FREQUENTLY ASKED QUESTIONS ABOUT

GFR Estimates

NATIONAL KIDNEY FOUNDATION®

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ASSESSMENT OF KIDNEY FUNCTION

1] What is GFR?

GFR (glomerular filtration rate) is equal to the total of the filtration rates of the functioning nephrons in the kidney. GFR is considered the most useful index of kidney function in health and disease, which in conjunction with albuminuria, generally assessed from urine albumin-to-creatinine ratio (uACR), can help determine the presence and severity of chronic kidney disease (CKD).

2] Why assess GFR as an index of kidney function?

GFR is considered the best index of kidney function in health and disease. The level of GFR and its magnitude of change over time are important to:

- Detect CKD
- Understand the severity or stage of CKD
- Make decisions about diagnosis, prognosis, and treatment of CKD.

Normal GFR varies according to age, sex, and body size; in young adults, it is approximately 120 mL/min/1.73 m^2 and declines with age. A decrease in GFR precedes the onset of kidney failure. Therefore, a persistently reduced GFR is a specific diagnostic criterion for CKD. Below 60 mL/min/1.73 m^2, the prevalence of complications of CKD increases, as does the risk of cardiovascular disease (CVD).

Table 1 lists clinical conditions where assessment of GFR is important.

3] How does age affect GFR in adults?

GFR generally declines with age. However, there appears to be substantial variation among individuals, and reasons for decline are not completely known (healthy aging, disease, or other factors). The threshold to diagnose CKD does not differ by age. At all ages, GFR is an independent predictor of adverse outcomes, such as death, cardiovascular disease, and other CKD complications. In addition, decreased GFR in the elderly may require adjustment in drug dosages, as with younger patients with decreased GFR. Some have proposed age-stratified GFR criteria for the diagnosis of CKD.

4] How is GFR assessed?

GFR cannot be measured directly. It can be assessed as measured (mGFR) or estimated (eGFR) from the clearance or serum (plasma) concentration of a filtration marker, respectively.

5] What is a filtration marker?

Filtration markers are exogenous or endogenous solutes with molecular weight less than approximately 20,000 Daltons whose serum concentration varies inversely with GFR and can be used to measure or estimate GFR. An ideal filtration marker is freely filtered by the glomeruli (not protein-bound), is not reabsorbed or secreted by the tubules, does not affect kidney function, and is easy to measure. Exogenous filtration markers include inulin (the gold standard), iothalamate, iohexol, EDTA, DTPA, and synthetic polymers. Endogenous filtration markers include

TABLE 1: CLINICAL CONDITIONS WHERE ASSESSMENT OF GFR IS IMPORTANT*

CLINICAL DECISIONS	CURRENT LEVEL OF GFR	CHANGE IN LEVEL OF GFR
Diagnosis	• Detection of CKD • Evaluation for kidney donation	• Detection of AKI • Detection of CKD progression
Prognosis	• Risk of CKD complications • Risk for CVD • Risk for mortality	• Risk for kidney failure
Treatment	• Dosage and monitoring for medications cleared by the kidney • Determine safety of diagnostic tests or procedures • Referral to nephrologists • Referral for kidney transplantation • Placement of dialysis access	• Treatment of AKI • Monitoring drug toxicity

Abbreviations: AKI: acute kidney injury; CKD: chronic kidney disease; CVD: cardiovascular disease.
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metabolites (creatinine is most commonly used) and low molecular weight proteins (cystatin C, beta-2 microglobulin, and beta-trace protein).

6] Why is GFR indexed for body surface area?

Kidney function is proportional to kidney size, which is proportional to body surface area (BSA). Adjustment for BSA is necessary when comparing a person's GFR to normal values, to the GFR criterion for the diagnosis of CKD, and to levels defining the stages of CKD. A BSA of 1.73 m^2 was the normal mean value for young adults when indexing was proposed. BSA can be computed using the formula of DuBois and DuBois.

$BSA\ (m^2) = 0.007184 \times W^{0.425} \times H^{0.725}$
(where height is measured in centimeters, and weight in kilograms)

Indexed GFR is less than non-indexed GFR in people with large BSA (tall or obese) and greater than non-indexed GFR in people with small BSA (short or very thin). Indexed GFR may be converted to non-indexed GFR by the formula:

non-indexed GFR = indexed GFR x BSA (m^2)/1.73 m^2

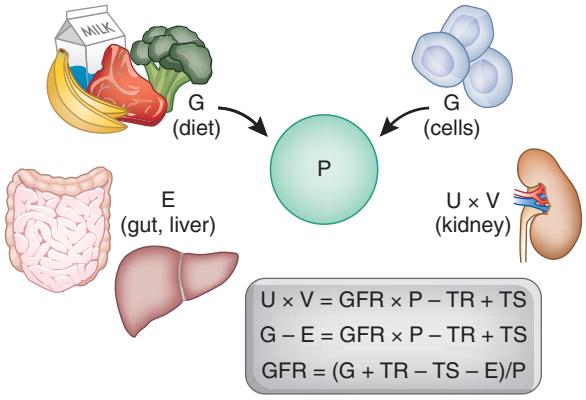
7] How is the accuracy of the GFR assessments described?

Errors in diagnostic tests can arise from systematic error (bias, average difference from the reference or "gold" standard) or random error (imprecision, variability of the differences about the average difference). Accuracy reflects a combination of absence of bias ("trueness") and precision; there are many metrics for describing accuracy. Common metrics for describing accuracy of GFR assessments are bias (mean or median difference) on the GFR scale (a lower value is more accurate), and the proportion of assessments that are within a specified percentage of the reference standard (for example, within 15% or 30%, a higher value is more accurate, see below).

8] How is GFR measured?

Measured GFR (mGFR) is determined from the urinary or plasma clearance of an exogenous filtration marker. However, these procedures are cumbersome and not used in routine clinical practice but may be used as confirmatory tests in special circumstances and in research studies. Urinary clearance of inulin during a continuous infusion is the classic method of Homer Smith. This procedure has limited precision; only approximately 90% of repeated measurements are within 15% of the initial measurement (P15= 90%). This mGFR procedure is rarely used, even in research studies. The following alternative clearance methods and filtration markers had strong to moderate evidence of accuracy compared to the classic method: urinary clearance of iothalamate, plasma clearance of iohexol, and urinary and plasma clearance of Cr-EDTA (not available in US). In general, plasma clearance methods have greater precision than urinary clearance methods. Special circumstances in which mGFR may be necessary in selected cases for clinical practice decision making include the assessment of a potential living kidney donor and infrequently for medication dosing for critical drugs.

FIGURE 1: DETERMINANTS OF THE SERUM LEVEL OF ENDOGENOUS FILTRATION MARKERS*



The plasma level (P) of an endogenous filtration marker is determined by its generation (G) from cells and diet, extrarenal elimination (E) by gut and liver, and urinary excretion (UV) by the kidney. Urinary excretion is the sum of filtered load (GFR x P), tubular secretion (TS), and reabsorption (TR). In the steady state, urinary excretion equals generation and extrarenal elimination. By substitution and rearrangement, GFR can be expressed as the ratio of the non-GFR determinants (G, TS, TR, and E) to the plasma level.
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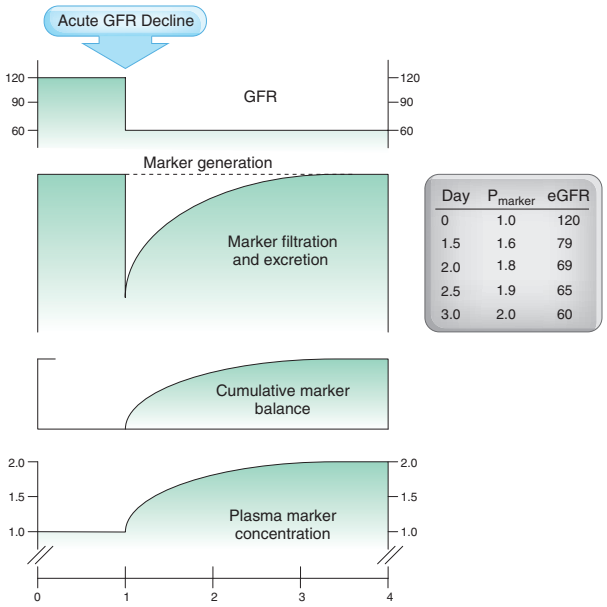
9] How is GFR estimated?

