

FREQUENTLY ASKED QUESTIONS ABOUT GFR ESTIMATES

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MEASUREMENT 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.

2) How is GFR measured?

GFR cannot be measured directly. The urinary or plasma clearance of an ideal filtration marker, such as inulin, iothalamate or iohexol, is the gold standard for the measurement of GFR.¹ However, this is cumbersome and not used in clinical practice. Instead, serum levels of endogenous filtration markers, such as creatinine, have traditionally been used to estimate GFR, along with urinary measurements in some cases. However, serum creatinine alone is not an adequate marker of kidney function.

3) What does GFR indicate?

GFR is usually accepted as the best overall index of kidney function. A clinician or medical laboratory can estimate GFR from a person's serum creatinine level and some or all of the following variables: gender, age, weight, and race.

- In most healthy people, the normal GFR is 90 mL/min/1.73 m² or higher.
- A result of 60–89 mL/min/1.73 m² without kidney damage may be normal in some people (such as the elderly, infants).

- A result of 60–89 mL/min/1.73 m² for three months or more, along with kidney damage (such as persistent protein in the urine), means the person has early kidney disease.
- When GFR is <60 for three months or more, chronic kidney disease (CKD) is present.

4) Why measure GFR as an index of kidney function?

The level of GFR and its magnitude of change over time are vital to:

- the detection of kidney disease
- understanding its severity
- making decisions about diagnosis, prognosis, and treatment

Normal GFR varies according to age, sex, and body size; in young adults it is approximately 120-130 mL/min/1.73 m² 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 chronic kidney disease (CKD). Below 60 mL/min/1.73 m², 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.¹

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

CLINICAL DECISIONS	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 • Detection of CKD progression
Prognosis	<ul style="list-style-type: none"> • Risk of CKD complications • Risk for CVD • Risk for mortality 	<ul style="list-style-type: none"> • Risk for kidney failure
Treatment	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Treatment of AKI • Monitoring drug toxicity

Abbreviations: AKI: acute kidney injury; CKD: chronic kidney disease; CVD: cardiovascular disease.

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5) Why are GFR estimates adjusted for body surface area?

Kidney function is proportional to kidney size, which is proportional to body surface area. A body surface area of 1.73 m² is the normal mean value for young adults. Adjustment for body surface area is necessary when comparing a patient's estimated GFR to normal values or to the levels defining the stages of CKD.

6) How does age affect GFR?

GFR declines gradually with age, even in people without kidney disease. However, there appears to be substantial variation among individuals and the reasons for decline are not known. Although the age-related decline in GFR was formerly considered part of normal aging, decreased GFR in the elderly is an independent predictor of adverse outcomes, such as death and cardiovascular disease. In addition, decreased GFR in the elderly requires adjustment in drug dosages, as with other patients with CKD.

Table 2 shows the average values of estimated GFR by decade in the general population, based on a small study of men.

TABLE 2: AVERAGE MEASURED GFR BY AGE IN PEOPLE WITHOUT CKD ²	
AGE (Years)	AVERAGE MEASURED GFR (mL/min/1.73 m ²)
20-29	116
30-39	107
40-49	99
50-59	93
60-69	85
70+	75

7) What is the difference between creatinine clearance and GFR?

Creatinine clearance exceeds GFR because creatinine is secreted by the proximal tubule as well as filtered by the glomerulus. Creatinine clearance can be measured from serum creatinine and creatinine excretion, or estimated from serum creatinine using estimating equations. Measurement

of creatinine clearance requires collection of a timed urine sample, which is inconvenient and frequently inaccurate. Repeated measurements of creatinine clearance may overcome some of the errors.

8) What is the currently recommended method to estimate GFR?

The National Kidney Disease Education Program (NKDEP) of 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. Two commonly used equations are the Modification of Diet in Renal Disease (MDRD) Study equation and Cockcroft-Gault equation.^{3,4} Both equations use serum creatinine in combination with age, sex, weight, or race to estimate GFR and therefore improve upon several of the limitations with the use of serum creatinine alone. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is a new equation based on serum creatinine.⁵

9) What is the Cockcroft-Gault formula?

The Cockcroft-Gault formula was developed in 1973 using data from 249 men with creatinine clearance (C_{Cr}) from approximately 30 to 130 mL/m². It is not adjusted for body surface area.

$$C_{Cr} = \left\{ \frac{(140 - \text{age}) \times \text{weight}}{72 S_{Cr}} \right\} \times 0.85 \text{ if female}$$

where C_{Cr} is expressed in milliliters per minute, age in years, weight in kilograms, and serum creatinine (S_{Cr}) in milligrams per deciliter (see Question 43).

10) What is the MDRD Study equation?

