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FAQs

FREQUENTLY ASKED QUESTIONS ABOUT GFR ESTIMATES

Frequently Asked Questions About GFR Estimates

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The following is a list of frequently asked questions pertaining to the current recommendations for the estimation of glomerular filtration rate (GFR). They are organized into three general topics: measurement and estimation of kidney function, interpretation of GFR estimates, and chronic kidney disease (CKD).

LIST OF FREQUENTLY ASKED QUESTIONS

Measurement and Estimation of Kidney Function

1) Why measure GFR as an index of kidney function?
2) Why are GFR estimates adjusted for body surface area?
3) What are the GFR changes with age?
4) How is GFR measured?
5) What is the difference between creatinine clearance and GFR?
6) What is the currently recommended method to estimate GFR?
7) What is the Cockcroft and Gault formula?
8) What is the MDRD Study equation?
9) Why are there different estimated levels of GFR for African Americans?
10) Are there terms for races or ethnic groups other than African Americans?
11) Why are there different estimated levels of GFR for males and females?
12) Why are there different estimated levels of GFR for people of different ages?
13) What is the recommended method for computing GFR using the MDRD Study equation?
14) Why do some laboratories only report a numerical value when estimated GFR is less than 60 mL/min/1.73 m^2?
15) What are the problems associated with using estimating equations?
16) What are the problems associated with the use of serum creatinine as a filtration marker?
17) What factors affect creatinine generation?
18) What factors affect creatinine secretion?
19) What is the impact of calibration and inter-laboratory variation of serum creatinine assays on the estimation of GFR?
20) What factors affect the creatinine assays?
21) What will be the effect of standardization of the creatinine assay on GFR estimates?
22) Are there any times when a 24-hour urine collection for creatinine clearance should be performed?
23) What is cystatin C?
24) Is cystatin C a more accurate filtration marker than creatinine?
25) Can cystatin C be used to estimate GFR?
26) What are the explanations for decreased accuracy of GFR estimates at higher levels of estimated GFR?
27) What problems are caused by non-steady state of filtration markers after a change in GFR?

Interpretation of GFR Estimates

28) To which populations does the MDRD Study equation apply?
29) To which populations or individuals does the MDRD Study equation not apply?
30) How do the Cockcroft and Gault and MDRD Study equations differ?

31) How can GFR estimates be used to detect CKD?
32) In patients not suspected of having CKD, how should estimates just below 60 mL/min/1.73 m^2 be interpreted?
33) What is the appropriate course of action for a suspected false positive test of GFR <60 mL/min/1.73 m^2?
34) What clearance measurements should be performed?
35) How can GFR estimates be used to detect progression?
36) Do some drugs affect the accuracy of GFR estimates from the MDRD Study equation?
37) How should estimates of GFR or creatinine clearance be used when dosing medications?
38) Should adjusted or unadjusted estimated GFR be used when dosing medications?
39) Can the estimating equations for GFR be used in acute kidney injury (acute renal failure)?
40) Can GFR estimates be used in hospitalized patients?

Chronic Kidney Disease

41) What is the public health problem associated with chronic kidney disease (CKD)?
42) What is the definition of CKD?
43) What are the stages of CKD?
44) What are markers of kidney damage?
45) What are complications of CKD?
46) What is the relationship between stages of CKD and complications of CKD?
47) When should patients with kidney disease be referred to a nephrologist?

MEASUREMENT OF KIDNEY FUNCTION

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

GFR is usually accepted as the best overall index of kidney function in health and disease. Normal GFR varies according to age, sex, and body size; in young adults it is approximately 120-130 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 cardio-vascular disease.

2) 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 m^2 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.

3) What are the GFR changes with age?

The GFR declines with age. Although the age-related decline in GFR has been considered part of normal aging, decreased GFR in the elderly is an independent predictor of adverse outcomes such as death and CVD. In addition, decreased GFR in the elderly requires adjustment in drug dosages, as in other patients with CKD. **Table 1** shows the average values of estimated GFR by decade in the general population, based on a small study of normal men.

