

# Department of Internal Medicine Grand Rounds

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R. Tyler Miller, M.D. has disclosed that he does not have financial interests or other relationships with commercial interests related directly or indirectly to this program. Dr. Miller will not be discussing off-label uses in this presentation.

Orson W. Moe, M.D. has disclosed that he does have financial interests or other relationships with commercial interests related directly or indirectly to this program. Dr. Moe will not be discussing off-label uses in this presentation.

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## **AGENDA**

- |      |                                         |                |
|------|-----------------------------------------|----------------|
| I.   | Introduction to KPMP and Kidney Disease | Robert Toto    |
| II.  | Precision Medicine                      | Orson Moe      |
| III. | KPMP Goals and Organization             | Tyler Miller   |
| IV.  | Using KPMP                              | Miguel Vazquez |

## **OBJECTIVES**

- I. Understand the definition and need for precision medicine
- II. Appreciate the impact of chronic kidney disease on patient survival and risk of kidney failure
- III. Know the value of performing kidney biopsy in patients with common causes of chronic kidney disease
- IV. Understand the role of UT Southwestern in the Kidney Precision Medicine Project

R. Tyler Miller, M.D. is a Professor of Medicine and Vice Chairman of Internal Medicine, VA North Texas Health Care System. Dr. Miller's research interests focus on regulation of epithelial electrolyte transport and the biophysical properties of normal and diseased renal tissues, especially glomeruli. He is active in various multicenter research consortia. Dr. Miller is also active in the education and training of the Internal Medicine housestaff at the VA of North Texas.

Orson Moe, M.D. is a Professor of Internal Medicine and Physiology and holds the administrative positions of Chief of Nephrology and Director of the Charles and Jane Pak Center of Mineral Metabolism and Clinical Research. His research is in fluid-electrolytes and mineral disorders, and extra-renal complications of acute kidney injury and chronic kidney disease. His research is supported by the National Institutes of Health, Department of Defense, and the Charles Pak Foundation.

Robert Toto, M.D. is a Professor of Internal Medicine and Population and Data Sciences and is Associate Dean for Clinical and Translational Research. His research interests include the detection, diagnosis, management and prevention of acute and chronic kidney disease and translation of scientific discoveries into practice. His research is supported by multiple NIH grants from NCATS, NIDDK and NHLBI.

Miguel A. Vazquez, M.D. is a Professor of Medicine and Clinical Chief Nephrology Division. His clinical and research interests focus on the care of patients with chronic kidney disease and end stage kidney disease. He is the Principal Investigator of the NIH – sponsored ICD-Pieces pragmatic trial. He is Co-Principal Investigator for the Kidney Precision Medicine Project at UT Southwestern and Co-Chair of Clinical Operations for the KPMP consortium.

## I. INTRODUCTION TO KPMP AND KIDNEY DISEASE

### Introduction:

Progressive chronic kidney disease (CKD) is a catastrophic condition that leads to end-stage kidney disease requiring very expensive therapies including dialysis and transplantation. Patients with progressive kidney diseases also suffer from excessive rates of depression, catastrophic cardiovascular events such as stroke, heart attack and heart failure and other comorbidities that are difficult and expensive to manage (e.g. anemia). Only 24% of adults with CKD have reported self-awareness of an existing diagnosis of CKD, underscoring the unmet need of improving health education and healthcare delivery (Vassalotti2016) Unfortunately, there are no effective approaches to slow or stop the inexorable increase in incidence of type 2 diabetes, the leading cause of CKD. The consequence of missed detection of CKD, diabetes and hypertension is higher morbidity, mortality and financial cost to our healthcare system. Many clinical trials in those with CKD not on dialysis and dialysis have failed to demonstrate benefit owing at least in part to heterogeneity of the study population and the lack of tissue proven cause of kidney disease. The purpose of the Kidney Precision Medicine Program is to perform kidney biopsies in patients with chronic kidney disease attributed to either diabetes mellitus or hypertension as well as people with acute kidney injury in order to discover new disease mechanisms that will lead to cures.

### Case Presentation:

History: The patient is a 68y/o white female with a history longstanding type 2 diabetes mellitus, hypertension and dyslipidemia who is referred for evaluation of elevated serum creatinine and proteinuria. Review of kidney function reveals serum creatinine in range of 0.6-0.8mg/dl from 2007-2009. A 24-hour creatinine clearance in 2010 was ~ 100 ml/min. In 2010, serum creatinine began to slowly and progressively increase to most recent value shows decrease at 1.47mg/dl.

