ACKNOWLEDGEMENTS

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His interests include reference intervals, diabetes and hemoglobin A1c analysis, and calibrator traceability/assay standardization/global harmonization in the clinical laboratory field.
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FACTS ABOUT CHRONIC KIDNEY DISEASE (CKD)

• More than 26 million American adults and thousands of American children have chronic kidney disease (CKD). Millions more are at increased risk for developing chronic kidney disease.

• It’s estimated that more than 500 million people worldwide have CKD, or about 10% of the adult population.

• About 1.5 million patients progress to end stage renal disease (ESRD) and require renal dialysis (hemodialysis or peritoneal dialysis) or kidney transplantation, both of which are expensive and clearly result in low quality of life for patients.

• Early detection can help slow the progression of kidney disease and help avoid kidney failure, but the signs and symptoms of CKD are not readily observable until the disease is advanced.

• Most people with chronic kidney disease do not die of end stage renal disease (ESRD; kidney failure); they die of heart disease or complications of diabetes. When all three conditions occur simultaneously, the CMR (cardiac/metabolic/renal) complex exists. In fact, heart disease causes 40%–50% of all deaths in patients with chronic kidney disease. Most of these deaths occur before dialysis or kidney transplant is necessary.

• When diabetes is present, the formation of advanced glycation end products (AGEs) occurs and results in abnormal changes in the glomerulus, the “filter” in the kidney.

• Persistent protein in the urine (proteinuria or albuminuria – two positive tests over approximately three months) is an early sign of chronic kidney disease.

• One of the best ways to measure kidney function is to calculate the estimated glomerular filtration rate (eGFR). An eGFR of less than 60 for three months or more is considered to be diagnostic of CKD.

• Only about 50% of dialysis patients and 82% of transplant patients are still alive three years after the start of ESRD therapy. ESRD means the glomerulus is so damaged it can no longer filter blood effectively.

• According to the Centers for Disease Control and Prevention (CDC), the “burden of CKD, in terms of human suffering and economic costs, is exploding as we move through the early years of the 21st century, making it a major public health issue.”
Shedding Light on Renal Disease

OVERVIEW OF CHRONIC KIDNEY DISEASE

Although chronic kidney disease (CKD) is a worldwide health issue, many healthcare providers and the general public are largely unaware of its increasing prevalence and consequences. CKD is insidious, gradually impairing kidney function over a period of years. It can lead to complications as diverse as cardiovascular disease (CVD), bone disease and anemia, greatly affecting quality of life. CKD often progresses to end stage renal disease (ESRD), requiring renal function replacement by dialysis or kidney transplant. If CKD is diagnosed early and properly managed, the need for renal replacement can be deferred for many years or even avoided altogether. CKD is underdiagnosed and undertreated, due to a number of factors, including the silent nature of the disease, a poorly standardized definition of renal impairment, and the previous lack of consistently applied clinical diagnostic criteria. Recent studies show that many adults with mild to moderate CKD are not aware they have the disease, and 50% of kidney function can be lost before symptoms or signs are apparent.

Clinical laboratories are key allies of patients and clinicians for screening, early diagnosis and management of CKD. New practice guidelines and the standardization of renal function tests offer an opportunity to greatly improve the health of CKD patients and reduce the cost of care. Information and resources in this monograph describe the incidence and physiology of CKD and associated complications, CKD diagnostic guidelines and tests, and laboratory assessment of renal function.

Diagnosis of CKD is based on laboratory criteria and has important implications for the patient, with emotional, pharmacological and socioeconomic impact. Many widely disseminated guidelines use discrete laboratory cutoffs to trigger therapeutic decisions in management of CKD, but most clinicians remain unaware of the uncertainty associated with the laboratory assessment of CKD. Utilization of laboratory test results is optimized when clinicians understand the meaning, as well as limitations, of these tests. Clinical labs have a great opportunity to improve care by educating clinicians about laboratory tests. With proper interpretation, physicians can recognize at-risk patients, monitor their renal function, and delay or avoid the need for renal replacement therapy.
WHO IS AT RISK FOR GETTING CHRONIC KIDNEY DISEASE?

Anyone can develop chronic kidney disease at any age. However, some people are more likely than others to develop kidney disease. The risk is greater if a person:

- Is African-American, Hispanic, Asian, Pacific Islander or American Indian.
- Has diabetes, high blood pressure or hepatitis C.
- Has a family member with kidney disease.
- Is 65 or older.
- Has used medications that damage the kidneys over the course of many years.

Each risk factor listed above increases a person's chances of developing kidney disease. The more risk factors a person has, the greater the risk.

WHAT SHOULD BE DONE IF A PERSON IS AT INCREASED RISK FOR KIDNEY DISEASE?

Individuals who have risk factors for developing kidney disease should:

- Be tested regularly for kidney disease. This should include testing for markers of kidney damage, such as blood, urine creatinine and proteinuria; estimating GFR; and checking blood pressure.
- Take precautions to avoid developing diabetes, or control diabetes, if present. Diabetes is a leading cause of chronic kidney disease. In fact, about a third of people with diabetes may get chronic kidney disease. Strict control of blood glucose has been proven to lower the risk of developing kidney disease.
- Control high blood pressure. High blood pressure is another leading cause of kidney disease. Lowering blood pressure and keeping it under control can help reduce that risk.

STEPS TO REDUCE BLOOD PRESSURE

- Take antihypertensive medication, if necessary.
- Avoid tobacco. Smoking raises blood pressure.
- Eat less salt. Keeping salt intake low reduces blood pressure.
- Avoid alcohol. Alcohol increases the chance of developing high blood pressure; it can also affect medicines and make it harder to control blood pressure.
- Lose excess weight to help control blood pressure and diabetes.
- Follow a program of regular physical exercise approved by a doctor. Regular exercise helps control blood sugar and blood pressure, two major risk factors for developing kidney disease. Even mild exercise, such as walking or strolling, can be helpful.

