The International Society of Nephrology's International Consortium of Collaborators on Chronic Kidney Disease of Unknown Etiology: Report of the working group on approaches to population-level detection strategies and recommendations for a minimum dataset

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ABSTRACT

There is an epidemic of chronic kidney disease of unknown cause (CKDu) clustering in rural communities of low-and-middle income countries. The International Society of Nephrology's International Consortium of Collaborators on CKD of Unknown Etiology established a workgroup to develop uniform approaches to detecting CKDu at a population-level. The group have outlined methodologies to detect CKDu using routine data or population-based studies along with elements of minimal data sets that could be used to provide robust and comparable measures of CKDu burden. Use of these common approaches will allow the international nephrology community to speak with a single voice when advocating for resources to support research, prevention and treatment of CKD in low-income settings and CKDu specifically.

1. INTRODUCTION

There is an epidemic of chronic kidney disease (CKD) clustering in rural communities, predominantly in a number of low-and-middle income countries[1]. Tens of thousands of working-aged adults are estimated to have died from the disease in Central America[2] with similar numbers in Sri Lanka[3]. Similar diseases have been reported elsewhere, e.g. rural regions or communities in India[4], North[5] and West[6] Africa. Those affected do not have common risk factors or underlying conditions that lead to CKD, e.g. diabetes, immune-mediated glomerulonephritis or structural renal disease. In instances where histopathology is available, the predominant feature is tubular atrophy and interstitial fibrosis[7-10]. Although it is currently unclear whether there is a unified underlying cause, these conditions have been collectively termed CKD of unknown cause ("CKDu"). Other terms used include CKD of non-traditional Cause[11], Mesoamerican Nephropathy[12], Chronic Intestinal Nephritis in Agricultural Communities[13] and Kidney Disease of Unknown Cause in Agricultural Laborers[14] but we have chosen CKDu as the most agnostic terminology.

The current clinical and research landscape in CKDu consists of multiple similar, but non-concordant approaches to individual-level diagnosis[11,15] and detection at the population-level[15-17]. In combination with the ongoing lack of treatment or prevention strategies the heterogeneity in identification of CKDu is a significant obstacle to combating the disease.

A uniform approach to detecting CKDu on a population-level would allow comparisons between studies and regions, providing valuable data for healthcare agencies and a basis for understanding key risk factors for disease. However even when "gold-standard" diagnostic investigations are available, no single approach will capture CKDu with complete certainty, and, depending on the reasons for evaluation, clinicians or researchers may accept differing levels of uncertainty. Nonetheless a uniform approach enables comparability and allows the international nephrology community to speak with a single voice in attempts to advocate for research, prevention and treatment resources.

To this end the International Society of Nephrology's International Consortium of Collaborators on Chronic Kidney Disease of Unknown Etiology (i3C) created a workgroup to guide a common approach to the detection of CKDu. This work shares many goals, and aims to be complementary to, the recent Resolution on Chronic Kidney Disease[18] from the Pan American Health Organization. We list different study populations that might be of interest alongside kidney-specific and other measures that could be used to determine the burden of disease.

Finally, we recommend a number of elements for a 'minimum dataset' endorsed by the i3C, for use in studies aimed at quantifying and comparing disease burden.

Key to this work is the recognition that there is currently no consensus on the case definition(s) for CKDu, and existing definitions may be refined in future[11,19]. Therefore the aim should be to obtain key information that can be used in a variety of definitions of CKDu now and going forward. Hence this approach is designed to estimate the extent of ESRD or impaired kidney function in a specific region of interest, and then determine the proportion of that estimate attributable to the "CKDu" as later defined.

We selectively focus on detection, rather than surveillance, as an initial step to building consensus approaches. Although the methodologies described could be part of wider surveillance efforts, systems required for continual monitoring, real-time data interpretation and reporting are not discussed. Furthermore we also recognize diagnosis of CKDu in individuals can be challenging, particularly in resource-constrained settings; potential strategies are discussed further in the Supplementary Material.

We have divided detection efforts into:
(i) *Passive detection* based on routine data collected for clinical or administrative purposes, and,
(ii) *Active detection* undertaken specifically for the purposes of determining disease prevalence (based on prospective epidemiological studies or extant datasets for the study of non-communicable diseases in general).

Recommended approaches and the minimum dataset are highlighted in the tables.

