Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy

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The global nephrology community recognises the need for a cohesive plan to address the problem of chronic kidney disease (CKD). In July, 2016, the International Society of Nephrology hosted a CKD summit of more than 85 people with diverse expertise and professional backgrounds from around the globe. The purpose was to identify and prioritise key activities for the next 5–10 years in the domains of clinical care, research, and advocacy and to create an action plan and performance framework based on ten themes: strengthen CKD surveillance; tackle major risk factors for CKD; reduce acute kidney injury—a special risk factor for CKD; enhance understanding of the genetic causes of CKD; establish better diagnostic methods in CKD; improve understanding of the natural course of CKD; assess and implement established treatment options in patients with CKD; improve management of symptoms and complications of CKD; develop novel therapeutic interventions to slow CKD progression and reduce CKD complications; and increase the quantity and quality of clinical trials in CKD. Each group produced a prioritised list of goals, activities, and a set of key deliverable objectives for each of the themes. The intended users of this action plan are clinicians, patients, scientists, industry partners, governments, and advocacy organisations. Implementation of this integrated comprehensive plan will benefit people who are at risk for or affected by CKD worldwide.

Introduction

Defining the problem

Chronic kidney disease (CKD) is increasingly recognised as a global public health problem.[1] Kidney failure is the most severe form of CKD, and is fatal if not treated by renal replacement therapy (RRT), which can be dialysis or kidney transplantation. The prevalence and associated burden of CKD is rising worldwide;[2–4] with the fastest growth occurring in low-income and middle-income countries. The incidence of acute kidney injury (AKI) has also substantially increased over the past two decades, and AKI is now recognised as an important cause of CKD and kidney failure.

Key messages

- A global collaborative effort of all stakeholders is required for a multifaceted action plan to combat the growing burden of CKD and its complications
- More work is needed to understand the causes and pathophysiology of CKD at the individual patient level, and at the population level in regions where CKD is endemic
- Existing data and biomaterial sources must be better used by promoting collaborative efforts and reducing administrative hurdles
- The clinical and research workforce needs to grow substantially in order to address the global burden of CKD, especially in low and middle income countries
- A concerted effort is required to increase the number, size, and quality of clinical trials investigating how to reduce the burden of CKD and its complications

CKD=chronic kidney disease.

Background statements

- CKD affects as many as 10–15% of the population worldwide, and is due to multiple causes
- CKD is associated with impaired quality of life and strongly reduced life expectancy
- CKD is associated with increased risk of cardiovascular disease, different disease manifestations, and more frequent and severe cardiovascular disease outcomes
- CKD reflects a serious complication of many different diseases, including diabetes, hypertension, and systemic immune disorders
- The cause of CKD remains uncertain in a large proportion of affected individuals, hindering specific therapeutic approaches
- The mechanisms that cause progressive kidney failure and associated systemic complications, including cardiovascular disease, remain incompletely understood, resulting in few available targeted therapies
- Nephrology lags behind other medical disciplines with respect to the number, size, and quality of clinical trials undertaken
- CKD and acute kidney injury are related manifestations of renal impairment with mutual predisposition, functional and structural overlap, and potentiating adverse consequences
- The costs of treating CKD-associated complications (including kidney failure) provide a challenge for health-care budgets that cannot be met in many parts of the world
- Successful prevention and treatment of CKD is strongly linked to progress on the Sustainable Development Goals

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CKD is associated with impaired quality of life and substantially reduced life expectancy at all ages. It is also associated with excess risk for cardiovascular disease and other conditions such as diabetes, infection, and cancer.[5] Even patients in wealthy countries do not always have optimal access to preventive treatment and methods for the early detection of CKD. There are few strategies currently available to slow CKD progression. Although RRT has been available for decades in high-income countries, relatively little is known about the benefits of RRT compared with conservative care in some patient groups, such as those with multi-morbidity, or advanced age. In low-income and middle-income countries, most people with kidney failure have insufficient access to life-saving dialysis and kidney transplantation.[6,7] Worldwide, only half of those people requiring RRT can be treated; estimates of the number who are untreated range from 2·5 million to 5 million.[6] The costs of treating CKD and its complications are unaffordable for governments and individuals in many parts of the world. Annual costs of dialysis and kidney transplantation alone range between US$35 000 and $100 000 per patient. Although better access to dialysis and transplantation in low-income and middle-income countries reflects progress on development goals, the associated costs have profound consequences for families and health-care systems, and the provision of RRT depends on sustainable health-care infrastructure, personnel, and supplies.[8] Medications that attenuate the course of CKD and its consequences are substantially less expensive than RRT, but still out of reach of many patients with CKD.[9]

CKD is defined by the Kidney Disease: Improving Global Outcomes (KDIGO) CKD guideline as abnormalities of kidney structure or function, present for more than 3 months, with implications for health.[10] Although there are issues in identifying population prevalence based on this definition,[11] as much as 10–15% of the adult population are affected worldwide.[12–17] Nevertheless, CKD is not included in most priority lists of non-communicable diseases, and few countries have explicit policies or public programmes aimed at CKD prevention and control. This is despite the fact that the presence of impaired kidney function is a risk amplifier of all non-communicable diseases, and is associated with the use of more resources.[3,8,18–23] Acute events such as infection, dehydration, and exposure to toxins or contrast media during imaging can affect kidney function, especially in people with underlying CKD. Recognising the need for action, an increasing number of global advocacy initiatives such as World Kidney Day, International Society of Nephrology (ISN) 0by25, and the *Lancet* Kidney Campaign aim to raise public awareness of the consequences, costs, and importance of both CKD and AKI.

Despite the many recognised causes of CKD such as diabetes, hypertension, vascular disease, or glomerulonephritis, the aetiology of CKD remains uncertain in most affected individuals, which hinders research about how to prevent, mitigate, and cure CKD. Knowledge about mechanisms that cause progressive loss of kidney function and its complications is also insufficient. Inconsistency and variability of clinical information between studies hinder pooling of data that could enable analyses with sufficient statistical power and adequate representation of less common diseases. Several high-profile interventional trials of promising therapies did not show a significant benefit, which discourages the search for innovative treatment approaches.[24–29] Nephrology lags behind other medical disciplines in terms of the number, size, and quality of completed clinical trials. There are many reasons for this, including few promising molecular targets, the slow rate of progression in many forms of CKD that require long observation periods, uncertainty about the potential of surrogate markers, a culture that does not foster the robust testing of focused hypotheses, and a failure to recognise clinical equipoise that would justify such trials. Since 2014, several international initiatives have emerged to foster collaboration in observational and interventional research, including KDIGO, ISN Advancing Clinical Trials (ISN-ACT) and International Network of CKD cohort studies (ISN-iNET CKD), the CKD Prognosis Consortium (CKD-PC), and the Kidney Health Initiative (KHI).

The need for a plan

In view of the need for a cohesive plan to address the problem of CKD, the ISN organised a summit in

Panel: **Key areas and themes**

Improve the identification of CKD and reduce risk factors for CKD

Theme 1: Strengthen CKD surveillance
Theme 2: Tackle major risk factors for CKD
Theme 3: Reduce acute kidney injury—a special risk factor for CKD

Improve the understanding of causes and consequences of CKD

Theme 4: Enhance understanding of the genetic causes of CKD
Theme 5: Establish better diagnostic methods in CKD
Theme 6: Improve understanding of the natural course of CKD

Improve outcomes with current knowledge

Theme 7: Assess and implement established treatment options in patients with CKD
Theme 8: Improve management of symptoms and complications of CKD

Develop and test new therapeutic strategies

Theme 9: Develop novel therapeutic interventions to slow CKD progression and reduce CKD complications
Theme 10: Increase the quantity and quality of clinical trials in CKD

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For more on **World Kidney Day** see www.worldkidneyday.org

For more on **0by25** see www.0by25.org

For the ***Lancet* Kidney Campaign** see www.thelancet.com/campaigns/kidney

For more on **KDIGO** see www.kdigo.org

For the **ISN** see http://www.theisn.org

For the **CKD Prognosis Consortium** see http://www.jhsph.edu/ckdpc

For the **Kidney Health Initiative** see https://www.asn-online.org/khi/mission.aspx

See Online for appendix

Vancouver, BC, Canada, in July, 2016, co-chaired by authors AL, MT, and K-UE. Participants included more than 85 individuals with diverse international expertise (clinicians, basic scientists, clinical researchers, epidemiologists, methodologists, and industry scientists). The purpose of the meeting was to identify and prioritise key activities for the next 5–10 years in clinical care, research, and advocacy; to identify potential partners within and outside the nephrology community; and to create an action plan and performance framework. This was the first time that such an activity has been undertaken by the global nephrology community.

Brief methods

Participants met for 2·5 days to develop the plan, which was based on ten themes predefined by the three co-chairs with input from the ISN Executive Committee (panel). All delegates participated in two of ten working groups, each of which addressed a single theme. We identified key issues and did supporting literature searches before the meeting to facilitate the working groups. By use of an iterative process, each group produced a prioritised list of key issues, goals, activities, and deliverable objectives. Special emphasis was placed on aligning these objectives with the Sustainable Development Goals (SDGs).[30]

The next sections of this Review elaborate on the specific themes discussed at the ISN summit, describing the current knowledge gaps and activities required to move the field forward. The performance framework is articulated to facilitate tracking of the activities, since "what gets measured gets done". Progress will be reported regularly at national and international meetings, in peer-reviewed publications, and as part of the Global Kidney Health Atlas (GKHA), to be updated every 2 years. The GKHA describes updates on CKD-relevant access to care, health infrastructure, national and regional policies, and research capacity.

Improve the identification of CKD and reduce risk factors for CKD

Theme 1: Strengthen CKD surveillance

Although the number, geographical distribution, size, and quality of the studies examining CKD prevalence and incidence have increased over the past decade, global capacity for CKD surveillance remains far less developed than that for disorders such as hypertension, diabetes, and cardiovascular disease. Moreover, fewer data on prevalence are available in low-income and middle-income countries as compared with high-income countries.

A 2010 systematic review identified 33 studies that reported age-specific and sex-specific prevalence of CKD in representative populations worldwide.[31] The global prevalence of CKD was estimated at about 10%, corresponding to almost 500 million people, with similar estimates in men and women, and in high-income countries compared with low-income countries. A meta-analysis of 100 studies of CKD prevalence resulted in an estimate of global CKD prevalence of 13% (appendix p 5),[32] which might overestimate the true prevalence given the limitations in the source literature. Other work has documented substantial variation in the apparent prevalence of CKD across studies done in different European populations (eg, the prevalence of CKD in northern Germany is five times higher than that in Italy and Norway).[33] It is unclear how much of this variation is because of research methods and how much caused by true population differences.[34] Data published in 2016 from the USA[13] suggest that initial increases in CKD prevalence[12] have plateaued since the mid-2000s,[13] largely due to a decrease in CKD in people older than 65 years. However, CKD prevalence in high-risk groups (such as African-Americans and people with diabetes) has continued to rise.

Dialysis and kidney transplantation registries are non-existent in many countries, and in many countries, there is no mandate to enter patient data into registries, nor to ensure the accuracy of them. Furthermore, RRT is only one measure of the burden of kidney failure—many patients worldwide are unable to receive or choose not to have RRT. Population-based registries of less severe forms of CKD are infrequent in most countries.

Identification of individuals with CKD relies primarily on serum creatinine measurements and equations to estimate glomerular filtration rate (GFR). Measurement of creatinine and albuminuria are central to the diagnosis and stage classification of CKD. Prevalence estimates remain sensitive to calibration errors in creatinine measurement.[35] The CKD Epidemiology Collaboration equation for estimating GFR is becoming the global standard, but much of the older literature used the Modification of Diet in Renal Disease Study equation, which results in somewhat higher prevalence estimates.[36,37] Urine measures of protein for CKD (protein-to-creatinine ratio, albumin-to-creatinine ratio [ACR], and qualitative dipstick for protein or albumin) are more difficult to standardise and suffer from high physiological variation of ACR,[38] with dipsticks providing even lower accuracy. Few studies have fully staged CKD by cross-classifying GFR and ACR categories, as recommended by the most recent KDIGO CKD guideline.[10] Estimates of reduced GFR or increased albuminuria have not been confirmed in most studies, which might have led to overestimation in prevalence figures.[11,39]

The first step to making progress in improving CKD monitoring activities (table 1) is to fully engage stakeholders by making sure the rationale for monitoring programmes is clear and tailored appropriately for different settings (appendix p 6).

