

## The Kidney Research National Dialogue: Gearing Up to Move Forward

Joseph V. Bonventre, L. Ebony Boulware, Laura M. Dember, Barry I. Freedman, Susan L. Furth, Lawrence B. Holzman, Christian J. Ketchum, Melissa H. Little, Rajnish Mehrotra, Sharon M. Moe, Jeff M. Sands, John R. Sedor, Stefan Somlo, Robert A. Star, and Krystyna E. Rys-Sikora on behalf of the Kidney Research National Dialogue (KRND)

### Abstract

The National Institute of Diabetes and Digestive and Kidney Diseases–supported Kidney Research National Dialogue asked the scientific community to formulate and prioritize research objectives that would improve our understanding of kidney function and disease; >1600 participants from >30 countries posted >300 ideas and >500 comments covering all areas of kidney research. Smaller groups of investigators interrogated the postings and published a series of commentaries in *CJASN*. Additional review of the entire series identified six cross-cutting themes: (1) increase training and team science opportunities to maintain/expand the nephrology workforce, (2) develop novel technologies to assess kidney function, (3) promote human discovery research to better understand normal and diseased kidney function, (4) establish integrative models of kidney function to inform diagnostic and treatment strategies, (5) promote interventional studies that incorporate more responsive outcomes and improved trial designs, and (6) foster translation from clinical investigation to community implementation. Together, these cross-cutting themes provide a research plan to better understand normal kidney biology and improve the prevention, diagnosis, and treatment of kidney disease, and as such, they will inform future research efforts supported by the National Institute of Diabetes and Digestive and Kidney Diseases through workshops and initiatives.

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### Introduction

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-supported Kidney Research National Dialogue (KRND) asked the renal community to identify research objectives that would improve our understanding of basic biology and normal kidney function and aid in the prevention, treatment, and reversal of kidney disease. KRND welcomed all interested parties to submit, discuss, and prioritize ideas through an interactive website (1). A smaller group of investigators reviewed postings to identify research gaps and potential strategies. Ten commentaries have been published in the following areas: AKI (2), CKD (3), diabetic nephropathy (4), dialysis (5), glomerular disease (6), normal kidney biology (7), pediatric nephrology (8), polycystic kidney disease (9), training (10), and translation research to improve outcomes (11).

A comprehensive review of these commentaries revealed six cross-cutting themes holding the promise for catalyzing advances in basic kidney research and improving clinical outcomes (Figure 1). Basic fundamental research is central to unifying these themes and driving scientific advancement. Tomorrow's opportunities to reshape nephrology will require continued, steady investment in basic, translational, and clinical research.

### Strengthen Nephrology Workforce

Marked growth in CKD, ESRD, and elderly populations requires nurturing a robust and diverse nephrology workforce performing basic, translational, and clinical

research and working in conjunction with those involved in care and education of individuals affected by renal disease. Declining interest in nephrology as a subspecialty because of a diminished biomedical workforce pool in general and renal-specific factors (*e.g.*, a limited therapeutic armamentarium) threatens progress and innovation.

### Recruit a National Diverse Workforce by Expanding Opportunities for Broad-Based Research Experiences

Initiation and maintenance of a long-term interest in kidney research could be influenced by trainees' early exposures to renal physiology and pathophysiology. Investments made in recruiting and training a wide spectrum of talented people with diverse backgrounds in basic science, clinical research, and applied technical fields are imperative to widen participation in kidney research. Focused efforts to include more underrepresented minorities are needed to better reflect kidney patient populations and assure that the community uses all of its talent. Various initiatives to increase participation in nephrology research programs have introduced students to kidney research at key points in their education, starting in high school. These programs include exposure to scientific approaches and techniques used in bench and translational research. Understanding the effectiveness of programs that initiate and maintain long-term commitments to kidney research would be enhanced by tracking the progress of trainees throughout their careers.

Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

**Correspondence:**  
Dr. Krystyna E. Rys-Sikora, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 6707 Democracy Boulevard, Bethesda, MD 20892. Email: RysSikok@nidk.nih.gov



**Figure 1.** | Six cross-cutting themes of the Kidney Research National Dialogue (KRND) commentaries and basic science research form a pinion that can move toward the goal of enhancing knowledge of kidney health and disease to improve clinical outcomes. Today's opportunities frequently resulted from advances in basic fundamental research into kidney function (central axle), and tomorrow's opportunities will require continued investment in basic, translational, and clinical research. The six cross-cutting objectives of KRND commentaries are (1) increase training and team science opportunities to maintain/expand the nephrology workforce, (2) develop novel technologies to assess kidney function, (3) promote human discovery research to better understand normal and diseased kidney function, (4) establish integrative models of kidney function to inform diagnostic and treatment strategies, (5) promote interventional studies that incorporate more responsive outcomes and improved trial designs, and (6) foster translation from clinical investigation to community implementation. Together, these cross-cutting themes provide a research plan for improving the prevention, diagnosis, and treatment of kidney disease, and as such, they will inform future research efforts supported by the National Institute of Diabetes and Digestive and Kidney Diseases through workshops and initiatives. These combined efforts support the main goals mentioned through the KRND commentaries: to enhance knowledge of kidney health and disease, improve clinical outcomes, and support the future of nephrology research.

### Train and Support Successful Mentors

Mentors who engage and excite students are integral to steering interest toward kidney research. In the past, mentors often engaged in both clinical care and research. However, increasing commitments for other activities have reduced the time available for and quality of mentoring. Mentoring workshops and programs should target physician scientists, particularly mentors of underrepresented minorities, and junior faculty. Recognizing and funding mentoring effort on grants (including funds on the mentees award), celebration of mentoring accomplishments in print and at scientific meetings, accepting mentoring effort as a criterion for promotion, and increased unstructured academic time that is protected by the institution might reverse this trend.

### Allow Non-United States Citizens to Take Advantage of National Institutes of Health-Sponsored Training Programs

The majority of nephrology trainees is now foreign medical graduates. Barriers to immigration impede the ability of these individuals to remain in the research workforce. Despite clear evidence of successful research careers by similarly trained individuals, support of many such trainees on National Institutes of Health (NIH) training grants is

prevented by law. Several members of the NIH Biomedical Workforce Committee have argued that non-United States citizens should be eligible for NIH training grant support (12).

### Promote Multidisciplinary Team Science Training

Diversity powers innovation and discovery. Multidisciplinary teams allow the kidney research community to address increasingly complex clinical and scientific problems. Trainees will require experiences with collaborative approaches and translation of information between disciplines. Programs should provide didactic training on leadership and the benefits and challenges of team science and reward collaboration. All institutions supporting research should genuinely tackle barriers to team science and support multidisciplinary efforts. Universities should adopt promotion criteria that recognize faculty who contribute to team science.

### Develop Novel Technologies

Advances in imaging technologies and cell-based techniques have led to the detection and deciphering of many genetic and molecular mechanisms underlying kidney development, repair, and disease processes.

### Harness the Power of Novel Imaging Technologies

Efforts to use emerging technologies and develop novel methods to monitor and improve human kidney function should continue. Optimizing imaging techniques, such as magnetic resonance imaging, positron emission tomography, single-photon emission computed tomography, and optical imaging in animal models can provide novel insight that can then be translated to humans. The combined use of such imaging modalities holds significant potential for the non-invasive, real-time assessment of kidney function and disease pathogenesis in animals and humans. Qualitative and quantitative multiscale analyses of *in vivo* changes in kidney tissues and cells (renal architecture, renal cell number, compartmental volume, cell migration, and cellular dynamics) now can be reconstructed in three and four dimensions using high-speed bioinformatics software. Nanobiosensor technology may facilitate the detection of subthreshold changes in metabolites, especially after acute injury or exposure to toxins.

