INTRODUCTION: CHRONIC KIDNEY DISEASE AS A PUBLIC HEALTH PROBLEM

CHRONIC KIDNEY disease is a worldwide public health problem. In the United States, there is a rising incidence and prevalence of kidney failure, with poor outcomes and high cost. There is an even higher prevalence of earlier stages of chronic kidney disease.

Increasing evidence, accrued in the past decades, indicates that the adverse outcomes of chronic kidney disease, such as kidney failure, cardiovascular disease, and premature death, can be prevented or delayed. Earlier stages of chronic kidney disease can be detected through laboratory testing. Treatment of earlier stages of chronic kidney disease is effective in slowing the progression toward kidney failure. Initiation of treatment for cardiovascular risk factors at earlier stages of chronic kidney disease should be effective in reducing cardiovascular disease events both before and after the onset of kidney failure.

Unfortunately, chronic kidney disease is "under-diagnosed" and "under-treated" in the United States, resulting in lost opportunities for prevention. One reason is the lack of agreement on a definition and classification of stages in the progression of chronic kidney disease. A clinically applicable classification would be based on laboratory evaluation of the severity of kidney disease, association of level of kidney function with complications, and stratification of risks for loss of kidney function and development of cardiovascular disease.

CHARGE TO THE KDOQI WORK GROUP ON CHRONIC KIDNEY DISEASE

In 2000, the National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (KDOQI) Advisory Board approved development of clinical practice guidelines to define chronic kidney disease and to classify stages in the progression of chronic kidney disease. The Work Group charged with developing the guidelines consisted of experts in nephrology, pediatric nephrology, epidemiology, laboratory medicine, nutrition, social work, gerontology, and family medicine. An Evidence Review Team, consisting of nephrologists and methodologists, was responsible for assembling the evidence. The goals adopted by the Work Group are listed in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Goals of the CKD Work Group</th>
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<tbody>
<tr>
<td>Definition of chronic kidney disease and</td>
</tr>
</tbody>
</table>
classification of the stages of chronic kidney disease, irrespective of underlying cause

Evaluation of laboratory measurements for the clinical assessment of kidney disease

Association of the level of kidney function with complications of chronic kidney disease

Stratification of the risk for loss of kidney function and development of cardiovascular disease

Defining chronic kidney disease and classifying the stages of severity would provide a common language for communication among providers, patients and their families, investigators, and policy-makers and a framework for developing a public health approach to affect care and improve outcomes of chronic kidney disease. A uniform terminology would permit:

1. More reliable estimates of the prevalence of earlier stages of disease and of the population at increased risk for development of chronic kidney disease
2. Recommendations for laboratory testing to detect earlier stages and progression to later stages
3. Associations of stages with clinical manifestations of disease
4. Evaluation of factors associated with a high risk of progression from one stage to the next or of development of other adverse outcomes
5. Evaluation of treatments to slow progression or prevent other adverse outcomes.

Clinical practice guidelines, clinical performance measures, and continuous quality improvement efforts could then be directed to stages of chronic kidney disease.

The Work Group did not specifically address evaluation and treatment for chronic kidney disease. However, this guideline contains brief reference to diagnosis and clinical interventions and can serve as a “road map,” linking other clinical practice guidelines and pointing out where other guidelines need to be developed. Eventually, KDOQI will include interventional guidelines. The first three of these, on bone disease, dyslipidemia, and blood pressure management are currently under development. Other guidelines on cardiovascular disease in dialysis patients and kidney biopsy will be initiated in the Winter of 2001.

This report contains a summary of background information available at the time the Work Group began its deliberations, the 15 guidelines and the accompanying rationale, suggestions for clinical performance measures, a clinical approach to chronic kidney disease using these guidelines, and appendices to describe methods for the review of evidence. The guidelines are based on a systematic review of the literature and the consensus of the Work Group. The guidelines have been reviewed by the KDOQI Advisory Board, a large number of professional organizations and societies, selected experts, and interested members of the public and have been approved by the Board of Directors of the NKF.