The 4-variable MDRD Study equation was developed in 1999 using data from 1628 patients with CKD with GFR from approximately 5 to 90 milliliters per minute per 1.73 m². It estimates GFR adjusted for body surface area⁴ and is more accurate than measured creatinine clearance from 24-hour urine collections or estimated by the

Cockcroft-Gault formula.³ The equation is:

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

The equation was re-expressed in 2005 for use with a standardized serum creatinine assay, which yields 5% lower values for serum creatinine concentration:^{4, 6}

$$\text{GFR} = 175 \times (\text{Standardized } S_{Cr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

GFR is expressed in mL/min/1.73 m², S_{Cr} is serum creatinine expressed in mg/dL, and age is expressed in years.

11) What is the CKD-EPI equation?

The CKD-EPI equation was developed in 2009 to estimate GFR from serum creatinine, age, sex, and race.⁵ The CKD-EPI equation is as accurate as the MDRD Study equation in the subgroup with estimated GFR less than 60 mL/min/1.73 m² and substantially more accurate in the subgroup with estimated GFR greater than 60 mL/min/1.73 m². (Figure 1)

Table 3 shows the equation expressed as a separate equation by level of serum creatinine, sex, and race. The footnote at the bottom of the tables shows the equation expressed as a single equation.

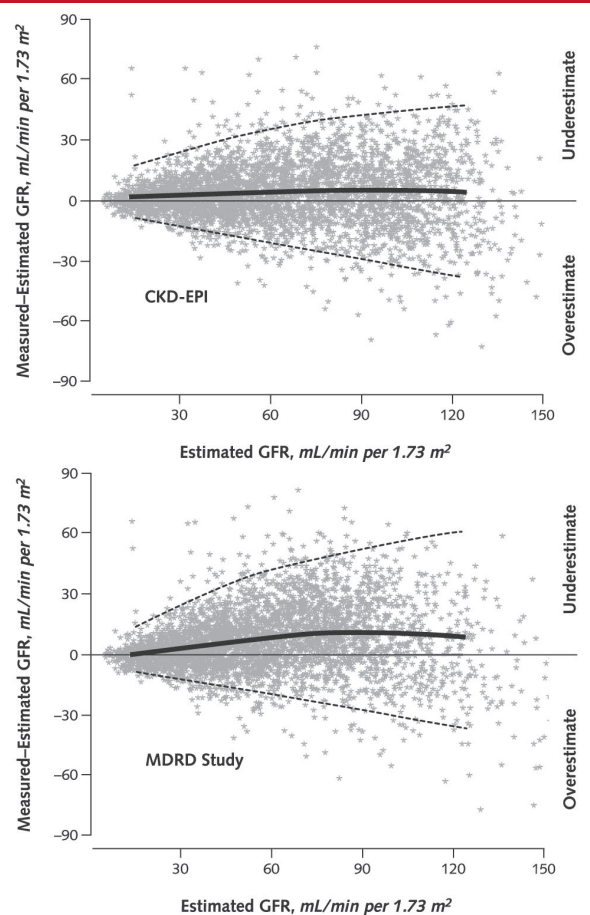
12) Why are there different estimated levels of GFR for African Americans, males and females, and people of different ages?

- African American patients:
The CKD-EPI and MDRD Study equations include a term for the African American race to account for the fact that African Americans have a higher GFR than Caucasians (and other races included in the CKD-EPI datasets and MDRD Study) at the same level of serum creatinine. This is due to higher average muscle mass and creatinine generation rate in African Americans. Clinical laboratories may not collect data on race and therefore may report GFR estimates using the equation for Caucasians. For African

Americans, multiply the GFR estimate for Caucasians by 1.16 for the CKD-EPI equation and 1.21 for the MDRD Study equation.

- Male and female patients:
The CKD-EPI and MDRD Study equations include a term for female sex to account for the fact that men have a higher GFR than women at the same level of serum creatinine. This is due to higher average muscle mass and creatinine generation rate in men.

FIGURE 1: 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 m² to mL/s per m², 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.

TABLE 3: CKD-EPI EQUATION FOR ESTIMATING GFR ON THE NATURAL SCALE EXPRESSED FOR SPECIFIED RACE, SEX, AND STANDARDIZED SERUM⁵

RACE	SEX	SERUM CREATININE (mg/dL)	EQUATION
Black	Female	≤0.7	$GFR = 166 \times (S_{Cr}/0.7)^{-0.329} \times (0.993)^{Age}$
Black	Female	>0.7	$GFR = 166 \times (S_{Cr}/0.7)^{-1.209} \times (0.993)^{Age}$
Black	Male	≤0.9	$GFR = 163 \times (S_{Cr}/0.9)^{-0.411} \times (0.993)^{Age}$
Black	Male	>0.9	$GFR = 163 \times (S_{Cr}/0.9)^{-1.209} \times (0.993)^{Age}$
White or other	Female	≤0.7	$GFR = 144 \times (S_{Cr}/0.7)^{-0.329} \times (0.993)^{Age}$
White or other	Female	>0.7	$GFR = 144 \times (S_{Cr}/0.7)^{-1.209} \times (0.993)^{Age}$
White or other	Male	≤0.9	$GFR = 141 \times (S_{Cr}/0.9)^{-0.411} \times (0.993)^{Age}$
White or other	Male	>0.9	$GFR = 141 \times (S_{Cr}/0.9)^{-1.209} \times (0.993)^{Age}$