To achieve valid comparisons over time (when meaningful trends in kidney function are often a small relative change of 2–10% per year[10]) and across regions, standardisation of measurements and methods must be

	Partners	Deliverables
Monitor the prevalence of CKD		
Develop and disseminate a clear rationale for monitoring CKD prevalence	Policy experts, third party payers	Published position statement; clarify the different measures of CKD burden (renal replacement therapy, CKD stages, use of health-care facilities, death from kidney failure, costs) in the general population and high-risk groups
Achieve a uniform measurement of CKD markers in CKD prevalence studies	International Federation of Clinical Chemists (IFCC)	Published position statement; develop and share quality control procedures and materials
Promote inclusion of measuring CKD and its awareness in all large chronic disease cohort or health surveys	Organisers of large studies, registries, such as WHO STEPS (102 countries), for cardiovascular disease, diabetes, and oncology surveillance	Inventory of studies of patients with and without CKD and CKD awareness; assembly of a task force to identify key contacts and include reporting of CKD and CKD awareness
Develop a plan to harness claims data for CKD surveillance	Health-care providers, aggregators of health data (eg, US Medicare, national health data repositories)	Established collaboration with regional and national societies and registries; workshop to assess feasibility and define action plan details; encourage validation of diagnostic codes in different regions; develop a plan to monitor strengths and limitations of claims data over time
Incorporate new CKD classification in WHO ICD coding	WHO	Incorporation into ICD-11
Establish CKD registries in special populations		
Establish registries of chronic dialysis and transplantation in all countries	Established registries	Inventory of CKD registries as part of the GKHA project; task force to explore the development of a generic software application; define minimal dataset required for these registries, facilitate implementation, suggest methods to assess comprehensiveness; encourage the use and usefulness of the registries to improve policy, observational research, and clinical trials
Establish registries for special CKD groups—eg, children, rare diseases, special causes, and regions where CKD appears to be endemic	Established registries, special interest groups	Inventory of CKD registries as part of the GKHA project; task force to explore the development of a generic software application to facilitate the establishment of CKD registries; define criteria for when a registry is high priority; encourage effective use of the registries to improve policy, observational research, and clinical trials
Identify individuals with CKD in high-risk groups		
Implement the respective KDIGO CKD guideline	Professional societies, medical and public health agencies	Implementation survey; case finding strategies in high-risk groups to be implemented in most countries
Support efforts to strengthen the evidence base underlying additional strategies for case finding in high-risk groups	Researchers and funding agencies	Research reports (focus on high-risk groups by condition, ethnicity, and region)
Ensure that wherever serum creatinine is measured, estimated GFR is reported	Clinical chemists (IFCC)	Focused extension of the GKHA project; IFCC committees; national and international laboratory professional groups and health-care institutions
Develop and share computer-assisted methods for identification and follow-up of CKD cases	Electronic medical record experts, health-care systems	Workshop to assess feasibility; position statement

CKD=chronic kidney disease. STEPS=STEPwise approach to Surveillance. ICD=International Classification of Diseases. GKHA=Global Kidney Health Atlas. KDIGO=Kidney Disease: Improving Global Outcomes. GFR=glomerular filtration rate.

Table 1: **Theme 1, goals and actions to strengthen CKD surveillance**

of high quality. To address this, large studies could consider shipping samples to a reference laboratory; reference materials could be prepared with known values for use in multiple studies worldwide; and where appropriate, point-of-care testing with reliable accuracy could be implemented that would increase the accessibility of diagnostic testing globally.

A systematic effort to ensure the inclusion of CKD measures in large ongoing or planned chronic disease studies could greatly enhance global efforts for CKD surveillance. The cost of including and standardising measurements of serum creatinine and albuminuria would be modest compared with the total cost of such surveys, especially if implemented in the context of other non-communicable disease-related initiatives. Systematic use of medical claims data for CKD surveillance would be complementary and should also be seriously considered. As electronic medical records are becoming standard worldwide, the potential for aggregating information is large, although the validity of claims or International Classification of Diseases (ICD)[40] codes for various medical conditions is limited. Codes for identifying CKD are often very insensitive, missing most diseases, but are quite specific.[41,42] Even unvalidated codes can give important clues to the evolving CKD epidemic. For example, a recent publication from China[43] showed that in 19 million people discharged from tertiary hospitals, the prevalence of CKD due to diabetes was higher than the prevalence of glomerulonephritis, in stark contrast to the situation a decade ago.[43] When electronic medical

records include laboratory data, researchers will be able to apply standardised definitions and staging of CKD to large populations. For example, Carrero and colleagues[44] tracked the prevalence of CKD in over 1 million people in the Stockholm region, and showed that even in a high-income country with universal health care, not all patients with advanced CKD consult a nephrologist for various reasons, including restricted access to services, personal choice, and physician's choice. Given the high cost of dedicated research studies and the increasing computerisation of health-care records, development of methods to increase the validity of imperfect health-care data appears to be a promising option for improving global CKD surveillance, especially in conjunction with focused validation studies.[45]

ICD coding forms the foundation for the systematic classification and enumeration of disease globally. Therefore, it is vital that the most recent KDIGO CKD classification scheme, which is based on estimated GFR (eGFR) and albuminuria, is integrated into the upcoming ICD-11 coding system. Additionally, a uniform system for specific coding of causes of CKD should be adopted worldwide; a potential candidate is the scheme by the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), which was developed in collaboration with the International Health Terminology Standards Development Organisation (IHTSDO).[46]

One special population of interest is people with kidney failure who receive RRT (ie, dialysis or transplantation); the prevalence of RRT reflects access to care and the burden of severe CKD—both of which are relevant to society and decision makers as well as to individuals. Therefore, emphasis should be placed on establishing registries of chronic dialysis and transplantation in all countries. Identifying patients who need RRT but do not receive it is an important, albeit challenging task. Given the specialised and expensive nature of RRT and the rapid conversion of medical care into the digital age, there is an excellent opportunity to improve the quality and coverage of such registries. Shared minimal data standards and architecture could greatly facilitate this work.

Simple registries for special populations such as children, patients with rare diseases, and residents of regions where CKD appears to be endemic (ie, hotspots) should collect data to support targeted efforts for improved care and prevention and clinical trials. Establishing and promoting a minimum dataset for registries (regardless of population or location) would enhance comparability across countries and facilitate global estimates of CKD prevalence.

A third population of interest is high-risk groups (eg, patients with known hypertension, diabetes, or cardiovascular disease) in which testing for CKD is already recommended. Supporting efforts to increase testing for both albuminuria and eGFR will help to understand and compare individual risk across countries and enable delivery of targeted therapies. Increasing efforts to use albuminuria and eGFR in combination should be coupled with reporting of eGFR whenever serum creatinine is measured. This is already the standard in much of the world and can be implemented at minimal cost elsewhere if digital data on age and sex are available.[47] Point-of-care testing is now available for use in rural and remote areas, which should improve ability to determine eGFR in low-income and middle-income countries, although the practicality and sustainability of long-term use in these settings has not been assessed.

Once CKD is identified, health-care providers might need support with management. Computer-assisted methods such as electronic decision support tools and protocols are being used in many settings to identify, follow, and care for patients with CKD.[48,49] Sharing these methods can be an efficient way to advance CKD monitoring and care; combining implementation efforts with cluster randomised designs to show efficacy should lead to continued improvement and further investment.

Although there is much enthusiasm for population-based CKD screening, the evidence base supporting this approach is insufficient. Since expectations for potential benefits of screening are often substantially different from true benefits, screening strategies should be developed and tested in a randomised setting so that efficacy can be appropriately measured. Although this has not yet been done for CKD, opportunities do exist to assess new strategies with control groups, possibly using a stepped wedge design with cluster randomisation—for example, CanSolveCKD aims to screen Indigenous communities for CKD comparing a standard and an enhanced approach.

For the **CanSolveCKD study Identifying diabetes and CKD in indigenous communities** see https://cansolveckd.ca/research/earlier-diagnosis/identifying-diabetes-and-ckd-in-indigenous-communities-case-finding-in-indigenous-communities/

Theme 2: Tackle major risk factors for CKD

CKD has multiple causes, both inherited and acquired. Some risk factors for CKD, particularly diabetes and hypertension, are well known; others are emerging, and yet others are presumably unknown (table 2). Including measures of kidney function (serum creatinine with eGFR or albuminuria) in population-based health surveys or assessments of non-communicable disease burden will not only facilitate CKD surveillance, but could also help to identify unknown risk factors and assist efforts to control known risk factors.

An example of unknown causes and risk factors for CKD is the hotspots of CKD of unidentified origin (CKDu) in specific regions close to the equator. These clusters of CKDu are an important and growing health problem; CKDu might be the leading cause of death affecting young field workers in parts of Sri Lanka, Central America, and South India.[50] Despite the recognition of these hotspots, there has been little success in identifying the root cause, which could include recurrent AKI; heat stress; dehydration; infections; exposure to agrochemicals, over the counter medication, heavy metal contamination, poor

	Partners	Deliverables
Identify unknown risk factors for CKD		
Promote inclusion of measuring CKD in all large communicable and non-communicable disease surveys	..	Inventory of studies including and not including CKD (and CKD awareness); task force to identify key contacts and include CKD and CKD awareness reporting
Establish and implement comprehensive research strategies to identify the causes of endemic CKDu hotspots using a lifecycle approach	ISN, WHO, and governments	Position statements and research reports including: case definitions, research agendas, standardisation of data collection tools; consistent framework for surveillance and investigation for epidemics of CKD around the world with reduction in time from identification to solving of problem, through this consistent approach
Mitigate known risk factors for CKD—diabetes		
Promote healthy lifestyles and food composition, implement prevention programmes, surveillance, case finding, and treatment according to local or regional needs and guidelines	Governments, payers, regulatory authorities, health-care organisations, patients, community groups, professional groups, global, regional, and national societies, public health practitioners	Appropriate references to the respective recommendations in publications, educational, and advocacy activities of nephrology organisations; reduction in proportion of patients with kidney failure and diabetes
Assess for the presence of CKD in individuals with diabetes	..	Implementation survey
Mitigate known risk factors for CKD—hypertension		
Promote healthy lifestyles and prevention programmes, implement surveillance, case finding, and treatment according to local or regional needs and guidelines	Governments, payers, health-care organisations, regulatory authorities, patients, community groups, professional groups, global, regional, and national societies for hypertension and cardiovascular health, public health practitioners	Appropriate references to the respective recommendations in publications, educational, and advocacy activities of nephrology organisations; improved blood pressure control in populations at risk
Assess the presence of CKD in individuals with hypertension	Governments, payers, regulatory authorities, health-care organisations, patients, community groups, professional groups, global, regional, and national societies, public health practitioners	Implementation survey
Mitigate known risk factors for CKD—prescribed medications		
Raise awareness of long-term medication use as a risk factor for CKD	Funding agencies, industry partners, and research networks	Research reports; reduction in proportion of patients with kidney failure attributable to medication overuse or misuse
Educate public and health practitioners about correct prescribing methods of potentially nephrotoxic medications, and need for surveillance	NGOs, governments, practitioners, pharmacists, CME organisations, communities, health insurance organisations	Inclusion in CME programmes
Mitigate known risk factors for CKD—traditional and alternative remedies		
Identify which (if any) traditional, alternative, and herbal remedies are risk factors for CKD	..	Research reports
Establish a health promotion and public education programme on the risk of the use of traditional and complementary medicine	NGOs, governments, traditional healers, alternative practitioners, media, communities, and public health practitioners	Inclusion in CME programmes
Require regulation of alternative medicine manufacture, labelling, and marketing	MOHs, industry partners, and alternative remedy manufacturers	Task force to establish a concrete strategy with tailored approaches
Assess the presence of CKD in individuals with significant exposure to remedies that have been shown to be risk factors for CKD	Governments, NGOs, practitioners, traditional healers, communities, global, regional, and national societies, and researchers	..
Mitigate known risk factors for CKD—kidney stones		
Promote access to adequate clean water, healthy diets (eg, those with sodium and protein), and work conditions that avoid dehydration	Communities, governments, professional associations (Centers for Disease Control and Prevention, American College of Physicians, Caring for Australians with Renal Impairment, Urology associations), health-care organisations, water companies, public health practitioners	..
Assess the presence of CKD in individuals that have previously had kidney stones	Urologists, primary care providers, and nephrologists	Survey existing guidelines on kidney stones for the inclusion of this recommendation and work towards its inclusion in future updates

(Table 2 continues on next page)

	Partners	Deliverables
(Continued from previous page)		
Mitigate known risk factors for CKD—infections		
Endorse population-level infection prevention and control policies and participate in educational activities	Public health providers and campaigners, Centres for Disease Control and Prevention, and primary care providers	..
Increase access to vaccinations against infections that are linked to AKI or CKD, or both	Public health providers and campaigners, Centres for Disease Control and Prevention, and primary care providers	..
Do studies to assess the effect of interventions that increase access to treatment for infections on the incidence and prevalence of infection-related AKI and CKD	Centres for Disease Control and Prevention (regional and national)	Epidemiological studies showing a positive effect of interventions that increase access to treatment for infections on the incidence and prevalence of infection-related AKI and CKD
Mitigate known risk factors for CKD—poor maternal and fetal health		
Increase the understanding of the link between variations in birthweight, gestational age, exposure to gestational diabetes or pre-eclampsia and the development of CKD in the fetus during childhood and adulthood	Obstetricians, paediatricians, epidemiologists, public health practitioners, and researchers	Research reports; increase surveillance practices of high-risk births and mothers in specific regions
Document each child's birthweight, gestational age at birth, exposure to gestational diabetes, pre-eclampsia, and any neonatal AKI, and maintain this information in their health record in high-income countries, and establish methods for data capture in low-income and middle-income countries	MOH, WHO, traditional birth attendants, community health workers, health information systems, paediatricians, neonatologists, obstetricians, patients (build upon MDG advances in maternal and child health)	Survey existing documentation policy as part of an extension of the Global Kidney Health Atlas project
Promote strategies to improve maternal and fetal health by reduction of risk factors—eg, smoking, obesity, diabetes, alcohol, and infections; and improve socioeconomic factors—eg, access to family planning, equity and education for women, reduction of poverty, and adequate nutrition	Patients, communities, public health practitioners, and WHO guidelines	Appropriate references to the respective recommendations in publications, educational, and advocacy activities of nephrology organisations

CKD=chronic kidney disease. CKDu=CKD of unknown cause. ISN=International Society of Nephrology. NGO=non-governmental organisation. CME=Continuing Medical Education. MOH=ministry of health. AKI=acute kidney injury. MDG=Millennium Development Goals.

