PART 4. DEFINITION AND CLASSIFICATION OF STAGES OF CHRONIC KIDNEY DISEASE

CHRONIC KIDNEY disease is a major public health problem. Improving outcomes for people with chronic kidney disease requires a coordinated world-wide approach to prevention of adverse outcomes through defining the disease and its outcomes, estimating disease prevalence, identifying earlier stages of disease and antecedent risk factors, and detection and treatment for populations at increased risk for adverse outcomes. The goal of Part 4 is to create an operational definition and classification of stages of chronic kidney disease and provide estimates of disease prevalence by stage, to develop a broad overview of a "clinical action plan" for evaluation and management of each stage of chronic kidney disease, and to define individuals at increased risk for developing chronic kidney disease. Studies of disease prevalence were evaluated as described in Appendix 1, Table 150. Data from NHANES III were used to develop estimates of disease prevalence in adults as described in Appendix 2.

GUIDELINE 1. DEFINITION AND STAGES OF CHRONIC KIDNEY DISEASE

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

- **The presence of chronic kidney disease should be established, based on presence of kidney damage and level of kidney function (glomerular filtration rate [GFR]), irrespective of diagnosis.**
- **Among patients with chronic kidney disease, the stage of disease should be assigned based on the level of kidney function, irrespective of diagnosis, according to the K/DOQI CKD classification (Table 10).**

Table 10. Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

BACKGROUND

Chronic kidney disease is a major public health problem. Adverse outcomes of chronic kidney disease can be prevented through early detection and treatment. Earlier stages of chronic kidney disease can be detected through routine laboratory measurements.

The USRDS provides reliable nationwide data regarding the incidence, prevalence, treatment patterns, outcomes, and cost of kidney failure treated by dialysis and transplantation, the most severe stage of chronic kidney disease. This guideline provides a definition of chronic kidney disease as well as definitions and estimates of prevalence of earlier stages of kidney disease.

Chronic kidney disease is defined according to the presence or absence of kidney damage and level of kidney function—irrespective of the type of kidney disease (diagnosis). Among individuals with chronic kidney disease, the stages are defined based on the level of kidney function. Identifying the presence and stage of chronic kidney disease in an individual is not a substitute for accurate assessment of the cause

0272-6386/02/3902-0105$35.00/0
doi:10.1053/ajkd.2002.30943

Table 11. Definition of Chronic Kidney Disease

Criteria
1. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by *either*: • Pathological abnormalities; or • Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
2. GFR <60 mL/min/1.73 m^2 for ≥3 months, with or without kidney damage

Methods to estimate GFR are discussed in Guideline 4. Markers of kidney damage are discussed in Guidelines 5–6.

of kidney disease, extent of kidney damage, level of kidney function, comorbid conditions, complications of decreased kidney function, or risks for loss of kidney function or cardiovascular disease in that patient. Defining stages of chronic kidney disease requires "categorization" of continuous measures of kidney function, and the "cut-off levels" between stages are inherently arbitrary. Nonetheless, staging of chronic kidney disease will facilitate application of clinical practice guidelines, clinical performance measures and quality improvement efforts to the evaluation, and management of chronic kidney disease.

RATIONALE

Definition and Classification

Definition of chronic kidney disease (O). Chronic kidney disease has been defined according to the criteria listed in Table 11.

Stages of chronic kidney disease (R, O). Among individuals with chronic kidney disease, the stage is defined by the level of GFR, with higher stages representing lower GFR levels. Table 12 illustrates the classification of individuals based on the presence or absence of markers of kidney disease and level of GFR, according to definition and staging of chronic kidney disease proposed by this guideline. In addition, it includes columns for the presence or absence of high blood pressure, because of the complex relationship of high blood pressure and chronic kidney disease.

All individuals with GFR <60 mL/min/1.73 m^2 for ≥3 months are classified as having chronic kidney disease, irrespective of the presence or absence of kidney damage. The rationale for including these individuals is that reduction in kidney function to this level or lower represents loss of half or more of the adult level of normal kidney function, which may be associated with a number of complications (Part 6).

All individuals with kidney damage are classi-

Table 12. Definition and Stages of Chronic Kidney Disease

GFR (mL/min/1.73 m^2)	With Kidney Damage*		Without Kidney Damage*	
	With HBP**	Without HBP**	With HBP**	Without HBP**
≥90	1	1	"High blood pressure"	"Normal"
60–89	2	2	"High blood pressure with ↓ GFR"	"↓ GFR"[a]
30–59	3	3	3	3
15–29	4	4	4	4
<15 (or dialysis)	5	5	5	5

Shaded area represents chronic kidney disease; numbers designate stage of chronic kidney disease.

* Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

** High blood pressure is defined as ≥140/90 in adults and >90th percentile for height and gender in children.

[a] May be normal in infants and in the elderly.

fied as having chronic kidney disease, irrespective of the level of GFR. The rationale for including individuals with GFR ≥60 mL/min/1.73 m^2 is that GFR may be sustained at normal or increased levels despite substantial kidney damage and that patients with kidney damage are at increased risk of the two major outcomes of chronic kidney disease: loss of kidney function and development of cardiovascular disease (Part 7).

The methods to estimate GFR and assess markers of kidney damage are not completely sensitive or specific in detecting decreased GFR and kidney damage, respectively. Thus, misclassification is possible, and clinicians should carefully consider all aspects of the patient's clinical presentation in interpreting test results and determining evaluation and management. For the definition of chronic kidney disease, the Work Group selected cut-off levels for GFR and markers of kidney damage that maximize specificity, acknowledging potential loss of sensitivity. Clinicians should be especially careful in the evaluation of individuals with borderline abnormal results for markers of kidney disease, mild decrease in GFR (60 to 89 mL/min/1.73 m^2), high blood pressure, and of other individuals at increased risk of chronic kidney disease. Risk factors for chronic kidney disease are discussed in Guideline 3.

Decreased GFR without kidney damage (R, O). Individuals with GFR 60 to 89 mL/min/1.73 m^2 without kidney damage are classified as "decreased GFR." Decreased GFR without recognized markers of kidney damage is very frequent in infants and older adults, and is usually considered to be "normal for age." The age-related decline in GFR in adults is accompanied by pathological findings of global glomerular sclerosis and cortical atrophy. The consequences of declining GFR with age have not been carefully studied. It is interesting to speculate whether the increasing incidence of end-stage renal disease in the elderly could be due, in part, to age-associated decline in GFR.

Other causes of chronically decreased GFR without kidney damage in adults include vegetarian diets, unilateral nephrectomy, extracellular fluid volume depletion, and systemic illnesses associated with reduced kidney perfusion, such as heart failure and cirrhosis. It is not certain whether individuals with chronically decreased GFR in the range of 60 to 89 mL/min/1.73 m^2 without kidney damage are at increased risk for adverse outcomes, such as toxicity from drugs excreted by the kidney or acute kidney failure. After much discussion and input from expert reviewers, the Work Group concluded that there is insufficient evidence to label individuals with GFR 60 to 89 mL/min/1.73 m^2, but without markers of kidney damage, as having chronic kidney disease. In clinical practice, it may be difficult to determine whether individuals with decreased GFR have chronic kidney disease. Recommendations for a clinical approach to elderly individuals with decreased GFR is given in Part 9.

High blood pressure in chronic kidney disease and in individuals with decreased GFR without kidney disease (R). High blood pressure is not included in the definition of chronic kidney disease or its stages. However, high blood pressure is a common cause and consequence of chronic kidney disease, and as reviewed later, patients with chronic kidney disease and high blood pressure are at higher risk of loss of kidney function and development of cardiovascular disease. High blood pressure is also common in older individuals without chronic kidney disease and is associated with accelerated GFR decline with age and more marked pathological abnormalities in the kidneys. Individuals with high blood pressure should be carefully evaluated for the presence of chronic kidney disease, especially those with decreased GFR.

Prevalence of chronic kidney disease and level of kidney function in the general population (S). The prevalence of chronic kidney disease, based on the definition above, was estimated using data from NHANES III and USRDS (Fig 7 and Tables 13 and 14). For the analysis of NHANES III data, GFR was estimated from serum creatinine concentration using a prediction equation derived from the Modification of Diet in Renal Disease (MDRD) Study,[17,18] elevated urine albumin-to-creatinine ratio was taken as a marker of chronic kidney disease, and high

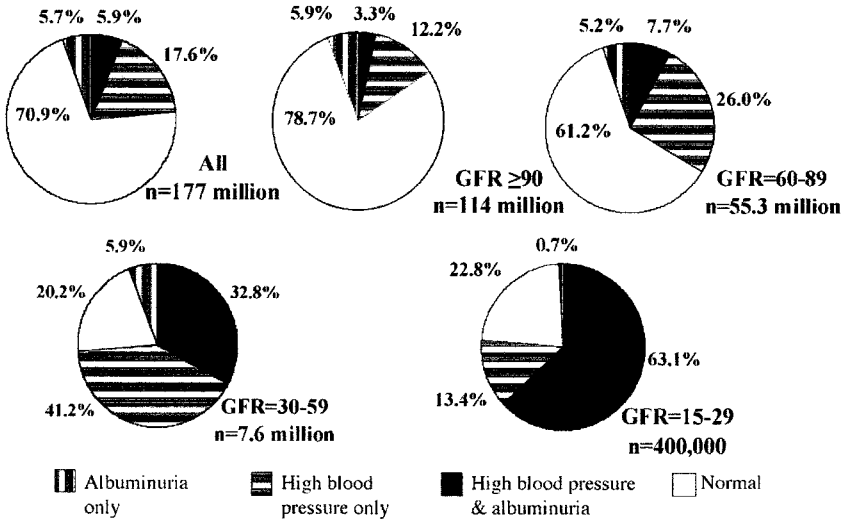


Fig 7. Prevalence of albuminuria and high blood pressure (%) in US adults age ≥20 years, NHANES III, 1988-1994. Based on one-time assessment of albuminuria, blood pressure, and estimated GFR.

blood pressure was defined as blood pressure ≥140/90 mm Hg or taking medications for high blood pressure. These parameters were ascertained on a single occasion. A subgroup of NHANES III participants underwent repeat measurement of albuminuria. Elevated albumin-to-creatinine excretion was persistent in 61% of the subjects with albuminuria (n = 163). Therefore, these estimates of prevalence should be considered as rough approximations of the true prevalence. The rationales for these assumptions and cut-off levels are discussed in more detail below.

Kidney Damage

Definition (O)

Kidney damage is defined as structural or functional abnormalities of the kidney, initially without decreased GFR, which over time can lead to decreased GFR. As described earlier, markers of kidney damage include abnormalities in the composition of the blood or urine or abnormalities in imaging tests. This section will emphasize proteinuria as a marker of kidney damage because it has been studied most thoroughly, including in NHANES III.

Proteinuria as a marker of kidney damage (R). Proteinuria is an early and sensitive marker of kidney damage in many types of chronic kidney disease. Albumin (molecular weight [MW] = 68,000 daltons) is the most abundant urine protein in most types of chronic kidney disease. Low molecular weight (LMW) globulins are the most abundant urine proteins in some types of chronic kidney disease. In this and later guidelines, the term proteinuria includes albumin-

Table 13. Prevalence of GFR Categories: NHANES III 1988–1994 US Adults Age ≥20

GFR (mL/min/1.73 m^2)	N*	Prevalence (95% CI)	Millions of Individuals (95% CI)
≥90	10,183	64% (63–66)	114 (106–122)
60–89	4,404	31% (30–33)	55.3 (50–61)
30–59	961	4.3 % (3.8–4.7)	7.6 (6.5–8.6)
15–29	52	0.2% (0.1–0.3)	0.4 (0.2–0.5)

GFR estimated from serum creatinine using MDRD Study equation based on age, gender, race and calibration for serum creatinine.

* N is based on number of individuals in each listed GFR range in NHANES III, 1988–1994. Prevalence and number of individuals estimated by extrapolation to population of US adults age ≥20 (N = 177 million). Based on one-time assessment of estimated GFR.

