Complementary Initiatives from the NIDDK to Advance Kidney Health

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Introduction

Despite the high prevalence and burden of acute and chronic kidney diseases, our understanding of appropriate clinical care and underlying disease pathology is far from complete. Nephrology clinical practice guidelines are littered with weak recommendations on the basis of low or very low evidence. No effective therapies currently exist for AKI, and the few drugs approved for CKD do not work consistently across the CKD population (1,2). Relatively few trials occur in nephrology compared with other medical specialties (3,4), and many of the interventions tested in recent AKI and CKD trials have had negative results—often sending us back to the drawing board.

Such setbacks in nephrology are not without explanation. Clinical nephrology research is impeded by a weak translational pipeline from bench to bedside. Our understanding of the pathophysiology of human AKI and CKD is poor (5), and existing animal models do not appropriately mimic human disease or accurately predict human drug effects (6). Growing consensus suggests that AKI and CKD each may be defined by a heterogeneous set of disease pathways. This incomplete understanding has hampered identification of pathway-specific drug targets.

After clinical trials are launched, nephrology lags behind other specialties in enrollment and adherence to protocols (7). Like many chronic diseases, CKD is typically characterized by a slow trajectory over decades and a relatively low rate of clinically important outcomes (*i.e.*, dialysis, death, or doubling of serum creatinine) compared with diseases like asthma and cancer. This low event rate requires long follow-up times to capture sufficient events. Surrogate outcomes are needed to facilitate clinical trials, but to date, such outcomes have been unsuccessful in predicting outcomes of clinical importance. For example, acute reductions in GFR may mask long-term improvements, which may have occurred in the HALT Progression of Polycystic Kidney Disease Trial of renin-angiotensin-aldosterone system blockers (8). In AKI, identifying participants for trials often requires seeking patients in the intensive care unit, but such patients are often too sick and enrolled too late to see benefits. Additionally, only recently have we begun to understand the relationship between AKI and CKD as interconnected syndromes (9).

Addressing these challenges will require novel approaches, involving large, community-wide efforts coordinated across numerous investigators and institutions. Over the next few years, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the *Clinical Journal of the American Society of Nephrology* plan to highlight a variety of NIDDK initiatives and how they integrate to advance kidney health. This manuscript discusses recent initiatives by the NIDDK that address these issues from the complementary perspectives of precision medicine, pragmatic clinical trials, and population health—each supported by efforts in health information technology (HIT) (Figure 1). Combined, these approaches will allow the kidney research community to identify, efficiently test, and implement treatments to potentially improve outcomes in kidney disease. Precision medicine will identify subpopulations of people with kidney disease and novel treatments targeting these subpopulations. Pragmatic trials and population health efforts will build on these findings by enabling more efficient testing of treatments and application.

Kidney Precision Medicine

Getting the right treatment to the right patient at the right time will require a deeper understanding of human kidney tissue, how its cells and interstitial components interact, and the heterogeneous pathways that lead to both AKI and CKD. Recent advances in multiscale interrogation of human tissue have set the stage for improving our understanding of kidney pathophysiology and ultimately, applying precision medicine to AKI and CKD. Given the poor fidelity of animal models and the limitations of tissue from transplant, nephrectomy, and autopsy, obtaining research biopsies from people with AKI and CKD is a necessary first step to fully leveraging these technologies and achieving precision medicine in nephrology. Access to research biopsies will enable understanding of the variation across AKI and CKD and identification of the disease pathways and appropriate drug targets to attain individualized care. Although our understanding of cancer has benefited greatly for having access to human tissue, it is important to acknowledge that application of precision medicine to nephrology will be less about genetic contributors (cancer model), focus more on omics (mRNA, protein, metabolites, and epigenetics), and likely require consideration of environmental factors (*e.g.*, viral exposures,

