National Kidney Foundation Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification

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Chronic kidney disease is a worldwide public health problem with an increasing incidence and prevalence, poor outcomes, and high cost. Outcomes of chronic kidney disease include not only kidney failure but also complications of decreased kidney function and cardiovascular disease. Current evidence suggests that some of these adverse outcomes can be prevented or delayed by early detection and treatment. Unfortunately, chronic kidney disease is underdiagnosed and undertreated, in part as a result of lack of agreement on a definition and classification of its stages of progression.

Recent clinical practice guidelines by the National Kidney Foundation 1) define chronic kidney disease and classify its stages, regardless of underlying cause, 2) evaluate laboratory measurements for the clinical assessment of kidney disease, 3) associate the level of kidney function with complications of chronic kidney disease, and 4) stratify the risk for loss of kidney function and development of cardiovascular disease. The guidelines were developed by using an approach based on the procedure outlined by the Agency for Healthcare Research and Quality.

This paper presents the definition and five-stage classification system of chronic kidney disease and summarizes the major recommendations on early detection in adults. Recommendations include identifying persons at increased risk (those with diabetes, those with hypertension, those with a family history of chronic kidney disease, those older than 60 years of age, or those with U.S. racial or ethnic minority status), detecting kidney damage by measuring the albumin–creatinine ratio in untimed ("spot") urine specimens, and estimating the glomerular filtration rate from serum creatinine measurements by using prediction equations. Because of the high prevalence of early stages of chronic kidney disease in the general population (approximately 11% of adults), this information is particularly important for general internists and specialists.

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Chronic kidney disease is a worldwide public health problem. In the United States, the incidence and prevalence of kidney failure are rising, the outcomes are poor, and the costs are high. The number of persons with kidney failure who are treated with dialysis and transplantation is projected to increase from 340 000 in 1999 to 651 000 in 2010 (1). The major outcomes of chronic kidney disease, regardless of cause, include progression to kidney failure, complications of decreased kidney function, and cardiovascular disease (CVD). Increasing evidence indicates that some of these adverse outcomes can be prevented or delayed by early detection and treatment (2). Unfortunately, chronic kidney disease is underdiagnosed and undertreated, resulting in lost opportunities for prevention (3–5), in part because of a lack of agreement on a definition and classification of stages in the progression of chronic kidney disease (6) and a lack of uniform application of simple tests for detection and evaluation.

In February 2002, the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) published 15 clinical practice guidelines on chronic kidney disease (7). The goals of the guidelines are to 1) define chronic kidney disease and classify its stages, regardless of underlying cause; 2) evaluate laboratory measurements for the clinical assessment of kidney disease; 3) associate the level of kidney function with complications of chronic kidney disease; and 4) stratify the risk for loss of kidney function and development of CVD. Our goal is to disseminate the simple definition and five-stage classification system of chronic kidney disease, to summarize the major recommendations on early detection of chronic kidney disease in adults (**Table 1**), and to consider some of the issues associated with these recommendations. Because of the high prevalence of early stages of chronic kidney disease in the general population, this information is particularly important for general internists and specialists.

METHODS

The guidelines of the K/DOQI are based on a systematic review of the literature. The approach used for the review was outlined by the Agency for Healthcare Research and Quality (formerly the Agency for Health Care Policy and Research) (46), with modifications appropriate to the available evidence and the goals of the K/DOQI Work Group.

The Work Group considered diverse topics, which would have been too large for a comprehensive review of the literature. Instead, a selective review of published evidence was used to focus on specific questions: a summary of reviews for established concepts and a review of original articles and data for new concepts. The strength of recommendations is graded according to a new classification (**Table 2**) recently adopted by the K/DOQI Advisory Board (see Appendix 1, available at www.annals.org).

FRAMEWORK

The Work Group defined two principal outcomes of chronic kidney disease: the progressive loss of kidney function over time (**Figure 1**) and the development and progression of CVD. **Figure 1**, which defines stages of chronic kidney disease, as well as antecedent conditions, outcomes, risk factors for adverse outcomes, and actions to improve

Table 1. **Guidelines, Recommendations, Ratings, and Key References***

Guideline Number and Description	Recommendations	Rating†	Key References
1: Definition and stages of chronic kidney disease	Definition of chronic kidney disease	A	8–15
	Classification of stages of chronic kidney disease	A	16, 17
2: Evaluation and treatment	Clinical action plan for chronic kidney disease	B	
	Referring patients with chronic kidney disease to nephrologists	B	4, 18–22
3: Persons at increased risk for chronic kidney disease	Assessing risk for chronic kidney disease	C	1, 23–31
	Testing persons at increased risk for chronic kidney disease	C	8, 9, 32
4: Estimation of GFR	Estimating GFR from prediction equations	A	33–36
	Not using serum creatinine concentrations alone to estimate GFR	A	37, 38
	Reporting estimated GFR by clinical laboratories	C	
	Calibration of serum creatinine measurements	A	39, 40
	Not using 24-hour creatinine clearance measurements to estimate GFR	A	34
5: Assessment of proteinuria	Quantitating proteinuria using untimed urine protein–creatinine ratio	A	41–45
	Not using 24-hour urine collections to quantitate proteinuria	A	41–45

* GFR = glomerular filtration rate.
† See Table 2 for guideline rating classification.

outcomes, is a model of the course of chronic kidney disease. This diagram provides a framework that has previously been lacking for the development of a public health approach to chronic kidney disease.

