Assessment of kidney function

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INTRODUCTION

Patients with kidney disease may have a variety of different clinical presentations. Some have symptoms that are directly referable to the kidney (gross hematuria, flank pain) or to extrarenal symptoms (edema, hypertension, signs of uremia). Many patients, however, are asymptomatic and are noted on routine examination to have an elevated serum creatinine concentration or an abnormal urinalysis.

Once kidney disease is discovered, the presence or degree of kidney dysfunction and rapidity of progression are assessed, and the underlying disorder is diagnosed. Although the history and physical examination can be helpful, the most useful information is initially obtained from estimation of the glomerular filtration rate (GFR) and examination of the urinary sediment.

Estimation of the GFR is used clinically to assess the degree of kidney impairment and to follow the course of the disease. However, the GFR provides no information on the cause of the kidney disease. This is achieved by the urinalysis, measurement of urinary protein excretion, and, if necessary, radiologic studies and/or kidney biopsy.

This topic will provide an overview of the issues concerning assessment of the GFR in the patient with chronic kidney disease (CKD). The utility of the urinalysis, radiologic studies, and kidney biopsy are discussed separately, as is the general approach to the patient with kidney disease:

- (See "Urinalysis in the diagnosis of kidney disease".)
- (See "Radiologic assessment of renal disease".)
- (See "The kidney biopsy".)
- (See "Diagnostic approach to adult patients with subacute kidney injury in an outpatient setting".)

OVERVIEW OF KIDNEY FUNCTION

Prior to discussing the evaluation of kidney function, it is helpful to first briefly review normal kidney physiology. The kidney performs a number of essential processes:

- It participates in the maintenance of the constant extracellular environment that is required for adequate functioning of the cells. This is achieved by excretion of some of the waste products of metabolism (such as urea, creatinine, and uric acid) and by specifically adjusting the urinary excretion of water and electrolytes to match net intake and endogenous production (table 1 and table 2). The kidney is able to regulate individually the excretion of water and solutes such as sodium, potassium, and hydrogen, largely by changes in tubular reabsorption or secretion.
- It secretes hormones that participate in the regulation of systemic and renal hemodynamics (renin, prostaglandins, and bradykinin), red blood cell production (erythropoietin), and calcium, phosphorus, and bone metabolism (1,25-dihydroxyvitamin D3 or calcitriol).

In the patient with kidney disease, some or all of these functions may be diminished or entirely absent. As an example, patients with nephrogenic diabetes insipidus have a decreased urinary concentrating ability, but other functions are entirely normal. By comparison, all kidney functions may be significantly impaired in the patient with end-stage renal disease, thereby resulting in the retention of uremic toxins, marked abnormalities in fluid and electrolyte balance, and anemia and bone disease.

GLOMERULAR FILTRATION RATE

Normal GFR — The glomerular filtration rate (GFR) is equal to the sum of the filtration rates in all of the functioning nephrons; thus, the GFR gives a rough measure of the number of functioning nephrons. The filtering units of the kidney, the glomeruli, filter approximately 180 liters per

day (125 mL/min) of plasma. The normal value for GFR depends upon age, sex, and body size, and is approximately 130 and 120 mL/min/1.73 m^2 for men and women, respectively, with considerable variation even among normal individuals [1].

Significance of a declining GFR — In patients with kidney disease, a reduction in GFR implies either progression of the underlying disease or the development of a superimposed and often reversible problem, such as decreased renal perfusion due to volume depletion. In addition, the level of GFR has prognostic implications in patients with chronic kidney disease (CKD), and such patients are staged, in part, according to GFR. These issues are discussed in detail separately. (See "Diagnostic approach to adult patients with subacute kidney injury in an outpatient setting" and "Definition and staging of chronic kidney disease in adults".)

However, there is **not** an exact correlation between the loss of kidney mass (ie, nephron loss) and the loss of GFR. The kidney adapts to the loss of some nephrons by compensatory hyperfiltration and/or increasing solute and water reabsorption in the remaining, normal nephrons [2-4]. Thus, an individual who has lost one-half of total kidney mass will not necessarily have one-half the normal amount of GFR. (See 'Using creatinine to estimate GFR' below.)

These concepts have important consequences:

- A stable GFR does not necessarily imply stable disease. Signs of disease progression other than a change in GFR must be investigated, including increased activity of the urine sediment, a rise in protein excretion, or an elevation in blood pressure.
- Similarly, an increase in GFR may indicate improvement in the kidney disease or may imply a counterproductive increase in filtration (hyperfiltration) due to hemodynamic factors. (See "Secondary factors and progression of chronic kidney disease".)
- Some patients who have true underlying renal disease may go unrecognized because they have a normal GFR.

ASSESSMENT OF GFR

How to evaluate GFR: Measurement versus estimation — Measurement of glomerular filtration rate (GFR) is complex, time consuming, and cumbersome to do in clinical practice. As such, GFR is usually estimated from serum markers (see 'Estimation of GFR' below). Clinical situations in which it is important to have more precise knowledge of the GFR include: prior to dose adjustment of medications, especially toxic medications with narrow therapeutic indices, such as chemotherapy; prior to kidney donation; and prior to determining the need for preemptive transplant. In such circumstances, it would be reasonable to consider measuring GFR.

Measurement of GFR — Although GFR cannot be measured directly, the best method for determining GFR is measurement of the urinary clearance of an ideal filtration marker. Using a filtration marker (x), the equation to calculate the clearance of x (Cx) is:

Equation 1: $Cx = (Ux \times V) \div Px$

Where Px is the serum concentration of the marker, Ux is the urinary concentration of x, and V is the urine flow rate.

An ideal filtration marker is defined as a solute that is freely filtered at the glomerulus, nontoxic, neither secreted nor reabsorbed by the kidney tubules, and not changed during its excretion by the kidney. If these criteria are met, the filtered load is equal to the rate of urinary excretion:

Equation 2: $GFR \times Px = (Ux \times V)$

Where GFR X Px is the filtered load, and Ux X V is the urinary excretion rate. By substitution into Equation 1:

Equation 3: $GFR = Cx$

Plasma clearance is an alternative to urinary clearance for measurement of GFR. It is performed by timed plasma measurements after administering a bolus intravenous injection of an exogenous filtration marker; the clearance equation is:

Equation 4: $Cx = Ax \div Px$

Where Ax is the amount of the marker administered, and Px is the plasma concentration computed from the entire area under the disappearance curve.

The gold standard of exogenous filtration markers is inulin. Inulin is a physiologically inert substance that is freely filtered at the glomerulus, and is neither secreted, reabsorbed, synthesized, nor metabolized by the kidney [5]. Thus, the amount of inulin filtered at the glomerulus is equal to the amount excreted in the urine, which can be measured. Inulin, however, is in short supply (and is no longer available in the United States), expensive, and difficult to assay. In addition, the classic protocol for measuring inulin clearance requires a continuous intravenous infusion, multiple blood samples, and bladder catheterization.

Various less cumbersome methods for measuring clearance are available: using alternative filtration markers (such as radioactive or nonradioactive iothalamate, iohexol, DTPA, or EDTA), bolus administration of the marker (subcutaneous or intravenous), spontaneous bladder

emptying, and plasma clearance [5-8]. While these methods are simpler, all have disadvantages that limit their application in clinical practice and affect the interpretation of research studies [8].

Estimation of GFR — In the United States, the most common methods utilized to estimate the GFR are: measurement of the creatinine clearance; and estimation equations based upon serum creatinine such as the Cockcroft-Gault equation, the Modification of Diet in Renal Disease (MDRD) study equation, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The abbreviated MDRD study and CKD-EPI equations are being increasingly utilized. (See 'Creatinine clearance' below and 'Estimation equations' below.)

Both measurement of the creatinine clearance and estimation equations rely upon creatinine as a marker of kidney function. Issues related to the use of creatinine to estimate GFR are presented below. (See 'Using creatinine to estimate GFR' below.)

Other markers of kidney function include the blood urea nitrogen (BUN), which is less useful than the serum creatinine, and serum cystatin C. (See 'BUN and GFR' below and 'Serum cystatin C' below.)

