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In the Clinic®

# Care of the Patient With Abnormal Kidney Test Results

Blood and urine tests are commonly performed by clinicians in both ambulatory and hospital settings that detect chronic and acute kidney disease. Thresholds for these tests have been established that signal the presence and severity of kidney injury or dysfunction. In the appropriate clinical context of a patient's history and physical examination, an abnormal test result should trigger specific actions for clinicians, including reviewing patient medication use, follow-up testing, prescribing lifestyle modifications, and specialist referral. Tests for kidney disease can also be used to determine the future risk for kidney failure as well as cardiovascular death.



CME/MOC activity available at Annals.org.

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An estimated 37 million adults (15%) in the United States have chronic kidney disease (CKD) ranging from mild to severe disease (1). CKD is most commonly associated with diabetes mellitus (approximately 24%) (2) and hypertension (35%–85% depending on CKD stage) which can be a cause and consequence of CKD (3). Diabetes is the most common cause of kidney failure (the most severe stage of CKD), followed by hypertension (4). These associated diseases and kidney failure are more common in persons of racial and ethnic subgroups (1, 4). Other causes of CKD (such as cystic and autoimmune disease) are less common but are important to identify, because targeted treatments can delay progression of kidney failure. Regardless of cause, CKD is an independent risk factor for cardiovascular disease and all-cause mortality (5). Early identification of kidney disease and active management are key to reducing these risks, which often require close collaboration between primary care clinicians and nephrologists.

## Kidney Function, Kidney Damage, and Definition of Chronic Kidney Disease

Functions of the kidney include selectively removing waste products while retaining important substrates, maintaining electrolyte and acid–base homeostasis, regulating systemic blood pressure (BP) and erythrocyte production, and assisting in metabolic functions. The mechanisms causing abnormal kidney function or damage are numerous and include nephron loss, nephron hypertrophy due to glomerular hypertension, inflammation, and scarring. These can affect any component of the nephron structure, including the glomerulus, vasculature, and tubule and its associated interstitium. The glomerular filtration rate (GFR) is the physiologic measure of the filtering function of all of the glomeruli of the kidney. It is measured in milliliters per minute and is often standardized to body surface area. Kidney damage is often manifested by leakage of protein into the urine, sometimes with erythrocytes. Both reduction in the level of GFR and increases in urinary protein over time can signify kidney disease.

CKD has heterogeneous causes and is characterized by decreased filtering function of the kidney and/or kidney damage sustained over a duration of 3 months regardless of the cause. Decreased kidney filtering function refers to a decreased GFR (<90 mL/min/1.73 $m^2$) with kidney failure defined by a GFR less than 15 mL/min/1.73 $m^2$ or treatment with renal replacement therapy (dialysis or transplant). Kidney damage refers to high levels of proteinuria. Abnormal GFR or proteinuria values for less than 3 months may indicate normal physiologic variation, acute or subacute kidney injury, or laboratory error.

## Tests for Kidney Disease

### How is glomerular filtration measured?

Direct measurement of GFR in humans is not possible. Assessment of GFR requires that an exogenous filtration marker (for example, iohexol or iothalamate) be injected intravenously and blood or urine collected at subsequent time intervals to assay either plasma clearance of the marker or urinary clearance, respectively. These methods are cumbersome. Therefore, in clinical practice, GFR is typically estimated (eGFR) using serum biomarkers (6).

The most common equation to estimate GFR uses serum concentration of creatinine, an endogenous filtration


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biomarker that is a byproduct of muscle. Serum creatinine can be used with the patient's age and sex to derive an estimated GFR (eGFRcr) in a practical, swift, and inexpensive way. Methods and standardization of creatinine assays have been refined over time, benchmarked to an international reference standard (7). The patient's race was previously included along with age and sex to calculate eGFRcr, but a newer equation released in 2021 without the use of race is now recommended by a national taskforce due to concerns about including a nonbiological factor in GFR estimation (8, 9). The serum concentration of cystatin C, a metabolite of all cells and an endogenous filtration biomarker, can also be used to estimate GFR along with age and sex ($eGFR_{cys}$), with assays also benchmarked to a reference standard (6) (**Appendix Table**, available at Annals.org).

Patient-specific, non-GFR determinants can influence serum biomarker concentrations; these are better understood for creatinine than for cystatin C (10). Antibiotics (trimethoprim), the $H_2$ blocker cimetidine, antiviral medications (dolutegravir, ritonavir, cobicistat), some antihypertensive agents, and the cholesterol-lowering agent fenofibrate can affect tubular secretion of creatinine. Gastrointestinal infection can cause gut elimination of creatinine. Cystatin C concentrations have been shown to be altered in persons who have obesity, who have inflammatory or endocrine conditions, and who smoke tobacco (**Table 1**). Estimation of GFR combining serum creatinine and cystatin C ($eGFR_{cr\text{-}cys}$) is more accurate than using either marker alone (8, 11). Other novel filtration markers (for example, $\beta_2$-microglobulin, β-trace protein) used in combination with creatinine and cystatin C have been studied but are not routinely available (12). Clinicians must take into account biological variation in GFR and non-GFR determinants that influence variation in eGFR when diagnosing kidney disease or confirming level of eGFR for clinical decision making (13, 14). Direct assessment of GFR is reserved to guide clinical decision making when errors in estimation are suspected.

## What are the signs and symptoms of kidney damage?

*Proteinuria* is the general term for the presence of increased amounts of protein in the urine. It may reflect abnormal loss of plasma protein due to increased glomerular permeability to large molecular weight proteins such as albuminuria (glomerular proteinuria); incomplete or insufficient tubular reabsorption of normally filtered low-molecular weight proteins (tubular proteinuria); increased excretion of low molecular weight proteins that exceed the normal proximal tubular reabsorptive capacity (overflow proteinuria); or abnormal loss of proteins derived from the lower urinary tract (post-renal proteinuria). The persistent presence of any type of proteinuria is pathognomonic of kidney damage. Because albumin is the principal component of urinary protein in most kidney diseases and quantity of albuminuria is strongly associated with risk for kidney disease progression and cardiovascular disease, the focus is on quantifying albuminuria rather than proteinuria (unless clinicians suspect a predominance of nonalbumin proteinuria) (15). The gold standard for quantifying albuminuria is via a 24-hour urine collection. However, this can be cumbersome to perform in routine clinical practice and is often performed incorrectly. Therefore, alternative methods using spot urine specimens are used. A urine dipstick provides a semiquantitative assessment of albuminuria but is not very sensitive to low levels of albumin excretion (16). The dipstick may also give false-positive results immediately after the use of iodinated radiocontrast, if urine is high alkaline (pH >8.0), or in the presence of gross hematuria. Qualitative presence of urine albuminuria by dipstick should be followed up by quantification. Of note, the dipstick may also identify the presence of hematuria,


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*Table 1.* **Non–GFR Determinants of Filtration Markers Used to Evaluate Kidney Function**

| *Endogenous Filtration Markers* | *Creatinine* | *Cystatin C* |
|---|---|---|
| Generation | Muscle mass | All nucleated cells |
| Tubular handling | Receptor-mediated tubular secretion (trimethoprim, cimetidine, fenofibrate, ritonavir, dolutegravir, cobicistat); level of GFR; cause of CKD (PKD vs. others); antihypertensive agents (diuretics, calcium channel blockers) | Receptor-mediated uptake and degradation in proximal tubular cells |
| Extrarenal elimination | Gastrointestinal (bacterial creatininase) | Possibly diaphragm, heart, liver, and lung |
| Clinical conditions associated with variation in non-GFR determinants | Chronic illnesses associated with malnutrition, inflammation, deconditioning | Fat mass, inflammation (higher CRP, lower serum albumin); smoking; thyroid and adrenal hormone status (including exogenous hormone supplementation) |

*CKD = chronic kidney disease; CRP = C-reactive protein; GFR = glomerular filtration rate; PKD = polycystic kidney disease.*

which may suggest glomerular pathology or a lesion lower in the genitourinary tract (such as ureters, bladder, urethra).