***Table 2*: Theme 2, goals and actions to tackle major risk factors for CKD**

quality drinking water; or some combination thereof.[51–60] Kidney biopsy samples in patients with CKDu show chronic interstitial nephritis. Because proteinuria is mild or absent, simple urinalysis is not effective in screening for these cases. Comparative studies of patients with CKDu from different areas are urgently needed to identify similarities and differences that could help to identify the cause or causes of CKD in these populations. Because of limitations in resources and infrastructure, diagnosing and characterising CKDu, determining its incidence and prevalence, and assessing exposures remains challenging, despite recognition of CKDu for over 10 years in several regions.

Diabetes and hypertension are the dominant global risk factors for CKD. Obesity is closely linked to diabetes and hypertension, and might also predispose people to CKD. Good management of diabetes, hypertension, and excess bodyweight reduces the risk of CKD and improves outcomes in patients with CKD.[61–67] However, several important questions remain. For example, only about a third of patients with diabetes develop CKD; identifying factors that protect against CKD in the presence of diabetes could inform novel therapeutic approaches. Studies are also still required to optimise risk factor targets (eg, Haemoglobin A1c, blood pressure [BP], bodyweight) for CKD prevention and variance of such targets, eg, by age, gender, and ethnic origin.

Nephrotoxin exposure is a common and under-recognised risk factor for AKI and CKD.[68–74] Nephrotoxic agents include prescribed medications—eg, non-steroidal anti-inflammatory drugs (NSAIDs), iodinated contrast media, and some traditional and alternative remedies. Over 80% of people in low-income and middle-income countries are estimated to use traditional remedies that are often the only affordable or accessible means of health care.[75] Many of these remedies are untested and unregulated, with potential for inter-product variability and high risk of toxicity.[76] Electronic prompting and prescription tracking might reduce medication errors, overuse, and nephrotoxicity, especially in high-income countries. Such efforts should be combined with education of the public and health practitioners about correct prescribing of potentially nephrotoxic medications and the need for surveillance. There is also increasing interest in de-prescribing medications, especially in the elderly due to high incidence of side-effects and questionable effectiveness.[77–80] Surveillance for CKD among those exposed to potential nephrotoxins (including traditional remedies) should be a priority, especially in low-income and middle-income countries.

Kidney stones are another important CKD risk factor.[81–83] Modifiable contributors to the risk of developing kidney stones include diet and environmental exposures.[82,83] Individuals who have had a kidney stone are at higher risk for another one, and secondary prevention is key to reduce risks of recurrent stones and CKD.[82,84] Activities to reduce the risk of kidney stones (eg, ensuring adequate intake of clean water and work conditions that avoid dehydration) together with appropriate follow-up of people with a history of kidney stones could prevent long-term complications of CKD.

Infections are a major cause of AKI and CKD, especially in resource-limited regions.[69,85–87] HIV, malaria, and tuberculosis—included in the Millennium Development Goals (MDGs)—and other infections such as impetigo, hepatitis B, hepatitis C, and various tropical diseases, have been shown to be associated with increased risk of CKD.[87–101] However, the regional CKD burden related to infections is not well documented, so the effect on CKD prevalence of prophylaxis (vaccines), clean water, or treatment of these infections remains unknown.

Low birthweight, prematurity, and high birthweight (eg, in infants born to mothers with diabetes) are associated with increased risks of hypertension, diabetes, obesity, cardiovascular disease, and CKD.[102–105] Childhood obesity and pre-term birth are important risk amplifiers for CKD.[106–108] Mothers who experienced pre-eclampsia or eclampsia have an increased life-time risk of hypertension and CKD.[109–112] Antenatal clinics and delivery sites could be central locations for identification of women and children at risk of AKI and CKD who will require long-term follow-up. Good pregnancy and delivery care reduce risks for AKI, but whether interventions during pregnancy or soon after birth could reduce subsequent CKD risk in mothers, babies, or both remains unknown. Research is required to better understand the pathophysiology of renal risk related to developmental programming; how to rescue kidney development; how premature babies should be optimally treated and nourished to avoid AKI and long-term metabolic consequences that might lead to CKD; how to reduce risks from pre-eclampsia; and how long-term risk might be modified through lifestyle or early interventions. Documentation of birthweight, gestation age at birth, exposure to gestational diabetes or pre-eclampsia, and any neonatal AKI should occur globally and this information maintained in health records. Strategies to improve maternal and fetal health through reduction of risk factors (including smoking, obesity, diabetes, alcohol, and infections) and improvement of socioeconomic factors (including access to family planning, equity and education for women, reduction of poverty, and adequate nutrition) will also improve kidney health.

Theme 3: Reduce AKI—a special risk factor for CKD and CKD progression

By contrast with what had been long assumed, episodes of AKI, even if they appear fully reversible with return of eGFR to baseline, are associated with long-term risk of de-novo CKD, CKD progression, and kidney failure in multiple clinical settings.[113–115] In a meta-analysis from 2012,[115] survivors of hospital-associated AKI were 8 times more likely to develop CKD. Occurrence of AKI in people without CKD is a risk factor for CKD, and pre-existing albuminuria and reduced eGFR are strong risk factors for AKI.[116–120] Chronic kidney damage, impaired renal reserve, and compromised vascular autoregulation might be contributors to AKI risk in the CKD population.

However, despite the epidemiological association of AKI and CKD, the effect of preventing AKI on long-term CKD remains to be shown. Patients who develop AKI often have other risk factors for CKD and CKD progression, so it is possible that the observed association between AKI and kidney function loss is confounded by illness severity. Moreover, it can be difficult to distinguish AKI from progression of CKD, and it is possible that the observed associations are to some extent due to misclassification—especially in low-income and middle-income countries, where laboratory testing is infrequent or unavailable and baseline kidney function is often unknown.[121] AKI is common in all populations irrespective of geographical location: although causes might vary, the effect of AKI events due to ischaemia, toxins, inflammation, or a combination of these factors is profound.

Progress in the management of people with CKD will require targeting of individuals who are at risk for AKI with preventive activities such as avoiding toxic drugs, identification of AKI events when they occur, and improvement in the quality of follow-up care after an episode of AKI (table 3). Greater recognition of CKD as a risk factor for AKI and selective assessment of kidney function before high-risk exposures (eg, cardiac catheterisation) is achievable through education, quality improvement processes, and leveraging of existing methods such as electronic medical records. The ability to identify and flag these patients allows an opportunity for intervention (such as prophylactic hydration, reduction in use of contrast during imaging, or non-contrast followed by contrast procedure, as necessary) and creates the opportunity for follow-up and specialist referral if required. Research collaborations using large population-based datasets (including participants from low-income and middle-income countries) might permit increased understanding of the exact contribution of CKD to global AKI risk and the attributable risk of AKI to CKD progression.

Educational tools for the lay public, patients with CKD, and their families might help to avoid high-risk exposures that could result in AKI (as proposed for the ISN-0by25 initiative for AKI).[122] Education for providers is also important. Most patients with CKD are managed by primary care providers and only a few are under specialist nephrology care, particularly in low-income and middle-income countries. Routine follow-up of patients with CKD

	Partners	Deliverables
Mitigate known risk factors for CKD—AKI		
Promote strategies to avoid and mitigate episodes of AKI in people without CKD according to regional needs and established guidelines	Non-nephrology disciplines, and 0by25	Progress reports of 0by25 initiative
Identify CKD patients at risk for AKI		
Develop and implement educational tools identifying known risk factors, including prediction equations	Health systems, and governments	Inventory of countries and regions and whether they have access to specific education tools for general use; improved ability to identify individuals at risk exists within all communities
Identify regional risk factors for AKI in individuals with CKD	Regional health systems, and industry partners	Research report; complete catalogue with participating countries within 2 years
Identify patient with CKD (tagging) to health-care providers	Health systems, primary care, and industry partners	..
Identify episodes of AKI in patients with CKD		
Monitor kidney function in high-risk clinical scenarios or exposures	Relevant non-nephrology specialties (radiology, cardiology, and infectious disease), and government	Demonstration of capacity to monitor kidney function longitudinally in high-risk populations; improved ability to identify people at risk exists within all communities
Identify and assess methods to better assess structural and functional aspects of the kidney in CKD and after AKI	Industry partners, and research funders	Advocate to funding agencies; improved access to diagnostic facilities in all regions of the world
Promote electronic medical record alerting—include kidney function in checklists for health-care workers who manage high-risk scenarios	Health systems, and government	Conference to discuss research and clinical possibilities
Educate patients and providers regarding AKI	Governments, health systems, and public health campaigners	Coordination of efforts such as educational initiatives and tool development as described in the 0by25 activities
Identify indications for biopsy sampling when patient diagnosis is not clear (AKI or progressive CKD)	Industry partners	Consensus conference with published report; increase access to diagnostic methods in all regions
Improve care during and after AKI		
Promote and monitor kidney function surveillance and CKD care after AKI	Governments, health systems, and primary care	Identify capacity for AKI care as part of the Global Kidney Health Atlas project
Promote or complete trials of appropriate interventions after AKI to minimise the risk of CKD progression	..	Adding representation to trials groups; improved evidence base for clinical decision making; better outcomes of AKI
Promote or complete trials of AKI prevention in patients with CKD	Industry partners, International Society of Nephrology—Advancing Clinical Trials, other interest groups such as international cardiology trials networks	Adding experts in AKI outcome ascertainment to clinical trials groups

CKD=chronic kidney disease. AKI=acute kidney injury.

Table 3: **Theme 3, goals and actions to reduce AKI, a special risk factor for CKD and CKD progression**

is often guided by the presence of comorbidities (eg, diabetes, heart failure, hypertension), and testing for albuminuria and reduced eGFR might be infrequent. It is therefore imperative that everyone with CKD be considered at risk for AKI by all providers caring for these patients. Education should include risk mitigation strategies and the need for ongoing monitoring of kidney function. Urinalysis for proteinuria and urine microscopy with assessment for eosinophils and casts are inexpensive methods for diagnosing AKI even in resource-poor settings.[123,124]

Patients should be encouraged to report symptoms (eg, diarrhoea, vomiting) that might facilitate earlier recognition of AKI.[69] Toolkits based on the 5R approach (risk, recognition, response, renal support, and rehabilitation) for AKI management described by the ISN-0by25 initiative[69,122] can be customised for this purpose. For instance, outpatient cardiac catheterisations and contrast CT scans are common procedures in high-income countries, and are frequently done in patients with or at risk for CKD. However, serum creatinine is not always tested for after a CT with contrast,[125] possibly because such testing is not reimbursed by insurance, or because there is an absence of awareness of the need for follow-up, so AKI that could contribute to CKD progression might go undetected. In low-income and middle-income countries or remote areas in high-income countries, innovative methods such as telemedicine could be useful to facilitate access to medical advice and guide management of AKI and CKD.

Even with optimal efforts at education and prevention, the prevalence of AKI is likely to increase further because of an ageing population and increased use of medicines, and parallel efforts are needed to improve the quality of follow-up care. The KDIGO guideline for

AKI management[126] recommends longitudinal patient follow-up after admission to hospital, targeted at providing appropriate care for patients with, or at high risk of, long-term sequelae of AKI. In settings where there is little access to medical care, the detection of AKI might represent the sole opportunity to identify and treat CKD. Several centres in Canada and the USA have established AKI survivor clinics,[127] but no interventions to manage AKI or its sequelae after discharge have been proven to improve outcomes so far. Since it is neither practical nor feasible for nephrologists to care for all patients with CKD who develop AKI, a targeted approach based on risk and opportunities for intervention is needed, based on evidence of effectiveness.

Improve the understanding of causes and consequences of CKD

Theme 4: Improve understanding of the genetic causes of CKD

Understanding the genetic contributors to kidney function in health and disease and the interaction between genetic susceptibility factors and the environment can provide insights into renal physiology and pathophysiology, including the identification of novel therapeutic or preventive targets. Genome-wide association studies (GWAS), as well as whole-exome and whole-genome sequencing, have become standard techniques to identify genetic loci in which variation is associated with complex forms of CKD and with impaired kidney function. These techniques can detect mutations that cause monogenic kidney diseases.[128–130] Several hundred genes are currently known in which mutations can cause single gene disorders with a kidney phenotype, as well as dozens of genetic loci in which common genetic variants are associated with kidney function and with complex diseases of the kidney[130] (appendix p 7).

However, there are five main limitations in understanding the genetic causes of CKD. First, awareness of the importance of genetic research is limited—especially of the initiation and type of genetic testing, assessment of the pathogenicity of detected genetic variants, and importance of patient counselling. Second, most existing genetic research has been done for individuals of European ancestry, despite the fact that indigenous populations of non-European ancestry often show high rates of kidney disease and that there is evidence for region-specific genetic risk factors for CKD.[131] The available knowledge, therefore, might not be representative globally, which could have substantial implications.[132] Third, genetic research can reach its full potential only through widespread data sharing, which currently is not commonly practised, and data are often available only in non-standard formats. Thus, comprehensive inventories of existing genetic datasets and their accessibility are important prerequisites to maximise the use of existing data. Fourth, the few methods available for functional genomics research, particularly in kidney cell types, hinders the identification of causal genes and variants, mechanistic insights, and ultimately translation to the clinic.[133] Finally, our current understanding of gene–environment interactions and their relevance for CKD is incomplete. A better understanding of these interactions will provide insights into patient subgroups and help in targeted therapy and prevention.