Requirement for stable kidney function — Endogenous filtration markers can only be used to estimate GFR in individuals with stable kidney function [9]. Early in the course of acute kidney injury, for example, the GFR is markedly reduced, but there has not yet been time for the filtration marker to accumulate and, therefore, for the filtration marker to reflect the degree of kidney disease severity. An equation has been developed that estimates the true GFR given the rate of change in creatinine [10].

Using creatinine to estimate GFR — Creatinine is derived from the metabolism of creatine in skeletal muscle and from dietary meat intake. It is released into the circulation at a relatively constant rate. Creatinine is freely filtered across the glomerulus and is neither reabsorbed nor metabolized by the kidney. However, approximately 10 to 40 percent of urinary creatinine is derived from tubular secretion by the organic cation secretory pathways in the proximal tubule [11]. Thus, if GFR, creatinine secretion by the renal tubules, creatine intake (ie, diet), and the creatinine pool size (ie, muscle mass) all remain constant, then the plasma creatinine concentration should remain constant.

Creatinine excretion (GFR x SCr), where SCr is serum creatinine, equals creatinine production in the steady state and creatinine production is relatively constant on a stable diet and with stable muscle mass. As a result:

$$GFR \times SCr = Constant$$

Thus, the serum creatinine concentration varies inversely with the GFR. If, for example, the GFR falls by 50 percent, creatinine excretion will initially be reduced. Assuming that tubular creatinine secretion, diet, and muscle mass do not change, this reduction in GFR will lead to creatinine retention and a rise in the serum creatinine until it has doubled (figure 1); at this point, the filtered load will again be equal to excretion:

$$GFR/2 \times 2SCr = GFR \times SCr = Constant$$

The shape of the curve relating the GFR to serum creatinine has an important clinical implication (figure 1): in patients with mild kidney disease, a small rise in serum creatinine usually reflects a marked fall in GFR, whereas a marked rise in serum creatinine in patients with advanced disease reflects a small absolute reduction in GFR.

However, this curve depicts a hypothetical relationship between GFR and serum creatinine (figure 1). In reality, a reduction in GFR results in increased tubular creatinine secretion that blunts the rise in serum creatinine. Thus, a 50 percent reduction in GFR does not produce a doubling of serum creatinine, but rather a smaller rise than would have occurred if the decrease in GFR had occurred without an increase in secretion.

Normal values — In the Third National Health and Nutrition Examination Survey in the United States, the mean serum creatinine values for men and women were 1.13 and 0.93 mg/dL (100 and 82 micromol/L), respectively (figure 2) [12]. The mean values also varied by race. For non-Hispanic Black American patients, the mean serum creatinine was 1.25 mg/dL in men and 1.01 mg/dL in women. The values were lower in non-Hispanic White American patients (1.16 mg/dL in men and 0.97 mg/dL in women) and in Mexican-Americans (1.07 mg/dL in men and 0.86 mg/dL in women) [12]. The mean values will all be lower with the adoption of newer creatinine assays traceable to reference materials. (See 'GFR estimation and race and ethnicity' below.)

Serum creatinine values are lower in women because they have less muscle mass and, therefore, a lower rate of creatinine excretion [13,14]. It is presumed that the higher values for Black American patients and lower values for Hispanic patients similarly reflect greater and lesser, respectively, muscle mass and creatinine excretion.

Limitations of using creatinine — There are several key limitations of using creatinine to estimate GFR. These include variations in creatinine production, variations in creatinine secretion, extrarenal creatinine excretion, and issues associated with creatinine measurement.

With stable kidney function, as seen in patients with normal kidney function or chronic kidney disease (CKD), a rise in serum creatinine almost always represents a reduction in GFR. However, certain drugs can interfere with either creatinine secretion or the assay used to measure the serum creatinine, and dietary changes or dietary supplements can alter creatinine production. In these settings, there will be no change in GFR and no concurrent elevation in the BUN. (See "Drugs that elevate the serum creatinine concentration".)

Variation in creatinine production — The production of creatinine differs among and within people over time. As examples, individuals with significant variations in dietary intake (vegetarian diet, creatine supplements) or reduction in muscle mass (amputation, malnutrition, muscle wasting) produce different amounts of creatinine than the general population. The accuracy of estimation equations is affected to a greater extent among lower extremity amputees, given the much greater reduction in muscle mass, compared with upper extremity amputations.

There are certain settings in which there may be an acute increase in creatinine load. One example is a recent meat meal. In addition, it has been suggested that the serum creatinine rises more rapidly with rhabdomyolysis (up to 2.5 mg/dL or 220 micromol/L per day) than with other causes of acute kidney injury [15]. Release of preformed creatinine from injured muscle and/or release of creatine phosphate that is then converted into creatinine in the extracellular fluid have been proposed as explanations for this finding. However, neither of these mechanisms appears to account for most of the increase in the serum creatinine concentration [16]. An alternative explanation is that rhabdomyolysis often affects otherwise healthy men with a high muscle mass and a higher rate of creatinine production while other forms of acute kidney injury frequently affect patients who are chronically ill [16].

Variation in creatinine secretion — The accuracy of GFR estimation with both the creatinine clearance and creatinine-based estimation equations is limited by the fact that as the GFR falls, the rise in the serum creatinine is partially opposed by enhanced proximal tubular creatinine secretion [2,3,6,17,18]. In early renal disease when the GFR is still near normal, an initial decline in GFR may lead to only a slight increase (0.1 to 0.2 mg/dL [9 to 18 micromol/L]) in the serum creatinine. The net effect is that patients with a true GFR as low as 60 to 80 mL/min (as measured by the clearance of a true filtration marker such as inulin or radioisotopic iothalamate or DTPA [6,19,20]) may still have a serum creatinine that is ≤1 mg/dL (88 micromol/L) [11]. Thus, a relatively stable serum creatinine in the normal or near-normal range does **not** necessarily imply that the disease is stable.

However, once the serum creatinine exceeds 1.5 to 2 mg/dL (132 to 176 micromol/L), the secretory process is effectively saturated. After this, a stable value usually represents a stable GFR [11].

The following clinical examples are illustrative:

- A man with unrecognized kidney disease and an initial serum creatinine of 0.9 mg/dL (79.6 micromol/L) has a decline in his true GFR from 120 to 70 mL/min per 1.73 m^2 (loss of 50 mL/min per 1.73 m^2, or approximately 40 percent of his GFR). Using the hypothetical relationship between GFR and creatinine (which ignores creatinine secretion), the serum creatinine multiplied by GFR is a constant, and the serum creatinine would be expected to rise to approximately 1.7 mg/dL (150.3 micromol/L) (figure 1). However, his actual rise in serum creatinine is much smaller, to 1.2 mg/dL (106.1 micromol/L), because of increased creatinine secretion. Although a serum creatinine of 1.2 mg/dL is in the normal range, this should **not** be mistakenly assumed to be normal or indicative of only mild disease. The severity of the GFR decline was not apparent due to an increase in creatinine secretion. Early detection of progressive kidney disease is particularly important because of the availability of therapies, particularly blood pressure lowering with angiotensin-converting enzyme inhibitors, which can slow the rate of progression in many patients. (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults".)

- In another patient with more advanced disease, the serum creatinine is 4 mg/dL (354 micromol/L) and the GFR 15 mL/min. Because creatinine secretion is saturated, a rise in serum creatinine (SCr) to 6 mg/dL (530 micromol/L) reflects a GFR of 10 mL/min or a loss of only 5 mL/min. Assuming that generation and extrarenal elimination of creatinine in this patient are constant, then GFR x SCr is constant, so: GFR x SCr = 15 x 4 = 10 x 6 = 60.

In addition, creatinine secretion may be enhanced or inhibited in certain clinical situations. As examples:

- Tubular creatinine secretion is significantly increased in patients with the nephrotic syndrome. In one study, in which GFR was determined by inulin clearance, decreased serum albumin levels were associated with a marked increase in tubular creatinine secretion (36 mL/min per 1.73 m^2 for nephrotic patients with serum albumin levels less than 2.6 g/dL versus 11 mL/min per 1.73 m^2 for normal controls) [21]. Patients with sickle cell disease may also have an increase in creatinine secretion. Thus, patients with nephrotic syndrome and sickle cell disease may have a GFR that is substantially lower than what can be estimated from the serum creatinine.

