



REVIEW

Kidney health for everyone everywhere - from prevention to detection and equitable access to care

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ABSTRACT

The global burden of chronic kidney disease (CKD) is rapidly increasing, with a projection of becoming the 5th most common cause of years of life lost globally by 2040. Aggravatingly, CKD is a major cause of catastrophic health expenditure. The costs of dialysis and transplantation consume up to 3% of the annual healthcare budget in high-income countries. Crucially, however, the onset and progression of CKD is often preventable. In 2020, the World Kidney Day campaign highlights the importance of preventive interventions – be it primary, secondary or tertiary. This article focuses on outlining and analyzing measures that can be implemented in every country to promote and advance CKD prevention. Primary prevention of kidney disease should focus on the modification of risk factors and addressing structural abnormalities of the kidney and urinary tract, as well as exposure to environmental risk factors and nephrotoxins. In persons with pre-existing kidney disease, secondary prevention, including blood pressure optimization and glycemic control, should be the main goal of education and clinical interventions. In patients with advanced CKD, management of co-morbidities such as cardiovascular disease is a highly recommended preventative intervention to avoid or delay dialysis or kidney transplantation. Political efforts are needed to support the preventive approach. While national policies and strategies for non-communicable diseases might be present in a country, specific policies directed toward education and awareness about CKD screening, management and treatment are often lacking. Hence, there is an urgent need to increase the awareness of the importance of preventive measures among populations, professionals and policy makers.

Keywords: World Kidney Day; chronic kidney disease.

INTRODUCTION

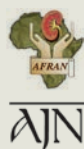
Around 850 million people currently are affected by different types of kidney disorders [1]. Up to one in ten adults worldwide has chronic kidney disease (CKD), which is invariably irreversible and mostly progressive.

The global burden of CKD is increasing, and CKD is projected to become the 5th most common cause of years of life lost globally by 2040 [2]. If CKD remains uncontrolled and if the affected person survives the

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ravages of the cardiovascular and other complications of the disease, CKD progresses to end-stage renal disease (ESRD), where life cannot be sustained without dialysis therapy or kidney transplantation. Hence, CKD is a major cause of catastrophic health expenditure [3]. The costs of dialysis and transplantation consume 2-3% of the annual healthcare budget in high-income countries, spent on less than 0.03% of the total population of these countries [4].

Importantly, however, kidney disease can be prevented and progression to ESRD can be delayed with appropriate access to basic diagnostics and early treatment including lifestyle modifications and nutritional interventions [4-8]. Despite this, access to effective and sustainable kidney care remains highly inequitable across the world, with kidney disease a low health priority in many countries. Kidney disease is crucially missing from the international agenda for global health. It is notably absent from the impact indicators for the Sustainable Development Goal (SDG) Goal 3, Target 3.4. "By 2030, reduce by one third premature mortality from non-communicable diseases (NCDs) through prevention and treatment and promote mental health and well-being," and the latest iteration of the United Nations Political Declaration on NCDs [9]. Current global political commitments on NCDs focus largely on four main diseases: cardiovascular disease (CVD), cancer, diabetes, and chronic respiratory diseases. Yet, it is estimated that 55% of the global NCD burden is attributed to diseases outside of this group [10]. Furthermore, kidney disease frequently co-exists with the 'big four' NCDs, which leads to worse health outcomes. CKD is a major risk factor for heart disease and cardiac death, as well as for infections such as tuberculosis, and is a major complication of other preventable and treatable conditions including diabetes, hypertension, HIV infection and hepatitis [4-7]. As the Sustainable Development Goals (SDG) and Universal Health Coverage (UHC) agendas progress and provide a platform for raising awareness of NCDs, targeted action on kidney disease prevention should become integral to the global policy response [1]. The global kidney health community calls for the recognition of kidney disease, effective identification and management of its risk factors and the implementation of an integrated and people-centered approach to care.