Table 1: Average estimated GFR by age[1]

Age (years)	Average Estimated GFR (mL/min/1.73 m^2)
20-29	116
30-39	107
40-49	99
50-59	93
60-69	85
70+	75

4) How is GFR measured?

GFR cannot be measured directly. The urinary clearance of an ideal filtration marker, such as inulin, iothalamate or iohexol, is the gold standard for the measurement of GFR. This is cumbersome in clinical practice and serum levels of endogenous filtration markers, such as creatinine, have traditionally been used to estimate GFR.

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

Creatinine clearance approximates GFR but overestimates it due to the fact that 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.

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

The National Kidney Disease Education Program (NKDEP) of the National Institute of Diabetes, 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 MDRD Study equation and Cockcroft and Gault equation. 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.

7) What is the Cockcroft and Gault formula?

The Cockcroft and Gault formula was developed in 1973 using data from 249 men with creatinine clearance (C_{Cr}) from approximately 30 to 130 mL/m^2. It is not adjusted for body surface area.

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

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 30).

8) What is the MDRD Study equation?

The 4-variable MDRD Study equation was developed in 1999 using data from 1,628 patients with CKD with GFR from approximately 5 to 90 milliliters per minute per 1.73 m[2]. It estimates GFR adjusted for body surface area[3, 4] and is more accurate than measured creatinine clearance from 24-hour urine collections or estimated by the Cockcroft and Gault formula.[3, 4] The equation is:

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

The equation was re-expressed in 2005 for use with a standardized serum creatinine assay, which yields 5 percent lower values for serum creatinine concentration [5, 6]:

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

GFR is expressed in mL/min/1.73 m[2], S_{Cr} is serum creatinine expressed in mg/dL, and age is expressed in years. In the MDRD Study, the equation has an R2 value of 89.2%, with 91% and 98% of the estimated values falling within 30% and 50% of measured values, respectively (see questions 26 and 28).

9) Why are there different estimated levels of GFR for African Americans?

The MDRD study equation includes 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 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 1.21.

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

A recent study developed a term for Chinese.[7] This has not yet been validated for Chinese people living in other countries, including the United States. Studies in other ethnic groups have not yet been performed.

11) Why are there different estimated levels of GFR for males and females?

The MDRD study equation includes 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.

12) Why are there different estimated levels of GFR for people of different ages?

The MDRD study equation includes 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) What is the recommended method for computing GFR using the MDRD Study equation?

The equation has been programmed into medical decision support software for PDAs and is available on internet Web sites such as **www.kidney.org/gfr** Some 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.

14) Why do some laboratories only report numerical values when estimated GFR is less than 60 mL/min/1.73 m^2?

The MDRD Study equation is less accurate at GFR estimates greater than 60 mL/min/1.73 m^2. At levels of estimated GFR less than 60 mL/min/1.73 m^2, 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 26, 28-29, 31, 32).

15) 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.

16) 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 extra-renal excretion of creatinine. 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. In addition, assays for serum creatinine vary across clinical laboratories, leading to differences in GFR estimates for the same patient when creatinine is measured in different labs. 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.

17) What factors affect creatinine generation?

The main factors affecting creatinine generation are muscle mass and diet. **Table 2** shows the effect on serum creatinine of factors affecting creatinine generation.

Table 2: Factors affecting serum creatinine concentration[8]

	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 Americans or Caucasians
Diet		
Vegetarian Diet	Decrease	Decrease in creatinine generation
Ingestion of Cooked Meat	Increase	Transient increase in creatinine generation; however, this may be blunted by transient increase in GFR
Body Habitus		
Muscular	Increase	Increased muscle 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

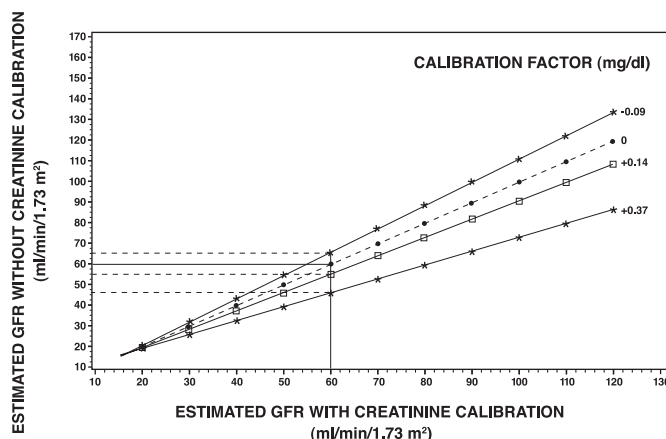## 18) What factors affect creatinine secretion?

