3

Assessment of Glomerular Filtration Rate

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The level of glomerular filtration rate (GFR) is widely accepted as the best overall index of kidney function in health and disease. GFR decline is correlated with decline in other excretory functions of the kidney, such as tubular reabsorption and secretion, and with decline in endocrine and metabolic functions of the kidney. Decreased GFR is strongly associated with complications of acute kidney diseases and disorders (AKD) and chronic kidney disease (CKD), and decreased GFR is one criterion in the definition and staging of AKD and CKD. GFR estimating equations are now recommended for routine use in clinical practice, and estimated GFR (eGFR) is routinely reported when serum creatinine is measured.

GLOMERULAR FILTRATION RATE

GFR is the product of the average filtration rate of each nephron, the filtering unit of the kidneys, multiplied by the number of nephrons in both kidneys. The normal level for GFR is approximately 130 mL/min/1.73 m^2 for men and 120 mL/min/1.73 m^2 for women, with considerable variation among individuals according to age, sex, body size, physical activity, diet, blood pressure, glycemia, pharmacotherapy, and physiologic states such as pregnancy. To standardize GFR for differences in kidney size, which is proportional to body size, GFR is indexed for body surface area (BSA), computed from height and weight, and expressed per 1.73 m^2 BSA. Even after adjustment for BSA, GFR is approximately 8% higher in young men than in women and declines with age; the mean rate of decline is approximately 0.75 mL/min/yr after 40 years of age, but the variation is wide and the sources of variation are poorly understood. During pregnancy, GFR increases by about 50% in the first trimester and returns to normal immediately after delivery. GFR has a diurnal variation and is 10% lower at midnight compared with the afternoon. In an individual, GFR is relatively constant over short intervals of time but varies considerably among people, even after adjustment for the known variables.

Reductions in GFR may result from reduced nephron number from prematurity, nephrectomy or kidney disease, or reduced single-nephron (SN) GFR from physiologic or hemodynamic alterations. An increase in SNGFR caused by increased glomerular capillary pressure or glomerular hypertrophy can compensate for a decrease in nephron number; therefore the level of GFR may not reflect the loss of nephrons. As a result, there may be substantial kidney damage before GFR decreases.

MEASUREMENT AND ESTIMATION OF THE GLOMERULAR FILTRATION RATE

The GFR cannot be measured directly in humans. Instead, it is assessed from clearance measurements or serum levels of filtration markers, which are exogenous or endogenous solutes that are mainly eliminated by glomerular filtration. Both measured GFR (mGFR) and eGFR are associated with systematic and random error (bias and imprecision, respectively) in their determination and thus may differ from the "true GFR."[1]

The classic method for GFR measurement described by Homer Smith is the urinary clearance of inulin and remains the reference (gold standard) against which other clearance methods and filtration markers are evaluated.[2] However, this technique is cumbersome in practice. Therefore many alternative clearance methods and filtration markers are used in clinical centers and as research tools (Table 3.1).[3] As discussed later, newer methods to measure GFR using plasma clearance of fluorescent tracer agents have been developed to shorten the measurement protocol, which might enable point-of-care GFR determination.

The GFR is generally estimated from serum levels of endogenous filtration markers to simplify GFR assessment without requiring administration of exogenous filtration markers and without performing clearance measurements.[4] The principles of GFR estimation are similar in adults and children.

CLEARANCE MEASUREMENTS

Concept of Clearance

Clearance of a substance is defined as the volume of plasma cleared of a marker per unit of time. The clearance of substance x (C_x) can be calculated as $C_x = A_x/P_x$, where A_x is the rate of elimination of x from the plasma, P_x is the average plasma concentration, and C_x is expressed in units of volume per time. Clearance does not represent an actual volume; rather, it is a virtual volume of plasma that is completely cleared of the substance per unit of time. The value for clearance is related to the efficiency of elimination: the greater the efficiency of elimination, the higher the clearance. Clearance of substance x is the sum of the urinary (renal) and nonurinary (extrarenal) clearance; for substances that are eliminated by both renal and extrarenal routes, plasma clearance exceeds urinary clearance. By convention we refer to concentration of the substance in plasma when discussing physiologic principles and serum when discussing

TABLE 3.1 Exogenous Filtration Markers for Estimation of Glomerular Filtration Rate

Marker	Clearance Method	Comments
Inulin	Urinary or plasma clearance during continuous IV infusion	Gold standard.
Iothalamate	Urinary or plasma clearance after bolus IV injection. Urinary clearance after subcutaneous bolus injection	Can be administered as radioactive compound with iodine 125 (^{125}I) as the tracer or in nonradioactive form, with assay using HPLC or MS methods in plasma and whole blood. In radioactive form, potential problem of thyroid uptake of ^{125}I. Iothalamate is secreted, leading to overestimation of GFR.
^{99m}Tc-DTPA	Urinary or plasma clearance after bolus IV injection	Dissociation of ^{99m}Tc leads to plasma protein binding and underestimation of GFR.
^{51}Cr-EDTA	Urinary or plasma clearance after bolus IV injection	10% lower clearance than inulin.
Iohexol	Plasma clearance after bolus IV injection	Low incidence of adverse effects; assay using HPLC or MS methods in plasma and whole blood. Research studies have used capillary blood spots. Iohexol may have extrarenal clearance, leading to overestimation of GFR.
Novel engineered markers conjugated to fluorescein[a]	Plasma clearance or transdermal fluorescence after bolus IV injection	Requires less time than plasma clearance of filtration marker alone. Neither are FDA approved for clinical use as of yet. Initial studies in small samples show strong correlation with iohexol plasma clearance.

[a]The two novel markers include relmapirazin (Lumitrace), a novel agent that has been engineered to not interact with the body and be excreted by the kidney, and visible fluorescent injectate (VFI), which consists of a 150-kDa rhodamine derivative, used to assess plasma volume, and a 5-kDa fluorescein carboxymethylated dextran, used to assess GFR.

^{51}*Cr-EDTA,* Chromium 51–labeled ethylenediaminetetraacetic acid; *GFR,* glomerular filtration rate; *HPLC,* high-performance liquid chromatography; *IV,* intravenous; *MS,* mass spectrophotometric; ^{99m}*Tc-DTPA,* technetium 99m–labeled diethylenetriaminepentaacetic acid.

clinical measures. In practice, laboratory measurements of markers of glomerular filtration are similar in plasma and serum and are generally referred to as serum concentrations.