Table 14. Prevalence of Stages of Chronic Kidney Disease and Levels of Kidney Function in the US

	Stages of CKD		Levels of Kidney Function		
	N (1000's)*	(%)	GFR (mL/min/1.73 m^2)	N (1000's)*	(%)
1	10,500[a] 5,900	5.9[a] 3.3	≥90	114,000	64.3
2	7,100[a] 5,300	4.0[a] 3.0	60–89	55,300	31.2
3	7,600	4.3	30–59	7,600	4.3
4	400	0.2	15–29	400	0.2
5	300	0.2	<15 (or dialysis)	300	0.2

* Data for Stages 1–4 from NHANES III (1988–1994). Population of 177 million with age ≥20 years. Data for Stage 5 from USRDS (1998),[2] includes approximately 230,000 patients treated by dialysis, and assumes 70,000 additional patients not on dialysis. Percentages total >100% because NHANES III may not have included patients on dialysis. GFR estimated from serum creatinine using MDRD Study equation based on age, gender, race and calibration for serum creatinine.

[a] For Stages 1 and 2, kidney damage was assessed by spot albumin-to-creatinine ratio >17 mg/g (men) or >25 mg/g (women) on one occasion (larger prevalence estimate) or on two measurements (smaller prevalence estimate). Albuminuria was persistent in 54% of individuals with GFR ≥90 mL/min/1.73 m^2 (n = 102) and 73% of individuals with GFR 60–89 mL/min/1.73 m^2 (n = 44).

uria, increased urinary excretion of other specific proteins, and increased excretion of total urine protein. On the other hand, the term albuminuria has been used only when referring to increased urinary albumin excretion. Older laboratory methods, such as the urine dipstick or acid precipitation, detect most urine proteins. Microalbuminuria refers to excretion of small but abnormal amounts of albumin, which requires recently developed, more sensitive laboratory methods that are now widely available.

Normal protein excretion (S, R). Normal mean value for urine albumin excretion in adults is approximately 10 mg/d. Albumin excretion is increased by physiological variables, such as upright posture, exercise, pregnancy, and fever. Normal mean value for urine total protein is approximately 50 mg/d. Major constituents of normal urine protein are albumin, LMW proteins filtered from the blood, and proteins derived from the urinary tract.

In practice, it is difficult to collect a timed urine specimen. As described in Guideline 5, the urinary excretion rate for albumin and total protein can be estimated from the ratio of albumin or total protein to creatinine concentration in an untimed ("spot") urine specimen. Because protein excretion varies throughout the day, the normal ratio varies throughout the day. The ratio in a first morning specimen correlates most closely with overnight protein excretion rate, whereas the ratio in mid-morning specimens correlates most closely with 24-hour protein excretion rate. Creatinine excretion is higher in normal men than women; therefore, the values in the general population (Fig 8) and cut-off values for abnormalities in urine albumin-to-creatinine ratio are lower for men than women (Table 15).

Definition of proteinuria and albuminuria in adults (R). Table 15 shows definitions for proteinuria and albuminuria, including gender specific cut-off values for microalbuminuria and albuminuria. Cut-points for definition of abnormal urine total protein and albumin are set to maximize specificity (avoid false positives), thus, the upper limit of "normal" typically extends far above the normal mean value, resulting in low sensitivity (many false negatives).

Normal albumin excretion in children (C). Normal values for albumin excretion in children are not well established. Although increased urine albumin excretion reflects glomerular injury better than other urinary proteins in both adults and children, many pediatric nephrologists continue to monitor levels of total protein rather than

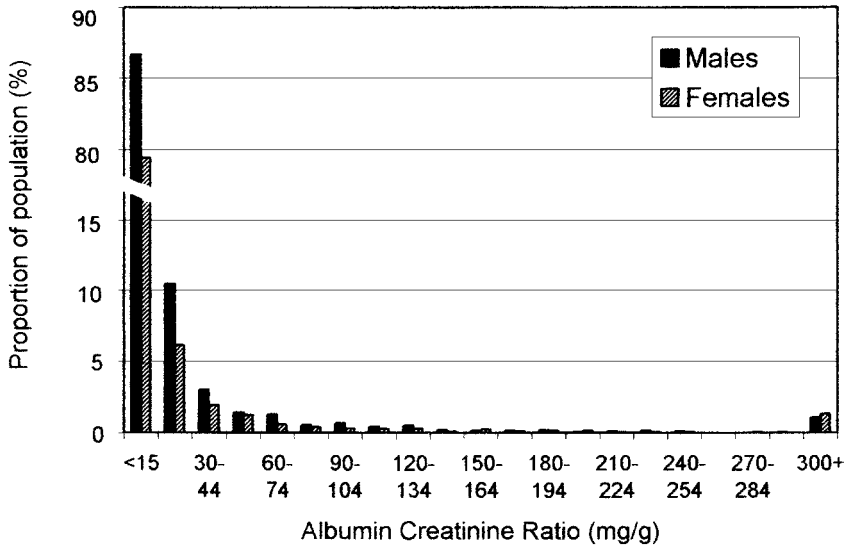


Fig 8. Distribution of albumin-to-creatinine ratio in US men and women, NHANES III (1988-1994), age ≥20. N = 14,836.

albumin in patients with proteinuria. Hence, reports of normal albumin rates in children are relatively few in number, and most have been published in the past 15 years. However, a literature search of articles describing albumin excretion in children revealed one study in 1970. This original paper[20] considered the best measurement of glomerular integrity to be albumin clearance factored by creatinine clearance. It concluded that the ratio of the concentration of albumin to creatinine in spot urine samples is the most accurate method for estimating albumin clearance and provides a better marker of glomerular permeability to albumin than the 24-hour albumin excretion rate. The results were expressed as mg albumin per mg creatinine, but subsequent papers have used a variety of methods to express albumin excretion, making comparisons between studies very difficult. Tables 16 and 17 give mean values and ranges for albumin excretion rate and albumin-to-creatinine ratio in children (neonates through age 20 years), and also emphasize some of the ways in which published reports have differed. Overall, the values appear similar to the values observed for adults.

Table 15. Definitions of Proteinuria and Albuminuria

	Urine Collection Method	Normal	Microalbuminuria	Albuminuria or Clinical Proteinuria
Total Protein	24-Hour Excretion (varies with method)	<300 mg/day	NA	>300 mg/day
	Spot Urine Dipstick	<30 mg/dL	NA	>30 mg/dL
	Spot Urine Protein-to-Creatinine Ratio (varies with method)	<200 mg/g	NA	>200 mg/g
Albumin	24-Hour Excretion	<30 mg/day	30–300 mg/day	>300 mg/day
	Spot Urine Albumin-Specific Dipstick	<3 mg/dL	>3 mg/dL	NA
	Spot Urine Albumin-to-Creatinine Ratio (varies by gender[a])	<17 mg/g (men) <25 mg/g (women)	17–250 mg/g (men) 25–355 mg/g (women)	>250 mg/g (men) >355 mg/g (women)

[a] Gender-specific cut-off values are from a single study.[19] Use of the same cut-off value for men and women leads to higher values of prevalence for women than men. Current recommendations from the American Diabetes Association define cut-off values for spot urine albumin-to-creatinine ratio for microalbuminuria and albuminuria as 30 and 300 mg/g, respectively, without regard to gender.[8]

Table 16. Albumin Excretion Rate: Normal Range in Children

Author, Year	No. of Subjects*	Applic-ability**	Urine Collection Method	Albumin Excretion Rate (mg/24 hr) Mean	Albumin Excretion Rate (mg/24 hr) Range	Albumin Excretion Rate (μg/min) Mean	Albumin Excretion Rate (μg/min) Range	Quality
Davies,[21] 1984	183 boys	↑↑	Split 24 hr	6.6[a] (Day: 8.2[a] Night: 4.0[a])	ND	4.6[a] (Day: 5.6[a] Night: 2.8[a])	ND	●
	191 girls			8.3[a] (Day: 11.1[a] Night: 4.3[a])		5.8[a] (Day: 7.7[a] Night: 3.0[a])		
Bangstad,[22] 1993	76: <13 y	↑↑↑	Overnight	5.3	0.3–34	3.7	0.2–23	○
	67: ≥13 y			8.4	1.6–50	5.8	1.1–35	
Cowell,[23] 1986	120	↑↑↑	24 hr	6.0	1–38	4.2	0.7–26.4	○
Salardi,[24] 1990	71	↑↑↑	24 hr	2.55	0.3–17.3	1.8	0.2–17.0	○
Marshall,[25] 1986	64	↑↑↑	Overnight	3.5[c]	0.6–13	2.4[c]	0.4–9.0	○
Ellis,[26] 1977	50	↑↑↑	24 hr	5.5	0–13.3	3.8	0–9.2	○
Mathiesen,[27] 1986	36	↑↑↑	Overnight	ND	1.5–20 (<15 in 97%)	ND	1–14 (<10 in 97%)	○
Brøchner-Mortensen,[28] 1979	28	↑↑↑	3 hr (supine)	ND	ND	8.3[b]	≈2–32[a,b]	○
Mortensen,[29] 1990	47 boys 4–12 y	↑↑	Overnight	1.9	ND	1.3	ND	○
	58 boys 13–19 y			3.9		2.7		
	30 girls 4–12 y			2.0		1.4		
	74 girls 13–19 y			3.3		2.3		
Dahlquist,[30] 1987	21	↑↑	24 hr	ND	ND	6	2–18.5	○
Erman,[31] 1990	32	↑	8 hr, overnight	5.7	1.8–16.5	3.9	1.3–11.5	○
Holl,[32] 1999	94	↑↑	Overnight	ND	0.3–17.3[a]	ND	0.2–12[a]	○
Huttunen,[33] 1981	68	↑↑	Short timed	7.0[c,d]	0.4–193[c]	4.9[c,d]	0.3–134[d]	○
Chiumello,[34] 1989	42	↑↑	Overnight	ND	ND	<10	ND	○
Laborde,[35] 1990	16	↑↑	3 hr	3.6	0.9–17.6	2.5	0.6–12.2	○
Mullis,[36] 1988	16	↑↑	12 hr overnight	3.5[a] 5.2[a]	0–6.6[a] 0–9.5[a]	2.4[a] 3.6[a]	0–4.6[a] 0–5.7[a]	○

* In all studies, each subject had one urine measurement.

** For this table, the generalizability scale was adjusted to reflect the broader target population (all healthy boys and girls) as follows:

↑↑↑ Sample is representative of a wide spectrum of healthy children, including both sexes and a range of ages.

↑↑ Sample is representative of a relevant subgroup of healthy children, such as a narrow range of ages, a homogenous ethnicity, or a single sex.

↑ Sample is representative of a narrow subgroup of healthy children not well generalizable to all healthy children (e.g., boys of a limited age range).

[a] per 1.73 m^2 BSA
[b] Estimate from graph
[c] Median
[d] Per m^2 body surface area

Abbreviations: hr, hour; y, year

Prevalence of proteinuria in adults (S). Table 18 shows the prevalence of albuminuria estimated from the albumin-to-creatinine ratio in a single spot urine collection in 14,836 adults studied in NHANES III. Based on these results, it is estimated that approximately 20.2 million adults (11.7%) have abnormal urine albumin excretion.