- The degree of creatinine secretion may vary with time, affecting the serum creatinine independent of the GFR [6,22]. In effectively treated lupus nephritis, for example, a rise in the GFR may not be accompanied by the expected reduction in the serum creatinine due to a fall (via an uncertain mechanism) in creatinine secretion [22]. In this setting, decreased activity of the urine sediment, diminished protein excretion, and lack of further elevation in the serum creatinine all point toward possible improvement.

- The presence of certain drugs may increase the level of the serum creatinine by decreasing creatinine secretion. These drugs include trimethoprim (which is most often given in combination with sulfamethoxazole) and the H2-blocker cimetidine, which result in a self-limited and reversible rise in the serum creatinine of as much as 0.4 to 0.5 mg/dL (35 to 44 micromol/L). (See "Drugs that elevate the serum creatinine concentration".)

Extrarenal creatinine excretion — Extrarenal creatinine elimination is increased in advanced kidney failure (eg, estimated GFR <15 mL/min per 1.73 m^2). In this setting, there is intestinal bacterial overgrowth and increased bacterial creatininase activity [23]. As a result, the serum creatinine concentration is lower than would be expected from the GFR.

Measurement issues — Serum creatinine is most often measured by the alkaline picrate method. Certain substances may interfere with the assay, thereby artifactually increasing the serum creatinine concentration. This colorimetric assay can recognize other compounds as creatinine chromogens, particularly acetoacetate in diabetic ketoacidosis, or bilirubin [24-27]. In this setting, the serum creatinine can rise by 0.5 to >2 mg/dL (44 to 176 micromol/L), a change that is rapidly reversed with insulin therapy. Cefoxitin and flucytosine are drugs that can produce a similar effect. (See "Drugs that elevate the serum creatinine concentration".)

Differences in method and equipment can lead to variation in reported serum creatinine values (random measurement error) [28]. In a study evaluating over 5000 laboratories using 20 different instruments to measure serum creatinine by up to three different methods (alkaline picrate and enzymatic), the mean serum creatinine concentration on a standardized sample ranged from 0.84 to 1.21 mg/dL (74.3 to 107 micromol/L) [25]. Bias related to instrument manufacturer was greater than that due to method. This variation has been substantially reduced by the national program established by the National Kidney Disease Education Program (NKDEP) to standardize creatinine assays so that they are all traceable to reference materials. Most manufacturers now use such calibrators and therefore most clinical laboratories in the United States have assays traceable to these reference materials [29].

The variation in serum creatinine measurement methods leads to variation in creatinine-based GFR estimation. This was shown in a study that examined frozen samples from 212 and 342 MDRD and NHANES III participants, respectively [28]. Creatinine was measured in MDRD and NHANES III with different assays. When creatinine was measured on the same blood samples using both assays, the serum creatinine was on average 0.23 mg/dL (20.3 micromol/L) higher with the NHANES III assay [28]. This difference can result in substantial variations in GFR estimation when the serum creatinine concentration is relatively normal. These data also suggest that changes in serum creatinine of ±0.3 mg/dL (26 micromol/L) measured in different laboratories may represent variations in the assay rather than variations in GFR; the variation is much smaller in repeated measurements in the same laboratory. The recognition that variations in serum creatinine measurements can have a substantial impact on the assessment of kidney function has led to ongoing efforts to standardize creatinine measurements across laboratories [1].

Creatinine clearance — Creatinine is freely filtered across the glomerulus and is neither reabsorbed nor metabolized by the kidney. However, approximately 10 to 40 percent of urinary creatinine is derived from tubular secretion by the organic cation secretory pathways in the proximal tubule [11].

If the effect of secretion is ignored, then all of the filtered creatinine (equal to the product of the GFR and the serum creatinine concentration [SCr]) will be excreted (equal to product of the urine creatinine concentration [UCr] and the urine flow rate). Thus:

$$GFR \times SCr = UCr \times V$$
$$GFR = [UCr \times V] \div SCr$$

This formula is called the creatinine clearance and tends to exceed the true GFR by approximately 10 to 20 percent or more since this is the fraction of urinary creatinine that is derived from tubular secretion [17]. However, historically, this error has been balanced by an opposing error of almost equal magnitude in the measurement of the serum creatinine using the Jaffe (alkaline picrate) method [28]. (See "Calculation of the creatinine clearance".)

National standardization of serum creatinine assays to creatinine reference materials should abolish this measurement error in serum creatinine. If so, creatinine clearance measurements utilizing urine collection will be consistently 10 to 20 percent higher than GFR, reflecting the impact of creatinine secretion. However, this effect is variable across laboratories due to the methods used to assay urine versus serum creatinine.

The creatinine clearance (CrCl) is usually determined from a 24-hour urine collection since shorter collections tend to give less accurate results. (See "Patient education: Collection of a 24-hour urine specimen (Beyond the Basics)".)

Suppose that the following results are obtained in a 60 kg woman:

$$SCr = 1.2 \text{ mg/dL } (106 \text{ micromol/L})$$
$$UCr = 100 \text{ mg/dL } (8800 \text{ micromol/L})$$
$$V = 1.2 \text{ L/day}$$

Thus:

$$CrCl = [100 \times 1.2] \div 1.2 = 100 \text{ L/day}$$

This value has to be multiplied by 1000 to convert into mL and then divided by 1440 (the number of minutes in a day) to convert into units of mL/min.

$$CrCl = [100 \times 1000] \div 1440 = 70 \text{ mL/min}$$

This unadjusted creatinine clearance value should be used for determination of drug doses (calculator 1). However, a patient's creatinine clearance should be adjusted to body surface area (BSA) when comparing it with normal values to determine the presence and severity of kidney disease (calculator 2).

As an example, a creatinine clearance of 70 mL/min in a small 50 year-old woman with a weight and height of 50 kg and 160 cm, who has a BSA of 1.5, is corrected to a body surface area of 1.73 m^2 as follows:

$$CrCl \times 1.73/BSA = [70\ mL/min \times 1.73] \div 1.5 = 80\ mL/min\ per\ 1.73\ m^2$$

In turn, for a large person with a body surface area of 1.9, the adjusted creatinine clearance would be 64 mL/min per 1.73 m^2.

Limitations of using creatinine clearance — There are two major errors that can limit the accuracy of the creatinine clearance: an inaccurate urine collection, and increasing creatinine secretion. (See "Calculation of the creatinine clearance".)

- An incomplete urine collection – The completeness of the collection can be estimated from knowledge of the normal rate of creatinine excretion (which is equal to creatinine production in the steady state). As a general rule in adults under the age of 50 years, daily creatinine excretion should be 20 to 25 mg/kg (177 to 221 micromol/kg) of lean body weight in men and 15 to 20 mg/kg (133 to 177 micromol/kg) of lean body weight in women. From the ages of 50 to 90 years, there is a progressive 50 percent decline in creatinine excretion (to approximately 10 mg/kg in men), due primarily to a fall in muscle mass. Formulas that incorporate race and weight with or without serum phosphorus in addition to age and sex may improve the estimation of creatinine excretion [13,30] (see 'GFR estimation and race and ethnicity' below):

$$\text{Estimated creatinine excretion (mg/day)} = 1115.89 + (11.97 \times \text{Weight in kg}) - (5.83 \times \text{Age}) - (60.18 \times \text{Phosphorus in mg/dL}) + (52.82 \text{ if black}) - (368.75 \text{ if fe}$$

  As an example, suppose a 50 year-old white woman weighing 50 kg excreted 1200 mg (10,600 micromol) of creatinine in 24 hours (24 mg/kg [177 micromol/kg]). According to the simple rule based upon age and sex alone, this patient provided an accurate collection. However, according to the formula above, the expected excretion for someone of her age, race, and weight would have been 844 mg/day [30], suggesting this may be an over collection. The clinical context, such as the muscle mass and diet of the patient compared with the average person, should be considered when determining the adequacy of collection. In addition, repeating the creatinine clearance and averaging the two would minimize the effect of any error.

