Kidney Precision Medicine Project

Clinical Protocol

July 13, 2023

Document ID: OPS001
Version #:10

Table of Contents

1 Introduction

1.1 Study Overview

The Kidney Precision Medicine Project (KPMP) is a prospective cohort study, whose goal is to use deep molecular phenotypes of kidney biopsies, along with longitudinally collected clinical phenotypic data, in order to develop new disease ontologies, classification systems, and treatments for acute kidney injury (AKI) and chronic kidney disease (CKD). Since its inception, the KPMP has sought out and included substantive patient-representative feedback regarding disease experience, lack of innovation in new kidney disease therapies and patient tolerance for risk levels in balance with potential benefits both to the individual and society. The KPMP has publicly and operationally committed itself to always put participants and their best interests first and this foundational principle informs and undergirds every facet of the study. Both AKI and CKD are conditions that impose a significant global health burden. Yet, no effective therapies currently exist for AKI, and only a few are available for CKD. To address this need, KPMP will obtain kidney biopsy tissue from study participants with AKI or CKD. The network will utilize state-of-the-art methods to perform molecular interrogation of the tissue and to link the molecular data to kidney structure and clinical information in the form of a human kidney atlas. Molecular and imaging data derived from kidney tissue will be integrated with clinico-pathologic and genetic information, as well as other data derived from analyses of fluid biospecimens, including peripheral blood, urine, and stool. Using advanced analytics to integrate the data, KPMP will aim to define kidney disease subgroups in molecular terms by identifying critical cells, pathways and targets for novel therapies. The general structure of the KPMP consortium is summarized in Figure 1. A detailed list of participating institutions is available on the KPMP website at https://www.kpmp.org/consortium-members.

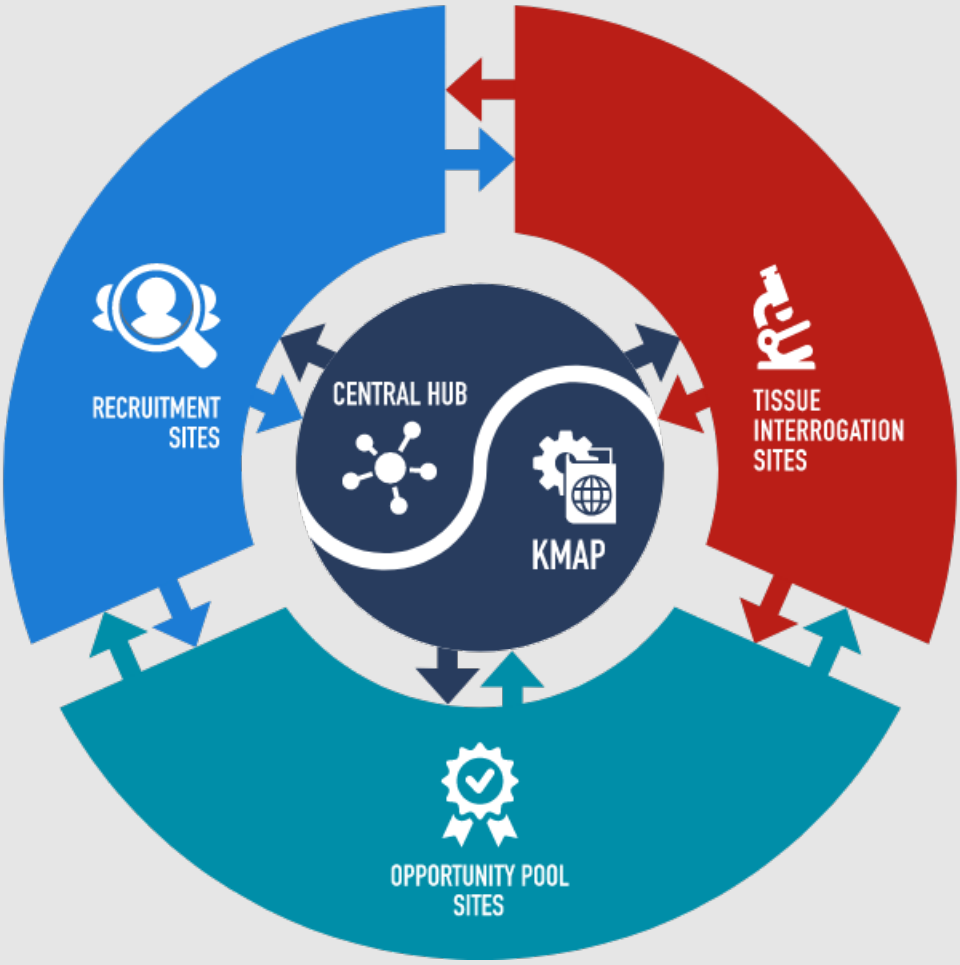

Figure 1: General structure of the KPMP consortium

Recent advances in multi-scalar interrogation of human tissue and single cells have set the stage for precision medicine to be applied to AKI and CKD. KPMP will provide a resource for advancing kidney research by providing high quality clinical, imaging, cellular and molecular data from normal and diseased kidneys to the broader research community.

The KPMP consortium consists of fourdistinct, but highly interactive, activities:

- Recruitment Sites will recruit participants with AKI or CKD for a kidney biopsy and longitudinal follow-up. They will also provide kidney tissue with no histopathological abnormality for generating a kidney reference atlas.
- Tissue Interrogation Sites will develop and use innovative technologies to analyze human kidney tissue and to provide high resolution structural, histologic and molecular data to develop a new molecular classification of kidney diseases.
- The Central Hub is responsible for aggregating, analyzing and visualizing all of the samples and data and provides scientific infrastructure and administrative support for the project.
- The Kidney Tissue Atlas Coordinating Center, a.k.a. Kidney Mapping Atlas Project (KMAP), is to clean, harmonize, store, and curate all de-identified KPMP data, perform integrative analyses, and create an interactive Kidney Tissue Atlas.

1.2 Purpose of the Study Protocol

The KPMP study protocol describes the cohort study of adult men and women participants with AKI and CKD, including the study design, visit schedule, study procedures, data collection, study outcomes and data management. Given the risk of potential complications from kidney biopsy, the protocol also reviews the published literature of biopsy complication rates and risk factors for adverse events, which informed the study inclusion/exclusion criteria and study design. In addition, it describes the safety and monitoring procedures to be implemented at all Recruitment Sites as KPMP holds ethical and participant safety considerations paramount. Finally, the protocol summarizes tissue processing, data quality control/assurance, return of results, and participant engagement after enrollment.

2 Background

2.1 Epidemiology of Chronic Kidney Disease (CKD)

Chronic kidney diseases (CKD) are a major public health problem in the United States (US). Current approaches to develop diagnostic and prognostic tools and targeted and effective therapies for common CKD are inadequate. Forty million Americans live with kidney diseases, and nearly 700,000 of those individuals have kidney failure, requiring kidney replacement therapies, dialysis or kidney transplantation, for survival.[1] The risk of death for patients receiving dialysis is nearly eight times higher than the general population, leading to a ~20% annual mortality rate. While patients who receive kidney transplants survive longer, a shortage of organs prevents transplantation for many patients and even individuals with successful transplants remain patients that require careful follow-up for complications and co-morbidities from lifetime immunosuppressive therapy.

Kidney disease treatment is expensive and the only disease entity uniquely tied to federal expenditures through a 1972 amendment (End Stage Renal Disease [ESRD] program) to the Medicare entitlement program.[2] In 2013, approximately 530,000 patients received dialysis or had a kidney transplant, costing the federal government nearly $31 billion, an expenditure that exceeded the FY2013 NIH budget.[1] ESRD expense is evident on a pie chart of the FY2015 Federal budget (Figure 2).(adapted from [3]) Patients with kidney failure represent only 1% of the Medicare population but costs associated with the condition accounted for more than 7% of Medicare's budget in 2013.[1] The cost of CKD is included in 4 of 5 most costly chronic condition combinations among Medicare beneficiaries.[4] Finally, advanced CKD is one of the starkest examples of racial and ethnic disparities in health.[5] CKD is more common among African Americans compared with other races.[6] Among patients with CKD, African Americans, Mexican Americans, patients with lower socioeconomic status, and other disadvantaged and

vulnerable patients are more likely to progress to kidney failure. [5, 6] Despite human burden, substantial health disparities, and remarkable cost of kidney diseases, innovation in the kidney disease space has been lacking due to chronic underinvestment in research compared to the burden of disease, and the paucity of clinical trials and new interventions compared to other diseases.[7-9]

2.2 Epidemiology of Acute Kidney Injury (AKI)

AKI is a common condition whose incidence has been rapidly increasing over the past decade.[10, 11] It is characterized by abrupt kidney function decline and is associated with increased morbidity, mortality and healthcare costs.[12] The overall incidence of AKI in the US is estimated to be about 2-3/1000 population, similar to that of acute myocardial infarction.[13] However, because of the silent nature of the syndrome, this is likely an underestimate. The percentage of patients with an AKI hospitalization in the Medicare Fee-for-service population has risen over the past decade, reaching 3.9% in 2013, compared to 1.5% in 2003. Additionally, older individuals are disproportionately affected. Among Medicare patients age 66–69, for example, the rate of AKI in 2011 was 14.9 per 1,000 patients, increasing to 18.8, 26.4, 35.9, and 49.6 respectively for ages 70–74, 75–79, 80–84, and 85 and older.[14]

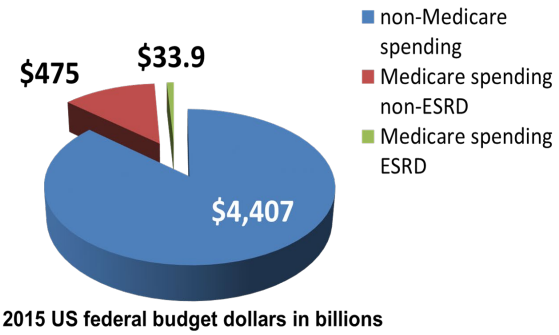

Figure 2: US ESRD Expense

Among hospitalized patients, AKI affects as many as one in five patients [15], increasing risk for additional complications, including death in up to 20-25% of patients. Recent evidence suggests that even mild forms of AKI are associated with increased risk of hospital mortality [16, 17] and AKI patients have higher long-term mortality compared to patients without AKI. [18] Although the reasons for this increased mortality are not fully understood, these studies and many others make a compelling argument that patients who develop AKI are at an additional increased risk of death that is in some way due to AKI itself.

AKI is also a major risk factor for the development and progression of CKD.[19] For example, acute tubular necrosis without recovery is the primary diagnosis for 2-3% of incident ESRD cases annually.[20] However, even if kidney function recovers, AKI increases the risk of CKD.[21] It is also a risk factor for cardiovascular events, 30-day re-hospitalization, and recurrent AKI, representing a significant individual and societal burden.

2.3 Rationale for This Study

Development of pharmacologic therapies for AKI and CKD has been hampered by animal models that fail to replicate the human disease phenotypes, the inability to identify and prioritize high value human targets, the limited availability of human kidney biopsy tissue, and a poor understanding of AKI and CKD

molecular heterogeneity. Combinations of serum creatinine concentration, urine volume and urine protein excretion define AKI and CKD but fail to cluster patients by common disease mechanisms. The resulting patient heterogeneity hinders novel drug target discovery, clinical trial design and success, and clinical care. Development of a kidney disease ontology based on molecular mechanisms will enable targeting of therapies to the patients most likely to benefit.[22]

3 Study Design

Since its inception, the KPMP has sought out and included patient-representative feedback regarding disease experience, lack of innovation in new kidney disease therapies and participant tolerance for risk levels in balance with potential benefits both to the individual and society. The KPMP has publicly and operationally committed itself to always put participants and their best interests first.[23] [24] The KPMP is a prospective cohort study of subjects with either AKI or CKD, who agree to a kidney biopsy using standardized KPMP procedures. Participants with AKI or CKD will be recruited from clinical care encounters (e.g. clinic visits for CKD patients, hospitalizations or emergency room visits for AKI patients) and from electronic resources (e.g. existing registries, electronic health records).

All study procedures are designed to optimize participant safety and will be ethically conducted, ensuring subjects fully understand the scope of the study and any possible risks.

For each participant, kidney tissue will be obtained for molecular phenotyping and clinical diagnosis. The diagnostic interpretation will be returned to the participant's caregiver to inform clinical care, but no treatment interventions will be prescribed by the KPMP. In addition to kidney biopsy, the study will involve collection of baseline (time of biopsy) and longitudinal biospecimens (including urine, plasma, serum, DNA, and stool) and demographic, clinical, and laboratory data. Participants will be followed through scheduled in-person and remote (telephone) study visits, as well as through periodic review of electronic health records (EHRs). The KPMP biorepository will contain biospecimens collected at the biopsy and follow-up visits for future studies. The biorepository will also contain reference kidney tissues to be used as comparators for the kidney biopsies obtained from the subjects with AKI and CKD.

