



Global Kidney Disease 6

Kidney failure: aims for the next 10 years and barriers to success

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Although in some parts of the world acute and chronic kidney diseases are preventable or treatable disorders, in many other regions these diseases are left without any care. The nephrology community needs to commit itself to reduction of this divide between high-income and low-income regions. Moreover, new and exciting developments in fields such as pharmacology, genetic, or bioengineering, can give a boost, in the next decade, to a new era of diagnosis and treatment of kidney diseases, which should be made available to more patients.

Introduction

Acute kidney injury and chronic kidney diseases are substantial health concerns. Acute kidney injury is still associated with high mortality, whereas chronic kidney disease is directly, or as a risk factor for cardiovascular disease, an economic burden to health systems.

Strategies are now available to slow down or stop the progression of chronic kidney disease, but poverty has prevented their application to most patients worldwide. Moreover, in low-income countries, several disorders that lead to acute kidney injury are potentially preventable or avoidable (panel 1).

Acute kidney injury: a preventable and treatable disorder

In low-income countries, acute kidney injury is usually associated with infections, nephrotoxins, or obstetric and surgical complications.¹⁻⁴ Limited resources for diagnosis, late or no referral to nephrology services, or lack of access to renal replacement therapy are key challenges. Renal replacement therapy is usually only obtainable in large cities for those who can afford to pay.

The challenge for the international nephrology community is how to support the development of strategies in low-income countries that allow timely diagnosis of acute kidney injury and provide access to renal replacement therapy for patients with potentially reversible disease.

Although highly specialised dialysis techniques are not feasible in low-income countries, peritoneal dialysis is affordable⁵⁻⁷ and appropriate in environments with limited technology. However, sustainability of peritoneal dialysis can only be achieved with full local commitment and availability of necessary professional skills. A peritoneal dialysis programme for acute kidney injury that does not

need electricity and machines can be started even in extremely low-technology environments. Compared with a haemodialysis programme, peritoneal dialysis is less costly to set up and maintain, although it can be sustainable only when governments include them in the national health-care budget. One important challenge is in being able to buy equipment for peritoneal dialysis.

Supporting the development of such programmes with educational grants for training and provision of start-up funds are appropriate objectives for the international community. Development of sustainable models from a resource and financial viewpoint is a bigger challenge, but is the ultimate objective; meeting this challenge will require co-operation and commitment of local health-care facilities, hospitals, and governments.

The Kilimanjaro Christian Medical Centre in Moshi, Tanzania, has developed a feasible programme for peritoneal dialysis in acute kidney injury, an initiative coordinated by the Sustainable Kidney Care Foundation in New York, and three universities in the USA and Canada, with the support of the International Society of Nephrology and the country's Ministry of Health.⁸

In summary, many patients with acute kidney injury in low-income countries will recover kidney function and

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This is the sixth in a **Series** of six papers about global kidney disease

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Key messages

The goals for nephrology in the next decade are:

- To reduce the burden of preventable causes of acute kidney injury in low-income countries and promote affordable renal replacement therapies
- To make worldwide interventions available that help combat the burden of chronic kidney diseases with selective screening, infant and maternal health care, and prevention and treatment of curable diseases
- To develop new drugs for kidney diseases
- To create new methods for diagnosis and treatments for inherited kidney disease
- To develop and apply bioengineering sciences to repair damaged tissues, and generate new organs

Search strategy and selection criteria

References included in this Series were identified by the authors, based on their respective areas of expertise and supplemented by unsystematic database searches.

Panel 1: Case report

A girl aged 15 years in Tanzania developed acute kidney failure with oliguria. Her recent medical history and her clinical and laboratory findings were compatible with more than one cause of acute kidney failure, including haemolysis, ischaemia associated with subacute bacterial infection, ischaemic sickle cell disease, and postinfectious glomerulonephritis. The availability of a small peritoneal dialysis programme at the hospital allowed the girl to have renal replacement therapy to treat acute kidney failure. After 14 days of treatment, her kidney function completely recovered. She was discharged and continued to attend school, receiving hydroxycarbamide for sickle cell disease.

