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## Rationale and design of the Kidney Precision Medicine Project.

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### Abstract

Chronic kidney disease (CKD) and acute kidney injury (AKI) are common, heterogeneous, and morbid diseases. Mechanistic characterization of CKD and AKI in patients may facilitate a precision medicine approach to prevention, diagnosis, and treatment. The Kidney Precision Medicine Project aims to ethically and safely obtain kidney biopsies from participants with CKD or AKI, create a reference kidney atlas, and characterize disease subgroups to stratify patients based on molecular features of disease, clinical characteristics, and associated outcomes. An additional aim is to identify critical cells, pathways, and targets for novel therapies and preventive strategies. This project is a multicenter prospective cohort study of adults with CKD or AKI who undergo a protocol kidney biopsy for research purposes. This investigation focuses on kidney diseases that are most prevalent and therefore substantially burden the public health, including CKD attributed to diabetes or hypertension and AKI attributed to ischemic and toxic injuries. Reference kidney tissues (for example, living kidney donor biopsies) will also be evaluated. Traditional and digital pathology will be combined with transcriptomic, proteomic, and metabolomics analysis of the kidney tissue as well as deep clinical phenotyping for supervised and unsupervised subgroup analysis and systems biology analysis. Participants will be followed prospectively for ten years to ascertain clinical outcomes. Cell types, locations, and functions will be characterized in health and disease in an open, searchable, online kidney tissue atlas. All data from the Kidney Precision Medicine Project will be made readily available for broad use by scientists, clinicians, and patients.

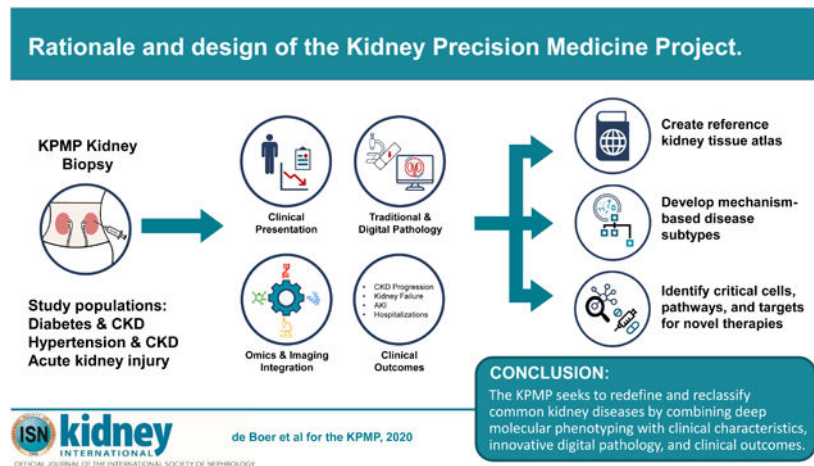
### Graphical Abstract

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#### Disclosures

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## Keywords

chronic kidney disease; acute kidney injury; precision medicine; diabetes; hypertension

## Introduction

Chronic kidney disease (CKD) and acute kidney injury (AKI) are common, morbid diseases that result in significant burdens on patients, their families, and society. Among adults in the United States, the prevalence of CKD is as high as 14% (37 million people), with a prevalence of 25% or more for those with diabetes or hypertension.<sup>1,2</sup> AKI affects 10–15% of all hospitalized patients, with particularly high incidence rates among patients with sepsis and other conditions requiring admission to intensive care units.<sup>3,4</sup> CKD and AKI can both progress to kidney failure, and people with CKD and AKI experience high rates of cardiovascular events, infections, and mortality.<sup>4–7</sup> Globally, as a result, CKD and AKI are associated with tremendous morbidity.<sup>6</sup>

Remarkable advances have been made in our understanding of CKD and AKI pathophysiology. For example, numerous pathways have been implicated in the development of CKD due to diabetes, *APOLI* genotype was identified as a strong determinant of CKD in African Americans, and molecular pathways mediating ischemic kidney damage have been delineated.<sup>8–11</sup>

Nonetheless, few therapies have been proven to prevent CKD or its progression, and there is currently no proven management approach to prevent or ameliorate the course of AKI.<sup>6</sup> Animal models, while critical to evaluating mechanisms of injury, often do not faithfully recapitulate human disease, and interventions effective in these models do not necessarily extend to humans.<sup>12,13</sup> In humans, individual disease states and affected pathways are rarely known, in part because kidney tissue is not routinely obtained for analysis in clinical care. Together, these hurdles make it difficult to prioritize targets for drug development, implement effective clinical trials of new therapeutic agents, and translate knowledge to human kidney health.<sup>14–17</sup>

## Rationale for kidney precision medicine

CKD and AKI are diagnosed and classified crudely, based predominantly on estimated glomerular filtration rate (eGFR) and urine protein excretion for CKD and short-term changes in serum creatinine and urine output for AKI.<sup>4,18,19</sup> While useful for staging and epidemiology, these clinical evaluations lack granular insight into the underlying molecular mechanisms or structural injury that contributes to heterogeneity of CKD and AKI, including differences that may contribute to known racial and ethnic disparities in kidney disease risk.

The lack of a mechanistic basis in the current kidney disease taxonomy has significant consequences for identification of novel disease mechanisms, development of therapeutic targets, and routine clinical care. For example, important molecular mechanisms of human kidney disease can be difficult to discover when present in a relatively small subset of patients. Moreover, if a therapy effectively targets a relevant molecular mechanism, the benefit of that treatment in a clinical trial or clinical practice may be diluted among patients with different disease pathways not targeted by the intervention.<sup>20</sup> This conundrum provides rationale for development of new molecular mechanism-based disease definitions, enabling therapy targeted to the specific molecular processes responsible for kidney injury and its progression in a patient or a subgroup of patients with similar molecular disease phenotype.

Precision medicine refers to prevention and treatment strategies that take individual variability into account.<sup>21</sup> When former President Barack Obama announced the Precision Medicine Initiative in 2015, he referred to precision medicine as “delivering the right treatments, at the right time, every time to the right person.”<sup>22</sup> This approach requires detailed understanding of the molecular basis of health and disease. Advances in technology now offer an unprecedented opportunity to interrogate critical cells and pathways using deep molecular phenotyping, including analysis of DNA, RNA, proteins, and metabolites.