All biological samples, biopsy slides, digital images and other relevant non-PHI clinical data will be deposited, harmonized, curated, and stored/tracked at the Central Biorepository at the University of Michigan. The Central Hub will manage and administer tissue distribution from the Recruitment Sites to the Tissue Interrogation Sites, where it will be interrogated using complementary, state-of-the-art platforms with rigorous quality control. Data generated at the Tissue Interrogation Sites will be transferred to KMAP, where it will be analyzed and visualized to further the scientific interests of the KPMP, including the building of a Kidney Atlas. Participant safety, satisfaction, participant reported outcomes, and the diagnostic yield of kidney biopsies will be systematically assessed. Curated and validated data will be available to the scientific community via an online portal and public research databases. The KPMP will prioritize dissemination of study results to all relevant stakeholders, including participants, patients, health care providers, researchers, and the broader scientific community.

4 Study Population

The KPMP will focus on participant populations that account for large proportions of the public health burden of acute and chronic kidney diseases as evidenced by research and federal data.

For CKD, high priority populations include CKD in the setting of diabetes (diabetic kidney disease, DKD) and hypertension-associated CKD (H-CKD). A special population of people with long-standing type 1 diabetes (more than 25 years) who remain free of clinically-evident DKD (i.e. DKD "resilient" individuals) will also be included. Study of the DKD resilient population using KPMP protocols offers a unique opportunity to identify protective factors against complications of diabetes mellitus. This cohort will also have detailed phenotypical evaluation including fundus imaging for retinopathy and examination for neuropathy.

For AKI, the focus will be on acute intrinsic non-glomerular disease, primarily on acute tubular necrosis (ATN). KPMP will also include a special population of patients at risk for AKI or with early AKI captured by an open (surgical) kidney biopsy performed at the time of clinically indicated laparotomy. The rationale for including this special AKI population is that AKI often occurs early in the clinical course of conditions like sepsis, major surgery and trauma. It is well recognized that elevations in serum creatinine lag behind the onset of AKI, both as a result of creatinine kinetics and changes in volume of distribution from volume resuscitation. Furthermore, even if early AKI can be identified by EHR alerts and biomarkers, obtaining percutaneous biopsies on this acute population will be challenging. Laparotomies are frequently performed for patients at high-risk for AKI (abscess, bowel perforation or infarction, trauma). The performance of an open kidney biopsy at laparotomy may enhance safety as compared to percutaneous biopsy, as the acute bleeding inherent with biopsy can be easily controlled with a variety of surgical techniques. Furthermore, it does not require a separate procedure. This special population has the potential to allow us to focus on patients who commonly develop AKI and in whom standard percutaneous biopsies may be difficult (e.g., the critically ill). It will also allow KPMP to obtain a novel type of 'reference tissue' in individuals who undergo this type of biopsy that do not subsequently meet criteria for AKI despite being at initial high risk.

4.1 KPMP Inclusion/Exclusion Criteria

4.1.1 Chronic Kidney Disease Subjects Inclusion Criteria

4.1.1.1 Diabetic kidney disease (DKD)

- Diagnosis of diabetes mellitus (type 1 or 2) established by at least one of the following criteria:
    - Hemoglobin A1C greater than or equal to 6.5%, confirmed with a repeat test within the past year
    - Fasting blood sugar greater than or equal to 126 mg/dL, confirmed with a repeat test within the past year
    - Use of glucose-lowering therapy (insulin or oral or other subcutaneous agents)
    - International Classification of Diseases (ICD) 9/10 diagnostic code for diabetes

- Evidence of persistent kidney damage, manifest as any of the following present on at least two clinic assessments prior to enrollment and at least 3 months apart and excluding subjects with acute medical illnesses and changing kidney function:
    - Estimated glomerular filtration rate 30-59 mL/min/1.73m2
    - Estimated glomerular filtration rate greater than or equal to 60 mL/min/1.73m2 with urine albumin excretion greater than or equal to 30 mg/g creatinine (or mg/day)
    - Estimated glomerular filtration rate greater than or equal to 60 mL/min/1.73m2 with urine protein excretion greater than or equal to 150 mg/g creatinine (or mg/day)

4.1.1.2 Hypertension-associated Chronic Kidney Disease (H-CKD)

- Diagnosis of hypertension (HTN) established by at least one of the following criteria:
    - BP greater than 140/90 mmHg measured on three occasions over at least 1 month
    - Taking antihypertensive medication for blood pressure (BP) control
    - International Classification of Diseases (ICD) 9/10 diagnostic code for hypertension
- Evidence of persistent kidney damage, manifested as any of the following present on at least two assessments at least 3 months apart and excluding subjects with acute medical illnesses and changing kidney function:
    - Estimated glomerular filtration rate 30-59 mL/min/1.73m^2 on two assessments at least 3 months apart with albuminuria or proteinuria less than 2000 mg/g creatinine (or mg/day)
    - Estimated glomerular filtration rate greater than or equal to 60 mL/min/1.73m2 with urine albumin excretion 30-2000 mg/g creatinine (or mg/day)
    - Estimated glomerular filtration rate greater than or equal to 60 mL/min/1.73m2 with urine protein excretion 150-2000 mg/g creatinine (or mg/day)

4.1.2 Acute Kidney Injury Subjects Inclusion Criteria

All three of the following criteria must be met:

- Baseline estimated glomerular filtration rate greater than 45 mL/min/1.73m2. Baseline defined by the median of the last three outpatient serum creatinine measurements from day 7 to 365 prior to enrollment.
    - If only two measurements are obtained within this window, the two results will be averaged.
    - If only one measurement was obtained within this window, this result will be used
    - If baseline is missing, the potential participant can be enrolled with an estimated baseline, but only if there is no past medical history of chronic kidney disease.
    - If the AKI RS PI believes that the baseline serum creatinine under or over-estimates baseline, a unanimous vote of AKI site PIs can confirm eligibility based on a review of deidentified serum creatinine values provided by the site PI.

- Elevated serum creatinine (greater than or equal to 1.5 times baseline as defined above).

- And at least ONE of the following:
    - A repeat serum creatinine within no less than 6 and no more than 48 hours of initial serum creatinine that is still greater than or equal to 1.5 times the baseline as defined above.
    - Positive kidney injury urine biomarker, as defined by any of the following:
        - NGAL level greater than or equal to 150 ng/mL by ELISA or clinical analyzer
        - KIM1 level greater than or equal to 2.8 ng/mL by ELISA
        - TIMP2 x IGFBP7 greater than or equal to 2.0 by NephroCheck®
    - Urine microscopy suggestive of acute tubular necrosis defined as a urine microscopy score of greater than or equal to 2. [25]
        - greater than or equal to 1 Renal Tubular Epithelial cells (RTE) per high powered field (HPF) AND greater than or equal to 1 granular cast/ low powered field (LPF); or
        - greater than or equal to 5 Renal Tubular Epithelial cells (RTE) per high powered field (HPF); or
        - greater than or equal to 5 granular cast/ low powered field (LPF)

4.1.3 Special Populations

4.1.3.1 Potential participants undergoing open laparotomy for a clinical indication and who are at high risk for acute kidney injury inclusion criteria

- Baseline estimated glomerular filtration rate greater than 45 mL/min/1.73m2 as defined above AND one of the following:
- Elevated serum creatinine (greater than 1.5 times baseline) or an increase in serum creatinine greater than or equal to 0.3 mg/dL within 48 hours, above admission serum creatinine.
  OR
- High risk for acute kidney injury defined by **TWO** or more criteria:
    - Positive kidney injury urine biomarker measured at the Recruitment Site, as defined by any of the following:
        - NGAL level greater than or equal to 150 ng/mL by ELISA or clinical analyzer
        - KIM1 level greater than or equal to 2.8 ng/mL by ELISA
        - TIMP2 x IGFBP7 greater than or equal to 2.0 by NephroCheck®
    - Urine microscopy suggestive of acute tubular necrosis:
        - Greater than or equal to 1 Renal Tubular Epithelial cells (RTE) per high powered field (HPF) AND greater than or equal to 1 granular cast per low powered field (LPF); or
        - Greater than or equal to 5 Renal Tubular Epithelial cells (RTE) per high powered field (HPF); or
        - Greater than or equal to 5 granular cast/low powered field (LPF)
    - Oliguria (less than 0.3mL/kg/hr) at least 1 hour after fluid resuscitation.
    - One or more exposure(s) known to cause acute kidney injury (major surgery not including index laparotomy, sepsis, nephrotoxic drugs, etc.).

4.1.3.2 Diabetic Kidney Disease Resilient Individuals Inclusion Criteria

A special population of people with long-standing type 1 diabetes (>25 years) who remain free of clinically-evident DKD (i.e. DKD "resilient" individuals) will also be included. Study of the DKD resilient population using KPMP protocols offers a unique opportunity to identify protective factors against complications of diabetes mellitus. Diabetic Kidney Disease Resilient individuals are defined as individuals with diabetes for more than 25 years that are free from clinical nephropathy

- Type 1 diabetes for over 25 years
- Estimated glomerular filtration rate greater than or equal to 60 mL/min/1.73m^2
- Urine albumin excretion less than 30 mg/d (or mg/g creatinine)

4.1.3.3 COVID Substudy Inclusion Criteria

In response to the COVID-19 pandemic, the KPMP temporarily added a flexible and modular COVID-19 substudy to address the critical need to understand the presentation of COVID-19 infection associated kidney complications, with the goal of improving diagnostics, therapeutics, and overall care. Participants from this substudy were asked to consider enrolling in the full KPMP (including kidney biopsy and follow-up visits for up to 10 years) at a baseline KPMP visit approximately three months after their COVID-19 Substudy visit. Inclusion Criteria for COVID-19 Substudy are patients greater than 18 years of age admitted to participating hospitals with a positive COVID-19 test result or Persons Under Investigation with suspected COVID-19 infection AND with AKI or at high risk of AKI in the setting of COVID-19 infection, as defined by any ONE of the following:

- pre-existing chronic kidney disease as defined by eGFR less than 60 ml/min/1.73 m2
- history of diabetes mellitus
- requiring use of vasopressors
- requiring use of mechanical ventilation

AKI is defined by temporal changes in serum creatinine meeting KDIGO Stage 1 criteria or greater. If a baseline serum creatinine is not available, the patient can be enrolled with an estimated Baseline serum creatinine (see KPMP COVID-19 Manual of Procedures for details).

For a participant to be considered enrolled in the COVID-19 Substudy the consent form must be signed and one or more participant procedures performed from the baseline module.

Recruitment for the COVID substudy ended in April 2022.

4.1.4 General Exclusion Criteria

- Under 18 years of age
- Severe allergy to iodinated contrast
- Pregnancy
- Transplant recipient (includes solid transplant and bone marrow)
- Additional vulnerable individuals (incarcerated, institutionalized, or otherwise unable to participate in the study)

- Inability to provide informed consent or obtain surrogate consent from a legally authorized representative (LAR)
- Clinical diagnosis of kidney disease from an autoimmune disease, dysproteinemia, viral disease or glomerular disease other than DKD or H-CKD
- Unwilling to receive blood transfusion (if needed)

4.1.5 Safety Exclusion Criteria

Potential participants will be excluded if the risk of kidney biopsy is considered too high by either the clinicians caring for the potential participant or the investigators at the RS.

4.1.6 Anatomic or Imaging Exclusion Criteria:

- Kidney depth more than 13 cm (percutaneous biopsies only)
- Kidney size less than 8 cm (percutaneous biopsies only)
- Solitary or single functioning kidney
- Evidence of urinary tract obstruction or hydronephrosis
- Multiple bilateral kidney cysts that will interfere with the safe performance of the biopsy
- Kidney infection, peri-renal infection, or cutaneous infection that overlies the kidney (percutaneous biopsies only)
- Any other imaging abnormality, which in the judgement of the operator, prevents biopsy being performed safely.

4.1.7 Bleeding Risk Exclusion Criteria:

- International Normalized Ratios (INR) greater than 1.4
- Platelet count less than 100,000/uL
- Hemoglobin less than 8.5 g/dL
- Chronic anticoagulation
- Inability to withdraw aspirin, clopidogrel, cilostazol, or similar anti-platelet agents for at least 7 days prior to biopsy (unless bleeding time is normal before open surgical biopsy); clinical judgement will be used in the case of nonsteroidal anti-inflammatory drugs (NSAID) exposure occurring less than 7 days before percutaneous biopsy.
- Blood pressure of more than 160 mmHg systolic or 100 mmHg diastolic.
    - Peri-procedure blood pressure fluctuations between 140-160 mmHg systolic and 90-100 mmHg diastolic require management, ideally to target, based on clinician/investigator judgment.
- Ventilator-dependent patient (does not apply to open biopsies)
- Hypotension or pressor support requirement (does not apply to open biopsies)
- Any other condition where in the judgement of the operator, biopsy cannot be performed safely.

