FOURTH INTERNATIONAL WORKSHOP ON CKDU:
TOPIC-BASED WORKING GROUPS

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CLINICAL DIAGNOSIS AND MANAGEMENT

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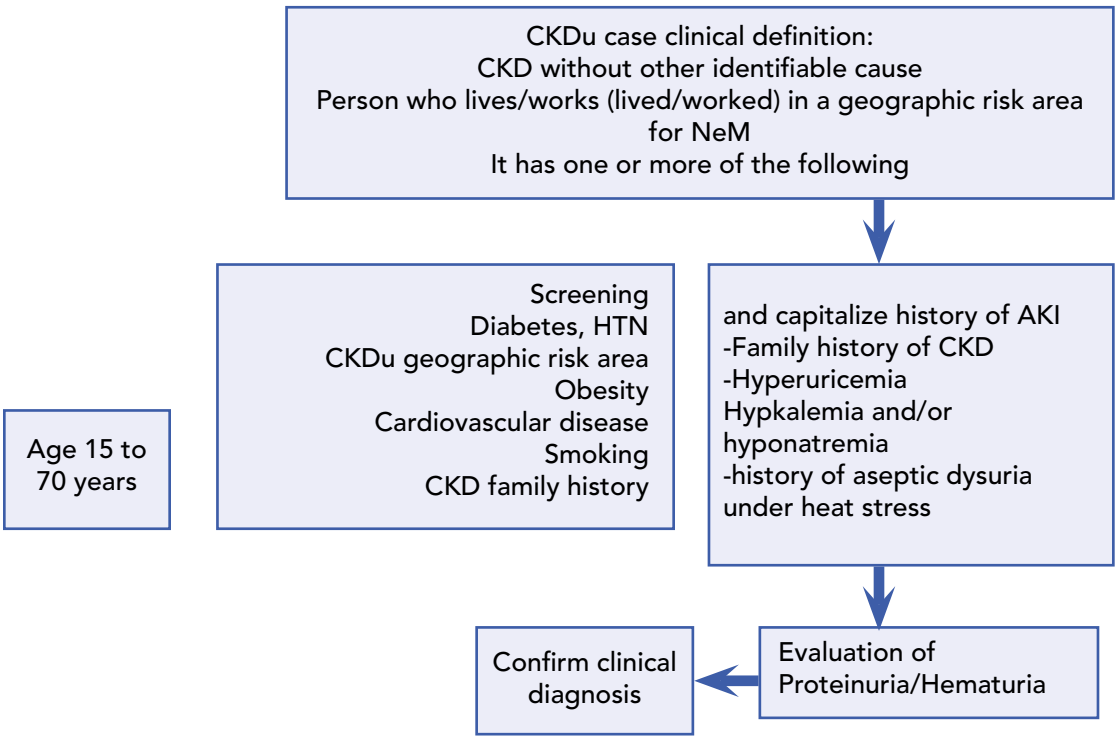
INTRODUCTION

Chronic Kidney Disease of unknown etiology (CKDu) is a serious public health concern, particularly in agricultural communities. Due to its unclear origins, accurate clinical diagnosis and management are crucial for slowing disease progression and improving patient outcomes. Early detection, proper treatment plans, and ongoing monitoring by healthcare professionals are essential for managing CKDu effectively.

Key Messages for Clinicians

- CKDu is a serious public health issue, particularly affecting agricultural communities.
- The cause of CKDu is still unknown, making diagnosis challenging.
- Clinical diagnosis and management are crucial for slowing disease progression and improving patient outcomes.
- Early detection, proper treatment plans, and ongoing monitoring by healthcare professionals are essential for managing CKDu effectively.
- It is important to have clinical suspicion in a patient who has occupational risks and findings of electrolyte abnormalities, even if they do not have symptoms.



Key Messages for Community Members

- CKDu is a serious kidney disease: it damages the kidneys over time, making it harder for them to filter waste products from the blood.
- Be aware of the symptoms: While symptoms may not appear early on, potential signs like fatigue, weakness, blood in the urine, urinating with pain or lose of appetite can occur.
- Highlight potential risk factors in your community, such as exposure to heat stress, dehydration, certain toxins in the environment, or use of some herbal medications.
- Emphasize the importance of regular health checkups, including kidney function tests, especially for those at higher risk.
- Promote healthy habits like staying hydrated, reducing heat stress, maintaining a healthy weight, and limiting exposure to potential toxins.
- Encourage anyone experiencing symptoms to see a healthcare professional for evaluation and diagnosis.

Key Messages for Policymakers

- Early detection, proper treatment plans, and ongoing monitoring by healthcare professionals are essential for managing CKDu effectively.
- Emphasize the primary challenge of CKDu diagnosis – the unknown cause. Traditional diagnostic tools for kidney disease may not be entirely suitable for CKDu.
- Supporting research and development of more specific and reliable diagnostic tools for CKDu is important.This could involve biomarker identification or improved imaging techniques.
- At this moment, it is important to do a syndrome-based approach, due to the unknown cause, treatment for CKDu often focuses on managing symptoms and preventing further kidney damage.
- Promoting healthy habits like maintaining a healthy weight, reducing heat stress, and staying hydrated is fundamental.
- It is essential to address other related health conditions, if present in that population, like having availability of medications to control blood pressure, manage diabetes (if present).
- Providing supportive care to manage symptoms like fatigue or anemia, and potentially offering dialysis or kidney transplant options in advanced stages is mandatory.
- It is important to do ongoing monitoring by healthcare professionals to track disease progression and adjust treatment plans as needed.

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OVERALL CAUSALITY

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The question "what causes CKDu?" does not have a simple answer. The CKDu literature contains valuable insights related to risk factors (such as heat stress and environmental exposures), injury mechanisms, and histopathologic characteristics that are all closely related to the question of causality. These topics are extensively discussed in other working group summaries. The Overall Causality group focused instead on overarching conceptual frameworks that integrate these findings into an comprehensive model of CKDu. Specifically, we applied both Directed Acyclic Graph analysis1 (DAG; Figure 1) and Causal Pie Model analysis2 (Figure 2) to examine the causal relationship within CKDu. **Please note that the DAGs and causal pies presented are meant to be illustrative, and not meant to be fully accurate and complete.** These models nevertheless serve as aids in conceptualizing where and how we can intervene to disrupt causal pathways, both at the individual and population levels, to reduce the burden of CKDu. By employing these models, we can better strategize and implement interventions aimed at mitigating the incidence and impact of CKDu.