FRAMEWORK
The Work Group defined “chronic kidney disease” to include conditions that affect the kidney, with the potential to cause either progressive loss of kidney function or complications resulting from decreased kidney function. Chronic kidney disease was thus defined as the presence of kidney damage or decreased level of kidney function for three months or more, irrespective of diagnosis.

The target population includes individuals with chronic kidney disease or at increased risk of developing chronic kidney disease. The majority of topics focus on adults (age ≥18 years). Many of the same principles apply to children as well. In particular, the classification of stages of disease and principles of diagnostic testing are similar. A subcommittee of the Work Group examined issues related to children and participated in development of the first six guidelines of the present document. However, there are sufficient differences between adults and children in the association of GFR with signs and symptoms of uremia and in stratification of risk for adverse outcomes that these latter issues are addressed only for adults. A separate set of guidelines for children will have to be developed by a later Work Group.

The target audience includes a wide range of individuals: those who have or are at increased risk of developing chronic kidney disease (the target population) and their families; health care professionals caring for the target population; manufacturers of instruments and diagnostic laboratories performing measurements of kidney function; agencies and institutions planning, providing or paying for the health care needs of the target population; and investigators studying chronic kidney disease.

There will be only brief reference to clinical interventions, sufficient to provide a basis for other clinical practice guidelines relevant to the evaluation and management of chronic kidney disease. Subsequent KDOQI clinical practice guidelines will be based on the framework developed here.

**DEFINITION OF CHRONIC KIDNEY DISEASE**

The Work Group developed the following operational definition of chronic kidney disease (Table 2).

<table>
<thead>
<tr>
<th>Table 2. Definition of Chronic Kidney Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criteria</strong></td>
</tr>
<tr>
<td>1. Kidney damage for ≥3 months, as defined by structural of functional abnormalities of the kidney, with or without decreased GFR, manifest by either:</td>
</tr>
<tr>
<td>• Pathological abnormalities; or</td>
</tr>
<tr>
<td>• Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests</td>
</tr>
<tr>
<td>2. GFR &lt;60 mL/min/1.73m² for &gt;3 months, with or without kidney damage</td>
</tr>
</tbody>
</table>

Abbreviation: GFR, glomerular filtration rate
### Table 3. Chronic Kidney Disease: A Clinical Action Plan

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73m²)</th>
<th>Action*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>≥ 90 (with CKD risk factors)</td>
<td>Diagnosis and treatment, Treatment of comorbid conditions, slowing progression, CVD risk reduction</td>
</tr>
<tr>
<td>2.</td>
<td>Kidney damage with mild ↓ GFR</td>
<td>60-89</td>
<td>Estimating progression</td>
</tr>
<tr>
<td>3.</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
<td>Evaluating and treating complications</td>
</tr>
<tr>
<td>4.</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
<td>Preparation for kidney replacement therapy</td>
</tr>
<tr>
<td>5.</td>
<td>Kidney Failure</td>
<td>&lt;15 (or dialysis)</td>
<td>Replacement (if uremia present)</td>
</tr>
</tbody>
</table>

Shaded area identifies patients who have chronic kidney disease; unshaded area designates individuals who are at increased risk for developing chronic kidney disease. Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m² 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: GFR, glomerular filtration rate; CKD, chronic kidney disease; CVD, cardiovascular disease.

Table 3 shows the classification of stages of chronic kidney disease, including the population at increased risk of developing chronic kidney disease, and actions to prevent the development of chronic kidney disease and to improve outcomes in each stage.

**Why “Kidney”?**

The word “kidney” is of Middle English origin and is immediately understood by patients, their families, providers, health care professionals, and the lay public of native English speakers. On the other hand, “renal” and “nephrology,” derived from Latin and Greek roots, respectively, commonly require interpretation and explanation. The Work Group and the NKF are committed to communicating in language that can be widely understood, hence the preferential use of “kidney” throughout these guidelines. The term “End-Stage Renal Disease” (ESRD) has been retained because of its administrative usage in the United States referring to patients treated by dialysis or transplantation, irrespective of their level of kidney function.