PMH is significant for Type 2 DM for 10 years with A1C ranging from 6-8% on insulin: hypertension for 10 years that has been well controlled and there is no history of stroke, MI or heart failure; and dyslipidemia. FH is negative for diabetes, kidney disease. SH: Non-smoker, non-drinker, Employed as nurse educator, no NSAIDS or OTC medications. Medications: Losartan-HCTZ (100 mg/25 mg) daily, Amlodipine 5 mg daily, Carvedilol 6.25 mg BID, Insulin, fenofibrate 48 mg once daily.

Physical Exam: BP 138/73, HR 86, 66 kg, BMI 25.6

Remarkable for absence of retinopathy, presence of pretibial edema

Laboratory data reveal: serum creatinine 1.47 mg/dl, eGFR 36, Urinalysis: remarkable for proteinuria 2+, urine albumin/creatinine = 486 mg/g, renal sonogram: no obstruction, kidneys 10 cm, no hydronephrosis.

**Differential diagnosis:** As illustrated below, the most likely diagnosis is diabetic nephropathy; however, other possibilities have to be considered. Diabetic kidney disease is the leading cause of kidney failure in the United

Differential Diagnosis	States accounting for ~ 40% of new cases of end stage kidney disease. In this case, the patient underwent a percutaneous kidney biopsy and was found to have <b>focal segmental glomerulosclerosis</b> and substantial interstitial fibrosis and tubular atrophy-indicating. The latter is both a sign of chronicity and likelihood that the disease will progress despite therapy.
Diabetic Nephropathy	<b>Why do a kidney biopsy in a patient with diabetes?</b> It was decided to perform a kidney biopsy in this patient to determine if she had a non-diabetic kidney disease The case
Diabetic Nephropathy	
Diabetic Nephropathy	
Membranous nephropathy	
IgA nephropathy	
Focal segmental glomerulosclerosis	
Other	

presented here makes two important points: 1) the clinical diagnosis of diabetic kidney disease is inaccurate and 2) without a tissue diagnosis, we will never understand the mechanisms of onset and progression of many progressive kidney diseases including focal segmental sclerosis (FSGS). Whereas we do not have specific treatment for FSGS or diabetes, obtaining tissue for studies beyond histologic description is critically important for advancing the field of kidney medicine.

In the overwhelming majority of cases the diagnosis of diabetic kidney disease is based on clinical findings and a biopsy is not required to make the diagnosis according to current National Kidney Foundation guidelines (Tuttle2007). The costs of care for people with DKD are extraordinarily high. In the Medicare population alone, DKD-related expenditures among this mostly older group were nearly \$25 billion in 2011. (Tuttle2014) Thus the standard of care for a patient with suspected diabetic kidney disease is to make the diagnosis on clinical findings and not perform a kidney biopsy to establish the diagnosis.

### National Kidney Foundation: Diagnosis of Diabetic Kidney Disease

In most patients with diabetes, CKD should be attributable to diabetes if:

- Macroalbuminuria ( $\geq 300$  mg/g) is present; or
- Microalbuminuria (30-299 mg/g) is present in the presence of
  - diabetic retinopathy
  - type 1 diabetes of at least 10 years' duration.

### What is the basis for the reticence to do kidney biopsies?

Because many patients present to nephrologists who are responsible for biopsies at relatively advanced stages of disease, there is reluctance to perform them when they are less informative and carry risk for

potential complications (e.g., hemorrhage). This reluctance is also driven by the fact that nephrologists have few specific treatment options to offer patients with CKD. There are two major problems: 1) few patients with diabetes or hypertension undergo kidney biopsy and 2) most kidney biopsy diagnoses use descriptive terms that do not guide clinical researchers and clinicians to discover disease pathways, new biomarkers, new diagnostic approaches, and mechanism-based therapies of human kidney disease.

### Burden of Chronic Kidney Disease

(CKD) is an important public health problem that afflicts millions of individuals worldwide. Not only is there no cure, the disease has catastrophic consequences: decreased quality of life, an alarming increase in cardiovascular morbidity and mortality, and frequent progression to end stage-kidney disease (ESKD). These human costs are associated with large healthcare financial burden with Medicare costs alone exceeding \$50B in 2014 per year. (USRDS., 2016)

