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Review

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Innovative directions of CKD prevention and treatment

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Summary. *Chronic kidney disease (CKD) is global challenge of health-care. Existence of CKD significantly increases total lethality risk as well as cardiovascular mortality risk. The issue is that current methodology does not ensure prevention, early detection of CKD and avoidance of its progression.*

Innovative patient-oriented approaches for solution of these issues must be realized through implementation of national screening programs, IT CKD self-testing, development of CKD-oriented drugs for new therapeutic targets.

If mentioned above problems will be solved, innovative modalities of prevention of steady progression of CKD and the new forms of medical care organization, at least, will help to decrease the level of CKD morbidity and decelerate its progression.

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Інноваційні напрямки превенції та лікування хворих на ХХН

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Резюме. Хронічна хвороба нирок (ХХН) є глобальною проблемою охорони здоров'я. Наявна ХХН значно підвищує частоту летальних наслідків незалежно від причин загалом, і особливо від кардіоваскулярних ускладнень зокрема. Основна причина, – застосовувані технології не дозволяють ефективно превентувати розвиток ХХН та зупинити її прогресування.

Інноваційні пацієнт орієнтовані підходи для вирішення цих проблем можуть бути реалізовані через здійснення національних скринінгових програм, ІТ самотестування ХХН, створення ХХН-спрямованих лікарських засобів для нових терапевтичних мішеней.

Якщо перелічені вище проблеми будуть вирішені, то інноваційні підходи до лікування та організації медичної допомоги зменшать розповсюдженість і захворюваність на ХХН та сповільнять її прогресування.

Ключові слова: хронічна хвороба нирок, організація нефрологічної допомоги, інноваційні технології.

Chronic kidney disease (CKD) is a public health problem worldwide with a global prevalence of 11% to 13% [1]. Cardiovascular diseases are being the major cause of mortality in these patients. CKD is associated with elevated risks of all-cause mortality, different adverse events and increased healthcare utilization [1]. The hazard ratios of death among individuals with CKD stages 3-5 vis-à-vis those without CKD ranged between 1.2 and 5.9 [1]. The majority of people with CKD have multiple comorbidities, placing them at high risk for complications. In addition, individuals with CKD were 1.6 – 2.2 times more likely to be hospitalized [1]. However, people with CKD are often excluded from clinical studies related to kidney disease. Given this, the evidence base for guiding care in CKD is small, and even in areas where evidence exists, uptake of evidence into clinical practice has been slow [2].

Compounding these complexities are the variable prognoses among patients with CKD and difficulties predicting who is most likely to develop complications over time. As such, health care professionals are unable to accurately inform patients of pertinent information such as time to dialysis and trajectories of disease progression. Many knowledge gaps remain, notably the underlying disease mechanisms, the epidemiology and burden in different locations, and genetic and environmental interactions [3]. The first step in addressing any care gap is identifying and quantifying the magnitude of the problem; this review achieves this goal by high-

lighting the consistency of the evidence regarding the hazards associated with CKD. The challenge that clinicians now face is to diagnose CKD early, to manage it aggressively, to evaluate novel means of detecting CKD and to expand the therapeutic strategies for patients with CKD. The evidence base for informing effective kidney care is limited, and the translation of existing knowledge to routine clinical care is slow.

Canada has great innovative experience of patient-oriented nephrologic care. The Canadian Institute of Health Research has launched the national Strategy for Patient-Oriented Research (SPOR), a coalition of federal, provincial, and territorial partners dedicated to integrating research into care, which has raised awareness of the need to generate knowledge that is more relevant to nephrologic patients and to accelerate the translation of evidence into improvement in kidney health and care [2]. The main objective of SPOR is to favour evidence-informed and patient-centered care by bringing innovative diagnostic and therapeutic approaches to the point of care, so as to ensure greater quality, accountability, and accessibility of care. As part of SPOR, Canadian Institute of Health Research is funding provincial SUPPORT (Support for People and Patient-Oriented Research and Trials) Units and national networks that will help advance patient-oriented research [4].