Some medications, including trimethoprim, cimetidine and some older cephalosporins, inhibit tubular secretion of creatinine, thereby decreasing creatinine clearance and increasing serum creatinine without a change in GFR.

19) 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 is not standardized across methods and laboratories. Since the concentration of non-creatinine chromogens does not increase as GFR declines, the difference in serum creatinine assays between laboratories is greater at low serum creatinine values; therefore, differences in GFR estimates related to differences in calibration are most apparent at higher levels of GFR.[9]

Figure 1 shows the GFR estimates with and without such calibration differences for a hypothetical 60-year-old black male across a wide range of GFR.[10] The effect of calibration on the Cockcroft and Gault equation cannot be similarly tested since the methods in the laboratory where this equation was developed have not been maintained.

Figure 1: Estimated GFR with and without creatinine calibration for a 60-year-old black male
Lines represent estimated GFR values with and without calibration of serum creatinine assay over the 95% confidence interval for calibration differences (factors) observed from the CAP survey for a 60-year-old black male. Calibration factor of zero indicates no difference between laboratories in serum creatinine assay. For estimated GFR <60 mL/min/1.73 m^2 a mean calibration difference of 0.14 mg/dL is associated with an error in GFR estimates of -9.1%. The upper and lower limits of the 95% confidence intervals are -0.09 mg/dL and +0.37 mg/dL respectively. The error in GFR estimates over this range is from +7.6% to -21.9%.
*To convert serum creatinine from mg/dL to μmol/L, multiply by 88.4.

20) 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.[11]

21) What will be the effect of standardization of the creatinine assay on GFR estimates?

The National Kidney Disease Education Program is leading the process of standardization of the creatinine assays in all clinical laboratories. This is expected to be complete in 2008. After standardization, most clinical laboratories' serum creatinine results will decline by 0.1-0.3 mg/dL. 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 and Gault equation has not been re-expressed

for use with standardized serum creatinine. GFR estimates using the Cockcroft and Gault equation with standardized serum creatinine will generally be higher and less accurate than with non-standardized creatinine.

22) 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 (see question 34) or for patients with estimated GFR >60 mL/min/1.73 m^2 when a more accurate clearance measure is required for clinical decision making. Such circumstance 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. (See question 34 regarding discussion of other clearance measurements).

Table 3: Indications for a clearance measurement because 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

23) 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 affecting 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 BMI, hyperthyroidism and steroid use. In addition, other studies suggest extra-renal elimination at high levels of cystatin C and higher intra-individual variation compared to serum creatinine, particularly among transplant patients.[12]

24) 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.[12] 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.[13, 14] 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.[12, 15, 16]

25) 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.[17] 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.

26) What are the explanations for decreased accuracy of GFR estimates at higher levels of estimated GFR?

There are several possible explanations for reports of decreased accuracy of higher GFR estimates, including: (1) inter-laboratory variation in the calibration of serum creatinine assays, which has a larger effect at higher GFR levels (see question 13). This is likely an important reason for the wide variation among published studies; (2) greater biologic and measurement variability of GFR at higher values; and (3) limitations of generalizing an equation developed in one population to another population.[9] These are the reasons that most clinical laboratories report GFR estimates as numerical values only when they are less than 60 mL/min/1.73 m^2 (see question 29). The latter two explanations are also likely to affect estimating equations based on cystatin C.

27) 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. 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.

