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# Unmet needs in clinical trials in CKD: questions we have not answered and answers we have not questioned

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## ABSTRACT

Many advances have been made in the field of nephrology over the last decade. These include an increasing focus on patient-centred involvement in trials, exploration of innovative trial designs and methodology, the growth of personalized medicine and, most importantly, novel therapeutic agents that are disease-modifying for large groups of patients with and without diabetes and chronic kidney disease. Despite this progress, many questions remain unanswered and we have not critically evaluated some of our assumptions, practices and guidelines despite emerging evidence to challenge current paradigms and discrepant patient-preferred outcomes. How best to implement best practices, diagnose various conditions, examine better diagnostic tools, treat laboratory values versus patients and understand prediction equations in the clinical context remain unanswered. As we enter a new era in nephrology, there are extraordinary opportunities to change the culture and care. Rigorous research paradigms enabling both the generation and the use of new information should be explored. We identify here some key areas of interest and suggest renewed efforts to describe and address these gaps so that we can develop, design and execute trials of importance to all.

**Keywords:** CKD, gaps, novel approaches, patient-centred outcomes

The last 10 years of nephrology have demonstrated amazing gains in the areas of clinical trials and novel therapeutic agents both for delaying the progression of chronic kidney disease (CKD) and associated cardiovascular disease and specific glomerulonephritis therapies. As a specialty, we have deepened our appreciation of the need for clinical studies, examined novel trial designs and methodologies [1–3] and increased the level and sophistication of patient engagement both in study design and research priority setting [4–10]. The quality and size of recent trials examining sodium–glucose co-transporter 2 (SGLT2) inhibitors and the new non-steroidal mineralocorticoid receptor antagonists (MRAs) have been remarkable, with >40 000 patients being enrolled in various studies on these agents around the world [11–15].

We should acknowledge how far we have come from the studies of the 1990s. There has been increasing attention to precision medicine and a renewed excitement about the value of kidney biopsies, characterizing kidney disease using advanced molecular and genetic technologies in the 'omics' field with the identification of novel therapeutic targets [16–23]. However, as a community, we need to reflect on unmet needs and critically evaluate what we are and are not studying, and why. We should ensure that we develop integrated research programs that benefit patients and advance our understanding of kidney

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diseases and their attendant consequences. Furthermore, the appreciation of how these impact individuals, populations and society may help us to focus on questions and outcomes of the greatest importance for so many.

Much of nephrology care has involved targeting specific numbers of laboratory values and titrating various therapies accordingly: haemoglobin, phosphate, potassium, bicarbonate and parathyroid hormone to name a few. Recognizing that each of these laboratory values is the result of complex physiological processes, subject to variability and instability, has not translated to more sophisticated approaches to study design, nor targeting of constellations of laboratory values, or a better appreciation of the relationship of these abnormalities to patient-centred outcomes. Indeed, a recent *Nature Medicine* article describes the value of patient-reported outcomes in early-phase clinical trials both for providing insights on therapies from the patient's experience and perspective as well as informing methodology development [24].

We know that haemoglobin varies in the normal population and that in large observational studies in CKD populations [25] haemoglobin and other laboratory values vary by the level of kidney function. However, we have targeted the same haemoglobin range for all CKD populations, irrespective of age, sex, modality of treatment, CKD stage or aetiology [26]. We do not phlebotomize patients who achieve higher than 'target range' haemoglobin, without therapy, so why do we have a treatment strategy that does not identify responders and non-responders to medications (iron, erythropoietin stimulating agents or hypoxia-inducible factor prolyl hydroxylase inhibitors) and then determine the lowest dose to achieve values that are associated with individual self-reported outcomes that are linked with these values (e.g. fatigue, exercise tolerance)? How should we design studies to determine the best target(s) for different patient phenotypes? Similar questions are being asked of phosphate [27–30], parathyroid hormone and perhaps other laboratory abnormalities: what is the right 'value' for an individual and in what context? Note that while multiple observational studies describe adverse outcomes at extremes of laboratory values, and there are treatments to address those specific laboratory values, we have not stopped to ask whom, to what target and why? We presume that benefits will accrue if we treat the abnormality. Our study designs have not addressed root causes, individualization or fixed-dose treatment strategies.