Panel 2: Steps to support and develop programmes of prevention and treatment of acute kidney injury in low-income countries

- Agreement by the physicians, hospital administration, and nursing staff on a regional level that treatment programmes for acute kidney injury be developed
- Assessment of available resources: medical and financial
- Development of programmes to diagnose acute kidney injury in a timely fashion at local health-care facilities
- Determination of the optimum renal replacement therapy to be provided
- Development of a viable financial model to support the programme
- Provision of training for appropriate individuals (physicians, nurses, other health-care providers, and administrators)
- On-going support by the international community; for example in terms of consultations and resource re-evaluation
- Involvement of the international community to assist in the planning, development, and implementation of these programmes

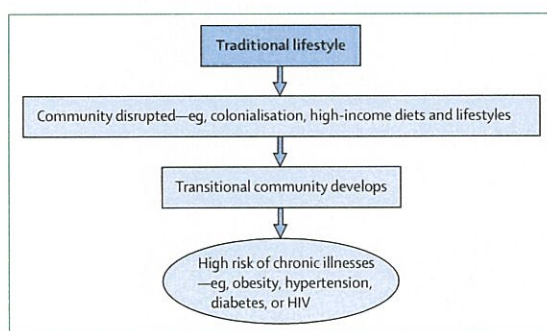


Figure: Transitional communities and the risk of chronic diseases including chronic kidney disease

survive if appropriate renal replacement therapy is provided. In the next decade the international community should support initiatives with the goal that nearly all patients with potentially reversible acute kidney injury should be offered appropriate supportive care, including dialysis, at a sustainable cost. Steps that need to be taken are summarised in panel 2. Saving Young Lives in Africa and Asia (2012–16), is one such programme for prevention and treatment of acute kidney injury.⁹

To achieve the goal of universal access to treatment, it is important that the international community is involved to ensure successful development of these programmes, and innovative partnerships among the

private sectors, foundations, academic institutions, and governments are incumbent.

Maternal and infant health promotion

In high-income countries, women are at the same risk of chronic kidney disease as men.¹⁰ However, unique to women is the development of pregnancy-associated kidney diseases and their sequelae. These challenges are magnified in developing countries.^{11,12} Another paper in this Series¹³ has alerted us to the importance of maternal diseases and early fetal and childhood development as a precursor of chronic non-communicable diseases. The cycle of poverty and lifestyle disruption, together with a high risk of second hits (ie, risk factors such as hypertension, diabetes, obesity, or HIV infection) increase the chance of chronic kidney disease (figure). Optimum maternal and early childhood health and nutrition is mandatory, particularly when considering the link between maternal malnutrition and hypertension, and kidney disease.¹⁴

Examples such as the Nepal's Safe Motherhood Programme suggest that maternal education, improved use of antenatal care, and maintenance of good health improves health in children.¹⁵ Such studies should be seen as an opportunity rather than a reason to remain inactive.

Moreover, maternal or childhood health promotion has a specific effect on kidney disease. Strategies should focus on primary prevention. Until now governments have not taken the opportunity to intervene in maternal and child promotion in association with future kidney and cardiovascular risk; the link with chronic kidney disease should be emphasised.

As with smoking and obesity, kidney disease will need to be approached as a broad public health issue, associated with chronic illnesses. Similar methods to those used in dealing with smoking and cardiovascular disease are needed.^{16–18} Unfortunately there is no radical approach in tackling kidney disease; like cardiovascular disease, kidney disease is not about one risk factor but rather about multiple strategies, which must be sustained. Proposed solutions to manage chronic illnesses should integrate all components of health care effectively.¹⁹ When empowered, women and mothers can substantially enhance the health of their families and communities.²⁰ This strategy is in keeping with the Millennium Development Goals' call for the efforts to reduce poverty, improve health, particularly for girls and women.²¹ When specifically focusing on chronic kidney disease, the words “chronic kidney disease” need to be embedded into future WHO charters and goals for health promotion.

Screening and prevention

In view of the adverse outcomes associated with kidney failure, early detection with screening for chronic kidney disease could prevent progressive loss of renal function and its consequences.²² This approach can also help with

appropriate dosing of medications, and with prevention of inappropriate exposure to nephrotoxic drugs, and allow timely preparation for dialysis or transplantation. Although screening programmes may be attractive at first glance, only a few lead to net benefits for health, and of these, only a few are economically appropriate. Wilson and Jungner²³ have suggested ten criteria to assess the potential merits of screening programmes. These criteria do not themselves justify the adoption of a screening service, rather, they identify promising areas for further study.