Urinary Clearance

The rate of urinary excretion of substance *x* can be calculated as the product of the urinary flow rate (V) and the urinary concentration (U_x). Therefore urinary clearance is defined as follows:

$$C_x = (U_x \times V)/P_x$$

The rate of urinary excretion of a substance depends on the rates of filtration, tubular secretion, and tubular reabsorption. Substances that are filtered but not secreted or reabsorbed by the tubules are ideal filtration markers because their urinary clearance can be used as a measure of GFR. For substances that are filtered and secreted, urinary clearance exceeds GFR, and for substances that are filtered and reabsorbed, urinary clearance is less than GFR.

Measurement of urinary clearance requires a timed urine collection for measurement of urine flow rate, as well as urine and plasma concentrations of the filtration marker. The classic protocol of Smith[2] used a continuous intravenous infusion to achieve a steady state and bladder catheterization with multiple timed urine collections. Alternative protocols to assess urinary clearance have been validated, including bolus intravenous or subcutaneous administration rather than continuous intravenous infusion and spontaneous bladder emptying rather than bladder catheterization.[3] Bolus administration of the marker results in declining plasma levels of the filtration markers during the clearance measurement, which may cause errors in determining the average plasma concentration during the clearance measurement.

Plasma Clearance

Measurement of plasma clearance avoids the need for a timed urine collection. GFR is calculated from plasma clearance (C_x) after bolus intravenous administration of an exogenous filtration marker, with the clearance (C_x) computed from the amount of the marker administered (A_x) divided by the average plasma concentration (P_x), which can be computed from the area under the curve of plasma concentration versus time.

$$C_x = A_x/P_x$$

The decline in the plasma level is secondary to the immediate disappearance of the marker from the plasma into its volume of distribution (fast component) and to renal excretion (slow component). Plasma clearance is best estimated by use of a two-compartment model that requires blood sampling early (usually two or three time points until 60 minutes) and late (one to three time points from 120 minutes onward).[5] Novel methods are under investigation to shorten the time required for clearance measurements.[6,7] As with urinary clearance, plasma clearance of a substance depends on filtration, tubular secretion, and tubular reabsorption, but, in addition, extrarenal elimination and the time course for equilibration of the filtration marker between plasma and its volume of distribution. Edematous conditions prolong the distribution from plasma to extracellular fluid and may cause error in GFR. Extrarenal elimination has been demonstrated for several filtration markers.

Accuracy of Clearance Measurements

Sources of errors in measuring GFR include biologic variation in GFR, "nonideal" handling of the filtration marker by the kidney (incomplete filtration, nonzero tubular reabsorption or secretion), measurement error in the serum or urine assays for filtration markers, and measurement error in serum or urine collections. By definition, the classic method of Smith is unbiased, but it may be imprecise. The coefficient of variation (CV) for repeated measurements in individuals using this method is approximately 7%. For other procedures, the smallest reported within-person CVs for repeated measures on different days range from approximately 5% to 15%, with larger values for urinary clearance than for plasma clearances. For a measurement method without bias compared with true GFR, a CV of 10% is equivalent to approximately 90% of measures being within 15% of true GFR (P_{15} of 90%).

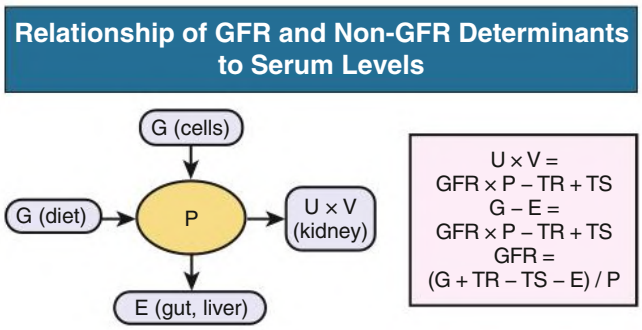

Fig. 3.1 Relationship of GFR and non-GFR Determinants to Serum Levels. *G,* Generation; *GFR,* glomerular filtration rate; *E,* extrarenal elimination; *P,* plasma; *TR,* tubular reabsorption; *TS,* tubular secretion. (Modified from Levey AS, Inker LA, Coresh J. GFR estimation: from physiology to public health. *Am J Kidney Dis.* 2014;63[5]:820-834.)

ESTIMATION OF THE GLOMERULAR FILTRATION RATE

Fig. 3.1 shows the relationship of plasma concentration of substance *x* to its generation (G_x) by cells and dietary intake, urinary excretion ($U_x \times V$), and extrarenal elimination (E_x) by gut and liver. The plasma level is related to the reciprocal of the level of GFR, but it is also influenced by generation, tubular secretion and reabsorption, and extrarenal elimination, collectively termed *non-GFR determinants* of the plasma level.[4]

In the steady state, a constant plasma level of substance *x* is maintained because the rate of generation is equal to the sum of the rates of urinary excretion and extrarenal elimination. Estimating equations incorporate demographic and clinical variables as surrogates for the non-GFR determinants and provide a more accurate estimate of GFR than the reciprocal of the plasma level alone. Most GFR estimating equations have been developed using linear regression to relate observed values of mGFR and serum concentration of the filtration marker, modified by demographic or clinical variables. Another method, as exemplified by the Full Age Spectrum (FAS) equations (see below), is based on hypothetical relationships based on assumptions about age- and sex-adjusted normal values for endogenous filtration markers, age-adjusted normal values for mGFR, and reciprocal changes in mGFR for deviations in observed filtration marker concentrations.[8] Recently, equations have been developed using some features of both methods.

Irrespective of the method for equation development, eGFR in an individual may differ from mGFR if a discrepancy exists between the true and average values of the surrogates for the non-GFR determinants of the filtration marker. Other sources of errors include measurement error in the filtration marker (e.g., failure to calibrate assay for filtration marker to assay used in development of equation), measurement error in mGFR method used in development of the equation, and regression to the mean. In principle, the absolute magnitude of these errors is likely to be greater at higher values for GFR, although such errors may be more clinically significant at lower mGFR. Accuracy of eGFR, as assessed as the percent of eGFR within 30% of mGFR (P_{30}) of 80% to 90%, is generally considered adequate for many clinical circumstances; P_{30} greater than 90% would be optimal.

For application to general populations, GFR estimating equations should be developed and validated in diverse populations including a wide range in age, race-ethnicity, and clinical conditions. To facilitate best practices and communication among patients, providers, and public, a single equation should be used for each filtration marker or combination of filtration markers, and clinical laboratories should automatically report eGFR whenever the filtration marker is measured.