### Develop Novel *In Vivo* Animal Models and *In Vitro* Cellular Systems

Conditional gene-deficient mice and high-throughput models (*e.g.*, drosophila and zebrafish) have been used to identify key regulatory hubs and therapeutic targets as well as test interventions. Work should focus on the development of humanized animal models that reflect the range, variety, and clinical characterization of human kidney disease. Also important is the creation of three-dimensional *in vitro* cell systems (*e.g.*, kidney on a chip), including those containing multiple cell types that adequately mimic epithelial and endothelial cell responses and epithelial, endothelial, and interstitial cell interactions with their extracellular matrix *in vivo*. These *in vitro* systems can be used to discover novel pathologic mechanisms and evaluate nephrotoxins and potential therapeutics. The capacity to generate pluripotent cells (*e.g.*, induced pluripotent stem cells) from patient somatic cells also provides the opportunity to model kidney disease using patient-specific material, potentially allowing the field to refocus on patient-relevant and individualized treatments. Advances in stem cell technology should also be used to facilitate kidney regeneration and *de novo* synthesis of kidney components.

### Improve Bedside Technologies

The development of bedside technologies to assess real-time changes in renal function, including stress tests for tubular function and reserve, renal perfusion, GFR, distribution of blood flow, oxygenation, inflammation, and pathophysiologic and therapeutic markers, is critical to understanding human phenotypic changes and responses to interventions.

### Promote Human Discovery to Spur Basic Research

The focus of kidney research shifted from the study of human physiology and disease (50 years ago) to rodent models to study biology and pathobiology and test potential therapeutic approaches (the last 10–40 years). With the burden of all types of kidney disease rising and the limited effect of currently available therapies, novel therapeutics are urgently needed. Successful drug development is predicated on a comprehensive understanding of the natural history of human

kidney function, disease progression, and systematic effects of uremia. Efforts have been hampered by recent failures of animal models to predict drug effects in humans and relatively small numbers of sets of longitudinally phenotyped individuals and banked biologic samples from carefully characterized patients. Investigators must complement basic cellular and mechanistic studies in improved animal models with studies using human samples to validate mechanisms of human disease and identify early indicators of disease progression and novel therapeutic targets.

### Leverage Human Cohorts

Existing cohort studies, such as the Chronic Renal Insufficiency Cohort, Chronic Kidney Disease in Children Prospective Cohort Study, and the Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury, explore the clinical history of disease for discovery and translational research. However, new human cohorts (with and without kidney disease) should be established with streamlined methods to obtain informed consent and patient data/samples. Future cohorts must include accurately phenotyped patients who are followed through disease progression, remissions, and exacerbations (including acute events) to dialysis. Greater focus is needed on specialized populations, such as children (including birth cohorts), the elderly, and those at high risk for AKI and progression of CKD and development of comorbid conditions associated with CKD. These cohorts might include smaller numbers of extensively phenotyped patients with biologic samples (see below) or large virtual electronic health record–generated phenotypic cohorts embedded in large health organizations with electronic or patient-centered registries. The former promotes understanding of the pathophysiology of disease. The latter might allow identification of novel risk factors to improve subsequent inclusion/exclusion criteria for clinical trials. Improvements to health information technology methods for identifying acute and chronic outcomes are needed.

### Increase the Study of Human Samples

More intensive efforts are needed to procure and use high-quality, large-scale, well characterized human biologic samples (tissue, blood, urine, and dialysate effluent) linked to comprehensive demographic, clinical, and phenotypic data. The samples should be widely accessible to the research community and used to support studies that explore novel hypotheses. For example, kidney biopsies are not routinely obtained, except in glomerular disease. Mindful of patient safety, reappraisal of the standard indications for biopsy is needed, especially in diabetic nephropathy, progressive kidney disease of any etiology, non-life-threatening forms of AKI, and perhaps, elderly patients with lower than expected GFR. Efforts should be made to obtain biologic materials from patients scheduled for nephrectomy and individuals identified with progressive disease beginning early in their course and when possible, longitudinally. Autopsy studies, although fraught with difficulty, have advanced scientific knowledge in other fields where samples cannot be obtained before death. The collection, processing, handling, and storage of human biologic materials must be universally standardized, and storage artifacts must be identified. Wide access will require better strategies to obtain preconsent and modifications