Risk factors for chronic kidney disease are defined as attributes associated with increased risk for adverse outcomes of chronic kidney disease (**Table 3**). The guidelines focus primarily on identifying susceptibility factors and initiation factors (to define persons at increased risk for developing chronic kidney disease) and progression factors (to define persons at high risk for worsening kidney damage and subsequent loss of kidney function). Because kidney disease usually begins late in life and progresses slowly, most persons in the stage of decreased glomerular filtration rate (GFR) die of CVD before they develop kidney failure. However, decreased GFR is associated with a wide range of complications, such as hypertension, anemia, malnutrition, bone disease, neuropathy, and decreased quality of life, which can be prevented or ameliorated by treatment at earlier stages. Treatment can also slow the progression to kidney failure. Thus, measures to prevent, detect, and treat chronic kidney disease in its earlier stages could reduce the adverse outcomes of chronic kidney disease.

Cardiovascular disease deserves special consideration as a complication of chronic kidney disease because 1) CVD events are more common than kidney failure in patients with chronic kidney disease, 2) chronic kidney disease seems to be a risk factor for CVD, and 3) CVD in patients with chronic kidney disease is treatable and potentially preventable (48–50). The 1998 Report of the NKF Task Force on Cardiovascular Disease in Chronic Renal Disease recommended that patients with chronic kidney disease be considered in the "highest risk" group for subsequent CVD events and that most interventions that are effective in the general population should also be applied to patients with chronic kidney disease (49).

Table 2. **National Kidney Foundation Kidney Disease Outcomes Quality Initiative Rating of the Strength of Recommendations***

Grade	Recommendation†
A	Strongly recommended that clinicians routinely follow the guideline for eligible patients; strong evidence that this practice improves net health outcomes.‡
B	Recommended that clinicians routinely follow the guideline for eligible patients; there is moderate evidence that this practice improves net health outcomes.§
C	Recommended that clinicians consider following the guideline for eligible patients; this recommendation is based on either weak evidence or on the opinions of the K/DOQI Work Group and reviewers that the practice might improve net health outcomes.‖

* See Appendix 1 (available at www.annals.org) for guideline rating classification. K/DOQI = Kidney Disease Outcomes Quality Initiative. Reprinted with permission from reference 47.
† Health outcomes are health-related events, conditions, or symptoms that can be perceived by persons to have an important effect on their lives. Improving net health outcomes implies that benefits outweigh any adverse effects.
‡ Strong evidence = Evidence includes results from well-designed, well-conducted studies in the target population that directly assess effects on net health outcomes.
§ Moderate evidence = Evidence meets any of the following criteria: 1) is sufficient to determine effects on net health outcomes in the target population, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; or 2) is from a population other than the target population but is from well-designed, well-conducted studies; or 3) is from studies with some problems in design or analysis; or 4) is from well-designed, well-conducted studies on surrogate end points for efficacy or safety in the target population.
‖ Weak evidence = Evidence meets any of the following criteria: 1) is insufficient to determine the effects on net health outcomes because it is from studies with some problems in design or analysis on surrogate end points for efficacy or safety in the target population; or 2) is only for surrogate measures in a population other than the target population, or 3) is from studies that are poorly designed or analyzed.

DEFINITION AND CLASSIFICATION OF STAGES OF CHRONIC KIDNEY DISEASE

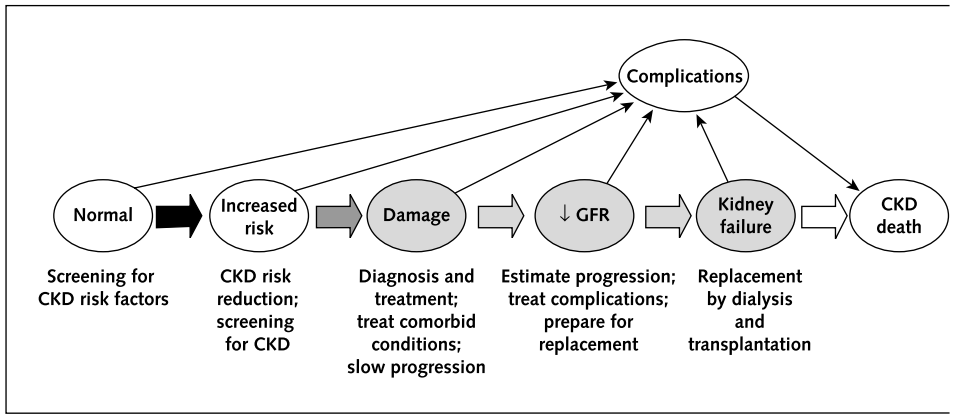
Guideline 1. Definition and Stages of Chronic Kidney Disease

Adverse outcomes can often be prevented or delayed through early detection and treatment of chronic kidney disease. Earlier stages of chronic kidney disease can be detected through routine laboratory measurements.

Chronic kidney disease is defined as either kidney damage or decreased kidney function (decreased GFR) for 3 or more months (level A recommendation).

Kidney disease can be diagnosed without knowledge of its cause. Kidney damage is usually ascertained by markers

Figure 1. **Evidence model for stages in the initiation and progression of chronic kidney disease (*CKD*) and therapeutic interventions.**



Shaded ellipses represent stages of chronic kidney disease; unshaded ellipses represent potential antecedents or consequences of chronic kidney disease. Thick arrows between ellipses represent risk factors associated with the initiation and progression of disease that can be affected or detected by interventions: susceptibility factors (*black*), initiation factors (*dark gray*), progression factors (*light gray*), and end-stage factors (*white*) (Table 3). Interventions for each stage are given beneath the stage. Persons who appear normal should be screened for chronic kidney disease risk factors. Persons known to be at increased risk for chronic kidney disease should be screened for chronic kidney disease. "Complications" refer to all complications of chronic kidney disease and its treatment, including complications of decreased glomerular filtration rate (*GFR*) (hypertension, anemia, malnutrition, bone disease, neuropathy, and decreased quality of life) and cardiovascular disease. Reprinted with permission from reference 7.

rather than by kidney biopsy. According to the Work Group, persistent proteinuria is the principal marker of kidney damage (8, 9). An albumin–creatinine ratio greater than 30 mg/g in untimed (spot) urine samples is usually considered abnormal; proposed sex-specific cut points are greater than 17 mg/g in men and greater than 25 mg/g in women (10, 11). Other markers of damage include abnormalities in urine sediment, abnormalities in blood and urine chemistry measurements, and abnormal findings on imaging studies. Persons with normal GFR but with markers of kidney damage are at increased risk for adverse outcomes of chronic kidney disease.