  However, variability in urine collections can lead to the following frequent misinterpretation. The 24-hour creatinine clearance is measured on two separate occasions in a patient with known kidney disease and a stable weight and diet. The serum creatinine is unchanged but the creatinine clearance has declined by 20 mL/min. The latter finding suggests that kidney function has deteriorated. However, if the serum creatinine concentration is stable, then from the formula for creatinine clearance ([UCr x V]/SCr), the only way for the measured creatinine clearance to fall is if creatinine excretion (UCr x V) has fallen. Assuming constant muscle mass and diet, the most likely explanation for reduced creatinine excretion is an incomplete urine collection. It is therefore likely that the stable serum creatinine in this patient represents a stable creatinine clearance (which, as described below, may or may not represent a constant GFR because of changes in creatinine secretion). Similar considerations apply to a rise in creatinine clearance without change in the serum creatinine. In this setting, an over collection increasing apparent daily creatinine excretion is most probable.

- Increasing creatinine secretion – The increase in creatinine secretion as GFR falls can limit the interpretation of the creatinine clearance. (See 'Variation in creatinine secretion' above.)

  As an example, if the true GFR falls to a range of 40 to 80 mL/min (as measured by an exogenous filtration marker), and the absolute amount of creatinine secreted rises by more than 50 percent, creatinine secretion would now account for as much as 35 percent of urinary creatinine [17]. Thus, in some patients with CKD, creatinine excretion may be much greater than the filtered load, resulting in a potentially large overestimation of the GFR when creatinine clearance is used to assess the level of GFR. The net effect is that the creatinine clearance may be normal (>90 mL/min) in approximately one-half of patients with a true GFR of 61 to 70 mL/min and one-quarter of those with a true GFR of 51 to 60 mL/min [18].

  Some patients with advanced disease have a creatinine clearance that exceeds the GFR by more than twofold [31]. This was best shown in a systematic review and meta-analysis of seven studies of 193 patients with liver cirrhosis in which the measured creatinine clearance was compared with true GFR (assessed by inulin clearance) [31]. Overall, the measured creatinine clearance overestimated inulin clearance by a mean of 13 mL/min per 1.73 m^2, with the overestimation being highest in those with the lowest true GFRs. Among those with inulin clearance of less than 30 mL/min per 1.73 m^2 (true stage 4 to 5 CKD), the measured creatinine clearance correctly classified 64 percent of patients, incorrectly classified 23 percent of patients as having GFRs between 30 to 59 mL/min per 1.73 m^2, and incorrectly classified 14 percent as having GFRs ≥60 mL/min per 1.73 m^2. Another method to help estimate the GFR in these patients is to average both the creatinine and urea clearances

From the above considerations, all that can be concluded is that the creatinine clearance represents an upper limit of what the true GFR may be. An alternative, although not widely used clinically, is to competitively inhibit creatinine secretion by the administration of cimetidine, which is

secreted by the same pathway [2]. However, there is inter- and intrapatient variability in the effect of cimetidine blockade, which can make the results difficult to interpret. (See "Calculation of the creatinine clearance", section on 'Use of cimetidine'.)

Issues concerning the use of the creatinine clearance in patients with liver disease and decreased GFR, a setting in which increased tubular secretion of creatinine is also observed, are discussed below. (See 'BUN and GFR' below.)

Estimation equations — GFR-estimating equations improve upon the serum creatinine by incorporating known demographic and clinical variables as observed surrogates for the unmeasured physiological factors other than GFR that affect the serum creatinine concentration, such as generation and tubular secretion. Estimation equations also appear to be reasonably accurate for following changes in GFR over time [32,33]. Similar to the serum creatinine, these equations do **not** provide accurate estimates of GFR in settings where the GFR is changing rapidly (eg, acute kidney injury).

The most common equations used in the United States are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, the MDRD study equation, and the Cockcroft-Gault equation. CKD-EPI is more accurate than the MDRD study equation, and both are more accurate than the Cockcroft and Gault equation. The MDRD study and CKD-EPI equations are normalized to body surface area.

Cockcroft-Gault equation — The Cockcroft-Gault equation allows the creatinine clearance to be estimated from the serum creatinine in a patient with a stable serum creatinine [34]:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{Age}) \times \text{Lean body weight [kg]}}{\text{Cr [mg/dL]} \times 72}$$

This formula takes into account assumptions that creatinine production decreases with advancing age, and is greater in individuals with greater weight. However, this equation was developed at a point in history when obesity was far less common. In the current era, higher weight may mean greater fat mass, and not greater muscle mass. For women, the formula requires multiplication by 0.85 to account for smaller muscle mass compared with men (calculator 3).

The equation is not adjusted for body surface area. Therefore, to compare with normal values, the result should be adjusted for body surface area. Normalization for body surface increases the accuracy of this equation, particularly among those with decreased kidney function [35]. (See 'Creatinine clearance' above.)

The Cockcroft-Gault equation was developed prior to the use of standardized creatinine assays, and has **not** been revised for use with creatinine values traceable to standardized reference materials. Thus, using the Cockcroft-Gault equation with creatinine values measured by most laboratories in the United States today will result in a 10 to 40 percent **overestimate** of creatinine clearance.

MDRD study equation — Several equations were derived from data on adult patients enrolled in the MDRD study who had GFR measured at baseline using urinary clearance of iothalamate [36].

The original MDRD study equation has been re-expressed for use with creatinine values that are standardized to creatinine reference materials measured using gold standard techniques (calculator 4) (www.cap.org). Standardized creatinine assays are used by most clinical laboratories in the United States.

$$\text{GFR, in mL/min per 1.73 m}^2 = 175 \times \text{SCr}^{(-1.154)} \times \text{Age}^{(-0.203)} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

Evaluation of the MDRD and Cockcroft-Gault equations in specific populations — The MDRD study equation was derived from primarily white subjects (mean age of 51 years plus/minus 12.7 years) who had nondiabetic kidney disease, with mean GFR of 40 mL/min per 1.73 m^2. Subsequently, there has been extensive evaluation of the performance of the equation in other populations including African Americans, Europeans, and Asians with nondiabetic kidney disease, diabetic patients with and without kidney disease, patients with liver disease, kidney transplant recipients, and potential kidney donors [20,37-58].

The following illustrate some of these important observations:

- The MDRD study equation is reasonably accurate in non-hospitalized patients known to have CKD, regardless of diagnosis [37-39,41].
- The MDRD study equation and Cockcroft-Gault equation appear to be somewhat less accurate in obese individuals [41,54,59].
- The MDRD study and the Cockcroft-Gault equations are less accurate in populations with normal or near-normal GFR [37,39-41,43,49,57].
- Among recipients of renal allografts, there have been variable results related to the accuracy of the MDRD study and other estimation equations [45,51,56,60-64]. Although the MDRD study equation has limitations in transplant recipients, most experts use the abbreviated formula in this setting.

- Estimation equations may also be less accurate in populations of different ethnicities and from outside of the United States [44,65-70]. Available data suggest that these equations overestimate GFR in Japan and some other Asian populations, possibly related to differences in body mass and diet [58,65-68,71-73], although a study in China showed that the MDRD study equation underestimated GFR [70]. Furthermore, the definition of what constitutes normal GFR is not well defined in some of these populations [68].

These examples illustrate the performance of estimating equations in specific populations. In addition, the performance of the MDRD study equation and Cockcroft-Gault equation may not be similarly accurate in different age groups [41,54,59,74,75]. In the Third National Health and Nutrition Examination Survey (NHANES III), for example, the abbreviated MDRD study equations and the Cockcroft-Gault equation provide similar values within a wide range of patient ages, which were consistent with age-specific historic inulin clearance values [74]. However, the Cockcroft-Gault equation provided higher estimates at younger ages, and lower estimates at older ages (eg, greater than 70 years of age) than that obtained with the simplified MDRD study equation.

CKD-EPI equation — Both the MDRD study and the Cockcroft-Gault equations are less accurate in populations with normal or near-normal GFR. (See 'Evaluation of the MDRD and Cockcroft-Gault equations in specific populations' above.)

CKD-EPI is superior when GFR is normal or mildly reduced — The CKD-EPI equation was developed to provide a more accurate estimate of GFR among individuals with normal or only mildly reduced GFR (ie, above 60 mL/min per 1.73 m^2) (calculator 5) [76]. This equation was developed using data pooled from 10 studies and validated against data derived from 16 additional studies, in which the gold standard was direct measurement of GFR using external filtration markers (eg, iothalamate). The study population included people with and without kidney disease who had a wide range of GFRs.