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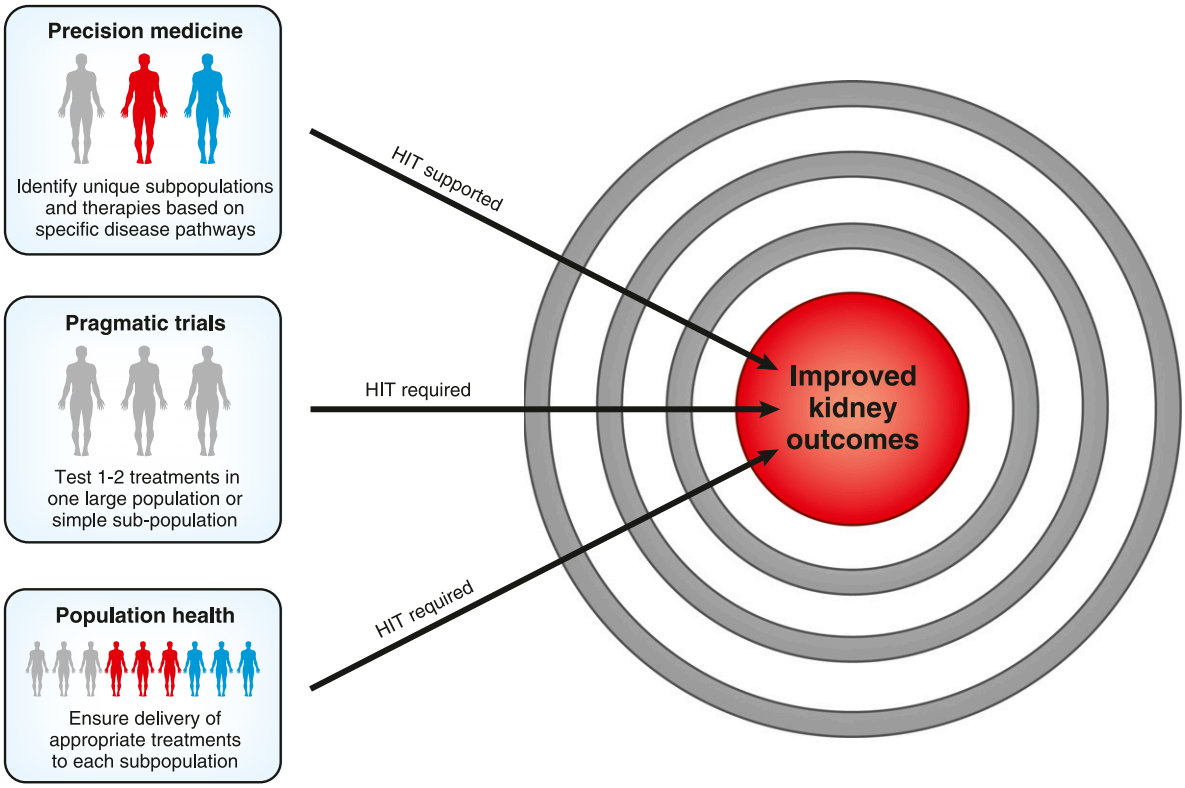

Figure 1. | **A theoretical model: complementary approaches to improve kidney outcomes and the role of health information technology (HIT).** Improved kidney outcomes may best be achieved through complementary approaches that include precision medicine, pragmatic trials, and population management. Precision medicine approaches to kidney research aim to identify unique disease subgroups and novel drug targets for each group. Pragmatic trials may cost effectively test identified treatments in large populations and simple subpopulations. Population health management efforts may be designed to ensure the appropriate delivery of treatments to all individuals within each subpopulation. HIT is critical to both pragmatic trials and population health management and can support precision medicine efforts.

obesity, and maternal/fetal factors) that may directly or indirectly contribute to kidney disease pathophysiology.

The NIDDK will launch the Kidney Precision Medicine Project (KPMP) in the summer of 2017 to ethically obtain and evaluate human kidney biopsies from participants with AKI or CKD; create a kidney tissue atlas (renal pathology of the future) to classify and locate different cell types and interstitial components within the kidney; define disease subgroups; and identify critical cells, interstitial components, and pathways that can be targeted for novel therapies.

Technologic challenges and needs will inevitably emerge over the course of the KPMP. To address these needs and help ensure that KPMP kidney biopsies yield useful research and clinical information, the NIDDK will routinely solicit and fund pilot projects and ancillary studies to the KPMP. The NIDDK is also supporting research to develop safer biopsy methods and novel techniques to interrogate human kidney tissue through its small business program. All deidentified data, samples, protocols, and technologies will be shared with the broader scientific community as soon as the appropriate quality control measures are met. We anticipate that findings and resources from the KPMP will invigorate kidney research, attract top talent from inside and outside nephrology, provide ample career development opportunities, and seed new investigator-initiated research.

