SUPPLEMENTARY MATERIAL

Annex 1: Current clinical case definitions

Although the i3C does not aim to agree on clinical or epidemiological case definitions, the World Health Organization, Centers for Disease Control (CDC), and other expert epidemiology organizations have created a template for a typical case definition for "an outbreak" investigations. It is arguable whether CKDu classifies as an outbreak but it is instructive to review these concepts and consider how they may apply to CKDu. The CDC for example advises that a case definition with two components: clinical and laboratory. The clinical criteria typically lay out person, place, and time. In addition to varying by levels of certainty (Annex Table 2), case definitions can (and likely should) vary over time as more information—typically diagnostic testing—becomes available.

Annex Table 2 CDC outbreak investigation categorization

		Advantage	Disadvantage	Applicable to CKDu?
Suspect	Typically based on one or two clinical criteria alone	Could be very sensitive—i.e., capture any and all at risk populations Useful in highly transmissible diseases, for purposes of isolation and prevention of further spread	Not specific, could be misleading by inflating numbers of afflicted persons	Probably, in specific areas if certain 'criteria' can be agreed upon
Probable	Based on several clinical criteria +/- one or two laboratory criteria	Offers an acceptable range of sensitivity *and* specificity	Requires additional resources	Yes, if can be operationalized to 'field conditions' in low-resource settings, for the purposes of surveillance, and management planning for nephrology services

Confirmed	Based on meeting all of the clinical criteria, and (typically) a diagnostic, "gold standard" laboratory criterion	Offers the highest specificity	Not feasible or practical in many instances	Yes, for clinical management, especially if a specific diagnostic tool that does not require biopsy can be developed. Biopsy confirmation—the current gold standard—not feasible in many areas

Recently, experts from Mesoamerica created a clinical and epidemiological definition for CKDu using a Delphi process, and further cited in the Pan American Health Organization's Resolution on Chronic Kidney Disease in Agricultural Disease. At a World Health Organization coordinated conference held in Sri Lanka in October 2016, experts proposed a 'suspected' and 'confirmed' classification system which builds on different sources of information to classify the condition (Annex table 3). These definitions are not identical, and the positive predictive value of these definitions against a biopsy is unknown but they indicate examples of systematic diagnoses and surveillance tools for CKDu.

Unique considerations that may be important in creating a clinical case definition of CKDu include:

- *Defining place or time period:* It is possible CKDu is unique to certain regions (Mesoamerican, Sri Lankan, Indian and other regions) and that "place or residence" needs to be part of the case definition. The limitations of this are that geography may change.
- *Limitations of diagnostic testing:* no "gold standard" except kidney biopsy, the availability of which is limited in Mesoamerican countries in particular
- *The existence of CKD without a known cause is widespread in clinical practice globally:* but must be differentiated from the epidemic levels of disease seen in rural communities as the former reflects late diagnoses and rarer diseases and in almost all cases will be a different clinical entity to CKDu
- *Low –income regions affected:* meaning agreed efforts aimed at labeling a patient as having CKDu need to be possible with limited resources

Annex 2: Comparison of case definitions for confirmed, suspect and probable cases of CKDu by Mesoamerican and Sri Lankan expert societies

	Meso America	Sri Lanka
Confirmed		
Presence of	• eGFR < 60 ml/min/1.73m^2 and/or albuminuria (30-to <3000 mg/g) and/or • Urinary sediment abnormalities including hematuria And/or • Renal tubular disorder And • Age 2 to 59 And • No ultrastructural abnormalities on kidney Ultrasound	• eGFR < 60 and/or albuminuria > 30 mg/g and • histopathological features consistent with CKDu on the biopsy
Exclusion of	• Diabetes with microvascular disease • Hypertension with target organ damage or BP≥160/100 • Autoimmune, hematologic, urologic or hereditary kidney disease • Repeated exposure to contrast	Criteria listed under suspect and probable CKDu
Suspect		
Presence of	• CKD as measured by eGFR < or albuminuria > 30 mg/g • Age < 60 years	• eGFR < 60 or albuminuria > 30 mg/g
Exclusion of	• Type 1 diabetes • Self reported hypertension • Self reported Autoimmune, hematologic or hereditary kidney disease	• Diabetes (self reported or diagnosed in clinic) • Hypertension on treatment or BP >=160/100 on two measurements • Proteinuria > 2 g/day
Probable		
Presence of	• A suspect case with CKD on repeat testing	• A suspect case with CKD on repeat testing performed 12 weeks later
Exclusion of	--	• Ultrastructural abnormalities on ultrasound • Clinical suspicion of other known causes of CKD • Diabetes based on fasting plasma glucose < 126 mg/dL. • Hematuria

