

## **KD:IGO Position Statement On**

### **The Definition and Classification Of Chronic Kidney Disease**

Abbreviated from Original version (Kidney International 2005, xx, xx-xx)

#### **I. Definition and Classification of CKD**

##### ***I.A Definition of CKD***

The K/DOQI definition of chronic kidney disease (Table 1), was accepted, with the following clarifications:

**Table 1. Definition of Chronic Kidney Disease Criteria**

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1. Kidney damage for  $\geq 3$  months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, that can lead to 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<sup>2</sup> for  $\geq 3$  months, with or without kidney damage
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*Abbreviation: GFR, glomerular filtration rate.*

*I.A.1. Retain the term “disease” to convey importance.* It is important that the definition use terms that reflect an appropriate balance between emphasizing need for diagnosis and treatment as opposed to that of labeling a risk condition as a disease. The K/DOQI definition of chronic kidney disease as a “disease” is consistent with current usage of this term. The Oxford English Dictionary (Compact Edition) defines a disease as “A disorder of structure or function in a human, animal, or plant, especially one that produces specific symptoms.” Evidence in support of a disease include clinical-pathological correlations (as defined by case series), associations with symptoms or findings (as

defined by cross-sectional analyses), and associations with outcomes (as defined by longitudinal analyses). The use of the term “disease” in CKD is consistent with: (1) the need for action to improve outcomes through prevention, detection, evaluation and treatment; (2) providing a message for public, physician and patient education programs; (3) common usage; and (4) its use in other conditions defined by findings and laboratory tests, such as hypertension, diabetes, and hyperlipidemia

I.A.2. Infer chronicity from documentation or presumption of kidney disease for >3 months.

This clarification allows clinical judgment about chronicity in the absence of past data on levels of GFR or markers of kidney damage. In the future, it will be important to link the definition of chronicity with definition of acute kidney disease.

I.A.3. Retain reduced GFR as a criterion for kidney disease. GFR is widely accepted as the best index of kidney function. The rationale for a threshold level of GFR <60 ml/min/1.73 m<sup>2</sup> is as follows:

- ❑ It is substantially above the level associated with kidney failure leaving time for treatment of kidney disease to prevent kidney failure
- ❑ It is less than half the adult level of GFR
- ❑ Lower levels are rare in young men or women (<40 years)
- ❑ Lower levels are associated with increasing complications of CKD
- ❑ Lower levels are associated with adverse outcomes, including cardiovascular disease morbidity and mortality in individuals with and without diabetes.

This threshold and lower levels can be detected with current estimating equations for GFR based on serum creatinine, but not by serum creatinine alone.

I.A.4. Retain albuminuria as a marker for kidney damage. Threshold values for spot urine albumin to creatinine ratio are discussed subsequently. The rationale for the recommended threshold (> 30mg/g) is as follows:

- ❑ The threshold level is 2-3 times greater than the normal value.
- ❑ Higher levels are infrequent in young men and women (<40 years).

- Higher levels are the earliest marker of kidney damage due to diabetes, glomerular diseases, and hypertension.
- Higher levels are associated with adverse outcomes, including progression of kidney disease and cardiovascular disease in individuals with and without diabetic mellitus.
- Therapies that reduce albuminuria are associated with slowing the progression of diabetic and nondiabetic kidney disease.

*I.A.5. Allow clinical judgment regarding the relevance of other markers of kidney damage.* Other markers of kidney damage include abnormalities in the urine sediment (casts, tubular epithelial cells); abnormalities in imaging studies (polycystic kidneys, hydronephrosis, small, "echogenic" kidneys); and abnormalities in the composition of the blood and urine that define "tubular syndromes" (renal tubular acidosis, nephrogenic diabetes insipidus, Fanconi syndrome, etc). The K/DOQI guidelines address the clinical relevance of these abnormalities based on whether they "can lead to decreased kidney function."