DEFINITION AND CLASSIFICATION OF CKD PREVENTION

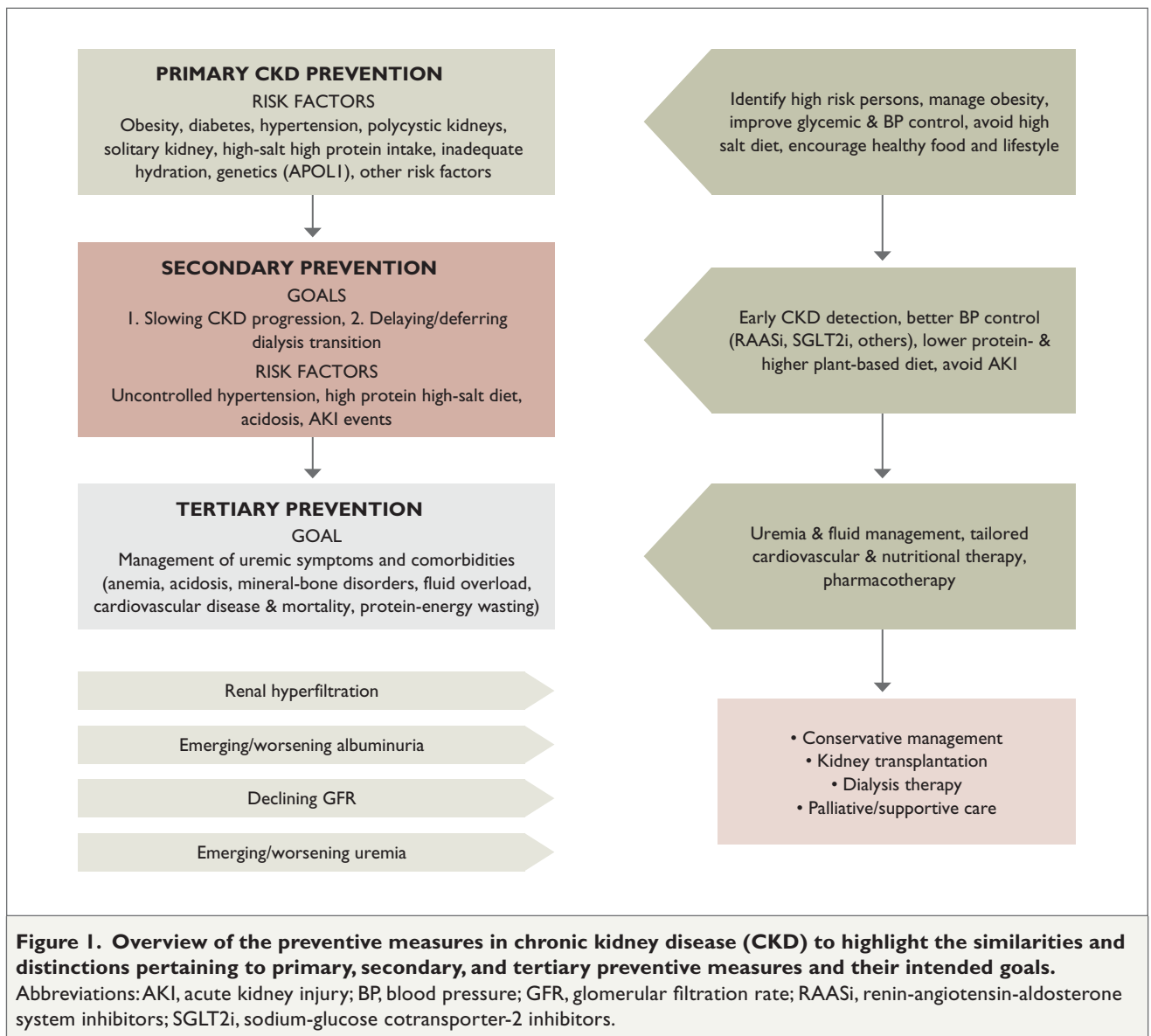
According to expert definitions, including that of the Centers for Disease Control and Prevention [11], the term "prevention" refers to activities that are typically categorized by the following three definitions: (i) primary prevention implies intervening before health effects occur in an effort to prevent the onset of illness or injury before the disease

process begins, (ii) secondary prevention suggests preventive measures that lead to early diagnosis and prompt treatment of a disease to prevent more severe problems developing and includes screening to identify diseases in the earliest stages, and (iii) tertiary prevention indicates managing disease after it is well established in order to control disease progression and the emergence of more severe complications, which is often by means of targeted measures such as pharmacotherapy, rehabilitation, and screening for and management of complications. These definitions have important bearing on the prevention and management of the CKD, and accurate identification of risk factors that cause CKD or lead to faster progression to renal failure, as shown in Figure 1, are relevant in health policy decisions and health education and awareness related to CKD [12].

