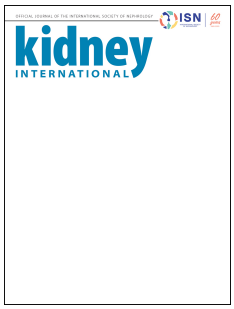

Kidney biopsies among persons living in hotspots of CKDu: A position statement from the International Society of Nephrology's Consortium of Collaborators on CKDu.

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Chronic kidney disease of unknown etiology (CKDu) is a progressive primary tubulointerstitial kidney disease affecting persons in rural, agricultural communities worldwide. Some of the other terms used to identify this disease include Mesoamerican nephropathy (MeN) in Central America, Uddanam nephropathy in India, and Chronic Interstitial Nephritis in Agricultural Communities (CINAC). Well-described hotspots exist in Central America, Sri Lanka, and India, with investigations to assess epidemiology and cause(s) ongoing in many regions of the world.[1,2] Although the disease is suggested in a person living in a CKDu endemic area and presenting with declining kidney function without alternative explanations (e.g., diabetes, heavy proteinuria or hematuria indicative of glomerulonephritis, or structural kidney disease), definitive diagnosis requires findings of chronic tubulointerstitial disease on kidney biopsy.

However, clinicians may not be enthusiastic about performing kidney biopsies among patients suspected to have CKDu for several reasons. These include: 1) undefined thresholds of kidney function decline at which to pursue biopsy, 2) the experiential evidence that a clinical diagnosis of CKDu is predictive of biopsy diagnosis, 3) the lack of a specific treatment for CKDu at present, and 4) concerns about safety and risk and cost to the patient. Kidney biopsies offer definitive diagnosis, provide prognostic information, and advance our knowledge about the spectrum of disease to putatively enable the institution of preventive and/or therapeutic strategies. The tension between limited resources, patient burden, and quest for accuracy in disease diagnostics leads to the question: are kidney biopsies clinically indicated among persons suspected of having CKDu in regions known to be CKDu hotspots?

In 2022 and 2023, the International Society of Nephrology's (ISN) i3C (International Consortium CKDu Collaborators) Working Group and the ISN Renal Pathology Working Group

held three consensus-building meetings to explore the pros and cons of pursuing kidney biopsies in CKDu hotspots. In addition, a survey was circulated to ISN members through three ISN regional boards (Latin America, South Asia, and Oceania and South-East Asia) to assess biopsy practices in non-proteinuric kidney diseases. Acknowledging that a group of research-intensive, internationally-engaged nephrologists and associated research scientists participated in this endeavor, we summarize the key considerations and describe the group's consensus. The contents of this draft were reviewed by the Chairs of the three ISN Regional Boards.

We note that ideally a rigorous, research-based approach to biopsies with will be pursued in many CKDu hotspots, but the reality on the ground, including the lack of resources to apply advanced tissue processing techniques, means that such studies may not have a broad or immediate reach, and in the meantime, clinicians are faced with counseling patients with CKDu. Thus our aim is to provide practicing clinicians with a framework around which to anchor personalized discussions with patients, and to maximize the clinical and scientific output of clinically-indicated biopsies in CKDu hotspots.

Clinical utility of kidney biopsy in a person suspected to have CKDu

Traditional indications for kidney biopsy emphasize proteinuria (with or without hematuria), or unexplained acute kidney injury. Persons with CKDu may not fall under any of these categories, as they may experience variable and insidious loss of kidney function without an active urinary sediment. We implemented a simple survey posing several scenarios of non-proteinuric kidney disease presentation at young and middle age and in patients of male and female sex (**Figure 1**). A total of 68 nephrologists responded, a majority from affected regions

(32% and 36% from South Asia and Latin America). 40% of the responding nephrologists would opt to recommend a kidney biopsy on a 36-year-old male or female, estimated glomerular filtration rate (eGFR) 80 ml/min/1.73m^2, and evidence of kidney function decline by eGFR change > 5 ml/min/1.73m^2 over a short time frame; fewer (~25%) would pursue a biopsy if the patient were a 60-year-old male. A similar pattern of responses held if eGFR were below 60 ml/min/1.73m^2 and no clear evidence of eGFR decline over a short time frame. More than 70% would pursue biopsy in patients, eGFR 58 ml/min/1.73m^2, and evidence of eGFR decline, independent of age or sex.