INTERPRETATION OF GFR ESTIMATES

28) 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 m^2) who were predominantly Caucasian, non-diabetic and did not have a kidney transplant.[3] The MDRD Study equation has now been evaluated in numerous populations, including African Americans, Europeans, and Asians with non-diabetic kidney disease, diabetic patients with and without kidney disease, kidney transplant recipients and 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.[17]

29) 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 of kidney donation.[17]

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 (see **Table 1**) (see question 17).

Despite these limitations, GFR estimates using equations are more accurate than serum creatinine alone. Understanding these limitations should help clinicians interpret GFR estimates. In particular, GFR estimates will be underestimates of true GFR in individuals with GFR levels >60 mL/min/1.73 m^2. As such, GFR estimates may not be useful for quantification of declines in GFR to levels of 60 mL/min/1.73 m^2 or more and may lead to a "false positive" diagnosis of CKD (GFR under 60 milliliters per minute per 1.73m^2) in people with mildly reduced GFR. However, even in the general population, an estimated GFR under 60 milliliters per minute per 1.73 m^2 is associated with an increased risk of adverse outcomes of CKD.[18] If more accurate estimation of GFR is necessary, then one should obtain a clearance measurement (see question 34).

30) How do the Cockcroft and Gault and MDRD Study equations differ?

The Cockcroft and Gault equation estimates creatinine clearance and is not adjusted for body surface area.[2] The MDRD Study equation estimates GFR adjusted for body surface area. GFR estimates from the MDRD Study equation can therefore be applied to determine level of kidney function, regardless of a patient's size. In contrast, estimates based on the Cockcroft and 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 37-38).

Many studies have compared the performance of the two equations to measured GFR. In some of these studies, the MDRD Study equation was more accurate than the Cockcroft and Gault equation. Other studies demonstrated similar performance. The Cockcroft and Gault equation appears to be less accurate than the MDRD Study equation, specifically in older and obese people.[10]

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

Persistent reduction in GFR to below 60 mL/min/1.73 m^2 is defined as CKD.[19-21]

Table 4: 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 26 and 29).[7]

32) In patients not suspected of having CKD, how should estimates just below 60 mL/min/1.73 m^2 be interpreted?

There will be some uncertainty for patients without markers of kidney damage and with GFR estimates just below 60 mL/min/1.73 m^2. Some of these patients may have a measured GFR above 60 mL/min/1.73 m^2 and therefore would not have CKD. Clinical decision making will depend on other patient characteristics, such as the presence or absence of risk factors for CKD or complications of CKD. In some patients, clinicians may decide to defer further evaluation for CKD, but it may be prudent to monitor estimated GFR more frequently, adjust the dosage of medications that are excreted by the kidney, and avoid medications toxic to the kidney (see questions 26, 29, 31).

33) What is the appropriate course of action for a suspected false positive test of GFR <60 mL/min/1.73 m^2?

If the GFR is near 60 mL/min/1.73 m^2 and the patient does not have any risk factors for CKD and is otherwise well, 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 monitor estimated GFR more frequently, adjust the dosage of medications that are excreted by the kidney and avoid medications toxic to the kidney (see questions 26, 29, 31). If an accurate measurement is required, a clearance measurement can be performed (see questions 22, 34). Referral to a nephrologist may also be indicated for decisions regarding diagnosis or further evaluation (see question 47).

34) What clearance measurements should be performed?

In patients where it is important to have an accurate level of GFR, clearance measurements should be performed. 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.

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

The reciprocal relationship between GFR and serum creatinine levels makes it difficult for clinicians to appreciate the level and rate of change in GFR by monitoring serum creatinine. 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 m^2 (from 84 to 38 mL/min/1.73 m^2), 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 m^2 (to 24 mL/min/1.73 m^2). Current guidelines recommend using GFR estimates to monitor progression of CKD.[19-21]

36) Do some drugs affect the accuracy of GFR estimates from the MDRD Study equation?

Drug-induced reduction in GFR raises the serum creatinine concentration and is detected by the 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.

37) 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 and Gault equation. For the majority of patients, the difference in GFR estimates based on the MDRD Study and the Cockcroft and Gault equations will not lead to a difference in drug dosages. If the estimates differ, the Cockcroft and Gault estimate should be used to be consistent with pharmacokinetic studies.