**Why Develop a New Classification?**

Currently, there is no uniform classification of the stages of chronic kidney disease. A review of textbooks and journal articles clearly demonstrates ambiguity and overlap in the meaning of current terms. The Work Group concluded that uniform definitions of terms and stages would improve communication between patients and providers, enhance public education, and promote dissemination of research results. In addition, it was believed that uniform definitions would enhance conduct of clinical research.

**Why Base a New Classification System on Severity of Disease?**
Adverse outcomes of kidney disease are based on the level of kidney function and risk of loss of function in the future. Chronic kidney disease tends to worsen over time. Therefore, the risk of adverse outcomes increases over time with disease severity. Many disciplines in medicine, including related specialties of hypertension, cardiovascular disease, diabetes, and transplantation, have adopted classification systems based on severity to guide clinical interventions, research, and professional and public education. Such a model is essential for any public health approach to disease.

Why Classify Severity as the Level of GFR?

Table 4. Stages and Prevalence of Chronic Kidney Disease (Age ≥ 20)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73m²)</th>
<th>Prevalence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>At increased risk</td>
<td>≥90 (with CKD risk factors)</td>
<td>N(1000s)</td>
</tr>
<tr>
<td>2.</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>&gt;90</td>
<td>5,900</td>
</tr>
<tr>
<td>3.</td>
<td>Kidney damage with mild ↓ GFR</td>
<td>60-89</td>
<td>5,300</td>
</tr>
<tr>
<td>4.</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
<td>7,600</td>
</tr>
<tr>
<td>5.</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
<td>400</td>
</tr>
<tr>
<td>6.</td>
<td>Kidney Failure</td>
<td>&lt;15 (or dialysis)</td>
<td>300</td>
</tr>
</tbody>
</table>

*Data for Stages 1-4 from NHANES III (1988-1994). Population of 177 million adults age ≥ 20 years. Data for Stage 5 from USRDS (1998) include approximately 230,000 patients treated by dialysis, and assume 70,000 additional patients not on dialysis. GFR estimated from serum creatinine using MDRD Study equation based on age, gender, race and calibration for serum creatinine. For stages 1 and 2, kidney damage estimated by spot albumin-to-creatinine ratio >17 mg/g in men or >25 mg/g in women on two measurements.

The level of glomerular filtration rate (GFR) is widely accepted as the best overall measure of kidney function in health and disease. Providers and patients are familiar with the concept that "the kidney is like a filter." GFR is the best measure of the kidneys' ability to filter blood. In addition, expressing the level of kidney function on a continuous scale allows development of patient and public education programs that encourage individuals to "Know your number!"

The term “GFR” is not intuitively evident to anyone. Rather, it is a learned term, which allows the ultimate expression of the complex functions of the kidney in one single numerical expression. Conversely, numbers are an intuitive concept and easily understandable by everyone. It is fortunate then that once the term “GFR” is learned, the expression “Know your number!” becomes intuitive and easily understood.

Why Include an “Action Plan”? 

Action is necessary to improve outcomes, which is the ultimate goal of the NKF. No clinical practice guideline, irrespective of the rigor of its development, can accomplish its intended improvement in outcome without an implementation plan. This has been the charge of the Advisory Board. The process has been set in motion in parallel with that of development of the guidelines.

PREVALENCE OF CHRONIC KIDNEY DISEASE IN THE UNITED STATES
Using the definition and stages of chronic kidney disease, the Work Group was able to provide rough estimates of the prevalence of each stage in adults from the Third National Health and Nutrition Examination Survey (NHANES III) (Table 4). Methods for estimating prevalence are detailed in Part 10, Appendix 2. The prevalence of chronic kidney disease in children is too low to provide accurate estimates of prevalence of each stage based on data from NHANES III.

**FUTURE DIRECTIONS**

The framework that has been adopted can be used to develop an evidence model of the course of chronic kidney disease (Fig 1). It is anticipated that clinical practice guidelines for interventions to reduce adverse outcomes in patients with chronic kidney disease can be based on this model.

