National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases

Reimagining Kidney Function Assessment

Virtual Workshop
February 5–6, 2024

EXECUTIVE SUMMARY

Introduction

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored the Reimagining Kidney Function Assessment workshop on February 5 and 6, 2024. The purpose of the workshop was to bring together experts to evaluate the limitations of current methods for measuring kidney function and discuss potential paths toward a more thorough assessment of various kidney functions. The goal of the meeting was to propel a paradigm shift toward comprehensive approaches to assessing kidney function and an improved ability to describe pathophysiologic mechanisms, trajectories, and subgroups. Broadening the approaches and tools used to measure the functions of the entire nephron will allow researchers and clinicians to refine disease classification and enable better targeting of treatments at the right time and for the right patients. Approximately 319 participants from across the United States and other countries registered and attended the workshop.

Background and Meeting Objectives

Renal function is dynamic and influenced by a variety of factors. In addition to filtering and excreting waste products and toxins, the kidneys are involved in regulating extracellular fluid volume, contributing to glucose homeostasis, and producing hormones (e.g., calcitriol, erythropoietin, klotho, renin), as well as influencing several blood parameters (e.g., ionic composition, osmolality, pH, pressure). Assessment of renal physiology and pathophysiology currently is limited by static and partial measures that focus on serum creatinine (SCr)—as well as its derivative equation, estimated glomerular filtration rate (estimated GFR, or eGFR)—and proteinuria as measures of kidney function status. These measures do not always reflect the range of important renal mechanisms that may be affected early or differentially in varying disease states. More comprehensive tools and techniques are needed to phenotype the full spectrum of kidney disease.

Several current limitations in evaluating renal function have been identified:

1. *Inability to capture specific functions of renal compartments*. The lack of generally accepted or standardized protocols for capturing the full range of functions of critical renal compartments (e.g., proximal tubule, thick ascending limb, collecting duct, microvasculature) hinders the ability to measure a comprehensive suite of renal functions, prevents thoughtful endophenotyping of common kidney diseases, impedes recognition of variant and early forms of kidney disease, and thwarts the development of targeted interventions.
2. *Difficulty in estimating average GFR*. Prior measured GFR (mGFR) approaches do not account for the high biological variability in true GFR. Inaccurate estimations of GFR hinder the ability to understand the average true GFR and prevent the assessment of overall kidney function that is essential for early disease recognition.
3. *Lack of a gold standard for GFR measurement*. The absence of a practical gold standard complicates the accurate measurement of GFR and impedes the development of reliable and

universally accepted benchmarks for GFR assessment and the development of robust estimating equations and biomarkers.

4. *Lack of established models for assessing renal reserve functions*. Current methods do not assess glomerular renal reserve functions to the degree necessary for determining early loss of function and thus result in missed opportunities for early intervention and understanding the progression of kidney diseases.
5. *Challenges in assessing kidney function and reserve during acute injury*. Current methods are inadequate for reliably assessing kidney function and reserve during acute kidney injury (AKI), preventing timely and accurate management of AKI, a critical aspect of overall kidney health.
6. *Inability to integrate various kidney function measures*. Lack of integration of diverse kidney function measures into a single, individual-level global assessment impedes the development of a holistic understanding of an individual's renal health status and limits the use of personalized treatment strategies.

The identified limitations collectively contribute to a significant gap in the ability to comprehensively and dynamically assess various renal functions. To overcome these challenges, clinicians and researchers must integrate detailed molecular profiling and clinical phenotyping to establish reliable tools, standardized procedures, and new tailored approaches that address the multifaceted nature of renal function assessment.

The major themes of the scientific sessions included the following:

1. Measuring Tubular Functions
2. Measuring Glomerular Filtration
3. Glomerular Charge and Size Selectivity
4. Measuring Glomerular Capacity and Reserve
5. New Technologies

Breakout groups on the themes of Glomerular Filtration, Glomerular Permselectivity, Tubular Function, and Renal Reserve met on the second day of the workshop and supported discussion of key considerations for the field.

Scientific Sessions

Meeting speakers presented on topics under each main theme listed above. Following the scientific sessions, moderated discussions were used to identify knowledge gaps and research opportunities relevant to these topics.