Accordingly, future activities should work toward five goals (table 4): to increase awareness about the importance of genetics for understanding and treating CKD; to increase the diversity of genotyped populations beyond those of European ancestry; to increase accessibility of genetic data to a broader range of scientists; to generate new methods for functional genomics; and to promote better understanding of gene–environment interactions that are relevant to causes and consequences of CKD.

Professional organisations including patient advocacy organisations, scientific journals, the media, the pharmaceutical industry, medical schools, teaching hospitals, and the ISN should develop and disseminate relevant educational materials. Topics should include the discussion of challenges in genetic research (eg, privacy, how to report incidental findings)[134,135] and opportunities (eg, discovery of novel pathophysiological mechanisms; development of new therapies). Educational activities in countries of all income levels[136] should include the communication of realistic timelines for the translation of genetic findings (appendix p 8).[133]

Findings from large-scale sequencing projects of patients with CKD and healthy individuals can provide adjusted estimates of the prevalence and penetrance of suspected pathogenic variants and give insights into the phenotypic presentation spectrum for variants of a given gene, which would help in counselling and risk prediction.[134,137–140] Knowledge of mutation prevalence and penetrance can also guide the choice of which variants to pursue experimentally, the timing and scope of genetic testing, and pharmacogenomic decisions.[132]

The *APOL1* gene for apoliporotein 1 has been identified as a major susceptibility gene for kidney disease in individuals of African ancestry,[131,141] which shows that ancestry-specific determinants exist. Genetic research in indigenous populations with high rates of CKD could be particularly informative about susceptibility genes or gene–environment interactions, and might lead to a better understanding of allelic diversity, reducing the risk of false attribution of pathogenicity to ancestry-specific variants.[132] Genetic investigations in populations at high risk for CKD can also help understanding of whether kidney function variants identified in the general population[142–145] contribute to endemic or advanced CKD.

To increase the application of clinical genomics to populations at high risk of developing CKD (such as indigenous populations, groups with rare diseases, and some ethnic groups), study protocols and policies must

	Partners	Deliverables
Increase awareness about the value and importance of genetics for understanding and treating CKD		
Educate clinicians and researchers about the value and importance of clinical genomics and genetic research for CKD, including challenges (eg, ethical aspects, limitations in variant interpretation), opportunities, and realistic timelines for mechanistic understanding and translation	Nephrology fellows, medical schools, geneticists, professional organisations, patient advocacy organisations groups, industry partners, and technology and biotechnology companies	Inventory of existing training and educational programmes; double the number of programmes in 5 years; offer training programmes in nephrogenetics at international nephrology meetings or as stand-alone meetings; increase in proportion of patients who participate in genetic research *vs* those who decline
Educate patients and the public about the value of clinical genomics and genetic research	Geneticists, professional organisations, patient advocacy organisations groups, journals, offprint media, and industry partners	Increased media coverage in the next 2–5 years; increase in proportion of patients who participate in genetic research *vs* those who decline
Educate clinicians and researchers about findings from large-scale sequencing projects of nephrology patients and asymptomatic individuals that provide adjusted estimates of prevalence and penetrance of presumably pathogenic variants necessary for counselling and risk prediction	Medical schools, teaching hospitals, university and hospital nephrology divisions, professional societies, patient advocacy organisations and groups, industry partners, and nephrology journals	Research reports and review articles in the next 2 years, including discussion of potential implications for counselling; increase in proportion of patients who participate in genetic research *vs* those who decline
Educate clinicians about the diverse clinical presentations of genetic kidney disease and revise genetic testing accordingly	Medical schools, teaching hospitals, professional societies, patient advocacy organisations, industry partners, journals, and clinical sequencing laboratories	Research reports and reviews on spectrum of clinical presentations for kidney disease genes; published recommendations about which genes to sequence for which presentation; and development of standard gene panels for different nephrological diseases (tubular, FSGS) with region-specific content
Increase diversity of genotyped populations beyond European ancestry		
Protect indigenous populations, rare disease groups, ethnic minorities, small communities, family or heritage beliefs to enable their inclusion in genetic analysis and increase diversity of genotyped populations	Communities, governments, regulatory authorities, and Institutional Review Boards	Inventory of genotyped populations and their diversity in CKD hotspots; review of existing protocol or policy recommendations and publication of recommendation about where to focus genotyping efforts in the next 2 years; increase in proportion of patients who participate in genetic research *vs* those who decline
Improve SNP diversity on commercially available chips; and improve imputation reference panels for ethnically diverse populations	Genotyping companies (Affymetrix, Illumina), and computational biologists (for improved and diverse imputation platforms)	Development of affordable genotyping for worldwide populations; provision of improved genotype imputation for non-European ancestry populations; promote comprehensive SNP array genotyping for CKDu in CKD hotspots to identify a potential major gene effect; produce timely research reports
Educate groups, patients, populations, and other stakeholders about the value of genetic research in diverse populations	Communities, governments, regulatory authorities, Institutional Review Boards, genotyping companies (Affymetrix, Illumina), computational biologists (for improved and diverse imputation platforms), and media	Increase media and journal coverage of the value of genetic research in diverse populations
Increase accessibility of genetic data		
Increase accessibility and usability of existing and future datasets by promoting standardised format, broad data sharing, and increased usage	International Society of Nephrology-iNET CKD, journal editors, technology companies, CKDGen, biobanks and biorespositories, dbgap, Big Data 2 Knowledge initiative, Accelerating Medicines Partnership portal, Cohorts for Heart and Aging Research in Genomic Epidemiology consortium, and National Human Genome Research Institute and Genome-Wide Association Studies Catalog (now European Bioinformatics Institute)	Development and publication of position statement on standardised format for data sharing; tracking of number of publications, number of requests for data, review of catalogued resources, and reduction of redundancies
Develop data mining tools and search functions to catalogue existing datasets	Computational scientists, and industry partners	Shared tools (eg, search functions) to investigate publicly available data; research publications based on existing datasets (secondary use)
Promote common data elements, phenotypes, or standards in existing and future datasets (eg, age, sex, serum creatinine, urine albumin-to-creatinine ratio, and ethnicity); improve renal phenotype harmonisation and lab assays used to measure renal function parameters; and develop EMR search tools for renal patients	Clinical chemistry, epidemiologists, and lab assay developers	Establishment of consensus on a set of core nephrological parameters to enable kidney disease genetics research and consensus on how to identify patients with CKD from EMR; more focused research in genetics within the field of renal medicine
Create incentives for data sharing	Journals and industry partners	Develop journal guidelines that require data sharing for publication; sponsor platforms, portals, and infrastructure to share data; more focused research in genetics within the field of renal medicine
Catalogue and aggregate existing data repositories and biobanks or biospecimens to enable more rapid and accessible research	Computational scientists, and industry partners	Develop concept for centralised platforms, portals, and infrastructure to share data and identify funding mechanisms; more focused research in genetics within the field of renal medicine
Link biomarkers to genetic data to attribute causality (Mendelian randomisation) using publicly available summary statistics databases	Statisticians, and industry partners	Development of software that facilitates Mendelian randomisation analyses and make publicly available

(Table 4 continues on next page)

	Partners	Deliverables
(Continued from previous page)		
Generate tools for functional genomics		
Develop methods for applying function of genetic findings to identify the causal gene or variant, and the genetic mechanism of action to facilitate translational research; methods should be shared broadly	Geneticists, bioinformaticians and computational biologists, technology companies, industry partners, and funding agencies	Inventory of available tools, cell types, cell lines in the next 2–5 years; tracking of published papers with mechanism of action of genetic findings and collection in a centralised resource; faster time from discovery to phase 1 clinical trials and phase 2 trials in nephrology with less failure of compounds
Promote the creation of disease-relevant cellular assays, bioinformatics pipelines, and tools for use in the scientific community	Geneticists, bioinformaticians and computational biologists, technology companies, industry partners, and funding agencies	Published research reports elucidating mechanism of action of newly uncovered genetic loci; development of assays that are available upon request; faster time from discovery to phase 1 and phase 2 trials in nephrology with less failure of compounds
Generate tools to study genetic modifiers, including epigenetic effects to understand mutations in their genomic context and identify potential therapeutic targets	Geneticists, bioinformaticians and computational biologists, technology companies, industry partners, and funding agencies	Creation of tools as documented in published research reports of epigenetic catalogues of different kidney cell types; faster time from discovery to phase 1 and phase 2 trials in nephrology with less failure of compounds
Promote better understanding of genes by environment interactions		
Promote existing large initiatives such as the Precision Medicine Initiative or the UK Biobank data to elucidate genes by environmental interactions	CKDGen, iNET CKD, biobanks and biorespositories, CKDu investigators	Research reports
Develop EMR search tools for the most common environmental CKD risk factors	Computational scientists, specialists for environmental risk factors, and epidemiologists	Consensus on a small set of potentially most important interactors and standardisation of their definition and methods for data capture
Develop renal endophenotypes to increase the power of GXE interactions; use renal endophenotypes (including genetics) to identify more homogeneous subgroups of patients to facilitate GXE discoveries	..	Use of biomarkers and genomics, proteomics, and metabolomics data for the identification of more homogeneous subgroups of CKD to identify novel genes and GXE interactions; produce timely research reports
Promote comprehensive SNP array genotyping for CKDu in CKD hotspots to identify a major gene effect present in populations exposed to a specific environment	Environmental scientists	Research report

CKD=chronic kidney disease. SNP=single-nucleotide polymorphism. GXE=genetics by environment. FSGS=focal segmental glomerulosclerosis. CKDu=CKD of unknown cause. CKDGen=CKD Genetics consortium. EMR=electronic medical records.

Table 4: **Theme 4, improve understanding of the genetic causes of CKD**

ensure the protection of each of these unique groups from exploitation and misuse of data by including them in specific patient engagement activities, while being mindful of family or heritage beliefs to allow for culturally sensitive genetic research. The development and implementation of culturally sensitive methods by which to engage communities worldwide is imperative if new knowledge is to be comprehensive and applicable to multiple populations.

To broaden the knowledge base of genetic variants in high-risk populations, researchers need to work with genotyping companies and computational scientists to provide affordable and comprehensive genotyping for worldwide populations, and to improve reference panels for non-European ancestry populations. As outlined in the FAIR (findability, accessibility, interoperability, reusability) guidelines,[146] individual and aggregate datasets should be available with few barriers to access in a useful, standardised format. The accessibility and effectiveness of existing and future datasets could be increased by promoting standardised formats, common data elements and standardised phenotype definitions, and broad data sharing. Data sharing could also be complemented by cataloguing and aggregating existing data repositories and specimens for correlation of biomarkers to genetic data to identify causality (eg, Mendelian randomisation).

There are tremendous potential benefits from developing common data elements relevant to kidney research. The use of similar measurements and definitions maximises the potential for the use of datasets in different centres as well as in combination, to increase power of under-represented groups. Important potential partners in this process are biomedical journals, which could insist on data access for all original publications as a condition for publication, international research collaborations (eg, CKD Genetics Consortium, CKD-PC, ISN-iNet CKD) for the definition of common renal phenotypes, and the data scientists who develop and maintain resources for the establishment of data sharing formats (eg, the National Human Genome Research Initiative GWAS Catalogue).[147] Governments and the pharmaceutical industry should support data sharing infrastructure, as they have already done with platforms generated through the Big Data to Knowledge (BD2K) project[148] or the Accelerating Medicines Partnership project for type 2 diabetes.[149] Many of these resources already exist in high-income countries, but in low-income and middle-income countries, primary data generation can be challenging.

New methods for functional genomics will be needed to enable the translation of loci uncovered through genetic screens including GWAS and sequencing studies[133] (appendix p 8). Functional genomics methods are used to identify causal genes and variants and to elucidate their mechanisms of action, to focus on

translation of the most promising findings.[150,151] One example is the original discovery of the *APOL1* gene region, where the signal was initially attributed to a neighbouring gene, *MYH9*, illustrating that causal genes are not always the ones that are initially suspected on the basis of proximity.[152]

Emerging technologies such as epigenetics,[153] metagenomics, metabolomics,[154,155] and proteomics[156] will help further with interpretation of genetic data. The Genotype-Tissue Expression (GTEx) project[157] currently has only a few kidney samples available; development of libraries of kidney cell types with epigenetic maps and robust cellular assays in models for disease and cell-types will be necessary to realise the full potential of kidney disease genetics. The short-term deliverables for this goal include the tracking of published datasets and accessible methods; the ultimate goal is to gain insights into biological pathways and novel biomarkers to enable prevention of disease and improve drug development. Drug targets with underlying human genetic support are twice as likely to be approved as those that are not supported by genetic evidence.[158]

Additional efforts will be needed to better understand how environmental factors interact with genetic variants to modify the risk of CKD. Examples of such interactions include IgA nephropathy and the intestinal immune response to helmintic infections that correspond to higher prevalence of IgA nephropathy in east Asia[159] (appendix p 9), and *APOL1*-associated kidney disease and trypanosomiasis that correspond to higher rates of kidney failure in individuals of African ancestry.[131,160] Other interactions of gene and environmental risk variants could include diabetes and hypertension,[161,162] the main causes of CKD in many regions of the world, and other yet unknown environmental factors that contribute to CKD hotspots.[163,164] Unravelling the effects of genes and environment can be challenging when their interaction is required to cause disease or when the genetic effect or interaction is small.