Screening the general population for chronic kidney disease by measuring serum creatinine or albuminuria does not meet several of the Wilson and Jungner criteria (table). Although some attribute reduced incidence of treated kidney failure to a population-based screening programme for chronic kidney disease in Japan,²⁴ the declining incidence cannot confidently be attributed solely to screening. A recent systematic review reported evidence

that screening for chronic kidney disease did not improve clinically relevant outcomes, such as kidney failure, cardiovascular events, and death.²⁵ Because kidney failure is immediately fatal in much of the developing world, it is easy to speculate that screening should be prioritised in these countries.²⁶ However, adequate treatment of known non-communicable diseases (previously diagnosed chronic kidney disease, diabetes, hypertension or vascular disease) is more efficient for preventing death and disability than detecting new cases of kidney disease, and so the former should be the priority when resources are limited. Therefore, it would be premature to recommend general population screening for chronic kidney disease in both high-income and low-income countries. Conversely, identifying people at increased risk of chronic kidney disease (so-called selective screening or case finding) meets many of the Wilson and Jungner criteria. This suggests that further study is necessary,²⁷ particularly in high-risk minority groups.²⁸ Patients with chronic

	Developed countries		Developing countries	
	General population	Selective screening	General population	Selective screening
1 Condition sought to be an important health problem; the primary aim of screening for chronic kidney disease is to prevent kidney failure and complications of advanced kidney disease such as accelerated atherosclerosis	Yes	Yes	Yes	Yes
2 There should be effective treatment for patients with recognised disease; an important caveat is that several key treatments for chronic kidney disease are also indicated for treatment of non-communicable diseases that cause or frequently coexist with chronic kidney disease. Therefore, detection of chronic kidney disease through screening will not necessarily change management if the other non-communicable diseases have been previously identified	Yes	Yes	Yes	Yes
3 Facilities for diagnosis and treatment should be available	Yes	Yes	No	Not universal
4 There should be a recognisable latent or early stage of the disease; precisely which early stage of chronic kidney disease should be targeted for detection is uncertain. Possibilities include stage 4 chronic kidney disease or stage 3 chronic kidney disease, or heavy albuminuria. The more inclusive the definition, the less likely that criterion number 3 will be met, especially in developing countries or with general population screening	Yes	Yes	Yes	Yes
5 There should be a suitable test; screening for chronic kidney disease should be based on blood tests (estimating equations for glomerular filtration rate in conjunction with serum creatinine assays), urine tests (albuminurias as assessed by dipstick urinalysis or specific assays), or combinations thereof (sequential or simultaneous testing), with or without follow-up testing for confirmation. The optimum testing strategy is unknown and will depend on setting, available resources, and the screened population	Yes	Yes	Yes	Yes
6 The test should be acceptable to the population	Yes	Yes	Yes	Yes
7 The natural history of the disease should be understood; much has been learned about the natural history of chronic kidney disease, but important gaps remain—especially for milder forms of disease, and in people with competing comorbidities. Whether available data about the natural history of chronic kidney disease (largely gathered in developed countries) can be applied to case finding in developing countries (where competing risks, available treatments for comorbidities and the absolute risk associated with chronic kidney disease may vary) is uncertain, especially for the general population. Importantly, how the natural history should influence the ideal frequency for population-based screening (in developed or developing countries) is unknown	No	Yes	No	No
8 There should be an agreed policy on whom to treat as patients; there is general agreement that advanced forms of chronic kidney disease or those with severe albuminuria should be treated, if identified. More remains to be learned about the potential benefits of treating people with very early forms of chronic kidney disease (such as those with normal glomerular filtration rate and persistent mild albuminuria). In view of the large number of such people, the feasibility of screening for and treating these abnormalities is uncertain even if such treatment were known to be helpful	Yes	Yes	Yes	Yes
9 The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in association with possible expenditure on medical care as a whole; studies show that screening the general population is not cost effective. Although studies suggest that case finding in developed countries may be economically attractive, these studies have made assumptions that may overestimate benefits. Even in developing countries where the prevalence of chronic kidney disease and other non-communicable diseases is higher than expected (thereby increasing the yield of case finding), it is uncertain whether this represents a wise use of resources, given that treatment of patients with clinically obvious non-communicable diseases (usually more economically efficient) is relatively rare in such settings	No	Yes	No	Uncertain
10 Case finding should be a continuing process and not a once and for all project; the logistical difficulties associated with population-based screening and the large number of cases identified mean that the feasibility of such programmes are uncertain even in developed countries. For the reasons given in criterion 9, the feasibility of ongoing case finding in developed countries is uncertain	Feasibility uncertain	Feasible	Not feasible	Feasibility uncertain