In 2016, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) convened a workshop to explore whether and how precision medicine could be used to improve the diagnosis and management of CKD and AKI. In the workshop, patients, clinicians, academic researchers, bioethicists, and industry representatives discussed opportunities, resources, and barriers for obtaining and interrogating human kidney tissues to advance kidney precision medicine. In the same year, the NIDDK released a series of Requests for Applications for the Kidney Precision Medicine Project (KPMP), which commenced in the fall of 2017.

## Overall goals

The KPMP seeks to redefine CKD and AKI by integrating deep molecular phenotypes with clinical characteristics, digital pathology, and clinical outcomes. Specifically, the overall goals of the KPMP are to (1) ethically and safely obtain kidney biopsies from participants with CKD or AKI, (2) create a reference kidney atlas, (3) characterize disease subgroups to stratify patients based on molecular mechanisms of disease and associated outcomes, and (4) identify critical cells, pathways, and targets for novel therapies. Ultimately, this approach

may allow diagnosis of key disease pathways on the individual level, identify promising targets for intervention, facilitate evaluation of new interventions through targeted clinical trials, help validate biomarkers for diagnosis and treatment, and promote the application of precision medicine to patients with CKD and AKI.

Achieving the goals of KPMP requires kidney tissue from humans with common forms of CKD and AKI. Patients who have CKD attributed to diabetes or hypertension or AKI attributed to ischemic or toxic injury rarely undergo kidney biopsy, or do so only when their clinical presentation is unusual. As a result, studies of clinically indicated kidney biopsies may over-represent unusual causes of disease or fail to identify the most common disease mechanisms. Effectively evaluating the heterogeneity of CKD and AKI presentations therefore requires enrolling a new cohort of people willing to volunteer to donate kidney tissue who otherwise would likely not undergo kidney biopsies as part of usual clinical care. Accordingly, the first goal of the KPMP is to ethically and safely obtain tissue from such study participants.

A key deliverable of the KPMP is a kidney atlas that charts cell types and functions in health and disease. The atlas will be an interactive tool that integrates molecular data with clinical presentation, imaging data, and clinical outcomes. A standardized and machine-interpretable kidney nomenclature (ontology) will be developed to support data sharing and integration and construction of new tools for data analysis. Molecular data generated by new assays that are developed, optimized, and implemented by KPMP investigators will be integrated with digital pathology and clinical phenotypes using a systems biology approach to generate new disease subtypes and targets for therapy (Figure 1).<sup>23,24</sup>

## Study organization

The KPMP is broadly inclusive of patients, nephrologists, radiologists, pathologists, primary care providers, intensivists, research coordinators, project managers, ethicists, informaticians, research scientists from different disciplines, and others invested in improving health for people with kidney disease. Recruitment sites and tissue interrogation sites are linked and organized by a central hub that contains an administrative core, data coordinating center, and data visualization center (<https://kpmp.org/consortium-members/>). The study is overseen by three independent bodies, including a Data Safety Monitoring Board, central Institutional Review Board (Washington University, St. Louis), and an NIDDK-convened External Expert Panel.

## Patients drive the KPMP

A defining feature of the KPMP has been the establishment of an equitable partnership with patients who have kidney disease. Patients have been integrally involved in the KPMP throughout the full duration and at all levels of the design process.<sup>25</sup> Patients with kidney disease were included in the 2016 NIDDK workshop on kidney precision medicine to guide an ethical and feasible approach to research-focused kidney biopsies. Patients from all KPMP sites also were invited to attend the first KPMP Steering Committee meeting, and initial patients subsequently worked with investigators to recruit other representatives to

exemplify the diversity of KPMP target populations. As the research protocol was developed, patients informed the study on best practices for engagement and participated in drafting the KPMP informed consent form (Table 1). Protocol development was influenced by patient perspectives on merits and burdens of study procedures. Patients advocated strongly for enrolling a diverse and representative study population, engaging enrolled study participants as research partners, and returning study results in a fully transparent and timely manner. Patients are represented in every KPMP Committee, including the Steering Committee, where they actively participate and lead as peers. These contributions have helped to make the research protocol appropriate for potential participants and ensure that the ultimate products of the KPMP will be optimally oriented toward patient values and preferences.

## Study design

The KPMP is a multicenter prospective cohort study of people with CKD or AKI who undergo a protocol kidney biopsy at study entry. The full study protocol and detailed manuals of procedures are freely available at [kpmp.org/researcher-resources](http://kpmp.org/researcher-resources). The KPMP focuses on kidney diseases that are most prevalent and therefore substantially burden the public health. For CKD, these are presentations attributed clinically to diabetes, hypertension, or both. For AKI, these are presentations attributed to sepsis, ischemic, or toxic injury. Some patients who have been offered a kidney biopsy for clinical indication may elect to participate in the KPMP research protocol instead of a standard clinical biopsy and provide additional tissue for research purposes. However, it is anticipated that most participants who volunteer to participate in the KPMP would not have otherwise undergone a kidney biopsy.

Enrollment strategies include recruiting from clinical care encounters (e.g. clinic, emergency room, or hospital stay), electronic health information resources (e.g. existing registries and electronic health records), and community networks and outreach. Site-specific approaches optimize recruitment strategies according to their local health care settings and target study population(s). The KPMP data coordinating center monitors demographic and disease characteristics of enrolled participants, compares these characteristics to those of the underlying target populations, and feeds these data back to recruitment sites to prioritize recruiting efforts as needed. To this end, community advisory boards at each recruiting site facilitate engagement of local patient populations and advocacy groups.

Informed consent is viewed as a longitudinal process that includes patients, patients' trusted advisors, clinical providers, and trained KPMP staff and spans days (for AKI) to weeks (for CKD), depending on clinical presentation. The process includes providing access to extensive educational materials in addition to written informed consent and is designed to ensure that participants fully understand the scope of the study and its possible risks.