Glomerular filtration rate is the best measure of overall kidney function in health and disease (12). The normal level of GFR varies according to age, sex, and body size. Normal GFR in young adults is approximately 120 to 130 mL/min per 1.73 m^2 and declines with age (12–15). A GFR level less than 60 mL/min per 1.73 m^2 represents loss of half or more of the adult level of normal kidney function. Below this level, the prevalence of complications of chronic kidney disease increases.

Although the age-related decline in GFR has been considered part of normal aging, decreased GFR in the elderly is an independent predictor of adverse outcomes, such as death and CVD (51–53). In addition, decreased GFR in the elderly requires adjustment in drug dosages, as in other patients with chronic kidney disease (54). Therefore, the definition of chronic kidney disease is the same, regardless of age. Because GFR declines with age, the prevalence of chronic kidney disease increases with age; approximately 17% of persons older than 60 years of age have an estimated GFR less than 60 mL/min per 1.73 m^2 (16).

The guidelines define kidney failure as either 1) GFR less than 15 mL/min per 1.73 m^2, which is accompanied in most cases by signs and symptoms of uremia, or 2) a need to start kidney replacement therapy (dialysis or transplantation). Approximately 98% of patients with kidney failure in the United States begin dialysis when their GFR

Table 3. **Risk Factors for Chronic Kidney Disease and Its Outcomes***

Risk Factor	Definition	Examples
Susceptibility factors	Increase susceptibility to kidney damage	Older age, family history of chronic kidney disease, reduction in kidney mass, low birthweight, U.S. racial or ethnic minority status, low income or education
Initiation factors	Directly initiate kidney damage	Diabetes, high blood pressure, autoimmune diseases, systemic infections, urinary tract infections, urinary stones, lower urinary tract obstruction, drug toxicity
Progression factors	Cause worsening kidney damage and faster decline in kidney function after initiation of kidney damage	Higher level of proteinuria, higher blood pressure, poor glycemic control in diabetes, smoking
End-stage factors	Increase morbidity and mortality in kidney failure	Lower dialysis dose (Kt/V), temporary vascular access, anemia, low serum albumin level, late referral

* Kt/V = dialyzer urea clearance multiplied by time divided by volume of distribution of urea. Modified and reprinted with permission from reference 7.

Table 4. **National Kidney Foundation Kidney Disease Outcomes Quality Initiative Classification, Prevalence, and Action Plan for Stages of Chronic Kidney Disease***

Stage†	Description	GFR, *mL/min per 1.73 m²*	Prevalence, *n (%)*‡	Action§
—	At increased risk	≥60 (with chronic kidney disease risk factors)	—	Screening; chronic kidney disease risk reduction
1	Kidney damage with normal or increased GFR	≥90	5 900 000 (3.3)	Diagnosis and treatment; treatment of comorbid conditions; slowing progression; CVD risk reduction
2	Kidney damage with mild decreased GFR	60–89	5 300 000 (3.0)	Estimating progression
3	Moderately decreased GFR	30–59	7 600 000 (4.3)	Evaluating and treating complications
4	Severely decreased GFR	15–29	400 000 (0.2)	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	300 000 (0.1)	Kidney replacement (if uremia present)

* CVD = cardiovascular disease; GFR = glomerular filtration rate. Modified and reprinted with permission from reference 7.
† Stages 1 to 5 indicate patients with chronic kidney disease; the row without a stage number indicates persons at increased risk for developing chronic kidney disease. Chronic kidney disease is defined as either kidney damage or GFR less than 60 mL/min per 1.73 m^2 for 3 or more months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.
‡ Prevalence for stage 5 is from the U.S. Renal Data System (1998); it includes approximately 230 000 patients treated with dialysis and assumes 70 000 additional patients not receiving dialysis. Prevalence for stages 1 to 4 is from the Third National Health and Nutrition Examination Survey (1988 to 1994). Population of 177 million adults age 20 or more years. Glomerular filtration rate is estimated from serum creatinine measurements by using the Modification of Diet in Renal Disease study equation based on age, sex, race, and calibration for serum creatinine. For stages 1 and 2, kidney damage is estimated by using untimed urine samples to determine the albumin–creatinine ratios; greater than 17 mg/g in men or greater than 25 mg/g in women on two measurements indicates kidney damage. The proportion of persons at increased risk for chronic kidney disease has not been estimated accurately.
§ Includes actions from preceding stages.

is less than 15 mL/min per 1.73 m^2 (17). Kidney failure is not synonymous with end-stage renal disease (ESRD). "End-stage renal disease" is an administrative term in the United States. It indicates that a patient is treated with dialysis or transplantation, which is the condition for payment for health care by the Medicare ESRD Program. The classification of ESRD does not include patients with kidney failure who are not treated with dialysis and transplantation. Thus, although the term ESRD provides a simple operational classification of patients according to treatment, it does not precisely define a specific level of kidney function.

The level of kidney function, regardless of diagnosis, determines the stage of chronic kidney disease according to the K/DOQI chronic kidney disease classification (level A recommendation).