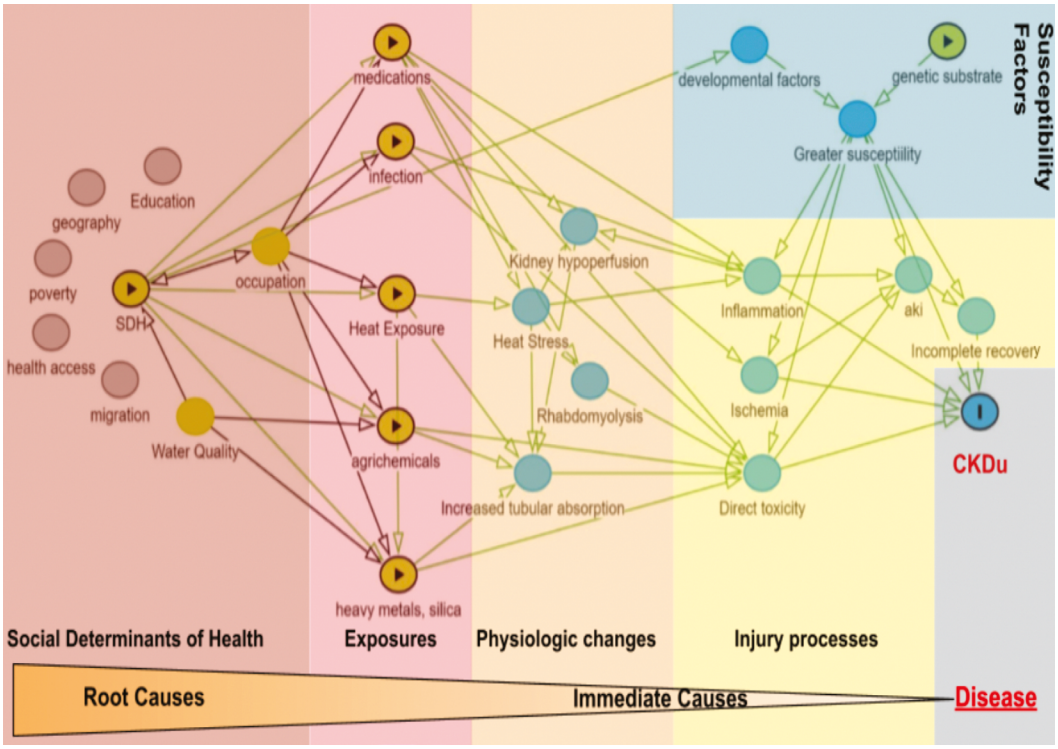

Figure 1. Directed Acyclic Graph (DAG) of CKDu Causality. Postulated causes of CKDu are diagrammed with those factors that are more immediate causes clustering further to the right, and underlying or root causes clustered further to the left. Factors that may increase the likelihood of a root or immediate cause leading to CKDu are in the top right. The Directed Acyclic Graph shown in Figure 1 conveys a number of key messages:

- The causality of CKDu is complex, with multiple factors that may function independently or in concert to contribute to disease development.
- Social determinants of health (SDH), in particular social factors linked to poverty and low education level, are the fundamental root cause of CKDu.
- Different exposures may interact in ways which increase the chance that each will cause kidney injury.
- Each region of the DAG provides potential opportunities for intervention to disrupt CKDu development:
- Programs to target poverty, improve healthcare and education, and prevent unsafe living and working environments
- Policy implementation and educational campaigns to help reduce possibly harmful exposures
- Identification of interventions (behavioral, pharmacologic) to mitigate physiologic changes and injury processes that lead to CKDu development

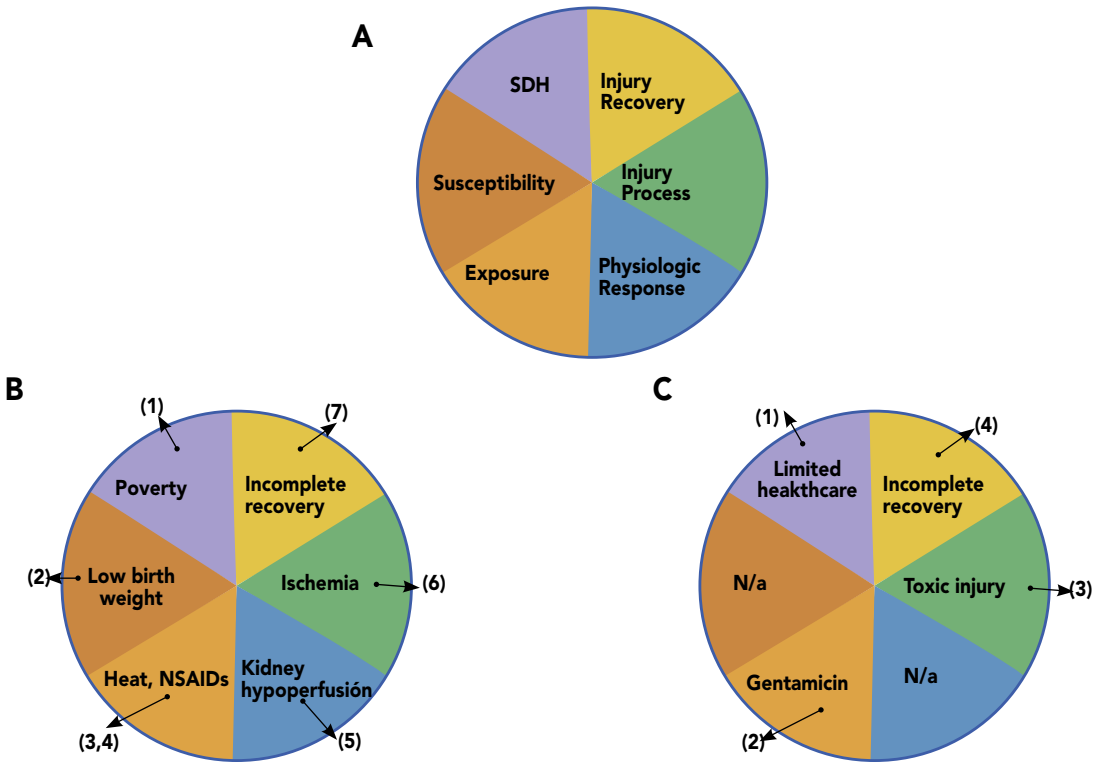

Figure 2. Causal Pie Models. (A) A causal pie model of CKDu, again demonstrating a range from root causes to immediate causes which broadly align with the different groups of causes shown in the DAG in Figure 1. If any one piece of the pie model can be eliminated, then disease cannot develop. (B), (C) Two examples of the causal pie model applied to an individual, discussed in greater detail in the text.

The Causal Pie Model provides a framework for thinking about causality complementary to the DAG, emphasizing how disease development can only occur when all necessary causal factors are present. To illustrate:

- Individual 1 (Figure 2B) has 7 elements causing CKDu, where eliminating any one of them would prevent his disease: He lives in poverty (1) and as a result had low birth weight leading to lower nephron number at birth (2) and therefore greater susceptibility to kidney disease; works in a job that exposes him to significant heat stress (3) and uses NSAID medications (4) which intersect to lead to poor kidney blood flow (5) and ischemic injury (6); and because he needs to work every day to support his family he never has a chance to fully recover from repeated ischemic injury (7).
- Individual 2 (Figure 2C) has only 4 identifiable elements causing CKDu: He has limited healthcare access (1) and takes frequent courses of gentamicin (2) for urinary symptoms without the opportunity for further diagnostic workup, leading to toxic injury to the kidney (3) that eventually leads to chronic disease (4).

Note that neither susceptibility or physiologic response were elements of causality in this second person; not all factors need to be identified for the causal pie model to be applied. Considered on a population scale, identifying factors that are part of the causal pie for large portions of the population can help prioritize targets for intervention.

The key message from both of these conceptual models is that it is not necessary to understand CKDu causality in its entirety in order to intervene to combat the disease. We would like to highlight three "causes" as illustrative examples of how risk factors may be prioritized as the target of interventions to prevent CKDu.

- Heat Stress: Likely to provide high benefit. There is strong evidence to justify interventions that are likely to be effective. See the Heat Stress Working Group recommendations for a full discussion.
- Nephrotoxic Medications: Likely to have low financial and political cost. There is weaker evidence that nephrotoxic medications play a key role in CKDu. However, educational programs emphasizing avoidance of nephrotoxic medications (particularly NSAIDs and Gentamicin) and use of non-nephrotoxic alternatives are likely to be more straightforward and easier to implement than interventions against many other causes of CKDu.
- Social Determinants of Health: Likely to provide broad-reaching benefit. The central role of poverty, lack of healthcare access, and poor education in CKDu is vital to recognize, particularly among policymakers seeking to achieve a broad-reaching impact. The benefits of interventions targeting social determinants of health will certainly extend far beyond CKDu.

Ongoing longitudinal, mechanistic, and animal model research remains crucial, as it may discover new information related to causality that can inform interventions to combat CKDu. Particular priorities include research on:

- The molecular mechanisms of injury in CKDu - the immediate cause(s)
- Susceptibility factors to CKDu
- The intersection between causal factors, particularly exposures, driving CKDu development

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HEAT EXPOSURE AND INTERVENTIONS

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INTRODUCTION:

Occupational heat stress, which is a function of both environmental (external) heat and metabolic heat production (Box 1), is becoming increasingly evident as a significant contributor to chronic kidney disease of non-traditional or uncertain origin (CKDnt/CKDu). Observational studies have identified workers performing heavy work under hot conditions as being at a high risk of CKDu. Heat-stressed workers have a high rate of acute kidney injury (AKI), an observation that has been confirmed in well controlled human subjects and preclinical lab studies. Importantly, a few interventional studies have reported beneficial effects of structured rest-shade-hydration-hygiene programs (Box 2) on reducing the occurrence of AKI, and thereby potentially preventing CKDu.