Canadians Seeking Solutions and Innovations to Overcome Chronic Kidney Disease (Can-SOLVE CKD) is one of five pan-Canadian chronic disease networks supported through SPOR. The vision of Can-SOLVE CKD is that by 2020, every Canadian with or at high risk for CKD will receive the best recommended care, experience optimal outcomes, and have the opportunity to participate in studies with novel therapies, regardless of age, sex, gender, location, or ethnicity. The network is led by a steering committee that includes a broad range of patients affected by a representative mix

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of medical conditions, policy makers, researchers, and charitable foundations [3].

The goal of patient-oriented research is “to better ensure the translation of innovative diagnostic and therapeutic approaches to the point of care, as well as to help the provinces and territories meet the challenge of delivering high quality, cost-effective health care” [5]. The highest priority areas identified by patients and policy makers were those pertaining to early diagnosis and prognosis – improved understanding of pathobiology and stratifying patients based on risk; treatment options for CKD and comorbidities, and how best to address physical and emotional symptoms; and optimal models of care in chronic disease. Two examples of the research projects conducted under Can-SOLVE CKD – Identifying diabetes and chronic kidney disease in Indigenous communities and Increasing the use of living donor kidney transplantation [3].

Patients have been integrated into the research teams, bringing the patient voice to all aspects of the research: design, development, recruitment, implementation, and KT. This partnership is an innovative way of performing research, requiring a culture change for all involved. To help effect this change, Can-SOLVE CKD is hosting training workshops to help enable a truly effective and meaningful partnership. For example, 56 network members have received training in patient-oriented research at sessions facilitated by Can-SOLVE CKD [3].

Policy makers are also integral partners and engaged in all aspects of the work: identifying health issues of strategic importance, designing and implementing interventions, and translating findings into practice. [2, 3].

So, the innovative approach in Canadian nephrologic patient-oriented care includes: *training patients and their informal caregivers* to engage as full partners in the Can-SOLVE CKD Network, and to serve as mentors for other patients, ensuring program sustainability; *training researchers* to develop expertise in patient-centered research and how to work in research teams effectively with patients; *training nephrologists* to develop skills in patient engagement and patient-oriented care; *training policy makers* on key aspects of the full spectrum of patient-oriented research, including the use of health research data to produce evidence-based policy [3].

The organizational structure is developed around patients including both the Patient Council and the Indigenous Peoples' Engagement & Research Council (IPERC). At least two patients serve on all Can-SOLVE CKD committees, thus enabling bidirectional communication between committees, the Patient Council and IPERC. The Patient Council is the core and the heart of Can-SOLVE CKD. The Council is co-chaired by 3 patients with unique lived experience of CKD [3]. Membership includes a broad range of patients affected by a representative mix of medical conditions (eg, diabetes, heart disease, polycystic kidney disease) as well as care-

givers and kidney donors. All committees report to the Steering Committee through the respective committee co-chairs [3]. The Steering Committee is ultimately accountable to the Board of Directors of the CSN and the Kidney Foundation of Canada. Committee Chairs are nominated by the respective committees and appointed by the Executive Committee. The Can-SOLVE CKD International Research Advisory Committee provides advisory support to the network, and the Core Operations Team provides the infrastructure support to keep the network functioning on a day-to-day basis. [3].

Network activities will be tracked and reported according to a performance measurement framework with a series of process and outcome measures. Examples of these measures include number of patient partners engaged; experiences of patients engaged in research teams; percentage of partners trained in patient-oriented research; numbers of Indigenous people screened, triaged, and treated; number of living donor and preemptive kidney transplants; and uptake of home therapies as measures of informed decision making and an appropriately resourced health care system [6].

The Can-SOLVE CKD Network will provide the infrastructure necessary to drive patient-oriented research and implement evidence into clinical practice. By linking patients, caregivers, policy makers, researchers, and clinicians, the network promotes a cultural shift from care which is disease-centered and provider-focused to care which is patient-centered, informed by evidence, and coordinated across the health care system. [3]. By focusing on the patient's voice and implementing relevant findings in real time, Can-SOLVE CKD will transform the care that CKD patients receive, and will improve kidney health for future generations.

Multidisciplinary CKD clinics improve patient outcomes, but there is variability in clinic structure and function across Canada. Exploring optimal CKD patient care practices from the patient, physician, and provincial renal program perspective is important in the development of multidisciplinary CKD clinics and to identify what practices are effective in improving outcomes [7].