PRIMARY PREVENTION OF CKD

Measures to achieve effective primary prevention should focus on the two leading risk factors for CKD, diabetes mellitus and hypertension. Other CKD risk factors include polycystic kidneys or other congenital or acquired structural anomalies of the kidney and urinary tract, primary glomerulonephritis, exposure to nephrotoxic substances or medications (such as nonsteroidal anti-inflammatory drugs), having one single kidney (for example, after cancer nephrectomy), high dietary salt intake, inadequate hydration with recurrent volume depletion, heat stress, exposure to pesticides and heavy metals (as has been speculated as the main cause of Mesoamerican nephropathy), and possibly high protein intake in those at higher risk of CKD [8]. Among non-modifiable risk factors are advancing age and genetic factors such as apolipoprotein I (APOI) gene variants mostly encountered in those with sub-Saharan African ethnicity, especially among African Americans. Table 1 shows some of the risk factors of CKD.

Among measures to prevent emergence of de novo CKD are screening efforts to identify and manage persons at high risk of CKD, especially those with diabetes mellitus and hypertension. Hence, targeting primordial risk factors of these two conditions including metabolic syndrome and overnutrition is relevant to primary CKD prevention, as is correcting obesity [14]. Promoting healthier lifestyles is an important means to that end including physical activity and healthier diet. The latter should be based on more plant-based foods with less meat, less sodium intake, more complex carbohydrates with higher fiber intake, and less saturated fat. In those with hypertension and diabetes, optimizing blood pressure and glycemic control has shown to be effective in preventing diabetic and hypertensive nephropathies. Persons with a solitary kidney should avoid high protein intake above 1 gram per kilogram body weight



per day [15]. Obesity should be avoided, and weight reduction strategies should be considered [14].

SECONDARY PREVENTION IN CKD

Evidence suggests that among those with CKD, the vast majority have early stages of the disease, that is, CKD stages 1 and 2 with albuminuria or CKD stage 3A (estimated glomerular filtration rate (eGFR) of 45 to 59 mL/min/1.73 m²) [16]. For these earlier stages of CKD, the main goal of kidney health education and clinical interventions is to slow disease progression. Uncontrolled or poorly controlled hypertension is one of the most established risk factors for faster CKD progression.

The cornerstone of the pharmacotherapy in secondary prevention is the renin-angiotensin-aldosterone system inhibitors (RAASi). Low protein diet appears to have a synergistic effect on RAASi therapy [17]. Recent data

suggest that a new class of anti-diabetic medications known as sodium-glucose cotransporter-2 inhibitors can slow CKD progression, and this effect may not be related to glycemic modulation by the medication. Whereas acute kidney injury (AKI) may or may not cause de novo CKD, AKI events that are superimposed on preexisting CKD may accelerate disease progression [18]. A relatively recent case of successful secondary prevention that highlights the significance of implementing preventive strategies in CKD is the use of vasopressin receptor antagonists in adult polycystic kidney disease [19].

TERTIARY PREVENTION IN CKD

In patients with advanced CKD, management of uremia and related comorbid conditions such as anemia, mineral and bone disorders, and cardiovascular disease is of high priority, so that these patients can continue to achieve the

Table 1. Risk factors for *de novo* CKD and pre-existing CKD progression.