In the validation dataset, the CKD-EPI equation was as accurate as the MDRD study equation among individuals with estimated GFR less than 60 mL/min per 1.73 m^2 and somewhat more accurate in those with higher GFRs (figure 3).

Although the CKD-EPI equation was more accurate and less biased than the MDRD equation [76], precision was not substantially improved. Half of the study population had an estimated GFR that differed from the measured GFR by at least 16 mL/min per 1.73 m^2 using the CKD-EPI equation, and by 18 mL/min per 1.73 m^2 or more using the MDRD study equation (figure 3). Similarly, the percentage of patients whose estimated GFR differed by more than 30 percent of the measured GFR was similar with the two equations (12 versus 15 percent).

The accuracy and bias of the CKD-EPI equation as compared with the MDRD study equation may differ according to the GFR and to various patient characteristics [77-79]. The CKD-EPI equation, for example, performs better at higher levels of GFR and in subgroups defined by sex, race, diabetes and transplant status, in older adults, and at higher levels of BMI [78,79]. By contrast, the MDRD study equation performs better at lower levels of GFR [78]. (See 'GFR estimation and race and ethnicity' below.)

CKD-EPI results in lower prevalence of CKD and better risk prediction — When both equations were used to estimate GFR in over 16,000 NHANES participants, GFR estimates by CKD-EPI were higher than estimates obtained using the MDRD study equation among individuals with a measured GFR greater than 30 mL/min per 1.73 m^2. As a result, the overall prevalence of CKD was lower when the CKD-EPI equation was used to define the CKD population (13 versus 11.5 percent).

The finding of a lower overall prevalence of CKD in the general population with the CKD-EPI equation was confirmed in additional studies. These studies also demonstrated a lower risk of adverse outcomes in people who were reclassified to a lower CKD stage using the CKD-EPI equation [80-86].

The most comprehensive data comparing the CKD-EPI and MDRD equations with respect to CKD stage and risk prediction come from a meta-analysis that included 1.1 million adults from 25 general population cohorts, 7 vascular disease high-risk cohorts, and 13 CKD cohorts [80]. Individuals in this meta-analysis had GFR estimated by both the CKD-EPI and MDRD equations, and were followed for a median of 7.4 years (interquartile range, 4.2-10.5 years) for all-cause mortality, cardiovascular mortality, and end-stage renal disease (ESRD). The following observations were made:

- Compared with the MDRD study equation, 24.4 and 0.6 percent of participants from general population cohorts were reclassified to a higher and lower estimated GFR category, respectively, by the CKD-EPI equation; the prevalence of CKD stages 3 to 5 (estimated GFR <60 mL/min/1.73 m^2) in these general population cohorts was reduced from 8.7 to 6.3 percent when the CKD-EPI equation was used.
- Of those whose estimated GFR was 45 to 59 mL/min/1.73 m^2 according to the MDRD study equation, 35 percent were reclassified to an estimated GFR of 60 to 89 mL/min/1.73 m^2 by the CKD-EPI equation. These individuals who were reclassified had a significantly lower risk for all-cause mortality (9.9 versus 34.5 events per 1000 patient years), cardiovascular mortality (2.7 versus 13 events per 1000 patient years), and ESRD (0.5 versus 0.8 per 1000 patient years) compared with those whose estimated GFR was 45 to 59 mL/min/1.73 m^2 with both equations
- The findings were similar in the high-risk and CKD cohorts.

These data show that, across multiple populations, the use of the CKD-EPI equation results in a lower prevalence estimate of CKD and more accurate risk prediction for adverse outcomes compared with the MDRD study equation [87].

Choice of equation — Given the data on the improved performance, especially at higher levels of GFR, we and others suggest using the CKD-EPI equation for the general population (calculator 5). This includes people with a GFR near or above 60 mL/min per 1.73 m^2, as specific values in that range can be used with somewhat more confidence. The CKD-EPI equation has a similar performance to the MDRD study equation for people with lower levels of GFR, and therefore can be used for people with lower levels of GFR as well.

Other equations have also emerged using standardized serum creatinine assays, such as the Lund Malmo Revised (LMR) and Full Age Spectrum (FAS) equations, which were developed in Caucasian populations. These equations performed as well as, but not better than, the CKD-EPI equation, although they would not be applicable for use in diverse populations [88-90].

Limitations of estimation equations — The three creatinine estimation equations described above are limited by the limitations inherent in the use of serum creatinine (see 'Limitations of using creatinine' above). This is particularly true when there are variations in creatinine production. Given these variations, all serum creatinine equations will be less accurate in certain populations. These include diabetic patients with high GFR [91], specific ethnic groups (eg, Asians), pregnant women, and those with unusual muscle mass, body habitus, and weight (eg, morbid obesity, amputees). In all of these settings, use of a confirmatory test such as estimated GFR from cystatin C or creatinine-cystatin GFR estimating equations (see below), collection of a 24-hour urine sample for measurement of creatinine clearance, or measurement of clearance of an exogenous filtration marker will provide a more accurate assessment of GFR than estimated GFR from creatinine. (See 'Variation in creatinine production' above.)

Drug dosing — Drug dosing guidelines have historically been developed using the Cockcroft-Gault equation to estimate kidney function. This practice had been consistent with the original recommendation of the US Food and Drug Administration (FDA) to pharmaceutical industries to use an estimating equation, rather than serum creatinine alone, in pharmacokinetic studies to determine drug dosing in kidney disease. Most pharmacokinetic studies for drug dosing in renal disease were performed using the Cockcroft-Gault equation since this equation was suggested by the FDA prior to publication of the MDRD study equation [92].

The move toward standardizing all creatinine assays so that they are traceable to reference materials creates a problem with drug dosing according to estimated GFR. The pharmacokinetic studies were performed using serum creatinine values that were highly variable (before standardized reference materials were available), and therefore the results of these pharmacokinetic studies **cannot** necessarily be reliably translated into current clinical practice [93]. This could lead to inaccuracies in drug dosing in patients with kidney disease.

A large simulation study showed that there was greater concordance between the MDRD study equation and measured GFR than the Cockcroft-Gault equation and measured GFR [94]. Concordance was lower for the Cockcroft-Gault equation at older age but was consistent for the MDRD study equation. Unpublished data show comparability between the MDRD study equation and the CKD-EPI equation. Thus, for most patients, the MDRD study or CKD-EPI equation can be used to estimate kidney function for drug dosing [95]. Given these and other data, the Kidney Disease Improving Global Outcomes (KDIGO) 2011 clinical update on drug dosing in patients with acute and chronic kidney diseases recommended using the most accurate method for GFR evaluation for each patient (rather than limiting the evaluation to the Cockcroft-Gault formula) and specifically including estimated GFR as it is reported by clinical laboratories or measured GFR if creatinine-based estimates are not accurate for individual patients [96].

If estimated GFR is used for drug dosing in very large or small patients, the reported estimated GFR (which is normalized to body surface area) should be multiplied by the estimated body surface area and then divided by 1.73 to obtain an estimated GFR in units of mL/min (ie, not normalized to body surface area).

As noted above, for patients at the extremes of muscle mass, with unusual diets, or with conditions associated with changes in creatinine secretion, all estimation equations that use the serum creatinine are limited. In such cases, dosing decisions should be made based upon GFR estimated with cystatin- or creatinine-cystatin-based equations, with measured creatinine clearance, or with measured GFR using exogenous filtration markers, particularly if prescribing drugs with a narrow therapeutic window. (See 'Measurement of GFR' above and 'Creatinine clearance' above.)

BUN and GFR — Although the blood urea nitrogen (BUN) also varies inversely with the GFR, it is generally less useful than the serum creatinine because the BUN can change independently of the GFR. Two factors contribute to this phenomenon [6,97]:

- The rate of urea production is not constant, increasing with a high-protein diet and with enhanced tissue breakdown due to hemorrhage, trauma, or glucocorticoid therapy. By comparison, a low-protein diet or liver disease can lower the BUN without change in GFR. Thus, liver disease may be associated with near-normal values for both the BUN (due to decreased urea production) and the serum creatinine (due to muscle wasting) despite a relatively large reduction in GFR [98,99].