CKD-EPI equation expressed as a single equation: $GFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [if black] where S_{Cr} is standardized serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of S_{Cr}/κ or 1, and max indicates the maximum of S_{Cr}/κ or 1.

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• Age:

The CKD-EPI and MDRD Study equations include a term for age to account for the fact that younger people have a higher GFR than older people at the same level of serum creatinine. This is due to higher average muscle mass and creatinine generation rate in younger people.

13) Are there terms for races or ethnic groups other than African Americans?

Modifications of the CKD-EPI and MDRD Study equations have been developed for Japanese and Chinese people.^{7, 8, 9, 10} They have not yet been validated for Japanese or Chinese people living in other countries, including the United States. Studies in other ethnic groups have not yet been performed.

14) Are calculators available for the CKD-EPI or MDRD Study equations?

The CKD-EPI and the MDRD Study equations have been programmed into medical decision support software for PDAs and are available on internet Web sites, such as www.kidney.org/gfr.

Most clinical laboratories are now reporting GFR estimates using the MDRD Study equation. The National Kidney Disease Education Program, American Society of Nephrology, and National Kidney Foundation have all recommended that

laboratories automatically report estimated GFR whenever a serum creatinine is ordered. The NKF recently recommended that clinical laboratories should begin using the CKD-EPI equation to report estimated GFR.¹¹

15) Why do some laboratories only report numerical values when estimated GFR is <60 mL/min/1.73 m²?




The MDRD Study equation is less accurate at GFR estimates >60 mL/min/1.73 m². At levels of estimated GFR <60 mL/min/1.73 m², the equation is accurate for most persons of average body size and muscle mass, and therefore these estimates can be used to guide clinical decision making (see Questions 28, 30-31, 36-37). Values for the CKD-EPI equation can be reported throughout the range of GFR.

16) What are the problems associated with using estimating equations?

Estimating equations are limited by:

- (1) use of serum creatinine as a filtration marker;
- (2) decreased accuracy at higher levels of estimated GFR; and
- (3) non-steady state conditions for the filtration marker when GFR is changing.

TABLE 4: THE SAME SERUM CREATININE: VERY DIFFERENT eGFR

	 22-YR-OLD BLACK MAN	 58-YR-OLD WHITE MAN	 80-YR-OLD WHITE WOMAN
Serum creatinine	1.2 mg/dL	1.2 mg/dL	1.2 mg/dL
GFR as estimated by the MDRD equation	98 mL/min/1.73 m ²	66 mL/min/1.73 m ²	46 mL/min/1.73 m ²
Kidney function	Normal GFR <i>or</i> stage 1 CKD if kidney damage is also present	Stage 2 CKD if kidney damage is also present	Stage 3 CKD

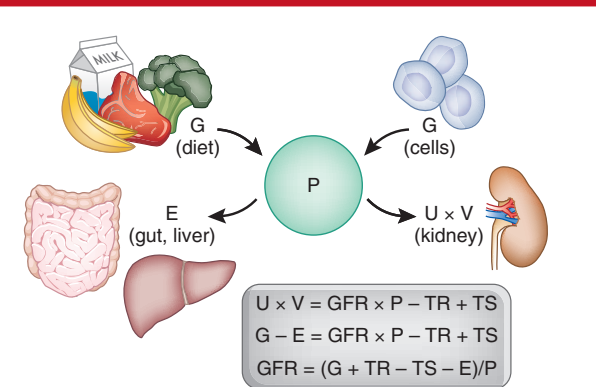
17) Can serum creatinine alone be used to estimate kidney function?

No. Serum creatinine alone is not the best way to detect kidney disease, especially in the early stages. This is because a rise in blood creatinine levels is observed only after significant loss of functioning nephrons.

18) What are the problems associated with the use of serum creatinine as a filtration marker?

Creatinine is a 113 dalton amino acid derivative that is generated from the breakdown of creatine in muscle, distributed throughout total body water, and excreted by the kidneys primarily by glomerular filtration. Although the serum level is affected primarily by the level of GFR, it is also affected by other physiological processes, such as tubular secretion, generation, and extrarenal excretion of creatinine (Figure 2).¹ Due to variation in these processes amongst individuals and over time within individuals, particularly the variation in creatinine generation, the cutoff for normal versus abnormal serum creatinine concentration differs among groups. 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.