Estimated GFR (eGFR) is determined from estimating equations that incorporate the steady-state serum concentration of one or more endogenous filtration markers. However, the serum concentration alone is not an adequate marker of GFR as the serum concentrations of all filtration markers are affected by physiological processes in addition to GFR (non-GFR determinants): generation from cells and diet, tubular secretion and reabsorption, and extra-renal elimination (**Figure 1**). GFR estimating equations include demographic and clinical variables as surrogates of these non-GFR determinants. Accuracy of GFR estimates is limited by non-GFR determinants of filtration markers; only approximately 80–90% of eGFR are within 30% of mGFR (P30= 80–90%) (**Figure 2**).

FIGURE 3: EFFECT OF AN ACUTE GFR DECLINE ON GENERATION, FILTRATION, EXCRETION, BALANCE, AND SERUM LEVEL OF ENDOGENOUS FILTRATION MARKERS*



Effect of an acute GFR decline on generation, filtration, excretion, balance, and serum level of endogenous filtration markers. After an acute GFR decline, generation of the marker is unchanged, but filtration and excretion are reduced, resulting in retention of the marker (a rising positive balance) and a rising plasma level (non–steady state). During this time, eGFR is lower than GFR. Although GFR remains reduced, the rise in plasma level leads to an increase in filtered load (the product of GFR times the plasma level) until filtration equals generation. At that time, cumulative balance and the plasma level plateau at a new steady state. In the new steady state, eGFR approximates mGFR. GFR is expressed in units of milliliter per minute per 1.73 m^2. Tubular secretion and reabsorption and extrarenal elimination are assumed to be zero. *Modified and reproduced with permission from Kassirer JP.
N Engl J Med. 1971;285:385–389.

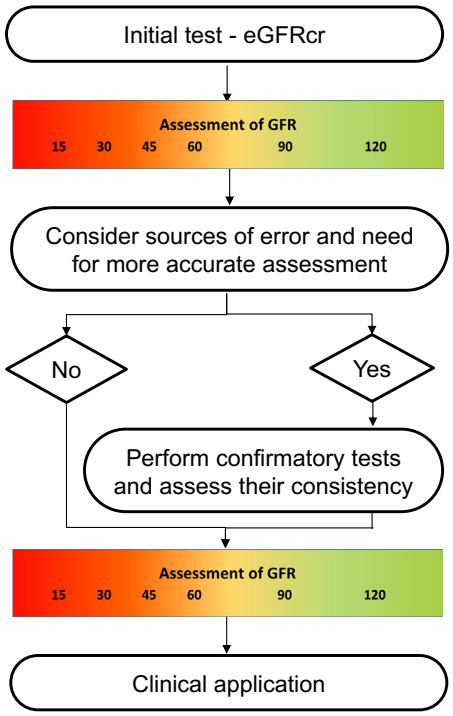
10] What problems are caused by the non-steady state of endogenous filtration markers after a change in GFR?

Accurate estimation of GFR from the serum level of an endogenous filtration marker (creatinine or cystatin C) requires a steady state; that is, the serum level is stable from day to day. This is true whether the serum level alone is used to estimate GFR or the serum level is used in an estimation equation. After a decline in GFR, the serum level rises until a new steady state is achieved **(Figure 2).** When the serum level is rising, the GFR estimate based on the non-steady state serum level overestimates the measured GFR. Conversely, after a rise in GFR, the serum level declines until a new steady state is achieved. When the serum level is declining, the GFR estimate based on the non-steady state serum level underestimates the measured GFR. In the non-steady state, the direction of change in the serum level indicates the direction of change in GFR, and the rate of change in the serum level provides some indication of the magnitude of the change in GFR.

11] What is the recommended approach for evaluation of GFR?

The *2012 Kidney Disease Improving Global Outcomes (KDIGO) CKD Guidelines* recommend eGFR from Scr (eGFRcr) to be the initial test in the assessment in adults since eGFRcr is the simplest, least expensive, most widely available method worldwide, allowing GFR estimation with satisfactory bias and accuracy in most clinical settings. If eGFRcr is thought to be potentially inaccurate, confirmatory testing using cystatin C to estimate GFR, measured creatinine clearance (see Question 8), or mGFR should be performed (**Figure 3**).

FIGURE 3: ASSESSMENT OF GFR



12] What is creatinine and how is serum creatinine used in creatinine-based GFR estimating equations (eGFRcr)?

Creatinine is a 113 Da amino acid derivative that is generated from the breakdown of creatine in muscle, distributed throughout total body water, and excreted by the kidneys by glomerular filtration and tubular secretion. Although the serum concentration of creatinine is affected primarily by the level of GFR, it is also affected by other physiological

TABLE 2: THE SAME SERUM CREATININE: DIFFERENT eGFR		
	58-YR-OLD MAN	**80-YR-OLD WOMAN**
Serum creatinine	1.20 mg/dL	1.20 mg/dL
GFR as estimated by the 2021 CKD-EPI equation	70 mL/min/1.73 m^2	49 mL/min/1.73 m^2
Kidney function	Mild reduction in GFR Stage G2 CKD if kidney damage is also present such as albuminuria	Moderate reduction in GFR Stage G3a CKD whether or not kidney damage is present

processes (non-GFR determinants): generation from muscle or diet, tubular secretion by active transport, and extrarenal elimination by gastrointestinal bacteria or loss of "third-space" extracellular fluid. GFR estimating equations convert the serum creatinine concentration to the GFR scale and adjust for variation in non-GFR determinants that vary by age and sex, which provides a more meaningful assessment of GFR.

13] Can serum creatinine be used alone for GFR estimation?

No. Due to variation in these processes among individuals and over time within individuals, particularly the variation in creatinine generation, the cutoff for normal versus abnormal serum creatinine concentration differs among groups (**Table 2**); however, clinical laboratories generally report a single reference range for all adults. Because of the wide range of normal for serum creatinine in most clinical laboratories, GFR must decline to approximately half the normal level before the serum creatinine concentration rises above the upper limit of normal. Thus, an increase in serum creatinine almost always reflects a reduction in GFR, but people with decreased GFR may have normal serum creatinine.

14] What is the difference between creatinine clearance and GFR?

Creatinine is secreted by the proximal tubule as well as filtered by the glomeruli, thus creatinine clearance (Clcr) exceeds GFR by about 10% to 40% at all levels of GFR (the difference is higher at higher GFR and lower at lower GFR). Clcr can be measured (mClcr) from serum creatinine and creatinine excretion in a timed urine collection or estimated from serum creatinine using estimating equations (eClcr), such as the Cockcroft-Gault or Jelliffe equations. As with other clearance measurements, mClcr is inconvenient and frequently inaccurate. mClcr does not meet the criterion for acceptable accuracy compared to mGFR.