KIDNEY PHYSIOLOGY AND FUNCTION

Each kidney has about 1.5 million nephrons, and slow loss of function may not be noticeable. Because the kidney has a large physiologic reserve, CKD may be asymptomatic until more than 50% of renal function is lost.

The human body has two kidneys. Each kidney is about the size of a fist. The kidneys are located near the middle of the back, just below the rib cage.
Each kidney has about 1.5 million filters, called nephrons. Nephrons remove waste and extra fluid from blood, in the form of urine. The urine flows through two tubes, called ureters, to the bladder. The urine is stored there until it is passed during urination. The waste comes from the breakdown of food eaten and medicine taken, plus normal muscle and organ activity.

**HOW DO THE KIDNEYS FUNCTION?**

Kidneys are important because they keep the rest of the body’s systems in physiologic balance by:

- Removing waste products from the body.
- Regulating blood levels of chemicals, such as potassium, sodium, calcium and magnesium.
- Balancing the body’s fluids.
- Helping to keep blood pressure under control.
- Keeping bones healthy.
- Helping in the production of red blood cells.

**WHAT IS CHRONIC KIDNEY DISEASE?**

The definition of chronic kidney disease is:

- Kidney damage lasting longer than three months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR and

**Manifested by either:**

- Pathological abnormalities and
- Markers of kidney damage, including abnormalities in the composition of blood or urine, or abnormalities in imaging tests

Or

- GFR less than 60 mL/min/1.73 m² for more than three months, with or without kidney damage, and
- The persistent and usually progressive reduction in glomerular filtration rate (GFR less than 60 mL/min/1.73 m²)

And/or

- Albuminuria (more than 30 mg of urine albumin per gram of urine creatinine)
Chronic kidney disease means the kidneys have been damaged, perhaps due to a physical injury or a disease such as diabetes or high blood pressure. Once the kidneys are damaged, they cannot filter blood or perform their other functions as well as they should. CKD is defined as kidney damage for three months or longer, as determined by pathological abnormalities in the kidney, presence of markers of kidney damage in the blood or urine, or abnormalities in imaging tests (even if the GFR is not decreased), or a GFR of less than 60 mL/min/1.73 m² for three months or longer. In the early stages of the disease, most people do not have any symptoms, but as kidney disease gets worse, wastes and fluid may build up in the blood and cause symptoms, such as swelling, increased blood pressure, nausea and vomiting, and poor appetite. Chronic kidney disease is a serious, life-threatening disease that requires treatment. With early detection and treatment, it may be possible to prevent chronic kidney disease and its complications from getting worse. Without treatment, CKD can progress to kidney failure. A person who has kidney failure will need regular dialysis treatments or a kidney transplant to stay alive. Lab tests are critical for detecting CKD. They give physicians information about the severity of each patient’s condition and guidance in selecting the best treatments.

ARE THERE DIFFERENT STAGES OF KIDNEY DISEASE?

There are five stages of chronic kidney disease (see table below). A doctor determines which stage of kidney disease a person has, based on the presence of kidney damage and glomerular filtration rate (GFR), which is a measure of kidney function.

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<th>AND FREQUENCY OF eGFR TESTING</th>
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<td>eGFR (mL/min/1.73 m²)</td>
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<tr>
<td>1</td>
<td>≥90</td>
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<td>2</td>
<td>60–89</td>
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<td>3A</td>
<td>45–59</td>
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<td>3B</td>
<td>30–44</td>
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www.nice.org.uk, NICE Clinical Guideline

WHAT ARE THE TESTS FOR CHRONIC KIDNEY DISEASE?

The guiding principle for the clinical laboratory is to provide the right test, at the right time, for the right patient. There are two simple tests to screen for CKD:

1. Blood test for creatinine to estimate GFR – The patient’s blood is tested for a waste product, called creatinine. Creatinine is formed from breakdown of muscle tissue. When the kidneys are damaged, they have difficulty removing creatinine from blood. The creatinine test result is used in a formula to calculate the GFR (estimated GFR, or eGFR).

2. Regular blood pressure checks – High blood pressure puts people at risk for chronic kidney disease. High blood pressure can also be caused by chronic kidney disease. It is both a risk factor for kidney disease and a complication of kidney disease. Regular blood pressure checks help doctors find and treat high blood pressure. This lessens the risk of kidney damage and the worsening of kidney damage.

THE CREATININE ASSAY

Creatinine is a breakdown product of creatine and is related to muscle mass and protein intake. The creatinine concentration in blood is inversely proportional to the GFR. The most common tests for renal function are serum/plasma and urine creatinine. Creatinine is freely filtered by the glomerulus; is not actively secreted or reabsorbed intact by the kidney or metabolized; is produced at a constant rate; and is tied to muscle mass and turnover, exercise, and the growth hormone. Creatinine can be accurately measured using modern methods, with precision of routine assays less than 2% CV.
The traditional creatinine assay is the Jaffe alkaline picrate method. The Jaffe method cross-reacts with glucose, ketones, cephalosporins and other interferents, which falsely elevates creatinine values. More recently, enzymatic creatinine assays have been developed. The enzymatic assays use the enzyme creatininase and, thus, are much more specific and less prone to interference than the Jaffe methods.