This line of logic allows for the ultimate construction of a list of modifiable risk factors at each stage of chronic kidney disease, as shown in Table 5.
REVIEW OF EVIDENCE

The guidelines developed by the Work Group are based on a systematic review of the literature using an approach based on the procedure outlined by the Agency for Healthcare Research and Quality (formerly the Agency for Health Care Policy and Research) with modifications appropriate to the goals. An Evidence Review Team was appointed by the NKF to collaborate with the Work Group to conduct a systematic review of the literature on which to base the guidelines. A detailed explanation of these methods is provided in Part 10, Appendices 1 and 2; Table 6 provides a brief listing of the steps involved in this approach.

Table 6. Approach to the Evidence Review

<table>
<thead>
<tr>
<th>Develop and refine topics;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine approach to topics:</td>
</tr>
<tr>
<td>Established concepts - summary of published reviews and selected original articles;</td>
</tr>
<tr>
<td>New concepts - systematic review of original articles and analysis of primary data, if available.</td>
</tr>
<tr>
<td>Retrieval of evidence (literature review);</td>
</tr>
<tr>
<td>Analysis of primary data from the Third National Health and Nutrition Examination Survey (NHANES III) and other sources;</td>
</tr>
<tr>
<td>Evaluation of evidence (types and quality);</td>
</tr>
<tr>
<td>Synthesis of evidence (tables);</td>
</tr>
</tbody>
</table>
A uniform format for summarizing the strength of evidence has been developed using four dimensions: study size, applicability, results, and methodological quality.

An example of an evidence table is shown in the above table. Within each table, studies are ordered first by methodological quality (best to worst), then by applicability (most to least), and then by study size (largest to smallest). Detailed evidence tables are on file at the National Kidney Foundation.

**Applicability**

Applicability (also known as generalizability or external validity) addresses the issue of whether the study population is sufficiently broad so that the results can be generalized to the population of interest at large. The study population is typically defined by the inclusion and exclusion criteria. The target population was defined to include patients with chronic kidney disease and those at increased risk of chronic kidney disease, except where noted. A designation for applicability was assigned to each article, according to a three-level scale. In making this assessment, sociodemographic characteristics were considered, as were the stated causes of chronic kidney disease and prior treatments.

**GFR Range**
For all studies, the range of GFR (or creatinine clearance [CCr]) is represented graphically when available (see table above). The mean or median GFR is represented by a vertical line, with a horizontal bar showing a range that includes approximately 95% of study participants. Studies without a vertical or horizontal line did not provide data on the mean/median or range, respectively. When GFR or CCr measurements are not available, serum creatinine levels are listed as text.

Results

Results are represented by prevalence levels, proportions (percents) for categorical variables, mean levels for continuous variables, and associations between study measures. Symbols indicate the type and significance of associations between study measures:

- Sample is representative of the target population, or results are definitely applicable to general chronic kidney disease population irrespective of study sample.

- Sample is representative of a relevant sub-group of the target population. For example, sample is only representative of people with a narrow range of GFR, or only a specific relevant subgroup, such as elderly individuals or patients with diabetic kidney disease. In addition, studies of association of level of kidney function with complications that report serum creatinine levels rather than estimated GFR are assigned to this category.

- Sample is representative of a narrow subgroup of patients only, and not well generalizable to other subgroups. For example, the study includes only patients with a rare disease. However, studies of such narrow subgroups may be extremely valuable for demonstrating “exceptions to the rule.”
The specific meanings of these symbols are explained in the footnotes of tables where they appear. Some informative studies reported only single point estimates of study measures (e.g., mean data) rather than associations. Where data on associations were limited, evidence tables provide these point estimates. Studies that provide data on associations and studies that provide only point estimates are listed and ranked separately, with shading used to distinguish them (as in the table, Example of Format for Evidence Tables).

**Quality**

Methodological quality (or internal validity) refers to the design, conduct, and reporting of the clinical study. Because studies with a variety of types of design were evaluated, a three level classification of study quality was devised:

- **Least bias; results are valid.** A study that mostly adheres to the commonly held concepts of high quality, including the following: a formal study; clear description of the population and setting; clear description of an appropriate reference standard; proper measurement techniques; appropriate statistical and analytic methods; no reporting errors; and no obvious bias.

- **Susceptible to some bias, but not sufficient to invalidate the results.** A study that does not meet all the criteria in category above. It has some deficiencies but none likely to cause major bias. Includes retrospective studies and case series.