Filtration Markers

Solutes with molecular weight less than approximately 20,000 Da and not bound to plasma proteins are freely filtered by the glomeruli and are candidate filtration markers.

Exogenous Filtration Markers

Iothalamate, iohexol, ethylenediaminetetraacetic acid, and diethylenetriaminepentaacetic acid, often chelated to radioisotopes for ease of detection, are commonly used alternatives to inulin (see Table 3.1).[3] Deviations from ideal behavior of the filtration marker can be inferred from differences from inulin clearance during simultaneous clearance measurements. The most common methods used in the United States are urinary clearance of iothalamate after subcutaneous bolus administration and plasma clearance of iohexol after intravenous bolus administration.[9] Of note, the doses of iothalamate and iohexol that are used to measure GFR are far below the doses used for contrast imaging that have been associated with kidney toxicity and acute kidney injury. The challenge with both methods is assay of the exogenous marker using high performance liquid chromatography for iohexol in plasma samples or capillary blood spots, ^{125}I-labeling for iothalamate, or mass spectroscopy (for both).[10]

Endogenous Filtration Markers

Endogenous filtration markers are substances generated in the body at a relatively constant rate and eliminated largely by glomerular filtration. The plasma level correlates highly with mGFR after accounting for the non-GFR determinants. Currently identified endogenous filtration markers include metabolites (such as creatinine and urea) and low-molecular-weight plasma proteins (such as cystatin C) (Table 3.2). Filtered metabolites may undergo reabsorption or secretion, which may be assessed by comparing their urinary clearance to urinary clearance of exogenous filtration markers. By contrast, filtered plasma proteins are reabsorbed and degraded within the tubule with minimal appearance in the urine. For metabolites excreted in the urine, urinary clearance can be computed from a timed urine collection and a single measurement of serum concentration. If the serum concentration is not constant during the urine collection, as in acute kidney disease or when residual kidney function is assessed in patients undergoing intermittent dialysis, it is necessary to obtain additional blood samples during the urine collection to estimate the average serum concentration.

CREATININE

Metabolism and Excretion

Creatinine is a 113 Da end product of muscle catabolism. Advantages of creatinine include its ease of measurement and the low cost and widespread availability of assays (see Table 3.2). Disadvantages include the large number of conditions affecting its non-GFR determinants, leading to a wide range of GFR for a given serum creatinine level (Table 3.3). For example, a serum creatinine level of 1.5 mg/dL (132 μmol/L) may correspond to a GFR from approximately 20 to 90 mL/min/1.73 m^2.

Creatinine is derived by the metabolism of phosphocreatine in muscle, as well as from dietary meat intake or creatine supplements. Creatinine generation is proportional to muscle mass, which can be estimated from age, sex, and body size, but many other factors can affect creatinine generation. Creatinine is distributed in total body water, not protein bound, and freely filtered across the glomerulus and secreted by

TABLE 3.2 Creatinine, Cystatin C, and Urea as Endogenous Filtration Markers

Variable	Creatinine	Cystatin C	Urea
Molecular Properties			
Weight (Da)	113	13,000	60
Structure	Amino acid derivative	Nonglycosylated basic protein	Organic molecular product of protein metabolism
Physiologic Determinants of Serum Level			
Generation	Varies, according to muscle mass and dietary protein; lower in elderly persons, women, and Whites	Thought to be mostly constant by all nucleated cells; increases in hyperthyroid state and with steroid use; lower in elderly persons and women	Varies, according to dietary protein intake and catabolism
Handling by kidney	Filtered, secreted, and excreted in urine	Filtered, reabsorbed, and catabolized	Filtered, reabsorbed, and excreted in urine
Extrarenal elimination	Yes; increases at reduced GFR	Preliminary evidence of increases at reduced GFR	Yes; increases at reduced GFR
Use in Estimating Equations for GFR			
Demographic and clinical variables as surrogates for physiologic determinants	Age, sex, and race; related to muscle mass	Age, sex	Not applicable
Accuracy	Accurate for GFR <60 mL/min/1.73 m^2	Unknown	Not applicable
Assay			
Method	Colorimetric or enzymatic	PENIA, PETIA, or ELISA	Direct measurement, enzymatic colorimetric, and electrochemical
Assay precision	Very good except at low range	Precise throughout range, but difficult to standardize	Precise throughout range
Clinical laboratory practice	Multiple assays; widely used nonstandard calibration	Not on most autoanalyzers; not standardized	Multiple assays; enzymatic and colorimetric more common
Standardized recommendation materials (SRMs)	SRM 967	ERM-DA471/IFCC	SRM 912a
Reference assay	IDMS	PENIA, PETIA, or ELISA	IDMS

ELISA, Enzyme-linked immunosorbent assay; *GFR,* glomerular filtration rate; *IDMS,* isotope-dilution–mass spectroscopy; *PENIA,* particle-enhanced nephelometric immunoassay; *PETIA,* particle-enhanced turbidimetric immunoassay.

the tubules. Several medications, such as cimetidine, trimethoprim, and fenofibrate, competitively inhibit creatinine secretion, leading to a rise in the serum creatinine concentration without an effect on GFR.

In addition, creatinine is contained in intestinal secretions and can be degraded by bacteria; gastrointestinal elimination of creatinine is increased at higher levels of serum creatinine but can be reduced by changes in gut flora due to antibiotic use. Clinically, it can be difficult to distinguish a rise in serum creatinine concentration caused by inhibition of tubular secretion or extrarenal elimination of creatinine from a decline in GFR.

Creatinine clearance (Clcr) is usually computed from the creatinine excretion in a 24-hour urine collection and single measurement of serum creatinine in the steady state. Creatinine excretion rates vary with age and sex with mean levels of approximately 20 to 25 mg/kg/d and 15 to 20 mg/kg/d in a complete collection in healthy young men and women, respectively. Deviations from estimated creatinine excretion (based on age, sex, weight, and other variables)[11] can indicate errors in timing or completeness of urine collection but cannot be relied on because of wide variability in creatinine generation.

Creatinine Assay

Historically, the most common assay for measurement of serum creatinine was the alkaline picrate (Jaffe) assay that generates a color reaction. Chromogens other than creatinine can interfere with the assay, causing errors of up to 20% in normal individuals. Enzymatic methods are less susceptible to interference, and their use is increasing. Reference materials traceable to an isotope-dilution–mass spectrometry (IDMS) are now available to standardize creatinine measurements, and most manufacturers have now calibrated their instruments using these reference materials.[12,13] Standardization has reduced but not eliminated the error in estimating GFR at higher levels.