Preferred methods to quantify urine albumin are with spot urine specimens with measures of urinary concentrations of creatinine and albumin to allow the calculation of an albumin-to-creatinine ratio (uACR), expressed in milligrams of albumin per gram of creatinine. This ratio assumes a steady excretion of 1 g of urinary creatinine per day and correlates well with daily albumin excretion. However, it may be erroneous when applied to patients who consistently excrete more or less than 1 g of creatinine per day (such as younger persons and those who are losing or gaining muscle


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*Figure 1.* **CKD stages* defined by GFR and uACR categories and their risk of progressive CKD.**

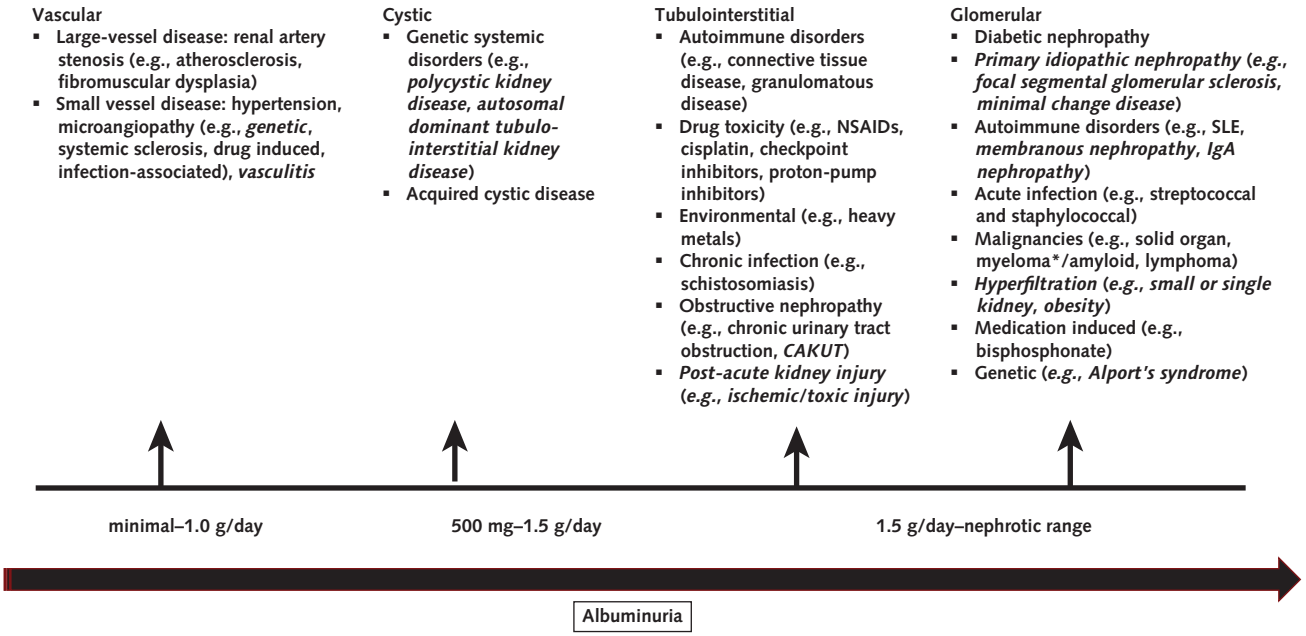
| GFR categories (mL/min/1.73 m²) Description and range | | | | Persistent albuminuria categories Description and range | | |
|---|---|---|---|---|---|---|
| | | | | A1 | A2 | A3 |
| | | | | Normal to mildly increased | Moderately increased | Severely increased |
| | | | | <30 mg/g | 30–300 mg/g | >300 mg/g |
| | G1 | Normal or high | ≥90 | | | |
| | G2 | Mildly decreased | 60–89 | | | |
| | G3a | Mildly to moderately decreased | 45–59 | | | |
| | G3b | Moderately to severely decreased | 30–44 | | | |
| | G4 | Severely decreased | 15–29 | | | |
| | G5 | Kidney failure | <15 | | | |

**Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.**

CKD = chronic kidney disease; GFR = glomerular filtration rate; uACR = urine albumin-to-creatinine ratio.

* Staging of CKD should also include cause of CKD assigned based on the presence or absence of systemic disease or the location of pathologic or anatomical abnormalities. Reproduced from Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int*. 2011;80:17–28; with permission.

*Figure 2.* **Illustrative causes of kidney disease and common levels of albuminuria.**




CAKUT = congenital disorders of the kidney and urothelial tract; IgA = immunoglobulin A; NSAIDs = nonsteroidal anti-inflammatory drugs; SLE = systemic lupus erythematosus. Italics denote primary diseases of the kidney vs systemic diseases that may affect the kidney.

* With myeloma, non-albumin proteins can predominate. Adapted from James MT, Hemmelgarn BR, Tonelli M. Early recognition and prevention of chronic kidney disease. Lancet. 2010;375:1296–1309.

mass). It can also be falsely increased immediately after vigorous physical activity.

## How is CKD staged?

For all causes of kidney damage, GFR category (assessing kidney filtration) and albuminuria category (assessing kidney damage) are used to classify and stage kidney disease according to risk for future adverse events and are helpful to guide management (**Figure 1**) (15). There are 6 GFR categories and 3 albuminuria categories that in combination yield 4 levels of risk: low, moderate, high, and very high (**Figure 1**).

The presence of systemic or specific causes of disease may modify expected prognosis and management, as compared with staging based purely on GFR and uACR (**Figure 2**). Diabetes mellitus and hypertension are the leading presumed causes of CKD, but other disease processes can cause CKD via different pathophysiologic processes in any anatomical component of the nephron. They are divided into vascular diseases, tubulointerstitial diseases, glomerular diseases, and cystic and congenital diseases and are often further classified as systemic diseases that affect the kidney or primary kidney diseases. Treatments and prognosis may differ by cause.