- **Significant bias that may invalidate the results.** A study with serious errors in design or reporting. These studies may have large amounts of missing information or discrepancies in reporting. Includes prospective and retrospective studies and case series.

**Strength of Evidence**

Each rationale statement has been graded according the level of evidence on which it is based.
Grading Rationale Statements

<table>
<thead>
<tr>
<th>Grade</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>Analysis of individual patient data from a single large, generalizable study of high methodological quality (for example, NHANES III)</td>
</tr>
<tr>
<td>C</td>
<td>Compilation of original articles (evidence tables)</td>
</tr>
<tr>
<td>R</td>
<td>Review of reviews and selected original articles</td>
</tr>
<tr>
<td>O</td>
<td>Opinion</td>
</tr>
</tbody>
</table>

GUIDELINE STATEMENTS

Guideline statements are grouped into four parts, corresponding to the four goals of the CKD Work Group. Guideline statements are reproduced in the Executive Summary. The reader is referred to specific pages for rationale, evidence tables and references.

DEFINITION AND CLASSIFICATION OF STAGES OF CHRONIC KIDNEY DISEASE (PART 4, p. S46)

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 147. 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 (p. S46)

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 KDOQI CKD classification:
Guideline 2.
Evaluation and Treatment (p. S65)

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 KDOQI CKD classification (see table below).

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; and
- 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/1.73 m² should be referred to a nephrologist.

**Guideline 3.**
**Individuals at Increased Risk of Chronic Kidney Disease (p. S72)**

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.
Guideline 4.
Estimation of GFR (p. S76)

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

- The level of GFR should be estimated from prediction equations that take into account the serum creatinine concentration and some or all of the following variables: age, gender, race and body size. The following equations provide useful estimates of GFR:
  - In adults, the MDRD Study and Cockcroft- Gault equations;
  - In children, the Schwartz and Counahan- Barratt equations.

- The serum creatinine concentration alone should not be used to assess the level of kidney function.

- Clinical laboratories should report an estimate of GFR using a prediction equation, in addition to reporting the serum creatinine measurement.

- Autoanalyzer manufacturers and clinical laboratories should calibrate serum creatinine assays using an international standard.
• Measurement of creatinine clearance using timed (for example, 24-hour) urine collections does not improve the estimate of GFR over that provided by prediction equations. A 24-hour urine sample provides useful information for:
  o Estimation of GFR in individuals with exceptional dietary intake (vegetarian diet, creatine supplements) or muscle mass (amputation, malnutrition, muscle wasting);
  o Assessment of diet and nutritional status;
  o Need to start dialysis.

Guideline 5.
Assessment of Proteinuria (p. S93)

Normal individuals usually excrete very small amounts of protein in the urine. Persistently increased protein excretion is usually a marker of kidney damage. The excretion of specific types of protein, such as albumin or low molecular weight globulins, depends on the type of kidney disease that is present. Increased excretion of albumin is a sensitive marker for chronic kidney disease due to diabetes, glomerular disease, and hypertension. Increased excretion of low molecular weight globulins is a sensitive marker for some types of tubulointerstitial disease. In this guideline, the term ÉproteinuriaÓ refers to increased urinary excretion of albumin, other specific proteins, or total protein; ÉalbuminuriaÓ refers specifically to increased urinary excretion of albumin. ÉMicroalbuminuriaÓ refers to albumin excretion above the normal range but below the level of detection by tests for total protein. Guidelines for detection and monitoring of proteinuria in adults and children differ because of differences in the prevalence and type of chronic kidney disease.

Guidelines for Adults and Children:

• Under most circumstances, untimed (ÉspotÓ) urine samples should be used to detect and monitor proteinuria in children and adults.

• It is usually not necessary to obtain a timed urine collection (overnight or 24- hour) for these evaluations in either children or adults.

• First morning specimens are preferred, but random specimens are acceptable if first morning specimens are not available.

• In most cases, screening with urine dipsticks is acceptable for detecting proteinuria:

  • Standard urine dipsticks are acceptable for detecting increased total urine protein.

  • Albumin-specific dipsticks are acceptable for detecting albuminuria.