FIGURE 2: 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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19) What factors affect creatinine generation?

The main factors affecting creatinine generation are muscle mass and diet. Table 5 shows the effect on serum creatinine of factors affecting creatinine generation.

20) 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. These medications include:

- cephalosporin and aminoglycoside antibiotics
- flucytosine
- cisplatin
- cimetidine
- trimethoprim

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

The most 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 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 should lead to less variation among clinical laboratories in GFR estimates using the same equation.

22) What factors affect the creatinine assays?

Proteins in the serum, as well as glucose and ketoacids in high levels (as occurring 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.¹³

TABLE 5: FACTORS AFFECTING SERUM CREATININE CONCENTRATION¹²

	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
Race		
African American	Increase	Higher creatinine generation rate due to higher average muscle mass in African Americans compared to Caucasians; not known how muscle mass in other races compares to that of African American or Caucasians
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

23) What was the effect of standardization of the creatinine assay on GFR estimates?

The National Kidney Disease Education Program led the process of standardization of the creatinine assays in clinical laboratories. This was completed in 2010. After standardization, most clinical laboratories' serum creatinine results 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.⁴ 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.¹⁴

24) Are there any times when a 24-hour urine collection for creatinine clearance should be performed?

Measurement of creatinine clearance 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, and a measured GFR using exogenous markers is not available.¹ Such circumstances may occur in people who are undergoing evaluation for kidney donation, treatment with drugs with significant toxicity that are excreted by the kidneys (for example, high-dose methotrexate), or consideration for participation in research protocols (Table 6).

25) What is cystatin C?

Cystatin C is a 13 kD, non-glycosylated, basic protein that is produced by all nucleated cells. It is freely filtered by the glomerulus and then reabsorbed and catabolized by the tubular epithelial cells, with only small amounts excreted in the urine. Its urinary clearance cannot be measured, which makes it difficult to study factors affect-

ing its clearance and generation. The generation of cystatin C appears to be less variable and less affected by age and sex than serum creatinine; however, 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. In addition, other studies suggest extrarenal elimination at high levels of cystatin C and higher intra-individual variation compared to serum creatinine, particularly among transplant patients.¹⁵

TABLE 6: INDICATIONS FOR A CLEARANCE MEASUREMENT WHEN ESTIMATES BASED ON SERUM CREATININE MAY BE INACCURATE

• Extremes of age and body size
• Severe malnutrition or obesity
• Disease of skeletal muscle
• Paraplegia or quadriplegia
• Vegetarian diet
• Rapidly changing kidney function
• Pregnancy

26) Is cystatin C a more accurate filtration marker than creatinine?

Some studies show that serum levels of cystatin C estimate GFR better than serum creatinine alone.¹⁵ Recent studies have clearly demonstrated that cystatin C is a better predictor of adverse events in the elderly, including mortality, heart failure, bone loss, peripheral arterial disease, and cognitive impairment, than either serum creatinine or estimated GFR.^{16, 17} These findings may be because cystatin C is a better filtration marker than creatinine, particularly in the elderly. An alternative explanation is that factors other than GFR that affect serum levels of creatinine and cystatin C differentially confound the relationships between these measures and outcomes.^{15, 18, 19}

27) Can cystatin C be used to estimate GFR?

Some studies have reported estimating equations based on serum levels of cystatin C, either alone or in combination with serum creatinine.²⁰ These equations have variable performance compared to serum creatinine and variable performance among populations. These equations need to be validated in other studies prior to use in clinical practice. In addition, calibration of assays of serum cystatin C will require standardization for routine use of estimating equations using cystatin C.

28) Why are GFR estimates at higher levels of estimated GFR less accurate?

There are several possible explanations for reports of decreased accuracy of higher GFR estimates, including:

- (1) inter-laboratory variation in the calibration of filtration marker assays, which has a larger effect at higher GFR levels. This is likely an important reason for the wide variation among published studies, and should diminish with standardization of assays.
- (2) greater biologic and measurement variability of GFR at higher values
- (3) limitations of generalizing an equation developed in one population to another population²¹

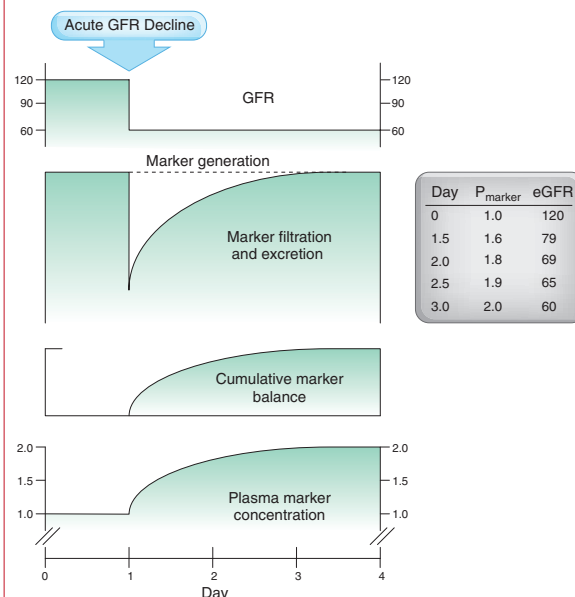
All three explanations are also likely to affect estimating equations based on cystatin C as well as creatinine.