## What is the role of screening in CKD?

CKD in its early stages is typically asymptomatic; laboratory examination with eGFR and albuminuria is essential for diagnosis. Screening of the general population for CKD was considered but not endorsed by the U.S. Preventive Services Task Force due to the lack of definitive evidence on the downstream benefits of screening. However, testing for CKD among persons with diabetes, hypertension, or cardiovascular disease who are at high risk for CKD and benefit from intervention is recommended in professional association guidelines (17–19).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# Evaluation

The history and physical examination are important in ascertaining the cause of kidney disease and in determining the accuracy of GFR estimates and the need for treatment with renal replacement therapy.

## How is the cause of kidney disease ascertained?

Evaluation for CKD should include ascertainment of risk factors for CKD (Table 2) through the medical history. These include important demographic characteristics that may predispose to kidney damage (older age, low birthweight) as well as a history of medical conditions that increase CKD risk, such as diabetes or hypertension for at least 5 years with evidence of retinopathy. Symptoms of ischemic heart disease, peripheral vascular disease, or heart failure including chest pain or dyspnea on exertion may suggest underlying cardiovascular pathology, which is also a risk factor for kidney disease. A personal history of autoimmune conditions (for example, systemic lupus erythematosus) or chronic viral infections (for example, hepatitis B) raises concern for glomerulonephritis. Presence of a family history of CKD and end-stage kidney disease (ESKD), in particular, raises concern for genetic causes of kidney disease (such as *APOL1* gene variants among Black Americans or Alport syndrome) or shared exposures that increase CKD risk directly (such as lead exposures) or indirectly (such as hypertension or obesity). The chronic use of over-the-counter medications such as nonsteroidal anti-inflammatory drugs or nephrotoxins such as dietary supplements or proton-pump inhibitors may also increase risk for CKD. Anatomical conditions that increase risk for CKD include congenital abnormalities or chronic urinary obstruction from benign prostatic hypertrophy.

Elements of the physical examination may point to different causes of kidney disease and identify signs that may indicate need for more aggressive treatment. An elevated BP or an abnormal finding on a fundoscopic eye examination suggests that CKD may be a sequela of hypertension or diabetes. Orthostatic vital signs may indicate volume depletion as a cause of acute kidney injury, whereas signs of volume overload (such as jugular venous distension, rales on pulmonary auscultation, and lower extremity edema) may suggest a contribution of heart failure

*Table 2.* **Common Risk Factors for Chronic Kidney Disease Development and Progression**

| | |
|---|---|
| **Demographic factors** | **Genetic conditions** |
| Older age | Autosomal dominant polycystic kidney disease |
| Smoking | Two APOL1 variant risk alleles |
| **Medical conditions** | Podocytopathies causing steroid-resistant nephrotic syndrome |
| Diabetes | Fabry disease |
| Hypertension (including hypertensive disorders of pregnancy) | Alport syndrome |
| Cardiovascular disease, including heart failure | Atypical hemolytic-uremic syndrome |
| Peripheral vascular disease | **Exposures** |
| Autoimmune conditions (i.e., systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disorder) | Lead and other heavy metals |
| Low nephron mass (i.e., low birth weight, history of nephrectomy) | Prolonged use of nephrotoxic drugs (i.e., nonsteroidal anti-inflammatory drugs, aristolochic acid, proton-pump inhibitors) |
| Viral infections (i.e., hepatitis B, hepatitis C, HIV) | Air pollution |
| Malignancy (i.e., multiple myeloma) | **Anatomical conditions** |
| Acute kidney injury | Congenital abnormalities (including congenital anomalies of kidney and urinary tract, and vesico-ureteric reflux) |
| Cirrhosis | Chronic urinary obstruction, including untreated nephrolithiasis |
| Overweight/obesity | Prior urologic or pelvic surgery |


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to acute kidney injury or CKD. Renal artery bruits may identify renal artery stenosis, and carotid or femoral bruits can indicate severe atherosclerotic disease potentially leading to CKD from cholesterol emboli. Small joint synovitis and presence of petechiae or purpura on the skin may elucidate an underlying autoimmune disorder.

## How is the accuracy of GFR estimates from creatinine ascertained?

Body composition with regard to large or small muscle mass (for example, certain athletes and limb amputees or frail persons, respectively) is another key element of the physical examination that gives insight into creatinine generation by an individual person. This is an important consideration when placing serum creatinine test results in context to detect and stage CKD.

## What factors are involved in determining need for management of advanced CKD?

Although many of the physical examination findings may be normal among persons in the early stages of kidney disease, some elements suggest more advanced kidney disease. The presence of a pericardial rub, fruity odor, uremic frost on the skin, asterixis and clonus, and general confusion are signs of uremia from kidney failure. Pallor may indicate presence of anemia (a common complication of kidney disease) and painful indurations, nodules or plaques, or skin lesions may suggest calciphylaxis (a rare complication of kidney failure).

## What is the role of further testing beyond eGFR and uACR to determine cause of CKD?

The presence or absence of hematuria on urinalysis and quantification of daily albumin excretion can help ascertain the anatomical component of the nephron that is injured. Low levels of albuminuria, whether quantified by uACR or timed urine collection, are suggestive of a vascular cause of kidney disease, whereas severely increased levels of albuminuria are suggestive of glomerular pathology (**Figure 2**). Additional diagnostic testing may be necessary to investigate possible systemic disorders that could lead to kidney damage (such as autoimmune disease, vasculitis, infection, malignancy) when history and physical examination findings are suggestive.

Kidney ultrasonography for patients with CKD assesses echogenicity, size, and symmetry of the kidneys, providing additional clues to identify the cause and chronicity of disease. Small kidneys are suggestive of long-standing CKD, regardless of cause. Large kidneys may suggest an infiltrative disorder (such as myeloma) or HIV-associated nephropathy. Asymmetrical kidneys may suggest a congenital disorder or renal artery stenosis (in the presence of difficult-to-control hypertension). Ultrasonography can also detect presence of hydronephrosis (suggestive of acute or chronic obstruction), numerous and bilateral cysts (suggestive of a genetic cystic disease), and nephrolithiasis. Computed tomography and magnetic resonance imaging scans without contrast may be useful for evaluation of anatomical features identified by ultrasonography (for example, cyst complexity, solid kidney masses). To detect vascular abnormalities not detected by ultrasonography, contrast scans may be used.

Genetic testing is increasingly being used to inform the diagnosis and clinical management of kidney disorders. A positive family history of disease, early-age onset of CKD in the absence of risk factors or family history, and presence of extrarenal symptoms (such as deafness, skin lesions, cognitive impairment) should prompt consideration of genetic testing (20). To date, more than 600 genes have been implicated in monogenic kidney diseases (21) and known single-gene disorders are associated with up to 30% of nondiabetic CKD in adults (20, 22, 23). Common genetic variants can interact with environmental factors, thus contributing to polygenic kidney diseases. In these circumstances, genetic testing may not yield a specific diagnosis but may be helpful in ruling out certain causes and risk-stratifying CKD. *APOL1* kidney risk variants, for example, are common among some populations of African ancestry and impart variable risk for


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**Kidney Failure Risk Equation (KFRE)**

Using the KFRE, a 50-year-old male patient with eGFR of 45 mL/min/1.73 $m^2$ and uACR of 500 mg/g has a predicted 8.0% chance of developing kidney failure at 5 years, compared to a 4.7% chance of kidney failure in a 75-year-old male patient with the same laboratory parameters (www.kidneyfailurerisk.com). By contrast, a 50-year-old male patient with an eGFR of 45 mL/min/1.73 $m^2$ and a uACR of 1200 mg/g has a 12.0% chance of kidney failure at 5 years.