Incorporating patient values and preferences, employing effective communication and education strategies, adopting SOPs, and utilizing CKD scorecards are all practices that are valuable in improving the care of patients in multidisciplinary CKD clinic settings [7].

The care of the CKD population is complex and requires many interactions between the patient, family, primary care provider, and multidisciplinary CKD clinic team as well as several inpatient and outpatient services. Optimal care is generally defined as care that leads to the best outcomes for the individual, population, and society; it is the goal of any health care system. However, patient-centered outcomes such as engagement, symptom control, and satisfaction may not necessarily align with the physician-centric priorities of slowing the progression of CKD, achieving clinical targets, and improving morbidity and mortality. Regardless, clinicians

seek to deliver effective and efficient care with the goals of identifying, risk stratifying, educating, and managing patients with CKD with appropriate preparation and transition to end-stage renal disease (ESRD) with renal replacement therapy (RRT: dialysis or transplantation) or conservative therapy.

Understanding patient values and exploring their perspectives are critical to caring for the CKD population [8,9]. Tong et al [9] identified 5 themes in CKD patient preferences and experiences including personal meaning of CKD, managing and monitoring health, lifestyle consequences, family impact and informal support structures. Five other topics emerged in adolescents and young adults including inferiority, insecurity, injustice, resilience and adjustment mentality. In the elderly, there is shock about a diagnosis, uncertainty about disease progression and a lack of preparation for living with dialysis. Thus, next innovation - **individualizing care by exploring the patient's values and perspectives** is important in improving their well-being and satisfaction [7].

The principles of care models designed for the elderly have relevance to the CKD population given that a significant portion of this population is considered elderly. Normal aging affects senses (vision, hearing, touch, reaction) and functions (cognition, spatial orientation, motor coordination, mobility, work rate, working memory, executive function, motor coordination and mobility) [1], which may create barriers to communication and education. Screening for sensory deficits [1], intervening with hearing or visual aids, and using other techniques (adequate lighting, appropriate sized print, adequate voice intensity, multimodal cues) may attenuate these barriers. Mood disorders and cognitive impairment are common in CKD patients and the elderly. Thus, such innovative approach as **screening for anxiety, depression [7] and cognitive impairment [10] on a routine basis** (or alternatively if a threshold pre-test probability exists) may be valuable, as these conditions may negatively impact patient interaction and ability to retain information presented. Compliance can be improved by simplifying instructions, reinforcing behavior on a regular basis and by checking/rechecking comprehension. As cognitive functions such as attention, concentration, comprehension and retention may be impaired, strategies to enhance communication are frequently necessary [19]. Information should be broken down into simple elements with each explained separately using techniques to ensure attention and retention of information such as “teach-back”, utilizing multiple senses (e.g. oral and written instructions), and the repetition of concepts over many sessions [11]. Ideally, education sessions should last less than 15 minutes and only address 3-5 points at a time to maximize concentration and retention. **Renal education – also mandatory innovative approach** - should also be individually tailored in format, length, frequency, and size (group vs. individual) using a patient-centered approach addressing feasibility and acceptability as soon as deficits

in health literacy are common in the CKD population, clinicians must be sensitive with their use of language complexity and terminology in all forms of communication [12]. In multilingual country, translators should be available during clinic visits and if not, caregivers can be utilized instead if language barriers exist. Additionally, educational materials including pamphlets, posters and education sessions should be offered in the languages most prevalent in the population [11].

Standardized operating procedures for physicians and multidisciplinary team members: defining inputs and outputs

Multidisciplinary CKD clinics improve clinical targets (blood pressure, ACE/ARB use, hemoglobin, calcium, phosphate, bicarbonate) and outcomes (rate of eGFR decline, acute renal replacement therapy, vascular access, hospitalizations, mortality, costs) in both adult and pediatric populations. However, it remains uncertain how to optimally structure multidisciplinary CKD clinics and what resources should be allocated to promote their operation [4, 13]. A time study and task consistency analysis demonstrated heterogeneity in practice, poor communication among the team with significant “down time” and wait times for patients and no clear dynamic monitoring of clinical and administrative outcomes. The goal of the clinic redesign by process engineering was to eliminate bottlenecks, improve patient flow and standardize quality of care through the elimination occupational uncertainty. A pre/post time study, task analysis and chart review for quality of patient care parameters must be performed. Mean throughput times (time for a patient to progress through the clinic) must be decreased and the standard deviation of mean cycle times and physician cycle time will decrease with adherence to time standards. It will help less variability of task performance and no changes in clinical targets. SOPs play an important role in multidisciplinary CKD clinics to optimize quality, efficiency and accountability.