Historically, creatinine results from different assays have not been comparable. The result for a patient tested using one assay might be elevated and indicate CKD, but results testing the same sample using a different assay might be either higher or lower, thus potentially resulting in conflicting clinical interpretation. An international effort resulted in the standardization of creatinine assays. The National Institute for Standards and Technology (NIST) developed a creatinine reference work, NIST SRM 967, that demonstrated commutability with patient samples for the most common creatinine assays. NIST SRM 967 provides metrological traceability for the calibration of routine creatinine methods and has been available since 2007. Traceability is also anchored by an isotope dilution mass spectrometry (ID-MS) reference method. Metrological traceability is consistent with the In Vitro Diagnostics Directive (IVDD) of 2003 and the goal of global harmonization for clinical laboratory methods. Both Jaffe alkaline picrate and enzymatic creatinine assays are in use. The creatinine assays from the major IVD manufacturers are now all standardized, which allows comparison of results from different tests, so changes in a patient’s creatinine values can be tracked reliably.

**SHOULD SERUM CREATININE ALONE BE USED TO ESTIMATE KIDNEY FUNCTION?**

No. Serum creatinine alone is not the best way to detect early stage kidney disease. This is because a rise in blood creatinine levels is observed only after significant loss of functioning nephrons, which are the filters of the kidneys. A better way to measure kidney function is to estimate glomerular filtration rate (GFR). GFR can be estimated with equations that use serum creatinine levels and some or all of the following variables: gender, age, weight and race.

However, sequential serum creatinine tests are informative. Creatinine can be a sensitive marker for changes in GFR if serial creatinine values are monitored. Sequential creatinine values eliminate the differences in eGFR, due to gender, ethnicity and age differences. A laboratory may determine a change in creatinine concentration between two samples that is clinically significant and not due to analytical noise.¹

**GLOMERULAR FILTRATION RATE (GFR)**

The GFR is a measure of how well the kidneys are functioning, specifically the efficiency of the glomerulus in filtering blood. The GFR is an important measure of renal health and is reported as a number.

- A GFR of 60 or higher is in the normal range.
- A GFR below 60 indicates kidney disease.
- A GFR of 15 or lower may mean kidney failure.

Patients can’t increase the GFR, but therapy can keep it from decreasing. The graphic below illustrates how GFR corresponds to renal function.

GFR can be measured by a clinical study involving injecting a patient with a marker of glomerular function and measuring its excretion in the urine. This is the most accurate means of measuring GFR, but it has several drawbacks. The GFR test requires the infusion of an exogenous radioisotopic or nonradioisotopic marker (i.e., a substance such as inulin or iothalamate that is not naturally occurring in the body but can be injected and is freely filtered by the glomerulus). The GFR study requires a steady-state concentration of the marker, reliable urine collection over a long collection period, adequate urine flow, and complete emptying of bladder by the patient. Due to the difficulties and variability of the GFR test, it is not commonly performed. The procedure is also costly, cumbersome, and inconvenient for both the patient and the laboratory. The traditional GFR test can be designated as mGFR (measured GFR) to distinguish it from eGFR.

Endogenous markers, molecules naturally found in the body, such as creatinine, are not as accurate as the exogenous markers but can be used to estimate the glomerular filtration rate (eGFR) and are a very practical alternative.
ESTIMATED GLOMERULAR FILTRATION RATE (eGFR)

One means of estimating the GFR is the creatinine clearance test, which measures how well creatinine is removed from the blood by the kidneys. Creatinine clearance provides more information than blood creatinine about kidney function, but it also requires measuring urine creatinine. Creatinine clearance is calculated using the formula:

\[
\text{Creatinine clearance, CrCl} = \text{urine volume} \times \frac{U\text{creatinine}}{P\text{creatinine}}, \text{expressed as mL/min or mL/min/1.73 m}^2
\]

Both blood and urine creatinine can be easily measured, but creatinine clearance requires a 24-hour urine sample. Collection of urine for 24 hours is not convenient for either the patient or the laboratory. The eGFR only requires a blood creatinine result, which is much more practical. Creatinine is measured by routine assays that are inexpensive and fast, and mathematical formulae can be used to estimate the GFR. The eGFR is not as accurate as a directly measured GFR (mGFR) and must not be confused with mGFR, but it offers many practical advantages and can be routinely reported for patients to detect early CKD and to monitor CKD progression and treatment. Various equations have been developed for eGFR derived from population-based studies. Performance of eGFR, equations is described by the P30 number. P30 refers to the percent of GFR estimates that are within 30% of the mGFR. Obviously, eGFR can vary considerably from mGFR, but it is considered clinically useful and much more practical than the mGFR. There are currently two common eGFR equations.

MDRD (MODIFICATION OF DIET IN RENAL DISEASE)

There is a 77.2% chance that the estimated GFR (for patients with eGFR below 60) is within 30% of the measured GFR (e.g., a patient with an eGFR of 59 has a 77.2% chance of having a measured GFR between 42 and 78).

\[
\text{MDRD eGFR (mL/min/1.73 m}^2) = 175 \times \left(\frac{\text{serum creatinine, mg/dL}}{1.154}\right)^{1.154} \times \left(\frac{\text{age}}{0.203}\right) \times [0.742, \text{if female}] \times [1.21, \text{if black}]
\]

Where:
\(\kappa\) is 0.7 for females and 0.9 for males, and
\(\alpha\) is -0.329 for females and -0.411 for males, and
min indicates the minimum of serum creatinine/\(\kappa\) or 1, and max indicates the maximum of serum creatinine/\(\kappa\) or 1

The eGFR values from both the MDRD and CKD-EPI equations are expressed as normalized for body surface area (BSA), based on an average BSA of 1.72 m² and reported as mL/min/1.73 m². After the age of 20–30 years, GFR decreases by about 1.0 mL/min/1.73 m² per year. The CKD-EPI equation has demonstrated improved accuracy in populations with eGFR levels above 60 mL/min/1.73 m² compared to the MDRD study equation.