Measuring Tubular Functions

Emerging Studies

- Secretion is a distinct mechanism of solute removal (apart from filtration) that involves active transport of solutes and drugs from the bloodstream to the proximal tubules, and methods to measure proximal tubule secretion would provide additional insight into kidney function and pathophysiology. To measure secretory clearance, targeted liquid chromatography–mass spectrometry assays were developed to measure and identify appropriate solutes for measuring proximal tubule secretion (i.e., protein-bound solutes with stable plasma concentration over the collection period). A national cohort study using these assays demonstrated correlation between secretory solute clearances and GFR by iothalamate clearance, yet considerable variation in

secretion was observed for any given GFR measurement. After adjustment for baseline eGFR, albuminuria, and other characteristics (e.g., age, race, sex, diabetes, blood pressure), lower clearance of secretory solutes was associated with a higher risk of chronic kidney disease (CKD) progression independent of GFR and albuminuria. In a cohort of stable outpatients with and without CKD, kidney clearance of endogenous secretory solutes predicted kidney elimination of two secreted drugs.

- Drug dosing often is based on estimates of GFR. To compare tubular secretory clearance with GFR for predicting kidney drug elimination, clearance of two administered drugs (furosemide and penciclovir) was compared to clearances of endogenous secretory solutes, as well as GFR by iohexol clearance. In a cohort of patients with and without CKD, kidney clearance of endogenous secretory solutes predicted kidney elimination of two secreted drugs, and some additional improvement in prediction was achieved by combining secretory solute clearances and GFR.
- Increased SCr (i.e., worsening renal function [WRF]) observed in patients who have chronic heart failure and have been treated with angiotensin-converting–enzyme inhibitors has been shown to represent a benign event that is not necessarily associated with a loss of benefit from continued drug therapy. Mechanisms underlying WRF in response to drug treatment are important in determining its prognostic significance.
- Furosemide is a loop diuretic that is secreted by the proximal tubule and used to assess renal tubular integrity. Furosemide-induced urine output can be used as a stress test to predict acute renal failure, as well as delayed graft function after kidney transplantation. The furosemide stress test outperforms several biomarkers and the fractional excretion of sodium test in predicting patient progression to AKI or the requirement for renal replacement therapy (RRT), and results from furosemide stress tests and biomarker data can be combined to enrich patient risk stratification.
- A natriuretic response prediction equation—which predicts urinary sodium output after administration of a loop diuretic—has been developed and validated and can be used to guide diuretic therapy during acute heart failure. Renal blood oxygen level–dependent (BOLD) magnetic resonance imaging (MRI) coupled with furosemide suppression of renal medullary oxygen consumption can serve as a kidney stress test in patients with flow-limiting renal artery stenosis.

Roadblocks, Gaps, and Opportunities

- No gold standard exists to confirm purely secretory kidney clearance, and current methods for measuring secretory solute clearance show only modest improvements in predicting kidney disease progression in stable outpatients when compared to GFR.
- The functional significance of genetic differences and effects of other factors (e.g., different disease states, expression of secretory transporters, agents that affect tubular metabolism, changes in renal blood blow) influencing secretory transport are not well understood.
- Data are lacking regarding the significance of WRF upon treatment with sodium-glucose cotransporter 2 inhibitors (SGLT2i) or mineralocorticoid receptor antagonists (MRA). Whether changes in SCr predict short- or long-term responses to these drugs remains unclear.
- Standardization of current biomarkers and measures (e.g., partial pressure of oxygen, BOLD MRI)—especially in patients experiencing various treatments in different settings—is needed. New biomarkers should be identified.