BOX 1. OCCUPATIONAL HEAT STRESS	BOX 2. BEST PRACTICES FOR HEAT STRESS PREVENTION AT WORK
Heat stress arises from the combination of heavy work, such as: • Digging, shoveling, cutting, chopping • Carrying, lifting, loading And a hot environment, such as: • In direct sunlight • Near a furnace or hot machinery Piece-rate labor and other forms of work incentivized by productivity or being forced to complete intensive work can increase heat stress.	Recognize the signs and symptoms of heat related illness Monitor ambient temperature, humidity and physical activity of workers to prevent heat stress conditions. **Rest:** 15-20 minutes of mandatory rest per hour for workers performing heavy work in heat. Always able to rest when feeling hot or ill. **Shade:** Should be accessible at all times. ***Hydration:*** Drinking water should be accessible, clean and safe. Electrolyte solution may provide further benefits. **Hygiene:** Latrines and handwashing facilities should be accessible to facilitate hydration. **Acclimate:** One week of gradually increasing workload.

Key Messages for Clinicians

Clinicians encountering a patient exposed to occupational heat stress (Box 1) presenting with symptoms like fever, headache, nausea, or signs of systemic or urinary tract inflammation (leukocyturia) should consider performing serum creatinine testing as AKI may be likely. If AKI is detected, they should recommend that the patient limit their workload and exposure to occupational heat stress until their AKI has resolved and provide counseling on occupational heat stress prevention (Box 2). Clinicians should use appropriate ICD codes for illness events caused by heat.

Nephrologists attending to CKD patients should take a comprehensive occupational history to identify the potential for heat stress exposure (Box 1), and when relevant, provide counseling on occupational heat stress prevention (Box 2). Nephrologists should recognize that AKI related to occupational heat stress is common in populations at risk of CKDu and be prepared to develop standards for the diagnosis and management of AKI accounting for local conditions.

Public and occupational health workers should be able to recognize populations at high risk of occupational heat stress (Box 1) and provide guidance on heat stress prevention for workers and employers (Box 2). They should also be able to provide education about early symptoms of heat illness, health promoting behaviors, and healthcare access.

Key Messages for Community Members

Workers exposed to heat stress (Box 1) should be trained on heat stress prevention (Box 2). However it should be recognized that the responsibility for safe working conditions lies with the employer. Workers need to be informed about risk factors of heat illness (e.g. fever, dehydration), early symptoms of heat illness, and adequate responses to such symptoms.

Employers need to be informed about links between heat stress and CKDnt and about occupational heat stress prevention (Box 2). Employers are responsible for implementing and enforcing heat stress prevention practices at the workplace and should be aware that interventions to reduce occupational heat stress may increase workforce productivity.

The general community, starting from an early age, needs to be informed about the relationship between occupational heat stress and CKDu so that future generations of workers are aware of and able to demand adequate workplace heat stress protections.

Key Messages for Policymakers

Scientific evidence has identified occupational heat stress as a preventable risk factor associated with AKI and likely CKDu Regulations concerning occupational heat stress exist in countries affected by CKDu but require implementation.

- Identify applicable regulations concerning heat stress.
- Implement existing regulations concerning heat stress prevention.
- Identify the authority responsible for enforcing heat stress regulations.
- Evaluate the impact of implementing workplace heat stress protections.
- Recognize that some populations are especially at risk of heat stress:
    - Informal/subcontracted workers - difficult to identify the employer responsible for implementing occupational heat stress protections.
    - Piece-rate laborers - consider other payment structures.
- Establish a regional early warning system to alert when heat waves are expected.
- Conduct broad educational campaigns on heat stress prevention, aiming to reach relevant populations through captivating, easily understood messaging.

Further resources: https://www.osha.gov/heat-exposure https://www.osha.gov/heat

ENVIRONMENTAL EXPOSURES

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INTRODUCTION

The rising prevalence of chronic kidney disease of non-traditional origin (CKDu) in underserved communities is a perplexing major public health threat disproportionately affecting vulnerable populations globally. This disease is not typically associated with traditional risk factors (i.e., diabetes and hypertension) of chronic kidney disease. Evidence indicates that heat strain plays a major role in this disease, whereas the contribution of many other environmental and occupational exposures is a topic of discussion and disagreement among investigators in the field. A list of alternative exposures were discussed by this working group. Albeit, no consensus was reached regarding the role of other exposures than heat strain for the development of CKDu recommendations are provided for various stakeholders.

KEY MESSAGES FOR CLINICIANS:

- Heat-strain is suspected of playing a major role in CKDu, but is not the sole causal factor. Clinicians should counsel their patients to reduce heat exposure and maintain hydration as much as possible to protect renal health.
- Poverty and poor socioeconomic conditions possibly contribute to CKDuand are important to consider.
- Other environmental exposures specific to high-risk areas (e.g., pesticides, metals) may increase individual susceptibility to CKDu itself or to renal harm from heat strain. Agricultural workers in particular are often exposed to mixtures of chemicals whose renal health implications are unclear.
- Ensuring access to quality healthcare, particularly in under-resourced communities, including early kidney health screening and diagnostic services, are key for early prevention and control of disease.
- Recognizing the role of environmental exposures in disease etiology can be challenging due to the latency period between exposure and onset of symptoms, as well as the lack of standardized diagnostic tests for many environmental illnesses. However, a thorough clinical history, including asking patients about occupational (e.g., workplace, job tasks, chemicals used, etc.) and residential exposure behaviors (e.g., chemicals used at home, drinking water source) can provide valuable clues for identifying potential environmental factors that could increase disease risk.
- Using standardized questions to evaluate environmental occupational and residential exposures specific for each area can improve exposure assessment efforts.

- Providing comprehensive kidney health and environmental health education for healthcare personnel in highly impacted regions can help with the early identification of environmental risk factors and disease symptoms.

KEY MESSAGES FOR COMMUNITY MEMBERS

While all factors that may increase risk of CKDuhave not been clearly elucidated, there are some precautions that community members can take while more local research is underway.

- Individuals that are in direct contact with environmental hazards, specifically to exposure to heat strain and chemicals, such as pesticides and metals in their environment (home, work), should take the proper precautions to reduce the risk of the potential adverse effects of these hazards, including:
    - Guaranteed access to safe drinking water is key to mitigate the negative consequences of heat.
    - For workers, ensure proper hydration throughout the workday and before and after the work shift.
    - Take breaks during heat-exposed work times and encourage your employer to incorporate breaks into the workday. It is highly desirable that work tasks and schedules can be adapted to the hours with less heat.
    - Use of personal protective equipment according to current regulations and guidelines in each country when available to minimize exposure to environmental hazards.
    - Wear protective clothing, including hats, long sleeves, and long pants, to protect your body from the sun.
    - Minimize the use of chemicals, when possible, at work and at home.
    - If you need to use chemicals, follow the instructions on handling and appropriate use, including wearing the proper personal protective equipment.
    - Take care to not bring workplace chemicals into the home:
    - If working around or handling chemicals, make sure that you wash your clothing separately and that you thoroughly wash your hands and shower before coming into contact with any household members.
    - Take off your shoes and work clothes before entering the home as these may have chemicals from the workplace and become a source of exposure for other household members.
    - Public actions could be developed with other key actors in health, environment, agriculture and educational entities to create a “safe work” culture.

KEY MESSAGES FOR POLICYMAKERS

- A comprehensive understanding of the causes of CKDuis not needed to take action to reduce environmental risk of CKDu. In particular, efforts to reduce exposure to heat strain for workers on the job and improve basic public health on the community level will reduce the risk of disease.