Risk factor	Contribution to <i>de novo</i> CKD	Contribution to CKD progression
Diabetes mellitus	Approximately 50% of all CKD	
Hypertension	Approximately 25% of all CKD	
Obesity	10-20%	
Age	Seen with advancing age, especially in the setting of comorbid conditions	Some evidence suggests that older patients may have slower progression.
Race, genetics and other hereditary factors: • APOL1 gene • Hereditary nephritis (Alport's)	Common among those with African American ancestors	
Acute glomerulonephritis: • Post-infectious GN • Rapidly progressive GN	< 10%	Recurrent GN or exacerbation of proteinuria
Polycystic kidney disorders	< 10%, family history of cystic kidney disorders	
AKI • ATN • Acute interstitial nephritis	Repeated AKI bouts can cause CKD	Repeated AKI bouts can accelerate CKD progression
Autoimmune disorders • Lupus erythematosus • Other connective tissue disorders		
Pharmacologic: • Medications causing interstitial nephritides (NSAIDs, calcineurin inhibitors, chemotherapy, PPIs, etc.) or ATN (aminoglycosides) • Herbs and herbal medication	Variable, e.g., in Taiwan, Chinese herb nephropathy may be an important contributor	
Environmental: • Heavy metal exposure	Rare	
Acquired or congenital solitary kidney • Cancer; donor or traumatic nephrectomy • Congenital solitary kidney, unilateral atrophic kidney		
Acquired urinary tract disorders & obstructive nephropathy	Benign prostatic hypertrophy and prostate cancer in men, gynecologic cancers in women	
Congenital anomalies of the kidney and urinary tract	Mostly in children and young adults	
Inadequate fluid intake • Mesoamerican nephropathy • Others	Unknown risk, but high prevalence is suspected in Central America	Whereas in earlier CKD stages adequate hydration is important to avoid pre-renal AKI, higher fluid intake in more advanced CKD may increase the risk of hyponatremia
High protein intake	Unknown risk, recent data suggest higher CKD risk or faster CKD progression with high protein diet, in particular, from animal sources	Higher protein intake can accelerate the rate of CKD progression
Cardiovascular diseases (cardiorenal)	Ischemic nephropathy	
Liver disease (hepatorenal)	NASH cirrhosis, viral hepatitis	
Malignancy (myeloma, light chain deposition disease, AL amyloidosis, etc.)		

Abbreviations: AKI, acute kidney injury; AL, amyloid light-chain; ATN, acute tubular necrosis; CKD, chronic kidney disease; GN, glomerulonephritis; NASH, nonalcoholic steatohepatitis; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Many of these risk factors contribute to both *de novo* CKD and its faster progression and hence are relevant to both primary and secondary prevention.

highest longevity. These measures can be collectively referred to as “tertiary prevention” of CKD. Whereas many of these patients will eventually receive renal replacement therapy in form of dialysis or kidney transplantation, a new trend is emerging to maintain them for longer without dialysis by implementing conservative management of CKD.

APPROACHES TO IDENTIFICATION OF CHRONIC KIDNEY DISEASES

The lack of awareness of CKD around the world is one of the reasons for late presentation of CKD in both developed and developing economies [20-22]. The overall CKD

awareness among the general population and even high cardiovascular risk groups across 12 low-income and middle-income countries was less than 10% [22].

Given its asymptomatic nature, screening for CKD plays an important role in early detection. Consensus and position statements have been published by the International Society of Nephrology [23], National Kidney Foundation [24], Kidney Disease Improving Global Outcomes (KDIGO) [25], NICE Guidelines [26] and Asian Forum for CKD Initiatives [27]. There is a lack of trials evaluating the screening and monitoring of CKD [28]. Currently most guidelines will promote a targeted screening approach to early detection of CKD. Some of the major groups at risk for targeted screening are patients with diabetes and hypertension, those with a family history of CKD, individuals receiving potentially nephrotoxic drugs or herbal medicines, patients with a past history of acute kidney injury and individuals older than 65 years [27,29]. CKD can be detected with two simple tests, a urine test for the detection of proteinuria and a blood test to estimate GFR [24,27].

Currently, population screening for CKD is not recommended [28, 30]. Low- to middle-income countries are ill-equipped to deal with the devastating consequences of CKD, particularly the late stages of the disease, and therefore effective preventative measures to avoid CKD or slow progression are of immense importance in these regions. There are suggestions that screening should primarily include high-risk individuals, but also extend to those with lower levels of risk, for example, those individuals with prediabetes and prehypertension [31].