2. PASSIVE DETECTION.

Death certification, and end-stage renal disease (ESRD) registries are potential data sources (Table 1) that can help identify regions as "hot spots" of kidney disease. Indeed, such approaches have been a key first step in recognising existing CKDu epidemics [20,21]. Two issues arise when using routine data:

1. Scarce and poor-quality routine data collection in many of the potentially affected regions. The World Health Organization (WHO) and Institute for Health Metrics and Evaluation have published global estimates on cause-specific deaths included those attributed to kidney disease[22]. The methodology underlying WHO estimates of cause-specific mortality is available elsewhere[22] however data-quality, including that based on verbal autopsy-based diagnosis of CKD[23], from almost all regions likely to be impacted by CKDu is suboptimal (Figure 1).

2. Difficulty differentiating whether recorded kidney disease is due to the CKDu. Misattribution of cause, a major challenge worldwide but particularly in settings where biopsies are not routinely obtained, could lead to misclassification as CKDu where a biopsy would have provided a diagnosis (e.g. IgA Nephropathy).

Additionally, CKDu is unlikely to be recorded specifically in death registries so underlying knowledge of diabetes, (and ideally rates of CKD attributed to diabetes) are key to generate useful estimates (as diabetes is the commonest cause of ESRD). Dialysis and transplant registries usually record cause-specific diagnoses albeit subject to misclassification as well; however terminology may vary and in most low-resource settings, the registries capture only a small fraction of patients reaching ESRD.

3. ACTIVE DETECTION

Active detection of CKDu will involve the systematic survey of populations to detect disease. This may involve new studies focused on CKDu or the use of existing datasets or plans for non-communicable disease surveillance, where minimum requirements are met. Indeed, there may be significant gains to be made in terms of rapid acquisition of prevalence data by accessing or modifying existing studies/processes (e.g. WHO STEPS[24] instruments or USAID Demographic and Health Surveys[25]).

Populations and study design

The possible populations and study approaches to active detection are outlined in Table 2. A critical feature of the reporting of all efforts is a description of the geographical area along with both the source population and the study responders so that conclusions about the representativeness of the study sample be drawn. These summary response rate data should be stratified by sex and age with adequate granularity to detect response bias (e.g. 10-year age bands).

Numerator (determined by measures of kidney dysfunction)

As alluded to in the introduction our aim is not to presuppose a definition of CKDu, but to provide a framework for the collection of data that will allow detection of CKD in a reproducible manner, to which a number of

definitions of CKDu to be applied (e.g. using different thresholds of kidney function or presence or absence of proteinuria or comorbidity). Importantly The Kidney Disease Improving Global Outcomes collaboration provides internationally accepted criteria for the clinical identification of CKD[26]. Given the asymptomatic nature and other attributes of CKDu population-based detection methods for this disease need to be based on measures of kidney function (estimated glomerular filtration rate, eGFR). Although the KDIGO definition of CKD requires two-measurements of eGFR[26] the multiplicative increase in resources required to re-contact participants after a prolonged period means that, in common with a large body of CKD-epidemiology, the i3C workgroup recommends accepting initial detection efforts based on a single eGFR estimate only. Furthermore, definitions of CKD use a threshold of GFR, however to allow maximum flexibility i3C advocates collection and reporting of the entire distribution of GFR values along with numbers below a particular (CKD) threshold. The different methods to quantify renal dysfunction are outlined in Table 3.

Other important data items

Key associations of CKDu at a population level are the absence of heavy proteinuria, and other causes of, or risk factors for, CKD and the socio-demographic characteristics of those that are affected. Therefore, information on these variables are needed to produce informative prevalence estimates (Table 3). The recommendations have been kept to a ***minimum*** to ensure minimal resource implications and allow the use of extant datasets.

4. APPLICATION OF SUGGESTED APPROACH

There is an urgent need for data that are comparable regionally and internationally, and the aim of a minimum data set(s) is/are to obtain the key information that can be used to define CKDu currently and in future (see supplementary material for an example). Such a dataset is contingent upon an international agreement to collect uniform data but it is **presumed and expected that researchers, agencies and service providers should collect additional data to meet their own specific needs.**.