Albuminuria was persistent on repeat evaluation

Table 17. Urine Albumin-to-Creatinine Ratio: Normal Range in Children

Author, Year	No. of Subjects*	Applicability**	Urine Collection Method	Albumin/Creatinine Ratio (mg/g) Mean	Albumin/Creatinine Ratio (mg/g) Range	Quality
Davies,[21] 1984	183 boys 191 girls	🧍🧍	Split 24 hr	6.1 8.9	1.7–21.8[a] 2.0–39.9	●
Elises,[37] 1988	377	🧍🧍🧍	AM spot	6.6	0.6–26.5	○
Ginevri,[38] 1993	368	🧍🧍🧍	2nd AM spot	21.5	105.0[b]	○
Houser,[39] 1986	108: 2 mo–4 y 171: 4–62 y	🧍🧍🧍	Random spot	17.1 12.9	4.2–62 3.0–37.8	○
Hjorth,[40] 2000	14: < 1 mo 35: 1–12 mo 66: 1–5 y 61: 6–10 y 71: 11–15 y	🧍🧍🧍	Random spot	ND	155[c] 33.6[c] 29.2[c] 23.9[c] 18.6[c]	○
Schultz,[41] 1999	208[d]	🧍🧍🧍	Overnight	8.1	1.8–38.2	○
Bangstad,[22] 1993	76: < 13 y 67: ≥ 13 y	🧍🧍🧍	Overnight	8.8 9.7	1.7–46 1.7–119	○
Gibb,[42] 1989	73[e]	🧍🧍🧍	AM spot	2.9	0.4–18.6	○
Marshall,[25] 1986	64	🧍🧍🧍	Overnight	8.4[f]	3.8–32.7[g]	○
Barratt,[20] 1970	58	🧍🧍🧍	AM spot	ND	≈ 10–300[h]	○
Schultz,[43] 2000	96 boys 113 girls	🧍🧍	AM spot	7.1 8.0	3.5–23.9 3.5–30.0	○
Yap,[44] 1991	28: neonate 29: 1–3 mo 28: 4–6 mo 26: 7–23 mo 28: 2–4 y	🧍🧍	Random/ AM spot	46.3 44.3 35.9 15.6 11.8	4.8–132.2[g] ND ND ND 4.9–29.1[g]	○
Jefferson,[45] 1985	21	🧍🧍	Random spot	11	4–32	○
Cesarini,[46] 1996	17	🧍🧍	Pre- and post-exercise spot	Pre-exercise: 14.8 Post-exercise: 6.6	ND	○
Erman,[31] 1990	10: 5–10 y 22: 10–20 y	🧍	8 hr overnight	11.5 6.0	4–28 2.2–11.6	○
Mullis,[36] 1988	16	🧍🧍	AM spot	8.8	0.3–20	◯

* Except where noted, each subject had one urine measurement.
** See footnote to Table 15 for explanation of applicability scale for this table.

[a] Geometric mean ×/÷ (tolerance factor)^2
[b] 97th percentile
[c] 90th percentile
[d] 602 urine measurements
[e] 171 urine measurements
[f] Median
[g] 95% confidence interval
[h] Estimated from graph

Abbreviations: hr, hour; AM, morning; y, year; mo, month

in only 61% of individuals; hence, these prevalence estimates based on a single spot urine are likely overestimates, especially for microalbuminuria. (Appendix 2 discusses the reproducibility of data on albuminuria and microalbuminuria.)

Among adults, the prevalence of albuminuria varies by age (Table 19) and presence (Table 20) or absence (Table 21) of diabetes. The prevalence is approximately 30% in adults with age ≥70 years: 26.6% with microalbuminuria and 3.7% with albuminuria. At all ages, the prevalence is higher among individuals with diabetes.

Table 18. Prevalence of Albuminuria in Adults: NHANES III

Albumin/ Creatinine Ratio	N	US Adult Prevalence (SE)
Normal	12,478	88.4% (0.4)
Microalbuminuria	2,040	10.6% (0.4)
Albuminuria	318	1.1% (0.1)
Totals	14,836	100%

This table shows prevalence of albuminuria detected in a single spot urine test.

Abbreviation: SE, standard error

Among individuals with a history of diabetes, the prevalence of microalbuminuria and albuminuria is 43.2% and 8.4%, respectively, at age ≥70 years. Among individuals without a history of diabetes the prevalence of microalbuminuria and albuminuria is 24.2% and 3.0%, respectively, at age ≥70 years.

Prevalence of proteinuria in children (C). Prevalence of proteinuria is lower in children. A compilation of studies shows that 1% to 10% of children may have proteinuria on initial screening using the urine dipstick, but that <1% have persistent proteinuria, as defined by positive results on repeated testing (Table 22). Similarly, the prevalence of increased urine albumin excretion on initial screening varies from 1% to 10% (Table 23).

Prevalence of Stage 1 and Stage 2 chronic kidney disease (S). The proportion of adults with GFR ≥90 and 60–89 mL/min/1.73 m^2 with albuminuria is shown in Fig 7. Among US adults with a GFR ≥90 mL/min/1.73 m^2, 9.2% had an

Table 19. Prevalence of Albuminuria by Age Group: NHANES III

Albumin/ Creatinine Ratio	Prevalence (SE) by Age Group (Years)			
	20–39	40–59	60–69	≥70
Normal	93.1% (0.6)	89.9% (0.7)	81.8% (1.4)	69.8% (1.3)
Microalbuminuria	6.6% (0.6)	9.1% (0.6)	16.2% (1.2)	26.6% (1.2)
Albuminuria	0.4% (0.1)	1.0% (0.2)	2.0% (0.4)	3.7% (0.5)

This table shows prevalence of albuminuria detected in a single spot urine test.

Abbreviation: SE, standard error

Table 20. Prevalence of Albuminuria Among Individuals with a History of Diabetes: NHANES III

Albumin/ Creatinine Ratio	Prevalence (SE) by Age Group (Years)			
	20–39	40–59	60–69	≥70
Normal	66.9% (10.5)	64.1% (3.8)	54.3% (4.2)	48.4% (3.6)
Microalbuminuria	28.0% (10.0)	30.0% (4.0)	39.1% (4.3)	43.2% (3.5)
Albuminuria	5.1% (3.0)	6.0% (2.0)	6.6% (1.9)	8.4% (2.3)

This table shows prevalence of albuminuria detected in a single spot urine test.

Abbreviation: SE, standard error

Table 21. Prevalence of Albuminuria Among Individuals without a History of Diabetes: NHANES III

Albumin/ Creatinine Ratio	Prevalence (SE) by Age Group (Years)			
	20–39	40–59	60–69	≥70
Normal	93.3% (0.6)	91.4% (0.7)	85.4% (1.5)	72.8% (1.4)
Microalbuminuria	6.3% (0.6)	7.9% (0.6)	13.2% (1.3)	24.2% (1.3)
Albuminuria	0.3% (0.1)	0.7% (0.2)	1.4% (0.3)	3.0% (0.5)

This table shows prevalence of albuminuria detected in a single spot urine test.

Abbreviation: SE, standard error

Table 22. Proteinuria: Prevalence in Nondiabetic Children

Author, Year	No. of Subjects	Applicability*	Method of Urine Collection	Proteinuria Definition	Prevalence of Proteinuria (%) 1 Test	2 Tests	≥3 Tests	Quality
Murakami,[47] 1991	7,349,928	♦♦♦	AM	≥15 mg/dL	1.2	0.17		●
Lin,[48] 2000	4,311,516	♦♦♦	AM	≥30 mg/dL	3.11	0.35		●
Vehaskari,[49] 1982	8,954	♦♦♦	Random/AM[a]	≥1+	3.5[b]	2.5	0.1	●
Wagner,[50] 1968	4,897	♦♦♦	Random	≥1+ ≥1+	5.4 1.7	1.1		●
Randolph,[51] 1967	3,628	♦♦♦	Random/AM	1+ 2+	6.3 2.1		0[c] 0[c]	●
Johnson,[52] 1974	3,626	♦♦	Random	≥1+	1.5	0.8	0.6	●
Wolman,[53] 1945	11,822	♦	Random/AM	30 mg/dL	2.6		0.07	●
Kunin,[54] 1964	3,429	♦♦♦	ND	ND	1.4–2.9	0.3	0.1	○
Meadow,[55] 1969	2,125	♦♦♦	Mostly AM	≥1+	"Often"	0.8	0.2	○
Mitchell,[56] 1990	732	♦♦♦	Random	≥1+	4			○
Hamill,[57] 1911	124	♦♦♦	Random	Trace	7			○
Dodge,[58] 1976	12,252	♦♦	Random	≥0 mg/dL	11.8	6.3	2.1–3.2	○
Hogg,[59] 1998	9,355	♦♦	AM	≥1+	0.25	0.08		○
Silverberg,[60] 1974	27,722	♦♦	Random	≥2 +/≥1+		0.5	0.16	○
Silverberg,[61] 1973	23,427	♦♦	Random	≥2 +/≥1+		1.6	0.5	○
Bashford,[62] 1926	1,000	♦	Random/AM[d]	ND[e]	5.8	0.4		○

* See footnote Table 15 for explanation of applicability scale for this table.

[a] Both random and AM studies were done in all subjects.
[b] Proteinuria in at least 1 of 4 specimens in 10.7%; 3.5% if only 1 specimen had been tested.
[c] 4 or more tests
[d] First test was random; "final" test was AM if random was positive.
[e] Article refers to trace as positive protein test in other subjects described in the same paper.

Abbreviation: AM, morning

elevated albumin-to-creatinine ratio (including 3.3% without hypertension and 5.9% with hypertension). As shown in Table 14, this group corresponds to approximately 5.9% of all US adults, or 10.5 million people in the years 1988 to 1994. On repeat examination, 54% (n = 102) of a subsample with albuminuria had a persistently positive result. Therefore, the prevalence of *persistent* albuminuria would be 3.3% of US adults with GFR ≥90 mL/min/1.73 m^2, or 5.9 million. This is the estimated prevalence of Stage 1 chronic kidney disease.

Among adults with GFR 60 to 89 mL/min/1.73 m^2, the prevalence of albuminuria was 12.9%, corresponding to 4.0% of all US adults, or 7.1 million people. On repeat examination, 73% of a subsample with albuminuria (n = 44) had a persistently positive test. Therefore, the prevalence of persistent albuminuria would be 3.0% of US adults with GFR 60-84 mL/min/1.73 m^2, or 5.3 million. This is the estimated prevalence of Stage 2 chronic kidney disease.

Note that persistent albuminuria is not the only marker of kidney damage. NHANES III

Table 23. Albuminuria: Prevalence in Nondiabetic Children

Author, Year	No. of Subjects	Applic-ability*	Method of Urine Collection	Proteinuria Definition	Prevalence of Albuminuria (%) 1 Test	Quality
Mueller,[63] 1999	4,088	†††	Random	$U_{Alb/Cr}$ > 30 mg/g $U_{Alb/Cr}$ > 200 mg/g	12 2.4	O
Pugia,[64] 1999	6,187	†††	AM	$U_{Alb/Cr}$ > 30 mg/g $U_{Alb/Cr}$ > 150 mg/g	2.6 0	O
Hoy,[65] 1998	405	††	Random	$U_{Alb/Cr}$ > 12 mg/g $U_{Alb/Cr}$ > 30 mg/g	24 7	O
Bernard,[66] 1997 (Study 1)	220	††	ND	UAC > 200 mg/L	6	O
Bernard,[66] 1997 (Study 2)	150	††	ND	UAC > 23.6 mg/L UAC > 200 mg/L	11.3 1.3	O

* See footnote Table 15 for explanation of applicability scale for this table.

Abbreviations: $U_{Alb/Cr}$, urinary albumin-to-creatinine ratio; AM, morning; UAC, urine albumin concentration

did not ascertain other markers of kidney damage, such as abnormalities of the urine sediment and abnormal imaging tests; thus, any estimate based on NHANES III data is likely to underestimate the true prevalence of chronic kidney damage.

Decreased GFR

GFR as an index of kidney function (R). The level of GFR is accepted as the best measure of overall kidney function in health and disease. In principle, the level of GFR is the product of the number of nephrons and the single nephron GFR. Therefore, GFR can be affected by chronic kidney disease, which reduces the number of nephrons, or by hemodynamic factors that affect single nephron GFR. In chronic kidney disease, as in normal individuals, GFR is modulated by hemodynamic factors.