29) What problems are caused by the non-steady state of 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 3). 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.

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 m². 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.

INTERPRETATION OF GFR ESTIMATES

30) To which populations does the MDRD Study equation apply?

The MDRD Study equation was developed in a group of patients with chronic kidney disease (mean GFR 40 mL/min/1.73 m²) who were predominantly Caucasian, non-diabetic, and did not have a kidney transplant.⁴ Since then, the MDRD Study equation has been evaluated in numerous populations, including:

- African Americans, Europeans, and Asians
- patients with and without diabetes or kidney disease
- kidney transplant recipients
- potential kidney donors

These studies have shown that the MDRD Study equation has reasonable accuracy in non-hospitalized patients thought to have CKD, regardless of diagnosis.^{20, 22, 23}

31) To which populations or individuals does the MDRD Study equation not apply?

The MDRD Study equation has been reported to be less accurate in populations without kidney disease, such as young patients with type 1 diabetes without microalbuminuria or people selected for evaluation for kidney donation.²²

The MDRD Study equation has not been validated in children (age <18 years), pregnant women, the elderly (age >85 years), or in some racial or ethnic subgroups, such as Hispanics. Furthermore, any of the limitations with the use of serum creatinine related to nutritional status or medication usage are not accounted for in the MDRD Study equation (Table 5) (see Questions 18-19).

32) To which populations does the CKD-EPI equation apply?

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 m²) and ages (18-97 years).⁵ The equation was validated in a separate cohort of 3896 people from 16 separate studies, GFR range (2 to 200 mL/min/1.73 m²) and age range (18-93 years) (Figure 1). 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 microalbuminuria, 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 and who have kidney disease.

33) To which populations does the CKD-EPI equation not apply?

The CKD-EPI equation has not been validated in children (age <18 years), pregnant women, or in some racial or ethnic subgroups, such as Hispanics. Furthermore, the CKD-EPI equation, like all creatinine-based estimates, including the MDRD Study equation and Cockcroft-Gault equation, cannot overcome the limitations of serum creatinine. Specifically, all equations will be less accurate in people with differences in nutritional status or muscle mass (Table 5) (see Questions 18-19).

34) How do the CKD-EPI, MDRD Study, and Cockcroft-Gault equations differ?

The Cockcroft-Gault equation estimates creatinine clearance and is not adjusted for body surface area.^{3, 24} The CKD-EPI and MDRD Study equations estimate GFR adjusted for body surface area.

GFR estimates from the CKD-EPI and MDRD Study equations can therefore be applied to determine level of kidney function, regardless of a patient's size. In contrast, estimates based on the Cockcroft-Gault equation can be used for drug dosage recommendations, whereas GFR estimates

based on the MDRD Study should be “unadjusted” for body surface area (see Questions 42-43).

Many studies have compared the performance of the MDRD Study and Cockcroft-Gault equations in measuring GFR. In some of these studies, the MDRD Study equation was more accurate than the Cockcroft-Gault equation. Other studies demonstrated similar performance. The Cockcroft-Gault equation appears to be less accurate than the MDRD Study equation, specifically in older and obese people.²²

A recent study of a large diverse population compared the performance of the two equations with the use of standardized serum creatinine values and showed that the performance of the Cockcroft-Gault was substantially worse with the standardized creatinine values, with the percentage of estimates within 30% of measured GFR falling from 74% before standardization to 69% after standardization. This suggests that the Cockcroft-Gault formula should not be used as clinical laboratories move to standard creatinine assays.¹⁴

35) If the Cockcroft-Gault equation is less accurate, why is it still used?

Pharmacokinetic studies over the last several years have used this equation to determine level of kidney function for dosage adjustment in drug labels. As a result, it has become the standard for drug dosing. However, given the variability in creatinine assays at the time, there was inconsistent translation from the pharmacokinetic studies into clinical practice, regardless of which equation was used. In addition, the difference in GFR estimates based on the MDRD Study and the Cockcroft-Gault equations will not lead to a difference in drug dosages for the majority of patients. Recent recommendations from the National Kidney Disease Education Program suggest that either equation can be used for drug dosing purposes.^{25, 26}

36) How can GFR estimates be used to detect CKD?