to biobank infrastructure to better coordinate storage and distribution. The NIDDK repository and other national biorepositories, such as the National Cancer Institute's Cancer Human Bio-Bank and the National Institute of Allergy and Infectious Diseases' National Disease Research Exchange, have ongoing programs to collect human samples that may be of interest to the renal community.

Meaningful discovery to improve clinical outcomes of patients with kidney disease requires access to health data and biologic samples to inform mechanistic studies in cell culture and animal models. Basic fundamental understanding of normal kidney biology is critical to translation from bench to bedside.

### Establish Integrated Models of Risk and Disease

The life course (progression) of kidney disease is affected by a cumulative series of overlapping and complicated risk factors and altered control pathways occurring throughout the lifespan of an individual that markedly amplify the likelihood of developing additional disease.

### Identify Risk Factors of Disease and Progression

Risk factors are spread throughout the individual's lifespan starting in fetal life (*e.g.*, genetics, epigenetics, nephron number, and maternal factors) and continuing into old age (*e.g.*, vascular disease, environmental and drug toxicities, sepsis, AKI, and ESRD). There may be critical and sensitive transitional periods where accumulating exposures to AKI and chronic kidney injury are especially deterministic and predispose individuals to subsequent development of CKD. Interactions between susceptibility genes, epigenetic modifications, cell fate determinants, and environmental exposure in the neonatal period are likely critical to the initiation and progression of CKD. Birth cohort studies may identify causative environmental and genetic factors and disease complications involved in later CKD. Studies on the influence of aging on normal function and CKD progression are increasingly important as the prevalence of CKD in aging populations rises. The effect of ethnic disparities and genetic variation among understudied population groups may also provide insight.

Methods of early detection of disease in affected individuals and identification of individuals at highest risk for progression are greatly needed. This will require going beyond pathologic observations to classify kidney diseases. Novel biomarkers and stress tests bridging clinical to animal studies are needed to fully identify the determinants of normal function, renal capacity, and productive and abnormal repair leading to fibrosis and CKD and evaluate pathologic processes that occur as result of AKI and other tissue damage. A better understanding of these processes is critical to characterize the window of opportunity in which recovery is possible and develop methodologies and drugs that stimulate repair and regeneration and minimize fibrotic responses.

### Use a Data Science Approach

Technologies are emerging to obtain comprehensive genomic, epigenetic, transcriptional, proteomic, and metabolomic data from specific kidney cell types and *in vivo* models. Integration of omics data with other biochemical, cellular, molecular, imaging, and pharmacologic information can generate new

ontologies for normal kidney function and disease at the molecular level and identify novel targets that are amenable to therapeutic manipulation. These efforts may enable nephrology to go beyond standard pathologic descriptions to develop phenotypes on molecular mechanisms, which ultimately will revolutionize clinical trial design. These findings also will inform the development of new animal models, including humanized and nonmammalian models, that better reflect the range, variety, and clinical characteristics of human kidney diseases. Nonmammalian models may be especially useful in defining the functional effects of disease-associated genetic variation and screening of small molecule libraries to identify new drugs. Presently, healthy and disease states are followed in individuals using a limited number of biomarkers and GFR monitoring. Multiscale analyses and computer modeling are expected to generate new knowledge about the dynamic interaction between the underlying genetics and changes in omics during health and disease, which in turn, can help identify biomarker sets and guide development of novel risk, diagnostic, and prognostic tools. These approaches can be used for more personalized phenotypes in clinical disease registries, health monitoring, and therapeutics. Scientists involved in this integrated research will require new levels of training and robust collaborations.