Measuring Glomerular Filtration

Emerging Studies

- Ideal GFR markers should be easy to measure; be removed from circulation by the kidney via the glomerulus; and not be protein-bound, metabolized, secreted, or reabsorbed. Historically, inulin has served as the gold standard for determining GFR, but inulin is problematic with respect to commercial availability, price, solubility, and administration. Such compounds as iohexol and iothalamate also are acceptable for calculating mGFR with plasma clearance or urinary disappearance protocols with sufficient precision. Urinary clearance approaches for determining mGFR are rapid, and the collection time does not depend on the patient's GFR. However, mGFR by urinary clearance can be invalid in several genitourinary conditions (e.g., urethral reflux, bladder diverticulitis); it requires accurate collection volumes; and some patients have difficulty voiding on demand. Plasma disappearance approaches for determining mGFR do not require urine collection, can be used in young children or patients with voiding difficulties, and are valid in patients with urethral reflux and bladder diverticulitis. However, this method can require collection times of up to 24 hours and requires precise measurement of the initial compound dose. Appropriate methods should be chosen and tailored toward patient populations as needed.
- True GFR can be estimated using mGFR or eGFR, but both methods are subject to analytical or biological variation that should be considered when interpreting these measurements. Additionally, exogenous substances and processes outside the kidney (i.e., non-GFR determinants) can alter endogenous filtration markers and interfere with eGFR assays. In a systematic review of studies performed in patients with a variety of acute and chronic illnesses, the GFR equations that use creatinine–cystatin C were more accurate than equations that use creatinine or cystatin C alone. Performance of eGFR (using creatinine, cystastin C, or both) was poor in many studies, suggesting the need for improved methods or more frequent use of mGFR.
- Various settings require different considerations when assessing GFR and estimating the difference between true GFR, eGFR, and mGFR. To control for physiological variation, standardized environments are necessary. In large clinical research studies, prolonged procedures (e.g., mGFR) are not practical, but not recognizing the potential for errors could lead to false results. Most clinical decisions can be made using eGFR, but mGFR might be required to assess interventions that affect non-GFR determinants of endogenous filtration markers.

Roadblocks, Gaps, and Opportunities

- Performance of eGFR (using creatinine, cystastin C, or both) was poor in many studies, suggesting the need for improved methods or more frequent use of mGFR. Appropriate methods for measuring GFR should be chosen and tailored toward patient populations as needed. Decision trees should be developed to assist clinicians with applying the right GFR method to the right patient.
- The goal for clinicians is accurate, precise, and reliable assessment of true or measured GFR that ideally is easy, inexpensive, and not time consuming to perform. Multiple markers might be useful in calculating an eGFR that converges on the true patient GFR, and untargeted metabolomic studies are being performed to develop improved GFR estimation methods using select biomarkers multiplexed in a single mass spectrometry assay.
- Stable supply chains and payment systems would encourage more widespread use of mGFR. Clearer indications for when to use creatinine, cystatin, or creatinine–cystatin in eGFR, as well as a better understanding of non-GFR determinants for cystatin, are needed. The field would benefit

from better methods to assess GFR (e.g., new methods using exogenous filtration markers or panels of endogenous filtration markers).

Glomerular Charge and Size Selectivity

Emerging Studies

- Increasing restriction to passage through the glomerular filtration barrier (i.e., reduced permselectivity) is observed with increasing size of neutral macromolecules. This "sieving curve" effect is described by the heteroporous model, in which most glomerular pores are small and restrictive, and a smaller number are large enough to allow passage of any size macromolecule into the urine through a shunt pathway. In long-term follow-up studies of human patients with a high incidence of kidney failure ascribed to diabetic nephropathy (DN), the fraction of glomerular filtrate that passed through the shunt (ω_0) was predictive of kidney failure independent of its effect on albuminuria: Although it is unlikely that this advantage would justify conducting technically demanding urinary dextran clearance studies on all patients with type 2 diabetes, a less involved method for obtaining similarly predictive information would help distinguish patients at high or low risk for developing kidney failure and enable personalized treatment and follow-up.
- Permselectivity can also be expressed in terms of the relative urine-to-serum ratios of endogenous serum proteins spanning a range of molecular sizes (as compared to transferrin). Higher protein selectivity (i.e., reduced protein clearance) is likely to be associated with reduced amounts of protein passing through the glomerular barrier; thus, an inverse relationship between protein selectivity and ω_0 is predicted and might offer a more tractable method of predicting kidney failure risk.
- Podocytes are terminally differentiated cells that cannot self-renew. They must maintain a stable proteome and metabolome for the lifetime of an organism while being exposed to enormous stress from blood pressure and filtration shear forces. Studies in murine models of late-onset kidney disease have demonstrated that the glomerular basement membrane (GBM) is compressed between fluid filtration forces in the capillary lumen and buttress force exerted by podocytes. Under disease conditions, loss of podocytes reduces the buttress force, enabling passage of macromolecules through the decompressed GBM. During later phases of disease, podocytes might be lost via detachment because of powerful shear forces through filtration slits, and, notably, GFR appears to provide a lower estimate of the extent of damage to the filter.
- Intraluminal pressure is converted into axial (longitudinal) and circumferential (hoop) stress in renal capillaries; circumferential stress exerts double the force of axial stress. Foot processes have a clear orientation preference along the longitudinal axis to protect against the stronger circumferential forces.