Persistent reduction in GFR to below 60 mL/min/1.73 m² is defined as CKD.²⁷⁻²⁹ A person with higher GFR does not have CKD unless he or she also has a marker of kidney damage (Table 7).

GFR estimates from the MDRD Study equation greater than 60 mL/min/1.73 m² underestimate measured GFR. As such, MDRD Study equation GFR estimates may lead to a “false positive” diagnosis of CKD in people with mildly reduced GFR. In addition, MDRD Study equation GFR estimates may not be useful for quantification of declines in GFR to levels of 60 mL/min/1.73 m² or more. However, an MDRD Study equation estimated GFR under 60 mL/min/1.73 m² has been shown to be associated with an increased risk of adverse outcomes of CKD in multiple populations.³⁰

The CKD-EPI equation provides more accurate estimates than the MDRD Study equation in this range of GFR, and consequently it will more accurately identify patients with CKD with estimated GFR (eGFR) around 60 mL/min per 1.73 m². In addition, it has been shown in several community-based cohorts, that people who were reclassified to a higher GFR stage using the CKD-EPI equation compared to the MDRD Study equation had lower risk for adverse events.^{31, 32}

37) How should mildly reduced GFRs in patients without kidney damage be interpreted?

There will be some uncertainty for patients without markers of kidney damage in whom GFR estimates are:

- Between 60-89 mL/min/1.73 m²
- or
- Slightly below 60 mL/min/1.73 m²

In these cases, clinical decision making will depend on other patient characteristics, such as the presence or absence of risk factors for CKD or complications of CKD (Table 7). In some patients,

clinicians may decide to defer further evaluation for CKD, but it may be prudent to:

- Check the person’s GFR more often.
- Counsel the person to avoid medications that can damage the kidneys (such as ibuprofen).
- Adjust the dosage of medications that are removed by the kidney.
- Consider co-consultation with a nephrologist regarding the patient’s lab and imaging studies.
- Refer the patient to a nephrologist.

(See Questions 28, 31, and 36.)

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 m² in patients without markers of kidney damage (see Questions 28 and 31).³³

38) What course of action should be taken for a suspected false-positive test of eGFR <60 mL/min/1.73 m²?

If the patient does not have any risk factors for CKD, is otherwise well, and if the GFR is near 60 mL/min/1.73 m², the next step is to check for markers of kidney damage. This should include a urinalysis and measurement of albumin-to-creatinine ratio in a spot urine sample.

If these are negative, then it is reasonable not to pursue other investigations at that time. However, it may be prudent to:

- Check the person’s eGFR more often.
- Adjust the dosage of medications that are removed by the kidney.
- Counsel the person to avoid medications that can damage the kidneys (such as ibuprofen).

If an accurate measurement is required, a clearance measurement can be performed. Referral to a nephrologist may also be indicated for decisions regarding diagnosis or further evaluation (see Question 53).

39) What clearance measurements should be performed?

For patients in whom it is important to have an accurate level of GFR, clearance measurements should be performed.¹ Clearance measurements using exogenous filtration markers, such as iohexol or iothalamate, are most accurate but are not readily available. Creatinine clearances can be performed in those circumstances. Repeating the creatinine clearance may reduce measurement errors in collection.

40) How can GFR estimates be used to detect progression?

Current guidelines recommend using GFR estimates to monitor progression of CKD.²⁷⁻²⁹ Clinicians should not rely on monitoring serum creatinine to detect the level and rate of CKD progression.

For example, for a 50-year-old white male:

- A change in serum creatinine from 1.0 to 2.0 mg/dl (88.4 to 176.8 μmol/L) **reflects a decline in GFR of 46 mL/min/1.73 m²** (from 84 to 38 mL/min/1.73 m²).
- Whereas a further increase in serum creatinine level from 2.0 to 3.0 mg/dL (176.8 to 265.2 μmol/L) **reflects a further decline of only 14 mL/min/1.73 m²** (to 24 mL/min/1.73 m²).

41) Do some drugs affect the accuracy of GFR estimates?

Drug-induced reduction in GFR raises the serum creatinine concentration and is detected by the CKD-EPI or MDRD Study equation; however, drugs that raise serum creatinine concentration without affecting GFR will give falsely low estimates of GFR. In most cases, GFR can be estimated after discontinuing the drug.

42) How should estimates of GFR or creatinine clearance be used when dosing medications?

In general, drug dosing is based on pharmacokinetic studies where kidney function was assessed using creatinine clearance levels estimated from the Cockcroft-Gault equation. For the majority of patients, the difference in GFR estimates based on the MDRD Study and the Cockcroft-Gault equations will not lead to a difference in drug dosages. Recent recommendations from the National Kidney Disease Education Program suggest that either value can be used to assign drug dosages.^{25, 26}

43) Should adjusted or unadjusted estimated GFR be used when dosing medications?