Table: Wilson-Jungner²³ principles of early disease detection and screening for chronic kidney disease

kidney disease who would usually go undetected as part of standard care could have a greater benefit than populations who are usually more likely to have serum creatinine or albuminuria measured. By contrast, the anticipated benefit of screening is lower in populations with a lower prevalence of chronic kidney disease. Several factors influence which high-risk populations should be selected for screening including the benefits and problems after treatment, the consequences of non-treatment, false-positive tests, and the feasibility of detecting the target population and treating identified patients. All these factors have been incompletely studied, and it is difficult to recommend groups for whom screening should be indicated or contraindicated. However, older age, diabetes, or hypertension are potentially attractive criteria—and selective testing for kidney disease in these populations seems likely to be beneficial.^{29–31}

The ideal frequency for screening measurements is unknown, but given the persistent nature of chronic kidney disease, covering a high proportion of people at risk should take precedence over frequent screening. Whether serum creatinine or albuminuria analysis, and which assays should be used is also unknown.^{22,32} Use of both strategies might be most sensitive (particularly as albuminuria does not universally accompany reduced glomerular filtration rate³³) but would lower specificity. Follow-up testing will probably be needed irrespective of which strategy is used initially. Finally, the best way to deal with cases identified through screening is uncertain, and will vary by setting: some countries may favour a public health approach (a generic bundle of effective therapies applied to all patients), whereas more individualised treatment (based on severity, stage or cause of chronic kidney disease) might be more appropriate in others.

Despite this uncertainty, effective treatment for diabetes, hypertension and cardiovascular disease will also have beneficial effects on chronic kidney disease, and vice versa. Because detection of chronic kidney disease is unhelpful if lifelong medical therapy is unavailable, establishing and maintaining access to effective treatments is a prerequisite for screening programmes for chronic kidney disease in low-income countries but also in high-income nations that lack universal health-care systems. The highest priority for controlling chronic kidney disease should be to ensure secure, sustainable access to low cost antihypertensive drugs (particularly angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers), which will prevent kidney failure and also reduce cardiovascular morbidity and mortality.³⁴ Improved access to treatments that control blood glucose and blood cholesterol, and those that tackle smoking will also improve renal and cardiovascular outcomes. Furthermore, serum creatinine and albuminuria measurements are commonly made in usual clinical practice; chronic kidney disease is usually identified in the absence of organised screening programmes. Management of chronic kidney disease is

often suboptimal, and therefore improving the care of all chronic kidney disease is important. Finally, in view of the common causes and consequences of chronic kidney disease with other non-communicable diseases, integration of screening into national or regional disease management programmes will be important.

New health service models for controlling chronic kidney disease

Treatment of chronic kidney disease is an important economic burden within health systems and is grossly inadequate in low-income countries.^{35,36} WHO has estimated that in two-thirds of low-income countries there is no access to renal replacement therapy for end-stage renal disease.³⁷ Therefore, addressing the burden of chronic kidney disease requires preventive measures that include control of generic risk factors (eg, smoke, high salt intake, or hyperlipidaemia) and, in some regions of the world, focusing on specific causes.³⁸

Multidisciplinary care and control of general risk factors

The increased awareness that death caused by cardiovascular disease is a more common outcome than progression to end-stage renal disease in patients with chronic kidney disease has led nephrologists to focus on the prevention of cardiovascular disease.³⁹ However, management of cardiovascular disease is fragmented (and sometimes divergent) among nephrologists, cardiologists, and diabetologists; these issues can be further complicated with the involvement of primary-care physicians, geriatricians, dietitians, pharmacists, and nurses. Two non-exclusive approaches might bring cohesion. The first is education of patients and support of self-management; the second is a multidisciplinary team approach. Interactions between informed patients and proactive multidisciplinary teams might improve health outcomes for people with chronic medical disorders.

Comprehensive, team-based, multidisciplinary interventions for chronic kidney disease are associated with improved blood pressure and metabolic control, preservation of glomerular filtration rate, a smaller percentage of patients needing dialysis, and reduced mortality.^{40–44} Multifactorial interventions including lifestyle changes^{45–48} and pharmacological interventions to reduce proteinuria and control blood pressure with angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers, tight diabetic control, and treatment of dyslipidaemia are not only cost-effective measures to reduce the burden of cardiovascular disease but have also a beneficial effect on chronic kidney disease.⁴⁹

The main expectation for the near future is building capacity to establish individualised multidisciplinary care programmes, adapted to the highly diverse medical needs of patients. For patients with chronic kidney disease, high comorbidity or specific frailty (the threshold beyond which the functional reserve of a person is critically reduced and

the tolerance of stress negligible), optimum care will probably be delivered with methods specific to the disorder, including multidisciplinary specialty clinics, aimed at reducing cardiovascular events and reducing or allowing transition to renal replacement therapy.