*I.A.6. Consider all kidney transplants recipients to have chronic kidney disease,* irrespective of GFR level or presence or absence of markers of kidney damage. The rationale for this is based on damage to native kidneys, presumed damage to the kidney transplant based on studies of "protocol biopsies," and need for life-long care caused by complications of prior CKD and chronic allograft nephropathy.

*I.A.7. Do not include cause of kidney disease in definition of CKD.* Identification of the cause of kidney disease is one of the goals of evaluation of CKD, and may lead to changes in management of CKD. However, CKD can be detected without knowledge of its cause, ascertainment of the cause may require specialized knowledge and procedures not available to the vast majority of clinicians who encounter and can detect CKD. Importantly, the cause of CKD cannot always be determined despite extensive evaluation. Thus, it is not practical to include the cause of CKD as part of the definition. However, CKD can be classified by cause, as described below.

### 1.B Classification of CKD (Table 2)

In principle, CKD could be classified according to severity, diagnosis, treatment and prognosis. Classification systems can be simple or complex. The choice of a classification system depends on answers to several questions:

- ❑ To whom is the classification system addressed?
- ❑ Can we build a system that is useful to most clinicians, with additional complexity that is useful to some?
- ❑ Can the classification system be linked to “Action Plans”? An action plan should be evidence-based, but modifiable based on considerations for different populations, and individualized based on patient circumstances.

**Table 2. Classification of Chronic Kidney Disease**

Stage	Description	GFR (mL/min/1.73 m <sup>2</sup> )	Related Terms	
1	Kidney damage with normal or ↑ GFR	≥90	Albuminuria, Proteinuria, Hematuria	T if kidney transplant recipient
2	Kidney damage with mild ↓ GFR	60–89	Albuminuria, Proteinuria, Hematuria	
3	Moderate ↓ GFR	30–59	Chronic renal insufficiency, Early renal insufficiency	
4	Severe ↓ GFR	15–29	Chronic renal insufficiency, Late renal insufficiency, Pre-ESRD	
5	Kidney failure	<15 (or dialysis)	Renal failure, Uremia, End-stage renal disease	D if dialysis (HD, PD)

*Abbreviations: GFR, glomerular filtration rate; ESRD, end-stage renal disease.*

*Related terms for CKD Stages 3-5 do not have specific definitions, except ESRD.*

*I.B.1. Retain classification based on severity.* There was agreement with initial classification based on level of GFR, using GFR estimating equations. This initial classification is simple, and can be linked to “Action Plans”. Because of imprecision of GFR estimates at higher range of GFR, it may be difficult to distinguish Stages 1 and 2. Alternative terms such as “stage, class, or grade“ can vary depending on local interpretation and language.

*I.B.2. Add classification based on treatment by dialysis or transplantation.* This is necessary to link with clinical care and policy, especially regarding reimbursement. To this end the use the following suffix:

- ‘T’ for all kidney transplant recipients, at any level of GFR (CKD Stages 1-5).
- ‘D’ for dialysis, for CKD stage 5 patients treated by dialysis. Irrespective of the level of GFR at which dialysis is initiated, all patients treated by dialysis are CKD Stage 5D.

*I.B.3. Encourage further consensus development on classification by cause of kidney disease.* Clinical evaluation for CKD should include elucidation of the cause of disease. As discussed above, cause of disease cannot be ascertained in all cases. Classification based on cause of disease would be desirable, but would require development of standard criteria for causes of CKD and a uniform taxonomy. These would be important areas for further research and consensus development.

*I.B.4. Further research is necessary to allow classification by prognosis.* Stratification of risk for the major outcomes of CKD (loss of kidney function and CVD) is based in part, on level of GFR (CKD stage) and cause of kidney disease. Other factors are also important and could be considered in risk stratification, such as magnitude of albuminuria. It is likely that these and other risk factors contribute differentially to the risk of different outcomes (Table 3). Research is needed to elucidate risk factors and develop risk prediction instruments for CKD progression and CVD.