- Heat-strain, poverty, environmental injustice, and social vulnerabilities are important risk factors for CKDu.
- Reducing poverty and provision of basic public health needs will likely reduce population-level susceptibility to CKDu, as these factors are intertwined with complex social risk factors that appear relevant in the disease emergence.
- Public health interventions ensure access to clean and safe drinking water, promoting worker safety and health, enhancing maternal well-being, and improving diet and nutrition.
- Individuals in under-resourced communities should have access to quality healthcare services that facilitate early screening, detection, and management of CKDu.
- Development and implementation of standardized workplace protections are paramount to ensure worker safety and not treat workers as disposable commodities. Absence of action will lead to financial losses at all levels. With CKDu, we are currently experiencing a loss of an essential workforce with many productive years ahead.
- Investment in research is necessary to understanding the mechanisms underlying CKDuand identifying effective prevention and management strategies.
- Funding for interdisciplinary, collaborative research initiatives focused on investigating the environmental and social determinants of CKDuis necessary to advance the research needed to protect vulnerable affected populations.

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SURVEILLANCE AND SCREENING

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INTRODUCTION

CKDu represents a significant public health challenge within Chronic Non-Communicable Diseases (NCDs). However, many countries lack dedicated surveillance programs for CKDu, with existing efforts often concentrated on recognized hotspots, potentially neglecting broader affected populations. To address this, it's advisable to broaden PAHO definition of CKDu, utilize existing surveillance systems, analyze national mortality statistics, and establish standardized protocols. Integrating CKDu surveillance, focused monitoring, and periodic population surveys can enhance understanding and guide appropriate actions to address this pressing issue.

Key Messages for Clinicians

For all clinicians:

- Emphasize the importance of early detection through routine screening for CKDu, particularly in high-risk populations or those acknowledged to be hotspots areas.
- Provide information related to screening results and the importance of identifying CKDu cases promptly for timely intervention and management either to reduce the already known risks, and if identified by a decline in eGFR, management should focus on delaying the progression of the disease
- Perform screening by conducting blood pressure, urine analysis, and creatinine determination in high-risk populations, such as agricultural and construction workers in regions with high prevalence of CKDu, to identify individuals with early signs of kidney dysfunction.

For general practitioners:

- Make sure that they are well aware of the signs and symptoms of CKDu, as well as the importance of incorporating CKDu screening into routine health assessments, especially for patients with relevant occupational or environmental exposures in hotspot areas.
- Provide resources and referral pathways for further evaluation and management of suspected cases.

For nephrologists:

- Confirm CKDu diagnoses through comprehensive clinical evaluations and specialized diagnostic tests.
- Encourage collaboration with primary care providers and public health to ensure a coordinated approach to CKDu surveillance, screening, and management.

For Public Health Workers:

- Stress the importance of surveillance data in informing public health policies and interventions aimed at preventing and mitigating the impact of CKDu.
- Provide training on surveillance and screening methods, data collection, and analysis to enhance capacity for monitoring CKDu trends and assessing the effectiveness of preventive measures.
- Track the prevalence of CKDu over time in a specific region using population-based surveys and health records for surveillance.
- Obtain statistics of mortality due to CKD compared to previous years in order to detect an increase in geographic areas not considered as hotspots.

Overall:

Develop packages of training for interested parties reinforcing community engagement working with nurses, public health educators, hygienists, community leaders. In the communities misinformed population may have the risk of using nephrotoxic medication or herbal remedies that could worsen the kidney health of at risk populations.

Key Messages for Community Members

Most important is the appropriate training of the whole personnel that might be in contact either to an exposed or at-risk in communities affected by CKDu" to the end of this sentence after the word individuals. That means to all possible health personnel that might have the opportunity for counseling and education. Exposed populations usually complain that they do not go to some health units or health post because there are no medications, no labs, nor timely advice from nurses or hygiene personnel.

Key communication targets:

- Individuals living in hotspots
- Individuals with leadership roles either in the heath system, industries, employers of any kind
- Healthcare personnel.

Key messages:

- Importance of regular health check-ups and screening for early detection of CKDu, especially for those living in high-risk areas or engaged in occupations associated with CKDu.
- Understanding of the signs, symptoms, and risk factors of CKDu, empowering community members to recognize potential warning signs and seek appropriate medical attention.
- Getting to know their traditions, use of remedies, learn from them to make sure that they will get a proper advice.
- Access to screening services, including information on where and how to access screenings, the benefits of early detection, and any associated costs or financial assistance programs available.

- The importance of collaboration to disseminate information about CKDu, promote participation in screening programs, and advocate for preventive measures and support services within the community.
- Surveillance systems and screening programs help identify individuals with CKDu at an early stage, enabling prompt diagnosis and intervention to prevent disease progression. Data obtained from surveillance provide insights into CKDu prevalence and risk factors within communities, guiding targeted preventive measures such as promoting occupational safety practices, improving access to clean water, and raising awareness about lifestyle modifications. Community-level support should focus on providing key information concerning findings, resources, education, and healthcare access to individuals and families affected by CKDu, thereby improving overall community health and well-being.

Surveillance in Central America, starting 2022

Aspects considered	Costa Rica	El Salvador	Guatemala	Panama	Dominican Republic
Epidemiological surveillance system					
Notification of Chronic Kidney Disease/Chronic Kidney Disease of non-traditional origin	CKD+CKD of non-traditional origin	CKD	CKD+CKD of non-traditional origin	CKD+CKD of non-traditional origin	CKD
Definition case CKD	Yes	No	Yes	Definition of the PAHO	No
	Cases of Chronic Kidney Disease of non-traditional origin suspected and confirmed		Cases of Chronic Kidney Disease of non-traditional origin suspected and confirmed	In the process of socialization	
Active surveillance or sentinel of CKD of non-traditional origin	Activate: CILOVISCIREVIS	No	Sentinel in 4 hospitals	No	No
Mortality surveillance CKD+CKD					
Analysis of demographic patterns	Yes	Yes	No	No	Yes
Use ICD 10 U50.X	(1023: 1 reported case)	No	No	Legally yes, in practice not yet.	No
Report to epidemiological surveillance	Sí	No	No	No	No

Key Messages for Policymakers

- Consideration should be given to the re-definition of a case of CKDu proposed by PAHO: It should not exclusively pertain to agricultural workers, as CKDu can also affect individuals in other occupations. The current age range starting from 12 years old may inadvertently include individuals with other renal pathologies unrelated to CKDu, potentially leading to misdiagnosis or overestimation of CKDu cases,
- Comparing statistics regarding the diagnosis of CKDu cases across countries poses challenges due to disparities in surveillance systems, inconsistent use of diagnostic codes, lack of reporting from certain regions, and variations or absence of standardized definitions. To address these issues, it is imperative to standardize reporting practices, establish a uniform registry system, and ensure inclusion of CKDu cases in compulsory notification systems. By implementing these measures, we can improve the accuracy and reliability of CKDu data collection and facilitate meaningful comparisons for effective public health interventions (see tables below showing the information gaps and differences in the surveillance systems).
- Surveillance and screening efforts contribute significantly to population-scale initiatives aimed at diagnosing, preventing, and treating CKDu, ultimately improving public health outcomes and reducing the burden of the disease on affected communities.

Note: Concerning surveillance, in the case of Costa Rica, CILOVIS stands for Local Inter-Institutional Commission on Health Supervision and CIREVIS stands for Regional Inter-Institutional Commission on Health Safety. Both are local and regional commissions that coordinate, supervise, analyze, and follow up both from passive and active surveillance.