Active or passive approaches may be more or less appropriate for these different aims including:

1. Alerting health services/communities/researchers to a possible problem of CKDu,
2. Estimating scope and scale of CKDu within populations
3. Determining secular trends in CKDu
4. Insight into disease aetiology

Therefore, it may be appropriate to apply two (or more) approaches in any single region. A protocol using a similar minimum dataset to undertake population-level detection has recently been published and is already being used in a number of settings in South Asia, Latin America and Sub-Saharan Africa[27].

5. SUMMARY

A uniform approach to detecting CKDu on a population-level allows the understanding key risk factors for disease, provides valuable data for healthcare agencies and establishes a basis for comparisons between regions and research studies. This document elaborates the methodology to detect CKDu via passive or active detection and suggests criteria for minimum data set. Such a common approach would allow the international nephrology community to speak with a single voice in attempts to advocate for research, prevention and treatment resources for CKD in general, and for CKDu in specific areas.

6. FIGURE LEGENDS AND TABLES

Figure 1. Map showing data-quality of cause-of-death by WHO member state as assessed by the 2016 Global Health Estimates project. Data from http://www.who.int/healthinfo/global_burden_disease/en/. WHO advises data from countries labeled in green (high completeness and quality) can be used for time or country comparisons whereas data from countries labeled yellow (moderate quality issues) or orange (severe quality issues) should only be used with caution. Estimates of cause-of death from countries labeled red (unavailable or unusable) should not be used for comparisons or policy purposes. Note: The impact of the availability of treatment for ESRD in a region may impact on estimates of the burden of chronic kidney disease (of any cause) from death registries as patients receiving renal replacement therapy may have a non-kidney related primary cause of death recorded and ESRD only recorded as a contributory cause (or not at all) .

Table 1 Passive detection approaches

Mortality registry	Deaths attributable to kidney disease#	National or regional mortality	Age-standardize* Subtract deaths attributable to diabetic kidney disease, or if not available, adjust for age-standardized diabetes prevalence^ Include only CKD not AKI	High-income countries mortality registries	A high-level, resource efficient approach to identify hot spots	Sometimes difficult to disaggregate to regional or state level Data are non-specific and not be able to differentiate CKDu from high rates of cause-specific kidney disease (e.g., IgA nephropathy).	Cause of ESRD or cause of kidney disease leading to death Data on the proportion of (non-CKD) deaths of unknown cause should also be reported as a quality indicator
Dialysis and transplant registry	Prevalent or incident numbers of patients with ESRD of unknown cause	Prevalent or incident ESRD population	Age standardize* Only include those with 'unknown' cause if registry provides these data	USRDS, ERA-EDTA, ANZDATA	A high-level, resource efficient approach to identify hot spots May also able to give a regional or state-level estimate if data are available.	Not available, or not representative of entire burden of (untreated) ESRD, in many low- and middle-income countries Attribution of kidney disease cause may be incorrect (or both known causes and CKDu may coexist)	Occupation of persons with ESRD Family history of persons with ESRD

We propose, that to the extent feasible, the data should be disaggregated to regional (in addition to national) levels and presented by age- and sex-strata so localized clustering can be identified.

The latest WHO and IHME Global burden of disease estimates include age-specific kidney disease attributable death estimates

*To referent World population as recommended by WHO http://www.who.int/healthinfo/paper31.pdf?ua=1

^These data are available on a national level at least via the IDF for many countries; the WHO also provides estimates for age-specific deaths due to diabetic kidney disease

Table 2 Study populations (denominator) and sampling approach

Population	Selection approach	Advantages/disadvantages	Recommended by i3C
Geographically defined community (aged>18)	**Random (or stratified random) sample or alternatively whole population***	**Representative of population prevalence Fieldwork can be challenging and response variable Requires new or existing census data**	**Yes**
Self-presenting or volunteer community population	All comers	Not representative and prone to major issues in interpretation due to selection bias	No
Workplace population	Random sample, whole population	Can be easier to capture participants than community based studies Investigators need to be sensitive to differing incentives between employees and employers to take part in studies Unlikely to be representative of community as a whole and may be misleading with regard to population prevalence and risk factors	May be useful if appropriate comparators can be identified

Table 3 Kidney function measures (to determine the numerator)