Data from the Third National Health and Nutrition Examination Survey (NHANES III) show the increasing prevalence of complications of chronic kidney disease at lower levels of GFR (7). These data and other studies provide a strong basis for using GFR to classify the stage of severity of chronic kidney disease. **Table 4** shows the classification of stages of chronic kidney disease and the prevalence of each stage, estimated by using data from NHANES III (16). Approximately 11% of the U.S. adult population (20 million persons from 1988 to 1994) have chronic kidney disease. The prevalence of early stages of disease (stages 1 to 4; 10.8%) is more than 100 times greater than the prevalence of kidney failure (stage 5; 0.1%). The burden of illness associated with earlier stages of chronic kidney disease has not been systematically studied (55, 56). The National Institute of Diabetes and Digestive and Kidney Disease has initiated a prospective cohort study, the Chronic Renal Insufficiency Cohort (CRIC) study, for this purpose.

Guideline 2. Evaluation and Treatment

The evaluation and treatment of patients with chronic kidney disease require understanding the separate but related concepts of diagnosis, comorbid conditions, severity of disease, complications of disease, and risks for loss of kidney function and CVD.

Each patient should have a clinical action plan based on the stage of disease, as defined by the K/DOQI classification (level B recommendation).

Starting treatment at the right point in the progression of chronic kidney disease is essential to prevent adverse outcomes. Defining the stage of chronic kidney disease is the key first step in developing the appropriate clinical action plan (**Table 4**).

Diagnosis of chronic kidney disease is traditionally based on pathology test results and etiology. A simplified classification emphasizes diseases in native kidneys (diabetic or nondiabetic in origin) and kidney diseases in the transplant. Diabetic kidney disease is the largest single cause of kidney failure in the United States; the earliest manifestation is microalbuminuria with a normal or elevated GFR (stage 1 according to the guidelines). Nondiabetic kidney diseases include glomerular, vascular, tubulointerstitial, and cystic kidney diseases.

The differential diagnosis of chronic kidney disease in a specific patient is based on the history, physical examination, and laboratory evaluation (**Tables 5** and **6**), as described in standard texts and recent reviews (57, 58). The remainder of the evaluation of chronic kidney disease is similar for most types of kidney disease. Specific treatment depends on the cause of kidney disease; a thorough search for reversible causes should be carried out in each patient. However, many aspects of treatment are not specific to the cause; these are reviewed in the NKF K/DOQI clinical

Table 5. **Clues to the Diagnosis of Chronic Kidney Disease from the Patient's History***

Clue	Potential Diagnosis
Review of systems	
Symptoms during urination	Usually suggest disorders of the urinary tract, such as infection, obstruction, or stones.
Recent infections	May suggest postinfectious glomerulonephritis or HIV-associated nephropathy.
Skin rash or arthritis	Suggests autoimmune disease, such as systemic lupus erythematosus or cryoglobulinemia.
Risk factors for parenterally transmitted disease	May suggest HIV, hepatitis B, or hepatitis C and associated kidney diseases.
Chronic diseases	
Heart failure, cirrhosis, or gastrointestinal fluid losses	Usually suggest reduced kidney perfusion (prerenal factors).
Diabetes†	As a cause of chronic kidney disease: Diabetic kidney disease usually follows a typical clinical course after onset, first with microalbuminuria, followed by clinical proteinuria, hypertension, and declining GFR.
Hypertension†	As a cause of chronic kidney disease: Hypertensive nephrosclerosis is usually characterized by severely elevated blood pressure readings over a long period, with associated end-organ damage in addition to kidney disease. Recent worsening of hypertension, in association with findings of diffuse atherosclerosis, suggests renal artery disease due to atherosclerosis. Recent onset of severe hypertension in young women suggests renal artery disease due to fibromuscular dysplasia.
Medical history	
Findings from previous routine examinations	May reveal a history of hypertension or proteinuria during childhood; during pregnancy; or on examinations for school, military service, or insurance.
Previous urologic evaluations	Details may disclose radiologic abnormalities associated with kidney disease.
Family history of kidney diseases	
Every generation: equal susceptibility in males and females	Suggests an autosomal dominant disease, such as polycystic kidney disease.
Every generation: predominant male susceptibility	Suggests a sex-linked recessive disease, such as the Alport syndrome.
Less frequent than every generation	Suggests an autosomal recessive disease, such as medullary cystic kidney disease or autosomal recessive polycystic kidney disease.

* GFR = glomerular filtration rate. Reprinted with permission from reference 7.
† Extremely common in elderly patients and often nonspecific.

practice guidelines on chronic kidney disease and other topics (available at www.kdoqi.org).

Treatment of comorbid conditions, interventions to slow progression of kidney disease, and measures to reduce the risk for CVD should begin during stage 1 and stage 2. Hypertension is both a cause and a complication of chronic kidney disease and should be carefully controlled in all patients. Evaluation and treatment of other complications of decreased GFR, such as anemia, malnutrition, bone disease, neuropathy, and decreased quality of life, should be undertaken during stage 3, as the prevalence of these complications begins to rise when GFR declines to less than 60 mL/min per 1.73 m^2. Preparation for kidney replacement therapy should begin during stage 4, well before the stage of kidney failure. Initiation of dialysis and transplantation is triggered by the onset of uremic symptoms. Preparations for these treatments should begin when GFR declines to less than 15 mL/min per 1.73 m^2 (stage 5). The clinical action plan for each stage should include actions begun in preceding stages.

Patients with chronic kidney disease should be referred to a specialist for consultation and comanagement if the patient's personal physician cannot adequately evaluate and treat the patient. A nephrologist should participate in the care of patients with a GFR less than 30 mL/min per 1.73 m^2 (level B recommendation).