**Table 3. Risk Factors for Progression of Chronic Kidney Disease, Cardiovascular Disease and Death**

Outcome	Importance for Different Outcomes		
	CKD Stage	Type of Kidney Disease (Diagnosis)**	Proteinuria
Concurrent complications*	+++	+	+
Prognosis (next 10-years)			
Risk of CVD or mortality	+++	+	+++
Risk of kidney failure	+++	++	+
Rate of decline in GFR	+	+++	++

\*Concurrent complications include hypertension, anemia, malnutrition, bone disease, neuropathy and decreased quality of life.

\*\*For example, diabetic kidney disease, glomerular diseases, vascular diseases (such as hypertensive nephrosclerosis), tubulointerstitial diseases (including disease due to obstruction, infection, stones and drug toxicity or allergy), and cystic disease (including polycystic kidney disease).

### **I.C. Research Questions**

- ❑ What is the relationship of body surface area (BSA) or total body water (V) to measured GFR in an individual patient. What is the impact on outcomes of adjustment by BSA or V?
- ❑ Should CKD Stage 3 be divided into two stages because of greater risk of CVD outcomes in patients with GFR 30-44 ml/min/1.73 m<sup>2</sup> compared to GFR 45-59 ml/min/1.73 m<sup>2</sup>?
- ❑ •Are different equations required for different populations and does that impact on utility of the system at the present time as a global tool?
- ❑ Do non-referred populations with low GFR have similar outcomes as referred populations?

- ❑ Are there different predictors of progression in different populations?
- ❑ What are the predictors of risk within each CKD stage that would change the treatment plans?
- ❑ What are the implications of different levels of GFR post transplant for CKD progression and CVD outcomes?
- ❑ If we use different or better tools to define kidney disease would we have different outcomes?
- ❑ What is the outcome of patients with increased GFR (hyperfiltration)?
- ❑ What are the long term outcomes of patients with acute kidney disease?
- ❑ What is the time course of chronic vs. acute kidney disease?
- ❑ Should the definition of chronicity vary among diseases or populations?
- ❑ Can chronicity be inferred by rate of change of kidney function over intervals shorter than 3 months?
- ❑ Can we identify markers that will predict 'rapid' progression?

## **II. Estimation of GFR**

### ***II.A. Standardization and Calibration of Serum Creatinine Assay:***

*II.A.1. Serum creatinine measurements should be standardized.* In the classic and modified Jaffé reaction, up to 20% of the color reaction in serum or plasma in normal subjects is due to substances other than creatinine ("non-creatinine chromogens"). Calibration of serum creatinine assays to adjust for this interference is not standardized across laboratories, such that systematic differences among laboratories account for most of the differences between observed and expected results compared to a reference standard. The lack of standardization can also cause differences in serum creatinine measurements within laboratories over time.

*II.A.2. Calibration should be traceable to an international reference creatinine method.* Isotope dilution mass spectrometry (IDMS) is an appropriate method. Cooperation from manufacturers is critical to this process.

## **II.B. Reporting Estimated GFR:**

*II.B.1. Estimated GFR should be reported automatically using an equation based on serum creatinine* following assay calibration and patient variables. Clinical laboratories are critical for the implementation. This recommendation does not preclude reporting GFR estimates prior to calibration, recognizing that GFR estimates  $>45\text{-}60$  ml/min/1.73 m<sup>2</sup> are sensitive to calibration differences.

*II.B.2. GFR estimates have been reported successfully using several different models.*

a. Interpretation of GFR estimates in the context of CKD definition:

“GFR  $<60$  ml/min/1.73m<sup>2</sup> for 3 or more months is consistent with CKD”

“GFR  $\geq 60$  ml/min/1.73m<sup>2</sup> and kidney damage that is present for 3 or more months is consistent with CKD”

“GFR  $\geq 60$  ml/min/1.73m<sup>2</sup> without kidney damage is not consistent with CKD”

b. Accounting for imprecision of GFR estimates at higher values:

If creatinine assay is calibrated,

Some labs report a numerical value for GFR  $<90$  and “GFR  $\geq 90$ ” for higher values.