Drug dosing is based on kidney function measurements or estimates that are not adjusted for body surface area. GFR estimates adjusted for body surface area will generally be adequate except in patients with body size that is very different than average.²⁵ In these patients, unadjusted estimated GFR can be computed by the following formulas:

$$\text{BSA (m}^2\text{)} = (\text{W}^{0.425} \times \text{H}^{0.725}) \times 0.007184$$

Where height is measured in meters, and weight in kilograms.

$$\text{GFR estimate (mL/min)} = \text{GFR estimate (mL/min/1.73 m}^2\text{)} \times \text{BSA/1.73}$$

44) Can the estimating equations for GFR be used in acute kidney injury (acute renal failure)?

GFR estimates are less accurate in the non-steady state; however, serum creatinine can provide important information about the level of kidney function even when it is not in a steady state. Estimated GFR overestimates measured GFR when serum creatinine is rising, and underestimates measured GFR when serum creatinine is falling. In general, if the serum creatinine rises at 2-3 mg/dl per day then the GFR is near zero.

45) Can GFR estimates be used in hospitalized patients?

GFR 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

46) What is the public health problem associated with chronic kidney disease?

CKD is a worldwide public health problem. Adverse outcomes of CKD include loss of kidney function, sometimes leading to kidney failure, and cardiovascular disease. Some of the adverse outcomes of chronic kidney disease 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 National Kidney Foundation’s Kidney Disease Quality Outcome Initiative (KDOQI) published guidelines for the classification and evaluation of CKD.^{27, 28}

47) What is the definition of CKD?

CKD is defined as either the presence of kidney damage or GFR less than 60 mL/min/1.73 m² for three or more months and can be diagnosed without knowledge of its cause.

48) What are the stages of CKD?

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

STAGE	DESCRIPTION	GFR	CLINICAL ACTION PLAN
1	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment, treatment of comorbid conditions, slow progression, CVD risk reduction
2	Kidney damage with mild ↓ GFR	60-89	Estimating progression
3	Moderate ↓ GFR	30-59	Evaluating and treating complications
4	Severe ↓ GFR	15-29	Preparation for kidney replacement therapy
5	Kidney Failure	<15	Kidney replacement therapy (if uremia present and patient consents)

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 scans ^c	May reveal asymmetry of kidney size or function, functional evidence of renal artery stenosis, acute pyelonephritis, or scars

^aThis modality has been largely supplanted by computed tomography, although it remains useful to describe fine detail in the collecting system.
^bWith or without contrast
^cCaptopril renography, mercaptoacetyltryglycine (MAG3), dimercaptosuccinic acid (DMSA)

49) 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)²⁷

50) What is the recommended method to screen for proteinuria?

The KDOQI Guidelines recommend that the following criteria be applied when evaluating the tests in random spot urine samples for CKD:

- albumin-specific dipstick positive
- albumin-to-creatinine ratio >30 mg/g
- routine dipstick (total protein) >1+
- total protein-to-creatinine ratio >200 mg/g

The screening for proteinuria in adults is done using an albumin-specific dipstick or an albumin-to-creatinine ratio on a random (spot) urine sample. A routine dipstick is not sensitive enough to detect small amounts of urine protein (as in “microalbuminuria”).

Measure urinary albumin-to-creatinine ratio (ACR) in spot urine sample	
CATEGORY	SPOT (MG/G CREATININE)
Normoalbuminuria	<30
Microalbuminuria	30–300
Macroalbuminuria	>300

*Because of variability in urinary albumin excretion, at least two specimens, preferably first morning void, collected within a 3–6 month period should be abnormal before considering a patient to have crossed one of these diagnostic thresholds.

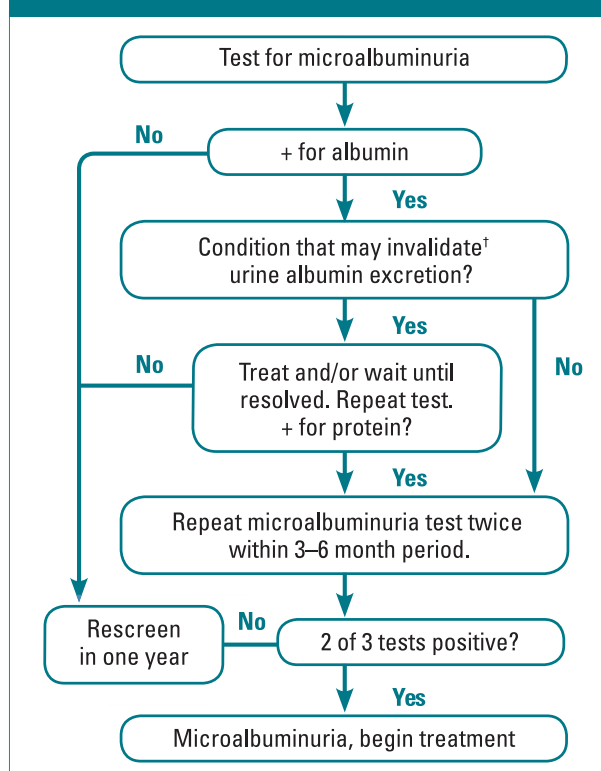
†Exercise within 24 hours, infection, fever, congestive heart failure, marked hyperglycemia, pregnancy, marked hypertension, urinary tract infection, and hematuria may increase urinary albumin over baseline values.

