Introduction: The case for updating and context

Kidney International Supplements (2013) **3,** 15–18; doi:10.1038/kisup.2012.63

Justification for updating the guideline for CKD Definition, Evaluation, Classification, and Stratification from an international perspective

In 2002, the US-based Kidney Disease Outcomes Quality Initiative (KDOQI) group published a guideline on definition, classification and evaluation of chronic kidney disease (CKD). The guideline proposed uniform definitions of CKD together with a staging system[1] and described issues related to measurement of kidney function that had not previously been identified by the clinical community. This publication revolutionized the concept and management of CKD, generating substantial research and controversy, stimulating discussion, and influencing public policy and laboratory practice. The research generated has led to new insights which require contextualizing in the current era, providing the evidence drivers for updating guidance for defining, diagnosing, staging and managing CKD, and promoting improved care of those with early CKD. Successive international controversies conferences, under the direction of Kidney Disease: Improving Global Outcomes (KDIGO), have shaped the scope of this international update through**:**

1. Facilitating global implementation of the definition and classification of CKD, identifying areas of uncertainty, and developing a collaborative research agenda to improve the evidence base and facilitate implementation (November 2004).
2. Evaluating the definition and classification of CKD from a global public health perspective (October 2006).
3. Reviewing the definition and classification of CKD based on data on patient prognosis derived from a unique research collaboration on prognosis (October 2009).

Given the *international* interest in understanding and improving the outcomes of people living with kidney disease and the tremendous amount of data generated since 2002, a need was identified to review, revise, and update the original 2002 KDOQI guideline.

There has been a wealth of published data highlighting the risk of adverse consequences and outcomes in people with albumin excretion rate (AER) >30 mg/24 hours and/or glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 (GFR categories G3a-G5), irrespective of the etiology or duration of reduced kidney function. Description of the relationship between GFR, albuminuria and prognosis has significantly improved the understanding of CKD in multiple populations.[2–5] Internationally, the widespread use of albumin-to-creatinine ratio (ACR) and reagent strip urine testing to detect elevated albuminuria together with reporting of estimated GFR (eGFR) has led to easier identification of people with CKD. However elevated albuminuria or reduced GFR alone are not necessarily indicators of need for specialist referral. Clinicians and medical systems are still adjusting to the improved "identification" of CKD and guidance about appropriate stratification of risk and modified action plans for different subgroups of individuals regarding further evaluation, referral, or treatment is needed.

The goal of this guideline is to clarify the definition and classification system of CKD, and to develop appropriate guidance as to the management and care of people with CKD. In addition, we present a framework which should foster an extended collaborative research agenda over the next decade and inform guidelines in the future.

Kidney disease is an important problem worldwide

Kidney disease is defined as an abnormality of kidney structure or function with implications for the health of an individual, which can occur abruptly, and either resolve or become chronic. CKD is a general term for heterogeneous disorders affecting kidney structure and function with variable clinical presentation, in part related to cause, severity and the rate of progression. The concept of CKD evolved after the recognition of the contribution of disordered kidney structure and function on the health of individuals across a wide range of severity.[1] The utility of the concept is that recognition of CKD will have implications for the individual and their care. Kidney failure is traditionally considered as the most serious outcome of CKD. Symptoms are usually due to complications of decreased kidney function and when severe, they can be treated only by dialysis or transplantation. Earlier stages of kidney disease are often asymptomatic, are detected during the evaluation of comorbid conditions, and may be reversible. Rapidly progressive diseases may lead to kidney failure within months but most diseases evolve over decades, and some patients do not progress during many years of follow-up.

Figure 1 shows a conceptual model for the development, progression, and complications of CKD.[1,6] The model includes antecedents associated with increased risk for development of CKD, stages of disease, and complications including death. Risks for development of CKD may be categorized either as susceptibility to kidney disease due to sociodemographic and genetic factors or exposure to factors that can initiate kidney disease. Abnormalities in kidney structure (damage) usually precede abnormalities in function. Outcomes of CKD may be progression, as shown by the horizontal arrows, and complications, as shown by the diagonal arrows, or both.