Aspects considered	Costa Rica	El Salvador	Guatemala	Panama	Dominican Republic
Dialysis and transplant records					
Active registry with protocol	Yes	Yes	Yes	Yes	Yes
National	Yes	Yes	Yes/No?	Yes	Yes
End-Stage Renal Disease Registry with and without RRT	No	Yes	No (nephrologists) Yes (commission)	Yes	Yes
Distinction CKD of non-traditional origin	No	No	Yes	Yes	No
Analysis by demographic variables	Yes	Yes	Yes	Yes	Yes
Analysis of demographic patterns	Yes	Yes	No	No	Yes
Report to the epidemiological surveillance system	Yes	Yes	Yes	No	No

QUALITATIVE METHODS: VOICES OF PATIENTS AND COMMUNITIES

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INTRODUCTION

Qualitative research methods or community participation can be a way to incorporate the voices of patients and communities not only in research on Mesoamerican Nephropathy but also in strategies for prevention, control, early diagnosis, and treatment of the disease. These methods, especially semi-structured interviews, have been modestly used in the last decade in studies on ethical aspects and best practices in the field of research, quality of life, perceptions of healthcare professionals and patients, and community participation and empowerment. (photovoice or photonovela methodology) in the field of Mesoamerican Nephropathy; however, given its potential, we recommend using it to describe and analyze the social determinants of this disease, to continue exploring its etiology, as well as to improve access and quality of health care, promote occupational health and prevent labor risks, and deploy socio-health resources and support at the family and community level.

Key messages to healthcare professionals

We recommend using qualitative and participatory methodologies throughout the research cycle (Fig. 1):[1]

- Invite community leaders to be part of kidney research projects to improve understanding of kidney disease, facilitate collaborative and equitable partnerships, and increase the ethical conduct and relevance of research projects.
- Use the principles of kidney research engagement as basic tools in kidney research projects.
- Continuously train community leaders on prevention programs and early recognition of kidney disease.
- Validate research or clinical practice questionnaires.
- Evaluate the impact of public health interventions, for example, using focus groups.
- To deepen the understanding of the social determinants of disease, as well as the subjective experience of illness by patients and communities (body mapping methodology).[2]
- Explore the stigma and discrimination associated with the disease.
- Identify and describe environmental and occupational exposures.
- Involve patients and communities in the design and collection of information in population screenings and epidemiological surveillance systems.
- Identify/improve information, health education needs, and formats/channels for health promotion programs.
- Active participation in social protection programs, alternative employment, etc.

- Further explore prevention strategies, access to, and quality of healthcare (e.g., nutritional counseling at all stages of the disease, with recommendations tailored to the cultural environment and affordability of patients and their families).
- Explore the acceptability and other social and cultural factors of procedures such as kidney biopsies, dialysis, or kidney transplants.
- Address the emotional and mental health aspects associated with the disease, using methodologies such as patient or peer support groups.

Key messages to community members

We recommend proactive engagement with patients and affected communities. We understand communities as groups of people who share a shared identity, for example, patients and their families, groups of workers, communities that share a geographic location, and religious or educational communities, including teachers and families. To achieve this, we recommend:

- Involve community leaders, community councils, and patient associations.
- Involve indigenous governance mechanisms, where appropriate.
- Involve unions and workers' associations.
- Involve community health agents/workers, health councils.
- Involve the education system: teachers, family associations.
- Promote patient support groups.
- Promote the leadership of disease champions in health and peer education.
- Develop educational materials inspired by real community participants.
- Conduct pilot interventions with focus groups.
- Use innovative media to disseminate information: social media, local radio or television, campaigns/marches, health fairs, commemorative events.

Key messages to public officials and political decision-makers

Key messages to public officials and political decision-makers

- Consultas públicas de nuevos procesos normativos/legislativos.
- Anonymous workplace comment/complaint boxes.
- Community and workplace advisory groups.

Furthermore, within the context of the COMISCA Strategy for Kidney Disease of Non-Traditional Causes, it is necessary to work on the following training strategies for healthcare professionals, the community, and social protection programs.
Continuing education for healthcare professionals:

- A comprehensive, interdisciplinary, and multidisciplinary approach, including social workers and mental health professionals.
- Developing care flowcharts for early-stage CKD cases, to be used by paramedical staff and/or primary care physicians.

- Prioritizing nutritional advice tailored to the local culture and patients' purchasing power. Specific interventions are tailored to the population's medical history.
- Possibility of community assistance from the authorities.

Fig. 1 Development of a community engagement program

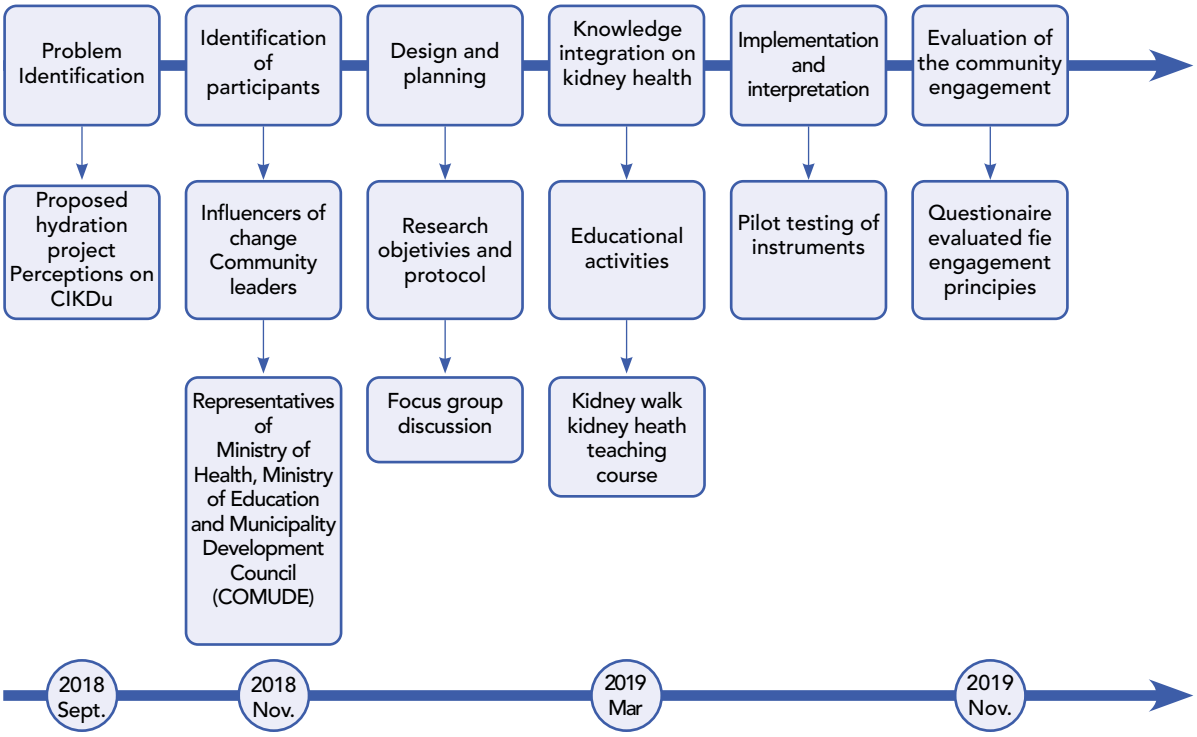

Fig.1 Development of a Community Engagement Program

In the Community Education Program:

- Work with the education sector.
- Use appropriate communication channels identified by the community.
- Promote self-care.

Design and seek commitment from countries to implement social protection programs that include:

- Disability, widowhood, and orphanhood pensions.
- Food packages.
- Subsidies for basic supplies.
- Transportation assistance, for example, to attend weekly dialysis sessions.
- Assistance with patient and family education.

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ANALYTICAL EPIDEMIOLOGY

David H. Wegman, Magdalena Madero, Ben Caplin, Sophie Claudel, Rebecca Fischer, Rolando Herrero-Acosta, Christer Hogstedt, Indiana López-Bonilla, iviana Loria-Carvajal, Dinesh Neupane, Maria Isabel Pedroza-Estrada, Ana Leonor Rivera-Chavarría, Dilcia Esperanza Sauceda- Acosta, Ajay Singh, Anna Strasma

INTRODUCTION

The mission of the Analytical Epidemiology working group was to provide insight into objectives and best practices for epidemiological studies to address the aetiology and prevention of work-related chronic kidney disease of undetermined cause (CKDu).