4.2 Recruitment Plans and Consent Process

Recruitment Sites will use similar recruiting strategies, but site-specific approaches will optimize effectiveness and efficiency according to their local health care settings and target study population(s). This may include collaboration with national patient and professional organizations that are part of the kidney community. Strategies will include both recruiting from clinical care encounters (e.g. clinic, emergency room, or hospital visits) and recruiting based on electronic health information resources (e.g. existing registries and EHR). Local recruiting networks will be utilized whenever possible at both CKD and AKI Recruitment Sites. Written informed consent will be obtained from all KPMP study participants or their LAR.

Recruitment of CKD participants will focus on the outpatient setting. Research coordinators will regularly attend nephrology clinics as well as other clinics that commonly care for patients with CKD and diabetes or hypertension. Identification of study candidates will be aided by use of EHR-based tools to screen potential participants for eligibility. Where possible, local CKD registries will be searched using the KPMP entry criteria to find potential participants. KPMP study candidates will be asked by their clinicians to agree to in-person or phone contact with a research coordinator. According to local site-specific procedures, other modes of outreach from the researchers to potential participants may also be considered for recruitment. If potentially eligible study participants are interested in learning more about the KPMP, they will meet with a research coordinator and/or study investigator to review the study in detail. They will be given information about the study verbally and in print. Study information will also be posted on the KPMP website.

Recruitment of AKI participants will be primarily in the inpatient setting. Some sites will utilize local EHR to identify potential participants for enrollment. Sites also will screen for potentially eligible participants across nephrology consultative services, emergency rooms, and intensive care units. If a patient is considered an appropriate candidate, the primary clinician will discuss the KPMP study with the potential participant. If the potentially eligible study participants are interested in learning more about the study, they will meet with a research coordinator and/or study investigator to review the study in detail. Recruitment of AKI participants for open kidney biopsy will include patients with established AKI as well as patients at high risk for AKI or in the earliest stages of AKI who undergo clinically indicated laparotomies. These potential participants will be identified through EHR alerts as well as by direct identification by participating intensivists and surgeons. The surgeon performing the laparotomy and kidney biopsy, accompanied by a KPMP research coordinator and/or study investigator, will discuss study procedures and risks directly with the potential participant. They will be given information about the study verbally and in print. Study information will also be posted on the KPMP website.

4.3 Recruitment Outreach

4.3.1 Participant Engagement

The KPMP formed a Community Engagement Committee (CEC) that will support participant engagement platforms at CKD and AKI sites in partnership with national and local community advisory groups. They

will provide specific input regarding strategies for contacting and interacting with prospective study participants for KPMP. The CEC and local community advisory groups will include experienced and new patient advisors as well as their family members with a diversity of backgrounds and kidney disease experiences. They will give voice to the patient perspective in order to address potential participant priorities and concerns regarding KPMP recruitment and retention.

4.3.2 Clinician Engagement

Clinicians will be included on the CEC and local advisory groups. They will give input on KPMP messaging, recruitment strategies, and methods for dissemination of results. Since participants will be drawn from a spectrum of academic and private practice primary care and specialty care clinics, a spectrum of clinicians reflective of those types of practices (e.g. nephrology, primary care, intensive care, endocrinology) will be represented.

4.3.3 Recruiting

Recruitment will focus on diversity that reflects typical populations with CKD and AKI. This will include focus on recruiting racial and ethnic minorities that are disproportionally affected by kidney diseases, particularly people of African ancestry, Hispanic ethnicity, or American Indians and Alaskan Natives. In addition, the representation of women should correspond to the fraction of women in the population diagnosed with CKD and AKI. While recruiting, reasons for non-participation will be tracked to mitigate selection bias and to optimize site recruiting practices. Participant and clinician engagement with ongoing dissemination of study progress and results, as well as engagement with national patient and medical professional organizations and societies, will enhance potential participant awareness and recruitment.

4.4 Sample Size

It is anticipated that the KPMP protocols will be active for over 10 years. The first two years of the KPMP (2017-2019) were devoted to establishing protocol safety; assessing feasibility of procedures for enrollment, tissue processing and technology development; and identifying and implementing quality control procedures. During years three through five of the KPMP (2019-2022), the KPMP accelerated the pace of recruiting. Currently, there are insufficient data available to estimate enrollment or calculate reliable power estimates for the novel goals of the KPMP, which include molecular as well as more traditional clinical endpoints (see Section 6). KPMP will prospectively gather molecular data from biopsies to develop disease sub-phenotypes and clinical study outcomes that will facilitate formal power and sample size requirements for an extension of procedures beyond 2022. The consortium will continuously evaluate sample size and power required to address specific hypotheses of interest.

4.5 Sampling plan

The KPMP will track consent rates, enrollment and retention according to stage and clinical diagnosis of CKD or AKI to ensure adequate sampling of the targeted disease phenotypes. Race/ethnicity and sex/gender will be tracked during recruitment to assure that KPMP achieves population-level demographics reflective of patients affected by the targeted cause of CKD or AKI. The KPMP will also strive to enroll participants residing across a broad geography, inclusive of residents in both rural and urban regions.

5 Study Procedures

5.1 Schedule of Study Procedures

5.1.1 Screening, Eligibility Assessment, and Informed Consent

A study team member will meet with each potential participant or their LAR to review the informed consent, determine the potential participant or LAR understands specifically what they are consenting to, invite and answer any questions regarding study protocol, and complete the KPMP informed consent process. Full review of inclusion and exclusion criteria will be performed. The risks and benefits will be discussed in detail as outlined in Section 10. The informed consent process may be completed at a single sitting or extend over multiple interactions of potential participants or LAR with study staff. Only participants who meet all eligibility criteria, provide written informed consent (in-person or by LAR), and who continue to express interest in participation will continue to kidney biopsy and baseline data collection.

5.1.2 Kidney biopsy and baseline data collection

The kidney biopsy is the primary focus of KPMP activities and the defining event for full enrollment into the KPMP. Detailed data regarding kidney disease course relative to timing of biopsy will be obtained, including nephrotoxic exposures and trends in renal function. Additional procedures will be performed at time of the kidney biopsy, which together will constitute the baseline study visit. These additional procedures include collection of demographics and past medical history, physical measurements (e.g. vital signs, height, weight, presence of lower extremity edema), measurements of kidney damage and function, and additional biospecimens for future examination (e.g. blood and urine). These biospecimens may be used to make immortalized cell lines and/or inducible pluripotent stem cells. Data will be collected from study participants and from the electronic health record (EHR).

For a participant to be considered fully enrolled in KPMP, the biopsy must be performed. Prior to the biopsy, a consented individual can be engaged in participant procedures including participant-completed questionnaires, physical measurements, and/or any biospecimen collection. If the individual is withdrawn or loses eligibility prior to the completion of the biopsy, they are not considered fully enrolled and will not be followed longitudinally.

5.1.3 Follow-up Visits

All participants will be asked to consent for follow up for up to 10 years (subject to continued NIH support) according to a standardized schedule of study visits. This schedule will include twice-yearly visits, every 6 months (+/- 3 months window), as summarized in Table 1. The visits will alternate between a remote (telephone, T) visit at 6, 18, 30, 42, etc. months post-biopsy and an in-person visit (V) at 12, 24, 36, 48 months, etc. post-biopsy. This schedule of follow up visits is expected to continue for the entire duration of the study (with alternating remote and in-person visits every six months), which we anticipate will be at minimum 10 years. Additionally, participants with AKI will have an additional in person visit (A2) at 3 months post biopsy.

In-person visits will include ascertainment of study outcomes (including dialysis/kidney transplant status, interval hospitalizations, and quality of life), physical measurements (vital signs), and collection of biospecimens (blood and urine to measure study outcomes including the extent of early recovery of

Table 1: AKI and CKD Participant Visit Schedule for first 10 years of study follow-up

Years 6-10 are planned to follow the same trajectory as years 1-5.

	Enrollment	Biopsy	Post-Bx Monitoring				Year 1		Year 2		Year 3		Year 4		Years 5	
Visit	**V0**	**V1**	**M1**	**A1**	**M2**	**M3**	**A2**	**R1***	**V2**	**R2**	**V3**	**R3**	**V4**	**R4**	**V5**	**R5**
Time	0	0	1d	5-7d**	14d	28d	3mo	6m	12m	18m	24m	30m	36m	42m	48m	54m
Window	0	0	12-48h	5-7d	10-20d	28-34d	2-4m	4-9m	9-15m	15-21m	21-27m	27-33m	33-39m	39-45m	45-51m	51-57m
Biospecimen	NO	YES	NO	YES	NO	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO

V = in-person visit with biospecimen sampling

A = AKI only in-person visit

M = Post-Bx monitoring phone calls

R = remote (e.g. telephone) visit; R1* Includes a 6-mo kidney function assessment for AKI participants

** = A1 occurs if participant is discharger prior to 5 days after biopsy

kidney function and for storage in the KPMP repository). Telephone visits will include assessment of dialysis/kidney transplant status and interval hospitalizations. The R1 contact for AKI participants includes ascertainment of kidney function.

5.2 Descriptions of Study Procedures

5.2.1 Baseline Demographics and Medical History

A study team member will review the medical record prior to participant visit and review the demographics and medical history to ascertain data elements required for enrollment. An interview will be conducted to confirm the variables obtained from the medical record and collect the remaining variables. These key variables are necessary for subsequent analyses, comparison of the study population with the larger CKD and AKI populations and for linkages to databases such as Centers for Medicare and Medicaid Services (CMS), the Scientific Registry of Transplant Registry (SRTR), the United States Renal Data System (USRDS), and the National Death Index (NDI.) If a participant is lost to follow-up, the study team will still look in their medical record and registries for this information, unless the participant specifically asks the study team not to. Protected health information (PHI) data elements will be collected for the study to enable participant tracking, contact, and linkages to national databases (**Table 2A**). PHI will be segregated on a secure server at the Central Hub but linked with other study data. In addition, complete information on baseline demographics, health status, exposures, and medical history will be obtained. **Table 2B** summarizes broad categories of clinical variables to be collected**.**

Table 2A. Protected Health Information

Protected Health Information (PHI)	Name and SSN to link with NDI, USRDS, SRTR
	Date of birth (DOB)
	Mailing Address, Zip Code, Census Tract
	Telephone contact information: home phone, cell phone, emergency contact
	Email contact information
	PCP & primary nephrologist: name, city, practice name, contact information

Table 2B. Broad categories of the collected health data

Demographics	Age, sex, race, ethnicity, marital status and other demographic variables as delineated in the Recruitment Site MOP
Socio-economic	For example, education level, occupation, work status, income, insurance status etc.
Medical History	Kidney disease history: e.g. prior AKI, UTI, hematuria, renal function, levels of proteinuria, kidney

	surgery, dialysis etc.
	Social history, smoking, alcohol, illicit substance use history etc.
	Family history with family tree
	Review of systems and complete list of comorbidities including surgical history
	Medication history and potential nephrotoxic iatrogenic or environmental exposures
	Reproductive health and pregnancy history

5.2.2 Physical Measurements

Vital sign measurement will be conducted on all participants at each visit. For outpatient participants, measurements of blood pressure (BP), weight, and height will be obtained at the time of the Baseline visit and on each subsequent visit. Edema, a sign identified as highly distressing by patients, will be noted as present or absent. Blood pressure will be measured using automated, validated blood pressure devices.

5.2.3 Kidney Biopsy Overview

The guiding principles in performing the kidney biopsy are participant safety and determination that the subject is both fully informed and completely knowledgeable of the scope and possible risks. Pre-procedure vital signs and laboratory values will be obtained and reviewed by the clinician performing the biopsy. Non-invasive biospecimens (urine, blood, and stool) will be collected before or after the biopsy procedure is performed. A qualified clinician (details in the Recruitment Site MOP) experienced in kidney biopsy procedures will perform a percutaneous kidney biopsy under direct imaging visualization with a 16G biopsy needle. Alternatively, a CT-guided percutaneous biopsy will be performed by a trained interventional radiologist, nephrologist, or clinical care provider according to local practice patterns and designated study personnel at Recruitment Sites.

All credentialed (e.g. Licensed Independent Providers) biopsy operators must have a minimum experience of 35 renal biopsies over 2 years, with at least 25 biopsies as the primary operator, an overall major complication rate of less than 10%, and more than 85% of biopsies deemed adequate for diagnosis. If the KPMP biopsy will be performed by a KPMP-certified physician's assistant, they must be accompanied by a KPMP-certified physician. In participants undergoing open laparotomy for a clinical indication and who are at high risk for acute kidney injury (see Section 4.1.3) a surgeon will obtain the kidney tissue via open biopsy.

A study goal is that three biopsy cores of kidney parenchyma will be obtained with a maximum of five passes and processed as detailed below. Hemostasis will be ensured and participants will be observed with frequent monitoring of blood pressure and heart rate. Participants will be monitored for post-procedural gross hematuria while in the hospital setting for up to 48 hours, and nursing will be available

continuously with on-call physicians available. dDAVP may be administered at the discretion of the biopsy operator when judged to be useful to reduce bleeding risk. A standard workflow for post-operative monitoring is further described in the Recruitment Site MOP. Ambulatory participants will be instructed to refrain from lifting anything heavier than 10 pounds for 48 hours post-procedure, no vigorous activity for 1 week, after which time they may resume usual activities. In addition, contact information with 24-hour coverage for study coordinator and study PI's will be provided for questions or problems post-procedure. For ambulatory participants, a follow-up phone call will be made in the morning post-procedure to answer any questions or concerns, and to verify no immediate complications. Once available, clinical biopsy results will be communicated to the participant's referring physician, who will then communicate the results to the participant. If necessary, the KPMP site team can facilitate referral to a nephrologist but will not themselves provide care to study participants. A copy of the final biopsy report will be included in the participant's medical record.