However, a programme of timely nephrology referral and specialised multidisciplinary follow-up for all patients with chronic kidney disease would quickly overwhelm available resources, and would not be realistic in many settings. Thus, in most parts of the world, primary-care physicians will have an essential role to play in the care of chronic kidney disease. Patients with stable renal disease, low comorbidity, those living in remote areas or in low-income countries could undergo comanagement, with regular monitoring by a primary-care physician, and future nephrology follow-up.⁵⁰ Similar considerations apply to the delivery of care to patients with acute kidney injury or with multiple organ failure syndromes (eg, combined hepatic and renal insufficiency; cardiorenal syndrome).

Care models that incorporate nurse practitioners are being increasingly used for the management of chronic diseases.⁵¹ In view of the success in other fields, the large population at risk for chronic kidney disease, and the low availability of trained nephrologists for the number of patients, it is important to test care models in which physicians partner with nurse practitioners to deliver care. The interface of nephrologists with primary-care physicians or other specialists could be implemented even in low-resource setting using new telecommunication technologies. Telehealth initiatives, in which nephrology specialists provide their expertise remotely over the internet, are a model that can be adopted in low-resource settings. This approach has been successfully applied in Bolivia where telehealth care is delivered using online applications to provide expertise at very low cost (Raul Plata Cornejo, Instituto de Nefrología, La Paz, Bolivia, personal communication). The programme not only permits individualised multidisciplinary care and the chance of follow-up by experienced off-site nephrologists, but minimises the burden of travel and its impact on family and employment (panel 3).

Control of region-specific risk factors for chronic kidney disease

In addition to global risk factors, the burden of chronic kidney disease has specific characteristics that should be recognised and addressed in certain regions of the world. Although most patients with chronic kidney disease in high-income countries have diabetes or hypertension, as many as 40–50% of patients have a different cause in low-income countries.⁵² Chronic glomerulonephritis and interstitial nephritis resulting from bacterial, viral, parasite or toxic causes represent a substantial proportion of chronic kidney disease in some areas of the world.⁵² An example is HIV infection.⁵³ Compared with controls without HIV, patients with HIV have an increased

Panel 3: Telemedicine for renal care

Low availability of specialist care in developing countries is one of the limiting factors for the prevention and cure of chronic kidney diseases or for proper management of acute events. Geographical barriers, lack of transport or infrastructure, and low availability of trained personnel are among the leading causes for varied management of kidney disease in developing countries. Rather than, or in addition to, providing resources or equipment, health-care systems' primary problem is effectively diffusing knowledge and information. Technology currently offers a chance for this to change.

In many developing countries the rate of growth of digital infrastructure has surpassed that of physical infrastructure. The deployment of mobile networks has reached an estimated 45% global population coverage in 2011, the largest rise in developing countries. Affordable connectivity has strong implications for the future of health care, in particular where accessibility to specialist care is limited.

The ability to communicate through rich, easy to use, multiuser applications capable of transmitting audio or video streams, once available in high-end teleconferencing or telemedicine systems, has become an integral part of everyday lives in both high-income and low-income countries. The availability of these technologies at the consumer level has largely contributed to reduce costs for developing these systems and making them available on a large scale, with minimum initial investments on the infrastructure of information technology as result of cloud computing and platform-as-a-service resources.

New models of specialist health-care provision could emerge from the integration of modern information technology and medicine. Renal care, in particular, is characterised by the need of regular follow-ups over long periods of time. Substantial improvements to morbidity and mortality can be achieved by simple and low-cost actions, if appropriately put in place.

In this setting, several small peripheral centres, typically led by primary-care physicians or nurse practitioners, could be pooled into centrally led virtual nephrology departments. Supported by rich web applications providing clinical information management, direct communication, and real-time data analysis, nephrologists located in these central facilities could lead patient care by relying on peripheral practitioners for in-loco operation.