• Patients with a positive dipstick test (11 or greater) should undergo confirmation of proteinuria by a quantitative measurement (protein-to-creatinine ratio or albumin-to-creatinine ratio) within 3 months.

• Patients with two or more positive quantitative tests temporally spaced by 1 to 2 weeks should be diagnosed as having persistent proteinuria and undergo further evaluation and management for chronic kidney disease as stated in Guideline 2.

• Monitoring proteinuria in patients with chronic kidney disease should be performed using quantitative measurements.

Specific Guidelines for Adults:
• When screening adults at increased risk for chronic kidney disease, albumin should be measured in a spot urine sample using either:
  o Albumin-specific dipstick;
  o Albumin-to-creatinine ratio.

• When monitoring proteinuria in adults with chronic kidney disease, the protein to-creatinine ratio in spot urine samples should be measured using:
  o Albumin-to-creatinine ratio;
  o Total protein-to-creatinine ratio is acceptable if albumin-to-creatinine ratio is high (>500 to 1,000 mg/g).

Specific Guidelines for Children Without Diabetes:

• When screening children for chronic kidney disease, total urine protein should be measured in a spot urine sample using either:
  o Standard urine dipstick;
  o Total protein-to-creatinine ratio.

• Orthostatic proteinuria must be excluded by repeat measurement on a first morning specimen if the initial finding of proteinuria was obtained on a random specimen.

• When monitoring proteinuria in children with chronic kidney disease, the total protein-to-creatinine ratio should be measured in spot urine specimens.

Specific Guidelines for Children With Diabetes:

• Screening and monitoring of post-pubertal children with diabetes of 5 or more years of duration should follow the guidelines for adults.

• Screening and monitoring other children with diabetes should follow the guidelines for children without diabetes.

Guideline 6.
Markers of Chronic Kidney Disease Other Than Proteinuria (p. S103)

Markers of kidney damage in addition to proteinuria include abnormalities in the urine sediment and abnormalities on imaging studies. Constellations of markers define clinical presentations for some types of chronic kidney disease. New markers are needed to detect kidney damage that occurs prior to a reduction in GFR in other types of chronic kidney diseases.

• Urine sediment examination or dipstick for red blood cells and white blood cells should be performed in patients with chronic kidney disease and in individuals at increased risk of developing chronic kidney disease.

• Imaging studies of the kidneys should be performed in patients with chronic kidney disease and in selected individuals at increased risk of developing chronic kidney disease.
• Although several novel urinary markers (such as tubular or low-molecular weight proteins and specific mononuclear cells) show promise of future utility, they should not be used for clinical decision-making at present.

ASSOCIATION OF LEVEL OF GFR WITH COMPLICATIONS IN ADULTS (PART 6, p. S111)

Many of the complications of chronic kidney disease can be prevented or delayed by early detection and treatment. The goal of Part 6 is to review the association of the level of GFR with complications of chronic kidney disease to determine the stage of chronic kidney disease when complications appear. As described in Appendix 1, Table 152, the Work Group searched for cross-sectional studies that related manifestations of complications and the level of kidney function. Data from NHANES III were also analyzed, as described in Appendix 2.

Estimated prevalence of selected complications, by category of estimated GFR, among participants age ≥20 years in NHANES III, 1988 through 1994. These estimates are not adjusted for age, the mean of which is 33 years higher at an estimated GFR of 15 to 29 mL/min/1.73 m² than that at an estimated GFR ≥90 mL/min/1.73 m².
Estimated distribution of the number of complications shown in figure by category of estimated GFR among participants age ≥20 years in NHANES III, 1988 through 1994. These estimates are not adjusted for age, the mean of which is 33 years higher at an estimated GFR of 15 to 29 mL/min/1.73 m² than that at an estimated GFR of ≥90 mL/min/1.73 m².

Because of different manifestations of complications of chronic kidney disease in children, especially in growth and development, the Work Group limited the scope of the review of evidence to adults. A separate Work Group will need to address this issue in children.

The Work Group did not attempt to review the evidence on the evaluation and management of complications of chronic kidney disease. This is the subject of past and forthcoming clinical practice guidelines by the National Kidney Foundation and other groups, which are referenced in the text.