5.2.4 Kidney Tissue Processing

5.2.4.1 Adequacy assessment of kidney biopsy tissue

The KPMP renal biopsy from participants with CKD and/or AKI is obtained at the Recruitment Sites. For each participant enrolled in KPMP, the target is to obtain three biopsy cores, preferably at least 1.4 cm in length. The fresh tissue will be rapidly evaluated by gross examination without compromising its integrity. An alternative option consists of ex-vivo imaging of the fresh tissue. The purpose of the gross examination or ex-vivo imaging, is to determine if each of the biopsy cores is composed of renal parenchyma, has a sufficient length (size), and contains an acceptable amount of renal cortex and glomeruli before being placed into the various transport media and processing solutions (fixatives and preservatives) as per protocol. The ex-vivo imaging will also provide information on tissue structural integrity. Additional details for determining adequacy of tissue, training of tissue processing technicians are described in the Tissue Processing MOP.

5.2.4.2 Triage of the renal biopsy

Biopsy core triaging protocols depend on tissue adequacy. In most scenarios three cores will be obtained. At least one core (goal minimum 1.4 cm length) will always be processed for clinical interpretation. The other cores will be immediately placed in the appropriate media or fixatives for molecular studies and distributed to the Tissue Interrogation Sites, according to a pre-specified tissue workflow (refer to the TP MOP). The specific steps in processing tissue cores designated solely for research cores (2 and 3) may vary over time, based on the needs of the KPMP consortium and the deliverables of the TISSUE INTERROGATION SITEs. Triage of limited cores will be guided by the principle that evaluation for clinical diagnosis will have primacy. Consequently, contingency plans have been developed in the event that fewer than 3 cores are obtained (because of technical difficulties, an emerging clinical situation, or biopsy complication). These contingencies are detailed in the KPMP TP MOP. Quality of tissue cores will be tracked prospectively.

5.2.5 Other Biospecimens

KPMP Recruitment Sites will collect blood, urine, and stool samples from study participants at baseline and follow-up visits. Sample type, volume, preservative, and priority of sample collection are described in the Biospecimen MOP (BS MOP). Biospecimen collection and banking will support future measurement of biomarkers to correlate with tissue findings, test diagnostic biomarkers associated with specific kidney diseases or prognostic biomarkers associated with outcomes, or develop predictive biomarkers in the pathway of novel therapeutic targets. The biospecimens will also enable discovery or validation of analytes indicative of aberrations in biological pathways that could provide clues to drug targets.

Quality control and quality assurance methods for biospecimen collection, processing and testing will be implemented with oversight by the appropriate KPMP committee in coordination with the Clinical Data Coordinating Center, Central Biorepository, and NIDDK Biorepository. The Clinical Data Coordinating Center will work closely with the appropriate committees to develop a high standard of data quality, document procedures in the Recruitment Site MOP, and then work with and monitor the Recruitment Sites and Central Biorepository to ensure that quality control protocols are meticulously implemented.

Quality assurance activities include technician training and certification, the production of clear, complete MOPs applicable to each Recruitment Site, planning of a complete data collection system with rigorous data quality checks, and monitoring of equipment calibration and maintenance.

Quality control activities, which occur during and after data collection, include monitoring data quality during data collection, incorporating replicate measurements to determine technician and device comparability, using statistical techniques to evaluate measurement quality, and implementing strategies to remedy any deficiencies. The Clinical Data Coordinating Center will implement quality control measures which are consistent with the QC plan developed prior to study initiation in order to ensure that the final data set is as complete and accurate as possible. While QC monitoring will be at committee discretion, it is anticipated that laboratory assay measures will undergo close QC scrutiny.

5.2.6 Measurements of Kidney Function

For primary analyses of study outcomes (Section 6), GFR will be estimated at baseline and longitudinally from serum creatinine and cystatin C concentrations measured at the KPMP Central Laboratory. Similarly, urine albumin and urine creatinine concentrations will be measured centrally. The Central Biorepository will employ strict quality control measures to minimize bias in blood and urine assays across sites and participants and within participants over time. Serum creatinine concentrations extracted from the EHR will be used when necessary to augment missing data and to perform secondary analyses that include a larger number of observations to increase temporal granularity. GFR will be estimated using CKD-Epi formula with: (a) serum creatinine (primary) and (b) creatinine and cystatin C combined (secondary). If improved GFR estimating methods become available over the time frame for data analyses, we will consider using the newer and /or additional methods assuming that necessary variables are available for the cohort.

5.2.7 Participant Provided Information

Participant questionnaires will supplement data collected through the EHR and in-person interviews and will reduce the time spent by study personnel during Baseline visit on data collection. Participants will be provided the option to fill paper or online questionnaires either before, during or after the Baseline visit. The list of questionnaires includes the following:

- Demographics
- Health literacy questionnaire
- PROMIS Global Health questionnaire
- Personal Health questionnaire

5.2.8 Electronic Health Record (EHR) Data

Participants will be asked to authorize linkage of their EHR information, if available, to study data. Although such linkage involves moderate risks to privacy and confidentiality (see Section 10), longitudinal tracking of health outcomes through EHRs is an important component of the KPMP Research Program. EHR data may be sent directly by the Recruitment Sites to the Central Hub or sent at the request of the participant through other means, such as via Sync for Science. If a participant is lost to follow-up, we will continue to track health outcomes through EHR, unless the participant specifically asks us not to.

Access to EHR data will be updated regularly throughout the lifespan of the KPMP. The scope of EHR data abstracted by the KPMP is expected to change over time. The initial data types to be included are demographics, visits, diagnoses, procedures, medications, laboratory tests, and vital signs. Initial efforts will be focused on longitudinal data on kidney function and damage (serum creatinine concentrations, urine albumin and protein measurements), medical history as defined by diagnosis codes, and hospitalizations. Data types may be expanded to all parts of the EHR, including health care provider notes or imaging data. The feed may include mental health data, HIV status, substance abuse and alcohol data, and genomic information stored in the EHR.

The KPMP Central Hub will create an informatics infrastructure to clean and standardize data from disparate EHR systems across the KPMP. The KPMP Recruitment Sites will extract data from the participant's EHR, format it according to the Observational Medical Outcomes Partnership [OMOP] Common Data Model (www.OHDSI.org) and transfer it to the Central Hub using secure protocols.

6 Study Goals

The primary study goal is to ethically obtain and evaluate human kidney biopsies from participants with AKI or CKD in order to create a kidney tissue atlas, define disease subgroups, identify critical cells and pathways driving disease, and discover targets for novel therapies. Specific goals of the KPMP include construction of a kidney atlas, development a molecularly based classification of common CKD and AKI, identification of molecular pathways associated with kidney disease progression and related clinical

events, and the identification of promising molecular pathways to target with therapeutic interventions. Given the novel application of the kidney biopsy within the KPMP and the imperative to monitor kidney biopsy safety, the KPMP will prospectively collect data on the safety and utility of kidney biopsy as part of its primary mission. The KPMP will evaluate a range of study outcomes to reflect these diverse goals and to accomplish the primary goal.

6.1 Biopsy-related outcomes

Incidence of biopsy-related complications:

- Macroscopic hematuria
- Requirement for a blood transfusion
- Unexpected requirement for ICU admission thought to be related to the biopsy procedure
- Requirement for renal angiographic intervention
- Requirement for nephrectomy to control bleeding
- Death associated with kidney biopsy procedure

Clinical utility of biopsy

- Change in management based on biopsy findings
- New (unsuspected) or confirmed (suspected) diagnosis

Participant-reported biopsy outcomes

- Participant satisfaction with the procedure (questionnaire-based)
- Participant perception of kidney biopsy impact on disease knowledge and management (questionnaire-based)

Biopsy-related complications will be collected by KPMP study staff using standardized case report forms. Clinical utility of the biopsy results will be assessed using standardized surveys of clinical providers, and participant-reported outcomes will be assessed using standardized questionnaires. All case report forms are detailed in the Recruitment Site MOP. Biopsy-related outcomes data will be collected around the time of the biopsy and within the six months following procurement of the kidney biopsy.

6.2 Kidney Tissue Atlas

The KPMP will create a set of maps used to classify and locate different cell types and interstitial components. The atlas will help define disease subgroups and identify cells, pathways, and targets for novel therapies. The KPMP Tissue Interrogation Sites will analyze tissue from kidney biopsies procured as part of the KPMP kidney tissue protocol as well as tissues obtained from other sources (Section 9). KMAP will then build the atlas using the multidimensional molecular data generated by the Tissue

Interrogation Sites. As with other products of the KPMP, the kidney tissue atlas will be made widely available to the broader scientific community through online resources.

6.3 Molecular Kidney Disease Subtypes

The KPMP will use all available data, focusing on novel molecular analyses of kidney tissue by Tissue Interrogation Sites and including data from the kidney tissue atlas, to define novel disease subtypes. These molecular kidney disease subtypes will be generated within clinical presentations (e.g. DKD, H-CKD, and AKI) and potentially across clinical presentations, when common disease pathways are identified. The short-term goals of the new molecular kidney disease subtypes are to facilitate patient stratification into distinct mechanism-based endophenotypes and to identify and understand healthy and disease pathways that are activated in a particular cell type in a particular subgroup of patients, which are further informed by clinical outcomes as described in 6.4 and 6.5. Diagnosis of molecular kidney disease subtypes will be facilitated by biomarkers that correlate with tissue-based molecular profiles. Development of appropriate biomarkers will be facilitated by analyses of blood and urine samples stored in the KPMP biorepository. The long-term goal of this work is to develop the knowledge basis whereby tailored treatment regimens can be based on individual patient disease pathogenesis and characteristics.

6.4 Kidney disease progression outcomes

6.4.1 Change in estimated glomerular filtration rate (eGFR):

- Primary composite longitudinal outcome, defined by any of the following:
    - ESRD, defined as initiation of maintenance dialysis or kidney transplantation
    - Sustained decline in eGFR by 40% or more from baseline
- Individual components of the primary composite outcome
- Slope of eGFR change (from baseline to the latest value)

6.4.2 Change in urine albumin excretion

- Slope of change in urine albumin-creatinine ratio
- Change in Kidney Disease Improving Global Outcomes (KDIGO) albuminuria stage

6.5 Additional Outcome Measures

- All-cause mortality, defined by death from any cause and validated through linkages with the National Death Index (NDI).
- Cardiovascular events, including heart failure, myocardial infarction, cerebrovascular event, transient ischemic attack, thromboembolic event, arrhythmia, and cardiac arrest.

- New AKI events after KPMP enrollment
- Hospital admissions and discharge diagnoses after KPMP enrollment.

Surveillance for mortality, cardiovascular events, AKI events, and hospitalizations will include questioning of participants at biannual study visits (in person or remote/telephone), monitoring of the EHR, and linkage to the National Death Index.

6.6 Outcomes specific to AKI

- Duration of AKI: number of days with elevated serum creatinine above baseline as defined in Section 4.1.3.1.
- Recovery of AKI: return of serum creatinine to greater than 125% of baseline by 3 months post-biopsy.
- ICU admissions: admissions to any intensive care unit during hospitalization.
- Need for dialysis: initiation and duration of any dialysis modality (CRRT, HD, or PD).
- Length of hospital stay: number of days in hospital during initial AKI episode.

Data to determine other AKI-related outcomes will be collected by KPMP staff using standardized case report forms at all visits.

7 Safety/Adverse Event Monitoring and Reporting Procedures

7.1 Adverse Events related to KPMP Biopsy Procedure

Recruitment sites will collect information in case report forms and report all deaths occurring within 28 days of a KPMP biopsy, all serious adverse events occurring within 28 days of a KPMP biopsy, and adverse events occurring within 28 days of a KPMP biopsy that are determined by site personnel to be possibly or definitely related to the biopsy procedure. All collected adverse events, (whether serious or non-serious, anticipated or unanticipated) will be reported to the DCC, DSMB, NIDDK and IRB according to the timeline for reporting as detailed in Table 4. All deaths and unanticipated non-fatal adverse events involving risks to participants or others that occur within 28 days of a KPMP biopsy will be reported to the Clinical Data Coordinating Center, DSMB, NIDDK, and IRB on an expedited basis. This will include both serious and non-serious adverse events that are assessed by the local site investigator and/or the Clinical Data Coordinating Center to be ***(a) an untoward event that is unexpected in terms of nature, severity, or frequency with respect to the KPMP kidney biopsy and related procedures and the characteristics of the CKD/AKI population being studied; and (b) definitely or possibly related to the KPMP kidney biopsy and related procedures.*** Anticipated non-fatal adverse events will be promptly reported to the Clinical Data Coordinating Center, and to the DSMB and NIDDK, in accordance with the time line shown in Table 4. These data will be reported in aggregate to the central IRB. The study will

systematically collect all serious adverse events, regardless of whether they are possibly or definitely related to the biopsy procedure, and will report these in aggregate to the DSMB, NIDDK, and IRB. The study will not systematically collect unrelated, non-serious adverse events.