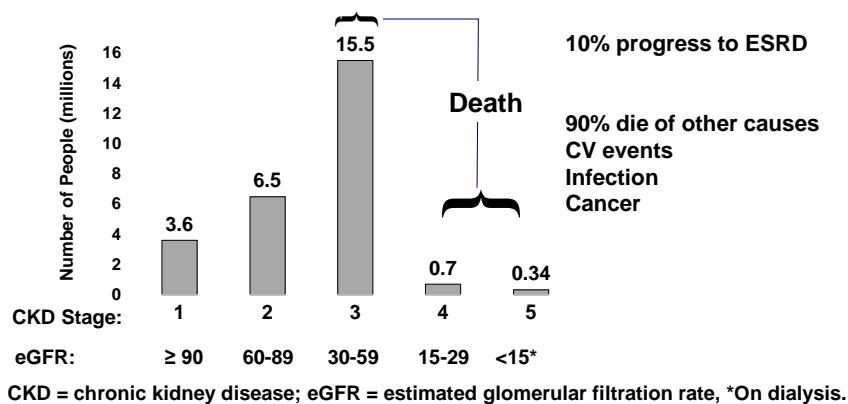
Unfortunately for most patients, CKD progresses over time, ultimately leading to increased disease burden and cost of care. It is estimated that approximately 15% (37 million) of the adult population in the United States have some degree of CKD (Coresh 2007; CDC, 2019). The National Kidney Foundation has staged kidney

disease based on the estimated glomerular filtration rate into 5 stages. It is clear that the prevalence of CKD increases with increasing stages 1-3. However, the prevalence of CKD sharply decreases in those with stages 4 and 5. Data indicate that whereas many people with CKD progress to end-stage, the overwhelming majority (~90%) die from cardiovascular events, infection, cancer or other causes before reaching end-stage.

Data to support this observation are provided in a large retrospective cohort study including about 1.2M people in the Kaiser health system. As shown, Go, et al, demonstrated that with increasing CKD stage the incidence of death, cardiovascular events and all-cause hospitalization. (Go 2004) Importantly, the incidence of all three of these outcomes sharply increase when the estimated GFR is below 45 ml/min/1.73 m<sup>2</sup>.

### Prevalence of CKD in the United States

Cross-Sectional Data (NHANES 1999-2004)



Coresh J et al. JAMA. 2007. USRDS, 2007.

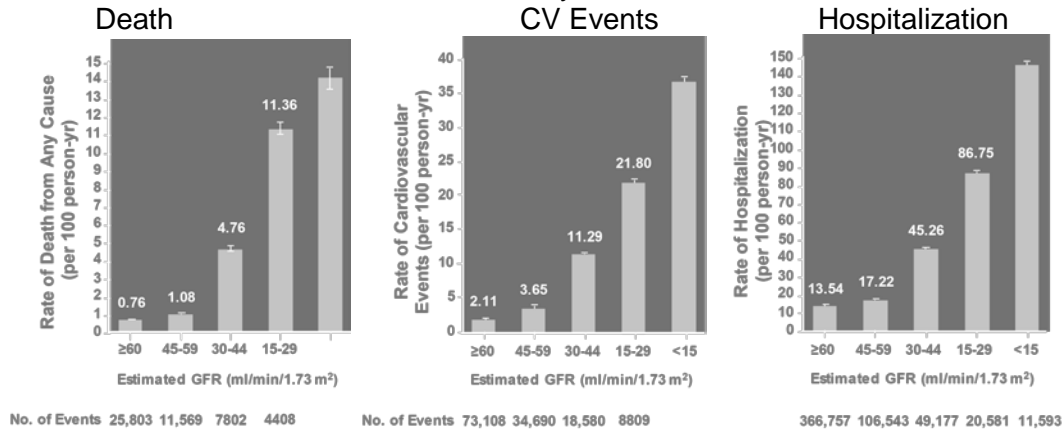
Unmet needs in the field of Chronic Kidney Disease

There is a dire unmet need to accelerate translation from disease mechanisms to therapeutic target identification and population health. Diabetic nephropathy is a common, prime, and compelling example. Despite considerable effort to develop disease models and numerous clinical trials with various interventions,

no new effective medical therapy has been introduced for more than 15 years. In the United States, diabetic kidney disease is the attributed cause of ESRD in ~ 40% of all new cases of ESRD, yet very few patients with this diagnosis is proven by kidney biopsy. Similarly, while we attribute ESRD to hypertension in over 25% of new cases of ESRD, few of these patients undergo kidney biopsy. Several studies of selected patients with diabetes and proteinuria demonstrated a variety of lesions other than typical diabetic glomerulosclerosis, including primary glomerular diseases (e.g. IgA nephropathy), vascular disease, and interstitial disease.