COST-EFFECTIVENESS OF EARLY DETECTION PROGRAMS

Universal screening of the general population would be time-consuming, expensive and not cost-effective, unless selectively directed towards high-risk groups [32-35]. The approach towards CKD early detection will include the decision for frequency of screening, who should perform the screening and intervention after screening [21]. Screening frequency for targeted individuals should be yearly if no abnormality is detected on initial evaluation. This is in line with the KDIGO guideline [25]. Patients detected to have CKD should be referred to primary care and general physicians with experience in management of kidney disease for follow up. Further referral to nephrologists for management will be based on the well-defined protocols [22,25,27].

INTEGRATION OF CKD PREVENTION INTO NATIONAL NCD PROGRAMS

Given the close links between CKD and other NCDs, it is critical that CKD advocacy efforts be aligned with existing initiatives concerning diabetes, hypertension, and cardiovascular disease, particularly in low- and middle-income countries. Some countries and regions have successfully introduced CKD prevention strategies as part of their NCD programs. As an example, in 2003, a kidney health promotion program was introduced in Taiwan, with its key components including a ban on herbs containing aristolochic acid, public-awareness campaigns, patient education, funding for CKD research, and the setting up of teams to provide integrated care [36]. In Cuba, the Ministry of Public Health has implemented a national program for the prevention of CKD [37]. It is hoped that the integration of CKD prevention into the NCD program may result in the reduction of renal and cardiovascular risks in the general population. Main outcomes have been the reduction in the prevalence of risk factors, such as low birth weight, smoking, and infectious diseases. There has been an increased rate of diagnosis of diabetes and of glycemic control, increased diagnosis of hypertension, higher rates of blood pressure control and more prescription of renoprotective treatment [38]. Recently, the US Department of Health and Human Services has introduced an ambitious program to reduce the number of Americans developing end-stage renal disease by 25% by 2030. The program, known as the Advancing American Kidney Health Initiative, has set goals with metrics to measure its success; among them more efforts to prevent, detect, and slow the progression of kidney disease, in part by addressing traditional risk factors like diabetes and hypertension [39]. Ongoing programs, like the Special Diabetes Program for Indians (SDPI) represents an important part of this approach by providing team-based care and care management. Since its implementation, the incidence of diabetes-related kidney failure among American Native populations decreased by over 40% between 2000 and 2015 [40].

INVOLVEMENT OF PRIMARY CARE PHYSICIANS AND OTHER HEALTH PROFESSIONALS

CKD detection and prevention programs require considerable resources and the availability of such resources will depend primarily on the leadership of nephrologists [41]. However, the number of nephrologists is not sufficient to provide renal care to the growing number of CKD patients worldwide. It has been suggested that most cases of non-progressive CKD can be managed without referral to a nephrologist, and specialist referral can be

reserved for patients with an eGFR < 30 mL/min/1.73 m², rapidly declining kidney function, persistent proteinuria, or uncontrolled hypertension or diabetes [42]. With an educational intervention, the clinical competence of family physicians increases, resulting in preserved renal function in diabetic patients with early renal disease [43]. The results were similar to those found in patients treated by nephrologists [44]. The role of primary health care professionals in the implementation of CKD prevention strategies in LMIC countries has been recently illustrated [45].

SHORTAGE OF NEPHROLOGY MANPOWER – IMPLICATIONS FOR PREVENTION

The resources for nephrology care remain at critical levels in many parts of the world. Even in Western developed countries, nephrologists are frequently in short supply. In a selection of European countries with similar, predominantly public, health care systems, there was a substantial variation in the nephrology workforce. Countries like Italy, Greece, and Spain reported the highest densities, while countries like Ireland, Turkey and the UK had the lowest [47]. In the USA, the number of nephrologists per 1000 ESRD patients has declined over the years, from 18 in 1997 to 14 in 2010 [48]. The situation in the developing world is even worse. With the exception of Nigeria, Sudan, Kenya and South Africa, in many countries of sub-Saharan Africa there are fewer than 10 nephrologists. The number of nephrology nurses and dialysis technicians is also insufficient [49]. In Latin America the average number of nephrologists is 13.4 pmp. However, there is unequal distribution between countries; those with <10 nephrologists pmp include Honduras (2.1 pmp), Guatemala (3.3 pmp) and Nicaragua (4.6 pmp), and those exceeding 25 pmp include Cuba (45.2 pmp), Uruguay (44.2 pmp) and Argentina (26.8 pmp) [50].