15] What is the currently recommended equation to estimate GFR from serum creatinine?

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Kidney Foundation (NKF), and American Society of Nephrology (ASN) recommend estimating GFR from serum creatinine using the 2021 CKD-EPI creatinine equations in people 18 years and older. This recommendation builds on prior recommendations as discussed below. In **Table 3** contains a summary of the previously recommended equations. See Questions 16 to 19 for details. For children, the recommended equations for estimating GFR are the 2009 Schwartz bedside creatinine equation or the 2012 CKiD creatinine-cystatin equation (Pediatric GFR Calculator | National Kidney Foundation).

16] What is the Cockcroft-Gault formula?

The Cockcroft-Gault formula was developed in 1976 using data from 249 men to estimate mClcr from approximately 30 to130 mL/min. It is not adjusted for body surface area and is not expressed for use with standardized Scr. In 1998, the US FDA recommended use of eClcr using the

TABLE 3: EQUATIONS TO ESTIMATE GFR				
EQUATION (YEAR)	CKD-EPI (2021)	CKD-EPI (2012)	MDRD Study (1999/2005)	Cockcroft-Gault (1978)
POPULATION	Diverse	Diverse	CKD	White men
REFERENCE METHODS	mGFR	mGFR	mGFR	mClcr
UNITS	mL/min/1.73 m^2	mL/min/1.73 m^2	mL/min/1.73 m^2	mL/min
FACTORS	Scr, age, sex	Scr, age, sex, race	Scr, age, sex, race	Scr, age, sex, weight
RECOMMENDATIONS (YEAR)	NKF-ASN Task Force Final Report (2021)	KDIGO (2013), KDOQI (2014), FDA (2020)	KDOQI (2002), FDA (2020)	FDA (1998), KDOQI (2002)

Cockcroft-Gault formula in drug development programs and for dose-adjustment of approved drugs in patients with decreased kidney function.

eClcr= {((140-age) x weight)/(72 SCr)} x 0.85 if female

where eClcr is expressed in milliliters per minute, age in years, weight in kilograms, and serum creatinine (SCr) in milligrams per deciliter. It was recommended by the 2002 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for routine GFR evaluation but is no longer recommended for this purpose (see Question 40.

17] What is the MDRD Study equation?

The 4-variable MDRD Study equation was developed in 1999 using data from 1628 patients with CKD, aged 18 to 70, predominantly Caucasian, nondiabetic, and with GFR from approximately 5 to 90 mL/min/1.73 m^2. It estimates mGFR adjusted for body surface area and is more accurate than mClcr using 24-hour urine collections or eClcr using the Cockcroft-Gault formula.[4] It underestimates mGFR at higher values of eGFR, so values above 60 mL/min/1.73 m^2 may not be reported as a numeric value. The equation is:

eGFR= 186 x (SCr) x (age) x (0.742 if female) x (1.210 if African American)

The equation was re-expressed in 2005 for use with a standardized serum creatinine assay, which yielded 5% lower values for serum creatinine concentration than in the MDRD Study laboratory:

eGFR= 175 x (Standardized S)-1.154 x (age)-0.203 x (0.742 if female) x (1.210 if African American)

eGFR is expressed in mL/min/1.73 m^2, SCr is serum creatinine expressed in mg/dL, and age is expressed in years.

The MDRD Study equation was initially recommended by the NKF-KDOQI CKD guideline of 2002 as an alternative to the Cockcroft-Gault equation but is no longer recommended.

18] What is the 2009 CKD-EPI creatinine equation?

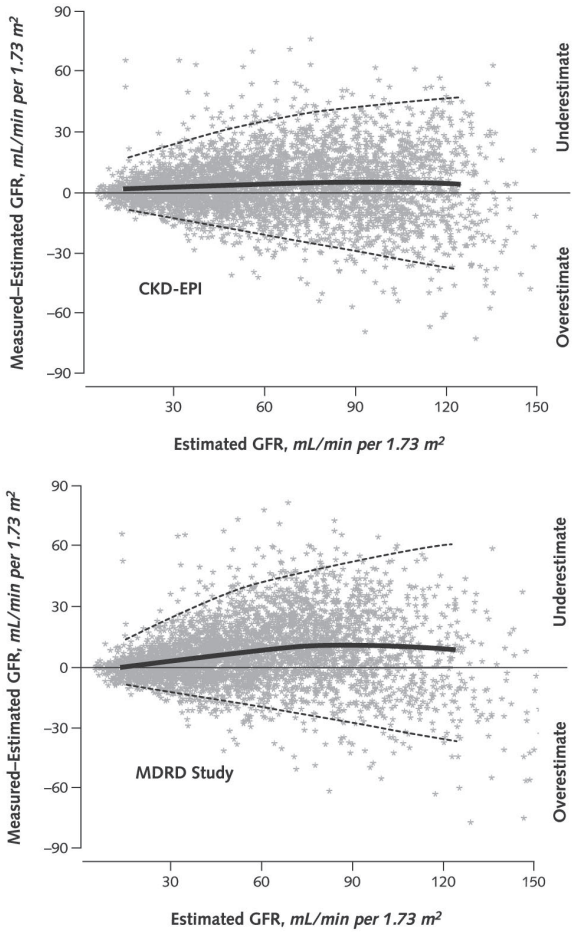
The CKD-EPI equation was developed in 2009 to overcome limitations of the MDRD Study equation. The CKD-EPI equation was developed in a cohort of 8254 people, predominantly Whites and Blacks with diverse characteristics, including people with and without kidney diseases, diabetes, and solid organ transplants who had a wide range of GFR (2 to 198 mL/min/1.73 m^2) and ages (18–97 years). The equation was validated in a separate cohort of 3771 people from 16 studies, GFR range (2 to 200 mL/min/1.73 m^2) and age range (18–93 years) **(Figure 4)**.

The CKD-EPI equation estimates GFR from serum creatinine, age, sex, and race.

$$eGFR= 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if Black]}.$$

eGFR is expressed in mL/min/1.73 m^2 SCr is serum creatinine expressed in mg/dL, and age is expressed in years.

FIGURE 4: COMPARISON OF PERFORMANCE OF MODIFICATION OF DIET IN RENAL DISEASE (MDRD) STUDY AND CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATIONS BY ESTIMATED GFR IN THE EXTERNAL VALIDATION DATASET*



Both panels show the difference between measured and estimated versus estimated GFR. A smoothed regression line is shown with the 95% CI (computed by using the lowest smoothing function in R), using quantile regression, excluding the lowest and highest 2.5% of estimated GFR. To convert GFR from mL/min per 1.73 m^2 to mL/s per m^2, multiply by 0.0167.

*Reprinted with permission from Levey AS, Stevens LA, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009:150.

The CKD-EPI equation is more accurate than the MDRD Study equation, particularly in people with higher levels of GFR, such as populations without kidney disease, young patients with type 1 diabetes without albuminuria, or people selected for evaluation for kidney donation. The CKD-EPI equation is as accurate as the MDRD Study equation in people with lower levels of GFR (populations with CKD). It estimates GFR from serum creatinine, age, sex, and race. The CKD-EPI equation is as accurate as the MDRD Study equation in the subgroup with estimated GFR <60 mL/min/1.73 m^2 and substantially more accurate in the subgroup with estimated GFR >60 mL/min/1.73 m^2 **(Figure 4)**. Thus, unlike with the MDRD Study equation, the CKD-EPI equation allows reporting of numeric values across the entire GFR range.