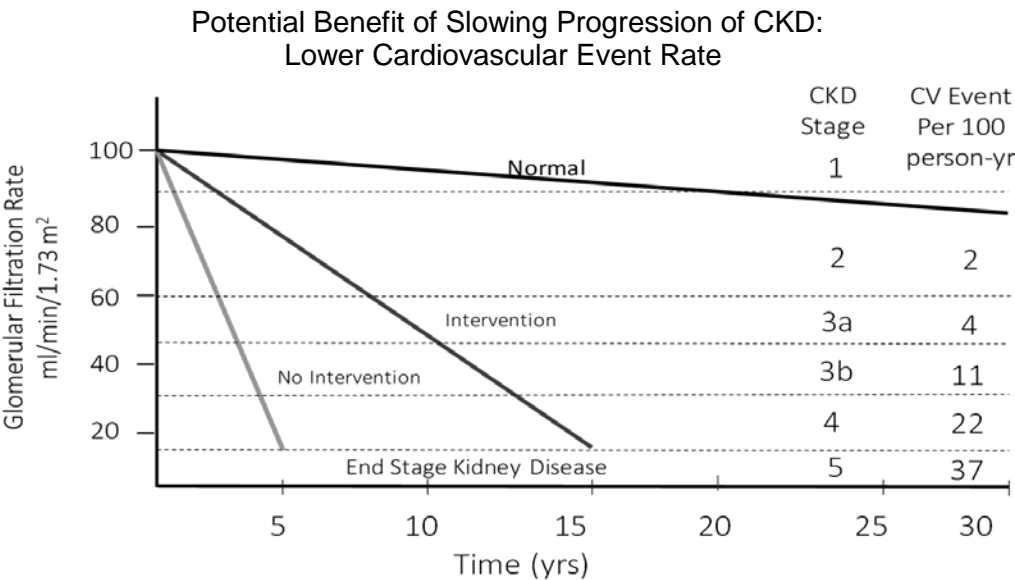
While modern technologies that can accurately phenotype people with CKD are widely available, they are not employed at a population level in a systematic or coordinated fashion, and are unavoidably superficial and unlikely to identify novel disease mechanisms. While patient registries, including some with kidney biopsies, have been established, a shared common data model and molecular diagnostic approach has not been taken.

Death, Cardiovascular Events and Hospitalization in CKD  
1,120,295 Ambulatory Adults



Slowing progression of Chronic Kidney Disease

Patients with progressive forms of CKD suffer from excessive rates of depression, catastrophic cardiovascular events such as stroke, heart attack and heart failure and other comorbidities that are difficult and expensive to manage (e.g. anemia and mineral metabolism disorders). The current approach to treatment of CKD is to slow



progression of the disease. Two benefits of interventions that slowing progression of CKD are 1) delay in development of end-stage kidney disease requiring very expensive therapies including dialysis and transplantation and 2) perhaps more importantly, lower risk for debilitating or fatal cardiovascular events. Ultimately early detection and management of risk factors including hypertension and proteinuria could go a long way to reducing the burden of CKD. Only 24% of adults with CKD have reported self-

awareness of an existing diagnosis of CKD, underscoring the unmet need of improving health education and healthcare delivery.

**How should this patient be treated?** Unfortunately, treatment options for most kidney diseases including DKD and focal segmental glomerulosclerosis are limited and include lowering blood pressure, proteinuria, blood lipid levels and in the case of diabetes, lowering blood glucose. The standard of care is to administer RAASi drug which lower BP and proteinuria.

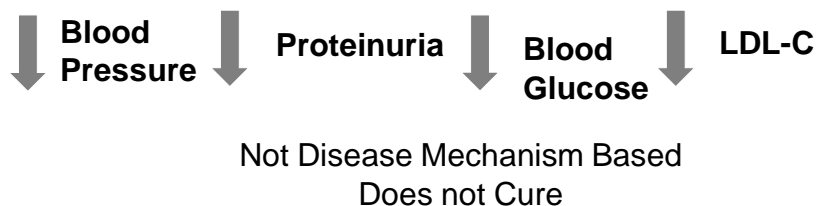
These agents have been shown to slow progression of kidney disease in diabetes, glomerular diseases and hypertensive nephrosclerosis.

(Lewis, 1993, 2001; Brenner. 2001; Jafar 2003; Wright 2002)

Unfortunately, none of these treatment options are mechanistic-based and none cure the kidney diseases. And, nephrologists have few pharmacologic interventions to treat most patients with CKD.