Key Messages for Public Health Workers and Leaders

An important underlying focus of Analytical Epidemiology is to contribute to understanding the causes of CKDu that inform prevention and then to evaluate the effectiveness of approaches or programs to prevent this disease. In the CENCAM context Analytical Epidemiology is distinct from clinical epidemiology which explores treatments to cure or prevent progression of the disease. Therefore, this working group addressed two primary questions.

1. How do we design and conduct good epidemiology studies to gain insight into the aetiology of CKDu moving forward?
2. How do we design and conduct good epidemiology studies to inform ways to control (or reduce the burden of) CKDu in the affected regions moving forward?

A. Two overarching conclusions resulted from the two days of discussions

Act on what we do already know:

- Those at risk of CKDu:
- Heat stress is sufficiently documented in epidemiologic studies to be an important factor in development of CKDu that current efforts should focus on interventions to reduce the impact of occupational or metabolic heat stress. Such interventions need to be evaluated through intervention research.
- Governments should prioritize implementation research to fully grasp the efficacy of interventions aimed at mitigating heat stress. This exploration is crucial to understanding why evidence-based interventions (EBI) can produce varied results when applied at the population level in real-world scenarios.
- Those with CKDu:
- Nephrotoxins (e.g. NSAIDs, aminoglycosides) are known contributors to kidney function decline. Interventions which reduce nephrotoxin use should be studied to identify priority intervention opportunities.

Alliances for intervention research:

- It is recommended that industry and public health engage with existing research teams, e.g. through CENCAM, SALTRA, to ensure optimal a priori research strategy, study design, exposure and outcome assessment, and control of confounding/bias.

B. The group agreed that early detection is critical for interventions that limit CKDu development or progression.

- A consensus was that eGFR decline is the most useful, easily available outcome, noting that even decline within the normal range could be important.
- A research priority is understanding rate of change in eGFR that could serve as an indicator of risk for CKD development
- Until rate of change is better understood, or another clinical marker is accepted we propose a concept labeled 'incident kidney injury (IKI)' as an epidemiologic (not a clinical) outcome to study in groups over a period of weeks to years. IKI is defined as an increase in SCr by 0.3 mg/dl or 1.5x the baseline SCr over the study period (the same values as KDIGO recommends for identifying AKI over a period ≤1 week).
- Research into early clinical markers is needed to assess disease initiation as well as disease progression. Ideal markers would be cheap, easy to measure, have low-technical needs, can be broadly accepted and implemented and non-invasive, if possible.

- Acute kidney injury (AKI) is often associated with CKD. There is an already accepted clinical diagnosis of AKI so cases could be enumerated and tracked in clinical records of relevant health centers or by well -planned short term measures of serum creatinine (cross-shift or cross-week) in populations at risk.

C. Important risk factors for eGFR decline amenable to intervention in populations at risk of CKDu have been identified, yet aetiology is not fully understood. Longitudinal studies with good exposure assessment aimed at providing insight into disease aetiology continue to be important. Fundamental principles of good epidemiological studies need to be a priority.

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HISTOPATHOLOGY

Carmen Ávila-Casado, Julia Wijkström, Manuel Cerdas,Zulma Cruz, Werner De León , Annika Östman Wernerson, Carmen Cajina-Aguirre

Histopathology investigation remains a key component of advancing our understanding of CKDu. The study of kidney tissue from biopsies may help to improve our ability to diagnose disease and provide information on prognosis; understand the contribution of possible causes to the development of disease; and understand the impact of interventions designed to prevent CKDu on the disease process. Key efforts related to histopathology that will help address CKDu include:

- Support for infrastructure and human resource development, particularly renal pathologists and laboratory facilities, in CKDu-affected regions. This can be accomplished through collaboration with existing societies (SLANH, ISN) and programs (the ISN Sister Renal Centers Program, ISN Educational Ambassadors, GlomCon) as well as development of new partnerships and programs.
  - Assessment of existing resources is a key first step, and should be a priority during the assessment stage of the "Support for the implementation of the strategy for the prevention, mitigation, and control of Chronic Kidney Disease of Non-Traditional Origin (CKDnT) in Central America and the Dominican Republic"
  - A SLANH-OPS agreement should be implemented
  - The ultimate goal should be to establish biopsy centers and local nephrologists in each CKDu-affected country

2. Development of a standardized biopsy template. This template will likely have different features when used for scientific research purposes versus diagnostic and patient care purposes.
   Ensures consistent data collection and reporting methods
   Improves communication across disciplines
   Enables analysis of trends, outcomes, and best practices

3. Construction of an educational atlas of CKDu histopathology for reference and training of pathologists working with CKDu.

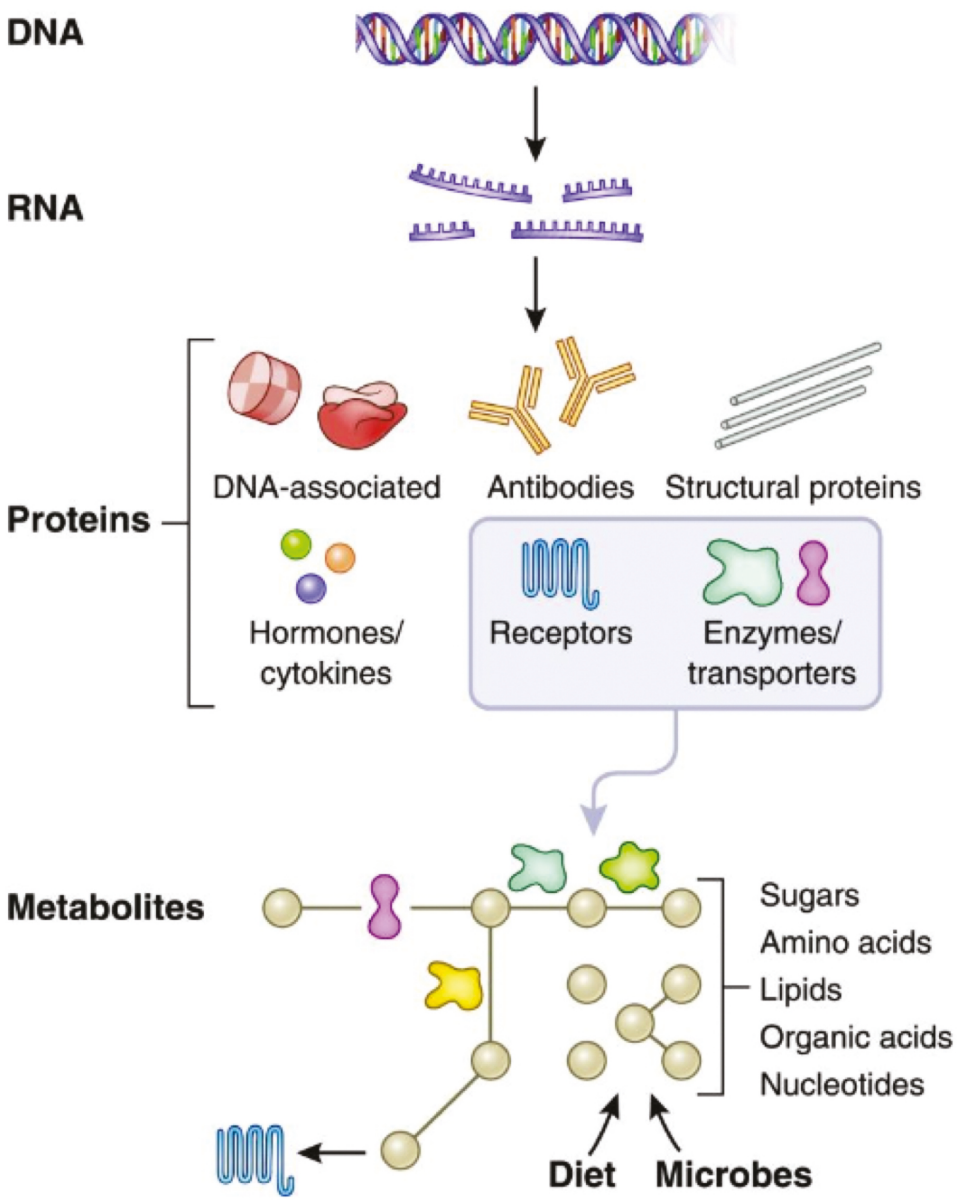
4. Development of renal tissue biobanks for research, and creating a Mesoamerican network registry with histopathological findings of biopsies, should be an additional goal to enhance our ability to study and understand CKDu.