  The presence of kidney disease in this setting can be documented by a reduction in creatinine clearance, but significant overestimation of GFR can still occur [31,48,99,100]. (See 'Limitations of using creatinine clearance' above.)

- Approximately 40 to 50 percent of the filtered urea is passively reabsorbed, mostly in the proximal tubule. Thus, when volume depletion is associated with enhanced proximal sodium and water reabsorption, there is a parallel increase in urea reabsorption. As a result, the BUN will

rise out of proportion to any change in GFR, and therefore to any change in the serum creatinine (SCr). This elevation in the BUN-to-SCr ratio is one of the suggestive clinical signs of decreased renal perfusion (prerenal disease) as the cause for renal failure. (See "Etiology and diagnosis of prerenal disease and acute tubular necrosis in acute kidney injury in adults".)

The measurement of the clearance of urea is useful in one setting. Among patients with severe kidney disease (eg, a serum creatinine greater than 2.5 mg/dL [220 micromol/L]), the urea clearance significantly underestimates the GFR. Since the creatinine clearance significantly overestimates this function, one method to estimate the GFR in patients with advanced kidney disease (for example, GFR <30 mL/min) is to average both the creatinine and urea clearances [101]:

$$\text{Estimated GFR} = \frac{\text{CrCl} + \text{CUrea}}{2}$$

The 2005 European Best Practices Guidelines suggest that this calculation is preferred for estimating GFR in advanced kidney failure [102]. As previously mentioned, the MDRD study equation can also be used in those with significantly decreased GFR. (See 'Estimation equations' above.)

Serum cystatin C — Because of the problems with changes in creatinine production and secretion, other endogenous compounds have been evaluated in an effort to provide a more accurate estimation of GFR, including cystatin C, beta trace protein, and beta 2 microglobulin.

Cystatin C is a low-molecular-weight protein that is a member of the cystatin superfamily of cysteine protease inhibitors. Cystatin C is filtered at the glomerulus and not reabsorbed. However, it is metabolized in the tubules, which prevents use of cystatin C to directly measure clearance. Cystatin C is believed to be produced by all nucleated cells. Its rate of production has been thought to be relatively constant, and not affected by changes in diet, although this is not proven. Equations that estimate GFR based upon cystatin C can be found here.

Although cystatin C has been purported to be unaffected by gender, age, or muscle mass, higher cystatin C levels have now been associated with male gender, greater height and weight, higher lean body mass [100,103,104], fat mass, diabetes, markers of inflammation (eg, C-reactive protein), and hyper- and hypothyroidism [100,105-107]. Cystatin C levels also increase with age [100].

Analysis of a subsample of 7596 participants drawn from NHANES III revealed that more than 50 percent of individuals over age 80 years have an elevated cystatin C level, and non-Hispanic White American patients and males have higher levels of cystatin C (figure 4) [108]. Since these data were not adjusted for GFR, it is unclear whether they are related to different levels of kidney function among the populations or differences in the non-GFR determinants of cystatin C. Together, these data suggest that levels of cystatin C are affected by many factors other than GFR.

As with creatinine, substantial variation in the cystatin C assay has been observed, even when using the same instrument and the same reagent type by the same laboratory [109]. In addition, substantial declines in cystatin C levels over time have been observed with a popular reagent and method. To correct these problems, certified reference materials for cystatin C assays have been generated by the International Federation for Clinical Chemists Working Group for the Standardization of serum cystatin C and the Institute for Reference Materials and Measurements (IRMM) [110,111]. This material, ERM-DA471/IFCC, was made available to laboratories in 2010. However, a survey conducted by College of American Pathologists in which ERM-DA471/IFCC standardized serum samples were sent to various clinical laboratories across the United States found a large amount of variability, suggesting that participating laboratories do not report accurate cystatin C results [112].

The serum cystatin C concentration may correlate more closely with the GFR than the serum creatinine concentration [113-121]. However, when comparing cystatin C-based GFR estimates to creatinine-based GFR estimates, there was no difference in the bias between the equations, and precision may be worse with cystatin C-based estimates. In one study of over 3000 patients with and without CKD, an equation for the estimated GFR based upon cystatin adjusted for age and sex was nearly but not as accurate as estimated GFR based upon serum creatinine adjusted for age, sex, and race, when compared with GFR measured by iothalamate clearance [121]. These same equations, without modification for ethnicity, performed well in a multiethnic Asian population in Singapore [122].

Creatinine and cystatin C in combination — Combining both the serum creatinine and cystatin C into a single equation appears to consistently provide more precise estimated GFR than equations that use either creatinine or cystatin C alone. A combined creatinine-cystatin C equation was initially developed among 5352 individuals who had both measured GFR and serum concentrations of creatinine and cystatin C [123]. This combined equation was then compared with the CKD-EPI creatinine- and cystatin C-based equations in a separate population of 1119 individuals. The combined CKD-EPI creatinine-cystatin C equation produced an estimated GFR that was within 20 percent of the measured GFR in a significantly higher proportion of individuals (77 as compared with 67 percent using equations based upon either creatinine or cystatin C alone). In addition to improved accuracy, the combined equation was more precise and no more biased than the equations using either creatinine or cystatin C alone. Other studies have also demonstrated the greater accuracy of the combined creatinine-cystatin C equation compared with equations that use either marker alone [124-127].

Assessment of GFR in clinical practice — Creatinine is widely available and inexpensive, and estimated GFR from creatinine using the CKD-EPI equation is accurate in most settings. For these reasons, the KDIGO 2013 guidelines on CKD recommend using the creatinine-based CKD-EPI equation as an initial test [128].

There are a few situations when a confirmatory test should be considered:

- Estimated GFR based upon the CKD-EPI equation will be less accurate in people with factors affecting serum creatinine other than GFR (eg, high or low muscle mass or creatinine intake, eg, children, patients with cirrhosis, serious chronic illness such as chronic heart failure, amputations or neuromuscular disease, or those with a high-protein or vegetarian diet). In these situations, confirmation of the estimated GFR is advised. Confirmatory tests could include estimation upon both cystatin C and creatinine, or a clearance measurement using either an exogenous filtration marker or a timed urine collection for creatinine clearance.

  It has been proposed that cystatin C-based equations would be more accurate in populations with lower creatinine production, such as older adults, children, kidney transplant recipients, or patients with cirrhosis [9,129,130]. However, the results from studies comparing creatinine- and cystatin C-based estimates in these populations have shown variable results [131-133]. As an example, whether cystatin C correlates better with GFR than serum creatinine in patients with diabetic nephropathy is unclear [134,135].

  In addition, steroid use may affect cystatin C levels, therefore limiting its use in transplant recipients. In one study, for example, for the same level of cystatin C, measured GFR was 19 percent higher in transplant recipients than in patients with native kidney disease [9].

  Although cystatin C appears to be more accurate for the assessment of GFR than serum creatinine in certain populations, whether measurement of cystatin C levels will improve patient care is at present unknown [136]. For this reason, GFR estimated based upon cystatin C is not recommended as a confirmatory test. However, it is reasonable to use cystatin C-based estimated GFR in patients with clear reductions in muscle mass and who are otherwise reasonably healthy. In support of this concept, in a study of other healthy amputees, estimation based upon cystatin C was substantially more accurate than estimation based upon creatinine [137].

- Estimated GFR based upon both cystatin C and creatinine can be used for confirmation of the diagnosis of CKD in patients with an estimated GFR of 45 to 60 mL/min per 1.73 m^2 and no other evidence of kidney disease, such as albuminuria or radiologic abnormalities.

- Kidney donor evaluation – In the United States, performance of a clearance measurement (24-hour urine for creatinine clearance or urinary or plasma clearance off exogenous filtration markers) is required for GFR evaluation. Given errors in these measurements, it is helpful to interpret clearance measurements in light of the estimated GFR results [138,139]. An online tool for performing this evaluation is available at http://ckdepi.org/equations/donor-candidate-gfr-calculator/. Very high post-test probabilities for eGFRcr or eGFRcrcys provide reassurance that measured GFR is above the threshold, while very low post-test probabilities provide reassurance that measured GFR is below the threshold.