The opportunity for the scientific community is unique. Information technology has the potential of delivering specialist health care in inaccessible areas, but it also represents a potential collector of data on unprecedented large scales. This collection is possible if data are public and if data collection systems are built with a high degree of interoperability (ie, their interfaces are fully disclosed and they are capable to interact and function with other systems without any access or implementation restrictions). The reliance on transparency and a consensus effort in the definition of the structure and the nature of data to be collected are important.

Telemedicine has had a rich history in the past two decades. For the first time, this model is becoming cost effective for developing and high-income countries, marking the path towards global health-care provision and new opportunities for scientific advancement.

prevalence of impaired kidney function (six times), albuminuria (five times), and end-stage renal disease (ten times).^{54,55} Between 770 000 and 2·6 million individuals in sub-Saharan Africa have HIV nephropathy. The existing guidelines for management and referral of patients with HIV for nephrology care in high-income countries are not applicable in sub-Saharan Africa and a recently proposed screening algorithm that starts with the determination of microalbuminuria deserves careful assessment.⁵³

Registries should be a key priority for control of chronic kidney disease, and could document the total burden of

kidney disease in each country or region and progress made over time—as well as quantifying the comparative contribution of common and specific regional risk factors. The feasibility of large, cross-sectional studies to assess the prevalence of chronic kidney disease was confirmed in a study^{56,57} done in several countries (Bangladesh, Bolivia, Georgia, and Nepal), with the support of the International Society of Nephrology in both the general population and in patients at high-risk of the disease. Advances in diagnostic testing will help the expansion of such programmes—including availability of cheap point-of-care testing for kidney function and albuminuria (with appropriate attention to assay standardisation and calibration), and validation of new creatinine-based or cystatin-based prediction equations for estimation of glomerular filtration rate in low-income countries.

New approaches for drug and clinical development

Drug and clinical development have become lengthy and expensive as a result of the number of newly marketed drugs by the pharmaceutical industry.⁵⁸ Few drugs to treat kidney disease have been developed in the past 15 years, despite a large number of potential beneficiaries.

Reduction in the time and costs of pharmacology research requires not only an understanding of the pathophysiology of the targeted disease but also an early test of the drug's effects on human physiology and pathology. Early clinical trials in patients are now more practical since there is new guidance from the international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use that introduces exploratory clinical trials as first-in-human studies that assess a drug's distribution *in vivo* as well as its physiological and pharmacological effects in a few patients.⁵⁹ These studies notably reduce the duration of preclinical assessment. These latest regulations for pharmaceutical practice as well as newer, state-of-the-art, efficient strategies for preclinical and clinical development require a thorough understanding by the investigator.⁶⁰

Exploratory clinical trials are important for drug development, especially in kidney diseases for which experimental animals mimicking human disease are difficult to obtain, and where clinical endpoints such as renal death are elusive.

A renewed partnership between pharmaceutical industry and academia is needed. Large clinical trials required for marketing authorisation are the responsibility of the pharmaceutical industry. By contrast, academia selects the compounds to be tested by industry, by assessing the physiological and pharmacological relevance of candidate molecules. Of importance, neither academia nor the pharmaceutical industry pay sufficient attention to orphan diseases⁶¹ or less common kidney diseases.^{62,63}

In the next few years, this new vision for the development of new drugs in clinical trials should be

extended from high-income to low-income countries. It will be important to ensure that the capacity for clinical trials is developed locally in low-resource regions. Thus, dissemination of clinical trials will require opportunities for training in clinical trial methodology, design, and statistics. Nevertheless, the important task will be to protect emerging countries from pharmaceutical companies taking advantage of patients in these countries who are rarely treated according to standard guidelines.

Focus on research for rare and genetic kidney diseases

The specialty of rare and genetic kidney diseases is expected to change fundamentally during the next decade. The International Rare Disease Research Consortium has formulated two key objectives to be reached by 2020: to establish diagnostic tests for most rare diseases, and to find medical treatments for 200 rare disorders.⁶⁴ These targets suggest the most important needs, and foreseeable accomplishments, in rare kidney diseases.