The CKD-EPI 2009 equation was recommended by the 2012 KDIGO CKD Guideline and the 2014 KDOQI CKD Guideline Commentary to replace the MDRD Study equation, with reporting of numeric values across the range. It was recommended by the 2020 FDA draft guidance update for drug development programs

19] Why was the CKD-EPI creatinine equation revised in 2021?

The inclusion of race in clinical algorithms in medicine is being questioned. Race is a social, not a biological construct; therefore, its definition lacks precision and tends to be dynamic over time and in different places. There is also a concern that use of race in clinical algorithms, such as GFR estimating equations, may increase disparities and lead to implicit bias in medical care. The CKD-EPI 2021 equation is a response to these questions and now provides a way to accurately estimate the GFR without need to specify race.

In 2021, a new equation was redeveloped from the same development data set as the 2009 equation, but without inclusion of race, and was validated in 4050 participants in 12 studies. Thus, GFR can now be estimated using serum creatinine, age, and sex alone. The 2021 equation averages observed differences across all individuals in the 2009 development data set, so it may be more equitable than the 2009 equation and may be more appropriate for the increasingly diverse US population.

eGFR=

$142 \times \min(Scr/k,1)^{\alpha} \times \max(Scr/k,1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female] where k is 0.7 for females and 0.9 for males, α is -0.241 for females and -0.302 for males, min indicates the minimum of Scr/k or 1, max indicates the maximum of Scr/k or 1

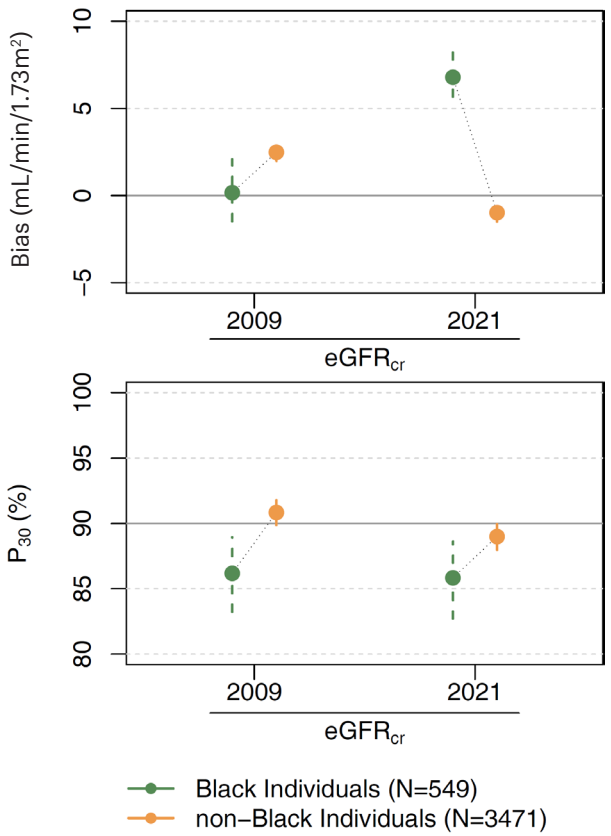
eGFR is expressed in mL/min/1.73 m^2, Scr is serum creatinine expressed in mg/dL, and age is expressed in years.

The 2021 CKD-EPI creatinine equation was recommended by the NKF-ASN Task Force based on a rigorous review process.

20] What is the difference in eGFRcr using the 2021 versus the 2009 equation?

Compared to the 2009 CKD-EPI creatinine equation, the 2021 CKD-EPI creatinine equation will lead to lower eGFR in patients who self-identify as Black race and to higher eGFR in patients who self-identify as non-Black race **(Table 4)**. Although the 2021 equation is less accurate than the 2009 equation, it is sufficiently accurate for clinical use in most routine circumstances and avoids the need to specify race **(Figure 5)**.

FIGURE 5: PERFORMANCE OF 2009 AND 2021 CKD-EPI CREATININE EQUATIONS COMPARED TO DIRECTLY MEASURED GFR



Top panel: Bias as measured as the median difference between measured and estimated GFR and units are in mL/min/1.73 m^2. The horizontal line at 0 indicates the optimal result of no difference between measured and estimated GFR for the group.

Bottom panel: P_{30} is measured as the percentage of estimates within 30% of measured GFR. The horizontal line at 90% represents the optimal result for P_{30}.

The lower eGFR in Black individuals would increase the estimated prevalence of CKD, could enable earlier diagnosis and treatment, but conversely could also lead to missed opportunities for treatments contraindicated at low GFR. In contrast, higher eGFR in non-Black individuals results in decreased estimated prevalence of CKD, and potentially missed diagnosis of CKD, and inappropriate exposure to medications or interventions that are contraindicated at lower levels of GFR.

21] Should clinical laboratories report eGFR when Scr is measured?

Most clinical laboratories are now reporting eGFRcr when serum creatinine is measured. The Kidney Disease Education Program, ASN, and NKF have all recommended that laboratories automatically report eGFRcr whenever a serum creatinine is ordered. The NKF and ASN Task Force on reassessing the inclusion of race in diagnosing kidney diseases recently recommended that clinical laboratories should begin using the 2021 CKD EPI creatinine equation to report estimated GFR.

22] Should clinical laboratories that use the MDRD Study equation for GFR reporting also change to the 2021 CKD-EPI creatinine equation?

According to the College of American Pathologists 2019 survey, many laboratories continue to report eGFRcr using the MDRD equation. The NKF-ASN Task Force final report recommendations present an opportunity to reinvigorate efforts to harmonize laboratory reporting of eGFRcr using 2021 CKD-EPI nationwide.

The NKF recommends transitioning to the 2021 CKD-EPI creatinine equation as it is more accurate than the MDRD eGFRcr, this clearly benefiting clinical decision making. In addition, the MDRD Study equation also includes race. Finally, with the MDRD Study equation, numeric values can only be reported for values <60 mL/min/1.73 m^2.

23] Why might different laboratories or health systems report different eGFR for the same patient?

There may be some variability in how laboratory or health information systems express age (as the nearest whole number or using 1 or 2 decimal points) or serum creatinine (1 or 2 decimal places). These differences are usually within 1–2 mL/min/1.73 m^2 of each other and not clinically significant.

24] Are calculators available for the CKD-EPI creatinine, MDRD Study, or Cockcroft-Gault equations?

All equations have been programmed into medical decision support apps for mobile devices and are available on Internet websites, such as https://www.kidney.org/professionals/kdoqi/gfr_calculator. Although all equations are included, the 2021 CKD-EPI creatinine equation is preferred.

TABLE 4: DIFFERENCE IN EGFR USING THE 2009 AND 2021 CKD-EPI CREATININE EQUATIONS FOR SELECTED AGE AND SERUM CREATININE VALUES, FOR MEN AND WOMEN AND FOR BLACK AND NON-BLACK INDIVIDUALS

RACE GROUPS	AGE		50 YEARS OLD				75 YEARS OLD			
	CREATININE (mg/dL)		0.6	1	1.5	2	0.6	1	1.5	2
Black	Men	2009 eGFRcr	136	101	62	44	114	85	52	37
		2021 eGFRcr	118	92	56	40	101	78	48	34
		Difference	***18***	***9***	***6***	***4***	***13***	***7***	***6***	***3***
	Women	2009 eGFRcr	124	76	47	33	104	64	39	28
		2021 eGFRcr	109	69	42	30	94	59	36	26
		Difference	***15***	7	***5***	***3***	***10***	***5***	***3***	***1***
Non-Black	Men	2009 eGFRcr	117	87	54	38	98	73	45	32
		2021 eGFRcr	118	92	56	40	101	78	48	34
		Difference	***-1***	***-5***	***-2***	***-2***	***-3***	***-5***	***-3***	***-2***
	women	2009 eGFRcr	107	66	40	28	89	55	34	24
		2021 eGFRcr	109	69	42	30	94	59	36	26
		Difference	***-2***	***-3***	***-2***	***-2***	***-5***	***-4***	***-2***	***-2***

25] What factors affect creatinine generation?