Roadblocks, Gaps, and Opportunities

- The relationship between protein selectivity and ω_0 can be tested in samples from ongoing studies using dextran sieving methods. The predictive power of ω_0 and the degree to which it can be replaced by an index of endogenous protein selectivity should be verified.
- Transient or partial pedicel/foot process detachment from podocytes, as well as the loss of entire podocytes, has been hypothesized to be the mechanism whereby large proteins permeate the glomerular barrier. With relative podocyte insufficiency, the frequency of detachment episodes might increase, increasing the size of the shunt. If this is the case, shunt magnitude (as measured by ω_0 or protein selectivity) might be a functional measure of podocyte loss.

- How to best measure podocyte depletion and/or ω_0—in addition to the power of this approach to predict outcomes in other glomerular diseases or long-term treatment responses—should be investigated.

Measuring Glomerular Capacity and Reserve

Emerging Studies

- Human kidneys have a functional reserve. Baseline GFR is not a fixed function, and renal functional reserve (RFR) can be quantified by measuring the increase in GFR after stimulation with protein loading or treatment with humoral or vasoactive mediators. RFR correlates with increased kidney size and lower GFR per kidney volume. Preliminary studies have demonstrated that RFR is reduced in young adults with congenital heart disease (CHD) compared to healthy young adults, and RFR appears to be predictive of AKI development in patients with CHD who undergo bypass surgery.
- Mechanical abdominal pressure—through compression of renal vessels—decreases blood flow and activates autoregulatory mechanisms that can be measured by a fall in renal resistive index (RRI), and the intraparenchymal renal resistive index variation (or IRRIV) test is a noninvasive method that exploits changes in RRI in response to mechanical pressure to measure RFR indirectly.

Roadblocks, Gaps, and Opportunities

- Knowledge of glomerular reserve can help in assessing the risk of AKI before high-risk kidney procedures (e.g., cardiopulmonary bypass, radiocontrast or nephrotoxin administration, transplant) and the level of recovery after an episode of AKI. Current studies are evaluating whether preoperative RFR can predict the development of postoperative AKI after cardiac surgery.
- RFR testing is time consuming, and the lack of standardized methods complicates comparisons among studies. More research on practical methods to quantify RFR and the use of RFR for patient stratification is needed.

New Technologies

Emerging Studies

- Intrinsic autoregulation is necessary to maintain homeostasis in the kidney by monitoring sodium chloride concentrations in the tubule. Resting-state MRI can be used to noninvasively detect spontaneous physiological fluctuations in the rat kidney. Spectral features of MRI signal oscillations within individual voxel clusters are specific to tissue compartments, and spectral power correlated with glomerular injury (and not tubular injury) in a rat model of DN.
- The equations from the Modification of Diet in Renal Disease Study and the Chronic Kidney Disease Epidemiology Collaboration are the most widely used equations for eGFR, but their precision remains suboptimal. Relmapirazin, a compound developed by MediBeacon Inc., is designed to exhibit a large Stokes shift with negligible protein binding and metabolism. Transdermal detection of relmapirazin fluorescence can be used across all skin tones to detect normal and impaired renal function.
- Noninvasive MRI can be used to quantify renal blood flow, a critical parameter for evaluating GFR. Dynamic susceptibility contrast imaging makes use of a gadolinium contrast agent and can determine renal blood volume, flow, and transit time. Deoxyhemoglobin dynamic susceptibility

(dDSC) contrast imaging leverages BOLD MRI to provide the same kidney function parameters in the absence of a contrast agent.