We had long believed in the value of dietary restrictions, especially regarding potassium, phosphate and protein. More recent data have reminded us of the complex relationship between intake to serum levels and the potential harm of excessive restrictions [31–33]. Interventional studies of the value of specific diets in specific individuals are few, yet given the fact that much clinical care and advice centres around diet and laboratory values, answering questions in the nutritional arena to critically rationalize or amend current practice and guidelines would be crucial.

SGLT2 inhibitors have been tested in diverse populations (CKD, diabetes and heart failure and people with more than one of these conditions) and the totality of the data suggests overwhelming benefits and minimal adverse events. In the current era, the treatment landscape has changed, as have many guideline recommendations (American Diabetes Association, Canadian Diabetes Association, Canadian Cardiovascular Society, Kidney Disease: Improving Global Outcomes) regarding the use of and indications for SGLT2 inhibitors. However, clinical practice lags due to some modifiable factors (reimbursement policies, physicians' attitudes, physicians' knowledge). Why have we not embraced 'implementation science' such that we can achieve the best penetration of disease-modifying drugs for our patients and determine the best methods to enable uptake [2, 34]?

In the era of deprescribing and recognition that polypharmacy is common and an issue for many of our patients [35–37], why have we not attempted to determine in whom or which context we may stop medications, especially with newer medications like SGLT2 inhibitors [15, 38–40] and MRAs [41, 42], which seem to address complex physiological processes and have pleiotropic effects? For example, with the successful introduction of SGLT2 inhibitors, in whom might we consider stopping uric acid–lowering medication and/or potassium binders, reducing diuretics and/or anaemia therapies and/or phosphate binders? Can we consider the value of SGLT2 inhibitors as not only a disease modifier but also an agent that may allow many to reduce other medications?

How do we test for the safety and efficacy of this strategy, and in whom?

Not yet known is the benefit of these medications in individuals with advanced CKD, those on dialysis and those with kidney transplants. Given the beneficial vascular and cardiac effects, these agents would seem ideal for these patients, who have a high risk and burden of cardiovascular disease [43]. Fortunately, dedicated studies are being planned for these groups [such as the RENAL LIFECYCLE trial (NCT05374291)]. The roles of glucagon-like peptide 1 receptor agonists in mitigating cardiovascular risk in advanced CKD are being determined in the FLOW trial (NCT03819153). Evidence for a novel and effective treatment to improve clinical outcomes in advanced CKD stages is urgently needed, thus this should be an important international effort supported by the community.

Long-term consequences of pre-eclampsia result in an increased risk of hypertension, cardiovascular disease and kidney disease [44]: why have we not developed simple strategies to risk stratify and provide targeted care for prevention in those individuals at highest risk? Further, both new and older agents known to reduce albuminuria, an early identifier of risk in those patients, could be tested in international collaborative studies.

Numerous investigators have suggested the value of the platform and adaptive trials to answer complex questions. In the area of acute kidney injury (AKI), there is recognized heterogeneity of causes and outcomes and a recent call for better design of clinical studies [45] to address questions of importance to patients and clinicians: survival may or may not be the appropriate outcome for all AKI studies, depending on aetiology, and an understanding of context, initiators and phenotypes and then focused strategies to address specific conditions is of utmost importance. While timing of dialysis initiation to impact outcomes has been the focus of many studies in AKI, there exists a need to better characterize and understand the pathophysiology, determine early interventions to delay progression to more severe stages and appreciate the true diversity of the condition.