38) 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. In these patients, unadjusted estimated GFR can be computed by the following formulas:

$$BSA = W^{0.425} \times H^{0.725} \times 0.007184 / 1.73 \text{ m}^2$$
$$\text{GFR estimate (mL/min)} = \text{GFR estimate (mL/min/1.73 m}^2) \times BSA/1.73 \text{ m}^2$$

39) 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 (see question 27); 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 doubles within one day then the GFR is near zero.

40) Can GFR estimates be used in hospitalized patients?

GFR estimates from the MDRD Study equation 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

41) What is the public health problem associated with chronic kidney disease (CKD)?

CKD is a worldwide public health problem. Adverse outcomes of CKD include loss of kidney function, sometimes leading to kidney failure, and cardiovascular disease (CVD) (see question 24). 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 published guidelines for the classification and evaluation of CKD.[19, 20]

42) 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 m^2 for 3 or more months and can be diagnosed without knowledge of its cause.

43) What are the stages of CKD?

Table 5 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.

Table 5: Stages of chronic kidney disease and clinical action plans

Stage	Description	GFR	Clinical Action Plan
1	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment, 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 desirable)

National Kidney Foundation. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification.[19]

44) What are markers of kidney damage?

The most common cause of CKD in North America is due to diabetes or hypertension; therefore, persistent proteinuria (albuminuria) is the principal marker of kidney damage. Other markers of damage include abnormalities in urine sediment, abnormal findings on imaging studies or abnormalities in blood and urine chemistry measurements that identify renal tubular syndromes (such as renal tubular acidosis).

The screening for proteinuria in adults is measured 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."). The NKF recommends that the following criteria are applied when evaluating the tests in random urine samples for CKD:

- albumin-specific dipstick positive
- albumin/creatinine ratio >30 mg/g
- routine dipstick (total protein) >1+
- total protein/creatinine ratio >200 mg/g
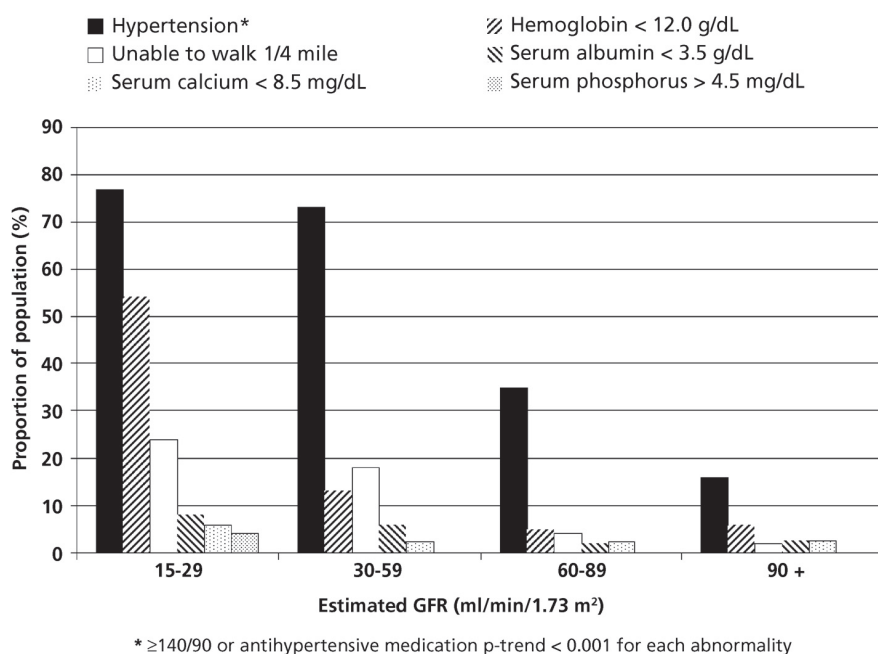
45) What are complications of CKD?