Estimated Glomerular Filtration Rate From Serum Creatinine

GFR can be estimated from serum creatinine ($eGFR_{cr}$) by equations that use demographic factors or body size as surrogates for the non-GFR determinants, principally creatinine generation. Despite ongoing refinements in recent years, GFR estimates remain imprecise; none of the equations is expected to work as well in patients with extreme levels for creatinine generation, such as large or small individuals, amputees, bodybuilders, patients with muscle-wasting conditions, or people with an atypical pattern of meat consumption (see Table 3.3). As discussed later, further improvements will probably require additional filtration markers.

Equations Currently Recommended for Use

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 and 2021 creatinine equations were developed from a large

TABLE 3.3 Factors Affecting Serum Creatinine and Cystatin C Concentrations Independent From Glomerular Filtration Rate

Factors	Effect on Creatinine (Direction/*Mechanism*)	Effect on Cystatin C (Direction/*Mechanism*)
Age	Decrease *Lower creatinine generation presumed due to decline in muscle mass. Effect on tubular secretion and extraelimination unknown.*	Decrease *Presumed lower cystatin C generation caused by decreased cellular mass, smaller influence than creatinine. Effect on extraelimination unknown.*
Female sex	Decrease *Lower creatinine generation presumed due to lower muscle mass. Effect on tubular secretion and extraelimination unknown.*	Decrease *Presumed lower cystatin C generation caused by lower cellular mass, smaller influence than creatinine. Effect on extraelimination unknown.*
Race		
Self-identified African American or Black in US or European studies, or African ancestry	Increase *Cause unknown; higher creatinine generation and lower tubular secretion of creatinine observed in some studies, but not consistent. Effect on extraelimination unknown. Factors less well known for race and ethnic groups other than African Americans or Whites.*	No effect
Diet		
Vegetarian	Decrease *Lower creatinine generation.*	No effect
Ingestion of cooked meats and creatinine supplements	Increase *Transient increase in creatinine generation, although this may be blunted by transient increase in GFR.*	No effect
Body Habitus		
Larger muscle mass	Increase *Higher muscle generation caused by increased muscle mass and/or increased protein intake.*	No effect
Smaller muscle mass (e.g., amputation, anorexia)	Decrease *Lower creatinine generation caused by reduced muscle mass and/or reduced protein intake.*	No effect
Malnutrition, muscle wasting, in context of chronic illness	Decrease *Lower creatinine generation caused by reduced muscle mass and/or reduced protein intake.*	Possible increase *Presumed higher cystatin C generation in conditions associated with inflammation.*
Obesity	No change *Excess fat mass, not muscle mass, which does not contribute to creatinine generation.*	Increase *Presumed higher cystatin C generation by excess fat mass.*
Medications		
Trimethoprim, cimetidine, fibric acid derivatives other than gemfibrozil, dolutegravir, and cobicistat PARP inhibitors,[a] tyrosine kinase inhibitors[b]	Increase *Reduced tubular secretion of creatinine.*	No known effects, not studied
Ketoacids, some cephalosporins	Interference with alkaline picrate assay for creatinine.	No known effects, not studied

[a]Such as olaparib and rucaparib.
[b]Such as imatinib, bosutinib, sorafenib, sunitinib, crizotinib, gefitinib, and pazopanib.
GFR, Glomerular filtration rate; *PARP,* poly-ADP ribose polymerase.

database of adults, including those with and without kidney disease, with and without diabetes, and with and without a history of organ transplantation.[14] The 2009 equation includes age, sex, and race (categorized as African American vs. non–African American), and standardized serum creatinine. It estimates mGFR assessed from urinary clearance of iothalamate. It uses a two-slope "spline" for serum creatinine and is accurate across the full range of eGFR. It has been extensively validated and is accurate across a wide range of patient characteristics, including age, sex, race, body mass index (BMI), and presence or absence of diabetes or history of organ transplantation. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that clinical laboratories use CKD-EPI creatinine equations to report eGFR in adults in North America, Europe, and Australia whenever serum creatinine is measured or to use other

BOX 3.1 Relevant Guidelines, GFR Calculators, and Other Information About Assessment of GFR

KDIGO Guideline 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease[15]: http://kdigo.org/guidelines/ckd-evaluation-and-management/

Guideline for Acute Kidney Injury[74]: http://kdigo.org/guidelines/acute-kidney-injury/

KDIGO Clinical Practice Guideline on the Evaluation and Follow-Up Care of Living Kidney Donors[78]: http://kdigo.org/guidelines/living-kidney-donor/

KDIGO Controversy Conference on Drug Prescribing in Kidney Disease: Initiative for Improved Dosing[82]: https://kdigo.org/conferences/drug-prescribing-in-ckd/

U.S. Department of Health and Human Services—Food and Drug Administration: Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing: https://www.fda.gov/media/78573/download

Chronic Kidney Disease Epidemiology Collaboration (CKP-EPI): https://www.tuftsmedicalcenter.org/CKDEPI

equations if they are shown to be superior to CKD-EPI equations in other populations (Box 3.1).[15]

The 2021 equation was developed from the same dataset used for development of the 2009 equation without inclusion of a term for Black race, in response to the call to remove race from clinical algorithms in medicine.[16–19] It is less accurate than the 2009 equation but sufficiently accurate for use in clinical practice and more accurate than prior equations. Importantly, it avoids potential for misclassification by race in a multiracial population.[20–22] The 2021 equation is now recommended for use by the American Society of Nephrology and National Kidney Foundation.[23]

There is insufficient information on racial and ethnic groups other than African-American and White individuals to be certain about the accuracy of GFR estimates in these populations.

The Chronic Kidney Disease in Children (CKiD) 2009 creatinine equation was developed from a moderate-sized study of children with CKD and decreased GFR.[24] The equation uses height and standardized serum creatinine to estimate mGFR assessed from plasma clearance of iohexol. It underestimates mGFR at higher eGFR. The 2012 KDIGO guidelines recommend its use for children with kidney disease but do not recommend reporting eGFR whenever serum creatinine is measured in children. An updated and more accurate equation (CKiD 2021) is based on a larger sample size with age up to 25 years, and uses age and sex in addition to height and recalibrated iohexol measurements.[25] Of note, the CKD-EPI and CKiD creatinine equations often give different results in the transition years from adolescence to young adulthood, reflecting their development in separate study populations.