- Glutathione-coated gold nanoparticles (GS-AuNPs) can be cleared by the kidney and detected by X-ray or fluorescent imaging. Unexpectedly, smaller GS-AuNPs get trapped in the glycocalyx layer of the glomerulus and get filtered at a lower rate than larger GS-AuNPs. Additionally, proximal tubular epithelial cells eliminate endocytosed gold nanoparticles from the kidneys into the urine within a month by transporting intact gold-containing endocytic vesicles into extrusions (along with mitochondria or other organelles) and pinching the extrusions off into the lumen. Proximal tubular extrusion has been observed independently of treatment with GS-AuNPs and disappears upon AKI, indicating that it is an intrinsic function of healthy proximal tubular epithelial cells.
- Approximately 0.3 percent of all cells found in urine are urine-derived stem cells (USCs). USCs have high proliferative capacity, express embryonic and mesenchymal stem cell markers, and are capable of *in vivo* multipotential differentiation (without teratoma formation) or *in vitro* renal organoid formation. USCs derived from older patients and patients with DN show decreased regenerative capacity and increased senescence and pathogenic factors (e.g., inflammation, oxidative stress, apoptosis) compared to USCs from young, healthy patients.
- Allograft biopsy is the standard of care for identifying kidney allograft injury, but this procedure is associated with complications. Shifts from oxidative phosphorylation to glycolysis and lactate dehydrogenation have been noted in AKI and CKD—as well as kidney transplant biopsies—and can be interrogated using hyperpolarized carbon-13 (^{13}C) MRI. Hyperpolarized ^{13}C probes for many endogenous metabolites (e.g., pyruvate, lactate, bicarbonate) are available. Preliminary hyperpolarized ^{13}C MRI studies show that elevated lactate-to-pyruvate ratios (indicating increased glycolysis) correlate with abnormal allograft biopsies.

Roadblocks, Gaps, and Opportunities

- Resting-state MRI–based oscillation detection has been demonstrated in human patients, and spectral features can be used to characterize unique physiological phenotypes and—when combined with pharmacologic challenge—identify functional kidney responses.
- Changes in transdermal-detected relmapirazin clearance occurred immediately with a change in continuous RRT rates and can provide real-time assessment of mGFR and drug elimination.
- Motion challenges must be overcome before dDSC imaging of kidney function can be used to calculate GFR.
- In a murine model of unilateral ureteral obstruction, GS-AuNPs accumulate in the medulla area of damaged kidneys. In combination with noninvasive fluorescence or photoacoustic imaging, nanoparticles likely can be used for functional kidney imaging (e.g., staging kidney dysfunction) in human patients.
- Potential applications for USCs include disease modeling, drug screening, tissue regeneration, correction of genetic defects, and predicting age-related CKD. Studies indicate that USCs may be useful as biomarkers for renal repair potential and irreversible renal dysfunction after injury.
- Technical development of hyperpolarized ^{13}C MRI is needed to further improve the technique's spatial resolution. The range of pyruvate metabolism in normal allografts should be established.

Breakout Discussions: New Approaches for Comprehensive Assessment

The breakout groups further discussed major themes to identify roadblocks to progress and opportunities for translating new insights into more effective strategies for measuring GFR, glomerular permselectivity, tubular function, and RFR. In particular, the groups focused on tools, resources, models, and other technological advances that will be needed for future success in addressing gaps in the field.

Group 1: Glomerular Filtration

- Use of SCr and/or cystatin C for eGFR is inexpensive and widely available but inaccurate under many circumstances (e.g., elevated GFR, early kidney disease) and influenced by confounding factors. Use of exogenous filtration markers to determine mGFR is more expensive and less accessible but provides more accurate measures across a range of conditions. No single GFR approach appears to be perfectly accurate in all settings.
- The current state of the science—with different techniques for measuring GFR providing varying outputs—is unsatisfactory. Causes of the variation observed in measures of GFR (because of biological variation, random and/or systemic methodological error, or assumptions built into calculations) should be investigated and accounted for in measurements of kidney function.
- The field currently is hindered by practical limitations. Improved standardization of GFR measurements is possible and desirable but will require an unknown amount of time and effort. The use of such outcomes as kidney disease progression or drug-level dosing as gold standards for measuring kidney function might be more informative, but collecting and analyzing this information is quite challenging.
- Additionally, health outcomes often are affected by extrarenal conditions, and bypassing GFR accuracy to focus on prediction might result in the loss of critical information that is specific to kidney function. For example, knowledge of kidney function is required to estimate renal clearance of a drug before determining appropriate dosage, especially for compounds with narrow therapeutic windows.
- Patients undergoing treatment can be leveraged for investigations that will improve measurement standardization and accuracy. For example, patients receiving extended infusion therapy can be monitored with exogenous filtration markers to measure kidney function.
- New techniques to measure kidney function easily and economically (e.g., transdermal detection of relmapirazin) hold great promise but require additional research before being implemented as GFR measures in the clinic.