Normal range and variability of GFR (S, R). The normal level of GFR varies according to age, gender, and body size. It is conventional to adjust GFR to "standard" body size (surface area of 1.73 m^2). Among normal adults, the inter-individual coefficient of variation (standard deviation divided by the mean) of GFR (adjusted for body surface area) within the normal population is approximately 15% to 20%.[67] The normal mean (standard devation) GFR in young adults is approximately 120 to 130 (20 to 25) mL/min/1.73 m^2. Children reach adult values for mean GFR by approximately age 2 years (Table 24).[68,69]

Figure 9 and Table 25 show the range of GFR in adults according to age, derived from normal men using inulin clearance.[72] Normal values in women are assumed to be 8% lower at all ages.[67,73] After approximately age 20 to 30 years, the normal mean value for GFR declines with age in both men and women, with a mean decrease of approximately 1 mL/min/1.73 m^2 per year. Thus, by age 70, the normal mean value is approximately 70 mL/min/1.73 m^2. At all ages, the range of normal GFR is wide.

Data from NHANES III are shown in Figs 9 and 10; these include men and women in the general population, including those with chronic

Table 24. Normal GFR in Children and Young Adults

Age (Sex)	Mean GFR ± SD (mL/min/1.73 m^2)
1 week (males and females)	40.6 ±14.8
2–8 weeks (males and females)	65.8 ±24.8
>8 weeks (males and females)	95.7 ±21.7
2–12 years (males and females)	133.0 ±27.0
13–21 years (males)	140.0 ±30.0
13–21 years (females)	126.0 ±22.0

*Data based on three studies.[69-71]

Abbreviation: SD, standard deviation

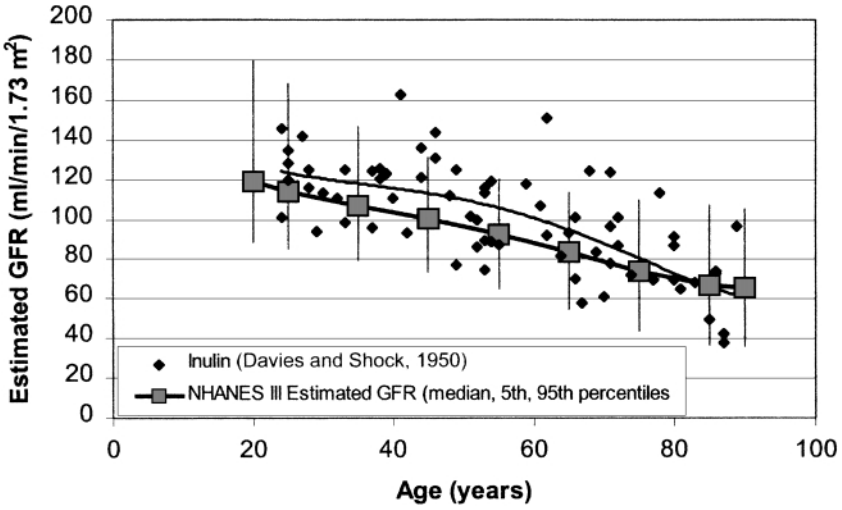


Fig 9. GFR versus age. Estimated GFR percentiles for the US population using NHANES III serum creatinine, age, sex, and race data (see Part 10, Appendix 2) by age compared to a regression of inulin clearance measurement of GFR on age among 70 healthy male participants. (Data abstracted from Davies and Shock.[72])

kidney disease. In part, the inclusion of women and individuals with chronic kidney disease may account for the slightly lower mean values observed in the NHANES III compared to the data from normal men in Fig 9.

Factors other than age also affect GFR. As shown in Table 24, GFR is slightly lower in young women than in young men. This difference appears to persist at older ages. Pregnancy has a major effect on GFR, with GFR reaching values of 140% of normal during the end of the second trimester.

Additional factors that may affect GFR to a lesser degree include: transient increases in GFR after a high protein meal, a lower GFR in individuals' following a habitually low protein diet, and antihypertensive agents (effect on GFR varies by class of agent), especially in patients with chronic kidney disease.

Definition of decreased GFR (R, O). The Work Group defined decreased GFR as <90 mL/min/1.73 m^2. The interpretation of decreased GFR varies depending on age, duration, and the presence or absence of markers of kidney damage.

The lower limit of normal GFR varies with age. For example, as shown in Table 25, GFR <90 mL/min/1.73 m^2 would be abnormal in a young adult. On the other hand, a GFR of 60–89 mL/min/1.73 m^2 could be normal from approximately 8 weeks to 1 year of age and in older individuals. It is possible that GFR 30 to 59

Table 25. Normal GFR in Adults Extrapolated from Data in 72 Healthy Men

	Men* GFR (mL/min/1.73 m^2)				Women** GFR (mL/min/1.73 m^2)			
Age (y)	Mean	SD	–2 SD	+ 2SD	Mean	SD	–SD	+2SD
20–29	128	26	77	179	118	24	71	165
30–39	116	23	70	162	107	21	64	149
40–49	105	21	63	147	97	19	58	135
50–59	93	19	56	130	86	17	51	120
60–69	81	16	49	113	75	15	45	104
70–79	70	14	42	98	64	13	39	90
80–89	58	12	35	81	53	11	32	75

* Values for GFR in normal men by age.[72] Mean GFR for age categories in men based on linear regression.[74] Regression equation is GFR = –1.163 (Age) + 157.0. GFR range assumes a standard deviation of GFR divided by the mean (SD/M, also known as the coefficient of variation) of 20%.

** Assumes that values for women are 8% lower at all ages.[67,73]

Abbreviations: y, years; SD, standard deviation(s)

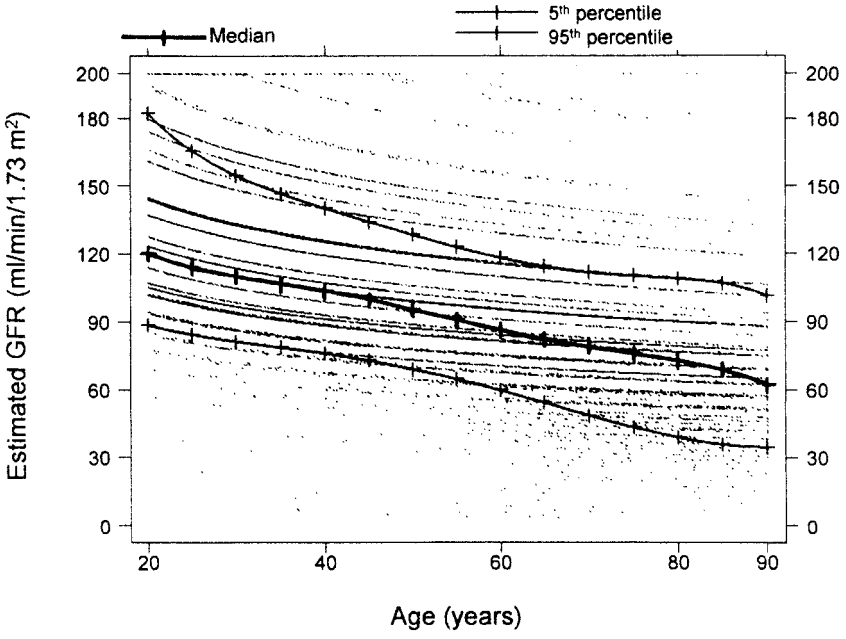


Fig 10. Percentiles of estimated GFR regressed on age (NHANES III). GFR estimated from serum creatinine using MDRD Study equation based on age, gender, and race (see Part 10, Appendix 3). Age ≥20, N = 15,600.

mL/min/1.73 m^2 could also be normal in individuals at the extremes of age, in vegetarians, after unilateral nephrectomy or in an older individual. It is likely that a GFR <30 mL/min/1.73 m^2 is abnormal at all ages other than neonates. For these reasons, the Work Group based the definition of chronic kidney disease solely on the level of GFR only in individuals with GFR <60 mL/min/1.73 m^2, whereas individuals with GFR 60 to 89 mL/min/1.73 m^2 were considered to have chronic kidney disease only if they also had a marker of kidney damage (see Table 12, p. S47).

Decreased GFR may be acute or chronic. An acute decrease in GFR does not necessarily indicate the presence of kidney damage. For example, it is well known that a brief period of mildly decreased blood flow to the kidneys or transient partial obstruction of the urinary tract may cause decreased GFR without kidney damage. However, a sustained decrease in blood flow or prolonged obstruction is often associated with kidney damage. Chronically decreased GFR is more often associated with kidney damage. The Work Group arbitrarily chose a cut-off value of greater than 3 months for the definition of chronic kidney disease.

As discussed earlier, individuals with decreased GFR should be evaluated for markers of kidney damage to determine whether they have chronic kidney disease and to determine the cause of reduced kidney function. Even if there is no evidence of kidney damage, individuals with chronically decreased GFR may be at increased risk for adverse outcomes (for example, toxicity from drugs excreted by the kidney, and acute kidney failure in a wide variety of circumstances).

Table 26. Prevalence of GFR Categories in Adults

GFR	Age Group (y)			
mL/min/1.73 m^2	20–39	40–59	60–69	≥70
≥90	86.0%	55.7%	38.5%	25.5%
60–89	13.7%	42.7%	53.8%	48.5%
30–59	—[a]	1.8%	7.1%	24.6%
15–29	—[a]	—[a]	—[a]	1.3%
N (millions):	82	55	20	20

GFR estimated from serum creatinine using MDRD Study equation based on age, gender, race and calibration for serum creatinine. Data from NHANES III (1988–1994). N = 15,000. Based on one-time assessment of estimated GFR.

[a] Fewer than 20 cases; data not considered reliable.

Association of level of GFR with complications (S, R, C, O). Decreased GFR is associated with a wide range of complications in other organ systems, manifested by high blood pressure, laboratory abnormalities, and symptoms. Severity of complications worsens as level of GFR declines (Part 6, Guidelines 7 through 12). The Work Group defined categories of decreased GFR as mild (Stage 2, 60 to 89 mL/min/1.73 m^2), moderate (Stage 3, 30 to 59 mL/min/1.73 m^2), and severe (Stage 4, 15 to 29 mL/min/1.73 m^2). Although these definitions are arbitrary, evidence compiled in later guidelines supports these broad categories and cut-off levels.

Prevalence of decreased GFR by age (S). The prevalence of decreased GFR is higher in the elderly (Table 26). Approximately 14.9 million individuals ≥70 years (74.5%) of age have decreased GFR. As already stated, not all individuals with decreased GFR have kidney disease. The prevalence of persistent albuminuria by GFR level and age group have not been determined, preventing an accurate estimate of the prevalence of chronic kidney disease among the elderly.

The prevalence of decreased GFR is lower in children. The Schwartz formula was used to estimate GFR in children aged 12 to 19 years in the NHANES III database. The lowest 1% of children had GFR below approximately 100 mL/min/1.73 m^2. Reliable estimates of prevalence of categories of decreased GFR (mild, moderate, or severe) in children are not available from NHANES III.

Kidney Failure

Definition of kidney failure (R, O). Kidney failure is defined as either (1) a level of GFR to <15 mL/min/1.73 m^2, which is accompanied in most cases by signs and symptoms of uremia, or (2) a need for initiation of kidney replacement therapy (dialysis or transplantation) for treatment for complications of decreased GFR, which would otherwise increase the risk of mortality and morbidity. Some patients may need dialysis or transplantation at GFR ≥15 mL/min/1.73 m^2 because of symptoms of uremia. The Work Group acknowledges that the level of GFR selected for this definition is arbitrary and may need to be modified based on advances in kidney replacement therapy.

End-stage renal disease (R). End-stage renal disease (ESRD) is an administrative term in the United States, based on the conditions for payment for health care by the Medicare ESRD Program, specifically the level of GFR and the occurrence of signs and symptoms of kidney failure necessitating initiation of treatment by replacement therapy. ESRD includes patients treated by dialysis or transplantation, irrespective of the level of GFR.