The most imminent progress is expected in the identification of causes for genetic disease. The advent of next-generation sequencing allows screening of the exome quickly and cost effectively.⁶⁵ This technique will accelerate the identification of new disease genes but also pose challenges in bioinformatic processing and define a need for new methods for high-efficiency functional assessment of gene variants by cell, tissue, and animal models. Cell and tissue modelling may be boosted by current advances in inducible stem cell and transdifferentiation technology. Conventional transgenic rodent disease models will probably be complemented by refined lower vertebrate models (such as zebrafish and xenopus frogs) suitable for rapid phenotypic and functional screening of candidate proteins and their mutants.⁶⁶

The proportion of patients with an unambiguous genetic diagnosis will increase notably. The development of targeted sequencing arrays covering all genes associated with a particular disease or disease group will substantially improve diagnostic time and cost efficacy. Targeted sequencing will also avoid the ethical dilemmas associated with incidental discovery of mutations in genes unlinked to the disease of interest that can occur with whole-exome sequencing.⁶⁷

In patients with rare kidney disorders in whom a genetic diagnosis cannot be made, new technologies with systems-biology approaches integrating DNA variants, gene transcript patterns, urine proteomic, and metabolomic profiles will soon be available to complement clinical trials by molecular phenotyping. These strategies will identify molecular markers that individually (as disease biomarkers) or in combination (as molecular signatures) will lead to a mechanistically based molecular spectrum of rare kidney diseases.

The availability of reliable genetic and molecular diagnostics will affect clinical disease management—eg, by replacing histopathology, accurately defining the need

for and susceptibility to pharmacological interventions, and by predicting the risk of post-transplant disease recurrence. In families with congenital kidney diseases, accurate prenatal diagnosis and risk assignment will allow individualised genetic counselling and help development of early intervention and secondary prevention strategies.

To date, the development of therapeutics in rare diseases has been lagging behind the advances in genetic and pathophysiological mechanisms, since the altered protein products of the disease-causing genes are commonly not treatable or there is no obvious molecular approach to bypass gene deficiencies. Notwithstanding these challenges, the widespread application of exome sequencing is expected to increase the number of molecular drug targets in rare kidney diseases.⁶⁸ Rare diseases with a renal phenotype are usually systemic disorders with multi-organ involvement. Hence, understanding the molecular pathophysiology of these diseases might contribute to knowledge about other organ-specific diseases. For example, research in rare complement kidney diseases will advance the global understanding of complement-mediated tissue and organ damage.⁶⁹ Furthermore, podocyte-specific proteins deficient in inherited glomerulopathies are also involved in acquired glomerulopathies, such as diabetic nephropathy, and study of these proteins could help understand the mechanism of glomerular disease.⁷⁰ Studying the pathophysiology of tubulopathies might have immediate relevance in understanding regulation of blood pressure, formation of kidney stones, and kidney disease progression. Finally, systems biology approaches that integrate molecular characteristics of different kidney disorders and phenotypes of disease progression may help identify common pathways that lead to kidney disease progression.^{71,72} If new targets for pharmacological nephroprotection can be identified, progress in research on rare kidney disease could help with understanding several progressive kidney disorders.

Promotion of research in developing countries

Local health problems in low-income countries indicate the importance of economic and social development: relevant research must focus on the biological causes of such illnesses, but also on how to break the vicious cycle of economic development and new emerging disease. For example, growing urbanisation and pollution have led to rising rates of environmental illness, including sick-building syndrome⁷³ and sick-house syndrome.⁷⁴ Several kidney diseases that are associated with environmental causes (such as glomerular nephropathies associated with organic solvents, common in high-income countries in the last century⁷⁵) have begun to emerge in low-income countries.

The number of researchers moving out of their home countries that are low income increases the gap between north and south, and reduces capacity to address local issues in these regions.^{76–79} Taiwan has implemented

several policies to keep researchers, including financial incentives reimbursement for the costs of repatriation and grants for business development, which reversed previous trends in migration of Taiwanese scientists.⁸⁰ Scientists, political leaders, and decision makers in low-income and high-income countries must collaborate to produce policies and education systems that promote and enable research and development. Easy communication, quick travel, and greater collaboration between high-income and low-income countries are increasingly common and should help expatriate professionals to contribute to their countries of origin.

A capacity gap remains between low-income or middle-income countries and high-income nations in health science, including nephrology. According to a WHO report⁸¹ public health-care systems receive only 4·3–6·3% of the GDP in low-income or middle-income countries compared with 11% in high-income countries. Physician density in low-income or middle-income countries was 10·1 per 10 000 population, as opposed to 28·6 per 10 000 population in high-income countries. High-income countries and the global kidney research community should help low-income countries to increase their funding for primary health systems but also to increase their local capacity for research on local problems. The fellowship, sister renal centres and educational ambassadors programmes from the International Society of Nephrology are important mechanisms to strengthen kidney research capacity in low-income countries.⁸² The global kidney research community should also focus on developing global clinical practice guidelines, which are suitable for patients in low-income countries.