GFR ESTIMATION AND RACE AND ETHNICITY

The Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine and creatinine-cystatin equations include a term for race that, for any given creatinine value, results in a higher estimated glomerular filtration rate (eGFR) for a black individual as compared with a non-black individual [38]. In our practice, we use the published, guideline-recommended equations that use the race correction factor, or cystatin C-based eGFR when patients prefer not to disclose or self-report their race or when their race is unknown. We consider confirmatory tests (eg, creatinine-cystatin C-based eGFR, measured creatinine clearance, or measured glomerular filtration rate [GFR]) when the accuracy of the GFR value would impact diagnosis, management, or prognostic decisions.

The rationale for using a race term in eGFR equations is based upon the empirical observation that the association between creatinine and GFR differs in self-reported black people compared with others. This difference was thought to reflect biologic variations in non-GFR determinants such as muscle mass or creatinine handling.

The ongoing use of a race term in these equations is debated [140]. First, race itself is a social construct, and including the coefficient for race ignores the substantial diversity within self-identified Black or African-American patients. Second, there are observations that the race term does not improve accuracy of eGFR based upon creatinine when applied in all populations, such as African populations, although there are substantial concerns about the methods across all of these papers [141,142]. Third, and most importantly, there is concern that the use of a race term may increase inequities and propagate race-based medicine [143]. Given these concerns, there is an increasing call for the elimination of the race term when using creatinine-based eGFR and creatinine-cystatin-based eGFR. The National Kidney Foundation and American Society of Nephrology have established a task force to address this issue in the context of addressing racial disparities and equitable care for all patients with chronic kidney disease (CKD).

While awaiting the recommendations, set to be released in 2020, we suggest full disclosure of the use of race in GFR estimation and shared decision-making between health care providers and patients regarding GFR estimation [144]. We recommend increased use of cystatin C-based eGFR, which does not include a race coefficient, when patients do not wish to report their race or it cannot be determined; in addition, we recommend increased use of creatinine-cystatin eGFR, measured creatinine clearance, or measured GFR using exogenous markers whenever clinical decisions would be impacted by the level of GFR [145].

There are also outstanding questions about the use of coefficients for other, non-black racial or ethnic groups when calculating creatinine-based eGFR (such as in Asian populations) [146]. In Japan, for example, a modified CKD-EPI equation is used that applies a correction factor of 0.813, thereby decreasing the eGFR for a given creatinine value in this population. Other calibration factors are not generalizable across countries, which may also reflect population differences in non-GFR determinants or differences in methods to measure GFR or assay creatinine. Cystatin C-based eGFR appears to be more accurate than creatinine-based eGFR in Asian countries and does not require a calibration factor.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Fluid and electrolyte disorders in adults" and "Society guideline links: Chronic kidney disease in adults".)

SUMMARY AND RECOMMENDATIONS

- The normal value for glomerular filtration rate (GFR) depends upon age, sex, and body size, and is approximately 130 and 120 mL/min/1.73 m^2 for men and women, respectively, with considerable variation even among normal individuals. GFR frequently decreases with age. (See 'Normal GFR' above.)
- In patients with kidney disease, a reduction in GFR implies either progression of the underlying disease or the development of a superimposed and often reversible problem. In addition, the level of GFR has prognostic implications in patients with chronic kidney disease (CKD), and such patients are staged, in part, according to GFR. However, there is **not** an exact correlation between the loss of kidney mass (ie, nephron loss) and the loss of GFR. The kidney adapts to the loss of some nephrons by compensatory hyperfiltration and/or increasing solute and water reabsorption in the remaining, normal nephrons. (See 'Significance of a declining GFR' above and "Definition and staging of chronic kidney disease in adults".)
- Measurement of GFR is complex, time consuming, and cumbersome to do in clinical practice. In addition, exact knowledge of the GFR is not required for most clinical settings. As such, GFR is usually estimated from serum markers. However, it is occasionally important to have more precise knowledge of the GFR (eg, prior to kidney donation). (See 'How to evaluate GFR: Measurement versus estimation' above.)
- GFR is measured by determining the urinary clearance of an ideal filtration marker. Inulin is the gold standard filtration marker, but iothalamate and iohexol are less cumbersome. (See 'Measurement of GFR' above.)
- The most common methods utilized to estimate the GFR are: measurement of the creatinine clearance; and estimation equations based upon serum creatinine such as the Cockcroft-Gault equation, the Modification of Diet in Renal Disease (MDRD) study equations, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. (See 'Estimation of GFR' above.)
- GFR-estimating equations used in practice rely upon creatinine as a marker of kidney function. Serum creatinine can only be used to estimate GFR in individuals with stable kidney function. In addition, creatinine-based estimations of the GFR are limited by variations in creatinine production, variations in creatinine secretion, extrarenal creatinine excretion, and issues associated with creatinine measurement. (See 'Using creatinine to estimate GFR' above.)
- Measurement of the creatinine clearance can be used to confirm estimated GFR from serum creatinine when there are variations in creatinine production. Measured creatinine clearance is limited by errors in urine collection, as well as creatinine secretion, extrarenal creatinine excretion, and issues associated with creatinine measurement. (See 'Using creatinine to estimate GFR' above.)
- Creatinine is freely filtered across the glomerulus and is neither reabsorbed nor metabolized by the kidney. However, approximately 10 to 40 percent of urinary creatinine is derived from tubular secretion by the organic cation secretory pathways in the proximal tubule. If the effect of secretion is ignored, then the creatinine clearance (calculator 1) will be equal to the GFR. However, the creatinine clearance tends to exceed the true GFR by approximately 10 to 20 percent or more since this is the fraction of urinary creatinine that is derived from tubular secretion. In addition, using the creatinine clearance to estimate GFR is limited by errors in urine collection and variation in the degree of creatinine secretion, which increases as GFR decreases. (See 'Creatinine clearance' above and 'Limitations of using creatinine clearance' above.)
- The most common equations used in the United States are the CKD-EPI equation, the Modification of Diet in Renal Disease (MDRD) study equations, and the Cockcroft-Gault equation. The CKD-EPI equation is more accurate than the MDRD study equation, and both are more accurate than the Cockcroft and Gault equation. The MDRD and CKD-EPI equations are normalized to body surface area. (See 'Estimation equations' above.)
    - The Cockcroft-Gault equation (calculator 3) was developed prior to the use of standardized creatinine assays, and has **not** been revised for use with creatinine values traceable to standardized reference materials. Thus, using the Cockcroft-Gault equation with creatinine

values measured by most laboratories in the United States today will result in a 10 to 40 percent **overestimate** of creatinine clearance. (See 'Cockcroft-Gault equation' above.)

- The MDRD study equation (calculator 4) is the most commonly used estimation equation, and has been re-expressed for use with creatinine values that are standardized to creatinine reference materials measured using gold standard techniques. (See 'MDRD study equation' above.)

- The CKD-EPI equation was developed to provide a more accurate estimate of GFR among individuals with normal or only mildly reduced GFR (ie, above 60 mL/min per 1.73 m^2) (calculator 5). Among patients with GFRs greater than 60 mL/min per 1.73 m^2, the CKD-EPI equation was associated with less bias, improved precision, and greater accuracy. The CKD-EPI equation results in a lower prevalence estimate of CKD and more accurate risk prediction for adverse outcomes compared with the MDRD study equation. (See 'CKD-EPI equation' above.)

- Given the data on the improved performance, especially at higher levels of GFR, we suggest using the CKD-EPI equation for the general population (calculator 5). (See 'Choice of equation' above and 'Assessment of GFR in clinical practice' above.)

- In addition to the problems associated with reliance upon serum creatinine, the commonly utilized estimation equations are less accurate in certain populations. These include individuals with normal GFR, children, older adult patients, specific ethnic groups (eg, Asians), pregnant women, and those with unusual muscle mass, body habitus, and weight (eg, morbid obesity, amputees). (See 'Limitations of estimation equations' above.)