The guidelines endorse a model in which primary phy-

Table 6. **Laboratory Evaluation of Patients with Chronic Kidney Disease and Persons at Increased Risk for Chronic Kidney Disease***

Laboratory Measurements	Patients with Chronic Kidney Disease	Persons at Increased Risk for Chronic Kidney Disease
Serum creatinine to estimate GFR	All	All
Albumin–creatinine ratio in a random untimed urine specimen	All	All
Examination of the urine sediment or dipstick for erythrocytes and leukocytes	All	All
Imaging of the kidneys, usually by ultrasonography	All	Selected patients (symptoms of urinary tract obstruction, infection, or stones or family history of polycystic kidney disease)
Serum electrolytes (sodium, potassium, chloride, and bicarbonate)	All	Selected patients (hypertension, diabetes, drug toxicity, edematous conditions)
Urinary concentration or dilution (specific gravity or osmolality)	All	Selected patients (polyuria, hypernatremia, hyponatremia)
Urinary acidification (pH)	All	Selected patients (metabolic alkalosis, metabolic acidosis, hypokalemia, hyperkalemia)

* Evaluations recommended in this table are based on the opinions of the Kidney Disease Outcomes Quality Initiative Work Group. GFR = glomerular filtration rate. Modified and reprinted with permission from reference 7.

Table 7. **Prevalence of Persons at Increased Risk for Chronic Kidney Disease***

Risk Factor	Prevalence	
	Estimated	Estimated, *n*
Diabetes mellitus (23)	Diagnosed: 5.1% of adults age ≥20 y Undiagnosed: 2.7% of adults age ≥20 y	10.2 million 5.4 million
Hypertension (24)	24.0% of adults age ≥18 y	43.1 million
Systemic lupus erythematosus (25)	Approximately 0.05% definite or suspected	Approximately 239 000
Functioning kidney graft (1)	Approximately 0.03%	88 311 (as of 31 December 1998)
African-American (26)	12.3%	34.7 million
Hispanic or Latino (of any race) (26)	12.5%	35.3 million
American-Indian and Alaska Native (26)	0.9%	2.5 million
Age 60–70 y (27)	7.3%	20.3 million
Age ≥70 y (27)	9.2%	25.5 million
Acute kidney failure (28, 29)	Approximately 0.14%	Approximately 363 000 nonfederal hospital stays in 1997
NSAID use (30, 31)		
Assumed daily use	Approximately 5.2% with rheumatoid arthritis or osteoarthritis	Approximately 13 million
Yearly use	Approximately 30%	Approximately 75 million

* NSAID = nonsteroidal anti-inflammatory drug.

sicians and specialists share responsibility for the care of persons with chronic kidney disease. Most patients with stage 1 to 3 chronic kidney disease are under the care of primary care providers, generalists, or specialists other than nephrologists. As kidney disease worsens, the need for consultation and comanagement with nephrologists increases. Recent studies show that many patients do not see a nephrologist until shortly before dialysis. Late referral is associated with increased mortality after initiation of dialysis (18–22). The Work Group identified a specific level of kidney function as a threshold for referral to a nephrologist in order to facilitate more timely preparation for kidney replacement therapy and perhaps improve outcomes.

Guideline 3. Persons at Increased Risk for Chronic Kidney Disease

Some persons who do not have kidney damage and who have normal or elevated GFR are at increased risk for development of chronic kidney disease.

All persons should be assessed as part of routine health encounters to determine whether they are at increased risk for developing chronic kidney disease on the basis of clinical and sociodemographic factors (level C recommendation).

Persons at increased risk for developing chronic kidney disease should undergo testing to identify markers of kidney damage and to estimate the GFR (level C recommendation).

Table 3 presents examples of clinical and sociodemographic factors that increase susceptibility to or initiate chronic kidney disease. The proportion of persons at increased risk for chronic kidney disease is not known. **Table 7** shows the large number of patients with risk factors for chronic kidney disease. Estimates indicate that the number of persons at increased risk may exceed the number of patients with chronic kidney disease (1, 23–31).

Table 6 presents recommendations for evaluating adults at increased risk for chronic kidney disease. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (32) and the American Diabetes Association (9) recommend testing adults with high blood pressure or diabetes for chronic kidney disease. Many other persons may also be at increased risk for chronic kidney disease (**Table 7**). Therefore, the Work Group also recommended testing persons who have a family history of chronic kidney disease, are older than 60 years of age, or who belong to U.S. racial or ethnic minorities.

The guidelines in **Table 6** are especially important for generalist physicians, who are uniquely positioned to detect chronic kidney disease in its earliest stages.

The NKF K/DOQI guidelines recommend testing more persons for chronic kidney disease than do other evidence-based guidelines. The U.S. Preventive Health Services Task Force (USPSTF) recommends testing patients with hypertension or diabetes but not other subgroups (59). However, data provided in the NKF K/DOQI guidelines suggest that the prevalence of earlier stages of chronic kidney disease is higher than previously suspected and that earlier detection and treatment can prevent or delay the loss of kidney function and development of chronic kidney disease. The Work Group calls upon the USPSTF to reevaluate its guidelines in light of the evidence cited in this report. The research community should evaluate risks and benefits of various testing schedules for specific subgroups of persons at increased risk for developing chronic kidney disease.

Evaluation of Laboratory Measurements for the Clinical Assessment of Kidney Disease

Guideline 4. Estimation of GFR

Estimates of GFR are the best overall indices of the level of kidney function.

Physicians should estimate the level of GFR from prediction equations that take into account the serum creatinine

concentration and some or all of the following variables: age, sex, race, and body size. The Modification of Diet in Renal Disease (MDRD) study and Cockcroft–Gault equations provide useful estimates of GFR in adults (level A recommendation).