Patient engagement has become an increasing focus for many granting agencies, in an attempt to directly ask and answer questions that matter to patients; examples include the Patient Centred Outcomes Research Institute [46] and the Canadian Institutes of Health Research Strategy for Patient-Oriented Research [47]. Specifically, in the kidney space, some very important initiatives have developed to focus research and development on questions of key importance to patients, such as the Kidney Health Initiative [48], Kidney Precision Medicine Project [49], Can-SOLVE CKD [50] and the Standardized Outcomes in Nephrology Group [51]. Patients and their caregivers, through

such initiatives, have prioritized the need for earlier diagnosis, better treatments for kidney disease symptoms and progression and innovative methods of care delivery [52–54]. Patients ask: Why was I not diagnosed sooner? What treatments can delay progression? Why do I feel so nauseous? Why am I so itchy? Why am I so tired?

As researchers and clinicians, we should prioritize answering these questions as well as developing and implementing validated patient-reported outcome measures to assess and address areas of life participation in routine care [55]. Important aspects include consideration of social and cultural backgrounds with an outcome measure flexible enough to encompass the activities valued by the individual. This will ultimately translate to better outcomes and build a community and culture of curious, disciplined researchers inclusive of basic and translational scientists, clinical researchers and social and implementation scientists.

From a diagnostic perspective, we as a specialty have failed to test or create methods that can be put into clinical practice and would help us to assess kidney functional reserve, tubular dysfunction and viability of kidney tissue. There are some ongoing efforts to address this void [56–58]. However, given the progress in imaging and dynamic assessment of so many other organs, we have not, as a community, necessarily recognized the value of improved assessment for both diagnosis and treatment and potential enrolment in clinical studies. There are individual groups who are committed to developing novel techniques and applications in this area, e.g. using functional intradialytic imaging to demonstrate the effect of haemodialysis on the circulatory and cerebral systems [59–62]. Unfortunately, without the support of the community to insist that we need better tools, these efforts will be isolated. Imagine oncology without positron emission tomography scans, cardiology without three-dimensional echocardiograms, cardiac magnetic resonance imaging and stress testing: should we not be advocating for such tests in the kidney space? What research would be required to ensure standardization and accessibility of such tools?

Lastly, we continue to develop and test prediction equations, which are powerful tools intended to facilitate the identification of important outcomes. We are using robust methodologies to validate prediction equations in diverse populations [63]. However, testing and modification of equations for use in the clinical setting versus enrolment into clinical trials versus policymaking have not been undertaken with the same rigour. It may be that equations of value for predicting outcomes on a population basis may need modification for use in individual clinical decision making, or at least need to be tested to determine their value [64].

We are entering a new era in nephrology, with excitement about new molecules for disease modification, increasing emphasis on sophisticated diagnostics and deep phenotyping of individuals to personalize treatment strategies. We are behind in testing different strategies for optimal medication initiation timing in specific conditions and the value of fixed versus escalated doses of medications to address complex conditions. It is important to describe and address the gaps in our knowledge, review our assumptions based on observational data and embrace new technologies and patient engagement so that we can design and execute trials of importance to all. There are questions we have not answered and answers we have not questioned over the years. The coronavirus disease 2019 pandemic has given us pause in many ways: to appreciate uncertainty, question what we know and adapt to changing challenges. Kidney disease remains an important global public health problem and addressing it and its attendant comorbidities requires a concerted effort among a galvanized community to ask and answer the questions of importance to so many.

### Box 1. A new era in nephrology: opportunities to change culture and care

Patient engagement in all research development and processes
Novel diagnostics
Novel trial designs
Novel therapeutics and strategies

### Box 2. Important areas for CKD research

Implementation science: What works to increase the uptake of proven therapies?
Personalized medicine: In whom, what, when and how?
- Individualization of care and treatment strategies throughout the age continuum.
- Understanding sex-specific conditions, responsiveness and evaluation strategies.

Patient-reported outcomes, validated tools and responsiveness to therapeutic interventions.
Reconsidering laboratory values as targets for care.
Predicting outcomes for patients, systems or clinical trial enrolment: when to use specific equations.
De-prescribing medications: benefits and risks.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

## CONFLICT OF INTEREST STATEMENT

None declared.

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