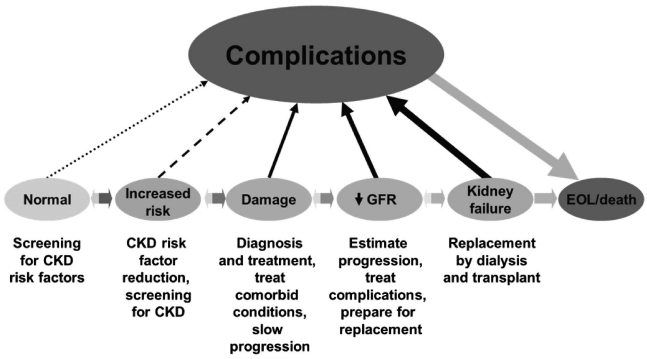

Figure 1 | Conceptual model of CKD. Continuum of development, progression, and complications of CKD and strategies to improve outcomes. Horizontal arrows between circles represent development, progression, and remission of CKD. Left-pointing horizontal arrowheads signify that remission is less frequent than progression. Diagonal arrows represent occurrence of complications of CKD, including drug toxicity, endocrine and metabolic complications, cardiovascular disease, and others such as infection, cognitive impairment, and frailty. Complications might also arise from adverse effects of interventions to prevent or treat the disease. CKD, chronic kidney disease; EOL, end-of-life care and/or conservative management; GFR, glomerular filtration rate. Adapted from Levey AS, Stevens LA, Coresh J.[6] Conceptual model of CKD: applications and implications. Am J Kidney Dis. 2009; 53:S4-16 with permission from the National Kidney Foundation; accessed http://download.journals.elsevierhealth.com/pdfs/journals/0272-6386/PIIS02726386080 17186.pdf

Although the need for treatment of chronic kidney failure with dialysis and/or kidney transplantation arises in only 1% of people with CKD, it remains the most expensive of chronic diseases and reduces lifespan significantly. The costs of dialysis and transplantation consume disproportionate amounts within the health-care budgets in all jurisdictions (5% of annual budgets consumed by less than 1% of the population). Failure to recognize CKD results in neglect of its consequences and complications, and late referral of people with advanced CKD resulting in worse renal replacement therapy (RRT) outcomes. In addition, there is a growing body of evidence that indicates people with CKD are at increased risk of acute kidney injury (AKI), which is also associated with poor outcomes and may accelerate progression of CKD. Therefore, identification of people at earlier time points in the trajectory of CKD, with appropriate management and earlier referral of those who would benefit from specialist kidney services, should lead to both economic and clinical benefits.

In those countries where access to dialysis and transplantation services may be limited or unavailable, the final consequence of progressive CKD is death. In all locations, irrespective of availability of dialysis and transplantation, early identification of CKD therefore assumes great importance, as delay or prevention of progression has the potential to prolong health and save lives for much lower cost than RRT. Although etiologies vary in frequency or absolute numbers in different countries, the proportion of people with important antecedents to CKD, such as diabetes, is growing alarmingly worldwide in both developed and developing countries.

Complications of CKD affect all organ systems. Kidney failure leads to the commonly recognized symptoms of uremia. Less severe CKD has been recognized as an independent risk factor for cardiovascular disease (CVD) and other common conditions affecting the elderly, such as infection and impairments in physical function and cognition. In addition, CKD is associated with increased risk from adverse effects of drugs, intravascular radiocontrast administration, surgery and other invasive procedures. Altogether, these complications are associated with higher morbidity, mortality and cost. If CKD is detected early, the associated complications and the progression to kidney failure can be delayed or even prevented through appropriate interventions. Regular testing of high-risk groups (i.e., people with diabetes, hypertension, CVD, structural renal tract disease, multisystem diseases with potential kidney involvement such as systemic lupus erythematosus, family history of kidney failure, hereditary kidney disease, the elderly, those receiving potential nephrotoxic drugs or those opportunistically found to have hematuria or proteinuria) can give an early indication of kidney damage, thus permitting the introduction of available interventions at an early stage, and the testing of novel interventions with potential added value.