ESKD depending on the nephropathy. Not all persons with 2 variant risk alleles experience rapid CKD progression or develop kidney disease (suggesting a potential role for gene–environment or gene–gene interactions), and new treatments to delay progression are promising but in the early stage of testing (24, 25). Thus, routine testing for *APOL1* is controversial at this time.

Nephrologists may opt to pursue a kidney biopsy for a more definitive diagnosis and to guide treatment when findings of history, laboratory tests, imaging, and genetic testing do not present a unifying diagnosis.

## What frequency of eGFR and uACR testing should be implemented for management of CKD?

The frequency of eGFR testing to monitor for CKD progression should be individualized based on the person's CKD stage, the underlying cause of kidney disease, rate of prior eGFR decline or increases in uACR, presence of comorbid conditions that can accelerate eGFR decline (such as diabetes, hypertension, heart failure), and intercurrent illness (15, 26). Among persons with CKD stages 1 and 2, eGFR testing should be performed on a regular basis because early-stage kidney disease in most individuals is asymptomatic. KDIGO (Kidney Disease: Improving Global Outcomes) recommends eGFR testing intervals for more advanced CKD as follows: CKD stage 3, 1 to 3 times per year depending on albuminuria category; CKD stage 4, 3 to 4 annual eGFR checks; CKD stage 5, quarterly monitoring (15). There are no recommendations to guide the frequency of uACR testing.

## When should primary care clinicians consider referring the patient to a specialist for diagnosis?

Individuals with eGFR less than 30 mL/min/1.73 $m^2$ or those with a greater than 5% risk for kidney failure over 5 years (see the **Box:** Kidney Failure Risk Equation) are likely to benefit from a nephrology consultation to slow CKD decline and allow sufficient time for patients to learn about their options for renal replacement therapy, including conservative management, dialysis, and transplantation. A consultation with a nephrologist should also be considered in individuals with eGFR greater than 30 mL/min/1.73 $m^2$ with persistent uACR greater than 300 mg/g without a clear cause; those with nephrotic syndrome (proteinuria >3500 mg/g, hypoalbuminemia, hypercholesterolemia); and those with sustained hematuria (erythrocyte count >20 per high power field) with a negative urologic work-up or rapid declines in kidney function (>5 mL/min/1.73 $m^2$ per year) because both characteristics are concerning for an underlying glomerulonephritis. Similarly, persons with diabetes and persistent uACR greater than 300 mg/g but without coexistent retinopathy may have a less common cause of CKD and should be referred to a nephrology specialist for diagnostic purposes.


48. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145:e895-e1032. [PMID: 35363499]
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Evaluation... A thorough history and physical examination can point to the mechanism causing CKD. A careful review of the patient's medication list, environmental exposures, uACR or additional laboratory tests, and noninvasive imaging can further narrow the differential diagnosis and location of injury along the nephron. Referral to a nephrologist may be required if noninvasive tests cannot provide a unifying diagnosis. GFR and uACR can be used to stage the disease and, along with cause of CKD, to identify risk for kidney failure, cardiovascular disease, and death.

**CLINICAL BOTTOM LINE**

## Management

### How is prognosis among persons with CKD determined?

Persons with more severe CKD are at the highest risk for poor outcomes with respect to acute kidney injury, progressive CKD, kidney failure, cardiovascular mortality, and all-cause mortality.

*In 2010, a KDIGO meta-analysis of 45 cohorts including 1 555 332 people found risks for all-cause and cardiovascular mortality were higher among persons with an eGFR of less than 60 mL/min/1.73 $m^2$ (vs >60 mL/min/1.73 $m^2$) and among those with a uACR greater than 10 mg/g (vs those below that threshold). Associations were stronger with progressive eGFR decline and uACR increases. Risks were highest among individuals with eGFR of 45 mL/min/1.73 $m^2$ or lower and with either uACR greater than 300 mg/g or dipstick albuminuria with 2+ or more (27).*

More recently, equations have been developed to give clinicians more precise estimates of risk for kidney failure, such as the Kidney Failure Risk Equation, which employs age and sex in addition to GFR and uACR to estimate risk for kidney failure within the next 2 years and 5 years (**Box**).

Prognostication assists with decisions to employ or intensify therapeutic interventions to delay kidney disease progression and to trigger shared decision making about treatment for kidney failure. Applying prognostication tools among older adults (age >75) may be difficult, however, given the controversy over whether GFR decline reflects normal aging or CKD in older adults (28).

### What lifestyle management changes are helpful for patients with CKD?

Lifestyle and dietary modifications that are effective for many chronic conditions are also helpful in CKD. Clinicians should advise all patients with CKD to quit smoking, engage in physical activity for 30 minutes most days of the week, limit alcohol and sodium intake, and maintain a body mass index within the normal range, as is done for patients with glucose intolerance and elevated BP (29). Several randomized controlled trials of diets high in fruits and vegetables have demonstrated efficacy in managing risk factors for CKD, including reducing weight and lowering BP (30, 31).

*A Cochrane review of 15 randomized controlled trials found high-quality evidence that salt restriction to approximately 4 g/day leads to short-term decreases in systolic and diastolic BP by −6.91/−3.91 mm Hg (95% CI, −8.82 to −4.99/−4.80 to −3.02) among persons with all stages of CKD. Salt restriction also led to a 36% reduction in albuminuria (CI, 26% to 44%) in 5 studies (32).*

KDIGO recommends lowering salt intake to less than 2 g of sodium per day (corresponding to <5 g of sodium chloride per day) among adults with any stage of CKD (15). The Dietary


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Approach to Stop Hypertension (DASH) diet, which is high in fruits, vegetables, whole grains, low-fat dairy, nuts, and legumes and is consistent with a low-salt diet, is recommended by the American College of Cardiology/American Heart Association for persons with hypertension and CKD stage G1 or G2 (33). Recent data suggest that the DASH diet might have protective effects on BP among persons with CKD stages G3 and G4 and is safe, despite its relatively high potassium and phosphorus content (34).

Limited evidence suggests that high-protein diets may accelerate renal function decline in persons with eGFR of 45 to 60 mL/min/1.73 $m^2$ (35). KDIGO weakly recommends that persons with CKD G3 or more advanced should avoid high protein intake (>1.3 g/kg of body weight per day) and consider plant-based diets to manage complications of CKD and to slow progression of kidney function decline, while being mindful of high potassium ingestion (36). Clinicians should recognize that lower creatinine level (and higher eGFRcr) in the context of lower protein consumption may reflect decreases in creatinine generation or improvements in kidney function. In the absence of definitive randomized controlled trials to guide dietary recommendations for persons with CKD with well-controlled BP, individualized nutritional monitoring under the guidance of a dietitian specializing in kidney disease may be helpful.