Glomerular filtration rate can be estimated from serum creatinine levels by using prediction equations that also take into account age, sex, race, and body size. Two such equations are:

Cockcroft–Gault equation (33):

$$C_{Cr}(\text{mL/min}) = \frac{(140 - Age \times Weight)}{72 \times S_{Cr}} \times (0.85 \text{ if female})$$

Abbreviated MDRD study equation (34, 35):

$$GFR(\text{mL/min per } 1.73\ m^2) = 186 \times (S_{Cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American})$$

where C_{Cr} is creatinine clearance, S_{Cr} is serum creatinine concentration in mg/dL, age is in years, and weight is in kg. **Appendix Table 1** (available at www.annals.org) shows the range of values of serum creatinine that correspond to an estimated GFR of 60 mL/min per 1.73 m^2, depending on age, sex, and race. Thus, minor elevations of serum creatinine concentration may be consistent with a substantial reduction in GFR.

The MDRD study equation has many advantages. It is more accurate and precise than the Cockcroft–Gault equation for persons with a GFR less than approximately 90 mL/min per 1.73 m^2 (34, 35). This equation predicts GFR as measured by using an accepted method (urinary clearance of ^{125}I-iothalamate). It was developed on a large ($n >$ 1000) database containing persons with various kidney diseases and was tested on a validation database containing more than 500 additional patients. It does not require height or weight and has been validated in kidney transplant recipients and African-Americans with nephrosclerosis (36). Nonetheless, questions remain about the equation's generalizability because it has not been validated in diabetic kidney disease, in patients with serious comorbid conditions, in normal persons, or in persons older than 70 years of age. Clinical conditions in which it may be necessary to measure GFR by using clearance methods include extremes of age and body size, severe malnutrition or obesity, diseases of skeletal muscle, paraplegia or quadriplegia, vegetarian diet, rapidly changing kidney function, and calculation of the dose of potentially toxic drugs that are excreted by the kidneys.

Clinicians should not use serum creatinine concentration as the sole means to assess the level of kidney function (level A recommendation).

The serum creatinine concentration is affected by factors other than GFR, such as creatinine secretion and generation and extrarenal excretion (37, 38). As a result, there is a relatively wide range for serum creatinine in normal persons. This wide range means that GFR must decline to approximately half the normal level before the serum creatinine concentration rises above the upper limit of normal (**Appendix Table 1**, available at www.annals.org). In the elderly, the serum creatinine concentration does not reflect the age-related decline in GFR because of a concomitant age-related decline in muscle mass that reduces creatinine generation. Thus, it is difficult to use the serum creatinine concentration alone to estimate the level of kidney function, to detect earlier stages of chronic kidney disease, or to adjust drug dosages.

Clinical laboratories should report an estimate of GFR using a prediction equation in addition to reporting the serum creatinine measurement (level C recommendation).

Use of GFR (rather than serum creatinine measurement) to characterize kidney function is a critical element in the Working Group's strategy for improving care of patients with chronic kidney disease. Clinical laboratories can help to implement GFR estimates. Laboratories should calibrate their serum creatinine results to the same level as the laboratory in which the MDRD prediction equation was developed. Clinical laboratories will need to work with physicians and administrators to develop reporting systems that meet their needs. In the interim, a GFR calculator with the abbreviated MDRD study equation is available on the NKF Web site (www.kdoqi.org).

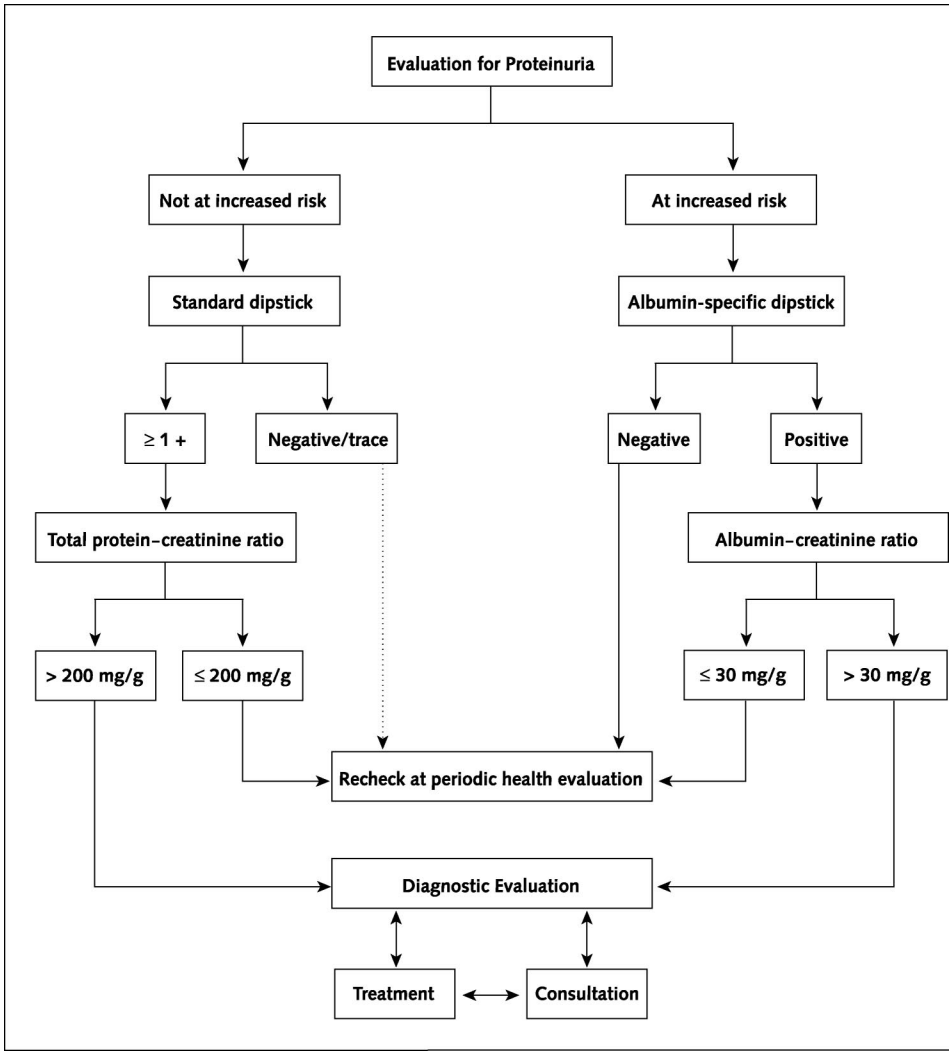
Autoanalyzer manufacturers and clinical laboratories should calibrate serum creatinine assays using an international standard (level A recommendation).