It is important to acknowledge that kidney biopsies pose a risk of complications. Therefore, ethical and participant safety considerations will be a primary concern. The KPMP will engage and acquire input from participants to ensure that all KPMP activities are informed by participant viewpoints, priorities, and preferences. Individuals who choose to participate will be provided with clear information about the risks associated with undergoing a kidney biopsy. Specific, validated protocols for tissue handling and interrogation will be developed and implemented to ensure that, when a participant donates his or her tissue to the KPMP, it yields the greatest possible benefit to that individual, the patient community, and society as a whole. Over time, we anticipate that nephrology practice will change as biopsy results become more informative to care and are incorporated into electronic health records (EHRs). The KPMP project is expected to collaborate with other tissue mapping projects at the National Institutes of Health (NIH), including the GenitoUrinary Development Molecular Anatomy Project (http://www.gudmap.org/), the Human Biomolecular Molecular Atlas Platform (https://commonfund.nih.gov/HuBMAP/index), and Cancer Moonshot (https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative)

Pragmatic Clinical Trials

Pragmatic clinical trials determine the effectiveness of interventions used to treat patients under real-life

conditions (10). Pragmatic trials are typically larger, simpler, more efficient, and less costly than randomized, controlled clinical trials and often involve cluster designs where sites—rather than patients—are randomized. Follow-up data are often collected during routine clinical care using EHRs. Pragmatic trials provide several potential benefits to CKD research, including enhanced external validity, ability to enroll traditionally hard to reach and disadvantaged populations who bear a disproportionate burden of CKD, lower barriers for translating findings to clinical practice, and reduced cost (11).

The NIDDK, along with the NIH Common Fund, is currently supporting two pragmatic clinical trials through the NIH Healthcare Systems Research Collaboratory including the Time to Reduce Mortality in ESRD (TiME) Trial and the Improving Chronic Disease Management with Pieces (ICD-Pieces) Trial. A new funding opportunity from the NIH Collaboratory seeks additional demonstration projects that include an efficient, large-scale pragmatic clinical trial conducted across two or more health care systems: https://grants.nih.gov/grants/guide/rfa-files/RFA-RM-16-019.html, and the NIDDK recently released a request for application focused on pragmatic research to improve kidney disease prevention and care: https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-17-008.html.

The TiME Trial aims to determine whether a minimum hemodialysis session duration of 4.25 hours has benefits compared with usual care on mortality, hospitalizations, and health-related quality of life among patients starting treatment with thrice weekly maintenance hemodialysis (12). The TiME Trial has several unique features. The study uses a cluster randomized design, whereby dialysis clinics are randomized to usual versus 4.25 hours of hemodialysis (approximately 30 minutes extra time); thus, the study does not require study coordinators at any sites, because all new patients are recruited into the study (7000 subjects to date). The study uses an opt-out consent, streamlining the consent process. As a pragmatic trial, the usual care group can change its practice over the course of the study in accordance with usual clinical care, thereby providing a more realistic comparison group. Finally, follow-up is obtained from data already collected in the dialysis centers' proprietary EHRs. Dialysis-related pragmatic trials may benefit from the consolidated nature of the United States dialysis industry, where relatively few large organizations provide the vast majority of dialysis care.

Outside of ESRD, greater challenges may exist in developing pragmatic trials given the more diffuse nature of care. Challenges and opportunities for conducting pragmatic trials in earlier stages of CKD may be identified through the ICD-Pieces Trial. The ICD-Pieces Trial aims to determine whether guideline care facilitated by an enhanced EHR ("Pieces") for people with diabetes, hypertension, and CKD improves rates of unplanned hospitalization, disease-specific hospitalization, 30-day readmission, or emergency room visits compared with usual care (13). This study also uses cluster randomization and an opt-out consent process. The study is more complicated than the TiME Trial, because the EHR system helps to identify patients (computable phenotype; see below; 11,000 subjects) to be included in the study, uses decision tools to suggest therapy, and identifies follow-up visits and hospitalizations. The ICD-Pieces Trial is ongoing in four different health systems that use four different EHRs. Pragmatic trials have significant potential to examine approaches to prevention and treatment of AKI as well.