## What pharmacologic management options are available for patients with CKD?

Medical treatment of kidney disease focuses on reduction of intraglomerular pressure to lower urinary albumin excretion. Renin-angiotensin system (RAS) blockers reduce intraglomerular pressure by decreasing efferent arteriole vasoconstriction and have been the cornerstone of therapy for decades. RAS blockade can slow progression of kidney disease, particularly among patients with albuminuria (37). Clinical guidelines published by KDIGO, the American Diabetes Association (ADA), and the American Heart Association recommend that angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should be prescribed to patients with CKD who have hypertension or diabetes, or both, with a uACR greater than 30 mg/g, titrated to the highest tolerated dose (potentially limited by BP and hyperkalemia), and maintained as therapy (38, 39). Combination therapy with an ACE inhibitor and an ARB is discouraged due to increased risk for adverse events, including large increases in serum creatinine and hyperkalemia (40, 41).

An active area of investigation is to identify newer agents that can decrease intraglomerular pressure for persons with persistent albuminuria despite ACE inhibitor/ARB therapy. Originally developed to lower blood glucose levels among persons with diabetes, sodium glucose cotransporter-2 (SGLT2) inhibitors decrease sodium reabsorption in the proximal tubule, leading to higher sodium delivery to the macula densa and, through tubuloglomerular feedback, reduce vasodilation of the afferent arteriole and decrease intraglomerular pressure.

*Meta-analysis of 4 randomized controlled trials among persons with diabetes and maximum tolerated RAS blockade showed that SGLT2 inhibitors reduce the risk for dialysis, transplantation, or death due to kidney disease by 33% (relative risk [RR], 0.67 [CI, 0.52 to 0.86]) (42). This benefit was seen across all eGFR subgroups, including those with a baseline eGFR greater than 90 mL/min/1.73 $m^2$ (RR, 0.37 [CI, 0.21 to 0.63]), eGFR of 60 to less than 90 mL/min/1.73 $m^2$ (RR, 0.60 [CI, 0.48 to 0.74]); eGFR of 45 to less than 60 mL/min/1.73 $m^2$ (RR, 0.55 [CI, 0.39 to 0.76]), and eGFR of 30 to less than 45 mL/min/1.73 $m^2$ (RR, 0.70 [CI, 0.54 to 0.91]). Similar findings were seen across all uACR subgroups.*

Although fewer trials of SGLT2 inhibitors have been conducted to judge the effectiveness among persons with


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nondiabetic CKD, the efficacy of SGLT2 inhibitors on reducing renal outcomes in this population appears just as strong (43, 44).

*DAPA-CKD was one of the first trials examining SGLT2 inhibitors with a primary kidney outcome of a sustained decline in eGFR of at least 50%, kidney failure, or death from kidney or cardiovascular causes. Over a median of 2.4 years, dapagliflozin reduced the primary kidney outcome by 39% (hazard ratio [HR], 0.61 [CI, 0.51 to 0.72]) compared with placebo. Findings were similar among patients with and without diabetes (45).*

Overactivation of the mineralocorticoid receptor, which regulates sodium and water transport in the kidney, contributes to CKD progression, suggesting that antagonism of this receptor could provide therapeutic benefit. Steroidal mineralocorticoid receptor antagonists (MRAs) include spironolactone and eplerenone. Meta-analysis has demonstrated that among adults with eGFR greater than 60 mL/min/1.73 $m^2$ who have persistent albuminuria despite receiving maximal doses of an ACE inhibitor or ARB, steroidal MRAs further reduce albuminuria and systolic and diastolic BP (46). These agents are also effective at reducing mortality and hospitalization in the treatment of heart failure, although their effects on major cardiovascular outcomes in patients with CKD are still unknown (47). Steroidal MRAs can induce substantial hyperkalemia, particularly when used as additive therapies to ACE inhibitors/ARBs; thus, alternatives have been sought for use among persons with CKD stages G4 and G5 (eGFR <30 mL/min/1.73 $m^2$).

Patients treated with ACE inhibitors, ARBs, SGLT2 inhibitors, and steroidal MRAs need to be monitored closely for side effects, specifically for hypotension and hyperkalemia. KDIGO guidelines recommend measuring BP, eGFR, and potassium level within 7 to 14 days of starting treatment or adjusting the dose of any of these medications, particularly if any of the following higher-risk characteristics are present: systolic BP lower than 120 mm Hg, eGFR less than 45 mL/min/1.73 $m^2$, decline in eGFR greater than 15% in the last 3 months, or a serum potassium level greater than 4.5 mEq/L. Declines in eGFR of less than 30% from baseline after initiation of an ACE inhibitor, ARB, SGLT2 inhibitor, or MRA and serum potassium level less than 5.5 mEq/L are deemed acceptable (33). Rather than immediate discontinuation of these effective medications, KDIGO recommends that hyperkalemia less than 5.5 mEq/L be managed with low-potassium diets, loop or thiazide diuretics, cation-exchange resins or binders (patiromer or sodium zirconium cyclosilicate), and correction of metabolic acidosis (48, 49). In addition to the potential side effects of newer SGLT2 inhibitors, the costs are considerably greater than for ACE inhibitors, ARBs, or steroidal MRAs. Formulary restrictions or medication insurance coverage may be a barrier for some patients to receive these medications. Patients may incur substantial out-of-pocket expenses depending on choice of treatment, making shared decision making essential to CKD management.

## What is the role of comorbidity risk reduction (BP control, glycemic control, cardiovascular disease) in patients with CKD?

Patients with CKD are at high risk for cardiovascular disease and often die or are disabled from a cardiovascular event before experiencing kidney failure. Thus, treatment of hypertension in all patients with CKD and appropriate use of HMG-CoA reductase inhibitors ("statins") among persons with eGFR of less than 60 mL/min/1.73 $m^2$ is indicated (15, 50, 51). Although the target BP goal for persons with kidney disease is controversial in part due to differences in how BP was measured across various clinical trials, there is consensus that a minimum target BP of less than 130/80 mm Hg is cardioprotective (17).


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Persons at highest cardiovascular risk, including those with significant albuminuria, may benefit from a more aggressive BP target of 120/80 mm Hg (29). ACE inhibitors or ARBs are first-line agents for BP management among persons with CKD, particularly among those with uACR greater than 300 mg/g. Often, combinations of medications are needed to achieve BP control. Diuretics are of particular importance because they reduce extracellular volume and potentiate the effects of ACE inhibitors and ARBs. Thiazide diuretics and loop diuretics can both be used for blood pressure control or volume reduction in patients with heart failure across CKD stages, though most clinicians opt for more potent loop diuretics when the eGFR is less than 30 mL/min/1.73 $m^2$ (52).