Group 2: Glomerular Permselectivity

- Evaluations of glomerular permselectivity might be predictive during early stages of kidney disease, and glomerular size and charge selectivity are potential druggable targets.
- Comprehensive assessment of glomerular size and charge selectivity likely will require a multimodal approach that considers mechanical forces, the role of podocyte attachment and GBM integrity, and hemodynamic stress.
- Proposed next steps to develop and establish techniques for assessing glomerular integrity included ultra resolution microscopy–based technology as a static measure of permselectivity; machine learning to determine the length of filtration slits and quantify podocyte numbers and GBM thickness; and integration of spatial transcriptomics, proteomics, and metabolomics for further mechanistic insights.

- Protein selectivity indexes (i.e., clearance of different sizes of proteins) and advances in proteomics (e.g., paired blood and urine) can be leveraged to identify novel biomarkers for assessing the integrity of the glomerular filtration barrier and assaying the function of its various components (e.g., glycocalyx, GBM, podocyte foot processes, filtration slits).
- Current models of glomerular sieving should be improved to represent physiology and biological variability more adequately.
- Such neutral molecules as dextran and Ficoll are associated with technical and safety challenges and likely will have limited clinical applications. Gold nanoparticles—a more tractable approach—can be detected easily and tailored to different clinical applications and research questions.

Group 3: Tubular Function

- Assessment of tubular function should quantify the ability of a tubular segment to perform a specific physiological function necessary for health.
- Biomarkers of tubular injury are not necessarily interchangeable with biomarkers of tubular function. Similarly, tubular function is separate from glomerular function. Not all patients with similar GFR are identical.
- Differentiating between glomerular and tubular albuminuria would be beneficial in assessing tubular reabsorption. The furosemide stress test is the best current marker of proximal tubule secretion, and tests of other functions of the proximal tubule (e.g., hormone synthesis), distal tubule, and collecting duct should be explored.
- Markers of tubular function and injury might be useful as prognostic tests and likely will provide information about the timeline of kidney injury or disease where secretion plays a larger role (e.g., AKI, DN, transplantation, advanced CKD, responses to chemotherapy, patients who do not respond to SGLT2i or MRA treatment).
- The functions and affinities of individual cationic transporters should be investigated, and the resulting data should be leveraged for further insight into tubular function.
- More research is needed to determine the source of USCs and to understand why more of these cells are present in patients with kidney disease.

Group 4: Renal Reserve

- No consensus exists on how to measure glomerular capacity and other types of RFR. Limited data related to the reproducibility of RFR measurements are available, and the most common method used to measure RFR has several limitations. The importance of controlling for changes in baseline GFR when measuring RFR has not been determined. A standardized RFR measurement protocol that can be used to predict meaningful patient outcomes would move this field forward. Different RFR reference ranges likely will be needed for different patient populations.
- Different types of RFR must be distinguished (i.e., glomerular reserve versus other functional domains), which might be possible by comparing stress tests involving salt or phosphate loading to stress tests of the glomerulus.
- Assessments of different RFR types might provide insight into the regenerative capacity of the kidney, as well as different functional domains that are affected unequally by kidney injury or disease. Associations between RFR and kidney histology or biomarkers could be valuable and should be explored.

- New technologies—particularly noninvasive, real-time GFR measures and MRI technologies that measure renal blood flow—will revolutionize the RFR field.

Summary and Conclusions

Reimagining kidney function assessment requires a broadened understanding of kidney function that extends beyond GFR and proteinuria. Standardized GFR assessment protocols that account for biological variation and minimize the gap between mGFR, eGFR, and true GFR in both research and hospital settings are needed. Advanced diagnostics and novel biomarkers are needed to evaluate the complex molecular and biophysical architecture of the kidney filtration barrier and related factors that govern permselectivity and the appearance of albuminuria. Measurements of tubular functions must account for the tubule's role in solute secretion and the subsequent implications for the clearance of protein-bound solutes and xenobiotics; biomarkers for tubular function should be explored for improved risk stratification and diagnostic precision. Methodological challenges in measuring RFR must be overcome to leverage the potential of RFR measurements in predicting kidney stress responses.

The meeting highlighted the limitations of current approaches and the urgent need to explore new avenues. Novel technologies and biomarkers for comprehensive assessment of all kidney functions should be developed to identify loci of dysfunction and gain insight into renal health. Collaborative efforts are needed to bridge the gaps and address the challenges identified during the workshop and achieve a paradigm shift in the classification and treatment of kidney diseases, with a goal of more precise and patient-tailored approaches.

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