Other labs report numerical value for GFR  $<60$  and “GFR  $\geq 60$ ” for higher values.

If creatinine assay is not calibrated, numerical value of value of GFR can be reported for GFR  $<60$  and “GFR  $\geq 60$ ” for higher values.

Numerical value of GFR at all GFR levels, with qualification that levels of GFR  $>60$  are imprecise

c. For all of the above, GFR levels of <60 have been highlighted as abnormal. Values from 45-59 are estimated with less precision. Some individuals with an initial abnormal GFR in this range will have a higher estimate on subsequent testing. Averaging of multiple measurements will improve the precision of estimated GFRs as it does that of measured inulin clearance.

## **II.C GFR Estimating Equations**

### *II.C.1. Estimating equations for GFR should have the following characteristics:*

- ❑ Developed in a large cohort, including a variety of racial and ethnic groups for international comparisons
- ❑ Evaluated in an independent cohort.
- ❑ Validated to have adequate precision and low bias against a gold standard measure of GFR (not creatinine clearance)

*II.C.2. Abbreviated MDRD Study equation meets these criteria.* The MDRD Study equation has been validated in patients with diabetic (type 2) and non-diabetic kidney disease and in kidney transplant recipients. It has been validated in U.S. whites and African-Americans, European whites, but requires verification for other groups, countries and racial and ethnic groups.

*II.C.3. Cockcroft-Gault formula is more difficult to implement in clinical laboratories.* It requires weight (and height for body surface area adjustment), which are usually not recorded on laboratory requisitions. Furthermore, the optimal calibration of serum creatinine for this equation is uncertain.

*II.C.4. Both MDRD Study and Cockcroft-Gault equations are imprecise at high values for GFR* (low values for serum creatinine). This may cause misclassification in selected groups, including

- ❑ normal individuals
- ❑ children
- ❑ pregnant women
- ❑ conditions associated with hyperfiltration

***II.D. Clinical Circumstances in which Clearance Measurements May Be Necessary to Estimate GFR*** (Table 4)

**Table 4. Clinical Circumstances in which Clearance Measurements May Be Necessary to Estimate GFR**

- Extremes of age and body size
- Pregnancy
- Severe malnutrition or obesity
- Diseases of skeletal muscle
- Paraplegia or quadriplegia
- Vegetarian diet
- Rapidly changing kidney function
- Prior to dosing drugs with significant toxicity that are excreted by the kidney
- Prior to kidney donation
- Clinical research projects with GFR as a primary outcome

***II.D.1. Situations in which GFR estimation may be unreliable:***

- Patients with grossly abnormal muscle mass (e.g. amputation, paralysis, muscular disease)
- Low body mass index (<18.5 kg/m<sup>2</sup>)
- High or low intake of creatinine or creatine (e.g. dietary supplements, vegetarians)
- Rapidly changing kidney function
- Pregnancy

*II.D.2. Situations when a high degree of accuracy may be needed:*

- Potential kidney donors
- Prior to dosing with medications that have high toxicity that are excreted by the kidneys

*II.D.3. Methods for measurement of GFR:*

Exogenous filtration markers including inulin, iothalamate (<sup>125</sup>I-labeled or unlabeled), <sup>51</sup>Cr-EDTA, <sup>99</sup>Tc-DTPA and iohexol provide good accuracy.

Urinary or plasma clearance of exogenous filtration markers can be used to measure GFR.

Urinary clearance of exogenous filtration markers is less susceptible to error than plasma clearance.

Accurate clearance measurement requires cooperation among nephrology, nuclear medicine, and clinical chemistry departments to establish protocols and training of personnel for proper administration and assay of the marker, patient preparation and sample collection. In particular, preparation of <sup>99</sup>Tc-DTPA requires careful attention to quality control.