The K/DOQI definition of kidney failure differs in two important ways from the definition of ESRD. First, not all individuals with GFR <15 mL/min/1.73 m^2 or with signs and symptoms of kidney failure are treated by dialysis and transplantation. Nonetheless, such individuals should be considered as having kidney failure. Second, among treated patients, kidney transplant recipients have a higher mean level of GFR (usually 30 to 60 mL/min/1.73 m^2) and better average health outcomes than dialysis patients. Kidney transplant recipients should not be included in the definition of kidney failure, unless they have GFR <15 mL/min/1.73 m^2 or have resumed dialysis.

The Work Group anticipated that most kidney transplant recipients would be considered to have chronic kidney disease according to the proposed classification. First, GFR is lower in patients with a solitary kidney and is even lower in kidney transplant recipients because of toxicity from immunosuppressive agents used to prevent and treat rejection, such as cyclosporine and tacrolimus. Second, biopsy studies demonstrate pathologic damage due to acute and chronic rejection in virtually all transplant recipients, even if serum creatinine is normal. However, because markers of kidney damage are not sensitive to tubulointerstitial or vascular damage, it is likely that some kidney transplant patients will have GFR ≥60 mL/min/1.73 m^2 without markers of kidney damage. Such patients would not be classified as having chronic kidney disease by the proposed classification. The Work Group would consider them to be at increased risk of chronic kidney disease. Thus, all patients with a kidney transplant would be considered either to

have chronic kidney disease or to be at increased risk of chronic kidney disease.

Relationship of GFR to other measures of kidney function in kidney failure (S). A number of measurements, including GFR, have been used to quantify the level of kidney function among patients with kidney failure. The K/DOQI Nutrition in Chronic Renal Failure Guidelines[75] and Peritoneal Dialysis Adequacy Guidelines Update 2000[16] recommend the decision to initiate dialysis in adults be based on a combination of measurements of kidney function, as well as nutritional status. These guidelines are reproduced here:

Peritoneal Dialysis Adequacy Guideline 1: When to Initiate Dialysis—Kt/V_{urea} Criterion (Opinion)

"Unless certain conditions are met, patients should be advised to initiate some form of dialysis when the weekly renal Kt/V_{urea} (Krt/V_{urea}) falls below 2.0. The conditions that may indicate dialysis is not yet necessary even though the weekly Krt/V_{urea} is less than 2.0 are:

1. Stable or increased edema-free body weight. Supportive objective parameters for adequate nutrition include a lean body mass >63%, subjective global assessment score indicative of adequate nutrition, and a serum albumin concentration in excess of the lower limit for the lab, and stable or rising; and;

2. Nutritional indications for the initiation of renal replacement therapy are detailed in Guideline 27 of the K/DOQI Clinical Practice Guidelines on Nutrition in Chronic Renal Failure, part of which is reproduced as Guideline 2 of the PD Adequacy Guideline.

3. Complete absence of clinical signs or symptoms attributable to uremia.

A weekly Krt/V_{urea} of 2.0 approximates a kidney urea clearance of 7 mL/min and a kidney creatinine clearance that varies between 9 to 14 mL/min/1.73 m^2. Urea clearance should be normalized to total body water (V) and creatinine clearance should be expressed per 1.73 m^2 of body surface area. The GFR, which is estimated by the arithmetic mean of the urea and creatinine clearance, will be approximately 10.5 mL/min/1.73 m^2 when the Krt/V_{urea} is about 2.0."

Peritoneal Dialysis Adequacy Guideline 2 and Nutrition in Chronic Renal Failure Guideline 27: Indications for Renal Replacement Therapy (Opinion)

"In patients with chronic kidney failure (e.g., GFR <15–20 mL/min) who are not undergoing maintenance dialysis, if protein-energy malnutrition (PEM) develops or persists despite vigorous attempts to optimize protein and energy intake and there is no apparent cause for malnutrition other than low nutrient intake, initiation of maintenance dialysis or a renal transplant is recommended."

The CKD Work Group searched for studies of measures of kidney function, dietary intake, and nutritional status at the onset of kidney replacement therapy. The largest and most comprehensive study is the one reported in abstract by the MDRD Study Group.[76] This study included 88 patients who were referred to their physicians by the MDRD Study investigators for initiation of dialysis because of symptoms or findings of uremia prior to the end of the study. Prescribed protein intake during the study was 0.6 g/kg/d, either as food or from food and a mixture of essential amino acids and ketoacids. The median interval from final GFR to initiation of dialysis in the study group was 89 days. Because these patients were participating in a clinical trial, the mean level of kidney function and nutritional status may be higher than in patients beginning dialysis in the general population. Tables 27 and 28 show measures of kidney function and nutri-

Table 27. Description of MDRD Study Participants Who Developed Kidney Failure: Kidney Function

Measurement	Mean	SD	Range
Serum creatinine (mg/dL)	6.9	1.9	3.3–11.5
BUN (mg/dL)	62	18	28–118
Kt/V_{urea}	1.7	0.6	0.8–3.2
GFR (^{125}I-iothalamate clearance)*	9.1	3.0	4.1–18.2
GFR (MDRD Study equation)*	9.6	3.3	4.9–18.3
C_{Cr} (measured)*	10.8	4.5	3.9–25.7
C_{Cr} (Cockcroft-Gault equation)*	12.6	4.2	6.2–25.3
$(C_{Cr} + C_{urea})/2$*	8.4	3.1	3.3–18.8

Data from Levey, 1998.[76]

* Units for clearance measurements: mL/min/1.73 m^2

Abbreviation: SD, standard deviation

Table 28. Description of MDRD Study Participants Who Developed Kidney Failure: Dietary Intake and Nutritional Status

	Men		Women	
Measurement	Mean	SD	Mean	SD
Energy Intake (kcal/kg/d)	22.0	6.2	20.1	5.9
Protein Intake (g/kg/d)	0.61	0.19	0.59	0.20
Weight (kg)*	80.7	10.9	65.5	12.0
BSA (m^2)*	1.97	0.15	1.69	0.14
BMI (kg/m^2)	26.1	2.8	25.2	4.9
V_{urea} (L)*	43.5	4.4	31.3	3.1
Albumin (g/dL)	4.0	0.4	3.9	0.4
Transferrin (mg/dL)	241	39	240	38
Arm muscle area (cm^2)*	40	11	28	11
Body fat (%)*	25	5.4	32	7.1
Urine creatinine (mg/kg/d)*	15.1	3.2	13.1	3.3

Data from Levey, 1998.[76]

* $p < 0.01$ for comparison of men vs. women

Abbreviation: SD, standard deviation

Table 29. Comparison of Kidney Function Measurements in MDRD Study Participants Who Developed Kidney Failure

Measurement	Correlation (R^2)	Mean Δ*	Median Δ*
$1/S_{Cr}$	0.65	—	—
BUN	0.25	—	—
Kt/V_{urea}	0.51	—	—
GFR (MDRD Study Eq.)*	0.71	0.54	1.32
C_{Cr} (measured)*	0.72	1.74	1.57
C_{Cr} (Cockcroft-Gault Eq.)*	0.68	3.56	3.54
$(C_{Cr} + C_{urea})/2$*	0.72	–0.71	0.96

Units for clearance measurements: mL/min/1.73 m^2; Correlations with measured GFR (^{125}I-iothalamate clearance). Data from Levey, 1998.[76]

* Δ is the difference between measured and estimated GFR.

tional status in these patients with kidney failure just prior to initiation of dialysis. The comparison of measured GFR to other kidney function measurements is shown in Table 29. These data show that estimated GFR provides only a rough approximation of other measures of kidney function. This provides additional justification for performing other measures of kidney function to assess the need for kidney replacement therapy, as recommended in the K/DOQI Peritoneal Dialysis Guidelines.[16] It was the opinion of the Work Group that these measurements should be obtained in patients with estimated GFR <15 mL/min/1.73 m^2, since, as described below, few patients begin dialysis at higher levels of GFR.

Level of GFR at initiation of replacement therapy (S, C). Clinicians initiate replacement therapy based on the level of kidney function, presence of signs and symptoms of uremia, the availability of therapy, and patient or surrogate preferences. There is variability among individuals in the relationship of level of kidney function to signs and symptoms of uremia. Notably, there is variability within and among health care systems in the availability of therapy.

The level of GFR at the beginning of dialysis has been estimated in more than 90,000 patients in the United States between 1995 and 1997, using data collected on the Medical Evidence Report (HCFA Form 2728) and the MDRD Study prediction equation (Fig 11).[77] The mean (SD) level of serum creatinine was 8.5 (3.8) mg/dL. The mean (SD) level of GFR at initiation of treatment was 7.1 (3.1) mL/min/1.73 m^2. The proportion of patients initiating dialysis with a predicted GFR of 10 to 15, 5 to 10, and <5 mL/min/1.73 m^2 was 11%, 63%, and 24%, respectively; 98% of patients began dialysis with predicted GFR ≤15 mL/min/1.73 m^2.

Tables 30, 31, and 32 summarize other studies

Table 30. GFR at Start of Hemodialysis

Author, Year	No. of Subjects	Applicability	Mean Kidney Function Measure	Quality
Arora,[78] 1999	135	🧍🧍	GFR = 7.8 mL/min/1.73 m^2	O

Table 31. Creatinine Clearance at Start of Hemodialysis

Author, Year	No. of Subjects	Applicability	Mean Kidney Function Measure	Quality
Jungers,[79] 1993	218	🧍🧍🧍	C_{Cr} = 6.9 mL/min	O
Sesso,[80] 1997	113	🧍🧍🧍	C_{Cr} = 6.1 mL/min	O

Table 32. Serum Creatinine at Start of Hemodialysis

Author, Year	No. of Subjects	Applicability	Mean Kidney Function Measure	Quality
Fink,[81] 1999	5,388	♀♀♀	S_{Cr} = 9.16 mg/dL	O
Jungers,[79] 1993	218	♀♀♀	S_{Cr} = 11.1 mg/dL	O
Sesso,[80] 1997	113	♀♀♀	S_{Cr} = 9.9 mg/dL	O
Iofel,[82] 1998	220	♀♀	S_{Cr} = 10.9 mg/dL	O
Ifudu, [83] 1996	139	♀♀	S_{Cr} = 12.6 ± 5.2 mg/dL	O

of the level of kidney function at initiation of dialysis. Overall, the results of these studies are consistent with the data from the MDRD Study (Table 27) and the large study shown in Fig 11.

Factors associated with level of kidney function at initiation of dialysis (R). Timing of initiation of replacement therapy varies by modality, clinical characteristics, and sociodemographic characteristics. Patients who receive a pre-emptive transplant or who are started on peritoneal dialysis begin replacement therapy at higher mean levels of GFR than patients starting hemodialysis. Dialysis is initiated at higher mean levels of GFR among patients who are older, or who have diabetes, cardiovascular disease, and other comorbid conditions.

Prevalence of kidney failure (S). The incidence and the prevalence of reported ESRD have doubled in the past 10 years in the United States (Fig 2). Data from the 2000 Annual Data Report of the USRDS documents the incidence of ESRD in 1998 of more than 85,000, or 308 per million individuals per year at risk. The point prevalence of ESRD on December 31, 1998 was more than 320,000, or 1,160 per million population, of whom 72% were treated by dialysis (230,000 patients, or 835 per million population) and 28% had functioning kidney transplants (90,000 patients, or 325 per 100,000). The number of individuals with GFR $<$15 mL/min/1.73 m^2 not on dialysis has not been estimated reliably.

The prevalence of kidney failure treated by dialysis varies by age. On December 31, 1998, there were approximately 75,000 adults over 70 years of age (97 per million) with kidney failure treated by dialysis, compared to approximately 1,800 children (2.1 per million).