Differences among clinical laboratories in calibration of serum creatinine assays can account for errors in GFR estimates as high as 20%, which are especially important in individuals with near-normal serum creatinine concentration (39, 40). Failure to adjust for differences in calibration accounts for some of the current controversy regarding the performance of prediction equations in selected clinical populations (60) or the prevalence of reduced GFR in the general population (61–63).

Measurement of creatinine clearance by using timed (for example, 24-hour) urine collections does not provide more accurate estimates of GFR than do prediction equations (level A recommendation).

Measurement of creatinine clearance requires collection of a timed urine sample, which is inconvenient and frequently inaccurate. In the MDRD study, predicted GFR provided a more accurate estimate of GFR (as measured by urinary clearance of ^{125}I-iothalamate) than measured creatinine clearance (34). Thus, the guidelines recommend obtaining 24-hour urine collections only for the special clinical circumstances discussed earlier.

Figure 2. **Evaluation of proteinuria in patients not known to have kidney disease.**



The Work Group recommends a cutoff value for an albumin–creatinine ratio greater than 30 mg/g in men and women. Some studies suggest sex-specific cutoff values for an albumin–creatinine ratio of greater than 17 mg/g in men or greater than 25 mg/g in women (10, 11). Reprinted with permission from reference 7.

Guideline 5. Assessment of Proteinuria

Persistently increased protein excretion is usually a marker of kidney damage.

Under most circumstances, untimed urine samples should be used to detect and monitor proteinuria (level A recommendation).

It is usually not necessary to obtain a timed urine collection (overnight or 24-hour) to measure proteinuria (level A recommendation).

Normal persons usually excrete very small amounts of protein in the urine. Increased excretion of albumin is a sensitive marker for chronic kidney disease due to diabetes, glomerular disease, and hypertension. Increased excretion of low-molecular-weight globulins is a sensitive marker for some types of tubulointerstitial disease.

In this guideline, the term "proteinuria" refers to increased urinary excretion of albumin or any other specific protein; "albuminuria" refers specifically to increased urinary excretion of albumin. "Microalbuminuria" refers to albumin excretion that exceeds the normal range but is below the minimum level for detection by tests for total protein.

The American Diabetes Association (9) and an earlier position paper by the NKF (8) recommend assessment of proteinuria to detect chronic kidney disease. The ratio of protein or albumin to creatinine in an untimed urine specimen has replaced protein excretion in a 24-hour collection as the preferred method for measuring proteinuria. Using a ratio corrects for variations in urinary protein concentration due to hydration and is far more convenient than timed urine collections. The ratio of protein or albumin to creatinine in an untimed urine sample is an accurate estimate of the protein or albumin excretion rate (41–45).

A proposed algorithm for testing for proteinuria distinguishes persons at increased risk for chronic kidney disease from asymptomatic, healthy persons (**Figure 2**). A sample of urine from the first voiding after awakening is preferred, but a random specimen is acceptable. The algorithm for adults at increased risk (**Figure 2**, *right*) begins with testing of a random untimed urine sample with an albumin-specific dipstick. Patients with a positive result on a disptick test for albuminuria (1+ or greater) should undergo confirmation of proteinuria by measuring the albumin–creatinine ratio on an untimed urine sample within 3 months. Alternatively, testing could begin with an untimed urine sample for the albumin–creatinine ratio. Patients with two or more positive results on quantitative tests temporally spaced over 3 months have persistent proteinuria and should undergo further evaluation for chronic kidney disease (as stated in Guideline 2).

The standard dipstick for protein and the untimed urine measurements for total protein–creatinine ratio are also useful for detecting proteinuria in adults not at increased risk for developing chronic kidney disease (**Figure 2**, *left*). However, adults at increased risk for chronic kidney disease with a negative result for protein on a standard dipstick test, especially those with diabetes, should undergo testing with either an albumin-specific dipstick or an untimed urine measurement for the albumin–creatinine ratio. It was the opinion of the Work Group that monitoring proteinuria in adults with chronic kidney disease should use the albumin–creatinine ratio or total protein–creatinine ratio if the albumin–creatinine ratio is high (>500 to 1000 mg/g). The guidelines review causes of false-positive and false-negative results in measuring urinary albumin or total protein.