Persons with CKD and diabetes benefit from enhanced glycemic control to reduce proteinuria, progression of CKD, and the incidence of kidney failure (53). However, strict glycemic control increases the risk for hypoglycemia. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, intense glycemic control with an $A_{1c}$ target of less than 6.0% was associated with increased all-cause mortality rate compared with a standard $A_{1c}$ target of 7.0% to 7.9% (54). As a result, the 2022 KDIGO and ADA guidelines recommend targeting an individualized $A_{1c}$ goal between 6.5% and 8.0% (18, 55). Metformin and SGLT2 inhibitors constitute first-line therapy for the management of persons with type 2 diabetes and CKD. Persons who are unable to tolerate these medications or who require additional glucose-lowering medications are recommended to receive glucagon-like peptide-1 receptor agonists (GLP1-RAs), incretin hormones that stimulate insulin release from beta cells, slow gastric emptying, and decrease appetite stimulation. GLP1-RAs improve glycemic control, confer weight loss, reduce major adverse cardiovascular events among persons at highest risk, and reduce albuminuria and slow the rate of eGFR decline (56, 57).

Finerenone is a nonsteroidal MRA that has also been approved for the management of diabetic kidney disease. Randomized clinical trials of finerenone have shown significant kidney and cardiovascular benefits among persons with diabetes when used in conjunction with RAS inhibition (58, 59). It is recommended by KDIGO as a second-line agent for management of albuminuria after RAS blockade and administration of an SGLT2 inhibitor for persons with diabetes (55). Further studies are under way to assess efficacy among persons with nondiabetic CKD.

*Pooled data from 2 large randomized controlled trials (FIDELIO-DKD [60] and FIGARO-DKD [58]) showed that finerenone reduced the risk for composite renal outcomes by 23% (HR, 0.77 [CI, 0.67 to 0.88]). The composite outcome consisted of kidney failure, a sustained decrease in eGFR of greater than 57% from baseline over more than 4 weeks, or renal death. Finerenone was also found to reduce the risk for composite cardiovascular outcomes by 14% (HR, 0.86 [CI, 0.78 to 0.95]) (61).*

## What factors should be considered with regards to medication safety in patients with reduced kidney function?

Patients with CKD are more likely to have acute kidney injury from nephrotoxic agents than persons with normal kidney function. Thus, use of known nephrotoxic medications such as nonsteroidal anti-inflammatory drugs, radiocontrast agents, aminoglycoside antibiotics, amphotericin B, and some dietary supplements (for example, chromium picolinate, creatine monohydrate, germanium, L-lysine) should be minimized (62). If radiocontrast is essential in a computed tomography study, then use of low-osmolar or iso-osmolar iodinated contrast media is preferred over high-osmolar agents, and volume expansion with 0.9% normal saline or iso-osmolar intravenous sodium bicarbonate is recommended by KDIGO among persons at high risk for contrast nephropathy (63). This includes persons with diabetes, elevated albuminuria, and an eGFR of less than 60 mL/min/1.73 $m^2$. Gadolinium contrast exposure for magnetic resonance images should also be avoided among persons with an eGFR of less than 15 mL/min/1.73 $m^2$ or among persons suffering from acute kidney injury, due to the risk for nephrogenic systemic fibrosis (64). Proton-pump inhibitors have also been associated with acute interstitial nephritis and CKD progression (65).

*A retrospective cohort study demonstrated an increased risk for incident eGFR of less than 60 mL/min/1.73 $m^2$ of 22% (HR, 1.22 [CI, 1.18 to 1.26]) among new proton-pump inhibitor users compared with new users of $H_2$ blockers. Persons treated with proton-pump inhibitors also had a significantly elevated risk for doubling of serum creatinine level (HR, 1.53 [CI, 1.42 to 1.65]) and incident kidney failure (HR, 1.96 [CI, 1.21 to 3.18]) (66).*

Clinicians are encouraged to re-evaluate the use of these medications periodically, deprescribe when appropriate, and consider substitution of a histamine $H_2$ antagonist for symptoms of gastroesophageal reflux. New oncologic medications, such as immune checkpoint inhibitors, can also

*Table 3.* **Common Complications of Advanced CKD and Possible Management Strategies**

| *CKD Complication* | *Mechanism and Contributors* | *Consequences* | *Possible Management Strategies* |
|---|---|---|---|
| Hyperkalemia | Decreased sodium delivery to the distal tubule, thus decreasing potassium secretion<br>Potassium-sparing diuretics<br>ACE inhibitors and ARBs decrease aldosterone levels and GFR<br>Concomitant acidosis with intra-to-extracellular shift | Cardiac hyperexcitability or depression<br>Death | *Mild or moderate (potassium level 5.3–5.9 mEq/L):* Dietary restrictions of potassium, kaliuresis via diuretics, intestinal cation exchange through potassium binders (e.g., sodium polystyrene sulfonate, patiromer, sodium zirconium cyclosilicate)<br>*Severe (potassium level ≥6 mEq/L) or ECG changes:* Consider urgent interventions, including IV calcium, inhaled albuterol, insulin with dextrose |
| Anemia | Decreased production of erythropoietin | Decreased quality of life<br>Cardiac ischemia and failure | *Hemoglobin ≤9.0 g/dL:* Administer an erythropoietin-stimulating agent with a target threshold of 10.0-11.0 g/dL (61, 62)<br>Oral or IV iron to maintain iron stores |
| Metabolic acidosis | Impaired acid excretion<br>Retention of hydrogen ions<br>Reduced tubular absorption of bicarbonate | CKD progression<br>Insulin resistance<br>Altered bone metabolism | *Serum bicarbonate level <22 mmol/L:* prescribe alkali therapy (e.g., sodium bicarbonate or meals that are high in fruits and vegetables) (64–66) |
| CKD–mineral bone disorder: altered calcium, phosphate, parathyroid hormone, and vitamin D metabolism | 1,25 dihydroxy vitamin D deficiency<br>Increases in fibroblast growth factor-23 secondary to impaired kidney secretion | Hypocalcemia<br>Hyperphosphatemia<br>Hyperparathyroidism | Dietary phosphorus restriction<br>Phosphorus binders<br>Vitamin D repletion with ergocalciferol [25-(OH)D] or calcitriol [1,25-$(OH)_2$D] |

*ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; ECG = electrocardiogram; GFR = glomerular filtration rate; IV = intravenous.*

cause acute kidney injury (67). Most often this represents acute interstitial nephritis, although the number of case reports of thrombotic microangiopathy and glomerular disorders continues to rise.

Clinicians must also be cautious about the dose of certain nonnephrotoxic medications at lower eGFRs. Metformin, for example, is first-line therapy along with SGLT2 inhibitors to manage diabetes among persons with an eGFR greater than 45 mL/min/1.73 $m^2$. A dose reduction of metformin is recommended at an eGFR of 30 to 44 mL/min/1.73 $m^2$, and discontinuation of the medication is recommended at an eGFR of less than 30 mL/min/1.73 $m^2$ due to possible metformin accumulation and its potential to cause severe, life-threatening lactic acidosis (15). SGLT2 inhibitor treatment should only be initiated among persons with an eGFR greater than 20 mL/min/1.73 $m^2$ and should be discontinued if a patient develops kidney failure. Other common medications that require dose reduction among persons with decreased kidney function include HIV medications, antibiotics, pain medications, and chemotherapeutic agents.