Annex 3: Clinical diagnosis of CKDu

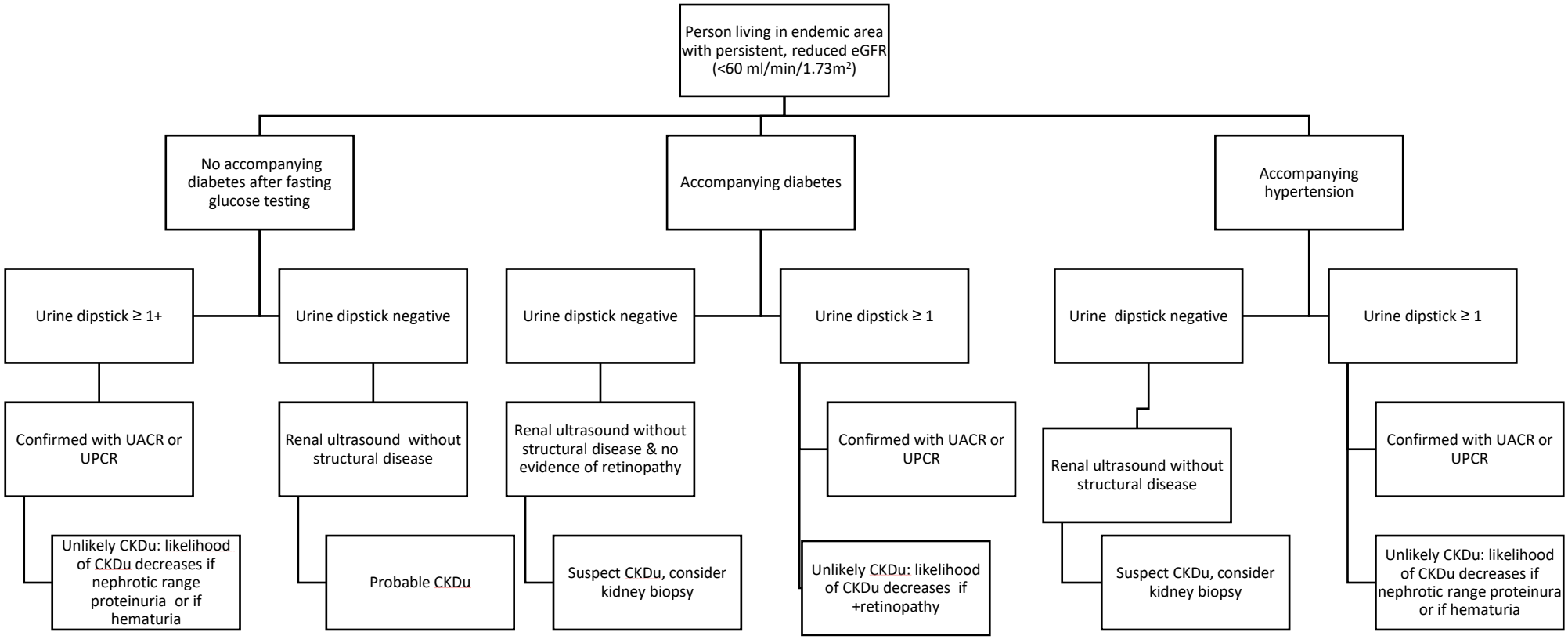
The i3C recognizes the challenges for nephrologists working in endemic regions and tasked with evaluating patients detected as having abnormal kidney function via population-based screening programs, or those presenting with symptoms of kidney disease. Given the controversy in consensus on a case definition, how does a nephrologist decide whether such a patient has CKDu (with the corresponding tubulo-interstitial disease), especially if kidney biopsy is not available? Another important diagnostic tool, urine albumin to creatinine ratios, is expensive and variably available in endemic regions.

With these considerations in mind, we outline the following principles if a non-biopsy based diagnosis is sought:

1. Confirmation of persistently abnormal serum creatinine (with repeat serum creatinine and eGFR assessment) is critical*. Proteinuria alone without abnormal serum creatinine is unlikely to be correlated with tubulo-interstitial kidney disease on biopsy. Since the diagnosis relies heavily on serum creatinine measurement, efforts to use laboratory equipment calibrated to IDMS standards are also essential.
2. Urinary assessment is required even if performed with a dipstick alone. Substantial proteinuria or hematuria should prompt work up for other forms of kidney disease. More and more data indicate that CKDu, especially in its earlier stages, is not associated with significant proteinuria or hematuria.
3. Diabetes and hypertension can co-exist with CKDu. In patients with these comorbidities, living in endemic areas but without significant proteinuria or hematuria, or evidence of end-organ damage from these diseases, CKDu should be considered.
4. Where possible, kidney biopsy confirmed diagnosis is ideal.