The causes of this shortage are multiple. Potential contributors include the increasing burden of CKD, erosion of the scope of nephrology practice by other specialists, lack of workforce planning in some countries, and the development of new care delivery models [48]. A novel strategy has been the successful ISN Fellowship program. Since its implementation in 1985, over 600 fellows from more than 83 LMICs have been trained. A significant number of fellowships were undertaken in selected developed centers within the fellow's own region. In a recent survey, 85% of responding fellows were re-employed by their home institutions [51,52].

THE INTERDISCIPLINARY PREVENTION APPROACH

Since 1994, a National Institute of Health consensus advocated for early medical intervention in predialysis patients. Owing to the complexity of care of CKD, it was recommended that patients should be referred to a multidisciplinary team consisting of nephrologist, dietitian, nurse, social worker, and health psychologist, with the aim to reduce predialysis and dialysis morbidity and mortality [53]. In Mexico, a nurse-led, protocol driven, multidisciplinary program reported better preservation in eGFR and a trend in the improvement of quality of care of CKD patients, similar to those reported by other multidisciplinary clinic programs in the developed world. Additionally, more patients started dialysis non-urgently, and some obtained a pre-emptive kidney transplant. For those unable to obtain dialysis or who choose not to, a palliative care program is now being implemented [54]. Future models should address region-specific causes of CKD, increase the quality of diagnostic capabilities, establish referral pathways, and provide better assessments of clinical effectiveness and cost-effectiveness [55].

ONLINE EDUCATIONAL PROGRAMS FOR CKD PREVENTION AND TREATMENT

E-learning has become an increasingly popular approach to medical education. Online learning programs for NCD prevention and treatment, including CKD, have been successfully implemented in Mexico. By 2015, over 5000 health professionals (including non-nephrologists) had been trained using an electronic health education platform [46]. It is equally important to promote "Prevention" with education programs for those at risk of kidney disease and with the general population at large. Education is key to engaging patients with kidney disease. It is the path to self-management and patient-centered care. Narva et al. found that patient education is associated with better patient outcomes [56]. Obstacles include the complex nature of kidney disease information, low baseline awareness, limited health literacy and numeracy, limited availability of CKD information, and lack of readiness to learn. New educational approaches should be developed through research and quality improvement efforts. Schatell et al. found that Web-based kidney education is helpful in supporting patient self-management [57]. Reputable healthcare organizations should facilitate easier access to health information on their websites (Appendix 1). Engagement of professional society resources and patient groups is a crucial step to promote community partnership and patient empowerment on prevention.

RENEWED FOCUS ON PREVENTION AND AWARENESS RAISING AND EDUCATION

Given the pressing urgency pertaining to the need for increasing education and awareness on the importance of the preventive measures, we suggest the following goals to redirect the focus on plans and actions:

- (i) Empowerment through health literacy in order to develop and support national campaigns that bring public awareness to prevention of kidney disease.
- (ii) Population-based approaches to manage key known risks for kidney disease, such as blood pressure control and effective management of obesity and diabetes.
- (iii) Implementation of the WHO “Best Buys” approach including screening of at-risk populations for CKD, universal access to essential diagnostics of early CKD, availability of affordable basic technologies and essential medicines, and task shifting from doctors to front-line healthcare workers to more effectively target progression of CKD and other secondary preventative approaches.

To that end, the motto “Kidney Health for Everyone, Everywhere” is more than a tagline or wishful thinking. It is a policy imperative which can be successfully achieved if policy makers, nephrologists and healthcare professionals place prevention and primary care for kidney disease within the context of their Universal Health Coverage programs.

Supplementary material

Appendix 1: Selected websites with information on CKD patient education.

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Disclosures

All the authors declared no competing interests.

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