### Promote Interventional Studies

Increasing our therapeutic armamentarium is critical. Clinical trials help elucidate the relative importance of risk factors, pathways, and targets in modifying and reversing human disease.

### Identify Responsive Outcomes and Novel Clinical Trial Designs

Renal outcomes take years to occur, thus necessitating clinical trials of long duration and limiting investment by industry in potential new therapeutics or predictive diagnostics. Therefore, we recommend development and subsequent use of a broader range of outcome metrics, especially patient-centered and reported outcomes and relevant intermediate outcomes. Patients with kidney disease are difficult to recruit. Pragmatic clinical trials that leverage the infrastructure of health care delivery systems, including dialysis providers, to evaluate interventions in the clinical setting using data obtained from electronic health records typically provide highly generalizable findings and are less expensive than explanatory trials. However, information technology challenges, study designs, statistical methods, and ethical/regulatory considerations need to be addressed to realize the full potential of this approach. The review of such studies must include clinical research experts and account for the effect on patient care in addition to the novelty of the hypothesis.

### Establish Clinical Trial Consortia for Multiple Simultaneous Pilot Studies

Many industry-sponsored large clinical trials seeking novel renal therapeutics have foundered because of recruitment difficulties, safety issues, and lack of detectable efficacy. This is, in part, because of a lack of cohort studies that allow identification of predictors of progressive disease

and/or biomarkers that help narrow phenotype or predict response. Initial testing of new pathways and targets is slow and arduous; subject and dose selections are critical. Additional clinical trial consortia (e.g., AKI and polycystic kidney disease) should be established for early phase and pilot studies. They should facilitate shared learning, coordinated recruitment, and comparisons across studies, where appropriate, thereby smoothing the pathway for evaluating novel therapeutics.

### Foster Translation from Clinical Investigation to Community Implementation

Individuals with kidney diseases require effective health care strategies along the disease continuum from early detection and treatment/management to end stage therapies. Benefits may be greatest in early-stage CKD, when effective interventions are most likely to slow progression. Translational studies (ranging from pragmatic studies establishing therapy effectiveness to population implementation approaches) provide opportunities to improve outcomes and reduce disparities through the development and testing of new approaches to deliver care. Special emphasis should be placed on disease education and adherence to prescribed therapies—especially in adolescents as they transition from pediatric care to adult-focused providers. Health care providers should be aware of the unique obstacles to achieving normal development for youth with CKD and innovative preventive approaches to nonadherence and risk-taking behaviors to lessen negative outcomes. Promoting self-management requires excellent provider-patient and provider-provider education and communication, especially between primary care providers and specialists. Qualitative studies measuring communication and testing interventions to improve provider-patient interactions to translate medical knowledge to patients are needed, especially in underserved communities. Approaches using new educational paradigms (including social media and technology-based approaches tailored to patients' different cultural norms, learning styles, and cognitive function levels) should be tested. Studies establishing the effectiveness of interdisciplinary collaboration among health care professions (primary care providers, specialists, allied health professionals, and lay health workers) to slow progression and improve outcomes are needed. Decision-support strategies to enhance patients' decision-making and self-management as well as enhance health care providers' population care management should be tested. Engagement of patients' family members and social networks to promote education and better adherence could improve self-management.

### Conclusion

The goal of the NIDDK for the KRND was to create a platform for discussion about how to make the most effect on kidney disease through research and compile input from the renal community as a service to the larger biomedical research community. This series of commentaries constitutes an integrated vision of future research opportunities identified by the community. As such, these ideas will inform future activities supported by the NIDDK, professional societies, and disease advocacy groups, including workshops

and research initiatives. All stakeholders are invited to continue the Dialogue by discussing these commentaries through PubMed Commons (<http://www.ncbi.nlm.nih.gov/pubmedcommons>).

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### Disclosures

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