GFR Measures	Advantages/disadvantages	Recommended by i3C for minimum data set
eGFR from creatinine - SINGLE MEASURE (CKD-EPI formula)*	**Serum creatinine measures available in most countries IDMS referenced methods critical to allow comparison between centres Population specific non-renal sources of creatinine affect estimates (meat consumption, muscle mass/breakdown)****	**Yes, if IDMS referenced measures**
eGFR from creatinine - REPEAT MEASURE	As above Reduces misclassification of AKI as CKD, aligns with KDIGO clinical guideline Requires recontact of all those with abnormal results after > 3 months.	Yes if resources allow but not as part of a minimum dataset
eGFR from cystatin C	Cystatin C based eGFR may be less dependent on non-renal factors Impact of ethnicity on equations used to calculate the eGFR using cystatin C are unknown No accepted method for standardization across laboratories yet Expensive	Not yet but may become the international standard Bio banking samples may be advised
measured GFR	Likely overcomes the ethnicity dependent bias in eGFR Not dependent on non-renal sources of analyte Invasive Expensive	No

We acknowledge that comparing GFR between populations internationally is problematic as the normal distribution of this variable is unknown in many of the groups/regions[28] and the implications for health of a particular GFR is also unknown. These issues are felt to be beyond the remit of the i3C and require substantial global efforts to address but are nonetheless accepted. Beyond this issue, the GFR is generally estimated from serum markers (the eGFR) and the GFR estimating equations have not been validated in many of the relevant populations[29], a particular issue when comparing eGFR distributions internationally as this will lead to ethnicity-specific differential bias. Validated eGFR equations in all relevant populations are unlikely to be available in the short term so this is again accepted as a limitation of the proposed collaborative approach. Furthermore although the i3C suggest estimates of the prevalence of impaired eGFR for the purposes of regional or international comparisons can be based on a single eGFR measurement only this does not detract from the responsibility to refer those with an abnormal finding (e.g. elevated creatinine, hypertension, protein/glycosuria) at initial survey to local health services and, it is recognized that investigators with resources may want to perform repeat measures in participants with abnormal results after an interval >3 months to reduce misclassification of episodes of acute kidney injury as CKD.

*CKD-EPI equation although not validated in many populations of interest has been shown to be more precise in the normal and near-normal GFR range that will be predominant in prevalence studies.

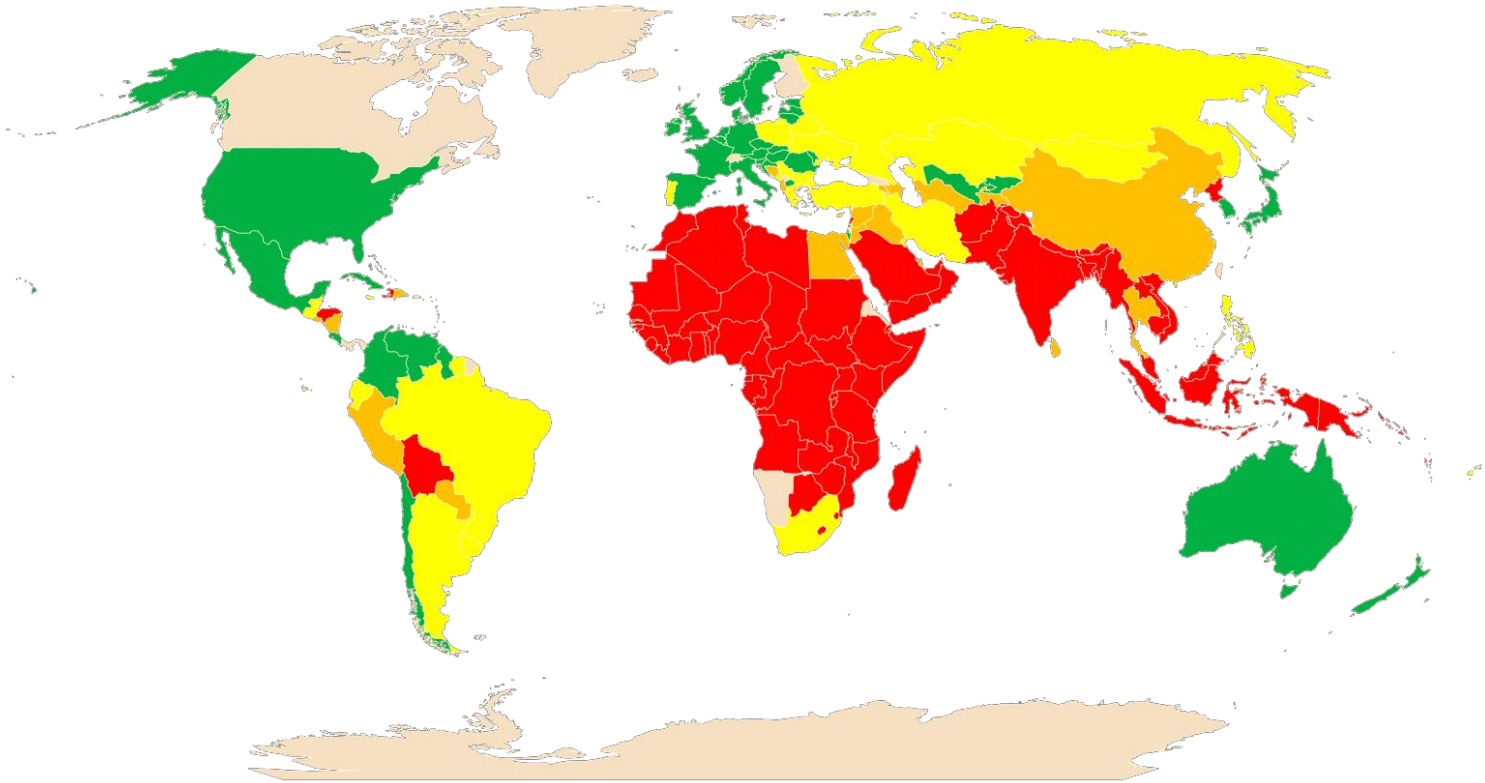
** Measures such as self-report of meat intake/vegetarianism[30] and estimates of body composition e.g. DEXA or bioelectrical impedance[31] measurements may be useful in adjusting for the impact of non-renal sources of creatinine when comparing eGFR distributions between populations. Similarly sampling should ideally occur in the morning, i.e. prior to large meals or physical work.