MDRD and CKD-EPI equations for creatinine results reported in umol/L (SI units) are also available. These equations should not be used under the following conditions:

- Rapidly changing creatinine levels (e.g., acute kidney injury)
- Extremes in muscle mass, body size or altered diet patterns
- Medications that interfere with the measurement of serum creatinine

Obviously, these are complex equations, and they are affected by several variables, including the accuracy of the creatinine test, age, ethnicity and gender. Given these limitations, it’s not surprising the eGFR is only expected to be accurate within ±30% of the mGFR. However, the advantages of the eGFR over mGFR are also obvious. Despite the variability of eGFR compared to mGFR, renal function can still be effectively monitored over time using eGFR, given that the variables remain reasonably constant. A laboratory
information system (LIS) can be programmed to automatically calculate eGFR (or even two eGFRs, both MDRD and CKD-EPI, if desired) for every patient or any selected group of patients that is tested for blood creatinine. The MDRD and CKD-EPI eGFR equations have replaced the Cockcroft-Gault and other dated equations.

**GFR LIMITATIONS**

Estimated glomerular filtration rate (eGFR), calculated using either the MDRD study equation or the CKD-EPI equation, is an estimate of GFR, not the actual GFR (mGFR). Both equations were derived from large population studies and will generate an estimate of the mean GFR in a population of patients with the same age, gender, race and serum creatinine. However, the actual GFRs of those individuals will be distributed around that eGFR. It’s analogous to the estimated delivery date for a pregnant woman, based on her last menstrual period. This is the best estimate of the delivery date, but in fact, only a small minority of women actually deliver on that date. As with creatinine values, an abnormal eGFR should be confirmed by one or two more values.

Although the best available tool for estimating kidney function, eGFR derived from the MDRD study or CKD-EPI equations may not be suitable for all populations. All creatinine-based estimates of kidney function are only useful when renal function is stable. Serum creatinine values obtained while kidney function is changing will not provide accurate estimates of kidney function. Additionally, the equations are not recommended for use with:

1. Patients under the age of 18. The Bedside Schwartz equation should be used to estimate GFR for patients under age 18. **Caution: It is important to know the method used to measure creatinine in a serum or plasma sample, as it will affect the formula for estimating GFR in children.**

2. Patients with unstable creatinine concentrations. This includes pregnant women, patients with serious comorbid conditions and hospitalized patients, particularly those with acute kidney injury.

3. Patients with extremes in body size or muscle mass or with altered dietary intakes. This includes, but is not limited to, individuals who are amputees, paraplegics, bodybuilders or obese; patients who have a muscle-wasting disease or a neuromuscular disorder; and those suffering from malnutrition, eating a vegetarian or low-meat diet, or taking creatine dietary supplements.

Use of either the MDRD study or CKD-EPI equation with these patient groups may lead to errors in GFR estimation. GFR-estimating equations have poorer agreement with mGFR for ill hospitalized patients and for people with near normal kidney function than for the patients in the MDRD or CKD-EPI study. For pediatric patients (under the age of 18), it’s recommended that the Bedside Schwartz equation (not the original Schwartz equation) be used for eGFR. Again, the creatinine results must be from methods with calibration traceable to the IDMS reference method. The Bedside Schwartz equation is:

\[
eGFR = 0.413 \times \left( \frac{\text{height}}{\text{Scr}} \right), \text{if height is expressed in centimeters, or } 41.3 \times \left( \frac{\text{height}}{\text{Scr}} \right), \text{if height is expressed in meters}
\]

\[
eGFR \text{ (estimated glomerular filtration rate)} = \frac{\text{mL/min}}{1.73 \text{ m}^2}
\]

\[
\text{Scr} \text{ (standardized serum creatinine)} = \frac{\text{mg/dL}}{}
\]

Note that the height is in SI units (centimeters or meters), not inches or feet.

Use of any serum creatinine-based estimate requires that kidney function be at a steady state. The eGFR should be used with caution for acutely ill or hospitalized patients, who may exhibit rapidly changing kidney function.

The Laboratory Working Group of the National Kidney Disease Education Program (NKDEP) published several recommendations for eGFR.² For both IVD manufacturers and clinical laboratories, the NKDEP Laboratory Working Group makes the following recommendations:

• Implement estimated GFR now, using the MDRD study equation for routine methods that have not been recalibrated to be traceable to IDMS until a revised MDRD study equation and routine methods traceable to IDMS are ready for use.

• IVD manufacturers should recalibrate serum creatinine methods to be traceable to IDMS and should coordinate the introduction of recalibrated serum creatinine methods with the introduction of a revised GFR-estimating equation appropriate for use with zero-biased routine methods. If coordination cannot be accommodated, IVD manufacturers should
collaborate with the NKDEP and other professional organizations to communicate to customers the clinical issues associated with recalibrating serum creatinine.

- Report estimated GFR values above 60 mL/min \(-1/(1.73 \text{m}^2)\)-1 as \(>60 \text{ mL/min}/(1.73 \text{m}^2)\)-1 and not as an exact number. For values \(<60 \text{ mL/min}/(1.73 \text{m}^2)\)-1, the report should give the numeric estimate, rounded to the nearest whole number, such as 35 mL/min\(-1/(1.73 \text{m}^2)\)-1.

- Report serum creatinine values as mg/dL to two decimal places (e.g., 0.92 mg/dL, instead of 0.9 mg/dL). Serum creatinine values reported as \(\mu\text{mol/L}\) should be reported as the nearest whole number (e.g., 109 \(\mu\text{mol/L}\), instead of 109.3 \(\mu\text{mol/L}\)).

- After recalibration to IDMS, a realistic total error goal for creatinine measurement is a maximum 10% increase in the relative error of the estimated GFR. Routine methods could achieve this total error goal if analytical imprecision (including between-laboratory calibration variability) is less than 8% and analytical bias (compared with an IDMS reference measurement procedure) is less than 5% at all serum creatinine concentrations of 88.4 \(\mu\text{mol/L}\) (1.00 mg/dL).