Complications of CKD may be a result of reduction in GFR, disorders of tubular function or reduction in endocrine function of the kidney. Complications include hypertension, malnutrition, anemia, low serum albumin, low serum calcium, high serum phosphate concentration, high serum parathyroid hormone concentration, reduced activities of daily living and lower quality of life. The complications may be problems in themselves or may increase risk for other adverse events (e.g., high blood pressure increases the risk of cardiovascular disease and stroke).

46) What is the relationship between stages of CKD and complications of CKD?

The prevalence of complications of CKD increases at levels of GFR less than 60 mL/min/1.73m^2. Therefore, patients at stage 3 CKD should be tested for the presence of these complications. **Figure 2** below shows the increased prevalence of the number of complications at each stage of CKD.

Figure 2: Relationship of estimated GFR to complications associated with chronic kidney disease[19]

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

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

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 less than 15 milliliters per minute per 1.73 m^2) is associated with a higher rate of morbidity and mortality.[22] Patients with GFR estimates less than 30 milliliters per minute per 1.73 m^2 should be referred to a nephrologist for co-management if they have not been referred earlier. Some of the many other reasons to refer to a nephrologist are listed in **Table 6**.[23]

Table 6: Recommendations for referral to specialist for consultation and co-management of CKD*

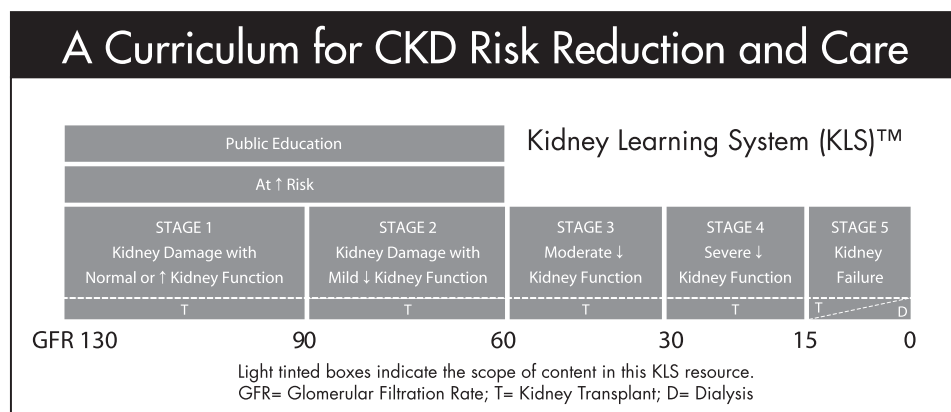| Indication	Specialist
Evaluation and management of CKD, as described in KDOQI CKD Clinical Action Plan	Kidney disease specialist (C) Other specialists as appropriate (C)
GFR <30 mL/min/1.73 m^2	Kidney disease specialist (B)
Urine total protein-to-creatinine ratio <500-1000 mg/g	Kidney disease specialist (C)
Increased risk for progression of kidney disease	Kidney disease specialist (C)
GFR decline >30% within 4 months without explanation**	Kidney disease specialist (C)
Hyperkalemia (serum potassium concentration >5.5 mEq/L) despite treatment	Kidney disease specialist (C)
Resistant hypertension	Kidney disease or hypertension specialist (C)
Difficult-to-manage drug complications	Kidney disease or hypertension specialist (C)
Acute presentations of CVD	Cardiovascular disease specialist (C)
Complex or severe chronic CVD conditions	Cardiovascular disease specialist (C)
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 m^2 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.
Letters in parentheses denote strength of recommendations.

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A Curriculum for CKD Risk Reduction and Care

Kidney Learning System (KLS)™

Public Education				
At ↑ Risk				
STAGE 1 Kidney Damage with Normal or ↑ Kidney Function	STAGE 2 Kidney Damage with Mild ↓ Kidney Function	STAGE 3 Moderate ↓ Kidney Function	STAGE 4 Severe ↓ Kidney Function	STAGE 5 Kidney Failure
T	T	T	T	T D

GFR 130   90   60   30   15   0

Light tinted boxes indicate the scope of content in this KLS resource.
GFR= Glomerular Filtration Rate; T= Kidney Transplant; D= Dialysis

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