The existence of multiple hotspots (eg, in Central and Latin America, Sri Lanka, India, and Malaysia) might allow the identification of a genetic cause of CKDu in a given population. Prerequisites for success include the availability of inexpensive and ethnicity-specific high-throughput genotyping arrays, the ability to identify individuals exposed to specific environmental factors (perhaps using existing data from populations surveys or electronic medical records), and pre-existing standardised data collection procedures.[165] Improved phenotyping can increase the power of detecting gene–environment interactions and allows for the completion of genetic studies in more homogeneous subgroups (ie, those exposed to a particular environmental factor), which should enhance the ability to identify CKD risk genes.[166]

Theme 5: Establish better diagnostic methods in CKD

The KDIGO definition enables the diagnosis of CKD in the absence of knowledge about the cause in individual cases.[10] This has been crucial in determining the incidence and prevalence of CKD, identifying CKD cases, and increasing disease awareness, but prognosis and treatment are highly dependent on the underlying aetiology and pathological mechanisms. Attempting to assess the cause of CKD is an explicit KDIGO recommendation. However, even in high-income countries, the cause of CKD remains unknown in about half of all patients, even in those under nephrology care.[167] In low-income and middle-income countries, where access to sequential laboratory assessments of eGFR, albuminuria, kidney biopsy samples, and other laboratory tests are limited or non-existent, the spectrum of diseases responsible for CKD in the population is usually unknown. Thus, there is a strong global need for increased use of existing diagnostic tests, including kidney biopsies, as well as for expanding the diagnostic armoury, including non-invasive imaging, biomarkers, functional and genetic testing (table 5). Consistent attempts to ascertain the aetiology of CKD in individuals should be made, to ensure the most appropriate therapies are implemented, and that information can be garnered from all patients.

Analysis of kidney biopsy samples can be used to stratify CKD into distinct subgroups of diseases on the basis of specific histological patterns, when combined with the clinical presentation. Additionally, kidney biopsies can provide information on disease activity, molecular mechanisms, and prognosis. However, even in high-income countries, renal biopsy is only done in a small number of patients with CKD—usually in patients with suspected glomerular disease in whom knowledge of biopsy findings—eg, confirmation of a specific cause, evidence for active inflammation and tubular damage, or sclerosis and fibrosis—might trigger a change in clinical management. For the more common causes of CKD such as diabetes and hypertension, renal biopsies are only done in instances for which the presentation or clinical course is atypical. Kidney biopsies are invasive, require resources and expertise in ultrasound and pathology, need special facilities, and create a risk of bleeding and pain for the patient, but they offer the possibility that specific causes and potential opportunities for treatment might be uncovered.

Even after categorisation by biopsy findings, there is substantial heterogeneity in pathophysiology and prognosis within a specific category of CKD. Most current histological diagnoses group diseases with multiple underlying mechanisms together into syndromic categories. Different, specific pathogenetic events show indistinguishable structural alterations in the kidney (eg, mutations in different genes causing familial nephrotic syndrome show the same pattern of focal segmental glomerulosclerosis). Conversely, the same single mechanism can give rise to different

	Partners	Deliverables
Promote diagnosis and staging of CKD as proposed by KDIGO		
Work towards global implementation of the diagnosis (assess or attempt to assess cause) and staging of CKD on the basis of measuring or estimating glomerular filatration rate and measuring albuminuria	Health-care providers, and clinical chemists	Increased ability to accurately diagnose CKD in different regions
Improve renal biopsy-based CKD diagnosis		
Endorse the need to obtain renal biopsy samples in a broader range of presentations, including CKD, AKI, and glomerulonephritis	KDIGO; health-care system, and pathology departments	Consensus conference with published report; increased ability to accurately diagnose CKD in different regions
Sustain or establish regional centres of excellence for renal biopsy sample analyses and interpretation worldwide	Ongoing efforts of the International Society of Nephrology Renal Pathology Committee	Consensus report with definition of standards for tissue processing and histological analyses; increase biopsy capacity in all countries
Support implementation of standards in renal biopsy reporting	RPS	Consensus report—eg, RPS, Mayo Clinic standardised reporting of glomerulonephritis
Sustain and expand efforts to increase capacity for performing renal biopsies worldwide	International Society of Nephrology Interventional Nephrology Committee	Offering of renal biopsy training courses, covering indication, risk, performance, and monitoring; increase biopsy capacity in all countries
Investigate and implement opportunities for molecular diagnosis of renal biopsies	Funding agencies, research networks	Produce timely research reports; increase biopsy capacity in all countries
Link existing and novel renal biopsy registries with clinical data	..	Establishment of a global network and exploration of opportunities for data sharing and joint analyses
Improve non-invasive imaging analyses of the kidney in patients with CKD		
Work towards global availability of diagnostic ultrasound imaging	Public policy	Monitoring of access to ultrasound diagnosis as part of the Global Kidney Health Atlas project
Develop better non-invasive imaging tools of renal structure and function	Funding agencies, and the Radiology Society	Research conference devoted to this topic; increase number and types of tools available for assessment of CKD
Facilitate identification, validation, and implementation of diagnostic biomarkers of CKD		
Sustain and increase efforts to identify and validate biomarkers that indicate cause, dominant pathophysiological mechanisms, or therapeutic responsiveness	Research networks, industry partners	Research reports; increase number and types of tools available for assessment of CKD
Advocate for local, national, and international biobanking efforts to include renal samples	..	Task force to explore opportunities and develop a concrete strategy
Provide guidance on biosampling for markers of renal structure and function	CKD research networks	Development of a consensus statement with minimum standards and outline of how sample collection and storage procedures affect sample utility; increase engagement of CKD networks in collaborative research
Promote sharing of biobanking inventories, protocols, and biosamples	Funding agencies and CKD research networks	Development of a guidance document for governance of research network: network internal policy developments, biosamples usage, sample sharing, and challenges of international collaboration
Improve the clinical assessment of renal function and the underlying mechanisms of pathology in CKD		
Endorse research efforts to assess renal functional domains and mechanisms of pathology with their interaction and complexity (function of different tubular segments, inflammation, fibrosis, and renal endothelial function)	Funding agencies	..
Assess the diagnostic and prognostic utility of renal functional reserve assessment	Funding agencies	..

CKD=chronic kidney disease. KDIGO=Kidney Disease: Improving Global Outcomes. AKI=acute kidney injury. RPS=Renal Pathology Society.

Table 5: **Theme 5, establish better diagnostic methods in CKD**

histological diagnoses in different patients (eg, biopsy samples from patients with mutations in podocin causing nephrotic syndrome, type 2, can vary from minimal change disease to focal segmental glomerulosclerosis). Thus, increasing the use of kidney biopsy samples to gain better diagnostic and prognostic insights into disease causes and mechanisms is an important goal.

Increasing the use of kidney biopsies will require education, capacity building, and enhanced efforts. Ideally, we will be able to compare biopsy findings across centres and settings, and support the implementation of

standards for renal biopsy reporting. Regional centres for renal biopsy procedures should be established worldwide, with appropriate access to expertise and supplies. Key elements will include technical expertise, with hands-on training of histology technicians in sectioning and staining technologies, including special stains beyond haematoxylin and eosin (eg, periodic acid–Schiff and silver stains). Sophisticated staining technology will be key to the success of regional centres because multiple steps are needed to detect focal lesions.[168] Renal pathology centres should also use electron microscopy for optimal diagnostic sensitivity, as some conditions—such as IgA nephropathy and membranous nephropathy—cannot be adequately diagnosed from light and immunofluorescence or immunohistochemistry alone; patients are misdiagnosed about 15–20% of the time when electron microscopy is unavailable.[169]

The potential of traditional pathological assessment of biopsy tissue would be magnified if analysis of kidney biopsy samples was coupled with broader availability of techniques for molecular diagnosis, and the capacity to link renal biopsy registries with clinical data. To ensure the effect of such registries standard values—such as minimum needed data and clinical follow-up variables—must be defined, as well as additional parameters for specific subcategories of diseases. After diagnosis the remaining tissue should be stored for potential future studies, to explore the aetiology and pathogenesis of CKD.

Current standards for biopsy reporting have been published by the Renal Pathology Society (RPS) and by a joint working group of renal pathologists and nephrologists from the Mayo Clinic.[170] The scarcity of well-trained renal pathologists, even in high-income countries, is a major obstacle to use of biopsy samples. The ISN is working worldwide to enhance development of local renal pathology expertise.

Ultrasound-guided visualisation of the kidney and the lower urinary tract is safe, requires minimal training, and can be done with low-cost equipment—but is rarely available in low-income and middle-income countries. Therefore, working towards global availability of diagnostic ultrasound imaging through the provision of equipment and training should be a priority, as well as developing better non-invasive imaging methods to monitor and assess renal structure and function.

On the basis of developments in other fields, it appears likely that blood-based and urine-based biomarkers will play an important role in the future.[171–175] This will require sustained and enhanced efforts to identify and validate biomarkers that indicate cause, dominant pathophysiological mechanisms, therapeutic responsiveness, or a combination of these factors. Networks of translational scientists and clinical investigators are needed that support sustainable and integrated biobanking and biomarker research—including the use of common protocols and practices.

As the research into CKD moves towards more complete assessment on the basis of imaging and tissue and fluid-based biomarkers, it will be important to incorporate assessments of functional status into diagnostic processes. Methods for assessing renal functional domains and pathological mechanisms are already available, and could be refined to target more specific parameters (such as function of different tubular segments, presence of inflammation or fibrosis, renal endothelial function, or renal functional reserve).

Theme 6: Improve understanding of the natural course of CKD

There is a well described variability in kidney and cardiovascular outcomes in patients with CKD. Thus, there is a need to identify and validate prognostic biomarkers that will help to predict risk of specific events and to better understand the underlying molecular mechanisms of cardiovascular disease and CKD progression (table 6).

Guidelines already recommend measurement of albuminuria over time in people with CKD.[176] This recommendation is inconsistently followed even in high-income countries, which compromises our understanding of CKD progression in individuals and populations. At the same time, more needs to be understood about to what extent changes in albuminuria and eGFR over time are clinically meaningful and how they should influence clinical management.

Current risk algorithms for cardiovascular disease in CKD are based on traditional cardiovascular risk factors and do not include albuminuria or eGFR. The ability to better predict cardiovascular disease in patients with CKD would permit assessment of targeted therapies in clinical trials and risk stratification in clinical practice. Given the different cardiovascular disease phenotypes observed with increasing severity of CKD, risk prediction instruments should be gauged for their ability to discriminate between events mediated by traditional atherosclerotic processes versus those mediated by CKD-specific processes. There is potential for developing a risk prediction method that integrates CKD markers with traditional cardiovascular disease risk factors, but the benefit of this approach would need to be shown, ideally through a well-designed prospective trial.[177]

The renal community should take advantage of existing large observational cohort studies with stored biomaterials and long-term follow-up to study and validate established and novel biomarkers. Testing of new web-based cardiovascular disease risk scores involving the renal risk markers albuminuria and eGFR can be accomplished with existing databases and collaborations (eg, EUTox),[178] industry partners, and CKD biomarkers consortia. It will be important to achieve agreement on strategy by which to investigate and validate the complex and diverse expression of cardiovascular disease in CKD. Given that cardiovascular

	Partners	Deliverables
Improve monitoring of kidney disease progression among patients with CKD		
Implement regular measurements of ACR and serum creatinine-based estimated GFR for monitoring CKD	Policy makers, professional societies, guideline developers, and WHO	Increase in number of countries able to measure ACR:estimated GFR ratio relative to current state
Increase awareness and empower patients in self-management and their understanding of their health (eg, by implementing health technology applications)	Patient organisations, print and electronic media, and the International Society of Nephrology	Formal interactions with partners to develop a collaboration to accomplish the goal (eg, International Federation of Kidney Foundation)
Define changes in albuminuria and GFR that are meaningful for individual patients and how they should relate to clinical action	Scientists, FDA, and EMA	Report on optimal change in albuminuria and association with outcome in 2018; international collaboration with ongoing initiatives (eg, National Kidney Foundation, FDA, and EMA workshop)
Improve cardiovascular disease risk prediction in patients with CKD		
Develop a risk prediction tool, integrating CKD markers in cardiovascular disease risk assessment in patients with CKD	Endocrinologists, cardiologists, general practitioners, and if possible, renal pharmacists	Web-based risk scores for cardiovascular disease involving renal risk markers (albuminuria or estimated GFR); evidence of use of risk scores in clinical practice
Facilitate identification, validation, and implementation of prognostic biomarkers in CKD		
Sustain and increase efforts to identify and validate biomarkers that indicate the progression or therapeutic responsiveness, or both, of CKD	Regulatory authorities (eg, FDA and EMA), industry partners, and payers	Conference with the partners to develop guidance and principles
Sustain and increase efforts to identify and validate biomarkers that indicate the development of cardiovascular disease events in patients with CKD	European Uremic Toxin working group, CKD biomarkers consortium, and industry partners	Conference with partners; correlation of uraemic toxins to phenotype; increased acceptance and uptake of diagnostic tests for specific conditions in many regions
Improve global access to strategies and agents that delay the progression of CKD		
Development of an early-stage CKD toolkit	Non-nephrology health-care providers, and health-care politicians	CKD toolkits for different regional settings; generation of toolkit that is multi-interventional, has specific goals, simple interventions, and simple measures such as blood pressure and urine tests; identification of workforce with capacity to deliver package; and translations into different languages
Work towards global access to affordable blood pressure-lowering and glucose-lowering drugs, renin–angiotensin system blockade for proteinuric diabetic kidney disease, and statins for cardiovascular disease prevention	WHO, and regional health-care providers	Monitor availability of the four treatments; assess change in implementation and uptake and publicise results; extend the GKHA project to include this monitoring; increase availability of these agents or polypill (eg, a combination tablet of statin, ACE-inhibitor, and aspirin) for at-risk populations
Develop and implement decision support tools	..	Create inventory of existing decision support tools for early CKD by country; extend the GKHA project

CKD=chronic kidney disease. ACR=albumin-creatinine ratio. GFR=glomerular filtration rate. US FDA=Food and Drug Administration. EMA=European Medicines Agency. GKHA=Global Kidney Health Atlas.