Equations Previously Recommended for Use

The Cockcroft-Gault equation for adults, developed in 1976, estimates measured Clcr from serum creatinine, age, sex, and body weight, in addition to serum creatinine.[26] Comparison to normal values for Clcr requires computation of BSA and adjustment to 1.73 m^2. The Cockcroft-Gault formula has several limitations. First, it is not precise, in particular in the GFR range above 60 mL/min. Second, it estimates Clcr rather than GFR and thus is expected to overestimate mGFR. Third, the formula was derived by older assay methods for serum creatinine, which cannot be calibrated to newer assay methods and would be expected to lead to variable systematic bias in estimating Clcr (generally an overestimate). Fourth, it systematically overestimates measured Clcr in edematous or obese patients. Fifth, the large age term means that all older adults will have lower levels of estimated GFR. The Schwartz equation for children, developed in 1976, estimates measured Clcr using serum creatinine and height.[27] When using standardized creatinine, it overestimates mGFR.

The Modification of Diet in Renal Disease (MDRD) study equation for adults was developed in 1999[28] and updated for use with standardized serum creatinine in 2006.[29] It is more accurate than the Cockcroft-Gault equation.[30] However, it was derived from a study population with CKD, so it underestimates the mGFR in populations with higher levels of GFR, and numeric values should not be reported for GFR levels greater than 60 mL/min/1.73 m^2.[31]

Other Equations That Could Be Considered for Use in Selected Populations

The Lund-Malmo Revised (LMR) equation for adults and the Berlin Initiative Study (BIS) equation for the elderly (age ≥70 years) use standardized creatinine and were developed in European and US populations that predominantly included White participants.[32,33] The FAS 2016 creatinine equation is based on hypothetical relationships rather than linear regression, which overcomes the limitation of discontinuity at the transition from adolescence to young adulthood.[34] Variations of the FAS equations combined with features of equations derived from linear regression have also been proposed.[35–37] These equations were derived from data on White persons from North America and Europe and appear as accurate as the CKD-EPI equation in White persons but less accurate in African-American persons.[38–41] Other equations have been developed in Asian and African populations that improve the accuracy of GFR estimates in the study population; however, the equations do not generalize well to other populations.[42–47]

CYSTATIN C

Metabolism and Excretion

Cystatin C is a 122–amino acid protein with molecular weight of 13 kDa (see Table 3.2).[48] Cystatin C is produced in all nucleated cells and is distributed in extracellular fluid. In health, approximately 99% of the filtered cystatin C is reabsorbed by the proximal tubular cells, where it is almost completely catabolized, with the remainder eliminated in the urine largely intact; in kidney disease, tubular uptake may be impaired, leading to an increase in urinary excretion.[49]

Some evidence suggests the existence of tubular secretion and extrarenal elimination. Smoking, inflammation, adiposity, thyroid diseases, certain malignant neoplasms, and use of glucocorticoids appear to be associated with higher cystatin C levels independent of mGFR.[50,51] Therefore factors other than GFR must be considered in interpreting cystatin C levels.

Cystatin C Assay

Several assays are available (all more expensive than those for creatinine). Reference materials for standardization of cystatin C from the International Federation of Clinical Chemists (IFCC) are now available, and standardization across clinical laboratories is improving.[52–54]

Estimated Glomerular Filtration Rate From Serum Cystatin C

Cystatin C is less affected by muscle than creatinine and is less affected by age, sex, and race than creatinine. However, eGFR based on serum cystatin C ($eGFR_{cys}$) is not more accurate than $eGFR_{cr}$, because of variation in other conditions affecting non-GFR determinants of serum cystatin C. Equations combining both these filtration markers ($eGFR_{cr-cys}$) appear to be more precise than equations using either marker alone. The 2012 CKD-EPI cystatin C and creatinine–cystatin C equations for adults were developed from a large database of adults, including those

with and without kidney disease or diabetes, are expressed for use with standardized serum creatinine and cystatin C and are recommended by the 2012 KDIGO guidelines (see Box 3.1).[15,55] The creatinine–cystatin C equation uses age, sex, and race, whereas the cystatin C uses age and sex without race. The 2021 creatinine–cystatin C equation was derived from the same dataset as the 2012 equation and is almost as accurate but does not use race. In patients with reduced muscle mass (e.g., neuromuscular or liver disease, low BMI) or in patients with diabetes, $eGFR_{cys}$ may be more accurate than $eGFR_{cr}$. Other recent equations using cystatin C have been developed; most but not all studies show that regional modifications appear to be less important for $eGFR_{cys}$ than for $eGFR_{cr}$.[33,56–58]

Some studies show that a lower $eGFR_{cys}$ is a better predictor of the risk for cardiovascular disease and total mortality than is a lower $eGFR_{cr}$.[59] In our view, this is likely due to confounding by non-GFR determinants of cystatin C and creatinine. Because of better accuracy and risk prediction, $eGFR_{cr\text{-}cys}$ is recommended as a confirmatory test for CKD, but full implementation will require standardization, greater availability, and cost reductions of cystatin C assays, as well as better understanding of non-GFR determinants of serum cystatin C (see Box 3.1).

The CKiD creatinine–cystatin C equation (also including urea nitrogen) for children was developed in 2009 and updated in 2012 but is not expressed for use with standardized cystatin C assays.[24,60] A CKiD 2021 cystatin C equation estimates mGFR and uses standardized cystatin C, age, sex, and height and recalibrated iohexol measurements.[25] Several equations are available for use in children and adults. The Caucasian Asian Pediatric and Adult (CAPA) equation, developed in 2014, estimates mGFR using variety of methods and includes only age and standardized serum cystatin C; the FAS 2017 cystatin C equation includes age, sex, and standardized serum cystatin C and performs similarly to the CKD-EPI 2012 cystatin C equation; and the FAS 2017 creatinine–cystatin C equation performs similarly to the CKD-EPI 2012 creatinine–cystatin C equation.[53,61]

UREA AND OTHER METABOLITES

The serum urea level has limited value as an index of GFR, in view of widely variable non-GFR determinants, primarily urea generation and tubular reabsorption (see Table 3.2).

Urea is a 60 Da end product of protein catabolism by the liver. Factors associated with the increased generation of urea include protein loading from hyperalimentation and absorption of blood after a gastrointestinal hemorrhage. Catabolic states caused by infection, corticosteroid administration, or chemotherapy also increase urea generation. Decreased urea generation is seen in patients with severe malnutrition and liver disease.