Factors associated with progression of CKD and with increased cardiovascular risk are overlapping to a large extent. Thus targeting of those risk factors that are modifiable may both reduce CVD in people with CKD and reduce progression of CKD to end-stage renal disease (ESRD). There is strong evidence that blockade of the renin-angiotensin-aldosterone system (RAAS) is a blood pressure (BP) lowering strategy which is more effective in reducing risk of kidney and cardiovascular disease in the presence of albuminuria.

The development of guidance for health-care providers will provide opportunities to improve the care of people with kidney disease. We hope that this publication serves to stimulate strategic research initiatives from basic, translational, clinical and health outcome perspectives.

General summary for the reader: what you will and will not find in this guideline

1. The guideline will offer best practice and evidence-based advice on the evaluation and approach to management of CKD.
   a. The target population for the guideline is all people identified with CKD who are not on RRT (i.e., not on dialysis or have not received a kidney transplant).
   b. The target population includes adults and children. The guideline will cover the spectrum of individuals with CKD, from children to the elderly who form important subgroups, underscoring current issues at the extremes of age with respect to the evidence base, especially in relation to implementation and management issues. Where the guideline does not apply to

children, statements to that effect will be made. It is beyond the scope of this guideline to address all issues related to children with CKD, given the heterogeneous nature of this group of individuals who range from newborn to post-adolescents, with specific physiological differences within each of those groups. Specific evidence and rationale will be articulated as appropriate in each section.

c. The target condition is CKD of any or unknown etiology. Identifying the cause of the CKD is strongly encouraged, both because treatment may need to be adjusted according to etiology and because it influences the prognosis and relative importance of risk factors associated with CKD. A comprehensive list of possible etiologies is not practical and guidance on detailed work-up for specific causes of CKD is beyond the scope of this document (readers will be referred to other pertinent sources). We will describe how knowledge of the etiology of CKD in an individual may be important in prognostication and management.

d. The target audience of the guideline includes nephrologists, primary care physicians, non-nephrology specialists (e.g., cardiologists, diabetologists, etc), clinical chemists and other practitioners caring for adults and children with CKD. The guideline is also expected to be suitable for use in public policy and other health-care arenas.

e. As a global guideline it is written for use in different health-care settings, but unavoidably its full implementation relies on health-care resources that are not universally available. We recognize this overtly in some of the discussion sections within the guideline.

f. The target health-care settings include primary, secondary, and tertiary care.

2. The guideline will provide information, advice, and education to support self-management for people with CKD and aid caregivers with the diagnosis and management of CKD. To avoid redundancy and potential for becoming outdated, the reader is asked to refer to existing KDIGO guidance on anemia, metabolic bone disease, BP, AKI, hepatitis C, lipid management, glomerulonephritis (GN) and other pertinent guidelines.
3. The guideline will provide a blueprint for an approach to CKD care in an international context. While the guideline will be sensitive to issues related to ethnicity and also geographical considerations, it is expected that subsequent regional adaptation will be required for specific health-care settings or contexts.
4. Research recommendations in general are described to inform a framework for ongoing research agendas in the international community. We have attempted to identify important study questions in need of answers. Through identification of gaps in knowledge, the reader will be better able to define methodologies, definitions of populations, and outcome measures of relevance to study designs in the future.

Topics that will not be covered

This document is not intended to provide enough detail to replace training and education in nephrology, nor is it intended to serve as a textbook of medicine or nephrology.