Factors affecting creatinine generation can include age, body habitus, muscle mass, or diet. **Table 5** shows the effect on serum creatinine of factors affecting creatinine generation.

26] What factors affect creatinine secretion?

Some medications inhibit tubular secretion of creatinine, thereby decreasing creatinine clearance and increasing serum creatinine without a change in GFR. Some commonly used medications include:

- Antimicrobial: trimethoprim
- Antiarrhythmic: dronedarone
- H2 blocker: cimetidine
- HIV treatment: dolutegravir and cobicistat and rilpivirine
- PARP inhibitors: olaparib and rucaparib
- Tyrosine kinase inhibitors: imatinib, bosutinib, and sorafenib. Sunitinib, crizotinib, gefitinib, and pazopanib may inhibit SLC47A1-mediated secretion of creatinine.

27] What is the impact of calibration and inter-laboratory variation of serum creatinine assays on the estimation of GFR?

The older now less commonly used assay for serum creatinine, the alkaline picrate ("Jaffe") assay, detects a color change when creatinine interacts with picrate under alkaline conditions and is subject to interference from substances other than creatinine ("non-creatinine chromogens"), such as proteins and ketoacids. Newer more commonly used enzymatic methods improve upon some of the non-specificities of the alkaline picrate assay, but some are subject to other interferences. Calibration of creatinine assays to adjust for this interference has been standardized across methods and laboratories as of 2010 and has reduced variation among clinical laboratories in GFR estimates using the same equation.

28] What factors affect the creatinine assays?

Serum proteins, as well as glucose and ketoacids in high levels (as occurs in diabetic ketoacidosis), interfere with the alkaline picrate assay, giving rise to false elevations in serum. There is thought to be less interference with enzymatic methods, but there are reports of interference by bilirubin and monoclonal IgG.

TABLE 5: FACTORS AFFECTING SERUM CREATININE CONCENTRATION

	Effect on Serum Creatinine	Mechanism/Comment
Older Age	Decrease	Reduction in creatinine generation due to age-related decline in muscle mass
Female Sex	Decrease	Reduced creatinine generation due to reduced muscle mass
Diet		
Restriction of Dietary Protein	Decrease	Decrease in creatinine generation
Ingestion of Cooked Meats	Increase	Transient increase in creatinine generation; however, this may be blunted by transient increase in GFR
Body Habitus		
Muscular	Increase	Increased creatinine generation due to increased muscle mass ± increased protein intake
Malnutrition/muscle wasting/amputation	Decrease	Reduced creatinine generation due to reduced muscle mass ± reduced protein intake
Obesity	No Change	Excess mass is fat, not muscle mass, and does not contribute to increased creatinine generation

*From Levey AS. *Am J Kidney Dis.* 1993;22:207–214.

29] What was the effect of standardization of the creatinine assay on GFR estimates?

The process of standardization of the creatinine assays in clinical laboratories was completed in 2010. After standardization, serum creatinine results in most clinical laboratories declined by 0.1–0.3 mg/dL. The CKD-EPI equation was developed for use only with standardized values. The MDRD Study equation has been re-expressed for standardized serum creatinine. Use of the re-expressed MDRD Study equation with standardized serum creatinine improves the accuracy of GFR estimates using that equation. The Cockcroft-Gault equation has not been re-expressed for use with standardized serum creatinine. GFR estimates using the Cockcroft-Gault equation with standardized serum creatinine will generally be higher and less accurate than with non-standardized creatinine. Biological variability of creatinine is not affected by standardization; therefore, use of creatinine assay in some populations having extreme ages or weights remains a limitation, e.g., children, elderly, obese, or malnourished. Alternative methods should be used when creatinine production or metabolism is impaired.

30] What are indications for confirmation of eGFRcr?

Confirmatory tests should be considered in circumstances when the estimating equation based on serum creatinine is suspected to be inaccurate or when highly accurate values are needed (**Table 6).**

TABLE 6: INDICATIONS FOR A CONFIRMATORY TEST*

Patient factor leading to inaccurate eGFRcr
Extremes of body size
Severe malnutrition or obesity
Disease of skeletal muscle
Paraplegia or quadriplegia
Vegetarian diet
Rapidly changing kidney function
Pregnancy
Transgender
Drug factors
Drugs that effect tubular secretion
Drugs that effect creatinine assay
Clinical settings in which accurate GFR assessment is required
Kidney donation evaluation
Treatment with drugs with significant toxicity that are excreted by the kidneys

*From Inker LA, Titan S. *Am J Kidney Dis*. 2021;78:736-749.

31] What is cystatin C and how is serum cystatin C used in cystatin C-based GFR estimating equations (eGFRcys)?

Cystatin C is a 13 kDa, non-glycosylated, basic protein that is produced by all nucleated cells. It is a member of the cystatin superfamily of cysteine protease inhibitors. Cystatin C is freely filtered by the glomerulus and then reabsorbed and catabolized by the tubular epithelial cells, with only small amounts excreted in the urine.

The generation of cystatin C appears to be less variable and less affected by age, sex, race, and diet than creatinine. Thus, the coefficients for age and sex in eGFRcys are smaller than in eGFRcr equations, and race is not required in eGFRcys. Some studies have reported increased cystatin C levels associated with higher levels of C-reactive protein or body mass index (BMI), hyperthyroidism, and steroid use, but these variables are generally not included in eGFRcys because they are not routinely available in laboratory information systems.

32] Is cystatin C a more accurate filtration marker than creatinine?

Some studies show that serum levels of cystatin C are more highly correlated with GFR than serum creatinine alone, however estimated GFR from cystatin C (eGFRcys) is generally not more accurate than eGFRcr. The combination of cystatin C and creatinine combined in an estimating equation (eGFRcr-cys) is more accurate than either eGFRcr or eGFRcys.

33] Can serum cystatin C (Scys) be used alone for GFR estimation?

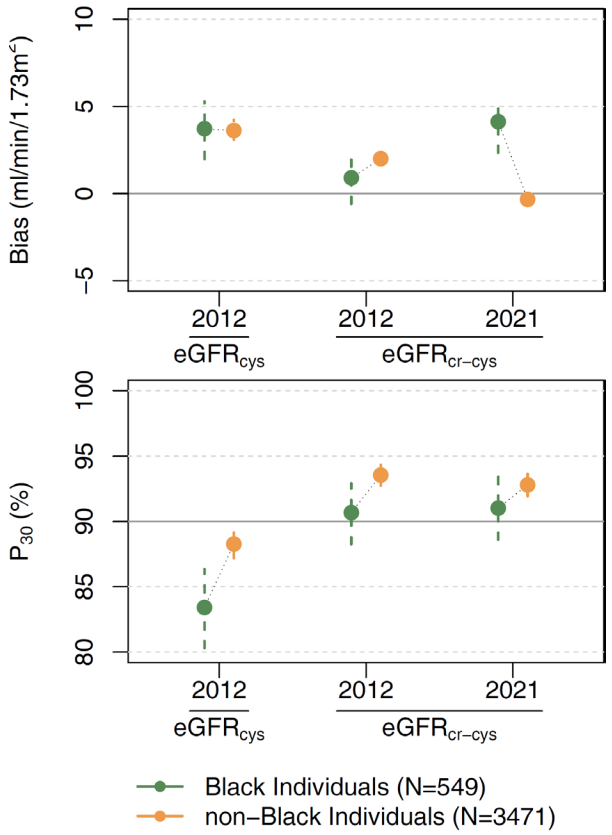
No. Like Scr, the normal range for Scys varies by age and sex (to a lesser extent than age).