**Cystatin C**

Cystatin C is a newer marker for renal function, with some advantages over creatinine. Cystatin C is a protease inhibitor secreted at a nearly constant rate by all nucleated cells in the body, and thus, it can reflect the constant state of kidney function. It’s a small (13 kD) single-chain non-glycosylated basic protein. Because it is freely filtered by the renal glomerulus, it has the ideal property of an endogenous kidney function marker. It is completely reabsorbed and degraded in the proximal tubules and, thus, does not appear in urine. Another advantage of the serum cystatin C concentration is that it appears to be independent of age (above 1 year of age), muscle mass, diet, gender and ethnicity. These properties make it more sensitive as an early marker of decreases in GFR, and it demonstrates the early, potentially reversible decrease in GFR before it would be observed using creatinine.

As with creatinine, a variety of eGFR equations have been developed using various cystatin C assays. Currently, several commercial cystatin C assays are not only available but have been standardized to the ERM-DA471 IFC C reference material through an initiative similar to that conducted for the standardization of creatinine. For assays traceable to ERM-DA471, an assay-independent cystatin C eGFR equation has been developed:

\[
e\text{GFR} = 130 \times \text{cystatin C}^{1.026}\text{Age}^{-0.117} - 7 \text{ mL/min}/1.73 \text{ m}^2, \text{ with cystatin C expressed as mg/L}
\]

This equation uses only two variables, the cystatin C concentration and age. Variables for ethnicity and gender are not required.\(^3\)

A triple-marker approach, consisting of creatinine, cystatin C and eGFR, can significantly improve CKD risk prediction. Cystatin C and albuminuria are both strongly and independently associated with all-cause mortality among subjects with or without CKD defined by creatinine. It’s been suggested that using both creatinine-based eGFR and cystatin C-based eGFR can aid in CKD diagnosis and prognosis.

**Urine Albumin**

Albumin is the major protein found in the blood. A healthy kidney does not let albumin pass into the urine. A damaged kidney lets some albumin pass into the urine. Albumin in the urine is a sign of kidney damage.

Albumin is preferred to urine total protein because the same protein is measured in blood and urine, and albumin assays are standardized. KDIGO (Kidney Disease: Improving Global Outcomes) recommends using urine albumin when using spot samples for detection of kidney disease and recommends reporting the urine albumin-to-creatinine ratio (UACR). KDIGO also recommends confirming an ACR above 30 mg/g from a random urine sample with a second early morning sample. An abnormal (elevated) urine albumin test once or twice confirms the result.

(continued)
Results may be referred to as microalbuminuria, macroalbuminuria, urine protein, proteinuria or albuminuria, all of which mean albumin has been detected in the urine. In the past, the test requested was sometimes called microalbumin. Microalbuminuria is a term used to describe urine albumin levels not detected by a dipstick test (i.e., 30 mg/g–300 mg/g). Macroalbuminuria is sometimes used to describe albumin levels above 300 mg/g. The assay is now ordered as urine albumin because microalbumin suggested the analyte was some smaller variant of albumin molecule, but micro only refers to a much smaller concentration of albumin found in the urine in comparison to the albumin concentration in the blood. Albuminuria is used to diagnose and monitor kidney disease. Changes in albuminuria may reflect response to therapy and risk for progression. A decrease in urine albumin may be associated with improved renal and cardiovascular outcomes. A urine albumin result below 30 mg/L is normal for a spot urine sample. A spot urine albumin sample with a result above 30 mg/L is abnormal and may mean kidney disease. Urine albumin is also measured in 24-hour urine collections. Of course, 24-hour urine sampling is not convenient for patients or laboratories. First-morning-void urine samples provide less variability than random urine samples. Second-morning voids can be used, although there’s no evidence to support superiority. Urine samples should not be frozen, and storage at 2°C–8°C for seven days is acceptable.

Cloudy urines should be centrifuged to eliminate precipitates or cellular fragments (precipitates absorb albumin). Refrigerated urine should be warmed to room temperature to dissolve any precipitate.

**URINE ALBUMIN-TO-CREATININE RATIO (UACR)**

In addition to creatinine and eGFR, urine albumin is another key marker for CKD. In fact, the combination of urine albumin and urine creatinine, in the form of the albumin-to-creatinine ratio (UACR), is another means to detect end stage CKD. Creatinine and eGFR measure the ability of the kidney to filter blood, and albumin detects the renal damage (i.e., loss of albumin from the blood to the urine when albumin should be retained and not leak into the urine). Chronic kidney disease (CKD) is usually detected by measuring creatinine and using the creatinine-based estimated glomerular filtration rate (eGFR), sometimes with the urine albumin-to-creatinine ratio (UACR).

\[
\text{UACR (mg/g)} = \frac{\text{Urine Albumin (mg/dL)}}{\text{Urine Creatinine (g/dL)}}
\]

The UACR is roughly equivalent to urine albumin excretion in mg/day. Because the UACR is a ratio between two measured substances, unlike a dipstick test for albumin, UACR is unaffected by variation in urine concentration. UACR above 30 mg/g indicates albuminuria and is a key marker for CKD.

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**Prognosis of CDK of GFR and albuminuria categories: KDIGO 2012**


| Persistent albuminuria categories: Description and range |
|---------------------------------|----------------|----------------|
| A1 Normal to mildly increased | A2 Moderately increased | A3 Severely increased |
| <30 mg/g <3 mg/mmol | 30–300 mg/g 3–30 mg/mmol | >300 mg/g >30 mg/mmol |

| GFR categories (mL/min/1.73 m²) Description and range |
|---------------------------------|----------------|
| 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
URINE PROTEIN (PROTEINURIA)

Total protein is a key constituent in the blood. No protein should be found in the urine. Protein in the urine (proteinuria) is a marker for kidney damage and can be a sign of early CKD. Albumin is the most common protein in the blood and is included in tests for total protein.