BASIC SCIENCE/OMICS

Amin Oomatia; Jared Brown; Werner González; Diane Santos; Iván Landires; Sushrut Waikar; Eugenio Vilanova Gisbert; Samira Salihovic; Samantha Hall; Yeimy Herrera

Scientific techniques that may help us learn more about CKDu include the application of "Omics" technologies and basic science techniques. Omics is an umbrella term encompassing (although not limited to) the following disciplines (Figure 1):

Figure 1: An overview of biochemical characteristics studied using "Omics" technologies. De Dubiny Rhee. 2020



From Dubin and Rhee, 2020.

- Genomics
- Epigenomics
- Transcriptomics
- Proteomics
- Metabolomics

Omics techniques have shown considerable promise in investigating numerous diseases. They have been effective in answering questions related to:
- Environmental exposures
- Genetic susceptibility
- Causation
- Case identification
- Risk prediction
- Treatment

These techniques have begun to be applied to CKDu already, identifying certain genetic predispositions, metabolic processes, and biomarkers that may be important in the disease. This work is stil in its infancy, but shows a great deal of promise.

Basic science techniques, using animal and cell models to study CKDu, have also been used effectively and will likely continue to be an important cornerstone of CKDu research. To date, investigators have investigated heat stress, metals, and pesticides as potential drivers of disease. They have also combined basic science and omics techniques to good effect.

Key messages related to the use of omics technologies and basic science techniques to study CKDu include:

1. There exist important considerations related to study design:
   - Appropriate case definition
   - Sufficient and appropriate referents for comparison
   - Sample storage, transportation, analysis
2. Study questions dictate which 'omics / basic science approach may be most useful
   - Metabolomics may be most useful to assess exposure
   - Proteomics may be most useful to identify early cases
   - Animal models may be useful to investigate mechanisms and exposure interactions
3. Rapid technological and analytical advances may continue to enhance the efficacy of these techniques

4. Publicly available datasets exist and should be studied in relation to CKDu

WORK INVOLVING BOTH GOVERNMENT/PUBLIC HEALTH SYSTEMS AND RESEARCHERS

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INTRODUCTION

Although decision-makers in the various ministries and government health institutions need to know and analyze the results of scientific research to make evidence-informed decisions, communication between the scientific community and decision-makers and those in government is not always optimal.

This clearly has room for improvement and represents an opportunity to establish collaboration and/or communication between government and academia to accelerate progress in the prevention, detection, and treatment of UCRD.

Main Objective

To offer recommendations on communication and collaboration mechanisms involving academia and governments in the field of chronic kidney disease of unknown causes (CKD) to:

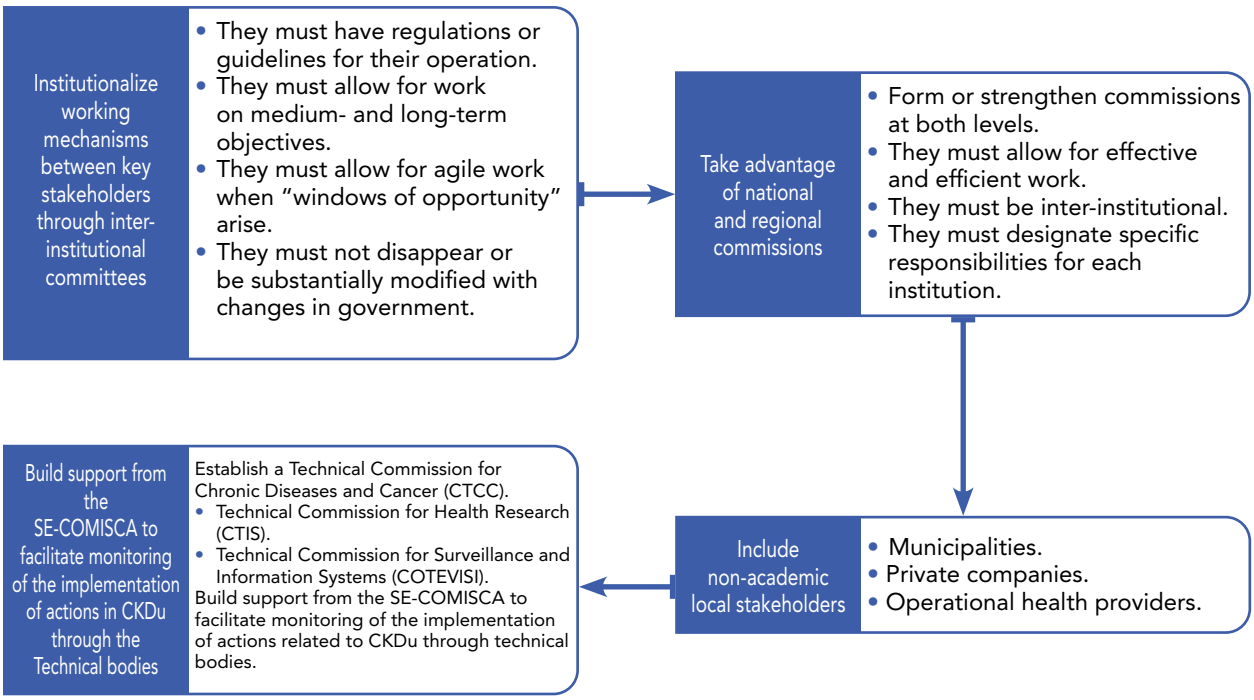
- **Improve communication** between academia and government for decision-making.
- Improve and expand opportunities for **collaborative work**
- **Support the project** "Support for the implementation of the Strategy for the Prevention, Mitigation, and Control of CKD in Central America and the Dominican Republic," proposed by AECID/SE-COMISCA/SLANH/ CENCAM/SALTRA
- **Propose a possible early detection and surveillance** system in the region (Central America and the Dominican Republic)

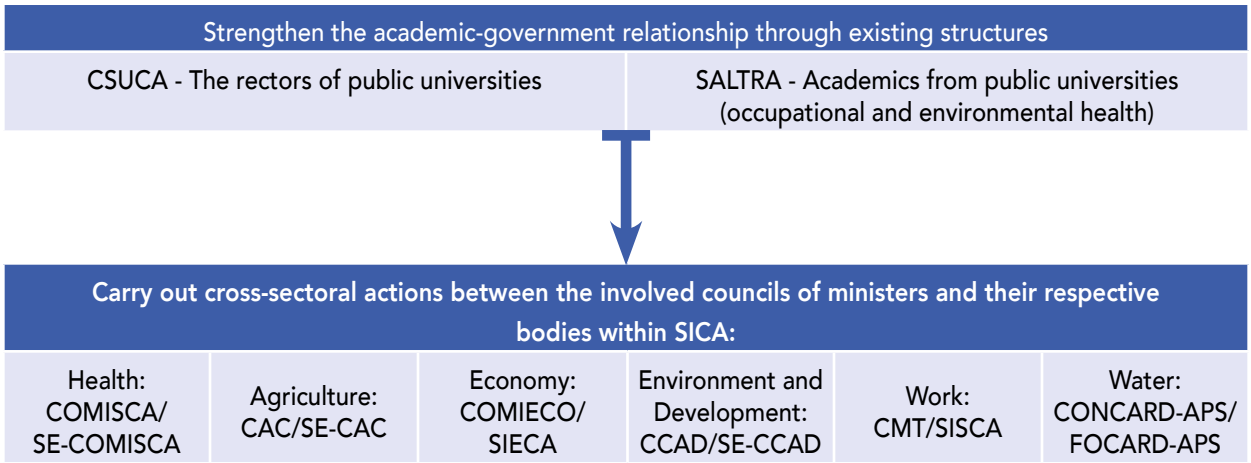
Key Messages for Medical Personnel

- **Incorporate this group's recommendations** into short-term training.
- **Emphasize prevention to prevent** more patients from requiring treatment.