Framework and goals of care: CKD scorecards

The BC Renal Agency Provincial Kidney Care Committee's (KCC) goal is to provide infrastructure and mechanisms to facilitate a provincial and interprofessional approach to improvements in CKD care [7]. Since the establishment of the provincial KCC in 2011, the group has involved all provincial health authorities in the creation of a formal framework including definitions, best practice documents, and a set of metrics to ensure accountability and enable quality improvement [7]. There is a systematic gathering of data using a provincial database, which permits a description of provincial CKD clinic demographics, comorbidities, and achievement of clinical targets and outcomes. In collaboration with provincial health authorities, KCC developed a work plan that included the creation of a document entitled “Best Practices in Organizing Kidney Care” (www.bcrenalagency.ca) that outlines guidelines, protocols, and algorithms for ordering

and reviewing of bloodwork, medication reconciliation, and modality education, and interprofessional team members' roles and responsibilities. In addition, the pathways for transitions between CKD and RRT modalities (hemodialysis, peritoneal dialysis, and renal transplantation) are well articulated, defining the roles for various team members. A scorecard approach in health care terms refers to the process of formally adjudicating systems for benchmarks of quality of care defined by guidelines. The KCC has developed and reported CKD scorecards for all clinics in an unblinded manner after establishing a set of indicators of quality of care and goals linked to best practices. For example, hemoglobin and iron target achievements would reflect implementation of anemia protocol; ACE/ARB use would reflect recommended best practice for delay of renal progression and cardiovascular health; the proportion of patients with eGFR<20ml/min and documented planned modality would indicate appropriate timing of education; the proportion of patients starting on the modality of their choice indicate appropriate timing and preparation; and independent modality rates of those attending clinics would be an 'integrated' measure of the entire process of care, including appropriate access creation and education, decision making and system functioning [7, 13]. Each of these measures can be mapped to a specific set of activities important to patient outcomes and system functioning. The value of the KCC provincial approach is that it has permitted knowledge translation, transparency, and standardization of CKD care with the use of the "plan, study, do, act" cycle as an iterative process. Future goals are to include measures of patient-oriented outcomes and other relevant metrics, and incorporate the assessment of how to address depression/anxiety, end of life, and advanced care planning activities into future metrics [7]. Unfortunately, a limitation of scorecards is the need for the infrastructure for information management.

The American Society of Nephrology (ASN) is a leader in the fight against CKD [14]. In February of 2017, the Veteran Association and ASN convened the inaugural Kidney Innovation Summit at the BAH Innovation Center in Washington D.C. to identify opportunities for innovation in the care of people with CKD. VA principles were applied as a roadmap for kidney innovation, aiming to make care patient-centered, collaborative, data driven, of high value, and continuously improving [15]. Four focus areas for innovation emerged from the Summit: (1) health system initiatives that foster early CKD detection, prevention, and treatment; (2) education and decision aids for people at risk for CKD and their caregivers; (3) data science developments that improve CKD care; and (4) rehabilitation of people with ESRD [14].

Health System Initiatives Targeting Early CKD

Health system initiatives targeting CKD prevention and early detection are vital to reduce health disparities and improve the overall population health

of veterans and other Americans. Models of care and technologies that surmount geographical barriers offer potential for reducing the adverse outcomes associated with late CKD detection and intervention. *Team-based models of care to facilitate rural veteran CKD screening and management* were among the Summit proposals. At home, *self-administered testing for kidney disease* was also proposed as an alternative to medical center-based CKD screening. Particular support was voiced for the *development of urine test kits of early biomarkers for kidney disease* and to monitor CKD's progression in high-risk patients.