Inclusion criteria were designed to enroll a population that is broadly representative of these clinical conditions, including early clinical presentations (Table 2). For CKD, participants are limited to those with estimated GFR  $\geq 30$  mL/min/1.73m<sup>2</sup> to increase the likelihood of identifying abnormalities that initiate and propagate relatively early disease, providing the

greatest opportunity for intervention. For AKI, eligibility criteria are designed to select participants with minimal underlying CKD, which could confound identification of mechanisms specific to AKI. Patients undergoing percutaneous kidney biopsy are further required to have elevated serum creatinine that is either sustained or accompanied by evidence of parenchymal injury,<sup>26</sup> while patients undergoing laparotomy kidney biopsy (usually in the acute emergency department setting) have a broader set of inclusion criterion designed to include early AKI or high risk of imminent AKI. Special populations are also enrolled. For CKD, people with longstanding type 1 diabetes without evidence of CKD (diabetic kidney disease “resistors”) are evaluated to search for pathways associated with protection from CKD. For AKI, people undergoing exploratory laparotomy who have evidence of early kidney dysfunction or are at high risk of developing AKI postoperatively undergo open biopsy at the time of surgery.

Exclusion criteria were designed primarily to protect participant safety. These exclusion criteria were based on published literature and clinical experience and focus largely on reducing the risk of bleeding (Table 2). Additional criteria exclude people with kidney diseases already under investigation by other large cohort studies (e.g. people with glomerular disorders and polycystic kidney disease) and those with unusual clinical scenarios for which unique abnormalities may underlie disease but for which an insufficient number of participants would be recruited to draw meaningful conclusions regarding pathogenesis.

Participants are followed for 10 years from the time of kidney biopsy through a combination of annual in-person study visits and interval remote visits to document clinically important events, including loss of kidney function, kidney failure, interval hospitalizations, cardiovascular events, and mortality (Table 3). Participants enrolled for AKI have an additional in-person study visit three months after kidney biopsy to establish a clinical post-AKI baseline. Surveillance of electronic health records and national databases such as the United States Renal Data System and National Death Index will supplement these approaches, especially for longer-term follow-up. An extensive biorepository of serum, plasma, circulating leukocytes preserved for DNA and RNA analysis, timed and spot urine samples, and stool samples is collected at the time of kidney biopsy and at in-person study visits. Biorepository samples are stored for future projects aiming to further understand disease pathogenesis and to develop and validate biomarkers reflecting disease heterogeneity. There are currently no plans to repeat kidney biopsies in the KPMP, but this may be considered in the future.

## Kidney biopsy

The centerpiece of the KPMP research protocol is the kidney biopsy, which is used to generate a traditional histology-based diagnosis as well as novel molecular phenotypes. The ethical conduct of kidney biopsies is an absolute requirement of the KPMP and has been a focus of discussion throughout planning and development. In general, during the planning process, physicians and scientists thought that while kidney biopsies in the planned populations may occasionally yield useful information for diagnosis or prognosis, most individual participants were unlikely to directly benefit from their biopsy. Patient

representatives expressed a broader concept of potential benefits, valuing knowledge of their disease process even if it does not alter medical therapy as well as the opportunity to contribute altruistically to their communities through new discovery. Regardless of potential benefit, kidney biopsies come with inherent risk, including risk of serious complications such as need for blood transfusions, hospitalization, kidney loss, and death.<sup>27,28</sup> The KPMP performed a systematic review of kidney biopsy complications to quantify these risks for potential participants and their providers.<sup>29</sup> Moreover, the KPMP aims to minimize these risks and to disclose them through a comprehensive informed consent process that is transparent and respects individual autonomy. In addition, the KPMP will prospectively collect data on both benefits (to participants and clinical providers) and risks in order to refine informed consent over time and better quantify biopsy outcomes for the broader community.

The guiding principle in performing the kidney biopsy is optimizing patient safety. Safety has been emphasized throughout the KPMP by developing a safety culture, specific safety-oriented protocols, and procedures to monitor and adapt the protocol as needed (Table 4). Many elements of the KPMP kidney biopsy protocol are standardized, while some elements are flexible in order to match procedural expertise at individual KPMP recruiting sites. All percutaneous kidney biopsies are performed by experienced, KPMP-certified operators using 16-gauge needles and real-time imaging guidance. KPMP-certified operators must demonstrate that they have completed 35 biopsies over the past two years with a major complication rate less than 10%, and 85% of the biopsies must have been adequate for diagnosis. A maximum of five passes is allowed to attain a goal of three biopsy cores. Operators may be nephrologists or radiologists. For participants undergoing open laparotomy, surgeons will perform biopsies using 16-gauge needles with direct visualization of the kidney. Checklists are used to ensure that all biopsies are only performed under appropriate conditions, including ensuring that vital signs and laboratory parameters are within safety limits. Adverse events are prospectively ascertained and monitored by an internal KPMP Safety and Adjudication Committee as well as an external Data Safety Monitoring Board and single Institutional Review Board.

## Kidney tissue processing and analysis

One of the major challenges for KPMP is maximizing the use of limited kidney tissue available for both traditional pathologic diagnosis and multiple molecular evaluations. To this end, pathologists, researchers and nephrologists spanning all KPMP sites undertook a collaborative effort to design a consensus protocol to process kidney biopsy tissue (Figure 2). The protocol was informed by a series of pilot studies and incorporates rigorous quality control at each step. Kidney biopsy tissue is triaged by a pathologist in the biopsy suite, and the most optimal biopsy core is selected for traditional histologic evaluation using algorithms available at [kpmp.org/researcher-resources/](http://kpmp.org/researcher-resources/). This diagnostic core is processed locally at the recruitment site for light microscopy, immunofluorescence, and electron microscopy, and a clinical pathology report based on this core is generated and returned to the participant and clinical care team. Any remaining tissue from this core is then sent to a central biorepository for research use to be made available to tissue interrogation sites for multiplexed imaging studies. Two other cores are processed expeditiously for deep



molecular phenotyping and frozen for transportation to a central biorepository at the University of Michigan.