A biopsy in any of these three scenarios, where CKDu is suspected, could address diagnostic uncertainty, and even in the case of pathologically-confirmed tubulointerstitial nephritis, could potentially point to known etiologies other than CKDu (e.g., nephrocalciniosis, oxalate nephropathy, granulomatous inflammation indicating tuberculosis or sarcoid, or plasma-rich infiltrate indicating IgG4 disease). In addition, kidney biopsy can provide valuable information for prognostication by quantifying the extent of tubular atrophy, interstitial fibrosis and secondary glomerulosclerosis, which is essential for developing a treatment plan. It is conceivable that clinical trials targeting either tubular inflammation or fibrosis may be offered in the near future, and a kidney biopsy could facilitate patient enrollment.

That uncertainty exists in the utility of kidney biopsy was acknowledged by ISN i3C Working Group discussants, especially in the context of socio-economic constraints of the patients, many of whom may need to travel or miss work to undergo the procedure. Some clinically important questions—e.g., does biopsy alter outcomes—remain unanswered, and in fact can only be answered with systematic approaches to biopsy. Furthermore the ISN i3C Working Group largely

consists of academically-focused nephrologists who aim to investigate CKDu in depth, and thus have an inherent bias towards gaining more information when feasible.

Ultimately, the decision to pursue biopsy in clinical encounters is reliant on physician-facilitated personalized discussion of risks and benefits, with patient autonomy at the center of these discussions.

Considering the safety of kidney biopsies in low-resource settings in general, and specifically for CKDu

The best-described CKDu hotspots exist in low and middle-income countries.[3] A recent review of 39 studies described safety data from 19,500 kidney biopsies performed in 18 low- and middle-income countries across 6 regions.[4] In comparison to a meta-analysis drawing the majority of its data from high income countries, the biopsy complication rates were similar (**Table 1**).[5] Complication rates were lower with real-time ultrasound guided biopsies as compared to pre-marked and blind procedures (12.4% *versus* 14.9% and 24.5% respectively).

The ISN i3C Working Group discussants noted that typical patients with suspected CKDu are young, normotensive, and have normal or low body mass index: thus, they do not have the well documented risk factors for bleeding complications post biopsy.[6] Furthermore, they are also less likely to be on antiplatelet or anticoagulant therapy or have severe acute kidney injury needing hospitalization. Thus, the ISN i3C Working Group concluded that a kidney biopsy is likely

to be as safe, if not safer, as for the traditional indications of kidney biopsy as long as there is a trained nephrologist or a radiologist performing the procedure with ultrasound guidance and using an automated biopsy gun.

Standardizing data collection during kidney biopsy

Should the patient and treating nephrologist mutually agree to proceed with a kidney biopsy, the group discussed approaches to maximizing both the clinical and research benefit of a biopsy. Through consensus we developed a case report form (**Supplemental Appendix A**) to collect relevant clinical information before and after the procedure. We prioritized this form to be concise and practical for clinicians practicing in regions with a high prevalence of kidney disease, but also to enable research outputs when collated across multiple suspected CKDu hotspots.

Several benefits exist for such standardized data gathering, some of which will be directly and immediately relevant to patient care. For example, we could inform the pre-test probability of kidney biopsy altering the diagnosis from primary tubulointerstitial kidney disease of unknown cause to a diagnosis attributable to specific cause or treatment. It is also conceivable that the diagnostic certainty affects prognosis, and again, systematic clinical data matched to briefly collected outcome data could answer this question. Although available literature supports that higher degree of fibrosis will be associated with worse prognosis, the precision with which we can make prognostic predictions will improve drastically with systematically available clinical data and standardized biopsy reporting. Finally, systematic approaches will elucidate the entire spectrum of pathology findings associated with the final clinical diagnosis of “CKDu” as both acute

and severely chronic presentations with substantial secondary glomerusclerosis have been described.