Table 4 Other important data items.

Non-GFR measures	Rationale / Advantages / Disadvantages	Method	Recommended by i3C for minimum data set
Age	Rates of CKD and CKDu are age- dependent	Self-report	Yes
Sex	Rates of CKD and CKDu are sex- dependent	Self-report	Yes
Ethnicity / racial group	Rates of CKD and CKDu are ethnicity dependent Can be difficult to capture and may be sensitive in some popualtions	Self-report	Yes
Occupation	CKDu has been mainly described in agricultural communities/workers. Occupational history can be very difficult to capture in many populations unless using detailed questionnaires	Self-report	Yes, although it is acknowledged that international comparisons of occupational categories are likely to be difficult
Education and income	Many studies demonstrate an association between social deprivation and CKDu Reasonably simple to capture using questionnaires.	Self-report	Yes, can be reported as primary/secondary education and/or quartiles/quintiles of income
Address or geolocation	CKDu has generally been described in rural populations and at low-altitudes	Self-report or cluster level data	Yes, can be captured at individual or population level.
Average temperatures	CKDu has been described in tropical regions	Regional routine data (e.g. average daytime and nighttime temperatures)	Yes
Diabetes	Although diabetes might co-exist with CKDu the high prevalence of diabetic nephropathy means most estimates of CKDu have excluded those with diabetes*	Self-report of diagnosis or medication	Yes, discriminate type 1 (insulin dependent at diagnosis) from type 2 if possible
		Glycosuria Fasting glucose or HbA1c,	No, except if performing urinalysis If resources allow
Hypertension	Severe hypertension appears atypical in CKDu and may indicate alternative causes of CKD.	Self-report of diagnosis or medication Direct measurement	Yes Yes (using calibrated devices and trained personnel).
Nephrotoxic drugs and traditional remedies	Drugs may cause CKD (or CKDu)	Self-report	If resources allow, recognising that international comparisons are likely to be difficult
Infections	Likely to differ by population Many of those affected will be undiagnosed	Self-report	No
Snake bite	Important cause of kidney injury	Self-report	If resources allow where relevant
History or cause of CKD	Many of those with CKD are unaware, or even if aware may not know the cause	Self-report	No
Family history of CKD	Family history of CKD has been described in CKDu	Self-report	If resources allow as prone to misclassification
Water source/ intake	Participants may have multiple water sources	Self-report	If resources allow, recognising that simple assessments are likely to be prone to misclassification
Agrichemical exposure	Difficult to capture	Self-report	If resources allow, recognising that simple assessments are likely to be prone to misclassification
Dipstick proteinuria	No or low-level proteinuria typical for CKDu urinalysis cheap but affected by urinary concentration	Urinalysis	Yes, or ACR
Quantified albuminuria	more expensive but quantitative	Albumin/creatinine ratio	Yes, or urinalysis
Quantified proteinuria	Less specific than ACR	Protein/creatinine ratio	No
Haematuria	May help exclude other forms of CKD e.g. Schistosomiasis	Urinalysis	Yes, if performing urinalysis for protein
Imaging	Smooth small kidneys; operator dependent expensive and difficult at scale	Ultrasound	No