Random urine specimens are convenient to collect and can be tested for both total protein and albumin. Both analytes may also be tested in 24-hour urine specimens, as well. Measurement of urine albumin is recommended instead of urine total protein.

RECOMMENDATIONS FOR THE USE OF ALBUMIN, PROTEIN AND UACR FOR CKD

In 2014, the National Kidney Foundation issued guidelines for the evaluation and management of CKD. Spot and untimed urine samples and early morning voids are preferred. There is no need for 24-hour urine collections. The preferred order of tests is:

1. Urine albumin:creatinine ratio (UACR).
2. Urine protein:creatinine ratio (UPCR).
3. Urine total protein (automated reading).
4. Urine total protein (manual reading).

Positive albumin and protein results from reagent strip tests should be confirmed by quantitative UACR or UPCR methods.

A UACR above-30 mg/g (above-3 mg/mmol) result on a random urine specimen should be confirmed with an early morning urine sample. The GFR and albuminuria should be assessed at least annually for patients with CKD and more often for those at higher risk of CKD progression.

OTHER COMMON LABORATORY TESTS

**Blood Urea Nitrogen (BUN)**

Urea nitrogen, or urea, is a normal waste product in the blood from breakdown of dietary protein and body stores of protein. Healthy kidneys maintain normal BUN, but when kidney function is impaired, BUN is elevated. In other words, the BUN concentration increases as kidney function decreases.

**BUN:Creatinine**

The ratio of BUN to plasma creatinine can be used in the differential diagnosis of acute kidney injury.

**Calcium**

Calcium is used to screen, diagnose and monitor a range of conditions relating to the bones, heart, nerves and kidneys. Blood calcium levels do not directly reflect how much calcium is in the bones but, instead, how much calcium is circulating in the blood. Patients with chronic kidney disease often develop problems with their bones, due to abnormal blood calcium levels. In CKD, calcium should be evaluated, along with phosphorus and PTH levels.

**Carbon Dioxide**

This test is used to detect acid-base disturbances, which are seen in patients with severe chronic kidney disease or kidney failure.

**Chloride**

Chloride helps evaluate electrolyte or acid-base balance. Some patients with kidney disease have an abnormal blood chloride level.

**Glucose**

This test determines if blood glucose is within the normal reference interval. Glucose is useful for screening, diagnosing and monitoring hyperglycemia, hypoglycemia, diabetes and prediabetes. Diabetes is a leading cause of chronic kidney disease.

**Phosphorus**

Blood phosphorus is usually controlled by the kidneys, which excrete phosphorus in the urine. A high phosphorus concentration can lead to weak bones in people with chronic kidney disease, for whom mineral and bone disorders are a complication. Phosphorus in blood aids in the diagnosis of conditions, such as kidney disease, known to cause abnormally high or low levels. In CKD, blood phosphorus should be evaluated, along with calcium and PTH levels.
Potassium

Potassium is a cation necessary for proper functioning of the heart and muscles. The kidneys are essential for maintaining potassium levels in balance. A potassium concentration too high (hyperkalemia) or too low (hypokalemia) can be harmful and needs to be treated to bring the concentration to the normal reference interval. Patients with more advanced chronic kidney disease can have abnormal potassium concentration.

Sodium

Sodium is used to monitor chronic or acute hypernatremia (high blood sodium) or hyponatremia (low blood sodium) and as part of an evaluation of electrolyte balance and kidney function. Patients with high blood pressure and chronic kidney disease may need to limit salt intake.

CAN KIDNEY DISEASE BE TREATED?

The earlier kidney disease is found, the better. If it is found and treated early, it may be possible to slow progression to the more advanced stages of kidney disease and reduce CKD complications. That is why it is so important for people with risk factors to be tested regularly. The success of treatment depends on a number of things:

- The person’s stage of chronic kidney disease when treatment is started. The earlier it’s treated, the better.
- How carefully a person follows the treatment plan. People with kidney disease should learn all they can about the disease and follow treatment carefully.

DOES KIDNEY DISEASE AFFECT THE BODY IN OTHER WAYS?

Chronic kidney disease may cause problems throughout a person’s entire body. Some of the most common complications are:

- Heart and blood vessel problems.
- Anemia (low red blood cell count).
- Mineral and bone problems.
- High blood pressure.
- Poor nutritional health.

As part of the treatment plan, a doctor will work closely with the patient to help prevent or treat these problems.

WHAT IS THE IMPACT OF KIDNEY DISEASE ON HEALTHCARE COSTS?

The impact of CKD on healthcare costs is high. CKD affects an estimated 11% of the U.S. population, and those affected are at increased risk of cardiovascular disease, kidney failure and premature death.

CKD is especially costly because it often involves more than one disease, occurring frequently with heart disease, diabetes, high blood pressure, anemia, bone and mineral disease, and other complications.

Kidney disease accounts for about 16.5% of Medicare expenditures, nearly double that of 10 years ago. Costs for Medicare patients with CKD exceeded $49 billion in 2006, nearly five times greater than costs in 1993. Expenditures for patients with CKD now account for nearly one quarter (24.5%) of Medicare spending.

It is estimated that, by 2030, more than 2 million people in the United States will have kidney failure, the form of CKD in which life can only be sustained by dialysis or renal transplantation.
KEY POINTS TO REMEMBER

• Most people with CKD are unaware that they have the disease. In fact, nearly half of people with an advanced form of kidney disease do not know they have weak or failing kidneys, according to recent research published in the *American Journal of Kidney Diseases*, the official journal of the National Kidney Foundation.