Key Messages for Policymakers

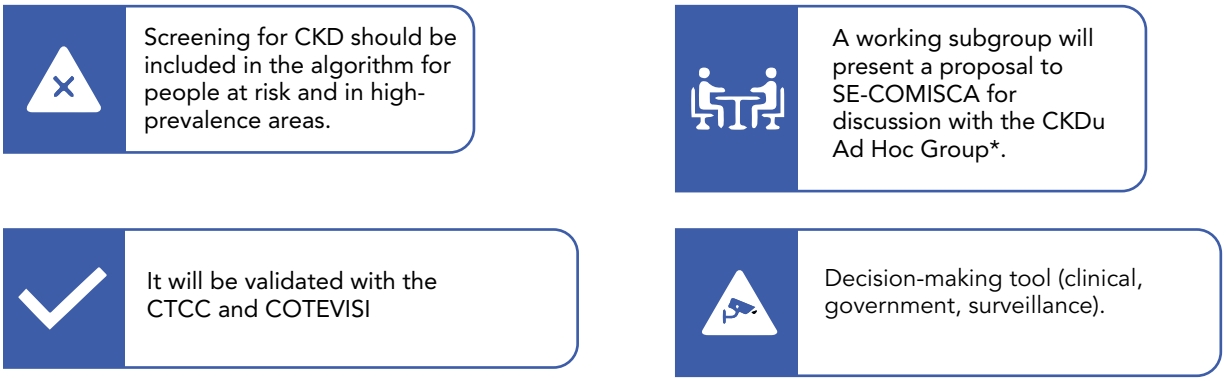
Recommendations on how to improve communication between the academic community, the health care community, and the government, in order to support evidence-informed decision-making and promote the implementation of actions and measures aimed at improving the CKDnT scenario:





Surveillance system for the region (Central America and the Dominican Republic)

The working group suggests creating a surveillance system by creating an integrative algorithm:



*The working subgroup will be coordinated by CENCAM, SALTRA, and SLANH, who will present the proposal to SE-COMSCA for discussion through the corresponding technical and operational bodies.

WORK INVOLVING INDUSTRY AND RESEARCHERS

Jason Glaser, Vidhya Venugopal, Juan Carlos Fernandez Quezada, Lourdes Doniz Lima, Julieta Granados Ramírez, Denis Chavarría, Thomas Boswell, John Adgate, Lee Newman, Ines Amenabar, Heath Prince

INTRODUCTION

Chronic Kidney Disease of Unknown Aetiology (CKDu) is a global public health issue, particularly in Mesoamerica, South Asia, and Africa. Industries and researchers must work together to treat CKDu due to its complicated aetiology and multifaceted character. Industry involvement provides researchers with big datasets, superior analytical tools, and specialised knowledge to improve study quality and scope. Research collaborations with companies can also speed up the development of preventive measures and technologies. These collaborations can understand CKDu's complex causes and find effective prevention and management methods by combining insights from nephrology, environmental epidemiology and implementation science.

Why work with Industry

- Demonstrate efficacy and viability of interventions to industry
- Reduce harm to the most exposed
- Increase productivity, a co-benefit of the research collaboration
- Provide an Return on Investment for the business
- Ethical and moral responsibility to improve OSH systems for workers while they are at work
- Capacity must be built so that adequate prevention systems carry on once research and/or consultancy has departed
- Through working with industry we can better understand who is most at risk and allow for targeting both occupationally based and community based interventions.

Additionally, it is imperative to consider that informal and migrant labourers, who are employed in Micro, Small, and Medium enterprises (MSMEs), are susceptible to exploitation on account of cultural and linguistic barriers, lack of access to social protection, and obstacles to healthcare. In addition to having an informal management structure and limited OSH awareness, MSMEs are frequently resource constrained and preoccupied with short-term issues. When it comes to labour inspectorates enforcing OSH legislation in smaller enterprises, government institutions frequently lack the resources necessary to ensure OSH compliance in MSMEs. The economies of the majority of LMICs are dependent on the labour force of MSMEs; therefore, the well-being of these workers will substantially impact the economic landscape of the region.

Key Messages for Clinicians

Clinicians are pivotal participants in the battle against CKDu, and it is critical for patient care that they comprehend industry-researcher collaboration. In order to tackle CKDu, these alliances combine knowledge, resources, and technologies from various sectors. Clinicians can enhance their comprehension of the underlying reasoning for industry-researcher collaborations in CKDu research and actively participate in cooperative endeavours that strive to elevate patient outcomes and public health by means of this partnership. These relationships should be regarded by clinicians as enduring commitments aimed at improving patient outcomes and public health through the comprehension, prevention, and management of CKDu.

Efforts to diagnose, prevent, and treat CKDu at the individual patient level are aided by collaborations between industry and research institutions. These partnerships develop personalised treatment approaches, identify risk factors, and enhance diagnostic tools. These collaborative efforts utilise assets and knowledge from diverse industries to improve the precision of diagnoses, guide the creation of innovative treatments customised to the specific requirements of each patient, and provide insights for preventative measures. Through the comprehension of the fundamental mechanisms of CKDu, these collaborations empower medical professionals to make earlier diagnoses, implement focused preventive strategies, and provide individualised therapeutic interventions—in essence, they enhance patient outcomes through the comprehension of CKDu's underlying mechanisms.

The key message for general practitioners, nephrologists and public health workers are as follows:

- **General practitioners** are strongly encouraged to remain updated on advancements in CKDu research and to actively engage in initiatives aimed at improving patient care in their respective communities.
- Understanding the complexities of industry-researcher collaborations concerning CKDu is critical for nephrologists to advance their specialty and enhance the quality of patient care.
- **Nephrologists** are strongly encouraged to engage in and provide backing for these collaborations, acknowledging their capacity to propel substantial progress in CKDu research and ultimately enhance patient results.
- **Public health professionals** need to be aware that these collaborations to provide access to vital resources, including funding, data, and advanced technology. These resources are indispensable for the execution of comprehensive research and the creation of efficacious interventions.

Key Messages for Community Members

An alliance between industry and researchers would yield significant advantages for the labour community. We wish to emphasise to these communities that worker communities can potentially enhance their health and well-being by actively participating in these partnerships that target the prevention, diagnosis, and management of CKDu.

- By participating in these collaborations, worker communities can assist in the prevention, management, and comprehension of CKDu, thereby enhancing their overall health and welfare.
- Addressing CKDu also requires effective communication with community leaders, such as civil society leaders, local government officials, and community organisers. In order to effectively communicate information regarding CKDu, including its risk factors and preventative measures, leaders ought to possess comprehensive knowledge.
- By actively interacting with government officials, one can advocate for the inclusion of CKDu in public health agendas and obtain financial support for research and interventions. Collaborating with community leaders can additionally facilitate the mobilization of community engagement, the promotion of policy reform, and the development of local capabilities to efficiently tackle CKDu.

Key Messages for Policymakers

- The key message to communicate to policymakers concerning collaborations between industry and researchers is the indispensable function that these alliances fulfil in tackling intricate public health issues, such as CKDu.
- Policymakers ought to recognise that industry-researcher collaborations facilitate the utilisation of knowledge, resources, and technologies from diverse sectors in order to carry out thorough investigations, devise inventive resolutions, and execute efficacious interventions. In doing so, they ought to give precedence to establishing a conducive atmosphere for collaboration, guaranteeing adherence to ethical principles, transparency, and community involvement, and allocating resources to support research endeavours.
- By acknowledging the significance of collaborations between industry and researchers, policymakers have the ability to make substantial advancements in the fight against CKDu and the advancement of public health.
- Occupational Health is every workers' RIGHT; no group, including marginalised migrants or informal labourers, may be excluded and policies pertaining to OSH must include these populations.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