* Note that CKDu can be seen in patients with diabetes, so although an individual with diabetes might be excluded from the denominator used in detection efforts a clinical diagnosis of CKDu may still be appropriate.

Figure 1



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SUPPLEMENTARY MATERIAL

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 categorisation

		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

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 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 < 60 ml/min 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

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https://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson1/section5.html

http://apps.who.int/iris/bitstream/10665/43541/1/9241547073_eng.pdf

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.

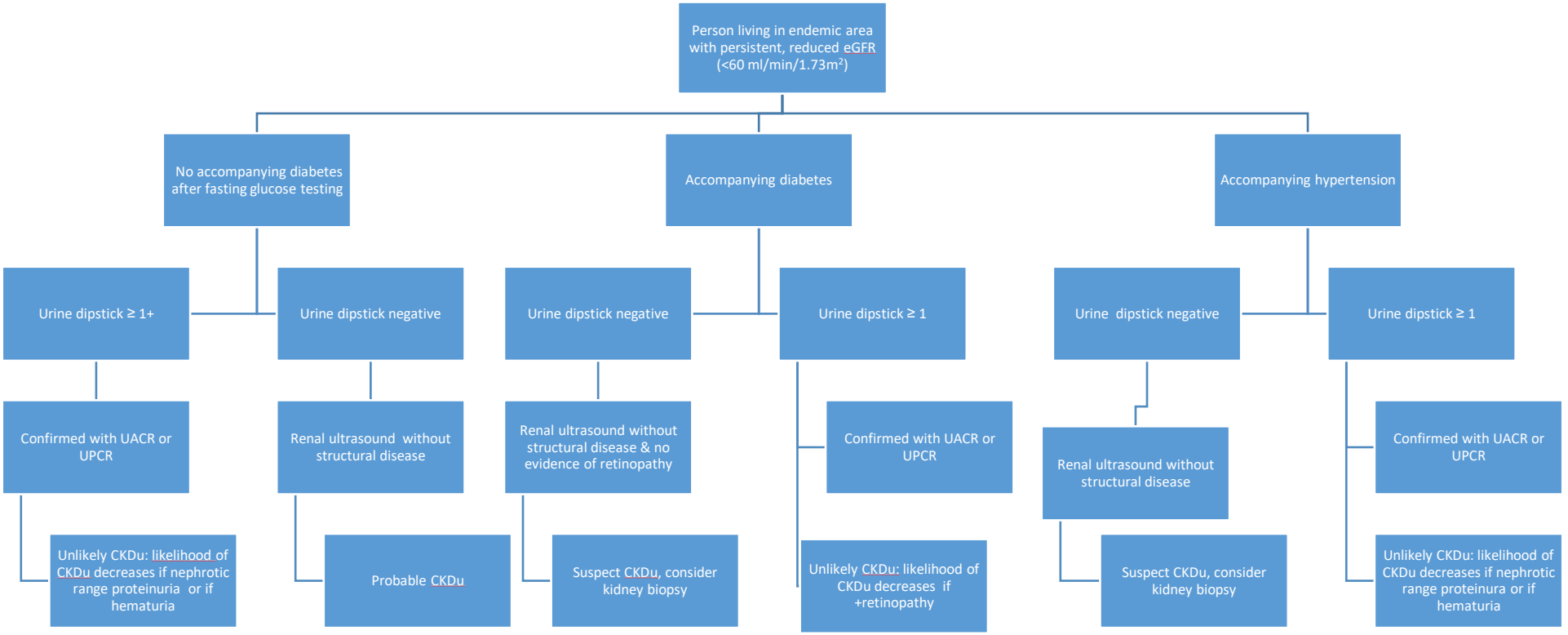
With these considerations in mind, we outline the following principles if a non-biopsy based diagnosis is sought:

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

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.

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).

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.