All sites formally demonstrate readiness for kidney biopsy and tissue preservation, including certification to maintain proficiency. All reagents and supplies are shipped as standardized, pre-labeled kits from the central biorepository. Slides generated at recruitment sites are scanned centrally for digital viewing and analysis, and tissue earmarked for research studies is sent to the central biorepository and then distributed to tissue interrogation sites.

Technologies applied to kidney tissue span imaging, transcriptomics, proteomics, and spatial metabolomics (Figure 2). These technologies are expected to evolve over time, and additional technologies will be added. Quality control is emphasized throughout processing and analysis, including close attention to preanalytic conditions such as tissue handling and storage, assay reliability, comparisons across technologies, and shift and drift in assays over time.

## Reference kidney tissues

Reference kidney tissues interrogated using KPMP technologies is needed to populate a kidney atlas in health and provide context for kidney diseases. Nephrectomy and deceased donor kidney tissues have been used in KPMP pilot studies for optimizing protocol and developing an initial version of a reference atlas.<sup>30,31</sup> However, these procurement methods are subject to artifacts including ischemia that may substantially change gene expression and protein and metabolite content in tissues. Therefore, the KPMP is developing partnerships and protocols to obtain better sources of healthy reference kidney tissues from living kidney donors as well as people without clinically evident kidney disease who undergo invasive kidney procedures, for example percutaneous nephrolithotomy for isolated nephrolithiasis. These reference tissues will be processed and interrogated using KPMP protocols and included in the KPMP tissue atlas.

## Study outcomes

The KPMP ascertains a range of outcomes consistent with its overarching goals (Table 3). These start with evaluation of the risks and benefits of the kidney biopsy itself because experience with kidney biopsies in the target populations is limited. Kidney biopsy outcomes are ascertained through prospective questionnaires administered to participants, clinicians, and study investigators as well as careful surveillance of adverse events. In addition, development of an open-source kidney tissue atlas and molecular-based disease subtypes are considered explicit deliverables of the KPMP.

The KPMP also follows participants for more traditional health outcomes, including progression of CKD, AKI outcomes (for AKI participants), and other health events, as defined in Table 4. Data for these outcomes are obtained through surveillance of electronic health records, the USRDS registry, and the national death index in addition to in-person and remote study visits. Comprehensive efforts are made to retain participants for clinical follow-up, with KPMP-wide patient representatives and recruitment site community

advisory boards playing key roles in developing and implementing comprehensive engagement and retention plans.

## Sample size

Currently, there are insufficient data to calculate reliable power estimates or sample sizes needed to achieve the goals of the KPMP. Therefore, the KPMP plans to enroll 200 participants, a number judged to be safe and feasible given the complexity of the clinical protocol, during its first phase (through mid-2022). Biopsies from these participants will be used to evaluate safety, generate initial versions of the reference kidney atlas (along with reference tissues), and identify initial mechanism-based disease subgroups. Moreover, biopsies from these participants will be used to understand variability within kidney cells of similar lineage, between different cell types, across tissue samples from the same individual, between individuals with the same kidney disease subtype, between disease subtypes, and in the associations of disease subtypes with clinical outcomes for the populations studied and technologies employed by the KPMP. These data will guide sample size calculations for future work.

## Kidney atlas

A novel kidney tissue atlas characterizing cell types, locations, and functions in health and disease will be a central product of KPMP efforts. The atlas will integrate digital pathology, transcriptomics, proteomics, and metabolomics with clinical data, present a set of curated multiscale two- and three-dimensional maps of kidney tissue, and offer analysis and visualization tools for users (Figure 3). Ontologies will be developed to semantically integrate these components and link to complementary data resources. The atlas will contain data on clinical disease-free reference tissue to help understand kidney structure and function in new detail as well as datasets containing results from enrolled KPMP participants with CKD or AKI, defined using kidney biopsy and detailed clinical characteristics. State-of-the-art algorithms will be employed to view digital histology and search structural features in real time. The kidney atlas will be accessible via [kmp.org](http://kmp.org) and will provide access to all processed and raw data (after cleaning) generated by the KPMP. Portals of entry will be established for common anticipated types of users, including clinicians, pathologists, scientists, and patients.

## Open source platform

The KPMP was conceived as an open-source platform to expeditiously share novel data with patients, clinicians, and scientists investigating kidney health and disease or broadly investigating human biology. As such, KPMP investigators are committed to making data publicly available as soon as it passes internal quality controls, beginning in spring, 2020, while protecting participant privacy. To that end, KPMP data are available for download, accessible through the KPMP website, [kmp.org](http://kmp.org). Data that carry risk of individual identification require a data use agreement for access that stipulates that no attempts will be made to re-identify participants. KPMP data sharing policies, protocols, and manuals of procedures are also freely available from the study website.

To maximize integration, dissemination, and collaboration, the KPMP developed and utilizes ontologies to classify all collected data. Ontologies are systems that classify symptoms, signs, conditions, and their relationships. Using common ontologies can facilitate combining of data across studies.<sup>32</sup> The KPMP has taken a leadership role in developing and refining kidney disease ontologies. For example, the KPMP hosted an international kidney-focused ontology meeting in Seattle, WA during the summer of 2018.

## Partnerships

The KPMP also encourages new partnerships, including partnerships with academic investigators, healthcare systems, and industry. Such partnerships are actively solicited through request for funding opportunity announcements (<https://kpmp.org/opportunity-pool/>) and can also be initiated through ancillary study applications to access KPMP participants or samples. Competitive travel grants are offered to present research posters at KPMP Steering Committee meetings, for which young investigators are particularly encouraged to apply. Additionally, KPMP is designed to integrate and synergize with other atlas efforts, such as the HuBMAP (<https://commonfund.nih.gov/hubmap>), GUDMAP (<https://gudmap.org>), and Human Cell Atlas (<https://www.humancellatlas.org/>). KPMP external collaboration and ancillary studies policies are available at [kpmp.org](https://kpmp.org).