Thus, there are some specific topics that will not be covered. Specifically we will not discuss:

1. Evaluation and management of people receiving RRT (management of kidney failure by dialysis or kidney transplantation).
2. Specific approaches to the diagnosis of people with AKI and other acute kidney diseases. This topic has been extensively reviewed in *KDIGO Clinical Practice Guideline for Acute Kidney Injury.*[7]
3. Diagnostic work-up or treatment of specific causes of CKD, including GN.[8]
4. Management of pregnancy in women with CKD or of pregnant women who develop kidney disease.
5. Detailed management of endocrine and metabolic complications of CKD. These are reviewed extensively by recent KDIGO guidelines on CKD-MBD,[9] management of BP[10] and anemia[11] in CKD.
6. Detailed management of CVD and CVD risk factors in CKD. This is reviewed in a recent KDIGO publication.[12]
7. Drug dosing in CKD. This topic has been addressed in a recent KDIGO publication.[13]
8. Details of resource implications and barriers to implementation are beyond the scope of this guideline. By virtue of its being international, the variability in these aspects by country, region, and even jurisdiction is vast. We look to the individual commentaries from around the world to inform those aspects more fully.

Brief overview on methodology

The Work Group included an international group of kidney specialists, primary care physicians, diabetologists, epidemiologists, clinical chemists, administrators, and a professional Evidence Review Team (ERT) who provided support and guidance to the group. Details of the methods used by the ERT are described in *Methods for Guideline Development*, along with the systematic searches for areas identified by Work Group members and performed by the ERT.

The recommendations and statements created herein will serve to direct both care and research in the next decade. Importantly, we expect the renewed classification system and risk stratification concepts to direct research and enrollment into trials which address test therapies to improve patient outcomes.

Statement grading and wording. The methods for formulating recommendations were based on modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, and have used the words

Table 1 | KDIGO nomenclature and description for grading recommendations

	Implications		
Grade*	Patients	Clinicians	Policy
Level 1 "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

*The additional category "Not Graded" was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

'recommend' when the balance of evidence would support the notion that the majority of patients would benefit from the implementation of this recommendation. The words 'suggest' are used when the balance of evidence would support the notion that some patients would benefit from the implementation of the recommendation, but that individual patient, physician and health-care system considerations would be necessary to adopt the practice. There are also ungraded statements many of which are often key practice points or educational issues (Table 1). The Work Group had struggled whether to organize them differently or move them to the rationale section. Ultimately they remain here in the guideline statement format so that they are not overlooked by those wishing to understand the condition better.

A significant proportion of statements in this guideline are ungraded because the grading system is most appropriate for statements of intervention. The international system, GRADE, allows for such statements which guide thoughts and attitude, and not specific actions. In the descriptive statements identifying, classifying, and defining the condition of CKD, grading is not possible. Since few studies have compared different methods of evaluation or care models, those statements too are difficult to grade. Thus, grading of specific statements is reserved for interventions or alternative diagnostic test strategies for which there is a substantial body of evidence.

Consideration of health benefits, side effects, and risks. These have been considered when formulating the recommendations but given the paucity of data in many of the areas reviewed, this has been less consistent than the Work Group would have liked. We see this as an area of research and future study that will inform future updates.

Review process. As with all KDIGO guidelines a two step process was used. This included a review by the Board of Directors, with feedback to the Work Group Chairs followed by revisions to the document. The public review, consisting of interested stakeholders from international communities, organizations and individuals, was then undertaken. The draft document was sent to a total of 2320 external reviewers, with 293 responses received and tabulated. The feedback was carefully reviewed and where appropriate, suggested changes were incorporated into the final document. In the interest of transparency, the Work Group prepared individual responses to each reviewer comment and these will be posted on the KDIGO website.

Planned update. At the current time there is no official plan to update the guideline in its entirety. Given the breadth and depth of the current undertaking and with knowledge of new studies and applications of some of these recommendations, the Work Group recommends that individual sections of this guideline be updated every 3-5 years as new evidence becomes available. We believe that this will be more practical for the readership.