Urea is freely filtered by the glomerulus and then passively reabsorbed in both proximal and distal nephrons. As a result of tubular reabsorption, urinary clearance of urea underestimates GFR. Reduced kidney perfusion in the patient with volume depletion and states of antidiuresis are associated with increased urea reabsorption. This leads to a greater decrease in urea clearance than the concomitant decrease in GFR. At mGFR of less than about 20 mL/min/1.73 m^2, the overestimation of mGFR by measured Clcr resulting from creatinine secretion approximates the underestimation of measured GFR by measured urea clearance from urea reabsorption; thus the average of measured creatinine and urea clearance approximates the mGFR.

Recent advances in assays for metabolites have revealed a number of compounds that are highly correlated with mGFR and could be used for GFR estimation.[62] An eGFR from a panel of four novel metabolites (pseudouridine, acetylthreonine, phenylacetylglutamine, and tryptophan) without demographic factors was as accurate as eGFRcr and eGFRcys but not more accurate than eGFRcr-cys; the most accurate equation included the four novel metabolites, creatinine, cystatin C, and demographic characteristics.[63] Assays for the four novel metabolites are not available.

OTHER LOW-MOLECULAR-WEIGHT SERUM PROTEINS

β2-Microglobulin (β2M) and β-trace protein (βTP) are low-molecular-weight serum proteins being evaluated as filtration markers for estimating GFR and for their role in prognosis. As with cystatin C, β2M and βTP are freely filtered by the glomerulus and extensively reabsorbed and degraded by the proximal tubule, with only small amounts excreted in the urine under normal conditions.

Serum β2M and βTP levels are more strongly correlated with mGFR than serum creatinine and, like cystatin C, they are less influenced by age and sex than creatinine. The CKD-EPI 2020 eGFR from a panel of all four markers, age, and sex without race is as accurate as the CKD-EPI 2012 creatinine–cystatin C equation that requires race.[64] In addition, studies have shown that β2M and βTP are better predictors of adverse health outcomes than creatinine and are potentially as accurate as cystatin C in the general population and in patients with CKD.[65] A recent study shows that serum β2M and βTP can be used to estimate residual kidney function in patients on dialysis.[66,67] The likely explanation is that they are too large to be filtered by conventional hemodialysis membranes or the peritoneum, so their serum concentrations reflect residual kidney function rather than the dialysis dose. β2M and βTP assays are not standardized across clinical laboratories, and further study of the usefulness of these equations in clinical practice is required.

CLINICAL APPLICATION OF ESTIMATED GLOMERULAR FILTRATION RATE

Chronic Kidney Disease

CKD is a heterogeneous group of disorders characterized by abnormalities in kidney structure or function for more than 3 months with implications for health. Estimation of GFR is necessary for the detection, evaluation, and management of patients with CKD. GFR less than 60 mL/min/1.73 m^2 for 3 months or longer is one of the criteria for the definition of CKD (see Box 3.1).[15] Guidelines recommend testing of patients at increased risk for CKD for decreased GFR and albuminuria, as a marker of kidney damage, and recommend staging of kidney disease severity and estimating prognosis using levels of albuminuria and GFR (see Box 3.1).[15] The Kidney Failure Risk Equation uses age, sex, GFR, and urine albumin-to-creatinine ratio to predict the risk for onset of kidney replacement therapy (KRT) within 2 or 5 years.[68]

Use of serum creatinine alone as an index of GFR is not recommended and can lead to delays in detection of CKD and misclassification of the severity of CKD. Use of estimating equations allows reporting of eGFR by clinical laboratories whenever serum creatinine is measured. Current estimating equations are less accurate in people with variation in non-GFR determinants of serum creatinine concentration (see Table 3.3). In these patients, more accurate GFR estimates require additional testing, such as measurement of cystatin C, measured Clcr, or mGFR. The KDIGO CKD guidelines recommend use of $eGFR_{cr}$ as an initial test followed by $eGFR_{cr\text{-}cys}$ or a clearance measurement for confirmation in conditions in which eGFR may be inaccurate (Fig. 3.2).[1] Examination of the consistency of GFR estimates and clearance measurements is recommended. If the results are inconsistent, clinicians should consider possible explanations, such as differences between observed and expected creatinine excretion for measured Clcr and non-GFR determinants of creatinine and cystatin C for eGFR, then eliminate the inconsistent value from consideration, repeat the measurement, or determine mGFR using an exogenous marker.