LIMITATIONS

There are a number of limitations to the proposed definition and classification of chronic kidney disease. The Work Group believes that these limitations should be identified, but does not think that they invalidate the proposal. Instead, these limitations should serve to stimulate

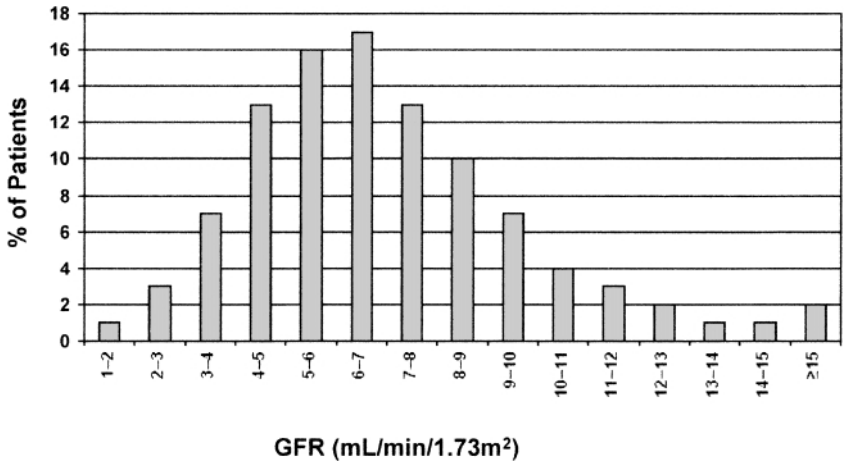


Fig 11. Level of GFR at initiation of replacement therapy (USRDS). Data from Obrador et al.[77]

further research to refine the definition and classification.

First, as described later in Guideline 6, the known markers of kidney damage are not sensitive, especially for tubulointersitial and vascular disease and for diseases in the kidney transplant. Thus, the prevalence of chronic kidney disease may be substantially higher than the Work Group has estimated, and recognition of patients with chronic kidney disease may be limited due to misclassification. Second, as described in Guideline 4, the MDRD Study prediction equation has not been validated extensively at levels of GFR $\geq$90 mL/min/1.73 m^2; thus, it is difficult to estimate the level of GFR above 90 mL/min/1.73 m^2, and it may be difficult to distinguish between Stage 1 and Stage 2 of chronic kidney disease. Third, as described earlier, the cause of age-related decline in GFR and high blood pressure is not known. Possibly, it may be due to chronic kidney disease. If so, it would be more appropriate to classify individuals with GFR 60 to 89 mL/min/1.73 m^2 without apparent markers of kidney damage as having chronic kidney disease rather than "decreased GFR." Fourth, the GFR cut-off values for Stages 3 to 5 have been selected based on limited data with respect to the relationship between complications and level of GFR. Further studies may permit refinement of these cut-off values. Fifth, the association of level of GFR with complications of chronic kidney disease does not prove a causal relationship between the two. Nonetheless, in many cases there is adequate evidence of a causal relationship, and even if there is not, the associations accurately describe the burden of illness associated with the severity of chronic kidney disease. Sixth, prevalence estimates for stages of chronic kidney disease and the associations of level of GFR with complications are based largely on an analysis of data from NHANES III that has not yet been peer-reviewed. However, the Work Group believes that Appendix 2 provides sufficient detail to evaluate the methods.

CLINICAL APPLICATIONS

There are a large number of clinical applications of the proposed definition and stages of chronic kidney disease. An overall approach to evaluation and treatment of patients with chronic kidney disease is given in Guideline 2, and recommendations for individuals at increased risk of chronic kidney disease are given in Guideline 3. Clinical applications are also given at the conclusion of each subsequent guideline. Finally, additional recommendations for evaluation, diagnosis, and treatment of chronic kidney disease are given in Part 9.

IMPLEMENTATION ISSUES

Implementation of a new approach to the patient, classification of severity, and assessment of risk for chronic kidney disease will require appropriate professional, patient, and public education effort, as well as administrative and regulatory changes.

Professional, Patient, and Public Education

Components of the implementation plan, which determined the success of K/DOQI, are under development and will be applied to these guidelines. They include: widespread dissemination and easy access to the guidelines; educational interactive programs aimed at health professionals, patients, providers, administrators, manufacturers, and policy makers; information tools and systems to facilitate adherence; development of clinical performance measures; incorporation of guidelines into continuous quality improvement programs; development of quality assessment instruments; and update and review of the pertinent literature on an ongoing basis.

Administrative and Regulatory Changes

Revision of Medicare forms and HCFA billing codes will be necessary. For example, classification of kidney disease by the International Classification of Disease (9th Edition) (ICD-9) is based on duration (acute versus chronic), diagnosis, clinical presentation, markers of damage, and kidney function impairment. The K/DOQI classification proposes that both diagnosis and stage (severity) should be included in the classification of chronic kidney disease. This would facilitate using administrative databases for epidemiological and outcomes surveys.

RESEARCH RECOMMENDATIONS

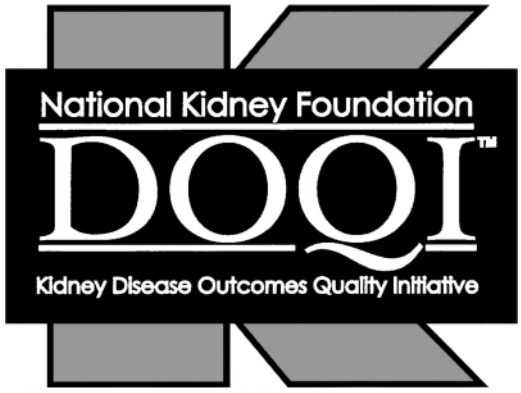
The Workgroup acknowledges that the proposed definition and classification chronic kid-

ney disease and stages is arbitrary and can be refined by further research.

The normal range for GFR was defined using a relatively small number of individuals. It would be useful to conduct a large cross-sectional study of GFR in general population, across the full range of age, gender, race, ethnicity, protein intake, with adjustment for other factors, including high blood pressure, diabetes, and other conditions that affect GFR. This study would permit validation of prediction equations based on serum creatinine or other filtration markers within the normal range of GFR.

The outcomes of individuals with various stages of chronic kidney disease are not defined. A cohort study of patients with chronic kidney disease would enable definition of the relationship between factors and outcomes of stages of chronic kidney disease. This would be particularly useful in defining the relationships among stages of chronic kidney disease, progression of chronic kidney disease, initiation and progression of cardiovascular disease, health service utilization, and barriers to care.

Age-related rise in blood pressure and decline in GFR may be responsible for a large number of individuals in Stage 3 (GFR 30 to 59 mL/min/1.73 m^2). There are even more individuals with high blood pressure and decreased GFR (GFR 60 to 89 mL/min/1.73 m^2), who have not been classified as having chronic kidney disease. It would be useful to conduct cross-sectional and cohort studies of elderly individuals with normal and abnormal blood pressure and GFR to assess the effect of high blood pressure and decreased GFR in this population.



GUIDELINE 2. EVALUATION AND TREATMENT

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

- **Patients with chronic kidney disease should be evaluated to determine:**
  - **Diagnosis (type of kidney disease);**
  - **Comorbid conditions;**
  - **Severity, assessed by level of kidney function;**
  - **Complications, related to level of kidney function;**
  - **Risk for loss of kidney function;**
  - **Risk for cardiovascular disease.**
- **Treatment of chronic kidney disease should include:**
  - **Specific therapy, based on diagnosis;**
  - **Evaluation and management of comorbid conditions;**
  - **Slowing the loss of kidney function;**
  - **Prevention and treatment of cardiovascular disease;**
  - **Prevention and treatment of complications of decreased kidney function;**
  - **Preparation for kidney failure and kidney replacement therapy;**
  - **Replacement of kidney function by dialysis and transplantation, if signs and symptoms of uremia are present.**
- **A clinical action plan should be developed for each patient, based on the stage of disease as defined by the K/DOQI CKD classification (see Table 33).**
- **Review of medications should be performed at all visits for the following:**
  - **Dosage adjustment based on level of kidney function;**
  - **Detection of potentially adverse effects on kidney function or complications of chronic kidney disease;**
  - **Detection of drug interactions;**
  - **Therapeutic drug monitoring, if possible.**
- **Self-management behaviors should be incorporated into the treatment plan at all stages of chronic kidney disease.**
- **Patients with chronic kidney disease should be referred to a specialist for consultation and co-management if the clinical action plan cannot be prepared, the prescribed evaluation of the patient cannot be carried out, or the recommended treatment cannot be carried out. In general, patients with GFR <30 mL/min/**

Table 33. Stages of Chronic Kidney Disease: A Clinical Action Plan

Stage	Description	GFR (mL/min/1.73 m^2)	Action*
1	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment, Treatment of comorbid conditions, Slowing progression, CVD risk reduction
2	Kidney damage with mild ↓ GFR	60–89	Estimating progression
3	Moderate ↓ GFR	30–59	Evaluating and treating complications
4	Severe ↓ GFR	15–29	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	Replacement (if uremia present)

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

* Includes actions from preceding stages.

Abbreviations: CVD, cardiovascular disease

1.73 m^2 should be referred to a nephrologist.

BACKGROUND

Historically, the evaluation and management of chronic kidney disease has focused on diagnosis and treatment of specific kidney diseases and dialysis or transplantation for kidney failure. An action plan for patients with chronic kidney disease also requires interventions during the earlier stages of kidney disease, irrespective of the cause of kidney disease. This includes evaluation and management of comorbid conditions, slowing progression of kidney disease, cardiovascular disease risk reduction, preventing and treating complications of chronic kidney disease, and preparation for kidney replacement therapy.

RATIONALE

Diagnosis (R, O). Classification of the type of kidney disease is based on pathology and etiology. A simplified classification, and the distribution of types of kidney disease leading to ESRD are given in Table 34. The definitive diagnosis of the type of kidney disease is based on biopsy or imaging studies. Biopsy and invasive imaging procedures are associated with a risk, albeit usually small, of serious complications. Therefore, these procedures are often avoided unless a definitive diagnosis would change either the treatment or prognosis. In most patients, well-defined clinical presentations and causal factors provide a sufficient basis to assign a diagnosis of chronic kidney disease. An approach to diagnosis, based on concepts elaborated on in this report, is given in Part 9.

Diabetic kidney disease is a type of glomerular disease, but it is singled out here because it is the largest single cause of kidney failure. Both type 1 and type 2 diabetes cause chronic kidney disease. Because of the higher prevalence of type 2 diabetes, it is the more common cause of diabetic kidney disease. The clinical features, natural history and treatment for diabetic kidney disease are well known because it has been the subject of numerous epidemiological studies and clinical trials. Diabetic kidney disease usually follows a characteristic clinical course after the onset of diabetes, first manifested by microalbuminuria, then clinical proteinuria, hypertension, and declining GFR. Clinical trials have established a number of effective treatments to slow the development and progression of diabetic kidney disease, including strict glycemic control, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, blood pressure control, and perhaps dietary protein restriction.

A variety of diseases, including other glomerular diseases, vascular diseases, tubulointerstitial diseases, and cystic diseases, are often grouped together under the label “nondiabetic kidney diseases” for the purpose of epidemiological studies and clinical trials. Amongst these, hypertensive nephrosclerosis and glomerular diseases are the second and third most common causes of kidney failure. The various diseases in this group differ widely based on history, clinical presentation, risk for progression, and response to treatment. Differentiation among the diseases can be difficult, often requiring kidney biopsy or invasive imaging studies. An approach to diagnosis, based on the history, and a review of clinical presentations of chronic kidney disease, are given in Part 9. Specific therapies are available to reverse abnormalities in structure and function for some types of chronic kidney disease: for example, immunosuppressive medications for autoimmune glomerular diseases, antibiotics for urinary tract infections, removal of urinary stones, relief of obstruction, and cessation of toxic drugs. A thorough search for “reversible causes” of decreased kidney function should be carried out in each patient with chronic kidney disease.