Representative findings are shown by stage of chronic kidney disease in the figures above and below, showing a higher prevalence of each complication at lower GFR, and a larger mean number of complications per person and higher prevalence of multiple complications at lower GFR. These and other findings support the classification of stages of chronic kidney disease and are discussed in detail in Guidelines 7 through.

**Guideline 7.**
**Association of Level of GFR With Hypertension (p. S112)**

High blood pressure is both a cause and a complication of chronic kidney disease. As a complication, high blood pressure may develop early during the course of chronic kidney disease and is associated with adverse outcomes—in particular, faster loss of kidney function and development of cardiovascular disease.

- Blood pressure should be closely monitored in all patients with chronic kidney disease.
- Treatment of high blood pressure in chronic kidney disease should include specification of target blood pressure levels, nonpharmacologic therapy, and specific antihypertensive agents for the prevention of progression of kidney disease (Guideline 13) and development of cardiovascular disease (Guideline 15).
Guideline 8.
Association of Level of GFR With Anemia (p. S120)

Anemia usually develops during the course of chronic kidney disease and may be associated with adverse outcomes.

- Patients with GFR <60 mL/min/1.73 m² should be evaluated for anemia. The evaluation should include measurement of hemoglobin level.

- Anemia in chronic kidney disease should be evaluated and treated (see KDOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease, Guidelines 1-4).

Guideline 9.
Association of Level of GFR With Nutritional Status (p. S128)

Protein energy malnutrition develops during the course of chronic kidney disease and is associated with adverse outcomes. Low protein and calorie intake is an important cause of malnutrition in chronic kidney disease.

- Patients with GFR <60 mL/min/1.73 m² should undergo assessment of dietary protein and energy intake and nutritional status (see KDOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure, Guidelines 23 and 26).

- Patients with decreased dietary intake or malnutrition should undergo dietary modification, counseling and education, or specialized nutrition therapy (see KDOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure, Guidelines 24 and 25).

Guideline 10.
Bone Disease and Disorders of Calcium and Phosphorus Metabolism (p. S143)

Bone disease and disorders of calcium and phosphorus metabolism develop during the course of chronic kidney disease and are associated with adverse outcomes.

- Patients with GFR <60 mL/min/1.73 m² should be evaluated for bone disease and disorders of calcium and phosphorus metabolism.

- Patients with bone disease and disorders of bone metabolism should be evaluated and treated (see forthcoming KDOQI Clinical Practice Guidelines on Bone Metabolism and Disease in Chronic Kidney Disease).

Guideline 11.
Neuropathy (p. S156)

Neuropathy develops during the course of chronic kidney disease and may become symptomatic.

- Patients with chronic kidney disease should be periodically assessed for central and peripheral neurologic involvement by eliciting symptoms and signs during routine office visits or exams.

- Specialized laboratory testing for neuropathy in patients with chronic kidney disease is indicated only in the presence of symptoms.

Guideline 12.
Association of Level of GFR With Indices of Functioning and Well-Being (p. S161)
Impairments in domains of functioning and well-being develop during the course of chronic kidney disease and are associated with adverse outcomes. Impaired functioning and well-being may be related to sociodemographic factors, conditions causing chronic kidney disease, complications of kidney disease, or possibly directly due to reduced GFR.

- Patients with GFR <60 mL/min/1.73 m² should undergo regular assessment for impairment of functioning and well-being:
  - To establish a baseline and monitor changes in functioning and well-being over time;
  - To assess the effect of interventions on functioning and well-being.

STRATIFICATION OF RISK FOR PROGRESSION OF KIDNEY DISEASE AND DEVELOPMENT OF CARDIOVASCULAR DISEASE (PART 7, p. S170)

The major outcomes of chronic kidney disease are loss of kidney function, leading to complications and kidney failure, and development of cardiovascular disease. The goals of Part 7 are to define risk factors for progression of chronic kidney disease and to determine whether chronic kidney disease is a risk factor for cardiovascular disease. Because of the well-known association of cardiovascular disease and diabetes, the Work Group considered patients with chronic kidney disease due to diabetes separately from patients with chronic kidney disease due to other causes. As described in Appendix 1, Table 153, the Work Group searched primarily for longitudinal studies that related risk factors to loss of kidney function (Guideline 13) and that related proteinuria and decreased GFR to cardiovascular disease (Guidelines 14 and 15). It was beyond the scope of the Work Group to undertake a systematic review of studies of treatment. However, existing guidelines and recommendations were reviewed, as were selected studies, to provide further evidence of efficacy of treatment.