Table 6: **Theme 6, improve understanding of the natural course of CKD**

disease risk profiles, CKD populations, and health systems vary worldwide, special consideration should be given to whether recommendations should differ by setting (eg, in low-income countries *vs* high-income countries).[179]

Although additional benefit can be derived from consistent use of existing parameters such as eGFR and albuminuria, new prognostic biomarkers in CKD are needed to individualise patient management and enhance recruitment of patients with similar prognosis into clinical trials. Creating formal collaborations between existing research consortia will sustain efforts to identify and assess such biomarkers. Given the clinical heterogeneity of most unselected CKD populations, progress might be most likely to occur in well characterised cohorts of people with specific kidney diseases. Real-world assessments of new biomarkers should be done to identify whether or not they improve clinical care at reasonable cost before recommending their uptake into practice.[180] As for genetic epidemiology cohorts, efforts will be required to standardise outcomes, share protocols, protect the privacy of patients, and enhance relationships with regulatory authorities and industry partners.

Also important is the recognition of how biomarkers change with disease progression or with therapy, and whether such changes predict clinical outcomes, including CKD progression. High-throughput screening techniques (ie, transcriptomics, proteomics, and metabolomics) in conjunction with well phenotyped clinical cohorts offer an opportunity to achieve this objective.[181] Studies examining biomarker profiles should include populations from low-income and middle-income countries and people from diverse ethnic backgrounds. Young researchers should also be trained in all aspects of biomarker research, from discovery to clinical implementation.

Improve outcomes with current knowledge

Theme 7: Assess and implement established treatment options in patients with CKD

Although there is a huge unmet need for CKD therapies, some treatment options have been shown to reduce the risk of cardiovascular events and progression to RRT.

Such therapies include: lowering of blood pressure;[182,183] reduction of proteinuria;[182,184] treatment with angiotensin converting enzyme inhibitors or angiotensin 2 receptor blockers;[185] and treatment with statins to reduce atherosclerotic events (table 7).[186,187] Glycaemic control in patients with type 1 or type 2 diabetes also improves cardiovascular and clinical outcomes[188,189] and newer drugs such as sodium-glucose co-transporter 2 inhibitors and glucagon-like receptor agonists have the additional benefit of reducing albuminuria, cardiovascular outcomes, and progression of CKD in diabetes.[190–192] CKD caused by primary glomerular diseases is potentially curable with relatively short periods of treatment compared with CKD from other causes.

However, the implementation of established therapies is variable within and between regions. Physician, patient, and health-care system factors could all play a role in successful uptake of recommended treatment. Access to care or therapies is often restricted by poor availability, expense, or reduced access to specialist advice. Physicians might not adopt best practices, or might not have access to methods and equipment for standardised treatment. For example, the uptake of well established therapies such as renin–angiotensin blockade in patients with CKD followed up by nephrologists is less than 70%, partly[193] due to problems with tolerance of specific medications or adherence.[194]

So-called treatment gaps, defined as the difference between the number of people who have an indication for a therapy and those who actually receive it, represent opportunities to reduce morbidity and mortality.[195] The advent of electronic medical records and other internet-based frameworks offer potential mechanisms for surveillance of treatment gaps; at present, little is known about the magnitude and determinants of treatment gaps, particularly in low-income and middle-income countries. Most focus has appropriately been on which treatments are available or affordable; as access to care improves in low-income and middle-income countries, focus should shift to identifying and closing other potential causes.

	Partners	Deliverables
Increase global capabilities to treat glomerular diseases		
Establish best practices and indications for biopsy procedures and sample handling; increase capacity for trained pathologists to interpret specimens; establish key accessible medications for treatment of common glomerulonephritis	Pathologists and laboratory supporters	Inventory of current capacity and potential capacity; identification of barriers and work plans to address; extend the Global Kidney Health Atlas project
Sustain and increase development, dissemination, and awareness of clinical practice guidelines		
Continue to develop, update, and improve clinical practice guidelines pertinent to CKD on a global scale	KDIGO and other guideline organisations	Novel guidelines and guideline updates; conference sessions on guidelines; ensure global access to guidelines; international ambassador programmes to incorporate guideline education
Promote guideline dissemination and education	KDIGO and other guideline organisations	Task force to survey non-nephrology guidelines, to establish contacts with non-nephrology guideline organisations and to work towards the inclusion of CKD-related recommendations in future updates; inclusion of guidelines in Continuing Medical Education programmes and dissemination of nephrology guidelines to other specialty guideline groups; increase number of individuals being treated according to recommendations
Develop implementation science expertise in nephrology		
Develop and expand implementation science infrastructure within the nephrology community	WHO	Task force to explore opportunities and develop a concrete plan, taking into account experience in other fields; possibly supported by workshops or a consensus conference, or both; develop expertise through expert group, educational meetings, and training mechanisms; tool and curriculum or plan; funding for international and country-specific fellowships or ambassadors; regional presentations and collaboration on specific projects
Investigate implementation strategies pertinent to CKD in clinical trials, tailor effective trial design to local circumstances and scale or spread successful dissemination strategies for maximum worldwide effects	Government health ministries, industry partners, and funding agencies	Conduct a trial to assess pre-intervention use versus short-term and long-term effects of intervention; tailor effective trial designs to the local circumstances (eg, comparative effectiveness and step-wedge trials); partner with government and health services to embed research in clinical care—facilitation of comparative effectiveness studies when previously unused therapies are introduced to ensure focus of resources on high-yielding interventions
Inclusion of considerations related to implementation in guidelines	KDIGO and other guideline organisations	Future guidelines consider recommending an ideal and an absolutely acceptable minimum recommendation for increased uptake in high-income countries and low-income and middle-income countries alike
Identify indications for biopsy in individuals in whom diagnosis is unclear (AKI *vs* progressive CKD)	Industry partners	Consensus conference with published report; increase access to diagnostic methods in all regions

CKD=chronic kidney disease. KDIGO=Kidney Disease: Improving Global Outcomes.

***Table 7*: Theme 7, investigate and implement established treatment options in patients with CKD**

There are a variety of approaches to closure of treatment gaps, including reminders, checklists, and pre-printed orders, especially in high-income countries with universal health care.[196–198] Cost reduction or income supplementation is logical in situations where economic barriers are important. Affordable versions of drugs that control blood pressure and glucose metabolism and inhibit the renin–angiotensin system should be available in all health settings. The nephrology community should advocate for the widespread uptake of the Model List of Essential Medications by WHO,[199] which will help to achieve this objective. Making low-cost immunosuppressive medications more widely available is paramount to treat glomerulonephritis in low-income and middle-income countries, but their use also requires appropriate infrastructure for establishing the diagnosis.

Clinical practice guidelines and associated schemes are additional important mechanisms to assess the evidence for the benefits and risks of diagnostic and therapeutic strategies, and promote the uptake of beneficial treatments in clinical practice. Guideline development for patients with kidney disease is pursued at a global level by KDIGO and should continue, aiming to cover the major CKD management issues. There is an increasing need to ensure that guidelines and treatment strategies are also tailored to low-income and middle-income countries, and that decision makers and funders understand the clinical and socioeconomic benefits of improving access to care.

Guideline development must be complemented by effective knowledge translation efforts aimed at end users, including care providers, patients, and families. The introduction of any therapy represents an opportunity to assess implementation methods and to do comparative effectiveness studies, which should include a randomised and adequately controlled trial. A better understanding of the factors that drive effective implementation will lead to more effective dissemination of established therapies with an expansion of the number of people receiving current established therapies, reduction in the time to uptake of new therapies, and potentially increased efficiencies for health service providers. Nephrology-specific implementation activities should be actively developed and increased. Achievable short-term targets for building nephrology-specific capacity include formal curricula and the creation of training positions, perhaps within nephrology residency programmes. In low-income and middle-income countries, implementation science will also maximise the efficiency of health service investment as well as outcomes for patients.

It is important to recognise that worldwide, most people who have access to care for early CKD receive this care in primary and general health settings, so general providers have the greatest opportunity (and responsibility) to intervene in the course of CKD progression. A toolkit for these health-care workers that provides simple targeted advice regarding treatment and goals to slow common causes of CKD progression could reduce the global burden of CKD. Decision support toolkits where guideline-based advice is automatically generated from the entry of routine clinical data, for example in laboratory systems or electronic medical records, are also of potential importance. To promote uptake and effectiveness, the approach should be generalisable to different workforces and health-care settings.

Theme 8: Improve management of symptoms and complications of CKD

In addition to progressive loss of kidney function, CKD is associated with multiple complications that cause morbidity and mortality, and reduce health-related quality of life (HRQOL). These complications manifest as a variety of symptoms (eg, fatigue, pruritus, and nausea), abnormalities of physiological and laboratory parameters (eg, hypertension, anaemia, or hyperphosphataemia), and increased incidence of several adverse outcomes (eg, bone fractures, cardiovascular events).[200,201] Despite considerable research, the pathophysiological links between CKD and these complications remain incompletely understood; the benefits of correcting physiological and laboratory variables remain poorly defined, and strategies to reduce the cardiovascular burden associated with CKD are insufficient. Moreover, increasing investigation appears to be warranted into the causes and optimal treatment of CKD-associated symptoms (table 8).[200,201]

Pruritus, restless legs, nausea, poor appetite, and sexual dysfunction are common in patients with CKD, especially those with kidney failure.[201,202] These symptoms are likely to be multifactorial; their pathophysiology is incompletely understood, and little is known about their treatment.[201,202] How these symptoms influence HRQOL and other outcomes important to patients, such as employability and functional status, has not been completely studied. The relative importance of each symptom to the total symptom burden is not well understood; this information is necessary to prioritise future studies. Few, if any, drugs have been approved for the treatment of uraemic symptoms and there is little evidence to support the off-label treatments that are recommended. Appraising the best candidates for well-designed clinical trials should be a high priority, which could include treatments for similar symptoms associated with other conditions (eg, chemotherapy-associated nausea or phototherapy for pruritus not associated with CKD). These approaches should be complemented by research efforts that capitalise on new technologies, such as metabolomics and proteomics, to link uraemic toxins with symptoms and to identify the pathophysiology that causes or exacerbates symptom burden.

Data showing that management of hypertension, anaemia, and metabolic bone disease improves outcomes have been sparse, and the results of randomised trials

	Partners	Deliverables
Improve symptoms associated with CKD		
Develop better understanding of symptoms associated with CKD and their effect on health-related quality of life, employability, and functional status	Patients and caregivers	Task force to establish interaction and joint plan with patient groups; symptom survey of patients with CKD; review summarising current evidence and gaps in knowledge; reduction in suffering of patients with CKD
Promote basic and clinical research about understanding the pathophysiology of the key symptoms, to better target therapeutic efforts	Industrial partners and funding agencies	Produce timely research reports
Improve symptom management in patients with CKD	..	Multidisciplinary meetings; educational materials for different target groups; consider educational and advocacy activities about the symptom burden—eg, World Kidney Day
Optimise the management of haematological, hormonal, and metabolic abnormalities associated with CKD		
Promote research to understand the links between laboratory abnormalities and clinically relevant outcomes (symptoms, cardiovascular disease outcomes, and progression of CKD)	Funding agencies and industry partners	Research reports; more research funding spent on this area
Promote consistent assessment and documentation of laboratory abnormalities in CKD populations according to KDIGO guideline	Patients	Survey of guideline implementation
Promote research and education into region-specific causes of abnormalities in patients with CKD (eg, nematode infection causing anaemia)	KDIGO	Produce timely research reports; educational toolkits
Promote availability of affordable point-of-care measurement devices and treatments for hormonal, haematological, and biochemical abnormalities	Policy makers	Survey availability as part of the Global Kidney Health Atlas project; access to point-of-care testing in many areas where it does not exist now
Improve prevention and management of cardiovascular complications in people with CKD		
Develop an integrated research programme to better understand vascular and cardiac diseases occurring in the context of CKD populations	Funding agencies and industry partners	Research reports; research conferences
Improve understanding of global variation in cardiovascular disease associated with CKD	Cardiologists	Analysis of cardiovascular disease morbidity in cohort studies in different regions
Identify barriers to dissemination and implementation of existing guidelines on dyslipidaemia and hypertension management to reduce cardiovascular risk in CKD, and implement strategies to overcome those barriers	KDIGO	Produce timely research reports; more patients receive appropriate care (current reports <65%)
Develop new therapeutic approaches to reduce cardiovascular disease risk in patients with CKD	Funding agencies, industry partners	New therapeutic agents; clinical trials focusing on cardiovascular disease outcomes in patients with CKD
Promote further research into optimal therapeutic targets for cardiovascular disease risk factor management (eg, blood pressure control) and how best to achieve them	Policy makers	Produce timely research reports; complete well-designed large clinical trials

CKD=chronic kidney disease. KDIGO=Kidney Disease: Improving Global Outcomes.