At the same time, a new gap in capacity has appeared between scientifically proficient emerging countries (Argentina, Brazil, Chile, China, India, Malaysia, Mexico, and South Africa) and other emerging countries, the so called South–South gap. However, there are examples of increasing South–South cooperation that are helping to close this gap:⁸³ these initiatives must be promoted in renal medicine as well.

Today, even important ideas and studies from low-income or middle-income countries have little chance to reach international journals and are ignored.⁸⁴ Access to health information in low-income and middle-income countries should be improved. The gap between evidence and practice can have profound health effects when highly effective interventions exist.⁸⁵ Encouraging original research in low-income or middle-income countries should also increase visibility in these ideas to a wider audience—perhaps providing specific space in international journals for papers focusing on local problems needing specific solutions.

Renal replacement therapies

Despite the success of strategies for preventing progression of chronic nephropathies,⁸⁶ kidney failure

remains an important clinical problem. The outcomes associated with chronic dialysis have not substantially improved over the past two decades and further work is needed in this area to improve renal replacement therapy, either for acute kidney injury and chronic kidney injury.

New dialysis research includes cheaper treatments, home-based therapies, and simpler methods of blood purification, objectives that can be achieved with new disciplines such as miniaturisation and nanotechnology. In the field of renal replacement therapy, technical innovation can be the result of a joint effort of not-for-profit organisations, rather than industrial investment, when considering the needs of small populations. For example, the development of equipment for miniaturised renal replacement therapy for newborn babies and very young infants.⁸⁷

Although kidney transplantation is the best available treatment for kidney failure, the supply of renal allografts is insufficient to meet the demands. New and more effective strategies are needed, including the use of self-repair of human tissues and organs.

The human kidney has an intrinsic capacity to repair after injury.⁸⁸ The repair process is accomplished by migration of stem or progenitor cells into the damaged region, with eventual reconstitution of a functional epithelium. Such progenitors have been identified in resident epithelial cells⁸⁹ and glomerular parietal epithelial cells,^{90,91} but stem cells with broader regenerative properties are also found in the proximal tubuli, glomeruli, papilla, and peritubular capillaries, and in urine.⁹²

Understanding how these unspecialised precursors are maintained and regulated has practical implications, as the regenerative potential of tissue-specific progenitor cells can be therapeutically used to boost the repair activity of cells in models of chronic kidney disease.^{91,93} Efforts are also directed to replenish the renal stem-cell pool and potentiate the regenerative repairing process by transplantation of mesenchymal stromal cells from bone marrow or other tissue sources. This regenerative cell-based approach has been applied in rodent models with damaged renal tissue and is more effective in acute kidney injury than in chronic kidney injury.^{94–96} However the main barrier to effective implementation of therapies based on mesenchymal stromal cells is the absence of specific homing of exogenously infused cells and the inability to direct these cells to the diseased tissue. Genetic modification of mesenchymal stromal cells with retroviral vectors that encode homing receptors⁹⁷ or preconditioning of mesenchymal stromal cells before infusion with compounds possessing promigratory properties (and possibly without side-effects)⁹⁸ are now being explored to direct therapy to diseased cells. Stem-cell therapies, however, might not be acceptable since some studies have suggested an increase in interstitial fibrosis.⁹⁹

Investigators are trying to bioengineer kidneys¹⁰⁰ but this work is in its infancy and ex-vivo kidney regeneration with extracellular matrix scaffolds will probably not be clinically viable for at least a decade, despite a recent clinical attempt.¹⁰¹

Recently in-vivo experiments in athymic rats showed the development of renal organoids from embryonic murine cells, indicating that generation of vascularised glomeruli attached to nephrons with filtration and active re-uptake, from simple cell suspension is possible.¹⁰² As engineering and nanotechnology advance, implantable artificial devices that could provide both glomerular and tubular function may be developed.

Whether and when these new technologies will result in significant clinical applications cannot be determined at present. Even more difficult is to predict how much such technologies would cost when applied on a large scale, and whether they would be affordable in low-income countries.

Contributors

All authors contributed to writing and conceptualisation of the report. GR and AS revised and did final editing of the various contributions.

Conflicts of interest

We declare that we have no conflicts of interest.

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