## Challenges

The initial challenges of the KPMP include developing a novel protocol that is safe, ethical, rigorous, feasible, and acceptable to participants. This report highlights basic aspects of this protocol, and further reports will provide additional details regarding patient engagement, tissue processing and pathology, molecular interrogation, and data visualization. Numerous additional challenges remain. Quality control must be maintained throughout the collection and analysis of tissue and data. Finite amounts of kidney tissue must be divided among multiple informative technologies, including promising new technologies that emerge during the study. Sufficient numbers of participants must be enrolled to address all sources of variability, the scope of which is not yet fully defined. Kidney tissue status at a single snapshot in time must be related to diseases that evolve over time and to long-term clinical outcomes. Rich clinical phenotype data on kidney function above and beyond eGFR and albuminuria may be required to create new disease classifications. Data will be made available for public use in a manner that promotes integration with complementary resources, relying on common metadata and ontologies that require further development.

## Vision for the future

The KPMP is a new initiative that seeks to redefine and reclassify common kidney diseases by combining deep molecular phenotyping with clinical characteristics, innovative digital pathology, and relevant clinical outcomes. Data generated by the KPMP will improve the knowledge base for a wide range of research within and beyond nephrology, organized in a kidney tissue atlas and disseminated through an open source platform. Near-term goals of this work include developing new mechanism-based subtypes of kidney diseases that are common but heterogenous and to help identify and prioritize targets for intervention. Such

advances would support clinical trials, enabling platform trials and other innovative methods of testing new diagnostics and treatments.<sup>33</sup>

In the process, the KPMP aims to redefine the diagnosis and understanding of both CKD and AKI. It will comprehensively assess the role for kidney biopsy in the diagnosis and treatment of these kidney diseases. New methods of molecular analysis, digital pathology, imaging techniques, and bioinformatics are expected to become standard for diagnosis of kidney disease, and new protocols may be developed to reduce risks of kidney biopsy, facilitate proper selection of patients, and identify those who may benefit the most from the procedure. These contributions should improve the benefit-risk profile of kidney biopsy and increase its use in clinical practice. Patients themselves may be empowered to request the option of a kidney biopsy from their providers. In addition, biomarkers may be developed to accurately identify kidney pathology. Kidney precision medicine offers myriad opportunities to improve science and health, and the KPMP along with similar research initiatives will stimulate interest in nephrology to entice a new generation to innovate upon the KPMP foundation.

Ultimately, the goal of the KPMP is to improve the health of patients with and at-risk for kidney diseases by enabling individual-level diagnosis and treatment. To achieve this goal, KPMP investigators intend to advance kidney precision health by classifying disease subgroups to stratify patients based on molecular mechanisms of disease and identifying critical cells and pathways as targets for novel clinical strategies. Data will be visualized and disseminated through a new kidney tissue atlas and shared openly to catalyze new diagnostic and therapeutic approaches for CKD and AKI.

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## Appendix:

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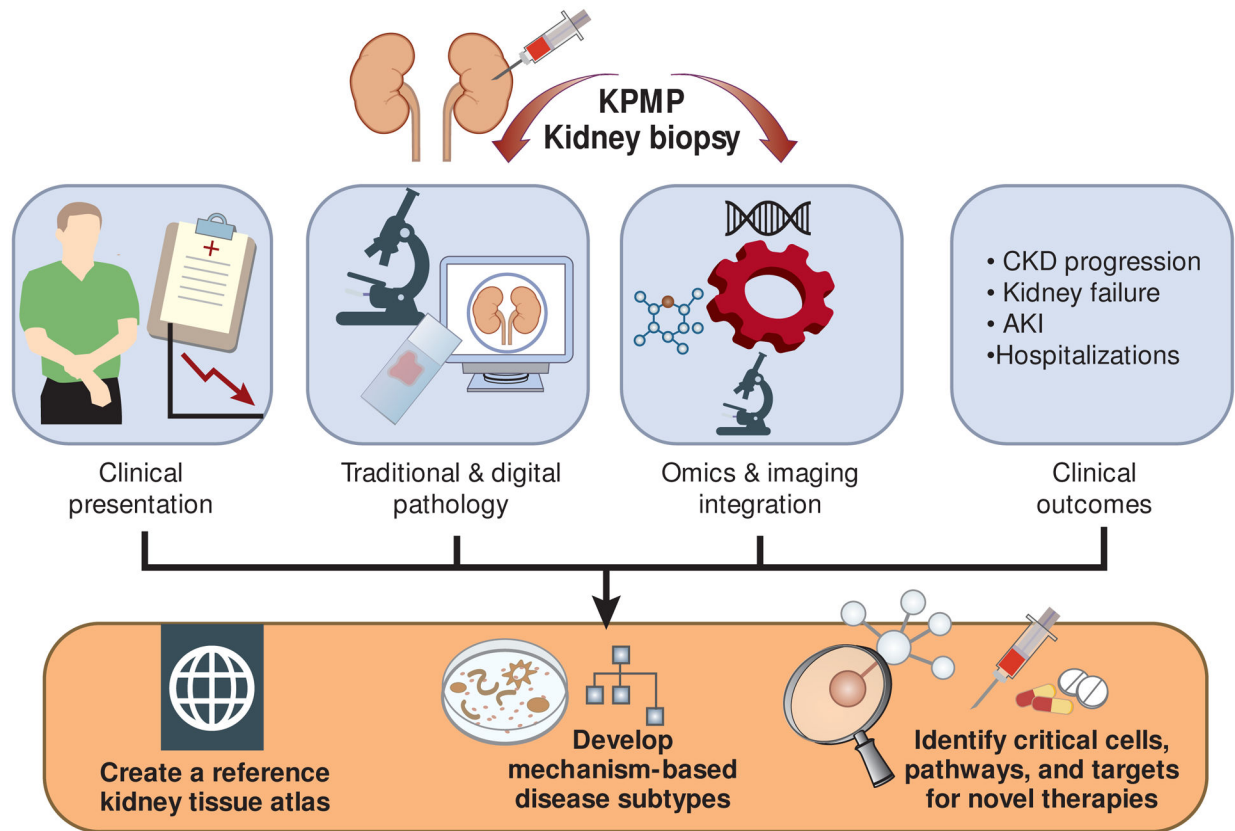
*Yale University, New Haven, CT:* Randy Luciano, Dennis Moledina, Ugwuowo Ugochukwu, Francis Perry Wilson, Sandy Alfano