Enhanced health system teletextology was also identified as a means to extend care to rural patients with CKD. For example, augmenting the VA *e-Kidney mobile application* prototype to feature biometrics reporting, medication and appointment reminders, and access to virtual nutrition clinics would expand its functionality beyond static education to empower active patient self-management [16].

Kidney Disease Education and Decision Aids

Proposed aids to enhance healthy food decision-making ranged from virtual nutrition clinics and grocery store tours, to cooking demonstration classes for patients and their families, and automated monthly nutrition report cards.

Decision aids to assist patients in managing their expectations and experience with self/home care dialysis and kidney donation were also identified as learning opportunities in need of innovation. Suggested home dialysis education aids included peer-to-peer coaching programs and booster training curricula for patients and caregivers to diminish the loss of skills over time reported by patients. To expand kidney donation opportunities, a living donation fact sheet, standardized screening process, and central education portal were cited as essential tools to develop.

Data Science to Advance Kidney Health Care

As emphasized at the Summit, the rapidly evolving field of data science offers unparalleled opportunities to enhance the wellbeing of populations and individuals with kidney disease and to substantially reduce avoidable health care utilization and expenditures. The feasibility of leveraging VA's vast data resources to comprehensively assess the population health of patients with CKD and provide insight into best practices is emerging [17, 18]. High priority for data science innovation was assigned to analytics techniques using artificial intelligence, including machine learning and natural language processing. In addition, data science developments in aggregation of big data to improve kidney health care was identified as a need. And, novel data science methods to identify individuals at risk for kidney disease and enable deep phenotypic stratification were deemed essential by Summit panelists to advance precision medicine related to CKD [16].

Rehabilitation of People with ESRD

Impaired health-related quality of life and other poor outcomes characterize many people suffering from ESRD or its burdensome treatment. Processes of care and tools that promote personalized RRT and preemptive kidney transplantation were favored solutions. Examples included *incremental dialysis*, which if shown to preserve residual renal function, offers an alternative paradigm for incident ESRD care. Tailoring of RRT via *suppression of colonic uremic toxins* was another testable hypothesis proposed. Currently undergoing regulatory review, *wearable artificial kidney devices* would facilitate rehabilitation through enhanced patient autonomy. Additionally, patient-centered decision-making tools related to RRT and strategies to improve living donation transplantation awareness were cited as rehabilitation opportunities [16].

Although dialysis and kidney transplantation were ground-breaking advancements in the past, little innovation has occurred in the last few decades, especially when compared with revolutionary high-tech advancements in other areas, and for other diseases such as cancer and diabetes. The result we anticipate, will be an ecosystem that accelerates innovation toward the development of new therapies. This exciting new wave of research programs is multidisciplinary, designed to unite the nation's sharpest minds to address the challenges in creating kidney replacement systems that are patient-centered to developing targeted therapies that lead to cures [19].

The National Institutes of Health (NIH) **All of Us Research Program** is a groundbreaking scientific effort to gather data from at least a million Americans to develop precision medicine techniques – with far-reaching implications. A second, more kidney-focused project – the **Kidney Precision Medicine Project** – aims to secure and evaluate human kidney biopsies from participants with acute kidney injury or chronic kidney diseases, with the goal of developing a sound scientific understanding of the kidney and opportunities for novel therapies [19].

The broader kidney community is united in advocating for the **Chronic Kidney Diseases Improvement in Research and Treatment Act (H.R. 2644)**, which if enacted will have a positive influence on research in our field. This Act would complement current kidney research efforts by requiring the U.S. Department of Health and Human Services (HHS) to study crucial issues facing kidney patients, such as factors influencing why minority populations are at greater risk for kidney diseases and what actions HHS could take to reduce barriers to transplantation [19].

Perhaps most excitingly, the federal government of USA has also engaged with the private sector in unique partnerships to spur innovation and accelerate therapies for people with kidney diseases. HHS has partnered with ASN to establish **KidneyX** – a kidney innovation accelerator. Through a series of prize competitions, KidneyX will work to accelerate the development of drugs, de-

vices, and other therapies across the spectrum of kidney care including diagnostics, prevention, and treatment. The result, we hope, will be therapies that could reduce or eliminate patients' time on dialysis, slow or stop the progression of kidney diseases, improve patient outcomes, and provide a better quality of life [19].