Table 8: **Theme 8, improve management of symptoms and complications of CKD**

have typically been disappointing.[203–205] Guidelines advising on management of these abnormalities suffer from limited evidence and do not usually account for practice conditions in low-income and middle-income countries.[203,205,206] Moreover, underlying causes of these abnormalities can vary by country. For example, parasitic infections or nutritional deficiencies can cause or exacerbate anaemia in patients with CKD in low-income and middle-income countries. Global guidelines also assume the availability of sophisticated laboratory assays and treatments, which are often not available or affordable in low-income or middle-income countries. Developing adequate, affordable point-of-care devices should be a high priority for future research and could provide an incentive for public–private partnerships.

Additionally, haematological, hormonal, and metabolic abnormalities are not necessarily important to patients per se; yet monitoring and treating these abnormalities accounts for a substantial proportion of the costs of CKD care, especially for patients with kidney failure. However, it seems clear that these abnormalities contribute to symptom burden and possibly outcomes in patients with CKD.[207] More research is needed to assess the mechanisms by which these abnormalities affect outcomes, and identify how they can best be treated. Establishing how to reduce the clinical and economic burden of appropriate monitoring of laboratory abnormalities and clinical symptoms, especially in low-income and middle-income countries, is an important goal.

Cardiovascular disease in patients with CKD is more frequent, more severe, and shows different manifestations compared with the non-CKD population. Atypical coronary disease, uraemic cardiomyopathy, and peripheral vascular disease are major causes of mortality in patients with CKD. Although the risk of conventional atherosclerotic events does increase when kidney function is reduced,

most of the excess risk associated with CKD is due to so-called non-Framingham or non-atherosclerotic pathologies, such as left ventricular hypertrophy with diastolic and systolic dysfunction, dysrhythmia, sudden cardiac death, valvular calcification, arterial calcification, and haemorrhagic stroke. The pathophysiology of these conditions appears due in part to a high burden of traditional cardiovascular risk factors as well as uraemia-specific factors.[201] Although there is some evidence that management of traditional cardiovascular risks improves outcomes in earlier forms of CKD, it is unknown how best to reduce cardiovascular risk in advanced CKD or kidney failure.[208] The well documented but poorly understood regional variations in cardiovascular disease in populations with CKD might offer new insights into how outcomes can be improved—eg, Japanese haemodialysis patients appear to have a much lower risk of sudden death than those patients in other countries. Much remains to be understood about fundamental aspects of vascular risk reduction in CKD (eg, optimal target blood pressure, benefits of aspirin in patients on dialysis, implantable defibrillators to prevent sudden cardiac death).[209]

In addition to a high burden of traditional risk factors, cardiovascular disease in CKD appears to be driven by risk factors specific to CKD. For example, abnormalities in phosphate, fibroblast growth factor 23, and Klotho all appear to contribute to cardiovascular disease in populations with renal abnormalities. Continued work is needed to translate discoveries from biomedical science into treatments that address these risk factors and mitigate the burden of cardiovascular disease.

Although controlling traditional risk factors has not been as successful in reducing mortality in patients with kidney disease as it has in the general population, control of blood pressure,[210] treatment with statins,[211] and blockade of the renin–angiotensin–aldosterone axis[212,213] have reduced cardiovascular events. However, the evidence base varies across CKD stages. For example, in dialysis patients, the target for control of blood pressure is unknown, but severe hypertension is clearly harmful—and organised programmes should encourage better blood pressure control strategies that minimise harmful side-effects. There is general consensus about the merits of controlling blood pressure, blood sugar, and dyslipidaemia in most people with CKD—yet worldwide people consistently do not receive these treatments.

Develop and test new therapeutic strategies

Theme 9: Develop novel therapeutic interventions to slow CKD progression and reduce CKD complications

Better treatments to reduce the risk of progression from CKD to kidney failure are needed, and—as mentioned in Theme 8—there is only a small evidence base for therapies that reduce cardiovascular mortality in CKD. Progress will require research consortia to be developed among academia, industry partners, biotechnology companies, philanthropic and funding bodies, policy makers, and governments. Scientists from varied backgrounds will need to be engaged, and clinicians across the world will require education to involve both themselves and patients in the necessary clinical trials to develop the evidence base for new treatments to be introduced into clinical practice. Consortia members will inevitably be required to design, develop, and conduct trials differently, since current strategies have not led to the development of many new therapeutics in CKD. Hence, a focused strategy with local and regional adaptation by high-income countries and low-income and middle-income countries is required. Breaking down structural impediments, and opening up scientific, regulatory, financial, management, and legal silos represents a formidable but not insurmountable challenge.

To drive the availability of new treatments for CKD, three linked sets of activities are required: identifying therapeutic drug targets, enhancing capacity for pre-clinical and early clinical development, and encouraging increased investment in the development of CKD therapies (table 9).

The likelihood of identifying potential drug targets will be enhanced by coordinated efforts to analyse samples of human kidney tissue and other biomaterial (urine and blood) using state of the art genomic, proteomic, and metabolomics approaches, in conjunction with detailed patient phenotyping and use of existing biomarkers to identify and qualify new therapeutic targets. Such efforts should link genetic data with existing phenotypic information or generate personalised human tissue models, using induced pluripotent stem cells and targeted mutation followed by differentiation to human kidney tissue. To support these efforts, better models of disease are needed to reflect the complexity of CKD (eg, AKI in the setting of CKD, CKD in the setting of vascular disease, diabetes, and the metabolic syndrome).

Building capacity for pre-clinical (ie, animal and in-vitro models) and early clinical development could be facilitated by better use of existing infrastructure (eg, leveraging research networks for CKD to facilitate data acquisition), as well as developing new infrastructure to collect and analyse biological materials (eg, kidney biopsy specimens). Human capacity will also be crucial—there is a need to facilitate interaction and exchange of ideas between academic researchers and drug, device, and diagnostic manufacturers, to promote collaborations and mutual understanding of each other's environments and objectives.

Partnerships with industry are crucial for drug discovery, but existing frameworks for academic–industrial collaboration do not encourage (and might even inhibit) such collaborations. Work is needed on how best to recognise and support academic nephrologists and researchers who move in and out of an industry or biotechnology research environment. An essential element will be identifying how to give academic credit to researchers who participate in such interactions,

	Partners	Deliverables
Improve identification of potential therapeutic drug targets		
Investigate human samples using state of the art genomics, proteomics, and metabolomics approaches, merged with detailed patient phenotyping and existing biomarkers to identify and qualify new therapeutic targets	Research consortia, industry or biotechnology companies, systems biologists, and geneticists	Inventory of current capacity and activities, with annual updating of changes in capacity or activities and outputs
Increase participation in cross-disciplinary research on pathophysiological mechanisms relevant for CKD and other diseases (eg, fibrosis research)	Global, regional, and national societies, networks, and ISN	Development of series of meetings with non-renal scientists around areas or mechanisms (new meeting format or strategy); number of new targets increased since 2016
Focus academic preclinical research on identification of druggable targets	Funding agencies and research networks	..
Improve models of disease (animal and human) to better reflect the complexity of human CKD (eg, acute kidney injury in the setting of CKD, CKD in the setting of vascular disease, diabetes, and metabolic syndrome)	Scientists, industry partners, and biotechnology companies	Research reports
Increase the capacity for preclinical and early clinical development		
Promote research networks for CKD and segmented disease populations to facilitate data acquisition and trial recruitment	ISN and industry partners	Inventory of current capacity and changes over time (1–3 years)
Develop infrastructure to do state of the art analyses of human tissue (CKD biopsy sample collections) to better understand the pathobiology of CKD and its progression	..	Increase in number of new drugs available for specific causes of CKD since 2016
Facilitate interaction and exchange of ideas between academic researchers and drug, device, or diagnostic manufacturers, aiming to promote collaborations and mutual understanding of each other's environment and objectives	ISN, industry partners, and scientists	Development of innovative meeting formats, such as Pitch for Partners as stand-alone meetings or in conjunction with major conferences
Recognise and support academic nephrologists and kidney PhD scientists to move in and out of an industry or biotechnology research environment	Industry partners and academic institutions	Establish special scholarships to increase capacity
Give credit to ongoing involvement of academic, industry, and biotechnology collaborations in therapeutic development and in academic career development	Academic institutions and health sector, biotechnology companies, and industry partners	Policy statement at academic institutions recognising activities and tabulating towards career development
Increase the availability of novel therapeutic approaches		
Investigate opportunities for repurposing of existing drugs for diverse disease for treatment of CKD and its complications	Industry partners and system biologists	Workshops or conferences for establishing programme of work and for reporting of results
Improve access to effective but costly drugs or biologics and devices, especially in low-income and middle-income countries; support from Organisation for Economic Co-operation and Development countries to low-income and middle-income countries, aiming to target prevention and treatment of CKD	Industry or biotechnology companies, governments, international and national agencies, ministries of health, corporations, and foundations	Inventory of current availability of any therapeutics, regular update (via GKHA or targeted ancillary survey) in specific low-income and middle-income countries within the next 3–10 years
Encourage increased investment in the development of CKD therapies		
Document differences in CKD practice patterns and therapeutic needs in different countries	ISN, global, regional, and national nephrology societies	Extension of the GKHA project
Encourage industry, biotechnology, and government investment in the development of new therapies for CKD	Industry, government, researchers, biotechnology, and venture capitalists	Tailored plans and strategies accepted by funders, governments, WHO, World Bank, and foundations
Market economic opportunity and develop business case	Academic institutions and industry partners	..
Assess opportunities for repurposing of existing drugs for diverse diseases for treatment of CKD and its complications	Industry partners and system biologists	Workshops or conferences for establishing programme of work and for reporting of results

CKD=chronic kidney disease. ISN=International Society of Nephrology. GKHA=Global Kidney Health Atlas.

Table 9: **Theme 9, develop novel therapeutic interventions to slow CKD progression and reduce CKD complications**

which might not always yield traditional scholarly deliverables such as publications.

Development of effective drug delivery systems is as important as identification of novel targets, and advances in therapeutics beyond small molecules to DNA and RNA therapeutics should help in this regard, together with targeted bioavailability to reduce side-effects and enhance efficacy. Although the focus of improving therapeutic strategies has usually been on scientific development, development of novel therapeutics has also been hindered by identification of project funding sources, availability of suitable manufacturing companies that are compliant with Good Manufacturing Practice, and protection by investigators and industry of

intellectual property generated from scientific studies. Taxation and regulatory policies, including offering patent exclusivity and expedited review for breakthrough therapies for CKD, should provide incentives to develop innovative therapeutics in CKD. Clinical trials repurposing generic therapeutics—such as allopurinol and metformin, both of which have shown potential in the attenuation of progression of CKD through mechanisms related to oxidative stress and fibrosis[215,216]—should be prioritised where there is sufficient scientific evidence. Strategies that extend the patent life of drugs without commitment to assess repurposing should be discouraged. If the above goals are achieved, treatment to stop, slow, or reverse CKD might become accessible to populations worldwide.

Theme 10: Increase the quantity and quality of clinical trials in CKD

High-quality clinical trials are the cornerstone of evidence-based prevention and treatment of disease, but nephrology has a strikingly weak base of these trials. The number of trials in nephrology is less than any other specialty, and shows little evidence of improvement.[216] Trials in populations with kidney disease tend to be smaller than those in other specialties, and are less likely to be randomised or masked.[217] Building the evidence base to improve outcomes for people with kidney disease requires both greater quantity and better quality of trials (table 10).

Most phase 2–4 trials in populations with CKD have not shown benefit for their primary endpoint and several have been stopped due to safety concerns (appendix pp 10–11). Different causes of CKD will probably require different targeted therapies to alter initiation and persistence of kidney injury. However, some mechanisms for progression of CKD might be similar (regardless of cause) and require an inclusive approach by those involved in clinical trials and regulatory authorities. Industry investment in new therapies for CKD is driven by large clinical need, but hampered by the high risk of failure, which has been reinforced by the history of disappointing large studies.

Among a number of factors that have contributed to this situation, the selection of valid and appropriate endpoints in kidney disease trials has been especially problematic. The most clinically important outcome in patients with CKD is kidney failure requiring renal replacement (dialysis or transplantation), which can lead to death. However, this endpoint typically develops over many years (or decades), so defining the effects of interventions on this endpoint is often difficult, if not impossible. The long-term nature of trials required to generate regulatory approval and allow revenue generation also presents a key barrier because kidney-relevant outcomes thought to be of importance often take 5–10 years to manifest—which is far beyond the duration of clinical trials in other fields, such as oncology. To make trials feasible, many studies enrol large numbers of people with advanced CKD in whom progression is considered to be more predictable than in patients with earlier stages of CKD—but interventions that slow progression during earlier stages might not be effective in later stages, and vice versa. A doubling of serum creatinine (equivalent to a 57% decline in eGFR) has been accepted as a surrogate for the development of kidney failure for many years. A workshop convened by the US National Kidney Foundation and Food and Drug Administration (FDA) recommended that the threshold might be reduced to a decline of GFR by 30–40% under specific circumstances, to improve trial feasibility.[218] This reduction is clinically meaningful because it is established to be on the causal pathway to RRT or death. In addition, this 30–40% reduction metric is used in clinical practice, and trials are being planned using it.