Kidney disease in the transplant is probably the fourth largest cause of kidney failure. Both immunologic and non-immunologic factors appear to play an important role. The most common causes are chronic rejection, toxicity due to cyclosporine or tacrolimus, recurrent disease, and transplant glomerulopathy. In addition, differential diagnosis includes all the diseases that can occur in the native kidney. For a variety of reasons, especially the ease and safety of kidney biopsy, there is generally a much lower threshold for performing invasive procedures to establish a definitive diagnosis in kidney transplant recipients.

Comorbid conditions (R, O). Patients with chronic kidney disease have a large number of comorbid conditions. Comorbidity is defined as

Table 34. Classification of Chronic Kidney Disease by Pathology, Etiology and Prevalence in Patients with End-Stage Renal Disease

Pathology	Etiology (Examples*)	Prevalence Among Patients with ESRD**
Diabetic Glomerulosclerosis	Diabetes Mellitus Type 1 Type 2	33%
Glomerular Diseases (Primary or Secondary)		19%
Proliferative glomerulonephritis Mesangial proliferative glomerulonephritis Membranoproliferative glomerulonephritis Focal proliferative glomerulonephritis Diffuse proliferative glomerulonephritis Crescentic glomerulonephritis	Systemic lupus erythematosis, vasculitis, bacterial endocarditis, chronic hepatitis B or C, HIV infection	
Noninflammatory glomerular diseases		
Minimal change disease	Hodgkin's disease	
Focal glomerular sclerosis	HIV infection, heroin toxicity	
Membranous nephropathy	Drug toxicity, solid tumors	
Fibrillary glomerular diseases	Amyloidosis, light chain disease	
Hereditary nephritis (Alport's)		
Vascular Diseases		21%
Diseases of large-size vessels	Renal artery stenosis	
Diseases of medium-size vessels Nephrosclerosis	Hypertension	
Diseases of small vessels Microangiopathy	Sickle cell disease, hemolytic uremic syndrome (including cyclosporine or tacrolimus toxicity)	
Tubulointerstitial Diseases		4%
Tubulointerstitial nephritis		
Pyelonephritis	Infection, stones	
Analgesic nephropathy	NSAID	
Allergic interstitial nephritis	Antibiotics	
Granulomatous interstitial nephritis	Sarcoidosis	
Autoimmune interstitial nephritis	Uveitis	
Noninflammatory tubulointerstitial diseases		
Reflux nephropathy	Vesico-ureteral reflux	
Obstructive nephropathy	Malignancy, prostatism, stones	
Myeloma kidney	Multiple myeloma	
Cystic Diseases		6%
Polycystic kidney disease Tuberous sclerosis Von Hippel Lindau Medullary cystic disease	Autosomal dominant or recessive	
Diseases in the Transplant		—[a]
Chronic rejection		
Drug toxicity	Cyclosporine or tacrolimus	
Recurrent disease	Glomerular diseases	
Transplant glomerulopathy		

* Examples of some causes for specific pathologic types

** Approximate, based on USRDS Annual Data Report 1998[2] (on the Internet, see www.usrds.org/2kpdf/oo_precis.pdf#p1). Prevalence varies with age.

[a] Not recorded as a cause of ESRD in USRDS.

Abbreviations: HIV, human immunodeficiency virus; NSAID, non-steroidal anti-inflammatory drug

conditions other than the primary disease (in this case, chronic kidney disease). Complications of chronic kidney disease, such as hypertension, anemia, malnutrition, bone disease and neuropathy, are not considered as comorbid conditions. It is useful to consider three types of comorbid conditions (Table 35).

Diseases which cause chronic kidney disease. Evaluation and management of these diseases is important for patients' well being and may improve the course of chronic kidney disease. This is particularly important for patients with diabetes and high blood pressure, the leading causes of chronic kidney disease and cardiovascular disease in the United States.

Unrelated diseases, which may lead to impairments of functioning and well being but do not affect the course of chronic kidney disease. Evaluation and management is important for patients' health and well being.

Cardiovascular disease. Cardiovascular disease is singled out from among the possible comorbid conditions to emphasize its complex relationship with chronic kidney disease, and its importance as a preventable cause of morbidity and mortality in patients with chronic kidney disease.

In all cases, management of comorbid conditions must be integrated into the overall care of patients with chronic kidney disease. Examples include adjustment of drug dosages, interpretation of symptoms, and minimizing treatment complications, including acute decline in kidney function. In patients with normal or mildly decreased GFR (CKD Stages 1-2), integration of care for chronic kidney disease and these comorbid conditions may be relatively simple. However, in patients with moderate to severe reduction in GFR (CKD Stages 3-4) and in patients with kidney failure (CKD Stage 5), integration of care is complex and requires careful coordination among all providers.

Risk of loss of GFR (R, O). Risk of kidney failure depends on the level of GFR (severity) at detection of kidney disease and the rate of loss of GFR thereafter. Level of GFR can be improved by specific treatment in some chronic kidney diseases, but not in most others.

Rate of loss of GFR (progression of kidney disease) is affected by diagnosis and by modifiable and nonmodifiable patient factors. These factors can be assessed even before the decline in GFR, thereby allowing implementation of interventions to slow progression while GFR is still normal. Some therapies to prevent or slow the loss of GFR are specific for the diagnosis, while others are non-specific. Factors associated with progression of kidney disease are discussed in Guideline 13.

It is difficult to estimate the rate of progression until there has been a decline in GFR. In diseases

Table 35. Classification and Management of Comorbid Conditions in Chronic Kidney Disease

Type of Comorbid Condition	Examples	Management Goals
Diseases causing CKD	Diabetes High blood pressure Obstruction of the urinary tract	Improve CKD, Improve functioning and well-being, Integration of care with management of CKD
Diseases unrelated to CKD	Chronic obstructive pulmonary disease, Gastroesophageal reflux disease, Degenerative joint disease, Alzheimer's disease, Malignancies	Improve functioning and well-being, Integration of care with management of CKD
Cardiovascular disease (CVD)	Atherosclerotic CVD Coronary heart disease Cerebrovascular disease Peripheral vascular disease Left ventricular hypertrophy Heart failure	Evaluation and management of traditional and CKD-related CVD risk factors, Possibly improve CKD, Improve functioning and well-being, Integration of care with management of CKD

characterized by a quantifiable marker of damage—for example, albuminuria in diabetic kidney disease—progression, stability, or regression can be estimated by change in the marker. For most diseases, however, quantitative relationships between changes in markers and progression have not been established.

Severity of disease and complications (R, O). Decreased GFR is associated with a wide range of complications due to disorders in other organ systems, which are manifested by hypertension, laboratory abnormalities, and symptoms. Complications due to disorders in other organ systems are associated with worse outcomes. Early detection and treatment of complications can improve outcomes. The prevalence of complications of chronic kidney disease is mainly related to the level of GFR. Interpretation of signs and symptoms in patients with chronic kidney disease should be guided by the level of GFR.

Kidney functions other than GFR may be altered by chronic kidney disease. These include maintenance of the filtration barrier for plasma proteins (abnormalities include albuminuria and proteinuria), reabsorption or secretion of water or specific solutes (abnormalities include tubular syndromes), and various endocrine functions (erythropoietin deficiency causes anemia, parathyroid hormone excess causes bone disease, and vitamin D deficiency causes bone disease). For most chronic kidney diseases, severity in other abnormalities of function parallels the severity of decreased GFR. Prevention and treatment of complications of chronic kidney disease includes specific therapies related to the pathogenesis of complications—for example, erythropoietin for anemia and vitamin D for bone disease.

Table 36 shows the association of levels of GFR with complications of chronic kidney disease. Patients with GFR 60 to 89 mL/min/1.73 m^2 usually have hypertension and may have laboratory abnormalities indicative of dysfunction in other organ systems, but usually no symptoms. Patients with GFR 30 to 59 mL/min/1.73 m^2 have laboratory abnormalities in several other organ systems, but few symptoms. Patients with GFR 15 to 29 mL/min/1.73 m^2 usually have laboratory abnormalities in many organ systems and have mild symptoms. Patients with GFR $<$15 mL/min/1.73 m^2 usually have many symptoms and laboratory abnormalities in several organ systems, collectively known as the "uremic syndrome." The association of complications of chronic kidney disease with the level of GFR is discussed in Part 6, Guidelines 7 through 12.

Risk of cardiovascular disease (R, O). Cardiovascular disease may be a cause and compli-

Table 36. Association of Stages of Chronic Kidney Disease with Complications

Stage	Description	GFR (mL/min/1.73 m^2)	Complications	
			HBP or Lab Abnormality	Symptoms
1	Kidney damage with normal or ↑ GFR	≥90	–[a]	–[a]
2	Kidney damage with mild ↓ GFR	60–89	±	–
3	Moderate ↓ GFR	30–59	+	±
4	Severe ↓ GFR	15–29	++	+
5	Kidney failure	<15 (or dialysis)	+++	++

Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

[a] Manifestations of kidney damage may occur during this stage even though GFR is not decreased, as described in Guideline 6 (e.g., nephrotic syndrome, nephritic syndrome, urinary tract symptoms, tubular syndromes).

Abbreviations and Symbols: GFR, glomerlular filtration rate; HBP, high blood pressure; –, none; ±, possible; +, mild; ++, moderate; +++, severe

cation of chronic kidney disease. Irrespective of diagnosis, the increased risk of cardiovascular disease in individuals with chronic kidney disease can be attributed to: (1) a higher prevalence of "traditional" CVD risk factors; and (2) risk factors related to the hemodynamic and metabolic complications of chronic kidney disease ("CKD-related" or "nontraditional" CVD risk factors). Treatment and prevention of cardiovascular disease in chronic kidney disease includes risk factor reduction as well as specific therapies for cardiovascular disease and should begin as early as possible. CVD risk factors may become more prevalent or more severe as GFR declines; therefore, as GFR declines, treatment must intensify. Cardiovascular disease in chronic kidney disease is discussed in Guideline 15.

Kidney replacement therapy for uremia (R, O). Signs and symptoms of severe decrease in GFR, collectively, are known as "uremia" or the "uremic syndrome." Replacement therapy (dialysis and transplantation) is effective in improving the most serious features of uremia, irrespective of the type of chronic kidney disease. Patients require education and advance preparation to cope with the stresses of kidney failure, to choose a modality of kidney replacement therapy, and to undergo evaluation for that modality. It is recommended that preparation for kidney replacement therapy begin when GFR declines below 30 mL/min/1.73 m^2. All patients should probably be instructed to preserve suitable veins for possible future vascular access construction. The indications for initiation of kidney replacement therapy are based on the level of kidney function and presence of signs and symptoms of uremia. Most individuals begin dialysis or receive a kidney transplant when GFR is less than 15 mL/min/1.73 m^2.

Drug prescribing in chronic kidney disease (R). Patients with chronic kidney disease are prescribed a large number of medications. In addition, patients may take other medications, such as over-the-counter medications, "nontraditional" medications, vitamins and supplements, herbs, and drugs of abuse. A thorough review of the medication list and all other medications should be conducted at each visit. Drug dosage should be adjusted for the level of estimated GFR. Drugs with potentially adverse effects on kidney function or complications of decreased kidney function should be discontinued if possible. Drug-drug interactions should be considered. Because of possible alterations in volume of distribution, protein binding, drug elimination, and drug-drug interactions in chronic kidney disease, therapeutic drug monitoring should be performed, if possible. A large amount of information is available to providers in texts, manuals, and databases for handheld computers. Interpretation may be facilitated by the similarity between the classification of levels of kidney function proposed in this guideline and the recommendations for pharmacokinetic studies of drugs in patients with decreased kidney function made by the Food and Drug Administration[84] (on the Internet, *http://www.fda.gov/cder/guidance/1449fnl.pdf*).

Barriers to adherence in chronic kidney disease (R, O). Healthy people make choices that could ultimately shorten their lives, such as smoking, drinking or eating too much, not exercising, missing prescribed medications, and failing to get an annual physical. Those with chronic health conditions requiring lifestyle changes and clinician-initiated visits are more likely to be noncompliant.[85] Patients with chronic kidney disease live day-to-day with such a chronic condition. Other factors linked with noncompliance are shown in Table 37.[85-98]

Because the terminology "noncompliance" or "nonadherence" often leads to prejudice and negative stereotyping, it is recommended that "self-management behaviors" be substituted.[99] The Work Group recommends assessment of barriers to adherence in all patients with chronic kidney disease and incorporation of self-management behaviors into the treatment plan at all stages.