34] What is the currently recommended equation to estimate GFR from serum cystatin C?

The NKF and ASN recommend estimating GFR from serum creatinine and cystatin C using the 2021 CKD-EPI creatinine-cystatin C equation, which does not require use of race (**Figure 6**). The 2012 KDIGO CKD guideline recommended estimating GFR from cystatin C using either than the 2012 CKD-EPI Cystatin C equation or 2012 CKD-EPI creatinine-cystatin C equation; the latter equation includes a term for Black race.

eGFR= 135 x min(Scr/κ,1)α x max(Scr/κ,1)-0.544 x min(Scys/0.8,1)-0.323 x max(Scys/0.8,1)-0.778 x 0.9961Age x 0.963 [if female]

FIGURE 6



Top panel: Bias as measured as the median difference between measured and estimated GFR and units are in mL/min/1.73 m^2. The horizontal line at 0 indicates the optimal result of no difference between measured and estimated GFR for the group.

Bottom panel: P_{30} is measured as the percentage of estimates within 30% of measured GFR. The horizontal line at 90% represents the optimal result for P_{30}.

eGFRcys, estimated GFR from cystatin C; eGFRcr-cys, estimated GFR from creatinine and cystatin C together. The vertical bars indicate 95% confidence intervals. The dotted black line between the green and orange symbols represents the difference in the GFR equation performance between race groups.

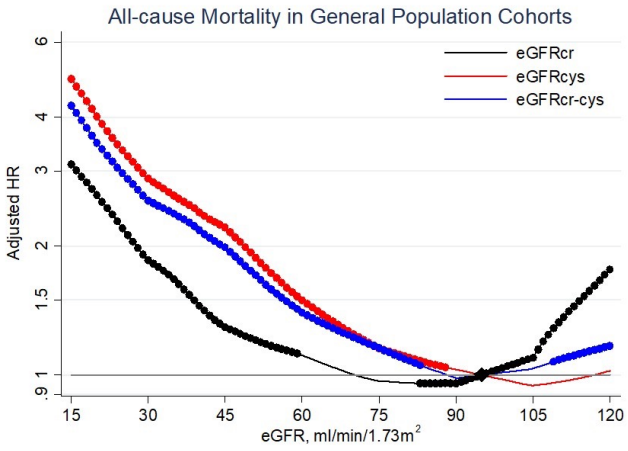
35] Why is eGFRcr-cys more accurate than either eGFRcr or eGFRcys?

In general, the use of multiple filtration markers in an estimation equation is more accurate than either single marker, if the non-GFR determinants of the filtration markers are not correlated with each other, as in the case of creatinine and cystatin C. This is the rationale for the development of equations using panels of filtration markers (panel eGFR) including metabolites in addition to creatinine and low molecular proteins in addition to cystatin C.

36] Cystatin C and risk

eGFRcys is a better predictor of adverse events in the elderly, including mortality, heart failure, bone loss, peripheral arterial disease, and cognitive impairment, than eGFRcr (**Figure 7).**

FIGURE 7



Shown are hazard ratios for death from any cause, according to whether the eGFR was calculated with the measurement of creatinine, cystatin C, or both. The graph shows associations by plotting the adjusted hazard ratio versus the reference point, which is indicated by a black diamond (at 95 ml/min/1.73 m2of body-surface area for death from any cause. The hazard ratios were adjusted for age, sex, race, body-mass index, systolic blood pressure, total cholesterol, presence or absence of a history of cardiovascular disease, smoking status, presence or absence of diabetes, and level of albuminuria. Solid circles indicate that the adjusted hazard ratio at the indicated eGFR level was significant, as compared with the reference point. For death from any cause, the meta-analysis included 11 general-population cohorts with 90,750 participants, of whom 12,351 died during follow-up. Modified and reproduced from Shlipak M, Matsushita K, Ärnlöv J, et al. N Engl J Med. 2013;369:932–934.

37] When should cystatin C be measured?

Accurate GFR estimation includes both serum creatinine and cystatin C for initial diagnosis and staging. KDIGO currently recommends cystatin C as a confirmatory test in the following clinical circumstances:

1. eGFRcr 45–59 mL/min/1.73 m^2 without markers of kidney damage to confirm CKD stage G3a
2. Clinical conditions associated with variation in non-GFR determinants of serum creatinine not associated with age and sex (diet, muscle mass, drugs that affect creatinine secretion, increased extra-renal elimination)
3. Clinical circumstances when more accurate levels of GFR are required, e.g., dosing of chemotherapy or antibiotics cleared by the kidney (see Question 30 and **Table 6**).

In addition, clinicians could consider:

4. eGFRcr 60–74 mL/min/1.73 m^2 without markers of kidney damage to confirm no CKD.

INTERPRETATION OF GFR ESTIMATES

38] How should differences in a patient's eGFR be interpreted during the transition from the old to the new equations?

The rationale for the development of the 2021 CKD-EPI equations is to avoid classification by race. On average, for patients who previously identified as Black, eGFR using the 2021 equations will be lower than eGFR using the 2009 creatinine or 2012 creatinine-cystatin C equation (**Table 4**). On average, for patients who previously identified as non-Black, eGFR using the 2021 equations will be higher than eGFR using the 2009 creatinine or 2012 creatinine-cystatin C equations. The magnitude of the difference will depend on age and sex (see **Table 5**). These differences may impact whether or not the patient has CKD, the CKD G stages, medication use and dosing, the need for interdisciplinary care and decisions about kidney replacement therapy planning and initiation. Given the limited precision of the equations, small differences in eGFR may not be clinically important. If there is uncertainty about clinical decision-making using the 2021 creatinine equations, it is recommended to measure serum cystatin C and use of the 2012 cystatin C equation and the 2021 creatinine-cystatin C equation. For the 2021 creatinine-cystatin C equation, the difference in eGFR compared to the 2012 creatinine-cystatin C equation is smaller than the difference between the 2021 and 2009 creatinine equations.

39] To which populations or individuals do the CKD-EPI 2021 equations not apply?

The equations should not be used in children (age <18 years); equations derived from the Chronic Kidney Disease in Children (CKiD) study are more accurate in children. The equations have not been validated in pregnant women. The equations are less accurate in the non-steady state and in patients with variation in non-GFR determinants of serum creatinine and cystatin C unrelated to age and sex (see Questions 12, 13, and 31).

40] Why is the Cockcroft-Gault equation still used, even though it is less accurate?

Prior to standardized calibration of creatinine assays, pharmacokinetic (PK) studies used the Cockcroft-Gault equation to estimate level of kidney function for dosage adjustment in drug labels. As a result, the Cockcroft-Gault equation was the standard for drug dosing. The variability in creatinine assays at the time led to inconsistent translation from the PK studies into clinical practice. With creatinine standardization, this inconsistency is worsened. Recommendations from the National Kidney Disease Education Program and KDIGO are to use the most accurate method of kidney function assessment for drug dosing purposes. Updated FDA guidance recommends using eGFR with standardized creatinine for drug development since it is more accurate and more widely used for GFR assessment than the Cockcroft-Gault equation. However, for previously approved drugs, there is no systematic method to update drug dosing recommendations using the Cockcroft-Gault equation.