Few intermediate, validated endpoints or biomarkers are accepted by the regulatory agencies for approval of new treatments. Change in albuminuria as an endpoint in kidney trials continues to be debated, with no clear consensus.[219,220] Other markers of kidney damage, such as biopsy findings, biomarkers of disease activity, or imaging results, might be suitable in some kidney diseases. For example, the US FDA has approved total kidney volume as a prognostic marker for polycystic kidney disease (PKD) trials, but this required substantial scientific collaboration by members of the PKD Outcomes Consortium.[221] In other areas of medicine, conditional approval is granted by regulatory agencies on the basis of benefits shown on approved surrogate outcomes, while requiring appropriate trials assessing effects on hard outcomes to be undertaken post approval. A similar approach in CKD would increase investment in the specialty and should be promoted. In any case, it is important that both efficacy and safety endpoints are developed with input from patients, which the Standardised Outcomes in Nephrology (SONG) initiative is trying to address.[222,223]

The likelihood of successful trials, and the appropriate generalisation of evidence from these trials to the clinic, will be enhanced if participants can be enrolled on the basis of the likelihood of a positive response as well as of risk of progression. More specific inclusion and exclusion criteria are required in clinical trials to improve the likelihood of answering the important research questions. The recognised variability in progress and response to therapy in a complex condition such as CKD requires studies designed to determine efficacy and safety in responders. This could affect generalisability but would answer clinically important questions and target populations that are likely to benefit. Active so-called run-in periods are one way that this is being done, but enrichment or adaptive approaches are likely to also add merit to the study. An adaptive approach assesses the treatment by observing participant outcomes, and possibly other measures, and modifying parameters of the trial protocol in accord with the observations.[224,225] An enrichment approach attempts to find a study population

	Partners	Deliverables
Strongly encourage and promote the conduct of clinical trials in people with CKD		
Develop value proposition for trials in kidney disease	Health economists and payers	Published position statement
Promote trials in areas of unmet need and orphan diseases, including outcome development (eg, biopsy and hospitalisation)	Advocacy organisations, regulatory authorities, and KDIGO	Consensus conference with published report
Engage activated patient groups, payers, and other stakeholders, aiming to substantially increase the number of clinical trials in CKD	Advocacy organisations, major payers, and WHO	Trial stakeholder workshop within 2 years; increase in number of clinical trials in nephrology
Promote models for early conditional approval of new therapies to encourage investment	Regulatory authorities and KHI	Position statement
Work to increase the number of people with CKD who are included in cardiovascular, diabetes, and oncology trials, aiming to reflect the prevalence of CKD in these patient populations	Regulatory authorities, FDA, EMA, and non-nephrology disciplines	Position statement; inventory of CKD-related inclusion and exclusion criteria in major non-kidney trials to monitor implementation; increase in number of clinical trials with CKD included (*vs* excluded) as an important subgroup
Develop a regular stand-alone meeting to review ongoing and planned clinical trials with patients with CKD on a global scale	KDIGO, KHI, global, regional, and national nephrology societies	First stand-alone meeting within 2 years
Optimise the design of clinical trials in people with CKD		
Develop and refine appropriate endpoints for CKD trials and promote their uptake and dissemination	NKF, FDA, EMA, KHI, Standardised Outcomes in Nephrology	Conference on albuminuria or estimated glomerular filtration rate in 2018 (US NKF, FDA, and EMA); position statement
Assess factors that lead to success or failure of clinical trials in CKD trials	Industry partners	Conferences, conference reports, and formal inclusion of this topic in proposed annual nephrology meetings
Facilitate strategies to pre-select patients for clinical trials according to their risk for progression or likelihood to respond to an intervention	Industry partners, bioinformaticians, clinicians, and scientists	Published reanalysis of selected trials to differentiate progressors or non-progressors and responders or non-responders
Develop innovative trial designs to increase feasibility and success of CKD trials	..	Integration into clinical trial meetings
Implement priority setting exercises for interventions to be tested in clinical trials worldwide and by region	ISN, KDIGO, global, regional, and national nephrology societies	Global exercise completed in 2 years; at least 2 regional processes within 3 years
Establish recommendations for clinical trials in people with CKD for use by ethical and regulatory boards, including opportunities for sample collection for future analyses	Industry partners, ISN, global, regional, and national nephrology societies	Convene a panel to address this topic, including stakeholders with appropriate expertise in relevant disciplines
Grow capacity in conducting clinical trials in people with CKD		
Develop networks of kidney clinical trialists, including community physicians, and other specialties	Funding agencies	Convene a meeting of established clinical trial groups
Catalogue sites or centres capable of participating in kidney trials	Academic research organisations	Catalogue and mechanism available by end of 2017, with mechanism for linking trials and centres; develop mechanisms for internationalisation of trials, particularly including low-income and middle-income countries
Develop and implement professional training in trial design and conduct, involving nephrology and related specialties	Trial training providers, global, regional, and national nephrology societies	First course at World Congress of Neurology 2017, put online by end 2017, rollout in at least two regions during 2018; award fellowships for the planning and completion of clinical trials; increase size and quality of clinical trials in nephrology

CKD=chronic kidney disease. KDIGO=Kidney Disease: Improving Global Outcomes. KHI=Kidney Health Initiative. FDA=Food and Drug Administration. EMA=European Medicines Agency. NKF=National Kidney Foundation. ISN=International Society of Nephrology.

Table 10: **Theme 10, increase the quantity and quality of clinical trials in CKD**

in which the effect of a treatment can be most readily demonstrated.[226,227] Enrichment or adaptive approaches will add complexity and further work to understand the trade-offs that will be required—eg, generalisability versus specificity, and effectiveness versus safety.

Compared with other specialties, the nephrology community has less experience, infrastructure, and capacity in doing clinical trials. The science of designing these trials has received little attention, with no dedicated discussion forum and a low profile at existing major kidney meetings. Until recently, most clinical trial designs have been static; but some studies that are in progress are using adaptive and enrichment protocols—eg, CREDENCE (NCT02065791) and SONAR (NCT1858532). Additionally, trials have mostly focused on the needs of high-income countries, with little input from (and limited relevance to) patients and health-care workers in low-income and middle-income countries. Development of a regular stand-alone meeting to review ongoing and planned clinical trials in CKD on a global scale is a priority for the field.

Discussions at such a meeting should also systematically include the analysis of outcomes, including evidence for harm and insufficient efficacy of treatments from terminated trials, to inform and improve future trial design.

Much of the infrastructure around existing trials in nephrology has grown from industry-sponsored trials, without an overarching framework for engagement of participating centres. Similarly, there is little support for multicentre clinical trial groups from the National Institutes of Health (NIH) or other government sponsors. Collaboration between national, regional, and global trial networks has been scarce and often ad hoc, leading to waste of existing resources. Much potential interaction with other health-care providers (nurses, allied health professionals, primary care, and other specialties) is also under-developed. A scarcity of training and capacity development opportunities has also meant that little infrastructure exists in many parts of the world, further limiting recruitment capacity and trial management. As a result, trials in CKD are not prioritised by funders, and are seen as a relatively high-risk endeavour compared with other therapeutic areas.

It is also important to recognise that many trials—particularly trials in cardiovascular disease—exclude participants with CKD, mainly because of concerns about the safety profile of novel therapies. However, given the high prevalence of CKD as a comorbid condition, this restriction limits the generalisability of the trial outcomes, and results in lost opportunities to generate evidence for optimal care of patients with CKD. The incorporation of people with CKD into any trial should be strongly requested by regulatory agencies if CKD is prevalent in the target groups.

Several new approaches to clinical trials might be particularly well suited to CKD. These include large simple trial designs, randomised registry trials, cluster randomised trials, and adaptive trials. Simple trials with minimal data collection would also increase the feasibility of multicentre trials with increased ethnic diversity, and thus improve the generalisability of studies.

The challenges to doing clinical trials in CKD could be addressed by the use of a broad, strategic, sustained, collaborative approach, encompassing better trial design and increased capacity and willingness to deliver these trials. Motivated people with kidney disease, advocacy organisations, and health-care funders are important stakeholders in this process, and need to be more engaged in all CKD research-related activities. Greater investment in kidney disease trials might require robust business cases, clearly articulating the size of the population affected, achievable benefits, and cost savings for health-care systems and patients by changing or delaying the progress of kidney diseases and reducing cardiovascular disease events and death.

As a stretch goal for the community, we propose that 30% of patients with CKD should be involved in relevant clinical trials by 2030. This will require transformative change and big ideas, but could greatly improve secondary prevention and treatment of CKD.

Summary and conclusions

There are substantial gaps in research, care, and policy that have severely compromised our ability to improve the outcomes of patients with CKD around the world. The international community recognises these gaps, and has developed a comprehensive plan to address them systematically.

We have involved many stakeholders: individuals with broad and diverse expertise and different professional, scientific, and cultural backgrounds. The content of this document, including the recommendations, was developed in a step-wise process, including several rounds of internal review, plenary discussion at the summit meeting hosted by the ISN, and subsequent working group deliberations. Despite this strength, the selection of goals and activities and their priorities remains subjective, and views on several issues are likely to differ throughout the community. In the current time of patient-centred care, many efforts to engage patients in these processes are ongoing. The broad scope of this Review precluded in-depth analysis of each topic, but inclusion of the full spectrum of themes relevant to the prevention and treatment of CKD is an important strength of this document.

Our proposed activities include education, research, policy creation, and implementation of these recommendations. Partners in these endeavours include academic institutions, health-care institutions, governmental agencies, industry partners, research funding agencies, clinicians, researchers, policymakers, and patients.

Targeted, culturally appropriate educational activities for patients, policy-makers, and clinicians in all areas of the world are crucial for progress. Education about risk factors, the importance of genetics, and the need to be involved in clinical studies will enhance the community's capacity to close many of the gaps identified.

Research activities that harness existing databases and biorepositories, both within and outside the nephrology community, will require the development of standardised definitions, improved methods of data collection and storage, and some minimal standard dataset that can be shared between countries. The development or enhancement of registries in countries around the world will be an important step forward in documenting current disease burden and changes. The ability to collaborate across borders and disciplines is predicated on a change in policies and attitude about data sharing and academic–industry collaborations. Progress towards this goal should be quantifiable using bibliometric indices.

Activities should be targeted to all regions of the globe, although toolkits, strategies, and research methods will need to be adapted for geographical, socioeconomic, cultural, and political considerations.

Given the potential granularity of each of the plans, we have been able to develop a performance measurement framework to document, identify timelines and responsible parties, and anticipate the effect on specific metrics.

Based on the key areas and specific theme-related action plans highlighted in this report we will hold the nephrology community to account (appendix pp 12–13). We are optimistic that tracking of events, activities, and desired outcomes will galvanise the medical community to close the identified gaps and reduce the burden of CKD worldwide.

Contributors

AL, K-UE, and MT were responsible for conception, organisation, writing, editing, and reviewing the manuscript. JD was responsible for organisation, revision, and logistic organisation, including reference validation. All other authors were responsible for initial drafts of specific sections of the manuscript, review, and validation after each review.

Declaration of interests

JB reports personal fees from AbbVie, Amgen, Astellas Pfizer, and Takeda, a grant from Boehringer Ingelheim, and equity in Medibeacon, Sentien, and Thrasos, outside the submitted work; additionally, JB has a patent KIM-1 Patents with royalties paid to R and D, Astute, Biogen, Sekisui, and Ortho. JC reports grants from the National Kidney Foundation and the Kidney Disease Improving Global Outcomes group, outside the submitted work. Additionally, JC has a provisional patent filed Aug 15, 2014 (PCT/US2015/044567). JD reports personal fees from The International Society of Nephrology and the International Society of Nephrology, outside the submitted work. CSF reports personal fees from and is employed by Merck Research Labs. HJLH reports consulting fees from Astellas, AbbVie, AstraZeneca, Boehringer Ingelheim, Janssen, Fresenius, and Merck outside the submitted work. MJ reports a Career Development Fellowship from the National Health and Medical Research Council of Australia and the National Heart Foundation; grants from the Cardiovascular Research Network, Gambro, Amgen, Eli Lilly, and Merck; advisory board fees from Boehringer Ingelheim, Fresenius, and Janssen; and speaker fees from Amgen, outside the submitted work. RM reports grants from the International Safety Adverse Events Consortium, Fresenius-Kabi, and Relypsa; personal fees from CSL Behring, GlaxoSmithKline, Baxter, Ferring Research, Ionis, Gambro, Relypsa, Eli Lilly, Ardea, AM Pharma, Quark, and AbbVie; and stock options in Astute Inc, outside the submitted work. CRP reports personal fees from AbbVie and Genfit outside the submitted work. VP reports grants from AbbVie related to a clinical trial in CKD, Janssen, the National Health and Medical Research Council, and Baxter; speaker fees from Bayer, Pfizer, Bristol-Myers Squibb, AstraZeneca, Novo Nordisk, Boehringer Ingelheim, Baker ISI, and Sanofi; and is a Steering Committee member for Astellas, GlaxoSmithKline, Eli Lilly, Janssen, Boehringer Ingelheim, Pharmalink, Relypsa, and Merck, outside the submitted work. DCW reports personal fees from Amgen, Sanofi, Mitsubishi, Otsuka, ZS Pharma, Akebia, UCB Celltech, Bristol-Myers Squibb, Fresenius, Vifor Pharma, Janssen, Boehringer Ingelheim, Alberta Innovates Health Solutions, GlaxoSmithKline, Vifor Fresenius Medical Care Renal Pharma, AstraZeneca, Bio Nano Consulting, and Semantics Market Research, outside the submitted work. All other authors declare no competing interests.

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