Top 5 Innovations for Patients with End Stage Renal Disease

New proposals such as the Dialysis Patients' Demonstration Act would truly revolutionize the way dialysis is paid for with the potential to improve lives, accelerating our efforts to reduce hospitalizations and readmissions [20].

When a medical provider does the right thing and avoids a hospital stay in a fee-for-service environment, the financial benefits typically accrue to the payor. **The healthcare economics change to the benefit of our patients in a value based program.** For example, a new innovative catheter cap has been shown to reduce dialysis-related infections. These more expensive caps are cost prohibitive in a fee-for-service model. But in a value based model, nephrologists would be free to implement this higher cost cap to reduce infections and hospitalizations.

There is increasing recognition of the benefits of **home dialysis**. These advantages include convenience, independence, privacy and a sense of autonomy for the patient [21]. We are committed to making home dialysis available to every patient for whom this therapy is appropriate. The options continue to increase for patients whether they choose at-home hemodialysis or at-home peritoneal dialysis. And in the past couple years, Medicare has stepped up to encourage more patients to try at-home dialysis and support more training so patients can be successful [21].

Improved Vascular Access for Hemodialysis

More reliable and less invasive vascular access for patients requiring hemodialysis has the potential to improve patient outcomes. Two types of hemodialysis vascular access designed for long-term use include the arteriovenous fistula (AVF) and the AV graft (AVG). A third type of vascular access – the central venous catheter (CVC) – is primarily intended for short-term use due to the number of complications related to this type of access [22].

Both the AVF and the AVG have significantly better outcomes and less complications than the CVC. An important goal is minimizing or eliminating the length of time that these patients are exposed to the CVC as their access. In the recent past there have been two new techniques developed that have demonstrated the potential to aid in reaching this goal: percutaneous anastomosis devices and bioengineered blood vessels created from human cells that help reduce the reliance on CVC's as a form of hemodialysis access. Promising research from Duke University has shown that these human derived vessels may be more durable and safer than synthetic alternatives [22].

Creating Insight from Information

The ability to capture information directly and indirectly and apply advanced analytical techniques (often referred to as machine learning or artificial intelligence) is coming into its own in medicine. These mathematical methods of capturing and extracting nuggets of critical insight will help provide people living with chronic illness more informed decisions on options for therapy, medication and clinical care [23]. This entire experience of care should be seen not only as therapeutic, but as a wealth of diagnostic information that will help to make personalized and more precise care choices to achieve the best outcome in the most effective and efficient manner [23].

Phosphate Control Improvement

Reducing the pill burden for dialysis patients has the opportunity to improve a patient's quality of life. Drugs that help patients better manage phosphate levels with fewer pills is something that may also help reduce the risk of cardiovascular events and bone fracture. Sucroferric oxyhydroxide is a novel, non-absorbable iron-based phosphate binder with high binding potency. In two years of real-world data, treatment with sucroferric oxyhydroxide increased the number of dialysis patients able to reach recommended levels of serum phosphorus with half the number of pills (four to five) compared to the most common phosphate binder (eight to nine pills per day) [24].

Novel therapeutic targets to retard progression of chronic kidney disease

Therapeutic strategies that positively impact the progression of CKD to inevitable renal replacement therapy are lacking. International Society of Nephrology CKD roadmap [13] was published recently to define goals and resulting action plans that can be collectively used by interested stakeholders to facilitate new therapeutic approaches to mitigate CKD progression.

Challenges and opportunities

There are many undisputed and complex reasons why patients with CKD remain bereft of treatment options despite an uncontroversial need to develop therapeutic interventions to impact the rising global burden of CKD. There is an acknowledged lack of coordination among scientists, investors, clinical trialists, pharmaceutical companies, regulatory authorities, policy makers, and governments to develop novel strategies to reduce the burden of CKD. It is also recognized that there are region-specific causes of CKD, requiring targeted therapies to alter the initiation of injury. Coupled to this is an incomplete understanding of the underlying multifactorial pathophysiological mechanisms that lead to CKD; this is explained in part by the inherent limitations in *in vivo* and *in vitro* models that are used to study acute and chronic diseases that converge on the entity that we collectively term as CKD. CKD is not one disease but rather the result of a variety of pathophysiological insults to the kidney, which ultimately result in

failure to function correlated with pathologic changes. It is conceded, however, that once CKD is established, the mechanisms for progression may be similar, and an inclusive approach by trialists and regulatory authorities is required [25].