41] How should GFR estimates be used to detect CKD?

Testing for CKD includes evaluation of GFR and markers of kidney damage. **Table 7** shows the interpretation of GFR and markers of kidney damage. eGFRcr is the first step in the evaluation of GFR; eGFRcys and eGFRcr-cys, mClcr and mGFR are confirmatory tests. Markers of kidney damage include albuminuria, urinalysis, imaging of the kidneys and urinary tract, serum electrolytes, and kidney biopsy (if the results would change management). There will be some uncertainty for patients without markers of kidney damage in whom eGFRcr is between 45 and 75 mL/min/1.73 m^2. Confirmatory tests for GFR evaluation can be useful for patients with eGFRcr 45–59 mL/min/1.73 m^2 (for confirmation of CKD) and for patients with eGFRcr 60–75 mL/min/1.73 m^2 (confirmation of no CKD).

TABLE 7: DETECTION OF CKD USING ESTIMATED GFR AND MARKERS OF KIDNEY DAMAGE

Marker of Kidney Damage	GFR	CKD	What to do?
+	<60	Y	Action Plan
+	>60	Y	Action Plan
-	<60	Y*	Action Plan*
-	>60	N	

*The differing accuracy of current estimating equations in people with and without CKD may make it difficult to interpret GFR estimates near 60 mL/min/1.73 m^2 in patients without markers of kidney damage (see Questions 28 and 31). [33]

From Stevens LA, Levey AS. Am J Kid Dis. 2009;53(suppl 3):S17–26.

Clinical decision making will also depend on other patient characteristics, such as age, the presence or absence of risk factors for CKD, or complications of CKD. In some patients, clinicians may decide to perform additional evaluation for CKD (for example, eGFRcr 60–74 mL/min/1.73

m^2 in younger patients) or to defer further evaluation for CKD (for example, eGFRcr 45–59 mL/min/1.73 m^2 in older patients). In either case, it may be prudent to:

- Perform periodic reassessment of GFR
- Counsel the person to avoid medications that can damage the kidneys (such as ibuprofen)
- Adjust the dosage of medications that are eliminated by the kidney
- Consider consultation with a nephrologist regarding the patient's lab and imaging studies
- Refer the patient to a nephrologist. (See Question 48 for indications.)

42] How can GFR estimates be used to detect progression?

Current guidelines recommend using GFR estimates to monitor progression of CKD. Clinicians should not rely on monitoring serum creatinine alone to detect the level and rate of CKD progression.

43] Do some drugs affect the accuracy of GFR estimates?

Drug-induced reduction in GFRcr may be caused by decreased GFR or inhibition of tubular serum creatinine. In most cases, these two conditions can be distinguished by repeating eGFRcr after discontinuing the drug. In addition, eGFRcys can distinguish between these conditions: eGFRcr and eGFRcys will be decreased by conditions that lower GFR, whereas eGFRcr but not eGFRcys will be decreased by conditions that inhibit tubular secretion of creatinine.

44] Should indexed or non-indexed eGFR be used when dosing medications?

Drug dosing is based on GFR measurements or estimates that are not indexed for body surface area. GFR estimates indexed for body surface area will generally be adequate except in patients with body size that is very large or very small. In these patients, non-indexed eGFR can be computed from indexed eGFR (see section above). The accuracy of non-indexed eGFR compared to non-indexed mGFR is similar to indexed eGFR compared to indexed mGFR.

45] Can the estimating equations for GFR be used in acute kidney injury?

Similar to serum creatinine, eGFRcr is less accurate compared to mGFR in settings where the GFR is changing rapidly, such as acute kidney injury. "Kinetic" eGFR equations have been proposed for this use but have not been widely validated.

46] Can GFR estimates be used in hospitalized patients?

eGFRcr estimates can be used in patients who are in the hospital; however, it is important to pay attention to potential inaccuracies due to the non-steady state of serum creatinine, comorbid conditions that cause malnutrition, and use of medications that interfere with the measurement of serum creatinine.

CHRONIC KIDNEY DISEASE

47] What is the public health problem associated with CKD?

CKD is a worldwide public health problem. Adverse outcomes of CKD include loss of kidney function, sometimes leading to kidney failure, cardiovascular hospitalization, premature death, and reduced quality of life. Some of the adverse outcomes of CKD can be prevented or delayed by early diagnosis and treatment. Unfortunately, CKD is under-diagnosed and under-treated. As a step toward improvement of this health care problem, the NKF published KDOQI guidelines for the classification and evaluation of CKD.

48] What is the definition of CKD and how is GFR used as a criterion for CKD?

CKD is defined as either the presence of kidney damage or GFR <60 mL/min/1.73 m^2 for 3 or more months and can be diagnosed without knowledge of its cause. (See Table 8.)

- In most healthy young people, the normal GFR is 90 mL/min/1.73 m^2 or higher.
- A GFR of 60–89 mL/min/1.73 m^2 without kidney damage may be normal in some people (such as the elderly, infants).

TABLE 8: CLASSIFICATION OF CKD

Cause (C)
GFR (G)
Albuminuria (A)

KDIGO 2012

GFR Categories, Description, and Range (mL/min/1.73 m^2)				Albuminuria Categories, Description and Range		
				A1	**A2**	**A3**
				normal to mildly increased	moderately increased	severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	normal or high	>90			
	G2	mildly decreased	60-89			
	G3a	mildly to moderately decreased	45-59			
	G3b	moderately to severely decreased	30-44			
	G4	severely decreased	15-29			
	G5	kidney failure	<15			

GFR Categories

Category	GFR (ml/min/1.73 m^2)	Terms	Clinical Action Plan*
G1**	>90	Normal or high	• Diagnose and treat the cause • Treat comorbid conditions • Evaluate for CKD risk factors • Start measures to slow CKD progression • Start measures to reduce CVD risk
G2*	60-89	Mildly decreased***	• Estimate progression
G3a	45-59	Mildly to moderately decreased	• Adjust medication dosages as indicated • Evaluate and treat complications
G3b	30-44	Moderately to severely decreased	
G4	15-29	Severely decreased	• Prepare for kidney replacement therapy (transplantation and/or dialysis)
G5	<15	Kidney failure (add D if treated by dialysis)	• Start kidney replacement therapy (if uremia present)

*Actions are cumulative. **GFR categories G1 or G2 without markers of kidney damage do not fulfill the criteria for CKD. ***Relative to young adult level.

Albuminurai Categories

Category	AER (mg/d)	Approximately Equivalent ACR (mg/mmol)	Approximately Equivalent ACR (mg/g)	Terms	Clinical Action Plan*
A1	<30	<3	<30	Normal to mildly increased	• Diagnose and treat the cause • Treat comorbid conditions • Evaluate for CKD risk factors • Start measures to slow CKD progression • Start measures to reduce CVD risk
A2	30-299	3-30	30-299	Moderately increased**	• Renin-angiotensin system blockers, sodium glucose transporter 2 inhbition, mineralocorticoid receptor antagonist in diabetic kidney disease
A3	>300	≥30	>300	Severely increased	• Treat nephritic syndrome or nephrotic syndrome (if present)

*Actions are cumulative. **Relative to young adult level.

- A GFR >60 mL/min/1.73 m^2 for 3 months or more, with kidney damage (such as persistent albuminuria), meets the criteria for CKD.
- A GFR <60 mL/min/1.73 m^2 for 3 months or more, even in the absence of kidney damage, meets the criteria for CKD.
- Because of variability in urinary albumin excretion, at least 2 specimens, preferably first morning void, collected within a 3- to 6-month period should be abnormal before considering a patient to have crossed 1 of these diagnostic thresholds.
- Exercise within 24 hours, infection, fever, congestive heart failure, marked hyperglycemia, pregnancy, marked hypertension, urinary tract infection, and hematuria may increase urinary albumin over baseline values.