The rationale for this approach is that adverse events that are unanticipated may change assessment of the risks and safety of the KPMP biopsy procedure and may therefore require prompt revision of study procedures and documents, including the informed consent form. In contradistinction, individual adverse events that are considered anticipated complications associated with the KPMP biopsy procedure or with the population of participants being studied cannot be meaningfully interpreted as individual events but need to be evaluated in aggregate to assess overall rates and trends within the study and at individual study sites.

Each site's Principal Investigator and their research team (co-Investigators, research nurses, clinical coordinators, and data managers) are responsible for identifying adverse events and determining if the event is anticipated or unanticipated as a complication of the KPMP biopsy or the nature of the CKD/AKI populations being recruited. A list of anticipated biopsy-related adverse events is provided in **Table 3**. Pain in the area of biopsy needle insertion and a feeling of internal discomfort on the side of the biopsy are common but generally mild complications that require only modest analgesia. These symptoms may occur only after the local anesthetic has worn off and will be assessed on a follow-up participant call or prior to discharge from observation the day after the procedure. Pain and discomfort should resolve within a few days of the biopsy. A small number of participants may have macroscopic hematuria, which usually occurs shortly following the biopsy. Subcapsular and perinephric hematomas are common, may be asymptomatic, but should be readily identified by the post-procedure kidney ultrasound, and usually do not require intervention. Some complications like soft tissue infection, arteriovenous fistula, and perhaps adjacent organ puncture may not be apparent at the time of biopsy or shortly thereafter but may develop over time. For any participant who develops late complications, assessment must be performed to determine relatedness to the KPMP biopsy; and if related, whether it constitutes an unanticipated event.

Table 3. Anticipated Kidney Biopsy-Related Adverse Events

Complication	Data collected	Type of Event
Death	Timing relative to biopsy, cause, autopsy	SAE
Soft tissue infection	Antibiotics required and duration. Hospitalization, LOS, nosocomial complications, white blood cell count, blood cultures, urine culture.	SAE
Puncturing of adjacent organs	Related complications – Rare but possible	SAE

Hemorrhage	Nature of bleed, baseline Hgb, pre-transfusion Hgb, number of units of blood transfused, other interventions to control bleeding (e.g., surgery, interventional radiology)	SAE, if requires transfusion, radiologic or surgical intervention
Arteriovenous fistulae	Hematuria, hypotension, high-output heart failure. Most clinically silent. Need U/S to diagnose.	SAE, if symptomatic. If incidentally found on an ultrasound and not associated with clinical manifestations, hospitalization or prolongation of hospitalization, it is a non-serious AE
Perinephric Hematoma	Transfusion support required (amount), imaging, hospitalization, LOS, intervention required, AKI, hypotension, Intensive Care Unit, nephrectomy, death, nosocomial complications, time to pain resolution, size of hematoma	Usually an AE, but if it requires intervention (pressor support or transfusion) or participant kept overnight instead of going home after 6 hours, or if resulting in prolongation of existing hospitalization, it becomes an SAE.
Subcapsular Hematoma	PRBCs, blood pressure, kidney function, imaging, hospitalization, LOS, nosocomial complications, time to pain resolution, size of hematoma	Usually an AE, but if it requires intervention (pressor support or transfusion) or participant kept overnight instead of going home after 6 hours, or if resulting in prolongation of existing hospitalization, it becomes an SAE.
Hematuria	Clots, obstruction, bladder irrigation, transfusions, hospitalization, length of stay (LOS), time to resolution	Usually an AE, but if it requires intervention (pressor support or transfusion) or participant kept overnight instead of going home after 6 hours, or if resulting in prolongation of existing hospitalization, it becomes an SAE.
Pain	Intensity and follow up, medication required to control pain	Usually a non-serious AE, unless resulting in change in plan of management with unplanned hospitalization or prolongation of hospitalization, in which case an SAE

7.2 Serious adverse events (SAE)

A serious adverse event (SAE) will be defined as any undesirable experience meeting one or more of the following criteria:

1. Death: all deaths within 28 days from the time of kidney biopsy regardless of relatedness to study participation will be reported to the DSMB.
2. New hospitalization: all new hospitalizations that occur that occur within 28 days from the time of kidney biopsy will be reported as SAEs.
3. Prolonged hospitalization: if a KPMP kidney biopsy is done in a hospitalized participant and the hospitalization is prolonged due to an adverse event occurring

within, this will be reported as an SAE.

4. Any life-threatening event that that occurs within 28 days of the kidney biopsy will be reported as an SAE.
5. Any other event occurring within 28 days of the kidney biopsy that results in persistent, significant, or permanent harm or disability will be reported as an SAE

All SAEs of any etiology that occur within 28 days of a participant undergoing a KPMP biopsy should be reported to the DSMB. Reporting timelines and responsibilities are listed in Table 4. Reporting to the Washington University single IRB will be consistent with current single IRB policies.

7.3 Non-serious Adverse Events

Adverse events (AEs) that do not meet the definition for an SAE will be considered to be non-serious AEs. Only non-serious AEs that occur within 28 days of a participant undergoing a KPMP biopsy and which are determined by site personnel to be possibly or definitely related to the biopsy procedure will be systematically reported. If a non-serious AE occurs in a hospitalized participant and it cannot be determined if it is due to a KPMP kidney biopsy or the participant's underlying condition, it should be reported.

Table 4. Proposed Reporting Timelines and Responsibilities

Event	Reporting to DCC	Reporting to SAC	Reporting to IRB	Reporting to DSMB and NIDDK
Death	1 business day	1 business day	1 business days	1 business day
Unanticipated non-fatal AE[a,b]	3 business days	1 week	10 business days	3 business days
Anticipated non-fatal AE[a,c]	3 business days	Weekly summary	Continuing Review	3 business days
Unrelated non-fatal AE[a,d]	3 business days	weekly summary	Continuing Review	3 business days

[a]All non-fatal SAEs regardless of relatedness and all non-serious AEs that are determined by site personnel to be possibly or definitely related and that occur within 28 days of the KPMP kidney biopsy will be systematically reported. Non-serious AEs in hospitalized participants whose relatedness to the KPMP kidney biopsy cannot be determined will be reported as possibly related.

[b]An unanticipated AE is defined by the KPMP IRB as an untoward event that is 1) unexpected in terms of nature, severity, or frequency with respect to the KPMP kidney biopsy and related procedures (see Table 3) and the characteristics of the CKD/AKI population being studied; and 2) is definitely or possibly related to the KPMP kidney biopsy and related procedures.

[c]An anticipated AE is an untoward event that is 1) definitely or possibly related to the KPMP kidney biopsy and related procedures; and 2) is expected in terms of nature, severity, or frequency with respect to the KPMP kidney biopsy and related procedures (see table 3) or the characteristics of the CKD/AKI population being studied.

[d]Non-serious AEs that are determined by site personnel to be unrelated to the biopsy procedure that are reported to the DCC will be included in reports to the SAC, IRB, DSMB and NIDDK.

7.4 Rules for Immediate Review by the DSMB

Although the data safety monitoring board (DSMB) will have the ultimate responsibility of deciding if an individual site or the whole study should be stopped on the basis of biopsy complications, the following rules may be used to trigger an immediate review by the DSMB.

For individual AKI recruiting sites:

- Occurrence of bleeding requiring transfusion in ≥20% of subjects
- Occurrence of intermediate bleeding requiring angiographic intervention in ≥10% of subjects
- Occurrence of any major bleeding requiring nephrectomy or other surgical intervention
- Occurrence of any death directly related to the biopsy

For individual CKD recruiting sites:

- Occurrence of bleeding requiring transfusion in ≥10% of subjects
- Occurrence of intermediate bleeding requiring angiographic intervention in ≥5% of subjects
- Occurrence of any major bleeding requiring nephrectomy or other surgical intervention
- Occurrence of any death directly related to the biopsy

Aggregate complication in the consortium-AKI

- Occurrence of bleeding requiring transfusion in ≥10% of subjects
- Occurrence of intermediate bleeding requiring angiographic intervention in ≥5% of subjects
- Occurrence of any major bleeding requiring nephrectomy.
- Occurrence of any death directly related to the biopsy.

Aggregate complication in the consortium-CKD

- Occurrence of bleeding requiring transfusion in ≥7% of subjects
- Occurrence of intermediate bleeding requiring angiographic intervention in ≥3% of subjects
- Occurrence of any major bleeding requiring nephrectomy.
- Occurrence of any death directly related to the biopsy

8 Post Enrollment Engagement Strategy

8.1 Community Engagement Committee (CEC)

The CEC, inclusive of patient-representatives, families, and clinicians will meet regularly by webinar/teleconference to review study progress and give input on KPMP engagement strategies. Dissemination of research progress and findings will be folded into each meeting as the study progresses.

8.2 Study participants

Summary study information will be communicated about the KPMP semiannually by printed materials distributed at participants' study visits and will be periodically updated on the KPMP website. Participant retention and ongoing engagement will be promoted through newsletters, personal recognition (e.g. birthday and holiday cards), and in-person and other protocol-directed interactions at the Recruitment Sites.

9 Reference kidney tissues

KPMP technologies need kidney tissue for feasibility testing and technology development. In addition, kidney tissue from people without diagnosed kidney disease is needed to generate a reference atlas of kidney tissue. The reference atlas of this control kidney tissue will serve as a benchmark for generating different kidney disease atlases as a part of the KPMP. For these purposes, the KPMP will obtain human kidney tissue collected from sources other than enrolled KPMP participants ("non-KPMP kidney tissue") that then becomes part of the KPMP. Such non-KPMP kidney tissues will be collected under separate IRB approved protocols, or under a waiver of human subjects regulation, and will only be contributed to the KPMP if such transfer is consistent with the informed consent signed by tissue donors or the waiver of informed consent as agreed upon by the IRB overseeing collection of these non-KPMP kidney tissues. The KPMP single IRB will review sources of non-KPMP kidney tissues on a case-by-case basis to ensure the collection protocols meet these requirements. While the consortium realizes the limitation of obtaining a true "normal" kidney, tumor nephrectomy tissue and living donor implant biopsies have been identified as sources of comparison kidney tissue that would aid in tissue processing and technology development, establishing quality assessment and control parameters, and contributing to a reference atlas. Other appropriate sources of previously-collected non-KPMP kidney tissue may also be identified for these purposes.

10 Human Subjects Considerations

10.1 Potential Risks and Benefits

10.1.1 Kidney Biopsy Risks

A review of the medical literature has identified the most common medical complications of kidney biopsy and their reported frequencies, which are listed in Table 5. We acknowledge that the literature on biopsy complication rates may suffer from publication bias. While these data demonstrate that kidney biopsy has a low incidence of serious complications (fall in hemoglobin necessitating transfusion, embolization or nephrectomy; or death), the general risk for these events is quantified in Table 5 and

study participants or their LAR will be fully informed of these risks through the informed consent process.

Table 5. Native Kidney Biopsy Bleeding Procedural Complication Rates* [26].

General Complications:	
Macroscopic Hematuria	3.5 (2.2-5.1)
Blood Transfusion	0.9 (0.4-4.1))
Hematoma	11.6 (7.0-18.4)
Angiographic Intervention	0.6 (0.4-0.8)
Urinary Tract Obstruction	0.3
Unilateral Nephrectomy	0.01
Death	0.08-0.1%
Transfusion rates for:	
14 vs 16 gauge needle	2.1 (0.9-3.8) vs 0.4 (0.0-1.4)
14 vs 18 gauge needle	2.1 (0.9-3.8) vs 0.6 (0.1-1.5)
Series with ≥ 10% AKI vs < 10% AKI	1.1 (0.6-1.8) vs 0.04 (0-0.3)
Transfusion rates for:	
Serum Creatinine ≥2 vs <2	2.1 (0.9-3.8) vs 0.4 (0.0-1.3)
Hemoglobin <12 vs ≥12	2.6 (1.4-4.0) vs 0.5 (0.1-1.1)

*Given as percentage; values in parentheses, when shown, are 95% confidence limits

10.1.2 Financial Risks

Participants and/or their insurance company(s) will not be charged for clinical care related to study participation, including services, supplies, and procedures. Participants may receive financial compensation who experience a burden as a result of participation in study activities. They may also receive reimbursement to cover travel and related expenses for study visits. The research staff will review the travel reimbursement policy with study participants at the Recruitment Sites.

If a participant suffers a complication, illness, or injury as a result of study participation, treatment will be provided through clinical services at the Recruitment Sites.