## What are the complications and management factors to consider in cases of advanced CKD?

Patients with a GFR less than 30 mL/min/1.73 $m^2$ may develop several metabolic abnormalities as a direct result of their kidneys' inability to maintain normal homeostatic mechanisms. Common complications include hyperkalemia, anemia (68, 69), metabolic acidosis (70–72), hyperphosphatemia, and hyperparathyroidism (73). Their presence should alert primary care physicians to seek nephrology consultation and co-management because of their clinical consequences (Table 3).

Shared decision making is at the forefront of a decision to initiate kidney replacement therapy and should include discussion of the options of in-center and home dialysis, transplant, and conservative medical management. Indications that kidney replacement therapy for stage G5 CKD is needed beyond medical management include hypervolemia unresponsive to diuretics, pericarditis, encephalopathy, uremic symptoms (for example, poor appetite, bitter taste sensation, weight loss), and metabolic derangements that are persistent despite medical management.

 

Management... The main goals of treatment are to slow CKD progression and prevent cardiovascular complications. All patients with CKD benefit from lifestyle modifications and control of comorbid conditions, including hypertension and diabetes. In addition to treating the cause of kidney disease and avoiding use of nephrotoxic medications, patients with abnormal kidney test results benefit from reduction in intraglomerular pressure using medications such as ACE inhibitors/ARBs, SGLT2 inhibitors, and steroidal MRAs. Such therapies can be safely prescribed in primary care. Patients with advanced CKD may develop metabolic abnormalities, which should prompt nephrology consultation.

**CLINICAL BOTTOM LINE**

## Practice Improvement

### What are the available guidelines on the evaluation of abnormal kidney function test results?

To encourage a more systematic and evidence-based approach to CKD, several national and international organizations have developed clinical practice guidelines for CKD or have embedded CKD recommendations in guidelines for treatment of other conditions. The Kidney Disease Outcomes and Quality Initiative in 2002 first provided guidelines for the diagnosis and classification of CKD, and these were enhanced and updated in 2012 by a global effort. With respect to diabetes management in the context of CKD, the American Diabetes Association and KDIGO recommend testing for albuminuria with uACR and eGFR in patients with type 1 diabetes of 5 years or more duration and in all patients with type 2 diabetes. They also recommend that patients with diabetes and uACR of 300 mg/g or greater and/or an eGFR of 30 to 60 mL/min/1.73 $m^2$ have their kidney function tested 2 times a year to guide therapy. With respect to hypertension management, current KDIGO guidelines recommend treatment to a blood pressure goal of 120/80 mm Hg in adults with hypertension and CKD, whereas the American Heart Association recommends a target of 130/80 mm Hg (29, 74). Both societies recommend treatment with an ACE inhibitor in adults with hypertension and eGFR below 60 mL/min/1.73 $m^2$ or eGFR greater than 60 mL/min/1.73 $m^2$ with uACR of 300 mg/g or greater, or treatment with an ARB if an ACE inhibitor is not tolerated.

#### *Patient Education*

Despite the high burden of CKD on the U.S. population and its association with excess cardiovascular morbidity and early mortality, awareness of CKD and its risk factors among patients is dismally low (75). Recent estimates of individual CKD awareness among diverse populations with CKD range from 6% to 12%, with higher levels of awareness among patients with more complications from severe kidney disease and other cardiovascular comorbid conditions (76, 77). Patient awareness with respect to the diagnosis of CKD is the necessary motivating step before engagement in shared decision making about treatment options that include adoption of self-management practices and adherence to therapies that can slow CKD decline (such as lifestyle modifications to maintain a healthy weight, control of hypertension and diabetes with pharmacologic agents, avoidance of nephrotoxic medications, and eating a healthy diet that can help manage the complications of CKD such as metabolic acidosis and anemia) and options for renal replacement therapy including conservative management. Patient education materials are available from various reputable organizations, but attention should be paid to the level of literacy (78). These organizations also provide access to peer groups to empower individuals to understand and manage their kidney disease. Increasing awareness of CKD to a target of 10% of adults with kidney disease is a U.S. Department of Health and Human Services Healthy People 2030 goal (79).

# In the Clinic
# Tool Kit

**Care of the Patient With Abnormal Kidney Test Results**

*Patient Information*

*https://medlineplus.gov/kidneytests.html*
*https://medlineplus.gov/languages/kidneytests.html*
Patient information and other reference sites on kidney tests from the National Institutes of Health's MedlinePlus in English and other languages.

*https://www.cdc.gov/kidneydisease/publications-resources/kidney-tests.html*
*https://www.cdc.gov/kidneydisease/spanish/publications-resources/kidney-tests.html*
Patient information and handouts on kidney tests from the Centers for Disease Control and Prevention in English and Spanish.

*https://www.niddk.nih.gov/health-information/kidney-disease/chronic-kidney-disease-ckd*
*https://www.niddk.nih.gov/health-information/informacion-de-la-salud/enfermedades-rinones/informacion-general*
Health information on chronic kidney disease from the National Institute of Diabetes and Digestive and Kidney Diseases in English and Spanish.

*https://www.kidney.org/atoz/content/kidneytests*
Information for patients on tests to measure kidney function from the National Kidney Foundation.

*Information for Health Professionals*

*https://kdigo.org/guidelines/diabetes-ckd/*
Kidney Disease: Improving Global Outcomes (KDIGO) 2022 clinical practice guideline for diabetes management in chronic kidney disease.

*https://kdigo.org/guidelines/blood-pressure-in-ckd/*
Kidney Disease: Improving Global Outcomes (KDIGO) 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease.

*https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease*
Kidney disease clinical tools and patient management information for health professionals from the National Institute of Diabetes and Digestive and Kidney Diseases.



 

# WHAT YOU SHOULD KNOW ABOUT ABNORMAL KIDNEY TEST RESULTS

## What Are Tests for Kidney Disease?

The kidneys play an important role in keeping the body healthy. They remove waste from the body, balance blood pressure, make important hormones, and help keep bones strong. Kidney tests show how well your kidney is working. They can help your doctor know if you have any kidney damage or disease.

## How Do They Work?

The most commonly used kidney tests are done by measuring the level of certain proteins in your blood (creatinine) and urine (albumin or protein). If your kidney is damaged, some of the protein levels might be higher than normal. These tests are used to calculate two measures that doctors use to determine severity of kidney damage and the risk of getting worse: estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (uACR).

## Do Abnormal Results Mean That I Have Kidney Disease?

Since tests and calculations are not perfect, people with healthy kidneys may occasionally have abnormal test results. Also, kidneys can recover from a brief injury.