Creatinine clearance may be a useful alternative when exogenous filtration markers are not available.

***II.E. Dosage Adjustment for Drugs Excreted by the Kidneys***

*II.E.1. Drug dosing should be based on GFR estimates without surface area adjustment.* The difference between adjusted and unadjusted GFR is largest for individuals with body size substantially different from 1.73 m<sup>2</sup> (children, obese, very large or small adults).

- Cockcroft-Gault equation provides unadjusted creatinine clearance.
- MDRD Study equation provides adjusted GFR.

*II.E.2. Recommendations for drug dosing* should be based on methods for measuring or estimating GFR that were used in pharmacokinetic studies. This is most important for narrow ranges of GFR or for drugs with significant toxicity. Otherwise, either MDRD Study or Cockcroft-Gault equation provides reasonable estimates.

*II.E.3. Most studies are based on creatinine clearance*. Many pharmacies use Cockcroft-Gault equation to estimate creatinine clearance before dispensing drugs. Future studies should provide drug dosing information based on both GFR and creatinine clearance. This will facilitate use of GFR estimates.

## **II.F. Research Recommendations**

Validating estimation equations for GFR in more diverse groups such as:

- ❑ Healthy populations
- ❑ Patients with BMI > 35 kg/m<sup>2</sup> and <19 kg/m<sup>2</sup>
- ❑ Elderly patients
- ❑ Type 1 diabetics
- ❑ Specific ethnic groups and nationalities (Southeast Asians, South Asians, Native Americans, Africans, Aborigines, Latin Americans)

Development of new equations to improve on the present equations.

Serum cystatin C alone and in combination with serum creatinine

Inclusion of variables to estimate lean body mass, such as anthropometry and imaging studies.

Determine the influence of patient referral source on estimated GFR for a given serum creatinine.

Use of repeated measurements of serum creatinine to improve precision of GFR estimates

Determine the accuracy of formulas to follow progression of CKD

Establish a database of research studies and clinical populations with GFR measurements and measurements of serum creatinine from a variety of countries, racial and ethnic groups to develop improved GFR estimating equations.

### **III. Assessment of Proteinuria**

#### ***III.A. Which urine protein should be measured and which measurement method should be used?***

*III.A.1. Albumin is the preferred urinary protein.* Increased urinary excretion of albumin is the earliest manifestation of chronic kidney disease due to diabetes, other glomerular diseases, and hypertensive nephrosclerosis. Albuminuria may also accompany tubulointerstitial diseases, polycystic kidney disease, and kidney disease in kidney transplant recipients.

Albumin measuring techniques should be traceable to the CRM 470 standard. If positive, may follow up with other protein measurements, for example total protein, or low-molecular weight proteins. Future research needs to focus on whether a urine albumin standard would be better than that of plasma albumin now used.

#### *III.A.2. Multiple methods are available to assay albumin:*

- ❑ Turbidometry (less sensitive and specific for albumin than other methods)
- ❑ Nephelometry
- ❑ Radioimmunoassay (RIA)
- ❑ Enzyme-linked immunosorbent assay (ELISA)
- ❑ If above unavailable an antibody-based dipstick can be used.
- ❑ Conventional dipstick in spot urine specimens is acceptable, if it is the only available option.

### III.B Collection and process

III.B.1. Random untimed “spot” urine samples are suitable for initial testing. A first morning urine sample is preferable, but not required if it poses substantial inconvenience compared to a random specimen.

III.B.2. Results should be expressed as albumin-to-creatinine ratio. Expression as a ratio corrects for variability due to hydration, diuretics, osmotic diuresis, concentrating defects.

III.B.3. For positive tests, rule out contamination from infection or menstrual blood with dipstick evaluation for leukocytes and erythrocytes.

III.B.4. Verification of increased albumin excretion requires 2 out of 3 positive tests. Patients with increased albumin excretion should be diagnosed as having CKD, and should undergo appropriate evaluation.