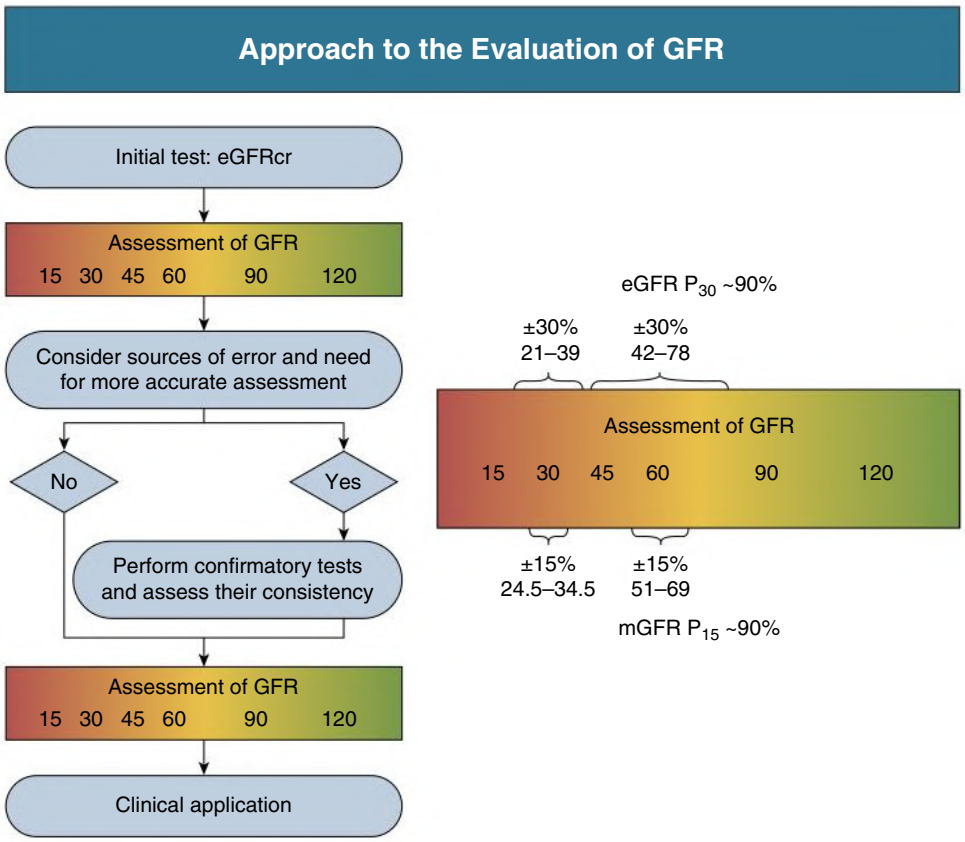

Fig. 3.2 An Approach to the Evaluation of GFR. Our approach is to use initial and confirmatory testing to develop a final assessment of true glomerular filtration rate (GFR) and to apply it in individual decision-making. *Left,* We would initially estimate GFR using serum creatinine ($eGFR_{cr}$)—the findings from this assessment must be interpreted in light of its limitations. Estimation of GFR based on serum cystatin C ($eGFR_{cys}$), both creatinine and cystatin C ($eGFR_{cr\text{-}cys}$), and measured creatinine clearance (Clcr) are useful confirmatory tests in some circumstances, and measured GFR (mGFR) is an appropriate confirmatory test if available and performed using an accurate procedure. We recommend using the most convenient confirmatory test that will enable clinical decision-making, recognizing that more than one confirmatory test might be required. Clinical application of the findings requires additional clinical information, for example, a clinical action plan based on chronic kidney disease GFR categories, drug-dosing recommendations, or use in predictive instruments. *Right,* It is important to determine how accurate an assessment of GFR needs to be for clinical decision-making. If accuracy within 30% is acceptable, eGFR may be sufficient, provided that there are not large deviations in non-GFR determinants of creatinine or cystatin C. If greater accuracy is needed, mGFR is recommended, and some methods can provide accuracy of within 15%. At a GFR of 60 mL/min/1.73 m^2, 30% accuracy for eGFR corresponds to an eGFR of 42 to 78 mL/min/1.73 m^2, and 15% for mGFR corresponds to 51 to 69 mL/min/1.73 m^2. At a GFR of 30 mL/min/1.73 m^2, 30% accuracy for eGFR corresponds to eGFR of 21 to 39 mL/min/1.73 m^2, and 15% for mGFR corresponds to 25.5 to 34.5 mL/min/1.73 m^2. (Modified from Levey AS, Coresh J, Tighiouart H, Greene T, Inker LA. Measured and estimated glomerular filtration rate: current status and future directions. *Nat Rev Nephrol.* 2020;16[1]:51–64.)

Change in serum creatinine is routinely used to assess the progression of kidney disease in populations, and quantitative associations with risk for KRT are now available. Changes in eGFR over 1 to 3 years were associated with higher risk for developing KRT in the subsequent time period compared with a stable eGFR for people at high and lower levels of eGFR.[69,70] The current level of eGFR was more strongly associated with risk of KRT than the rate of decline.[71] Similar results were observed for associations with mortality. A meta-analysis and statistical simulation from clinical trials demonstrates conditions in which an eGFR decline could be a valid surrogate endpoint for kidney disease progression.[72,73]

Acute Kidney Disease

AKD is a heterogeneous group of disorders characterized by abnormalities in kidney structure or function for 3 months or less with implications for health. Acute kidney injury (AKI) is a subset of AKD in which the decline in GFR is sufficient to cause an increase in serum creatinine by 0.3 mg/dL over 48 hours or by 50% over 7 days (see Box 3.1).[74] Change in GFR induces a nonsteady state in the serum levels of endogenous filtration markers (Fig. 3.3). After a decline in GFR, there is a lag before the rise in serum level because of the time required for retention of an endogenous filtration marker. Conversely, after recovery of GFR, there is a lag before the excretion of the retained marker. During the nonsteady state, neither the serum level nor the GFR estimated from the serum level accurately reflects the mGFR. Nonetheless, a change in the eGFR in the nonsteady state can be a useful indication of the magnitude and direction of the change in mGFR. If the eGFR is decreasing, the decline in eGFR is less than the decline in mGFR. Conversely, if the eGFR is increasing, the rise in eGFR is greater than the rise in mGFR. The more rapid the change in eGFR, the greater is the change in measured GFR. When eGFR reaches a new steady state, it more accurately reflects mGFR. A GFR estimating equation for use