10.1.3 Genetic risks

Even without personal health identifiers, genetic information is unique to each subject. There is a potential risk that a subject could be identified from genetic data generated by KPMP. In addition, the genetic data has ancestry and health information, which the subject may wish to keep confidential. These risks may increase in the future as technologies advance and more researchers study participant genetic information. The Genetic Information Non-discrimination Act is a federal law that prevents insurance companies from using genetic information to deny health insurance coverage. The law also prevents employers from getting or using genetic information for employment-related decisions. However, the law does not prevent companies that provide life insurance, disability insurance or long-

term care insurance from using genetic information and participants or their LAR will be fully informed of this potential risk through the informed consent process.

10.1.4 Confidentiality

Per the KPMP protocol, participant health records will not be shared directly with those not involved in participants' clinical care or in the KPMP, except as required by law. Some information from the participant's health record will be added to their KPMP record. Records relating to this study will be kept confidential, and all Personal Health Information (PHI) data will be protected according to the expectations under the HIPAA Privacy Rule. PHI will only be shared with additional consent from the participant. Only study identifiers will be used in study records. An encrypted database linking the study identifier to the subject's identifiers will be stored separately to facilitate linkages with recruitment sites. Only KPMP personnel will have access to this database. Paper records, if any, will be stored in a locked cabinet in a secure room. Publication of general study results will not identify individual study participants.

The following groups will have access to participant health records from the KPMP study: research staff at the recruitment site; Clinical Data Coordinating Center at the University of Washington. The following groups will have access to de-identified participant health records from the KPMP study: the National Institutes of Health/National Institute of Diabetes, Digestive, and Kidney Diseases and their representatives; Institutional Review Board at Washington University.

KPMP data are covered under a Certificate of Confidentiality agreement from the NIH (Section 2012 of 21st Century Cures Act as implemented in 2017 NIH Certificates of Confidentiality Policy). A Certificate of Confidentiality allows researchers to refuse to disclose identifiable research information in response to legal demands. Certificates are issued to researchers to help protect the privacy of human subjects enrolled in sensitive, health-related research. A description of the KPMP will be available on http://www.ClinicalTrials.gov. This website will not include information that can identify study participants or Personal Health Information. This website may include a summary of the study results.

As described in more detail below, biopsied tissue will be banked and subjected to detailed molecular biology investigation. Genetic information, particularly on a scale likely to be generated from genome-wide SNP arrays or whole exome and/or genomic sequencing, is individually identifying and the risks of re-identification of research participants from unauthorized access to their genomic information is a well-recognized potential privacy risk.[27] To protect participants from such risks, genetic information will be released only to researchers for KPMP-approved ancillary studies. These researchers will sign a data use agreement that includes a stipulation that prohibits attempts to re-identify study subjects.

Federal and State laws, including the Genetic Information and Nondiscrimination Act (GINA) which makes it illegal for health insurance companies, health plans, and employers to discriminate against individuals based on their genetic information, afford some measure of protection for participants in the event of an unintended disclosure of genetic data.

10.1.5 Potential benefits

Most participants in KPMP will not benefit directly from the kidney biopsy or the other KPMP-related procedures. Rather, the benefits of the study will primarily accrue to society in general through the advancement of basic science and medical knowledge regarding kidney diseases. It is hoped that the knowledge gained from KPMP will lead to treatments from which future patients will benefit, and it is this hope for future benefit that justifies asking participants to agree to the real, but small risk of kidney biopsy.

Although most participants are unlikely to benefit directly from KPMP participation, there are some situations in which direct benefit is possible (described below). In these circumstances, the KPMP investigators, the participant's clinical management team, or both will review the likelihood and nature of potential benefits as part of informed consent. However, the investigators will avoid exaggerating or unduly emphasizing these potential benefits because doing so could exacerbate therapeutic misconception on the part of potential participants. As the consent forms will make clear, the decision to participate in KPMP should not be influenced by an expectation of direct benefit. Participants should include only those who think the risks of biopsy are warranted by the potential benefit to society and future patients.

To allow for the possibility of direct benefit, the KPMP clinical pathology report will be provided to a physician chosen by the subject as soon as results are available. This clinical pathology report may provide or confirm a diagnosis of CKD or AKI, may provide prognostic information regarding the expected future course of CKD or AKI, or may be used to direct the participant's medical care. The KPMP clinical pathology report will become a part of participant's medical record. Results from the omics research may be shared at some time in the future, but there is expected to be a delay given all the steps in processing and analyzing information across samples.

A KPMP clinical pathology report is most likely to be useful for participants for whom the cause of CKD or AKI is uncertain based on clinical presentation. For some such participants, a kidney biopsy outside of the KPMP may be an alternative to participating in the KPMP. Even for participants with diagnostic uncertainty, however, the kidney biopsy may not determine a clear cause of CKD or AKI, or the underlying diagnosis may not directly change medical management.

A KPMP clinical pathology report is less likely to be useful for participants for whom a specific cause of CKD or AKI is already strongly suspected based on clinical presentation. For these participants, knowledge gained through the kidney biopsy may be of no benefit at all. However, for a small proportion of such participants, the kidney biopsy may reveal a cause of CKD or AKI that is not expected based on clinical presentation, which may substantially alter the prognosis or treatment of kidney disease. For many participants for whom a specific cause of CKD or AKI is already strongly suspected, a KPMP clinical pathology report may confirm the suspected cause of CKD or AKI and provide some information on the extent of kidney damage, refining prognostic expectations but not directly affecting medical management.

Beyond the KPMP clinical pathology report, KPMP participants will receive results of some standard clinical laboratory values, such as serum creatinine concentration and estimated GFR. In addition, participants may learn about kidney disease diagnosis, prognosis, and treatment through interactions with the KPMP study team. These sources of information may help increase some participant's understanding of their own kidney disease.

Additional knowledge may be gained from the research analyses of the kidney biopsies and other data sources that could identify causes of the kidney diseases studied by KPMP and improve the treatment of these diseases. However, this knowledge is not expected to benefit KPMP participants directly. The KPMP does not intend for research results to become part of a subject's medical record.

10.1.6 Risk Benefit Balance

As outlined above, relevant potential risks for participants include physical harms due to adverse events associated with complications from the kidney biopsy, financial risks associated with clinical care related to participation in the research, and risks to confidentiality of genetic information or other personal health information accrued in the course of study participation. Of these risks, the risk of injury or even death as a complication of kidney biopsy is low, but sufficiently serious as to warrant complete description as part of the informed consent process. It is important for the majority of participants for whom kidney biopsy is not clinically indicated to be aware that they are assuming risks that they would not otherwise assume in the course of their clinical care, for societal not individual benefit. Similarly, for those participants for whom kidney biopsy would ordinarily be conducted for clinical purposes, an incremental additional risk of injury is associated with the extra tissue collection required for research that is unlikely to yield clinical benefit.

To minimize the chance of therapeutic misconception on the part of participants, the consent process will focus on the modal case in which participants will not benefit directly from KPMP-related procedures. The consent form will clearly articulate the risks as well as the lack of anticipated benefit from participation. It will further specify that potential participant should consider participation only if they conclude that their desire to help people in the future outweighs the personal risks of participation.

The study team believes that substantial advances in kidney science require the kind of information obtained from the research-only biopsies proposed in this protocol. If realistic alternatives existed to advance science and therapeutics without subjecting participants to the biopsy-related risks, the study team would have adopted them. In the absence of these alternatives, the study team has chosen to appeal to the altruism of participants, many of whom are believed to be willing to help future generations by exposing themselves to the small but real risks of this study.

10.2 Clinically Actionable Findings

Clinical biopsy results will be communicated to the participant's clinician, who will then communicate the results to the participant. A copy of the final biopsy report generated by the site pathologist will be included in the participant's Electronic Health Record. The final report from the ultrasound or CT scan used to localize the kidney prior to biopsy will also be included in the participant's Electronic Health Record and any incidental findings based on these studies will be communicated to the participant's clinician. If necessary, the PIs can facilitate referral to a nephrologist or relevant sub-specialist but will not themselves provide care to participants.

Given the deep molecular phenotyping of the biospecimens and biopsies, there may be identification of potentially actionable, but currently "silent" incidental findings. Participants may be given the option to receive these data or indicate that they wish not to be informed of such findings. For those participants who agree to the receipt of individual results, any medically actionable incidental findings will be communicated to the participant, as well as the physician chosen by the subject. In particular, participants in KPMP are likely to undergo whole exome and/or whole genome sequencing. For those participants who agree to the receipt of individual results from genetic analyses, any medically actionable findings (as defined by the American College of Medical Genetics and Genomics or ACMG) may be communicated to the participant, as well as the physician chosen by the subject (as state laws allow). Additionally, participants may have the option of having information about risk alleles related to kidney function (for example risk variants of the APO-L1 gene) returned even if not clearly medically actionable. A process within the KPMP will assist in the decision how and when to return other research results to participants. The oversight process will include a designated panel of KPMP stakeholders, experts, and patient representatives, as part of KPMP operational oversight. Exactly when such incidental (molecular, genetic) results may become available in the course of KPMP research is uncertain. The KPMP return of results process will also include a periodic re-evaluation of risks and benefits associated with return of results from KPMP and from knowledge gained in other similar studies and as updated by the ACMG.

Since research methods often do not have the accuracy of diagnostic tests, any clinically actionable findings may need to be confirmed by a clinical test performed in a certified diagnostic laboratory. Therefore, if a potentially actionable finding is detected, study staff will recommend an appropriate diagnostic test to confirm the findings provided the participant has agreed to receive such information. If necessary, the study staff will facilitate referral to a nephrologist, clinical geneticist, or other relevant sub-specialist, but will not themselves provide care to study subjects. The participant and their treating physicians will together decide whether they want to perform such confirmatory test(s).

10.3 Data Sharing and Protection of Confidentiality

All molecular and genetic data will be stored centrally by the Central Hub and where appropriate will be deposited in the federal data repository, such as the database of Genotypes and Phenotypes (dbGaP),

for wider sharing and research use. In addition, data will be made available through the online KPMP Kidney Atlas.

10.3.1 KPMP Data Sharing via online KPMP Atlas

The Central Hub and the KPMP will develop the Kidney Tissue Atlas. This will be accomplished through developing a series of multi-scalar data integration models to define kidney disease mechanisms in their spatial context. The Kidney Tissue Atlas will be rooted in standard pathology images at the two dimensional level, and use serial sections for three dimensional reconstructions populated with orthogonal information sources. The static models will be extended using spatiotemporal computation, using techniques such as partial differential equation based dynamical modeling. To identify distinct cellular types, single-cell level -omics datasets will be used in probabilistic models to identify a hierarchy of cell types with a focus on disease-associated subtypes. Integrative, cell-type-specific networks will be generated to identify the patient-specific molecular characteristics of disease. The spatial information will be used to resolve the location of cell types and the expression of genes to particular regions in the kidney. A feature-rich, highly scalable and easily sustainable multi-site web platform will be deployed for visualization of the complex multiaxial two- and three-dimensional interrogations and visual concepts. These data will be broadly shared in a publicly available fashion and will be aggregated into summary metrics. However, underlying individual-level participant data will not be released publicly through the Atlas. Individual-level data will be available only to qualified researchers who have been approved by KPMP to conduct research on these data with appropriate privacy constraints.

10.3.2 KPMP Data Sharing with researchers

The KPMP data will be used as a resource for researchers nationally and internationally who are doing research broadly related to health and disease, precision medicine, technology development, drug discovery, or other research. The researchers may come from academic, private, government, pharmaceutical or other health care organizations. Investigators will be able to receive de-identified data for research under certain conditions. Data sharing and access to de-identified data will require an appropriate data request and approval by the KPMP Ancillary Studies committee and by the central IRB/ethics committee. Data provided to approved investigators will be stripped of personal identifiers. and the investigator(s) will sign a data use agreement that includes a stipulation that prohibits attempts to re-identify study subjects.

10.3.3 KPMP Data Sharing through public and NIH data repositories

In addition to the data sharing mechanisms described above, genomic sequence (whole exome sequencing and whole genome sequencing) and Genome Wide Association Study (GWAS) datasets derived from clinical research and funded by the NIH will be made available to investigators through a web portal called the Database of Genotypes and Phenotypes (dbGaP). Relevant datasets developed through the KPMP will be submitted to dbGaP or similar internationally recognized data repositories. Qualified investigators will be able to receive de-identified genomic and phenotypic data from these

dbGaP datasets. dbGaP has two access levels, open and controlled. Open data may be viewed by anyone. Controlled access is for downloading of de-identified participant level data and requires pre-authorization. Data releases to investigators for approved research purposes and analyses will be stripped of personal identifiers.

Eligible researchers may make an application to view individual level data that has been submitted to dbGaP and these applications are co-signed by both the investigator and the signing official at the investigators institution. These requests will be reviewed by the appropriate NIH Data Access Committee at the appropriate NIH Institute or Center.