Standardizing biopsy reporting

The value of standardized biopsy reporting has been demonstrated in several disease entities: specifically, the Banff classification for reporting of kidney transplant biopsies and the MEST-C score for IgA nephropathy scores are examples of standardized biopsy reporting that facilitated comparisons across sites/regions and have led to improved understanding of disease processes. Biopsy diagnosis and prognostication in presumed tubulointerstitial disease currently faces high inter-observer/pathologist variability. Having a pre-consensus overview with training sessions and using standardized descriptors to document the pathologic findings in the kidney biopsy has proven to be the best approach to improve concordance.[7] Thus, building on the pathology discussions at the NIH-Sponsored Third International Workshop on Chronic Kidney Disease of Uncertain Etiology in 2019, templates introduced by Wijkstrom and colleagues,[8] and input of pathologists in the ISN Renal Pathology Work Group, we present a reporting form which facilitates the systematic description of each compartment in the biopsy (**Supplemental Appendix B**). Electron microscopy capability may not exist in a majority of settings, but technology enables later review of Formalin Fixed Paraffin Embedded (FFPE) tissue for electron microscopy and increasingly the application of additional molecular techniques. Careful record keeping of procedures and conditions of tissue storage would enable the creation of a core tissue bank with potential to test multiple hypotheses.

Recommendations and way forward

The clinical scenarios of persons with suspected CKDu represent outliers to conventional indications for kidney biopsy. No disease-specific treatment exists at the present time, and many believe that there is a reasonable probability of clinical and pathologic diagnostic concordance in CKDu hotspots. However, without systematic clinical data and pathology review of kidney biopsies, we cannot be certain of such assumption. Until recently, the value of biopsies in people with presumed diagnoses (such as Diabetes and Hypertension) had not been thought to be of clinical value. With the Kidney Precision Medicine Program, and the advent of increasingly sophisticated technologies for assessment of kidney tissue, nephrologists need to re-examine previous attitudes toward performing biopsies in CKD.

The ISN i3C Working Group thoroughly considered the various perspectives on the risks and benefits of kidney biopsy in people with suspected CKDu. The Working Group concluded that kidney biopsies for clinical indication should routinely be considered in cases of suspected CKDu. Biopsies are justified given that there is a need to confirm a diagnosis, and assess prognosis based on the acuity and severity of histological features (**Table 2**). This justification was considered within the context of low risk for complications in a 'standard-of-care' setting of ultrasound-guided nephrologist or radiologist-performed kidney biopsies. The ISN i3C Working Group suggested an informed patient-centered discussion so that patients are aware of the current lack of disease-specific treatment, potential patient-borne costs, and individual risks for procedural complications.

Another major recommendation by the ISN i3C Working Group is for nephrology clinics in CKDu hotspots to standardize case report forms and pathology report forms. This standardization

will enable collaborative approaches to advancing knowledge about the disease (**Figure 2**). At minimum, such an approach would facilitate large-scale intra and cross-country comparisons on disease presentation, delineate spectrum of pathology findings, and correlate specific findings in the tubulointerstitial compartment to outcomes.

Summary:

CKDu remains an important unsolved problem in a number of regions around the world. This position statement prepared by the ISN i3C Working Group provides guidance to those working in endemic regions regarding clinical indications for kidney biopsies in individuals suspected of having CKDu.