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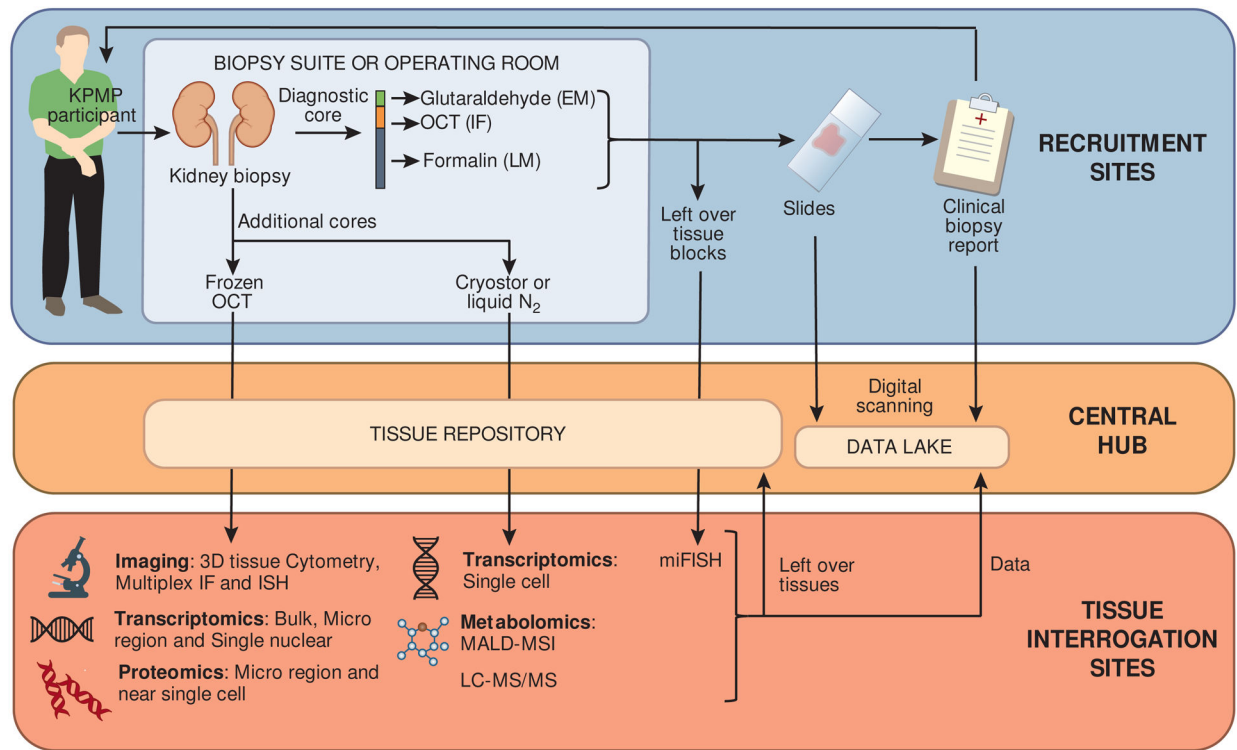
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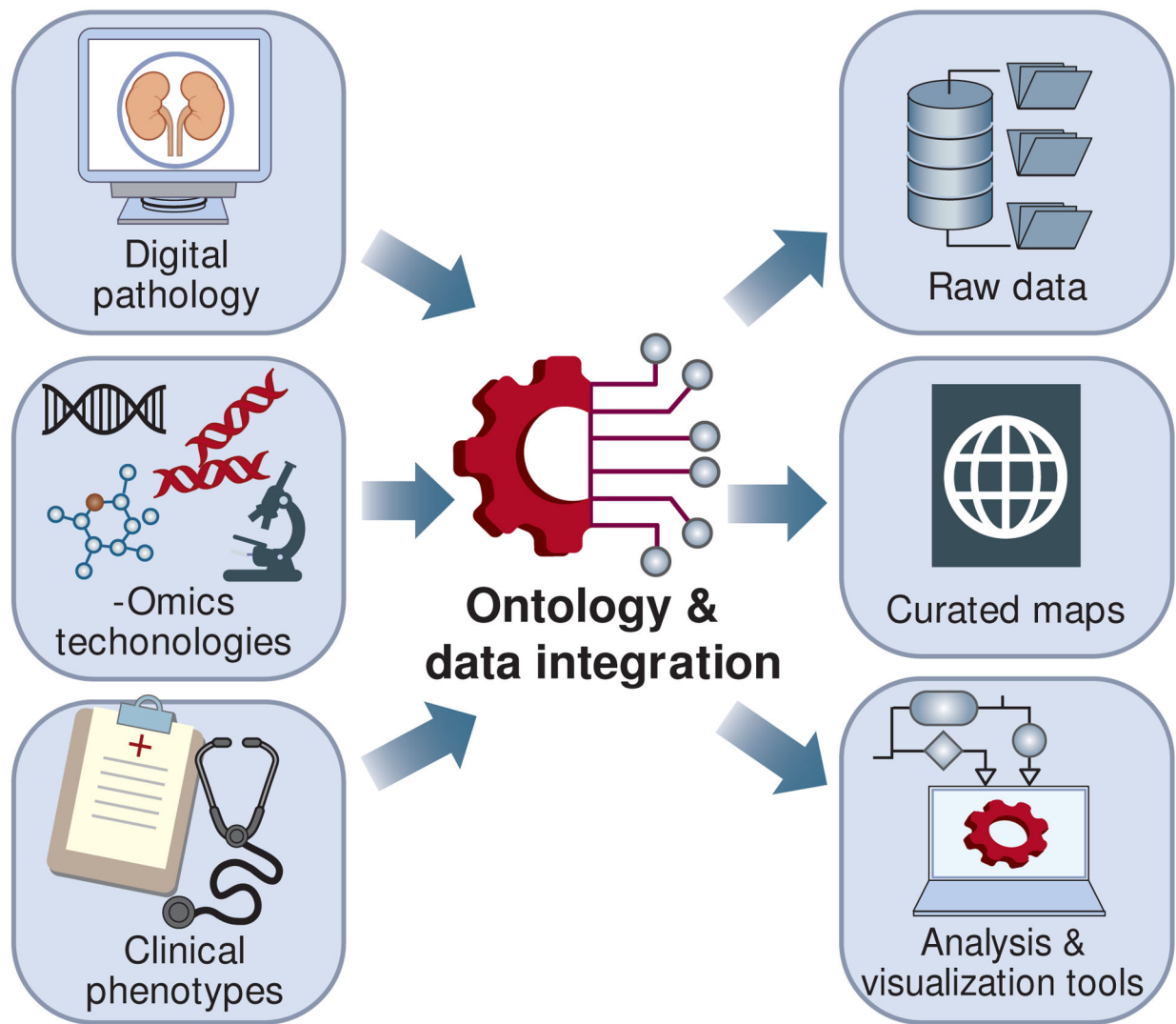