Submission of the data access request will constitute agreement and acknowledgment by both the PI and the institutional signing official to the terms of use for the specific dataset(s) requested, which are detailed in the "Data Use Certification" (DUC) documents that are provided on the dbGaP website. The DUC statements outline policies and procedures for using the data, such as limiting use to the project described in the Data Access Request form; not distributing the data beyond those permitted to handle it; not attempting to identify or contact study participants from whom phenotype data and DNA were collected; awareness of the specified principles regarding intellectual property; adhering to policies on the timeframe for publications stemming from the data; and other provisions designed to protect the confidentiality of study participants and to foster scientific advance.

10.4 Informed Consent

After reliance agreements are established with the CKD and AKI Recruitment Site IRBs and with approval by the single IRB for the KPMP, written informed consent will be obtained from all study participants or their LAR. Prospective participants will first be contacted by their treating clinician and/or a clinical team member before contact by KPMP-affiliated researchers. If they (or their LAR) express interest and willingness to be contacted about the KPMP, then potentially eligible study participants will meet with a research coordinator and study investigator to review the study in detail. They will be given information about the study both verbally and in easily understandable printed materials. Study information will also be posted on the KPMP website. KPMP investigators and staff will review potential risks and benefits, individualizing as applicable for each potential participant and including input from the treating clinician whenever appropriate. After sufficient time to review the KPMP study information, as well as ask questions and receive answers about the study, the potentially eligible study participant or their LAR will be asked to sign and date the consent form indicating their understanding and willingness to participate. Site investigators will be available to answer any questions or provide additional information to prospective study participants or their LAR. The biopsy operator will be available to explain the biopsy procedure and safety risks.

The Washington University (St. Louis) single Institutional Review Board will review and approve the KPMP Informed Consent Form along with patient-facing materials, the study protocol and all amendments or changes. The KPMP study will comply with the Declaration of Helsinki.

10.5 Withdrawal Procedures

During the recruitment and consent process, all potential participants will be informed that participation is voluntary, that they can change their mind at any time, and that their clinical care will not be affected regardless of their decision to participate or not participate in the KPMP. Research staff will emphasize that if a subject decides to enroll, he or she may withdraw from the study at any time, for any reason, specified or unspecified, and without prejudice. Subjects may wish to withdraw but permit ongoing contact by phone for limited clinical data collection. The site investigator will record the reason for the early termination and if the participant allows any further contact.

Participants are informed during the consenting process that data/specimens previously collected and already used in research cannot be withdrawn nor destroyed. For instance, it is not possible to destroy all sample remnants and information already distributed or analyzed. In contrast, stored biospecimens that have not been analyzed or distributed to qualified researchers will be destroyed. Existing datasets, including data from withdrawn participants, will remain available to promote reproducibility of research, a NIH priority. However, no new data or samples will be collected.

The withdrawal status of a given participant should be recorded within the KPMP database within two business days. Confirmation of withdrawal will be provided to participants via email and/or letter. Participants will be informed upon enrollment that their name and basic contact information will never be destroyed, even after withdrawal, due to regulatory requirements (e.g., as part of archived consent forms); however, the information will be maintained with the utmost security. The participant's records will be flagged to show that the participant withdrew and indicate if any further contact by study staff is permitted. The participant's KPMP record will no longer be available through the Participant Portal.

11 Study Administration

11.1 Organization and Participating Centers

11.1.1 Central Hub

11.1.2The overarching objective of the Central Hub of the KPMP is to create an environment to promote scientific rigor, participant safety, and the interdisciplinary team science necessary to successfully complete the aims of the KPMP. Two lead institutions (University of Washington andUniversity of Michigan) constitute the core of the Central Hub. The Central Hub is organized into twointerconnected components: an Administrative Core, and a Clinical Data Coordinating Center. The primary responsibilities of the Administrative Core are to support core functions of the KPMP (meetings and other functions within the KPMP and with the KPMP Observational Study Monitoring Board, DSMB, IRB, and sponsor; coordination of IRB interactions; enhancement of group dynamics and shared decision-making; and representing KPMP to the broader scientific and lay communities); to establish, organize, and support KPMP Committees and other work groups; to establish, organize, and support a Community Engagement Committee; and to manage and administer an Opportunity Pool to form new Partnerships for the KPMP. The primary responsibilities of the Clinical Data Coordinating Center are to coordinate and monitor recruitment, centralized training, sample collection, data quality, and longitudinal data collection; to provide statistical leadership; and to curate the longitudinal data resource by tracking all data and biospecimen transfers, repository impacts, uploads to public databases, and consulting with interested investigators in support of new research agendas. Kidney Tissue Atlas Coordinating Center

The Kidney Tissue Atlas Coordinating Center, a.k.a. Kidney Mapping Atlas Project (KMAP), will collaborate with the KPMP Recruitment Sites (RS), Tissue Interrogation Sites (TIS), and Central Hub (CH) to obtain and evaluate kidney biopsies from participants with acute kidney injury (AKI) or chronic kidney disease (CKD), create a Kidney Tissue Atlas, define disease subgroups, and identify

critical cells, interstitial components, pathways, and targets for novel therapies. The specific responsibilities of the KMAP will be to clean, harmonize, store, and curate all de-identified KPMP data and (1) use state-of-the-art computational approaches to carry out integrative analyses, and (2) build an interactive Kidney Tissue Atlas with FAIR principles (findable, accessible, interoperable, and reusable) to promote data retrieval, exploration, discovery, and analysis by the community. KMAP will include three different cores. The Data Management Core (DMC) will ingest, clean, harmonize, store, and archive all de-identified KPMP data and metadata with FAIR principles; optimize platforms for data integrity, dimensionality reduction, harmonization, scalability, security, accessibility, re-use, and potential migration to a cloud-based environment; actively biocurate data to ensure analytic pipelines produce biologically plausible results and that molecular, pathological, and clinical findings can be harmonized; use and enhance existing KPMP and other developed ontologies, controlled vocabularies and semantically indexed data across individuals, technologies, and disease, to develop a computational framework for the exploration of data and enable discovery; build and incorporate QA/QC tools that can determine missing, incomplete, and erroneous data and sources of technical noise to ensure that only high-quality is released and displayed to the public; and support and enhance a collaborative informatics community across the KPMP. The Data Analysis Hub (DAH) will develop computational and modeling strategies to integrate clinical phenotypic, physiologic, digital histopathologic and molecular data; harmonize with complementary datasets to maximize discovery (e.g., Human BioMolecular Atlas Program (HuBMAP), Human Cell Atlas (HCA), GenitoUrinary Development Molecular Anatomy Project (GUDMAP), ReBuilding a Kidney (RBK)); and execute a comprehensive systems-level and integrative analysis to uncover novel molecular pathways and define new sub-phenotypes of AKI and CKD. The Data Visualization Hub (DVH) will establish and/or maintain a Digital Pathology Bank of existing KPMP and new biopsy whole slide images and develop tools for accessing and analyzing image data, including the ability to perform comparisons and searches, and curation or quality control tasks such as de-identification and artifact detection; create and manage an interactive Kidney Tissue Atlas with FAIR principles representing health, disease, sex, age, race, and ethnicity; and lead and coordinate KPMP efforts to develop potential user personas for the Kidney Tissue Atlas and Digital Pathology Bank.

11.1.3 Recruitment Sites

KPMP Recruitment Sites were constituted based on the expertise of investigators and their commitment to the proposed study objectives as well as the size of target population, racial, gender, and age composition of their referral population base, their experience conducting clinical studies, and the quality of their existing clinical study infrastructure. The primary responsibilities of the Recruitment Sites include screening, recruiting, and enrolling study participants; ensuring participant safety and ethical acquisition of tissue; obtaining participants data and biospecimen; following study participants longitudinally over time; ensuring participant confidentiality; and participating in the broad overall functions of the KPMP.

11.1.4 Tissue Interrogation Sites

Tissue Interrogation Sites will receive, use and develop innovative technologies to analyze human kidney tissue to create a kidney tissue atlas, define disease subgroups, and identify cells, pathways and targets for novel therapies. The primary responsibilities of the TISs include analyzing kidney tissues; ensuring robust reproducibility and quality control; transmitting omics and other data to the Central Hub for analysis; and participating in the broader functions of the KPMP.

11.2 Committees

11.2.1 Steering Committee

The primary governing body of the study is the Steering Committee. The Steering Committee is comprised of the PIs of all KPMP sites, NIDDK staff, and patient representatives. For all issues requiring Steering Committee approval, voting is done either via webinar or electronically, and ideally through unanimous vote. Voting bodies include one patient representative vote, one vote on behalf of the NIDDK, and one vote from each grant. Joint sites have one vote in total. From September 2023 to present the voting body includes eight Recruitment Sites, seven Tissue Interrogation Sites, one patient, one NIDDK, one KMAP and one Central Hub to represent a total of 19 votes. From July 2017 – August 2022 the voting body consisted of six Recruitment Sites, five Tissue Interrogation Sites, one patient, one NIDDK and one Central Hub to represent a total of 14 votes. The Steering Committee will develop policies for the study pertaining to accessing participant data and specimens, ancillary studies, performance standards, publications and presentations. They will refine the study protocol, meet to discuss the progress of the study and resolve problems that arise. The Steering Committee may establish subcommittees on such topics as recruitment, measurement of kidney function, risk factor assessment for kidney disease, genetic studies, quality control, communications and ancillary studies. Small working groups may be established to prepare manuscripts, white papers, presentations, and other functions as needs determine.

11.2.2 Executive Committee

A KPMP Executive Committee will help implement the policies of the Steering Committee. The Executive Committee will include representatives from the Central Hub, KMAP, NIDDK, Recruitment Sites, and Tissue Interrogation Sites.

11.2.3 Additional Committees and Working Groups

The KPMP will constitute Committees and Working Groups will collaboratively develop, refine, and oversee the core functions of the KPMP. The Working Groups will be comprised of KPMP investigators from the Recruitment Sites, Tissue Interrogation Sites, KMAP and the Central Hub. The KPMP Executive and Steering Committee will nominate and elect one or more KPMP investigator(s) to lead

each Committee and Working Group and will be responsible for replacing a Committee or Working Group leader if necessary. Project Managers housed within the Central Hub and KMAP will support the Committees and Working Groups, coordinating meeting times and documents, preparing agendas and minutes, and helping to execute Committees and Working Group plans. Each Committee and Working Group will meet in person at the semi-annual KPMP Steering Committee meetings and regularly by teleconference. Teleconference minutes will be reviewed on a rolling basis by the Executive and Steering Committees. The number and functions of Committees and Working Groups will vary over time according to consortium needs and as directed by the Steering Committee. Quality control and ensuring the safety of participants and the confidentiality of their data will be key feature of protocol development for each Committee and Working Group. Overall Quality Assurance is overseen by the Quality Assurance Committee.

11.3 Policies

11.3.1 Ancillary Studies

To enhance the value of KPMP, the Steering Committee welcomes proposals from individual investigators to carry out ancillary studies. Nevertheless, to protect the integrity of the KPMP, such ancillary studies must be reviewed and approved by the Ancillary Studies (or equivalent) Committee and the Steering Committee before submission for external funding. The Steering Committee has developed a comprehensive policy that clearly defines requirements and describes a process for review and approval of ancillary study proposals. An ancillary study may use clinical or molecular data generated from the KPMP cohort to test hypotheses, which address study goals but are not part of the core study protocol. Ancillary studies derive support from non-KPMP study funds. A typical ancillary study will propose the collection of additional data not collected or analyzed as part of the routine KPMP data set. Ancillary studies may be submitted by investigators within the KPMP or investigators without a prior relationship to the KPMP. Ancillary studies require external funding. Examples include studies funded by investigator-initiated NIH research awards (R series awards, K series awards, and other career development awards) or grants from academic institutions or private sources (e.g. private foundations, pharmaceutical companies, etc.) Any ancillary study must have sufficient funding to cover the costs incurred by the KPMP Recruitment Sites, Tissue Interrogation Sites, and Central Biorepository (e.g. to process or ship samples), and by the Central Hub. The KPMP Ancillary Studies Policy is available on the KPMP website https://www.kpmp.org/for-researchers.

11.3.2 Publications and Presentations

It will be the policy of the KPMP study that preparation of all publications or presentations, other than materials prepared for local publicity purposes, must be assigned by the Publications and Presentations Committee to specifically appointed writing committees, and that all such materials must be reviewed and approved by the Committee before publication. A detailed description of

writing activities in KPMP as described in the KPMP Publication Policy is available on the KPMP website (https://www.kpmp.org/publications-presentations).

12 Data Management

12.1 Confidentiality and Security

12.1.1 Data Security

We will use HIPAA-aligned computing environments for managing KPMP data. All clinical data are encrypted with detailed access logs and audit trails. All systems are stored in a secure data center management by UW Information Technology. Research IT staff will perform regular maintenance, install upgrades, and implement a plan for secure and protected backups of KPMP data.

12.1.2 Participant Research Identifier

The Clinical Data Coordinating Center will create de-identifying participant identifiers that will be used for the purposes of data management. This identifier will be used within all parts of the data management process. The mapping between participant identity and the identifier will be managed by an honest broker within the Clinical Data Coordinating Center of the KPMP Central Hub.