The efficient design of pragmatic studies may enable limited research funding to address a larger number of clinical questions, helping the kidney community overcome some of the barriers to nephrology clinical trials. However, several challenges persist in the application of pragmatic clinical trials, including limited interoperability of data across sites, missing data from individuals who receive care at outside institutions, ethical challenges surrounding informed consent, limited expertise and training, uneven collection of follow-up information, difficulty in maintaining separation between groups, and lack of common data elements for research and care. Pragmatic trials are not appropriate for investigation and approval of investigational agents by the Food and Drug Administration. However, they may provide a less costly method for developing evidence for implementation and potential targeting of new therapies and comparing existing therapies (11).

Health Information Technology

HIT has the potential to improve care by facilitating pragmatic clinical trials in nephrology, supporting population health management activities, providing critical data for observational studies, identifying patients for research, and enabling national surveillance systems. CKD may represent an ideal target for HIT-supported care and research, because CKD is defined primarily by objective laboratory data that can be integrated into EHRs with relative ease, and optimal CKD care requires interdisciplinary and cross-setting collaboration that could be facilitated by interoperable HIT systems (14).

To advance efforts in the use of HIT in kidney disease research and care, the NIDDK's National Kidney Disease Education Program is working with volunteer patients, nephrologists, researchers, informaticists, health economists, federal agencies, and other CKD care providers to develop practical resources that will facilitate use of HIT systems to improve CKD research and care. Industry representatives—including EHR vendors and insurance providers—have also been engaged in these efforts. Resources include a computable phenotype to identify patients with CKD, an electronic care plan (e-care plan) to support communication across patient care transitions (*e.g.*, dialysis clinic to hospital to patient-centered home), and a business case to justify investment in CKD health management infrastructure. These efforts were the subject of a recent NIDDK workshop, which provided detailed updates on the efforts and solicited feedback from key stakeholders about obstacles and opportunities (15).

The computable CKD phenotype effort will provide the necessary EHR codes and logic to identify a candidate group of patients likely to have CKD (and their comorbid conditions) to facilitate population health management, surveillance, and research activities. Development of the CKD phenotype is challenged by incomplete race data, which limits ability to estimate the GFR; inconsistencies in GFR reporting (different estimating equations over time and across sites), and the low prevalence of urine albumin-to-creatinine

ratio (UACR) testing. Studies are being conducted to assess whether the more commonly collected urine albumin dipstick can substitute for UACR. The phenotype is being validated across multiple health systems using chart reviews.

The e-care plan aims to facilitate transfer of individual patient data—including clinical parameters (*e.g.*, BP), mental health status, quality of life metrics, laboratory values (*e.g.*, serum creatinine/eGFR and UACR), and personal health goals—across patients, providers, health care settings, and regional health information exchanges by automatically pulling and integrating data from the EHR. A draft CKD care plan dataset was recently published on the NIDDK website for public comment (16). Data displays will balance brevity and comprehensiveness, and they will be adapted to fit the needs of different users (*e.g.*, patients, nephrologists, and primary care providers). The e-care plan aims to be person- rather than disease-centric, thus enabling individuals with multiple chronic conditions to have a single e-care plan rather than numerous uncoordinated plans. The e-care plan will be validated in a variety of care settings.

To help health systems and payers evaluate investments in CKD population health management programs, an evidence-based business case model is being developed that will estimate the costs of CKD progression as well as savings from interventions to slow progression and improve ESRD transitions. The model can be individualized to a specific health system or plan on the basis of specific CKD populations and payment models, even in the face of shifting financial incentives (*i.e.*, transitions from traditional to alternative payment models).

Conclusion

We anticipate that these HIT tools will be useful for pragmatic clinical trials, surveillance, population health, and patient management efforts that aim to improve kidney health. Despite the significant burden of AKI and CKD, we still lack effective therapies. To address these challenges, the NIDDK is encouraging novel approaches to nephrology research on the basis of the complementary perspectives of precision medicine, pragmatic trials, and population management (Figure 1), enabling identification, efficient testing, and application of new treatments (including pathways of care) to improve AKI and CKD outcomes. Specifically, these NIDDK efforts aim to identify critical cells, pathways, and targets for novel therapies across subgroups of AKI and CKD; test simple interventions in large pragmatic trials; and simultaneously develop resources that will support population-level interventions in CKD. All three areas will be aided by advances in HIT.

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Disclosures

None.

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