Referral to specialists (O). Frequently the primary care provider will make the diagnosis of chronic kidney disease. Referral to a nephrologist or other specialist for consultation or co-management should be made after diagnosis under the following circumstances: a clinical action plan cannot be prepared based on the

Table 37. Factors Linked with Noncompliance in Chronic Diseases

Misunderstanding instructions[85]	Forgetfulness[94,95]
High stress[86]	Perception of negative side effects[90,94,95]
Depression[86-88]	Perception of less benefit from treatment[87]
Coping by avoidance[86]	Lessening of symptoms[94]
Belief that powerful others control health outcome[86,87,89]	Perception that illness affects work and life[96]
Unemployment[87,90]	Less confidence in care providers[87];
Lower income[86]	Less time with physicians[91]
Less social support[87]	Drug abuse history[97]
Less family support[85,87]	Male gender and medication compliance[87]
Many chronic illnesses[91,92]	Female gender and diet compliance[87]
Need for many medications[87,93]	Black race[87,97,98]
Limited medication access[87]	

stage of the disease, the prescribed evaluation of the patient cannot be carried out, or the recommended treatment cannot be carried out. These activities may not be possible either because the appropriate tools are not available or because the primary care physician does not have the time or information needed to do so. In general, patients with GFR <30 mL/min/1.73 m^2 (CKD Stages 4-5) should be referred to a nephrologist.

LIMITATIONS

This guideline provides a conceptual framework to the evaluation and management of chronic kidney disease, but does not provide sufficient details to guide health care providers in the management of individual patients with chronic kidney disease or the design of public policy to improve outcomes for the target population. Subsequent guidelines will elaborate on the concepts in this guideline, but it is beyond the scope of these guidelines to provide specific instructions for evaluation and management. This will be the topic of forthcoming K/DOQI guidelines and guidelines by other organizations. The ultimate goal is to develop specific guidelines for each action at each stage of disease.

CLINICAL APPLICATIONS

Almost all aspects of the evaluation and management of chronic kidney disease in textbooks of nephrology could be re-written to incorporate the stages of chronic kidney disease proposed in this guideline. Part 9 provides an approach to selected topics using this classification.

IMPLEMENTATION ISSUES

Development of a clinical action plan for all patients with chronic kidney disease is an enormous undertaking that will require coordinate effort of many government and non-governmental organizations. The National Institute of Diabetes, Digestive and Kidney Disease (NIDDK) has established a National Kidney Disease Education Program. The NKF is committed to developing an implementation plan for the K/DOQI CKD guidelines and to working with the NIDDK and other organizations to develop a national program.

RESEARCH RECOMMENDATIONS

Much research is needed to define diagnostic and therapeutic strategies to reduce adverse outcomes of chronic kidney disease at each stage of disease. It will also be important to assess the effect of implementing these guidelines on the outcomes of chronic kidney disease.

GUIDELINE 3. INDIVIDUALS AT INCREASED RISK OF CHRONIC KIDNEY DISEASE

Some individuals without kidney damage and with normal or elevated GFR are at increased risk for development of chronic kidney disease.

- **All individuals should be assessed, as part of routine health encounters, to determine whether they are at increased risk of developing chronic kidney disease, based on clinical and sociodemographic factors.**
- **Individuals at increased risk of developing chronic kidney disease should undergo testing for markers of kidney damage, and to estimate the level of GFR.**
- **Individuals found to have chronic kidney disease should be evaluated and treated as specified in Guideline 2.**
- **Individuals at increased risk, but found not to have chronic kidney disease, should be advised to follow a program of risk factor reduction, if appropriate, and undergo repeat periodic evaluation.**

BACKGROUND

Epidemiological studies show an increased risk for chronic kidney disease, especially kidney failure, among individuals with certain clinical and sociodemographic characteristics. This suggests that there are risk factors for chronic kidney disease. In principle, prevention of adverse outcomes of chronic kidney disease could be facilitated by evaluating individuals with risk factors, to enable earlier detection, and by risk factor reduction in individuals without chronic kidney disease, to prevent or slow the development of chronic kidney disease.

RATIONALE

Definition of Risk Factors (R)

A risk factor is defined as an attribute that is associated with increased risk of an outcome. In principle, the relationship between the risk factor and the outcome may be either *causal* or *non-causal.* Causal risk factors are determinants of the outcome, and successful intervention to reduce exposure to them would improve outcomes. Non-causal risk factors may be associated with the outcome through confounding or reverse causation. Interventions to reduce exposure to non-causal risk factors would not necessarily improve outcomes.

Classification of risk factors (R). A useful classification of risk factors has been used in cardiovascular disease epidemiology[100] and is shown in Table 38.

Risk factors for chronic kidney disease (R, O). In principle, risk factors for development of chronic kidney disease would include susceptibility factors and initiation factors. In addition, because it can be difficult to detect the onset of chronic kidney disease, some risk factors for faster progression may appear to be to susceptibility or initiation factors (Table 39). Note that progression factors may be associated with progression either because initial damage cannot be resolved or because damage is ongoing.

In addition, numerous factors have been shown to be associated with worse outcomes in patients with kidney failure, (such as inadequate dialysis dose, temporary vascular access, anemia, and low serum albumin concentration). These "end-stage" factors have been discussed in previous K/DOQI guidelines and are not relevant for this discussion.

Textbooks and reviews list a large number of potential risk factors for chronic kidney disease.

Table 38. Classification of Risk Factors

Classification	Definition of Risk Factor
Category I	Factors for which interventions have been *proven* to lower risk
Category II	Factors for which interventions are *likely* to lower risk
Category III	Factors for which modification *may* lower risk
Category IV	Factors for which modification is not possible

Table 39. Types and Examples of Risk Factors for Chronic Kidney Disease

	Definition	Examples
Susceptibility factors	Increase susceptibility to kidney damage	Older age, family history
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 level, poor glycemic control in diabetes, smoking

The difficulty of detecting the early stages of chronic kidney disease makes it difficult to determine whether the risk factors so far identified relate more to susceptibility, initiation, or progression. Table 40 contains a partial list of clinical and sociodemographic factors that have been implicated as susceptibility or initiation factors. Progression factors are discussed in more detail in Guideline 13.

Table 41 shows relationships between types of chronic kidney disease and CKD risk factors. For some of these factors (for example, diabetes), interventions (like strict glycemic control) have been *proven* to lower the risk of developing chronic kidney disease (Category I, Table 38). For other factors (for example, hypertension), interventions (like antihypertensive therapy) are *likely* to lower the risk of chronic kidney disease (Category II, Table 38). For other factors (for example, autoimmune diseases), modification of immune responses *might* lower the risk chronic kidney disease (Category III, Table 38). A number of these factors (for example, family history, age, race and ethnicity) are not modifiable (Category IV, Table 38).

Table 40. Potential Risk Factors for Susceptibility to and Initiation of Chronic Kidney Disease

Clinical Factors	Sociodemographic Factors
Diabetes	Older age
Hypertension	US ethnic minority status: African American, American Indian, Hispanic, Asian or Pacific Islander
Autoimmune diseases	
Systemic infections	
Urinary tract infections	Exposure to certain chemical and environmental conditions
Urinary stones	
Lower urinary tract obstruction	Low income/education
Neoplasia	
Family history of chronic kidney diseases	
Recovery from acute kidney failure	
Reduction in kidney mass	
Exposure to certain drugs	
Low birth weight	

Prevalence of individuals with risk factors for chronic kidney disease (R). The prevalence of individuals at increased risk for development of chronic kidney disease has not been studied systematically. However, some idea of the magnitude of the problem can be obtained by reviewing data from recent publications (Table 42).

LIMITATIONS

This guideline provides a conceptual framework to the definition, detection, and evaluation of individuals at increased risk of chronic kidney disease, but does not provide sufficient details to guide health care providers in screening individuals or developing screening programs. It is beyond the scope of these guidelines to provide specific instructions for screening.

CLINICAL APPLICATIONS

Universal screening for chronic kidney disease is recommended for children in the United States, but not for adults. However, the list of individuals at increased risk for chronic kidney disease includes a large fraction of the adult population (Table 42). Thus, it is important to carefully consider the definition of individuals at increased risk and meth-

Table 41. Relationship Between Types of Kidney Disease and Risk Factors for Initiation and Susceptibility to Chronic Kidney Disease

Type of Kidney Disease	CKD Risk Factors
Diabetes (Type 1 & Type 2)	Diabetes mellitus, HBP, family history, US ethnic minority
Glomerular Diseases	Autoimmune diseases, systemic infections, neoplasia, drug or chemical exposure, family history
Vascular Diseases	HBP, family history, US ethnic minority
Tubulointerstitial Diseases	Urinary tract infections, stones, obstruction, toxic drugs
Cystic Diseases	Family history
Disease in the Kidney Transplant	Prior acute rejection, greater HLA mismatches, cyclosporine or tacrolimus, glomerular disease in native kidneys

Abbreviations: HBP, high blood pressure; HLA, human leukocyte antigen

ods for testing them. Suggestions (based on opinion) for evaluation of individuals at increased risk for chronic kidney disease are provided in Part 9.

IMPLEMENTATION ISSUES AND RESEARCH RECOMMENDATIONS

Implementation of these guidelines will require education of all health care providers about risk factors for chronic kidney disease and methods of testing. The Sixth Report of the Joint National Committee for the Prevention, Evaluation, Detection and Treatment of High Blood Pressure (JNC-VI) and the American Diabetes Association have issued recommendations for the evaluation of patients with high blood pressure and diabetes, respectively, for chronic kidney disease. However, as indicated in Table 42, a large number of individuals without high blood pressure and diabetes may also be at increased risk. Thus, it will be important to test a larger population than currently targeted, which would increase the cost of health care.

The increased health care costs that would follow implementation of a screening program for chronic kidney disease may well require a more solid base of evidence than is currently

Table 42. Prevalence of Individuals at Increased Risk for Chronic Kidney Disease

	Prevalence	
Risk Factor	Estimated %	Estimated N
Diabetes mellitus[101]	Diagnosed: 5.1% of adults age ≥20	10.2 million
	Undiagnosed: 2.7% of adults age ≥20	5.4 million
Hypertension[102]	24.0% of adults age ≥18	43.1 million
Systemic lupus erythematosus[103]	~0.05% definite or suspected	~239,000
Functioning kidney graft[104]	~0.03%	88,311 as of 12/31/98
African American[105]	12.3%	34.7 million
Hispanic or Latino (of any race)[105]	12.5%	35.3 million
American Indian and Alaska Native[105]	0.9%	2.5 million
Age 60–70[106]	7.3%	20.3 million
Age ≥70[106]	9.2%	25.5 million
Acute kidney failure[107,108]	~0.14%	~363,000 non-federal hospital stays in 1997
Daily NSAID use[109,110]	~5.2% with rheumatoid arthritis or osteoarthritis (assumed daily use)	~13 million assumed daily use
	~30% yearly use	~75 million yearly use

Abbreviation: NSAID, non-steroidal anti-inflammatory drug

available. The Work Group recommends development of a clinical practice guideline focused on this issue in order to develop specific recommendations for evaluating adults for chronic kidney disease. In the past, universal screening was not recommended because of the low prevalence of chronic kidney disease and the lack of treatments to improve outcomes. Data provided in these guidelines suggests that the prevalence of earlier stages of chronic kidney disease is higher than previously known and that earlier detection and treatment to prevent or delay the loss of kidney function and development of cardiovascular disease in chronic kidney disease. If sufficient information is not available to assess the value of testing individuals at increased risk, or of universal screening, the Work Group suggests that research on evaluation programs should be conducted.