**Figure 1.** In the Kidney Precision Medicine Project, kidney biopsy tissues will be interrogated with multiple levels of omics technologies, and results will be integrated with digital pathology, clinical characteristics and outcomes to create a reference kidney atlas, develop mechanism-based disease subtypes, and identify critical cells, pathways, and targets for novel therapies. CKD = chronic kidney disease AKI = acute kidney injury.



**Figure 2. Kidney Precision Medicine Project tissue triage and interrogation schematic.**

Kidney biopsy tissues will be processed for local clinical pathology review and remote research interrogation according to a detailed, standardized protocol. KPMP = Kidney Precision Medicine Project; EM = electron microscopy; IF = immunofluorescence; LM = light microscopy; OCT = optimal cutting temperature compound; N<sub>2</sub> = nitrogen; ISH = in-situ hybridization; MALD-MSI = matrix-assisted laser desorption ionization mass spectrometry imaging; LC-MS/MS = liquid chromatography-mass spectrometry.



**Figure 3. Vision for a kidney tissue atlas.**

The Kidney Precision Medicine Project will integrate digital pathology, omics data, and clinical data using common ontologies, making raw data, curated maps, and analysis and visualization tools widely available to clinical and research communities.

**Table 1.**

Examples of patient influence on design of the Kidney Precision Medicine Project

<b>Design challenge</b>	<b>Patient input</b>
Protocol: balance of detail versus participant burden	Willing participants will accept additional procedures
Recruitment	Emphasize underrepresented populations, form Community Advisory Boards
Communications	Feature frequently asked questions and video testimonials
Informed consent process	Include all trusted advisors, including family members and personal physicians
Potential complications	Participants must not bear any direct financial costs
Return of results	Return all possible results, even if clinical implications are not clear
Data and tissue sharing	Make most extensive possible use of all donated tissue and data
Organization	Include patients in committees, provide explanations of terms and patient-level summaries

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Table 2.

## Selected eligibility criteria for the Kidney Precision Medicine Project

Inclusion criteria	AKI	Exclusion criteria
<b>CKD</b> One of the following: <ul style="list-style-type: none"> <li>• Diabetic kidney disease, defined as:               <ul style="list-style-type: none"> <li>- Type 1 or 2 diabetes, and</li> <li>- Evidence of persistent kidney damage:                   <ul style="list-style-type: none"> <li>◆ eGFR 30–59 mL/min/1.73m<sup>2</sup>,</li> <li>◆ eGFR 60 mL/min/1.73m<sup>2</sup> with urine ACR 30 mg/g, or</li> <li>◆ eGFR 60 mL/min/1.73m<sup>2</sup> with urine PCR 150 mg/g</li> </ul> </li> </ul> </li> <li>• Hypertension-associated kidney disease, defined as:               <ul style="list-style-type: none"> <li>- Diagnosis of hypertension, and</li> <li>- Evidence of persistent kidney damage:                   <ul style="list-style-type: none"> <li>◆ eGFR 30–59 mL/min/1.73m<sup>2</sup>,</li> <li>◆ eGFR 60 mL/min/1.73m<sup>2</sup> with urine ACR 30 mg/g, or</li> <li>◆ eGFR 60 mL/min/1.73m<sup>2</sup> with urine PCR 150 mg/g</li> </ul> </li> </ul> </li> <li>• Type 1 diabetes resilient to CKD, defined as:               <ul style="list-style-type: none"> <li>- Type 1 diabetes for 25 years</li> <li>- eGFR 60 mL/min/1.73m<sup>2</sup>, and</li> <li>- Urine ACR &lt;30 mg/g</li> </ul> </li> </ul>	For percutaneous kidney biopsy: <ul style="list-style-type: none"> <li>• Baseline eGFR &gt; 45 mL/min/1.73m<sup>2</sup></li> <li>• Elevated serum creatinine 1.5 times baseline</li> <li>• And at least ONE of the following:               <ul style="list-style-type: none"> <li>- A repeat serum creatinine within 48 hours of initial serum creatinine, showing a further increase of 0.3 mg/dL</li> <li>- Positive kidney injury urine biomarker:                   <ul style="list-style-type: none"> <li>◆ NGAL 150 ng/mL</li> <li>◆ KIM1 2.8 ng/mL</li> <li>◆ TIMP2 × IGFBP7 2.0</li> </ul> </li> <li>- Urine microscopy suggestive of ATN<sup>2,6</sup></li> </ul> </li> </ul> For open laparotomy kidney biopsy: <ul style="list-style-type: none"> <li>• Baseline eGFR &gt; 45 mL/min/1.73m<sup>2</sup> AND one of the following:</li> <li>• Elevated serum creatinine &gt;1.5 times baseline</li> <li>• Increase in serum creatinine 0.3 mg/dL within 48 hours, above admission serum creatinine, OR</li> <li>• High risk for acute kidney injury defined by TWO or more criteria:               <ul style="list-style-type: none"> <li>- Positive kidney injury urine biomarker:                   <ul style="list-style-type: none"> <li>◆ NGAL 150 ng/mL</li> <li>◆ KIM1 2.8 ng/mL</li> <li>◆ TIMP2 × IGFBP7 2.0</li> </ul> </li> <li>- Urine microscopy suggestive of ATN:</li> <li>- Oliguria (&lt;0.3mL/kg/hr) at least 1 hour after fluid resuscitation.</li> <li>- One or more exposure(s) known to cause acute kidney injury (major surgery not including</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Under 18 years of age</li> <li>• Body Mass Index (BMI) &gt; 40 kg/m<sup>2</sup></li> <li>• Allergy to iodinated contrast</li> <li>• Pregnancy</li> <li>• Malignancy - Receiving active chemotherapy or radiation to treat malignancy</li> <li>• Transplant recipient</li> <li>• Kidney depth &gt;13 cm</li> <li>• Kidney size &lt;8 cm</li> <li>• Solitary or single functioning kidney</li> <li>• Urinary tract obstruction or hydronephrosis</li> <li>• Multiple bilateral kidney cysts</li> <li>• Kidney infection, peri-renal infection, or cutaneous infection that overlies the kidney</li> <li>• Blood Urea Nitrogen &gt;80 mg/dL</li> <li>• International Normalized Ratios &gt;1.4</li> <li>• PTT &gt;35 seconds</li> <li>• Platelet count &lt;100,000/mL</li> <li>• Hemoglobin &lt;9 g/dL</li> <li>• Chronic anticoagulation</li> <li>• Inability to discontinue anti-platelet agents for 7 days prior to biopsy</li> <li>• BP that cannot be controlled to &lt;140/90 mmHg</li> <li>• Ventilator-dependent patient*</li> <li>• Hypotension or pressor*</li> </ul>