12.1.3 User Authentication

Access to secure systems will be authenticated through their home institutions using Single Sign On technology. This will be based on the Shibboleth identity management and will enable users to use the same credentials that are maintained for institutional computer resources, such as email. If a user comes from an institution that does not support Shibboleth technology, the KPMP Clinical Data Coordinating Center staff will create a University of Washington NetID for that individual. This NetID will be annually verified with the user for continued access or will be removed when the user leaves the KPMP project.

12.1.4 User Access Groups for Authorization

Access to specific systems and data will be provided through carefully maintained Access Groups and maintenance of institutional identify credentials as described above. Potential users will request access through an online form in REDCap and will be confirmed by Clinical Data Coordinating Center staff. Access Groups will be managed in the University of Washington's instance of the Internet2 Enterprise Grouper software. Grouper is an enterprise access management system designed for the highly distributed management environment and heterogeneous information technology environment common to universities. Access Groups will be defined for each application (Specimen tracking, EHR

database, etc.) and role in that application. Access level will be defined by predefined role (user, site, administrator, etc.)

12.1.5Web applications

The Clinical Data Coordinating Center will host various web applications in support of the KPMP protocol functions including Specimen Tracking, Clinical Trial Management tools and a Publications tracking system. All web applications and systems be HIPAA-compliant and meet CRF 21 Part 11 regulations. At the Clinical Data Coordinating Center all clinical data and data transmissions are encrypted with detailed access logs and audit trails. Servers are virtualized, running on systems in a locked, dedicated, climate-controlled server room located at the Sand Point campus with motion-activated video surveillance, a security alarm system and uninterruptible power supply units. Regular maintenance, upgrades, system monitoring and secure and protected backups including offsite backups are performed by Clinical Data Coordinating Center staff. These computing systems are on a private subnet behind a firewall. Network connectivity and monitoring is provided by the UW Network Operations Center.

12.2 Electronic Data Capture System (EDC)

12.2.1 Specimen Tracking System

The Clinical Data Coordinating Center will manage a custom in-house built web application to be used for tracking specimens in transit between the sites. This system will be tightly integrated with our primary EDC system and KMAP. This application will provide a communication and tracking layer between the sites that will help verify that all specimens are tracked, validated for quality issues, and data results are transferred to KMAP appropriately.

The specimen tracking website is built in Python using the Django framework with a MySQL database backend. It can be accessed only through a secure, 256-bit AES encrypted connection using SSL and the system is CFR-21 Part 11 compliant. The system tracks all access and changes to data, guards against excessive logins and requires site re-authorization after a period of inactivity.

12.2.2 UW Medicine REDCap System

The UW Medicine Research IT's instance of the REDCap System will be used for data collection, processing and management of clinical research information for this project. REDCap is a tool for electronic data capture in clinical research. The research team can create and design surveys and forms in a web browser and engage potential respondents using a variety of notification methods. The REDCap System provides secure, web-based applications that are flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry. REDCap offers easy data manipulation with audit trails and reporting for reporting, monitoring and querying participant records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). Our

administrators are actively involved in the global REDCap consortium by serving on various committees (FAQ, knowledge-base migration, Epic integration, new administrator workshop) and being active at the yearly conference (leading break-out sessions, creative use workshop, posters, presentations) and are always up to date on the latest best practices for use of REDCap. REDCap is managed in a secure data center and is regularly maintained and backed up. The system is regularly audited by the UW Medicine Chief Information Security Officer's office and is compliant with all policies and procedures for managing clinical research data.

12.3 Electronic Health Data (EHR)

Longitudinal Electronic Health Record data will be collected from KPMP Recruitment Sites as described in Section 5. These data will be collected at each Recruitment Site in accordance with both local and federal laws and institutional policy and procedures. At each site, it is likely an 'Honest Broker' model will be applied where a data services informaticist, who is not a part of the research team, will query and provide authorized data to the KPMP Central Hub. This data will be matched to a participant research ID.

12.3.1 Recruitment Site EHR Data Management

RSs will likely utilize an honest broker to query clinical systems and provide structured text files to the research team. These data will comprise the participant 'research' health record. The research record will be processed by the site research team in a secure and encrypted HIPAA aligned computer environment and the data will be stripped of identifiers (using the participant research ID) and will be checked for data quality and mapped to the KPMP common data model if it is not extracted in that form. Data will be uploaded securely using a specified text format to the KPMP Central Hub electronic data capture system or programmatically using a secure and encrypted Application Programming Interface.

12.3.2 KPMP EHR Data Management

Participant EHR data will be securely uploaded to a secure, enclave HIPAA aligned computing environment by Recruitment Sites without participant identifying information using an OMOP data model. Participant EHR-based observations may be annotated to the secured REDCap system for further data processing and transformations. All processing and management of the participant health records will be performed on secure, encrypted HIPAA-aligned computing environments within the Clinical Data Coordinating Center. Access to these systems will be limited to the appropriate access groups as described in Section 12.1. Processed data will be added to a database of participant electronic health record data that will be stored in a secure, encrypted relational database (likely MySQL or Microsoft SQL Server). This database will only be accessible by IT and informatics members in the KPMP Central Hub Clinical Data Coordinating Center. Access to clinical data and use by n other KPMP entitieswill follow an

honest broker model for the purposes of integrating with other KPMP datasets. All data integration will be performed using participant identifiers.

13 Quality Control/Quality Assurance

For data collection and management, we will assure high quality through several mechanisms. First, we will have documented standard operating procedures for all data entry and management as well as training for onboarding new users to systems. All systems will implement version control and other forms of tracking, so data provenance and history is auditable. We have developed well defined access control and use access control groups to define which individuals have access to which data and who is authorized to submit or change data. Within REDCap, we use best practices such as required fields, standard ontologies, forced fixed ranges and other methods for real time data checking and validation. We can use collected data to apply tools for identification of data inconsistency or quality, such as in EHR datasets. Finally, we can apply regular (possibly random) audits of submitted data to ensure data quality. The KPMP Quality Assurance Committee will develop and implement a formalized Quality Management Program that documents processes, procedures and responsibilities for achieving quality policies and objectives.

13.1 Data collection and management

Mechanisms to assure high data quality include: 1) Documentation of standard operating procedures for all data entry and management as well as training for onboarding new users to systems. 2) All systems will implement version control and other forms of tracking, so data provenance and history is auditable. 3) Access control and use access control groups will define which individuals have access to which data and who is authorized to submit or change data. 4) Within REDCap, best practices are used, such as required fields, standard ontologies, forced fixed ranges and other methods for real time data checking and validation. Collected data can be used to apply tools for identification of data inconsistency or quality, such as in EHR datasets. 5) Regular (possibly random) audits of submitted data will ensure that data quality standards remain over time.

13.2 Training and Certification Plan

Quality data collection and appropriate conduct of the study will require careful attention to the training of personnel at the Central Hub and participating sites. Training and certification sessions for Recruitment Site Research Coordinators and data entry personnel will be held prior to the initiation of participant recruitment. The protocol, manual of operations, forms and other materials will be distributed to the appropriate personnel prior to the training session. Each RS's personnel will be trained centrally in the study requirements, standardized measurement of height, weight, and blood pressure, requirements for laboratory specimen collection and processing, counseling for adherence and the eliciting of information from study participants in a uniform and reproducible manner.

During the training session, presentations will be made by staff members of the Central Hub, and the Central Biorepository. This training session will cover participant recruitment and participant eligibility and exclusion criteria. The study personnel will be shown how to enroll participants as uniformly as possible over time and ways to reach the recruitment goals in the allotted time period. The data to be collected and the procedures to be conducted at each visit will be reviewed in detail. Each of the data collection forms and the nature of the required information will be discussed in detail on an item by item basis. Entering data forms, responding to data discrepancy queries and general information about obtaining research quality data will also be covered during the training session.

13.2.1 Electronic Data Capture

UW Medicine Research IT has extensive training materials for users (both beginners and more advanced) across a variety of platforms (in-person classes, online videos, email newsletters and FAQ pages) for REDCap. Newsletters and online training material are also available.

13.2.2 Personnel Training

Investigators will maintain study documents on-site and in an orderly fashion for a prescribed period of time and will make available to the sponsor or the sponsor's representative the following documents: the signed study protocol, amendments, informed consent documents, and approval letters from the IRB, all primary source documentation, and all letters of correspondence. The Clinical Data Coordinating Center will maintain all study records for a period in accordance with their internal SOPs and applicable regulations.

14 References

1. USGAO, *Kidney disease research funding and priority setting*. 2017: [online] https://www.gao.gov/assets/690/681714.pdf.
2. RM, B., *Social security amendments of 1972: summary and legislative history*. 1973.
3. Rettig, R.A., *Special treatment--the story of Medicare's ESRD entitlement.* N Engl J Med, 2011. **364**(7): p. 596-8.
4. CfMaM., S., *Chronic Conditions among medicare beneficiaries*. Chartbook, 2012 Edition. Baltimore 2012.
5. Norris, K.C., et al., *Hemodialysis Disparities in African Americans: The Deeply Integrated Concept of Race in the Social Fabric of Our Society.* Semin Dial, 2017. **30**(3): p. 213-223.
6. Prevention, C.f.D.C.a., *National Chronic Kidney Disease Fact Sheet, 2017*, U.D.o.H.a.H. Services, Editor. 2017: Atlanta, GA.
7. Mendu, M.L., et al., *Federal Funding for Kidney Disease Research: A Missed Opportunity.* Am J Public Health, 2016. **106**(3): p. 406-7.
8. Linde, P.G., et al., *Overcoming Barriers in Kidney Health-Forging a Platform for Innovation.* J Am Soc Nephrol, 2016. **27**(7): p. 1902-10.
9. Inrig, J.K., et al., *The landscape of clinical trials in nephrology: a systematic review of Clinicaltrials.gov.* Am J Kidney Dis, 2014. **63**(5): p. 771-80.
10. Hsu, R.K., et al., *Temporal changes in incidence of dialysis-requiring AKI.* J Am Soc Nephrol, 2013. **24**(1): p. 37-42.
11. Lameire, N.H., et al., *Acute kidney injury: an increasing global concern.* Lancet, 2013. **382**(9887): p. 170-9.
12. Collister, D., et al., *Health Care Costs Associated with AKI.* Clin J Am Soc Nephrol, 2017. **12**(11): p. 1733-1743.
13. Kellum, J.A., R. Bellomo, and C. Ronco, *Kidney attack.* JAMA, 2012. **307**(21): p. 2265-6.
14. USRDS, *United States Renal Data Systems 2013 Annual Data Report. United States Renal Data Systems*. 2013: [online] http://http://www.usrds.org/2013/pdf/v1_ch6_13.pdf.
15. Waikar, S.S., K.D. Liu, and G.M. Chertow, *Diagnosis, epidemiology and outcomes of acute kidney injury.* Clin J Am Soc Nephrol, 2008. **3**(3): p. 844-61.
16. Sileanu, F.E., et al., *AKI in low-risk versus high-risk patients in intensive care.* Clin J Am Soc Nephrol, 2015. **10**(2): p. 187-96.
17. Murugan, R., et al., *Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival.* Kidney Int, 2010. **77**(6): p. 527-35.
18. Coca, S.G., et al., *Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis.* Am J Kidney Dis, 2009. **53**(6): p. 961-73.
19. Waikar, S.S. and W.C. Winkelmayer, *Chronic on acute renal failure: long-term implications of severe acute kidney injury.* JAMA, 2009. **302**(11): p. 1227-9.
20. Hsu, C.Y., et al., *Post-Acute Kidney Injury Proteinuria and Subsequent Kidney Disease Progression: The Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury (ASSESS-AKI) Study.* JAMA Intern Med, 2020. **180**(3): p. 402-410.
21. Coca, S.G., S. Singanamala, and C.R. Parikh, *Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis.* Kidney Int, 2012. **81**(5): p. 442-8.

22. Ong, E., et al., *Modelling kidney disease using ontology: insights from the Kidney Precision Medicine Project.* Nat Rev Nephrol, 2020.
23. Brown, K.D., C. Campbell, and G.V. Roberts, *Precision medicine in kidney disease: the patient's view.* Nat Rev Nephrol, 2020.
24. Kimmel, P.L., et al., *How Community Engagement Is Enhancing NIDDK Research.* Clin J Am Soc Nephrol, 2019. **14**(5): p. 768-770.
25. Perazella, M.A., et al., *Urine microscopy is associated with severity and worsening of acute kidney injury in hospitalized patients.* Clin J Am Soc Nephrol, 2010. **5**(3): p. 402-8.
26. Corapi, K.M., et al., *Bleeding complications of native kidney biopsy: a systematic review and meta-analysis.* Am J Kidney Dis, 2012. **60**(1): p. 62-73.
27. Rodriguez, L.L., et al., *Research ethics. The complexities of genomic identifiability.* Science, 2013. **339**(6117): p. 275-6.