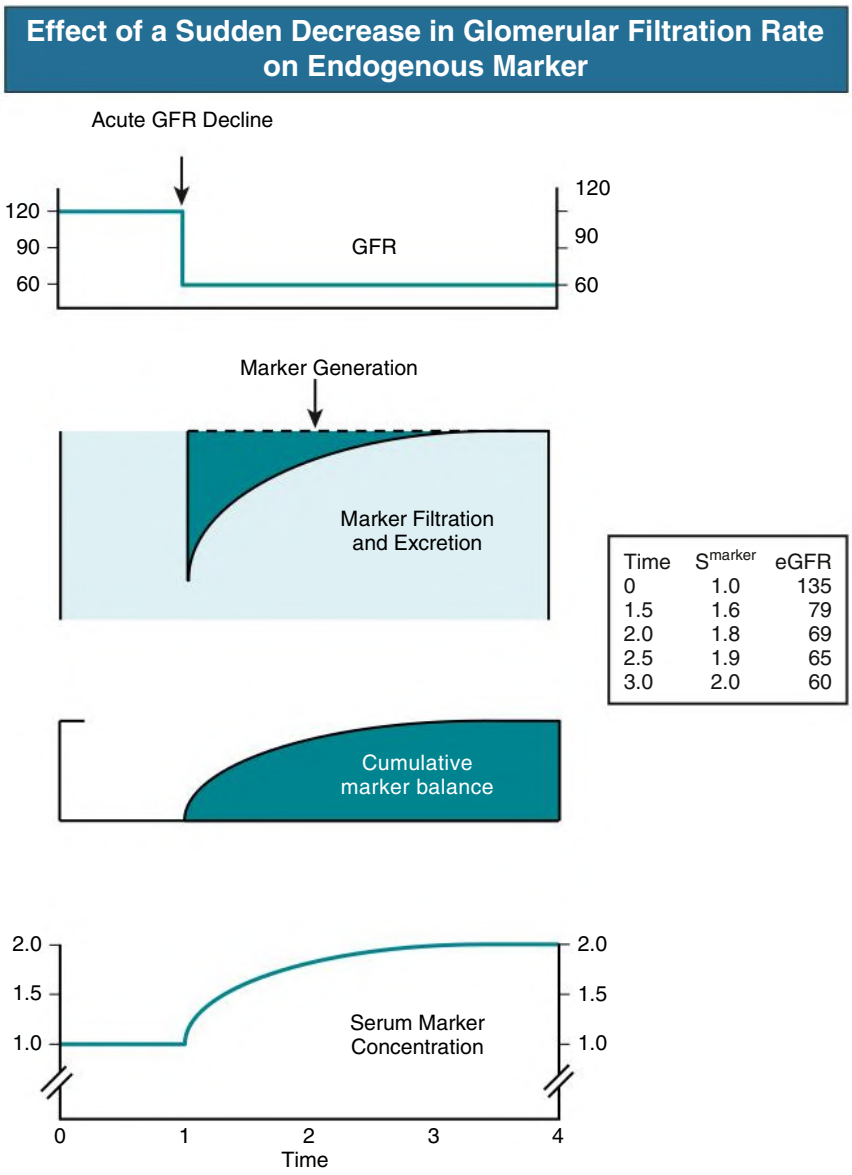

Fig. 3.3 Change in Serum Creatinine and eGFR after a Sudden Decrease in GFR. Graphs show the effect of acute GFR decline *(top)* on generation, filtration and excretion, balance of endogenous marker *(middle),* and concentration of serum marker (S^{marker}) *(bottom).*

in the nonsteady state has been proposed ("kinetic eGFR"), but has not yet been validated compared with change in mGFR.[75]

Simulations of creatinine kinetics after an abrupt GFR decline shows that the absolute and proportionate increase in serum creatinine are influenced by the baseline GFR and the magnitude of decline in GFR.[76] In patients with AKI, serum cystatin C appears to increase more rapidly than serum creatinine.[77] More data are required to establish whether changes in serum cystatin C are a more sensitive indicator of rapidly changing kidney function than changes in serum creatinine. In addition, similar to CKD, $eGFR_{cr}$ might be inappropriate in patients with differences in muscle mass or dietary protein intake, and in such patients it would be possible to confirm the change in $eGFR_{cr}$ with changes in $eGFR_{cys}$ or clearance measures (see Fig. 3.2).

LIVING KIDNEY DONOR CANDIDATES

KDIGO guidelines for the evaluation of the living kidney donor state that eGFR could be used in the evaluation of living kidney donor candidates (see Box 3.1).[78] In the United States, where evaluation of living kidney donor candidates requires a measured clearance, eGFR could be used as a first test with measured clearance as a confirmatory test.[79,80] Performance of multiple tests and assessment of the consistency of their results is helpful to identify possible sources of error. Elsewhere, if a clearance measurement is not required, eGFR could be used to accept or decline donor candidates if the probability is very high that mGFR is above or below, respectively, the thresholds for decision-making.[81]

DRUG DOSING

Pharmacokinetic properties of many drugs are affected by acute and chronic kidney disease. Drug dosing must be adjusted in patients with alterations in GFR to ensure therapeutic levels. The Cockcroft-Gault formula has been widely used to assess pharmacokinetic properties of drugs in patients with impaired kidney function, but, because of the limitations described previously, the KDIGO Controversies Conference Report recommended that GFR, as it is best evaluated in an individual patient, be used to assess kidney function for drug dosing, rather than a specific equation (see Box 3.1).[82] Using the MDRD Study or CKD-EPI

equation led to more accurate classification of mGFR categories for drug dosing adjustment than estimated Clcr using the Cockcroft-Gault equation.[83] In AKI, use of the kinetic eGFR may provide additional benefit.[84] Studies of predicted and observed vancomycin kinetics suggest that eGFRcr or eGFRcys using the CKD-EPI equations is more accurate than estimated Clcr using the Cockcroft-Gault equation.[85–87] The most recent update from the FDA acknowledges the importance of accurate GFR estimates for drug dosing and recommends eGFR using the MDRD Study or CKD-EPI equations rather than estimated Clcr using the Cockcroft and Gault equation for pharmacokinetic studies for drug development.[88] For drug dosing, GFR should be expressed without indexing for BSA for patients in whom BSA differs substantially from the index value of 1.73 m^2; to convert from mL/min/1.73 m^2 to mL/min, multiply by BSA/1.73 m^2. The accuracy of nonindexed eGFR compared with nonindexed mGFR is similar to the accuracy of indexed eGFR compared with indexed mGFR.[89]

SELF-ASSESSMENT QUESTIONS

1. A 59-year-old, 100-kg, 193-cm-tall man has a serum creatinine concentration of 1.5 mg/dL. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation and standardized serum creatinine is 53 mL/min/1.73 m^2, but measured GFR (mGFR) is 90 mL/min/1.73 m^2. What factor *most* likely explains the underestimation of mGFR?
   - **A.** Nonsteady state of serum creatinine.
   - **B.** Drug-induced inhibition of tubular secretion of creatinine.
   - **C.** Decreased extrarenal elimination of creatinine.
   - **D.** Increased creatinine generation from large muscle mass or diet.
2. An 80-year-old woman has a serum creatinine concentration of 1.0 mg/dL for 3 months. Her eGFR using the CKD-EPI creatinine equation and standardized serum creatinine is 57 mL/min/1.73 m^2. She has no chronic kidney disease risk factors. What laboratory tests could be performed to confirm the diagnosis of chronic kidney disease?
   - **A.** Measure urine albumin-to-creatinine ratio.
   - **B.** Measure GFR using an exogenous filtration marker.
   - **C.** Measure serum cystatin C and calculate estimation of GFR based on serum cystatin C ($eGFR_{cys}$).
   - **D.** Image the kidneys and urinary tract.
   - **E.** Examine the urine sediment.
   - **F.** Any or all of the above.
3. A 40-year-old man with type 1 diabetes mellitus and urine albumin-to-creatinine ratio of 450 mg/g begins angiotensin-converting enzyme (ACE) inhibitor therapy to slow the progression of kidney disease. Within 2 weeks, estimate GFR using serum creatinine ($eGFR_{cr}$) declines from 75 to 65 mL/min/1.73 m^2. What is the *most* likely cause for decline in eGFR?
   - **A.** Effect of ACE inhibitor on serum creatinine assay.
   - **B.** Effect of ACE inhibitor on GFR.
   - **C.** Effect of ACE inhibitor on tubular secretion of creatinine.
   - **D.** Effect of ACE inhibitor on muscle mass.

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