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Disclosure

EW reports to be Member of the DSMB for a CKDu project in Sri Lanka conducted by the Stanford University and the National Hospital Kandy, Deputy Chair of the i3C Working Group of the International Society of Nephrology (ISN i3C (CKDu) WG), and President-Elect of the Sri Lanka Society of Nephrology. BC reports to have received grants or contracts from UK Medical Research Council and Colt Foundation (both payments made to his institution). VSP reports to have received payment or honoraria from Bayer, AstraZeneca, Novartis and Sanofi; and to be the General Secretary of the Latin American Society of Nephrology and Hypertension (unpaid role). DF reports to have received grants or contracts from NIDDK, NIMHD, Dept. of Defense, royalties or licenses from Beth Israel Deaconess Medical Center, consulting fees from Vertex; payment or honoraria from Sanofi; to have patents related to APOL1; and to participate as a member for DSMB for NIH. MM reports to have received payment, grants, contracts, honoraria, and/or support for travelling/meetings from AztraZeneca and Boehringer; and to have a leadership role at ISPD Council, KDIGO writing group CKD Guideline, to be the KDIGO Chair Executive Committee and KI editor. VJ reports to have received grants, contracts, payment and/or consulting fees from GlaxoSmith Klein, Baxter Healthcare, Biocon, Vera, Biocryst, GSK, Bayer, Astrazeneca, Boehringer, Ingelheim, NephroPlus, Zydus and Cadilla (all paid directly to his institution); and to participate as a member for DSMB for Zydus Cadilla. NK reports to have received all support for this manuscript from 5R01DK12713803: NIH (Standford University), grants or contracts from 5U01DK13006002: NIH (Standford University), and payment from Elsevier: Amirsys series book on Renal Pathology. AL reports to have received support for attending meetings/travelling by International Society of Nephrology and MIH; to participate as a member for DSMB for NIH CURE

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All the other authors have nothing to declare.

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List of supplementary materials

Supplemental Appendix A

Supplemental Appendix B

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1. John O, Gummudi B, Jha A, et al. Chronic Kidney Disease of Unknown Etiology in India: What Do We Know and Where We Need to Go. *Kidney Int Rep*. Nov 2021;6(11):2743-2751. doi:10.1016/j.ekir.2021.07.031

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Tables

Table 1. Metanalyses data on the complication risk in kidney biopsies by setting

Complication	LMIC	HIC
Biopsy, *n*	19,500	118,064
Hematuria	1.48%	3.5%
Hematomas	2.4%	11%
Transfusion	0.24%	1.6%
Nephrectomy/ intervention	0.04%	0.3%
Death	0.01%	0.06%

Data from Kajawo et al *KI Reports* Jan 2021 (LMIC)[4]; Poggio et al *CJASN* 2020 (HIC).[5] LMIC – Low- and middle-income countries; HIC – high-income countries

Table 2. ISN i3C recommendations for kidney biopsy in CKDu endemic regions

Recommendation	Rationale
Kidney biopsies for clinical indication should routinely be considered in cases of suspected CKDu	Diagnostic uncertainty without biopsy Prognostic data Phenotype of potentially affected patients has low risk for complications
Standard of care for kidney biopsy safety must exist when offering kidney biopsies: ultrasound guidance, biopsy gun, trained nephrologist or radiologist, biochemical and bleeding risk profile review	Decreases risk for complications when these conditions are met, regardless of resource setting
Standard clinical data inclusive of occupational history and residence, biopsy processing protocol, and pathology review output should be gathered among all persons undergoing biopsy for any reason in CKDu endemic region	Standard minimal dataset and pathology scoring approach will enable optimal use of available clinical data with minimum additional resources

ISN -International Society of Nephrology; i3C – International Consortium of Collaborators on Chronic Kidney Disease of Unknown Etiology

Figure Legends

Figure 1. Survey results on kidney biopsy in non-proteinuric kidney diseases

Proportions indicate % of survey respondents indicating 'biopsy indicated' for these scenarios: eGFR 80, declining - eGFR 80 ml/min/1.73m2, and > 5 ml/min decline between two time points; Abnormal Cr - Serum creatinine higher than laboratory range, at two time points; eGFR 70, stable - eGFR 70 ml/min/1.73m2, stable at two time points; eGFR 55, stable - eGFR 55 ml/min/1.73m2, stable at two time points; eGFR 58 declining - eGFR 58 ml/min/1.73m2 and > 5 ml/min decline between two time points. The two time points were specified to be least 3 months apart.

Figure 2. Proposed work flow to maximize scientific output from kidney biopsies in CKDu hotspots

We propose that patients undergoing kidney biopsies in CKDu endemic region have standard clinical data stored in form amenable to aggregation across sites, and that the clinics note their standard biopsy processing protocol as well as cores obtained during the procedure. Pathologists working in these regions, or supporting these regions using telemedicine, follow standard pathology reporting, again to enable rapid aggregation and discernment of patterns.
LM – light microscopy; IF - immunofluorescence