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Inclusion criteria		Exclusion criteria	
CKD	AKI	index laparotomy, sepsis, nephrotoxic drugs, etc.)	

\* Does not apply to laparotomy biopsies

**Table 3.**

## Outcomes assessed by the Kidney Precision Medicine Project

Outcome	Metrics
Biopsy-related outcomes	<ul style="list-style-type: none"> <li>• Incidence of biopsy-related complications</li> <li>• Clinical utility of biopsy               <ul style="list-style-type: none"> <li>– Change in management based on biopsy findings</li> <li>– New (unsuspected) or confirmed (suspected) diagnoses</li> </ul> </li> <li>• Patient-reported biopsy outcomes               <ul style="list-style-type: none"> <li>– Participant satisfaction with the biopsy procedure</li> <li>– Participant perception of kidney biopsy impact on disease knowledge and management</li> </ul> </li> </ul>
Kidney tissue atlas	<ul style="list-style-type: none"> <li>• Development and implementation of a set of interactive data and maps used to classify and locate different cell types and interstitial components</li> </ul>
Molecular kidney disease subtypes	<ul style="list-style-type: none"> <li>• Mechanism-based endophenotypes to identify and understand healthy and disease pathways that are activated in particular cell types in particular subgroups of patients</li> </ul>
Kidney disease progression	<ul style="list-style-type: none"> <li>• Change in eGFR               <ul style="list-style-type: none"> <li>– Primary composite longitudinal outcome, defined by any of the following:                   <ul style="list-style-type: none"> <li>◆ ESRD, defined as initiation of maintenance dialysis or kidney transplantation</li> <li>◆ Sustained decline in eGFR by 40% from baseline</li> </ul> </li> <li>– Individual components of the primary composite outcome</li> <li>– Slope of eGFR change</li> </ul> </li> <li>• Change in urine albumin and protein excretion</li> </ul>
Outcomes specific to AKI	<ul style="list-style-type: none"> <li>• Duration of AKI</li> <li>• Recovery of AKI</li> <li>• ICU admissions</li> <li>• Need for dialysis</li> <li>• Length of hospital stay</li> </ul>
Additional clinical outcomes	<ul style="list-style-type: none"> <li>• New or recurrent AKI events</li> <li>• Cardiovascular events</li> <li>• Mortality</li> <li>• Hospital admissions</li> </ul>

**Table 4.**

Safety measures undertaken by the Kidney Precision Medicine Project

Safety domain	Measures
Safety culture	<ul style="list-style-type: none"> <li>• Patients and clinicians included from study start to assess feasibility and inform study design</li> <li>• Imperative to put patient safety first emphasized from study start-up</li> </ul>
Protocol development	<ul style="list-style-type: none"> <li>• Comprehensive literature review to ascertain complication rates and risk factors</li> <li>• Clear exclusion criteria based on bleeding propensity</li> <li>• Standardized needle gauge (16G) and maximum number of needle passes (5)</li> <li>• Comprehensive external review: <ul style="list-style-type: none"> <li>– Independent Institutional Review Board</li> <li>– Independent Data Safety and Monitoring Board</li> <li>– Independent External Expert Panel</li> </ul> </li> </ul>
Protocol implementation	<ul style="list-style-type: none"> <li>• Biopsy operators restricted to experienced, KPMP-certified physicians</li> <li>• Site visits evaluated facilities and safety plans prior to initiation</li> <li>• Biopsy safety checklist completed prior to every biopsy</li> </ul>
Surveillance for adverse effects	<ul style="list-style-type: none"> <li>• Known potential complications actively ascertained 24 hours and 2 weeks after kidney biopsy</li> <li>• Patient-reported outcomes actively ascertained 24 hours and 2 weeks after kidney biopsy</li> <li>• All related, unanticipated, or serious adverse effects within 28 days of kidney biopsy collected by recruitment sites</li> </ul>
Ongoing review of adverse events to adapt protocol if needed	<ul style="list-style-type: none"> <li>• Internal Safety &amp; Adjudication Committee</li> <li>• Independent Data Safety and Monitoring Board</li> <li>• Independent Institutional Review Board</li> <li>• Independent External Expert Panel</li> </ul>