If test results fall outside of the normal range, the tests should be repeated and followed up to see if you have chronic kidney disease. Depending on the specific test and result, your doctor may also need to perform one of the following tests to see if you have an underlying health condition:

- Kidney ultrasound
- Additional blood testing
- 24-hour urine collection
- Genetic testing
- Kidney biopsy

## What Causes Chronic Kidney Disease?

Kidney test results that remain higher or lower than normal may be due to damage from:

- Diabetes
- Hypertension
- Inflammatory conditions (autoimmune or infectious conditions)
- Medication (NSAIDs, bisphosphonates)
- Obstructions (kidney stones)
- Lack of blood flow
- Genetic disorders

## How Is Chronic Kidney Disease Treated?

Treating chronic kidney disease early can prevent or slow down more damage to the kidneys so that your kidneys keep working. Treatment can include:

- Taking medicine to protect the kidney
- Taking medicine to treat diabetes, high blood pressure, or other health problems that are damaging your kidneys
- Avoiding cigarettes and drugs that may harm your kidneys
- Exercising regularly, and maintaining a healthy weight
- Limiting salt and alcohol and following a healthy diet

## Questions for My Doctor

- Do I have kidney disease?
- How can I stop kidney disease from getting worse, or prevent kidney disease?
- What should I do to treat my diabetes or high blood pressure?
- Do I need to change my diet or alcohol intake?
- Do I need to adjust the medicines I normally take?
- Is there anything I should avoid, given my kidney function?
- What is my risk for worsening disease or other complications of kidney disease?

## For More Information

ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

**National Kidney Foundation**
www.kidney.org/kidneydisease/aboutckd

**National Kidney Disease Education Program**
www.nkdep.nih.gov

**American Association of Kidney Patients**
www.aakp.org

Patient Information

*Appendix Table.* **Current and New Equations to Estimate Glomerular Filtration Rate**

| *Model; Name of Equation** | *Intercept u (95% CI)* | *Coefficients for Creatinine (95% CI) †* | | *Coefficients for Cystatin C (95% CI)‡* | | *Coefficient c for Age (95% CI)* | *Coefficient d for Female Sex (95% CI)* | *Coefficient e for Black Race (95% CI)* |
|---|---|---|---|---|---|---|---|---|
| | | *a1* | *a2* | *b1* | *b2* | | | |
| 2009 CKD-EPI creatinine; eGFRcr (ASR), current | 141 (139 to 144) | F: −0.329 (−4.28 to −0.230)<br>M: −0.411 (−0.508 to −0.314) | −1.209 (−1.220 to −1.198) | – | – | 0.9929 (0.9925 to 0.9933) | 1.018 (1.007 to 1.029) | 1.159 (1.144 to 1.170) |
| 2009 CKD-EPI creatinine; eGFRcr (ASR-NB), new | 141 (139 to 144) | F: −0.329 (−4.28 to −0.230)<br>M: −0.411 (−0.508 to −0.314) | −1.209 (−1.220 to −1.198) | – | – | 0.9929 (0.9925 to 0.9933) | 1.018 (1.007 to 1.029) | 1 |
| 2021 CKD-EPI creatinine (2009 CKD-EPI creatinine fit without race); eGFR (AS), new | 142 (139 to 144) | F: −0.241 (−0.344 to −0.138)<br>M: −0.302 (−0.403 to −0.292) | −1.200 (−1.211 to −1.189) | – | – | 0.9938 (0.9935 to 0.9942) | 1.012 (1.000 to 1.023) | – |
| 2012 CKD-EPI cystatin C; eGFRcys (AS), current | 133 (130 to 136) | – | – | −0.499 (−0.610 to −0.388) | −1.328 (−1.344 to −1.312) | 0.9962 (0.9957 to 0.9966) | 0.932 (0.921 to 0.944) | – |
| 2012 CKD-EPI creatinine-cystatin C; eGFRcr-cys (ASR), current | 135 (132 to 137) | F: −0.248 (−0.364 to −0.132)<br>M: −0.207 (−0.308 to −0.107) | −0.601 (−0.630 to −0.571) | −0.375 (−0.477 to −0.274) | −0.711 (−0.744 to −0.678) | 0.9952 (0.9948 to 0.9957) | 0.969 (0.958 to 0.980) | 1.080 (1.067 to 1.093) |
| 2012 CKD-EPI creatinine-cystatin c; eGFRcr-cys (ASR-NB), new | 135 (132 to 137) | F: −0.248 (−0.364 to −0.132)<br>M: −0.207 (−0.308 to −0.107) | −0.601 (−0.630 to −0.571) | −0.375 (−0.477 to −0.274) | −0.711 (−0.744 to −0.678) | 0.9952 (0.9948 to 0.9957) | 0.969 (0.958 to 0.980) | 1 |
| 2021 CKD-EPI creatinine-cystatin C (2012 CKD-EPI creatinine-cystatin c without race); eGFRcr-cys(AS), new | 135 (132 to 137) | F: −0.219 (−0.336 to −0.101)<br>M: −0.144 (−0.245 to −0.042) | −0.544 (−0.572 to −0.515) | −0.323 (−0.426 to −0.220) | −0.778 (−0.809 to −0.746) | 0.9961 (0.9957 to 0.99675) | 0.963 (0.952 to 0.974) | – |

*Note: The cells show coefficients to use in the following formula: eGFR = u × min (Scr/k,1)$^{a1}$ × max (Scr/k,1)$^{a2}$ × min (Scys/0.8,1)$^{b1}$ × max (Scys/0.8,1)$^{b2}$ × c$^{age}$ × d[if female] × e[if Black]. Here, k is 0.7 for female participants and 0.9 for male participants, min indicates the minimum of Scr/k and 1, and max indicates the maximum of Scr/k and 1. The 2009 and 2012 models were developed previously. Sex differences for eGFRcr and eGFRcr-cys equations are modeled as sex-specific creatinine coefficients as well as female sex coefficients. CKD-EPI denotes Chronic Kidney Disease Epidemiology Collaboration, F female, and M male.*

** The equations are referred to by the filtration marker or markers (creatinine [eGFRcr], cystatin C [eGFRcys], or creatinine-cystatin C [eGFRcr-cys]) and the demographic factors (age, sex, and race [ASR] or age and sex [AS]) that were used in their development. Non-Black (NB) refers to equations in which the Black race coefficient was omitted in computation of the eGFR value.*

*† The coefficient a1 is used for levels of creatinine less than or equal to 0.8 mg/dL for male participants and 0.7 mg/dL for female participants. The coefficient a2 is used for levels of creatinine greater than 0.9 mg/dL for male participants and 0.7 mg/dL for female participants.*

*‡ The coefficient b1 is used for levels of cystatin C less than or equal to 0.8 mg/L, and the coefficient b2 is used for levels greater than 0.8 mg/L.*

*From Inker LA, Eneanya ND, Coresh J, et al; Chronic Kidney Disease Epidemiology Collaboration. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med. 2021;385:1737-1749. Copyright 2021 Massachusetts Medical Society. Reproduced with permission from Massachusetts Medical Society. The 2021 equations are recommended by the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases.*