• Early detection and treatment may help slow the progression of kidney disease and help avoid kidney failure.

• CKD is often not detected early enough to initiate treatment to prolong life and reduce disability.

• Kidney disease is listed as the ninth-leading cause of death in the United States by the Centers for Disease Control and Prevention.

• Heart disease is the major cause of death for all people with CKD.

• Hypertension causes CKD, and CKD causes hypertension.

• Diabetes is a leading cause of chronic kidney disease in developing countries. Today, it accounts for 45% of kidney failure — up from 18% in 1980.

• Persistent protein in the urine (two positive tests over approximately three months) is an early sign of chronic kidney disease.

• People with diabetes, hypertension and family history of kidney disease are at high risk for developing CKD.

• African-Americans, Hispanics, Pacific Islanders, Native Americans and seniors are at increased risk.

• Age alone is a key predictor of CKD. In fact, 11% of people in the United States age 65 years or older (without diabetes or hypertension) have moderately to severely decreased kidney function.

• Considering that kidney failure costs Medicare more than $20 billion every year — with rapid growth ahead — early detection means dollars saved (along with all those kidneys).

• One of the best ways to measure kidney function is to calculate estimated glomerular filtration rate.
**APPENDIX A: DESIRABLE KIDNEY DISEASE TEST RESULTS**

<table>
<thead>
<tr>
<th>Name</th>
<th>Results</th>
<th>Why It Is Important</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Albumin</td>
<td>Normal: 3.4 to 5.0*</td>
<td>Albumin is a protein that helps measure how well you are eating.</td>
</tr>
<tr>
<td>Urine Albumin-to-Creatinine Ratio (UACR)</td>
<td>CKD is more than 30</td>
<td>Urine albumin checks for kidney damage. The lower the result, the better.</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>Normal: more than 22</td>
<td>Bicarbonate measures the acid level in your blood.</td>
</tr>
<tr>
<td>Blood Urea Nitrogen (BUN)</td>
<td>Normal: less than 20</td>
<td>BUN checks how much urea, a waste product, is in your blood.</td>
</tr>
<tr>
<td>Calcium</td>
<td>Normal: 8.5 to 10.2*</td>
<td>Calcium keeps your bones strong and your heart rhythm steady. CKD can lower the amount of calcium in your bones.</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>Normal: less than 200</td>
<td>Cholesterol measures the amount of fat in your blood. Too much cholesterol can clog blood vessels or arteries in the heart and kidneys.</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>Normal: more than 40</td>
<td>HDL is the good cholesterol and clears bad fats out of your arteries.</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>Normal: less than 100</td>
<td>LDL is the bad cholesterol and can clog your arteries.</td>
</tr>
<tr>
<td>Serum Creatinine and Estimated Glomerular Filtration Rate (eGFR)</td>
<td>CKD is an eGFR less than 60</td>
<td>eGFR estimates how well your kidneys are filtering blood. As kidney disease gets worse, the creatinine goes up and the eGFR goes down.</td>
</tr>
<tr>
<td>Hemoglobin (Hgb)</td>
<td>Normal: 12 to 17*</td>
<td>Low hemoglobin is a sign of anemia. You may feel tired if you have anemia.</td>
</tr>
<tr>
<td>Parathyroid Hormone (PTH)</td>
<td>Normal: less than 65</td>
<td>PTH controls the calcium and phosphorus levels in your blood. It is needed to keep bones and blood vessels healthy.</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Normal: 2.7 to 4.6*</td>
<td>Phosphorus is important for strong bones and healthy blood vessels. High levels may cause soft bones, hard blood vessels and itchy skin.</td>
</tr>
<tr>
<td>Potassium</td>
<td>Normal: 3.5 to 5.0*</td>
<td>Potassium affects how your nerves and muscles are working. High or low levels can be dangerous.</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Normal: less than 150</td>
<td>Triglyceride is a type of fat in the blood.</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Normal: 20 or more</td>
<td>Vitamin D is important for bones and heart health.</td>
</tr>
</tbody>
</table>

*Normal ranges may vary.

APPENDIX B: GLOSSARY

ACUTE KIDNEY FAILURE – The loss of kidney function that occurs suddenly, sometimes because of surgery, illness, injury, drug reaction or other cause. It often resolves with treatment but sometimes does not. Acute kidney failure may be a risk for developing CKD. It is important to note acute kidney failure is not the same condition as chronic kidney disease.

ALBUMINURIA – The presence of albumin in the urine. Albuminuria may be an early sign of chronic kidney disease, especially in people with diabetes.

ANEMIA – A condition of a reduced number of red blood cells. People with chronic kidney disease develop anemia, due to insufficient amounts of a hormone needed to signal the body to make red blood cells.

ANTIHYPERTENSIVE MEDICATIONS – Medications used to lower high blood pressure.

BLOOD PRESSURE – The force of the blood pushing against the walls of the arteries.

CALCIUM – A mineral in the blood that is important for maintaining healthy bones and teeth. People with chronic kidney disease often develop problems with their bones, due to abnormal calcium levels.

CHRONIC KIDNEY DISEASE (CKD) – The irreversible loss of normal kidney function. In the United States, the two main causes of CKD are diabetes and high blood pressure.

CREATININE – A waste product in the blood that comes from muscle activity. Healthy kidneys remove creatinine from the blood, but when kidney function is reduced, the creatinine level in the blood rises.

CYSTATIN C – a marker of kidney function that has some advantages over creatinine because cystatin C is freely filtered by the glomerulus and better reflects the glomerular filtration rate.