51) What are the complications and common comorbidities associated with chronic kidney disease?

Chronic kidney disease 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
- hypoalbuminemia
- dyslipidemia (hypercholesterolemia, hypertriglyceridemia)
- cardiovascular disease [some examples include coronary heart disease (CAD), left ventricular hypertrophy (LVH), peripheral vascular disease (PVD), and valvular heart disease (VHD)]

FIGURE 4: SCREENING FOR MICROALBUMINURIA³⁴

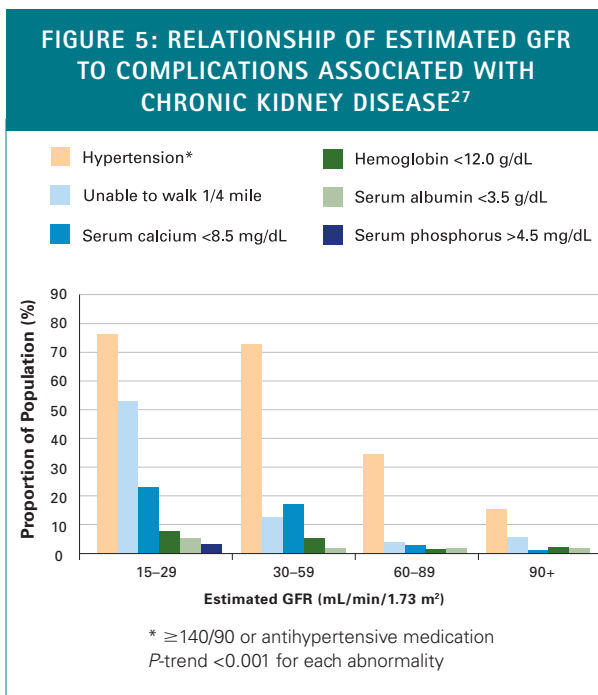


- vascular calcification
- neuropathy
- reduced ability to perform activities of daily living
- lowered quality of life

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.

52) Does the risk of complications increase as kidney disease progresses?

The prevalence of complications increases as GFR falls below 60 mL/min/1.73 m² (CKD stage 3 or higher). These patients should be evaluated for the presence of these complications. Figure 5 shows the prevalence of complications at each stage of CKD.



53) When should patients with kidney disease be referred to a nephrologist?

Patients should be referred to a nephrologist for co-management or consultation when:

- GFR is <30 mL/min/1.73 m²
- Assistance with creating the patient’s clinical action plan is needed.
- The prescribed evaluation of the patient cannot be carried out, or the recommended treatment cannot be implemented.

CKD-related complications and risk of development of kidney failure are highest among patients with CKD stages 4 and 5. Late referral to nephrologists prior to dialysis initiation (GFR <15 milliliters per minute per 1.73 m²) can result in a higher rate of morbidity and mortality.³⁵ Some of the many other reasons to refer to a nephrologist are listed in Table 11.³⁶

TABLE 11: RECOMMENDATIONS FOR REFERRAL TO SPECIALIST FOR CONSULTATION AND CO-MANAGEMENT OF CKD*	
INDICATION	SPECIALIST
Evaluation and management of CKD, as described in KDOQI CKD Clinical Action Plan	Kidney disease specialist, other specialists as appropriate
GFR <30 mL/min/1.73 m ²	Kidney disease specialist
Urine total protein-to-creatinine ratio >500-1000 mg/g	Kidney disease specialist
Increased risk for progression of kidney disease	Kidney disease specialist
GFR decline >30% within 4 months without explanation**	Kidney disease specialist
Hyperkalemia (serum potassium concentration >5.5 mEq/L) despite treatment	Kidney disease specialist
Resistant hypertension	Kidney disease or hypertension specialist
Difficult-to-manage drug complications	Kidney disease or hypertension specialist
Acute presentations of CVD	Cardiovascular disease specialist
Complex or severe chronic CVD conditions	Cardiovascular disease specialist
Age <18 years	Pediatric kidney disease specialist

*Availability of specialists may vary, depending on location.
** Defined as “fast” GFR decline (>4 mL/min/1.73 m² per year) or risk factors for GFR decline. Short-term decline in GFR up to 30% may be seen after initiation of ACE inhibitor and does not require referral to a specialist in the absence of other indications.

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