Moreover, there are recognized gaps in knowledge of the complications of CKD. Patients with CKD are at a high risk for cardiovascular disease yet are often and systematically excluded from cardiovascular outcome trials.

Four goals were identified as being necessary to achieve the objective of establishing and validating novel therapeutic targets to retard CKD progression [25]:

1. Improve the identification of "druggable" targets that are amenable to therapeutics
2. Enhance the capacity for preclinical and early clinical development
3. Broaden the availability of novel therapeutic approaches
4. Increase investment in the development of therapies to limit CKD.

To achieve these ambitious goals, it will be necessary to develop research consortium among scientists, pharmaceutical and biotechnology industries, funding agencies, policy makers, government. Only synergized effort will be successful [25].

The following actions are required to deliver the above goals [25].

Improve the identification of targets that are amenable to therapeutics (i.e., "druggable" targets)

To focus preclinical research in biotechnology and pharmaceutical sectors on the identification of "druggable" targets.

- Interrogate human samples using state-of-the-art omics and other advanced approaches to identify and validate new therapeutic targets; incorporate precision medicine-based approaches for target identification; assess the value in preclinical and pilot clinical studies of altering the gut microbiome through dietary strategies to improve CKD.
- Improve models of disease (animal and human) to include comorbidities that better reflect the complexity of human CKD and compare them with patient samples using cutting-edge technologies (e.g., omics, NextGen, etc.) to construct new models and to discover new biological pathways and targets.
- Generate personalized human tissue models using stem cell lines with targeted mutations followed by differentiation to human kidney tissue.
- Cross-disciplinary research on pathophysiological mechanisms relevant to CKD and other diseases [25].

Enhance the capacity for preclinical and early clinical development

- Increase the number, size, and quality of clinical trials.
- Develop infrastructure to collect and carry out state-of-the-art analyses of human biological materials. Include the identification of biomarkers as predictors of disease progression and/or response to treatment.
- Facilitate interaction and exchange of ideas between scientists and drug manufacturers.
- Recognize and support academic nephrologists to enable them to move more easily between academia, pharmaceutical and biotechnology research environment.
- Give grants to the ongoing involvement in academia and pharmaceutical and biotechnology collaborations in academic career development [25].

Broaden the availability of novel therapeutic approaches

- Evaluate opportunities of the new indications for existing drugs for the treatment of CKD and its complications (e.g., allopurinol, metformin).
- Collaborate with biotechnology and pharmaceutical industries to assess the availability of candidate drugs developed for nonrenal indications that passed phase 1 safety studies but did not meet phase 3 primary endpoints. Determine whether these assets may impact CKD and its complications, shortening the timeline from drug discovery to clinical development.
- Improve access to effective but costly drugs, biologics, and devices, especially in low- and middle-income countries. Aid from the Organization for Economic Cooperation and Development countries to low- and middle-income countries should be targeted for CKD prevention and treatment [24].

Increase investment in the development of therapies to limit CKD

- Document differences in CKD treatment approach and therapeutic needs in different countries in order to leverage patient populations available for potential treatment.
- Encourage pharmaceutical, biotechnology industries and governments to invest in the development of new therapies for CKD.
- De-risk costly and lengthy CKD trials by (i) improving patient stratification to enhance clinical success and (ii) identifying companion biomarkers that track with biological activity and efficacy and that can be independently monitored to predict clinical outcomes (death, dialysis, or change in estimated glomerular filtration rate) [25].

If the above goals are achieved, ultimately, new therapies will be available to stop, slow, or reverse CKD in all populations. Given this is a long-term outcome, intermediate deliverables are necessary [25].

Create multidisciplinary CKD consortia

National, regional, and global multidisciplinary consortia consisting of members representing diverse sectors – academia, biotechnology and pharmaceutical industries, regulatory agencies, policy makers, foundations, and nonprofit organizations – can be tasked with implementing approaches to address barriers to progress in the development of treatments to diminish or block CKD progression. An example of an attempt to do this on a national level is the establishment of the Kidney Health Initiative in the US. This is a collaborative effort between the US Food and Drug Administration and the greater nephrology community, formed to advance kidney health, patient safety, and new therapies for renal disease. Such national or regional consortia should work together across the globe to learn from other groups and be most efficient and productive in advancing drug development [25].