DIABETES – A disease in which the main problem is regulating blood glucose level. People with diabetes cannot make or effectively use the hormone insulin that is essential for regulating blood glucose. Type 1 diabetes occurs when the body does not make enough insulin. Type 2 diabetes occurs when the body cannot properly use the insulin it makes. Complications of diabetes affect many organs of the body, including the kidneys. Diabetes is the leading cause of chronic kidney disease in the U.S.

DIABETIC KIDNEY DISEASE – Kidney disease resulting from diabetes.

DIALYSIS – A treatment for kidney failure. The two major types of dialysis are hemodialysis and peritoneal dialysis.

ELECTROLYTES – The analytes found in the blood, usually regulated by the kidneys. Examples of electrolytes are sodium, potassium, calcium, magnesium, chloride and carbon dioxide. Electrolyte imbalances are common with kidney disease and can cause potentially serious illness.

ERYTHROPOIETIN – A hormone made by the kidney that signals the body to produce red blood cells. Lack of this hormone causes anemia (low red blood cell count).

GLOMERULAR FILTRATION RATE (GFR) – An estimate of kidney function. The GFR can be estimated (eGFR) from a person’s blood creatinine level, age, gender and race. Online calculators for eGFR are available on the website of the National Kidney Foundation at www.kidney.org.

HEMODIALYSIS (HD) – A treatment method for replacing the function of the kidneys by circulating blood through tubes made of porous membranes. These tiny tubes, which make up the dialyzers, are bathed by solutions that help remove wastes and excess fluids. Treatments typically last for 3–4 hours, three times each week, and take place at home or in a dialysis center. Treatments can also be done during the night while sleeping, lasting 6–10 hours.

HEMOGLOBIN – The compound in red blood cells that carries oxygen to the cells and tissues of the body. If the hemoglobin number is too low, the person has anemia.

HIGH BLOOD PRESSURE (HYPERTENSION) – A condition that occurs when the blood vessels become narrow or stiff, forcing the heart to pump harder to push blood through the body. High blood pressure is a leading cause of chronic kidney disease and also a complication of CKD.

HORMONE – A natural chemical produced in the body and released into the bloodstream to regulate particular body functions. The kidney releases three hormones: erythropoietin (for red blood cell production), renin (for blood pressure control) and vitamin D needed for healthy bones.
HYPERKALEMIA – An elevated potassium level in the blood that occurs in people with kidney failure when potassium is no longer removed sufficiently in the urine.

HYPOTENSION – Low blood pressure.

KIDNEY FAILURE – The stage of CKD at which a patient needs treatment with either dialysis or a kidney transplant to maintain life. Kidney failure occurs when GFR is less than 15 (CKD stage 5).

KIDNEYS – Two organs, each about the size of a fist, located on either side of the spine at the lowest level of the rib cage. Kidneys remove waste products from the body, balance the body’s fluids, and release hormones that control blood pressure, production of red blood cells and healthy bones.

MAGNESIUM – A mineral that helps maintain normal muscle and nerve function, keeps heart rhythm steady, supports a healthy immune system and keeps bones strong. Magnesium also helps regulate blood sugar levels, promotes normal blood pressure, and is known to be involved in energy metabolism and protein synthesis. Magnesium is excreted through the kidneys.

MICROALBUMINURIA – Condition of having a small but significant amount of albumin in the urine. This is an early sign of diabetic kidney disease. It is also an early warning sign of cardiovascular disease. The use of microalbumin is now discouraged and urine albumin is preferred.

NEPHROLOGIST – A physician who specializes in diagnosis and treatment of kidney and urinary tract disease.

NEPHRONS – The tiny structures of the kidney that perform the filtering and regulatory processes essential for health. Each kidney has about one million nephrons.

NEPHROTOXINS – Drugs or chemicals that are toxic or poisonous to the kidneys once levels are high in the blood.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) – A group of nonprescription drugs that helps to relieve pain and reduce inflammation. NSAIDs can cause kidney damage (they are nephrotoxic); examples are ibuprofen, ketoprofen and naproxen sodium.

PERITONEAL DIALYSIS (PD) – A dialysis treatment for kidney failure that removes wastes and excess fluids from the blood using the abdominal membrane as a filter.

POTASSIUM – A mineral in the blood that helps the heart and muscles work properly. Kidneys are essential to keeping blood potassium levels in balance. A potassium level that is too high (hyperkalemia) or too low (hypokalemia) can be harmful and needs to be treated to bring the level to normal range.

PROTEINURIA – The presence of protein in the urine. A simple test can be done to detect protein in the urine. Persistent protein in the urine is an early sign of chronic kidney disease.

RED BLOOD CELLS – The cells that contain hemoglobin to carry oxygen through the bloodstream to all cells and tissues of the body.

SODIUM – A mineral necessary for normal nerve and muscle function. Sodium is found in table salt and many foods, especially packaged and processed foods. High sodium intake causes the body to retain water, which may lead to edema and increased blood pressure.

TOXINS – Any drug or chemical that is poisonous to the body. A toxin may also be a waste product that builds up in the blood of patients with kidney disease.

UREA – A waste product found in the blood that comes from normal breakdown of protein in the body. It is normally removed from the blood by the kidneys and excreted in the urine. Urea builds up in the blood of people with severe kidney disease. High levels are associated with many adverse effects. Dialysis therapies remove urea from the blood. The analyte is often called blood urea nitrogen (BUN).

URINALYSIS – A urine test to detect abnormal substances or presence of cells that can indicate disease, infection, tumor and/or other disorders of the kidneys, ureter or bladder.

URINARY TRACT – The organs and structures responsible for the production, transport and elimination of urine. It comprises the kidneys, ureters, bladder and urethra.

URINE CULTURE – A urine test to identify bacteria or other organisms causing an infection in the urinary tract.
APPENDIX C: REFERENCES


GENERAL REFERENCES


