episodes of hypoglycemia.

Question 7: How will GFR assessment impact your decisions regarding medications in this patient?

For the answer to the question, see the following text.

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, especially those who are elderly or with obesity, and, importantly, is not accurate given the creatinine assays traceable to reference materials. In 2010, KDIGO convened a controversies conference with the goal of improving drug dosing in kidney disease. Regarding assessment of kidney function, the report states, “the pros and cons of the various GFR-estimating equations have been extensively reviewed, and there is no compelling evidence of the superiority of any given method for drug dosing in all patient populations or clinical situations. Most of these studies have all compared the equations with each other in hypothetical simulations and not with actual drug clearance.” It concludes that “clinicians should use the method that provides the most accurate assessment of GFR.” Recommendations on the assessment of GFR for drug dosing are given in Box 2. Recently, the FDA has updated its guidance (<https://www.fda.gov/media/78573/download>) and 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.

Additional Readings

- Matzke GR, Aronoff GR, Atkinson AJ Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2011;80(11):1122-1137. **★ESSENTIAL READING**
- Titan S, Miao S, Tighiouart H, et al. Performance of indexed and nonindexed estimated GFR. *Am J Kidney Dis.* 2020;76(3):446-449.
- Levey AS, Inker LA. Assessment of glomerular filtration rate in health and disease: a state of the art review. *Clin Pharmacol Ther.* 2017;102(3):405-419.

Supplementary Material

Supplementary File (PDF)

Table S1: Equations estimating GFR from endogenous filtration markers developed in specific populations outside North America.

Article Information

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