Develop clinical trial networks

These networks can be local to a country or set of countries with a particular concentration on CKD thought to be caused by factors particularly prevalent in that region. Alternatively, these networks can be international. Such networks can greatly facilitate the testing of new therapeutic agents and institutionalize “memory and experience” derived from failed and successful trials that will improve the success of future trials [25].

Programs to support the movement of academic scientists in and out of the industry and vice versa

These programs can include academic trainees or established investigators; alternatively, scientists from the pharmaceutical and biotechnology sector who are part of the drug discovery effort would benefit from being involved in renal biology and clinical nephrology in order to drive innovation that leads to new therapies [25].

Reports

- a. Collate recent progress in renal research and development and present at national and international meetings; publish research findings, including negative data that do not support successful clinical translation.
- b. Inventory the current capacity and activities of research networks for CKD with updating changes in capacity, activities, and outputs over time.
- c. Extend the International Society of Nephrology Global Kidney Health Atlas [26] project, currently tasked to map existing resources, structures, and organizations available globally to patients with CKD and acute kidney injury, to include novel drug development.
- d. Leverage investment from funders, governments, and international organizations with interests in investing in low- and middle-income countries to support better health outcomes [25].

Educational and collaborative activities

- a. Conduct multidisciplinary scientific meetings on targets and therapeutics, new or re-purposed, to draw on the collective experience of other disciplines (nonrenal) that have pursued diverse chronic diseases and have succeeded in clinical translation.
- b. Organize meetings to address barriers and solutions that hinder therapeutic success in order to broaden the cooperation and collaboration between commercial endeavors and academia.
- c. Promote collaborative efforts with existing consortia to better use the available data, resources, biomaterials, etc. for drug discovery and clinical development.
- d. Obtain policy statements from academic institutions that recognize engagement with the commercial sector as being meritorious for career advancement [25].

“Pitch for Partners” meetings among academic nephrologists, scientists, pharmaceuticals and biotechnology industries [26].

These meetings will allow worldwide access to key opinion leaders in order to facilitate interaction and the exchange of ideas to collectively define optimal strategies for programs in drug and clinical development. “Pitch for Partners” can be advanced either as a stand-alone meeting or in conjunction with major conferences.

In order to introduce new therapeutic agents to patients with kidney disease, there are many factors that need consideration beyond the development and validation of novel targets. Medicine has seen the introduction of many new therapeutics encompassing small molecules, antibodies, DNA, and RNA therapeutics. In addition, novel approaches to improve targeted bioavailability reduce side effects and enhance efficacy, making drug delivery systems of complementary importance to the identification of novel targets. Although the focus has been on scientific development, many of the challenges in developing novel therapeutics relate to identifying project funding sources; finding suitable contract manufacturing companies that are Good Manufacturing Practice compliant; and protecting intellec-

tual property generated from scientific advances while maintaining essential collaboration. 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. Trials with the aim of re-purposing of generic therapeutics should be prioritized if sufficient scientific evidence is available. Furthermore, strategies used to extend patent life of drugs, but without investment to assess re-purposing, should be discouraged.

Finally, if the above goals are achieved, new therapies will certainly become available to stop, slow, or reverse CKD. Most importantly, these therapies should be made accessible to populations around the globe.

Abbreviations

ACE/ARB	angiotensin converting enzyme/ angiotensin receptor blocker
ASN	American Society of Nephrology
AVF	arteriovenous fistula
AVG	arteriovenous graft
CANA	Canadian Association of Nephrology Administrators
Can-SOLVE	Canadians Seeking Solutions and Innovations to Overcome Chronic Kidney Disease
CKD	chronic kidney disease
CSN	Canadian Society of Nephrology
CVC	central venous catheter
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
HHS	Health and Human Services
KFOC	Kidney Foundation of Canada
RRT	renal replacement therapy
SOP	standardized operating procedure
SPOR	Strategy for Patient-Oriented Research
SUPPORT	Support for People and Patient- Oriented Research and Trials

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