49] What are the stages of CKD?

CKD is classified according to cause, GFR, and albuminuria (CGA classification system). **Table 8** outlines the stages of CKD and the clinical actions that are recommended at each stage. The action plan is cumulative in that recommended care at more severe stages of disease includes care recommendations for the less severe stages of disease, as well as additional interventions that are required for more advanced disease.

50] What are markers of kidney damage?

The most common causes of CKD in North America are diabetes and hypertension; therefore, persistent proteinuria (albuminuria) is the principal marker of kidney damage. Other markers of damage include:

- Abnormalities in composition of the blood or urine
- Abnormal findings on imaging studies (**Table 9**).

51] What is the recommended method to screen for albuminuria or proteinuria?

The KDIGO 2012 and KDOQI 2014 CKD clinical practice guideline and commentary, respectively, suggest using the following measurements for initial testing of proteinuria (in descending order of preference; in all cases an early morning urine sample is preferred).

1. urine albumin-to-creatinine ratio (uACR);
2. urine protein-to-creatinine ratio (uPCR);
3. reagent strip urinalysis for total protein with automated reading;
4. reagent strip urinalysis for total protein with manual reading.

The uACR in spot urine specimens is the preferred because this test is a more sensitive and specific measure of kidney damage than uPCR or urine protein dipstick testing. Another rationale for this recommendation is that urine albumin standardization efforts are ongoing and urine creatinine standardization is essentially established, whereas urine protein measurement is comprised of 3 assays that limit the feasibility of standardization across laboratories. In addition, the microalbuminuria term is to be avoided or replaced with the A CKD stages as part of the C-G-A CKD classification or with the familiar heat map for the G and A (see **Table 8**).

TABLE 9: INTERPRETATION OF ABNORMALITIES ON IMAGING STUDIES AS MARKERS OF KIDNEY DAMAGE

Imaging Modality/Feature	Associated Kidney Disease
Ultrasonography • General appearance • Increased echogenicity • Small, "hyperechoic" kidneys • Large kidneys • Size disparities and scarring • Doppler interrogation	May show nephrocalcinosis or discrete stones, hydronephrosis, cysts, or masses May indicate cystic disease or "medical renal disease" Generally indicate chronic kidney disease Generally indicate tumors, infiltrating diseases or diseases causing nephrotic syndrome Suggest vascular, urologic or tubulointerstitial diseases due to stones or infection May be useful in investigation of venous thrombosis, less so in arterial stenosis
Intravenous pyelography (IVP)a	May reveal asymmetry of kidney size or function, presence of obstructing stones, tumors, scars, or dilated collecting ducts in medullary sponge kidney
Computed tomography (CT)b	May show obstruction, tumors (eg. angiomyolipoma), cysts or ureteral calculi. Helical CT with contrast may show sites of anatomic renal artery stenosis.
Magnetic resonance imaging (MRI)	May show mass lesions, renal vein thrombosis, cysts, etc.
Nuclear scansc	May reveal asymmetry of kidney size or function, functional evidence of renal artery stenosis, acute pyelonephritis, or scars

[a]This modality has been largely supplanted by computed tomography, although it remains useful to describe fine detail in the collecting system.
[b] With or without contrast
[c] Captopril renography, mercaptoacetyltriglycine (MAG3), dimercaptosuccinic acid (DMSA)

52] What are the complications and common comorbidities associated with CKD?

CKD results in loss of kidney function, sometimes leading to kidney failure. A person with kidney disease may develop other serious complications including:

- Hypertension
- Malnutrition / poor nutritional health (negative metabolic balance)
- Anemia
- Mineral and bone disorders, including hyperphosphatemia, hypocalcemia, and vitamin D deficiency
- Secondary hyperparathyroidism
- Metabolic acidosis
- Hypoalbuminemia
- Dyslipidemia (hypercholesterolemia, hypertriglyceridemia)
- Cardiovascular disease [some examples include coronary heart disease (CAD), left ventricular hypertrophy (LVH), heart failure, peripheral vascular disease (PVD), and valvular heart disease (VHD)]
- Vascular calcification
- Neuropathy
- Reduced ability to perform activities of daily living
- Lowered quality of life.

Complications may be a result of reduction in GFR, disorders of tubular function, or reduction in endocrine function of the kidney. These may be problems in themselves or may increase risk for other problems. For example, hypertension is a complication of CKD, but also increases the risk of cardiovascular disease and stroke. Some of these complications can be prevented or delayed by early diagnosis and treatment.

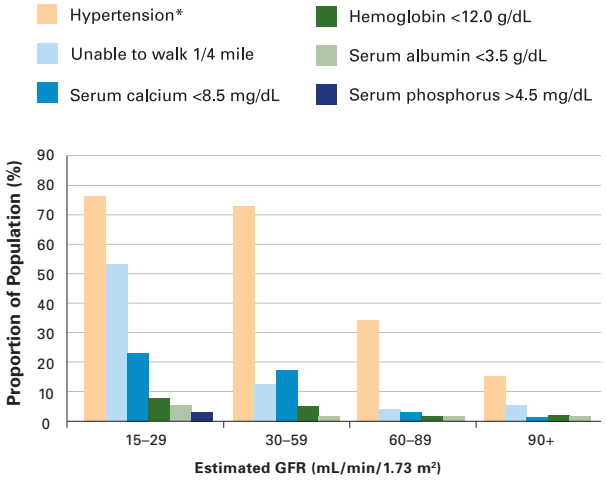
53] Does the risk of complications increase as kidney disease progresses?

The prevalence of complications increases as GFR falls below 60 mL/min/1.73 m^2 (CKD stage G3a or higher). These patients should be evaluated for the presence of these complications. **Figure 8** shows the prevalence of complications at each stage of CKD.

54] When should patients with kidney disease be referred to a nephrologist?

Patients should be referred to a nephrologist for co-management or consultation for the indications shown in **Table 10**.

FIGURE 8: RELATIONSHIP OF ESTIMATED GFR TO COMPLICATIONS ASSOCIATED WITH CHRONIC KIDNEY DISEASE



* ≥140/90 or antihypertensive medication *P*-trend <0.001 for each abnormality

From National Kidney Foundation: KDOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Kidney Disease Outcomes Quality Initiative. *Am J Kidney Dis.* 2002;39(suppl 1):S1–266.

TABLE 10: WHEN TO REFER A PATIENT TO A NEPHROLOGIST

AKI or abrupt sustained fall in GFR
GFR < 30 mL/min/1.73 m2 (GFR categories G4–G5)
Progression of CKD with a sustained decline in eGFR > 5 mL/min/1.73 m2/year per year
A consistent finding of significant albuminuria, uACR > 300
Urinary red blood cell casts or persistent unexplained hematuria
CKD and hypertension refractory to treatment with 4 or more antihypertensive agents
Persistent abnormalities of serum potassium or other difficult to manage CKD complications
Recurrent or extensive nephrolithiasis
Hereditary kidney disease or unknown cause of CKD
Uncertainty about GFR evaluation

CKD-related complications and risk of development of kidney failure are highest among patients with CKD stages G4 and G5. Late referral to nephrologists prior to dialysis initiation (GFR <15 mL/min/1.73 m^2) can result in a higher rate of morbidity and mortality. Some of the many other reasons to refer to a nephrologist are listed in **Table 10**.

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