Based on these principles, one possible algorithm for a diagnosis of CKDu in endemic is presented below.

*Within the framework of a clinical diagnosis, it is important to recognize that an acute tubulo-interstitial disease with some degree of recovery has recently been described in endemic regions. Patients are typically symptomatic with back pain or fever, and leukocytosis. Biopsy could be considered in such cases, especially if evidence of acute and persistent rise in serum creatinine is noted, albeit only for a short period.


Person living in endemic area with persistent, reduced eGFR (<60 ml/min/1.73m²)
No accompanying diabetes after fasting glucose testing
Accompanying diabetes
Accompanying hypertension
Urine dipstick ≥ 1+
Urine dipstick negative
Urine dipstick negative
Urine dipstick ≥ 1
Urine dipstick negative
Urine dipstick ≥ 1
Confirmed with UACR or UPCR
Renal ultrasound without structural disease
Renal ultrasound without structural disease & no evidence of retinopathy
Confirmed with UACR or UPCR
Renal ultrasound without structural disease
Confirmed with UACR or UPCR
Unlikely CKDu: likelihood of CKDu decreases if nephrotic range proteinuria or if hematuria
Probable CKDu
Suspect CKDu, consider kidney biopsy
Unlikely CKDu: likelihood of CKDu decreases if +retinopathy
Suspect CKDu, consider kidney biopsy
Unlikely CKDu: likelihood of CKDu decreases if nephrotic range proteinura or if hematuria

Annex 4: Example reporting of eGFR data from an active detection study using different definitions

Once primary data are acquired a number of analyses can be performed using both the distribution of eGFR in a population or numbers of participants below a certain threshold. For example, the prevalence of CKDu (as opposed to CKD of other causes) could be better approximated by excluding participants with diabetes or similarly restricting to those without heavy proteinuria. These criteria could be refined as additional information about the epidemiology of CKDu becomes available. Summary data from a simulated sample obtained from a hypothetical population with a high prevalence of CKDu amongst working age men is shown in the table below.

Data, collected with the same methodology, presented in this format can then be compared across time points and between regions. Further stratification by urban/rural residence or other proposed CKDu risk factors might be informative. Additional adjustment for meat-intake and body composition indices is likely to reduce bias due to non-renal sources of creatinine in these estimates.

Population		Definition 1: All		Definition 2: Excluding self-reported hypertension or diabetes[1]		Definition 3: As definition 2 but also excluding ACR>300mg/g	
	n	eGFR (SD)	n (%) with GFR<60	eGFR (SD)	n (%) with GFR<60	eGFR (SD)	n (%) with GFR<60
Men							
18-30	97	112 (16)	12 (12)	115 (17)	11 (11)	115 (17)	11 (11)
31-40	102	109 (15)	20 (20)	110 (18)	18 (18)	108 (18)	17 (17)
41-50	89	99 (15)	13 (15)	101 (15)	10 (11)	104 (15)	9 (10)
51-60	78	99 (13)	12 (15)	100 (13)	8 (10)	99 (13)	6 (8)
>60	97	88 (17)	19 (20)	95 (18)	10 (10)	88 (17)	6 (6)
Women							
18-30	111	121 (14)	4 (3)	125(10)	2 (2)	125(9)	2 (2)
31-40	101	119 (15)	4 (4)	123 (11)	2 (2)	120 (10)	1 (1)
41-50	96	117 (14)	4 (4)	120 (11)	1 (1)	118 (10)	1 (1)
51-60	89	101 (15)	5 (6)	110 (13)	2 (2)	110 (13)	1 (1)
>60	101	89 (16)	7 (7)	95 (14)	3 (3)	95 (14)	3 (3)

[1] It is important to underline the i3C group is not suggesting those with diabetes or high blood pressure cannot also get CKDu. However, the aim of this pragmatic type of analysis is to determine whether there is an excess of low eGFR across a population that is not attributable to another cause rather than to provide a clinical diagnosis at an individual level (for which approaches are outlined in Annex 2).