III.B.5. Timed urine collection for albumin and creatinine may be performed if increased precision is required.

### III.C. Thresholds for Abnormal Albumin-to-Creatinine Ratio (Table 5)

**Table 5. Threshold Levels for Abnormalities in Urinary Albumin**

24-hour Urine Collection	Spot Morning Urine Sample	Albumin-to-Creatinine Ratio*		Terms
Albumin Excretion Rate (mg/day)	Albumin Concentration (mg/l)	(mg/mmol)	(mg/g)	
<30	< 20	<3 M <2.0 F <3.0	<30 M <20 F <30	Normal
30-300	20-200	3-30 M 2.0-20 F 3.0-30	30-300 M 20-200 F 30-300	“Micro-albuminuria”**
>300	>200	>30 M >20 F >30	>300 M >200 F >300	“Macro-albuminuria”**

Abbreviations: M, male; F, female.

Threshold levels for albumin-to-creatinine ratios vary among guidelines. Threshold levels shown here are close to the various recommendations, but rounded to figures that are close to the threshold levels given in mg/day and mg/l

\*\*Terms are commonly used but should be avoided because they are misleading (see text).

*III.C.1. Threshold levels for diagnosis of CKD is >30 mg/g.* This is consistent with the definition in recommendations K/DOQI, JNC-7, and 2004 American Diabetes Association (ADA). This levels corresponds roughly to various definitions of "microalbuminuria." Sex-specific threshold levels (approximately 20 mg/g in men and 30 mg/g in women) adjust for greater average creatinine excretion in men than women [26-28]. However, there is some reluctance to recommend sex-specific threshold levels based on greater complexity, uncertainty regarding assay precision, and effect of factors in addition to sex on creatinine excretion, such as race, ethnicity, diet, and measures of body size.

*III.C.2. Levels of albumin to creatinine ratio >300 mg/g (>200 mg/g in men and >300 mg/g in women)* correspond roughly to various definitions of "macroalbuminuria", or "clinical proteinuria", which are associated with even higher levels of risk for kidney disease progression and cardiovascular disease.

*III.C.3. The term "albuminuria" should be substituted for terms "microalbuminuria" and „macroalbuminuria.“* These terms should not be retained because they are misleading.

### ***III.D. Testing for Albuminuria in Patients at Increased Risk of CKD:***

*III.D.1. High risk groups should be tested for presence of albuminuria:* These include patients with the following:

- diabetes
- hypertension
- family history of CKD
- past or family history of CVD

*III.D.2. Frequency of testing for albuminuria in high risk groups has not been rigorously studied.* Many recommendations suggest yearly testing based on opinion. This is an important area for future research.

### ***III.E. Research recommendations***

- ❑ Are some ranges of albuminuria or some urinary proteins other than albumin more sensitive as a risk factor for CKD progression vs. CVD morbidity and mortality?
- ❑ How does the different range for HPLC assay for urinary albumin affect risk for CKD progression and CVD morbidity and mortality?
- ❑ Are there particular settings when point-of-care measurement of albumin is more effective for particular settings than that in a central facility?
- ❑ Does screening for albuminuria, followed by appropriate therapy, improve outcomes, in the general population, or in subgroups of elderly or obese individuals?
- ❑ What is the recommended frequency of testing for albuminuria in high-risk subgroups?
- ❑ Is reduction of albuminuria a surrogate outcome for slowing progression of CKD in clinical trials?
- ❑ Develop risk prediction equations for CKD progression and CVD morbidity and mortality, including albuminuria.
- ❑ Harmonize CKD guidelines with those of other specialties: endocrinology, hypertension, diabetes, cardiology, internal medicine, primary care, family practice, pediatrics, and clinical chemists.
- ❑ Define relationships between total protein-to-creatinine ratio and albumin-to-creatinine ratio for various ranges of proteinuria, including “clinical proteinuria” and “nephrotic syndrome.”