- If the CKD-EPI equation or MDRD study equation is used for drug dosing in very large or small patients, the reported estimated GFR (which is normalized to body surface area) should be multiplied by the estimated body surface area and then divided by 1.73 to obtain an estimated GFR in units of mL/min (ie, not normalized to body surface area). For patients at the extremes of muscle mass, with unusual diets, or with conditions associated with changes in creatinine secretion, all estimation equations that use the serum creatinine are limited; thus, a measured creatinine clearance or GFR using exogenous filtration markers should be performed especially when prescribing drugs with a narrow therapeutic window. (See 'Drug dosing' above.)

- The measurement of the clearance of urea is useful in one setting. Among patients with severe kidney disease (eg, a serum creatinine greater than 2.5 mg/dL [220 micromol/L]), the urea clearance significantly underestimates the GFR. Since the creatinine clearance significantly overestimates this function, one method to estimate the GFR in patients with advanced renal disease is to average both the creatinine and urea clearances. (See 'BUN and GFR' above.)

- Cystatin C in combination with creatinine is more accurate for the assessment of GFR than serum creatinine in certain populations and can be used as a confirmatory test for diagnosis of CKD and for estimation of GFR. (See 'Serum cystatin C' above.)

Topic 2359 Version 43.0

GRAPHICS

Major functions of nephron segments

Nephron segment	Major functions
Glomerulus	Forms an ultrafiltrate of plasma
Proximal tubule	Reabsorbs isosmotically 60 to 65 percent of the filtered NaCl and H2O Reabsorbs 90 percent of the filtered HCO3- Major site of ammonia production in the nephron Reabsorbs almost all of filtered glucose and amino acids Reabsorbs K+, phosphate, calcium, magnesium, urea, and uric acid Secretes organic anions (such as urate) and cations (such as creatine); this pathway is also used for excretion of protein-bound drugs and toxins
Loop of Henle	Reabsorbs 25 to 35 percent of filtered NaCl Countercurrent multiplier as NaCl reabsorbed in excess of water Major site of active regulation of magnesium excretion
Distal tubule	Reabsorbs about 5 percent of filtered NaCl but almost no water Major site, with connecting segment, of active regulation of calcium excretion
Connecting segment and cortical collecting tubule	Principal cells reabsorb Na+ and Cl- and secrete K+ under the influence of aldosterone Intercalated cells secrete H+, reabsorb K+, and, in metabolic alkalosis, secrete HCO3- Reabsorb water in the presence of antidiuretic hormone
Medullary collecting tubule	Site of final modification of the urine Reabsorb NaCl, the concentration of which can be reduced to less than 1 meq/L Reabsorb water and urea relative to the amount of antidiuretic hormone present, allowing a concentrated or dilute urine to be excreted Secrete H+ and NH3; urine pH can be reduced to as low as 4.5 to 5.0 Can contribute to potassium balance by reabsorption or secretion of K+

Contribution of the different nephron segments to solute and water homeostasis.

Graphic 57561 Version 2.0

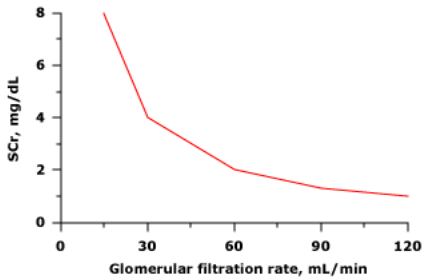
Solute reabsorption by the kidney

Substance	Filtered	Excreted	Percent net reabsorption
Water	180 liters	0.5-3.0 liters	98-99
Na+	26,000 meq	100-250 meq	>99
Cl-	21,000 meq	100-250	99
HCO3-	4,800 meq	0	~100
K+	800 meq	40-120 meq	80-95
Urea	54 grams	27-32 grams	40-50

Summary of the net daily reabsorptive work performed by the kidney. These values are for a normal adult man on a typical Western diet. The glomerular filtration rate and therefore the filtered load of solutes and water is approximately 25 percent lower in women.

Graphic 62415 Version 3.0

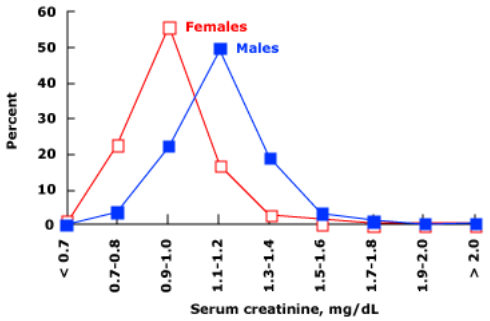
Serum creatinine and GFR



Idealized steady-state relationship between the serum creatinine concentration (SCr) and the GFR. A fall in GFR decreases creatinine filtration and produces a proportionate rise in the serum creatinine concentration.

Graphic 59518 Version 1.0

Distribution of serum creatinine among United States males and females

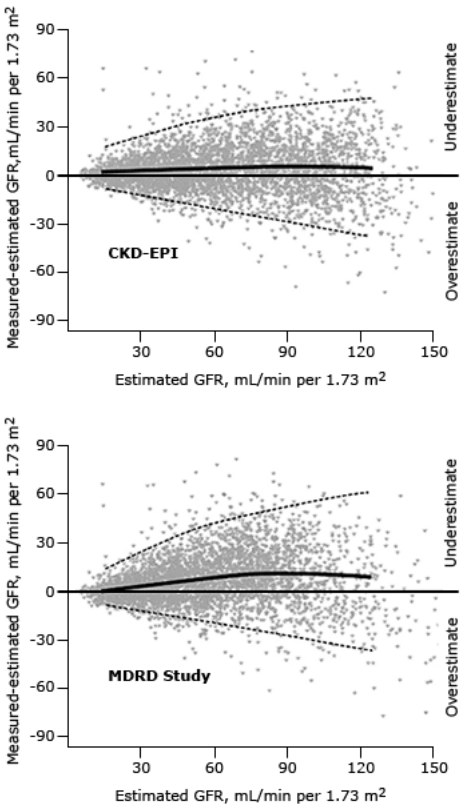


Distribution of the serum creatinine (in mg/dL) among United States males and females for the years 1988 to 1994 (age ≥12 years). Multiply values by 88.4 to convert to units of micromol/L.

Data from Jones CA, McQuillan GM, Kusek JW. Serum creatinine levels in the US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 1998; 32:992.

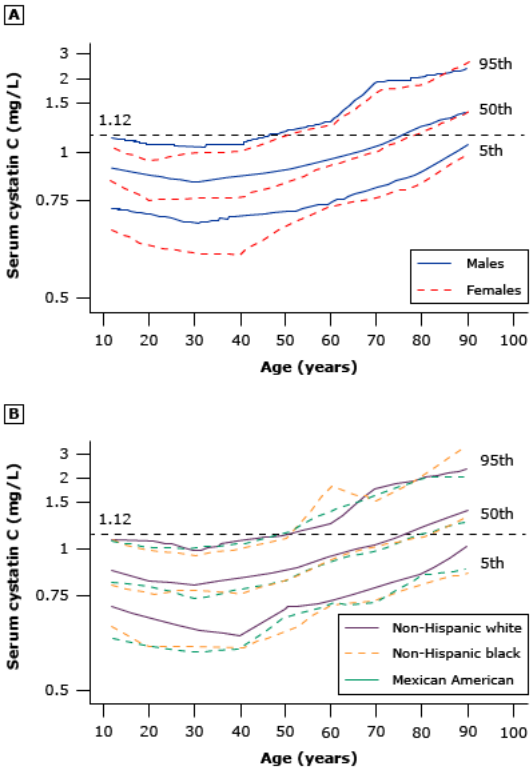
Graphic 76830 Version 3.0

Performance of the CKD-EPI and MDRD Study equations in estimating measured GFR



Graphic 78254 Version 12.0

Variations in cystatin C based upon sex, race, and ethnicity



Serum cystatin C percentiles (5th, 50th, and 95th) by age and (A) sex and (B) race/ethnicity graphed by using an inverse transformation. (-1/cystatin C) is analyzed and the corresponding values for serum cystatin C are shown on the y-axis. The horizontal line at a serum cystatin C value of 1.12 mg/L indicates the cutoff value for increased serum cystatin C level.

From: Köttgen A, Selvin E, Stevens LA, et al. Serum cystatin C in the United States: the Third National Health and Nutrition Examination Survey (NHANES III). Am J Kidney Dis 2008; 51:385.

Graphic 57111 Version 1.0

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