Guideline 13.
Factors Associated With Loss of Kidney Function in Chronic Kidney Disease (p. S170)

The level of kidney function tends to decline progressively over time in most patients with chronic kidney diseases.

- The rate of GFR decline should be assessed in patients with chronic kidney disease to:
  - Predict the interval until the onset of kidney failure;
  - Assess the effect of interventions to slow the GFR decline.

- Among patients with chronic kidney disease, the rate of GFR decline should be estimated by:
  - Computing the GFR decline from past and ongoing measurements of serum creatinine;
  - Ascertaining risk factors for faster versus slower GFR decline, including type (diagnosis) of kidney disease and nonmodifiable and modifiable factors.

- Interventions to slow the progression of kidney disease should be considered in all patients with chronic kidney disease.
  - Interventions that have been proven to be effective include:
    1. Strict glucose control in diabetes;
    2. Strict blood pressure control;
    3. Angiotensin-converting enzyme inhibition or angiotensin-2 receptor blockade.
  - Interventions that have been studied, but the results of which are inconclusive, include:
    1. Dietary protein restriction;
(2) Lipid-lowering therapy;
(3) Partial correction of anemia.

- Attempts should be made to prevent and correct acute decline in GFR. Frequent causes of acute decline in GFR include:
  - Volume depletion;
  - Intravenous radiographic contrast;
  - Selected antimicrobial agents (for example, aminoglycosides and amphotericin B);
  - Nonsteroidal anti-inflammatory agents; including cyclo-oxygenase type 2 inhibitors;
  - Angiotensin-converting enzyme inhibition and angiotensin-2 receptor blockers;
  - Cyclosporine and tacrolimus;
  - Obstruction of the urinary tract.

- Measurements of serum creatinine for estimation of GFR should be obtained at least yearly in patients with chronic kidney disease and more often in patients with:
  - GFR <60 mL/min/1.73 m2;
  - Fast GFR decline in the past (>4 mL/min/1.73 m2 per year);
  - Risk factors for faster progression;
  - Ongoing treatment to slow progression;
  - Exposure to risk factors for acute GFR decline.

Guideline 14.
Association of Chronic Kidney Disease With Diabetic Complications (p. S198)

The risk of cardiovascular disease, retinopathy, and other diabetic complications is higher in patients with diabetic kidney disease than in diabetic patients without kidney disease.

- Prevention, detection, evaluation, and treatment of diabetic complications in patients with chronic kidney disease should follow published guidelines and position statements.

- Guidelines regarding angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and strict blood pressure control are particularly important since these agents may prevent or delay some of the adverse outcomes of both kidney and cardiovascular disease.

Application of published guidelines to diabetic patients with chronic kidney disease should take into account their “higher risk” status for diabetic complications.

Guideline 15.
Association of Chronic Kidney Disease With Cardiovascular Disease (p. S204)

Patients with chronic kidney disease, irrespective of diagnosis, are at increased risk of cardiovascular disease (CVD), including coronary heart disease, cerebrovascular disease, peripheral vascular disease, and heart failure. Both “traditional” and “chronic kidney disease related (nontraditional)” CVD risk factors may contribute to this increased risk.

- All patients with chronic kidney disease should be considered in the “highest risk” group for cardiovascular disease, irrespective of levels of traditional CVD risk factors.
• All patients with chronic kidney disease should undergo assessment of CVD risk factors, including:
  o Measurement of “traditional” CVD risk factors in all patients;
  o Individual decision-making regarding measurement of selected “CKD-related” CVD risk factors in some patients.

• Recommendations for CVD risk factor reduction should take into account the “highest-risk” status of patients with chronic kidney disease.