SUMMARY

Chronic kidney disease affects approximately 11% of the U.S. adult population (20 million people from 1988 to 1994). The prevalence of earlier stages of disease (10.8%) is more than 100 times greater than the prevalence of kidney failure (0.1%). Adverse outcomes of chronic kidney disease, including loss of kidney function and development of kidney failure and CVD, can often be prevented or delayed through early detection and treatment. In particular, physicians should consider using interventions to slow the progression of kidney disease in all patients with chronic kidney disease and should place patients with chronic kidney disease in the highest-risk group for CVD risk factor reduction and other treatments for CVD. Each patient with chronic kidney disease should have a clinical action plan, based on the stage of disease, as defined by the NKF K/DOQI guidelines. All patients with chronic kidney disease and persons at increased risk for chronic kidney disease should undergo measurement of proteinuria (as a marker of kidney damage) and GFR. Quantitative assessment of proteinuria is useful for detection, differential diagnosis, prognosis, and treatment of chronic kidney disease. The ratio of concentration of albumin to creatinine in untimed urine samples should be used to detect and monitor proteinuria. Glomerular filtration rate, as estimated by prediction equations based on serum creatinine concentration, age, race, sex, and body size, is useful for detecting chronic kidney disease, classifying its severity, estimating progression, managing complications, and deciding on referral to a nephrologist.

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Appendix 1: Grading the Strength of Recommendations

Because of the nature of the questions addressed by the Work Group, evidence for the NKF K/DOQI guidelines on chronic kidney disease is based primarily on observational studies and is not readily graded according to the usual recommendations, such as those of the U.S. Preventive Services Task Force (USPSTF) (59).

The guidelines reference 667 articles, of which 367 are original articles tabulated and graded according to four dimensions: study size, applicability (generalizability) depending on study participants, results, and methodologic quality depending on type of study. In the original publication, strength of evidence for each link in the chain of reasoning was rated in the rationale accompanying each guideline (64). The body of evidence was classified according to whether it was based on an analysis of individual patient data from a single, large, generalizable study of high methodologic quality, such as the analyses of the NHANES III database; a compilation of original articles; a review of reviews and other selected original articles; or opinion. All statements represented the consensus of the Work Group, were reviewed by external reviewers, and were approved by the NKF K/DOQI Advisory Board.

In this paper, each guideline statement is classified according to a new classification recently adopted by the NKF K/DOQI Advisory Board (47). In this classification, each recommendation and the strength of evidence underlying each recommendation are rated separately. Ratings of recommendations are similar to that of the USPSTF (**Table 2**), but several key features of the rating of the strength of evidence differ from that of the USPSTF (**Appendix Table 2**). First, the classification of strength of evidence based on methodologic quality and applicability is explicitly identified. Second, high-level methodologic quality can be assigned to observational studies as well as to clinical trials. Third, applicability takes into account whether the outcomes measures are "hard" clinical outcomes or surrogates and whether the study population is the target population (in this case, patients with chronic kidney disease) or a population other than the target population. This latter distinction is particularly important in the study of CVD, in which extrapolation from studies in the general population contributes substantially to the body of evidence.

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Appendix Table 1. **Serum Creatinine Corresponding to an Estimated Glomerular Filtration Rate of 60 mL/min per 1.73 m^2 by the Abbreviated Modification of Diet in Renal Disease Study and Cockcroft–Gault Equations***

Age	Serum Creatinine Concentration					
	MDRD Study Equation				Cockcroft–Gault Equation	
	European-American		African-American		Men	Women
	Men	Women	Men	Women		
y	← *μmol/L (mg/dL)* →					
30	130 (1.47)	100 (1.13)	153 (1.73)	118 (1.34)	162 (1.83)	138 (1.56)
40	123 (1.39)	95 (1.08)	146 (1.65)	112 (1.27)	148 (1.67)	126 (1.42)
50	118 (1.34)	91 (1.03)	140 (1.58)	108 (1.22)	133 (1.50)	113 (1.28)
60	115 (1.30)	88 (1.00)	135 (1.53)	104 (1.18)	118 (1.33)	100 (1.13)
70	111 (1.26)	86 (0.97)	132 (1.49)	102 (1.15)	103 (1.17)	88 (0.99)
80	109 (1.23)	84 (0.95)	129 (1.46)	99 (1.12)	88 (1.00)	75 (0.85)

* Calculations in this table use serum creatinine values obtained in the MDRD study central laboratory, which were a mean of 0.23 mg/dL lower than duplicate samples analyzed at the Third National Health and Nutrition Examination Survey central laboratory. Calculations in this table assume a weight of 72 kg and body surface area of 1.73 m^2. MDRD = Modification of Diet in Renal Disease. Reprinted with permission from reference 7.

Appendix Table 2. **National Kidney Foundation Kidney Disease Outcomes Quality Initiative Rating the Strength of Evidence**

Outcomes	Population	Methodologic Quality*		
		Well-Designed and -Analyzed (Little, if Any, Potential Bias)	**Some Problems in Design or Analysis (Some Potential Bias)**	**Poorly Designed or Analyzed (Large Potential Bias)**
Health outcomes	Target population	Strong: 1	Moderate: 2	Weak: 8
Health outcomes	Other than the target population	Moderate: 3	Moderate: 4	Weak: 8
Surrogate measure for health outcomes	Target population	Moderate: 5	Weak: 6	Weak: 8
Surrogate measure for health outcomes	Other than the target population	Weak: 7	Weak: 7	Weak: 7, 8

* Strong: 1 = Evidence includes results from well-designed, well-conducted studies in the target population that directly assess effects on net health outcomes. Moderate: 2 = Evidence is sufficient to determine effects on net health outcomes in the target population, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies. 3 = Evidence is from a population other than the target population but is from well-designed, well-conducted studies. 4 = Evidence is from studies with some problems in design or analysis. 5 = Evidence is from well-designed, well-conducted studies on surrogate end points for efficacy or safety in the target population. Weak: 6 = Evidence is insufficient to determine the effects on net health outcomes because it is from studies with some problems in design or analysis on surrogate end points for efficacy or safety in the target population. 7 = Evidence is only for surrogate measures in a population other than the target population. 8 = Evidence is from studies that are poorly designed or analyzed.