Currently there are only 2 drug classes that are FDA approved for treating common causes of CKD in adults including diabetes: namely, RAAS inhibitors (captopril, irbesartan and losartan) and tolvaptan. The sodium-glucose transport-2 (SGLT-2) inhibitor canagliflozin has recently been shown to slow progression of kidney disease and reduce risk for cardiovascular events in people with CKD attributed to diabetes, this drug has yet to be approved by the FDA for this indication (Perkovic 2019). While canagliflozin slows disease progression, it does not stop it. And while SGLT-2 inhibition may slow progression of diabetic kidney disease, the mechanism of protection is not known but does not appear to be due to the lowering of blood glucose.

### Treatment for Diabetic Kidney Disease, Hypertension, FSGS, IgA nephropathy



### Rationale for Kidney Precision Medicine Program

Basic biomedical discovery in kidney disease has lagged behind other fields such as oncology because kidney diseases have been difficult to categorize pathogenetically, in large part because of limited availability of renal tissue at early stages of disease and lack of appropriate analytical methods to discover pathogenic mechanisms of disease. Even with more prevalent biopsies, the current practice of renal pathology offers limited help, with mainly descriptive histology-based diagnoses that lack mechanistic insight and that do not direct effective treatments. These factors lead to a vicious cycle that prevents advances in the diagnosis and treatment of kidney disease. As a consequence, very few patients with diabetes and chronic kidney disease undergo a kidney biopsy. We believe strongly that performing kidney biopsies in people with earlier stage kidney disease will 1) identify new categories of disease - defined by both morphologic and molecular parameters, coupled with and supplemented by clinical parameters (Lemlet 2016; Hogan2015) and will allow molecular studies that can be used to guide treatment. The purpose of the Kidney Precision Medicine Program is to perform kidney biopsies in patients with chronic kidney disease attributed to either diabetes mellitus or hypertension as well as people with acute kidney injury in order to discover new disease mechanisms that will lead to cures.

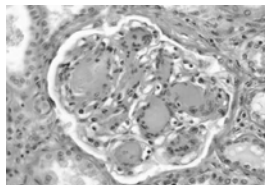
Basic biomedical discovery in kidney disease has lagged behind other fields such as oncology because kidney diseases have been difficult to categorize pathogenetically, in large part because of limited availability of renal tissue at early stages of disease and lack of appropriate analytical methods to discover pathogenic mechanisms of disease. Even with more prevalent biopsies, the current practice of renal pathology offers limited help, with mainly descriptive histology-based diagnoses that lack mechanistic insight and that do not direct effective treatments. These factors lead to a vicious cycle that prevents advances in the diagnosis and treatment of kidney disease. As a consequence, very few patients with diabetes and chronic kidney disease undergo a kidney biopsy. We believe strongly that performing kidney biopsies in people with earlier stage kidney disease will 1) identify new categories of disease - defined by both morphologic and molecular parameters, coupled with and supplemented by clinical parameters (Lemlet 2016; Hogan2015) and will allow molecular studies that can be used to guide treatment. The purpose of the Kidney Precision Medicine Program is to perform kidney biopsies in patients with chronic kidney disease attributed to either diabetes mellitus or hypertension as well as people with acute kidney injury in order to discover new disease mechanisms that will lead to cures.

### Only Two Drug Classes Approved to Treat Common Causes of Chronic Kidney Disease

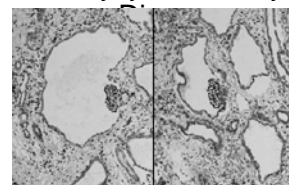
- Renin-Angiotensin Aldosterone System inhibitors

- AVP receptor Antagonist-Tolvaptan

Diabetic Nephropathy



Autosomal Dominant Polycystic Kidney

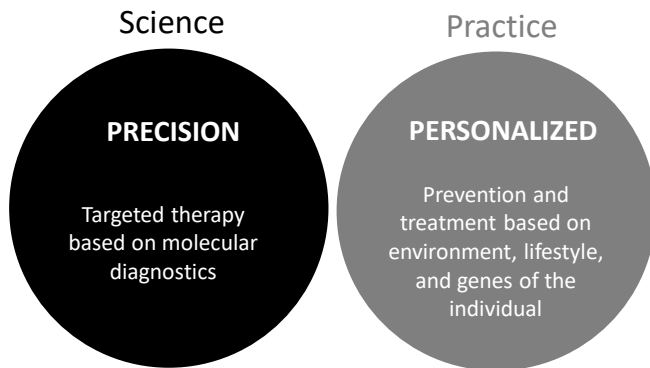


Desperately need to better understand the underlying molecular mechanisms of kidney disease

## II. PRECISION MEDICINE

## Definition of Precision Medicine

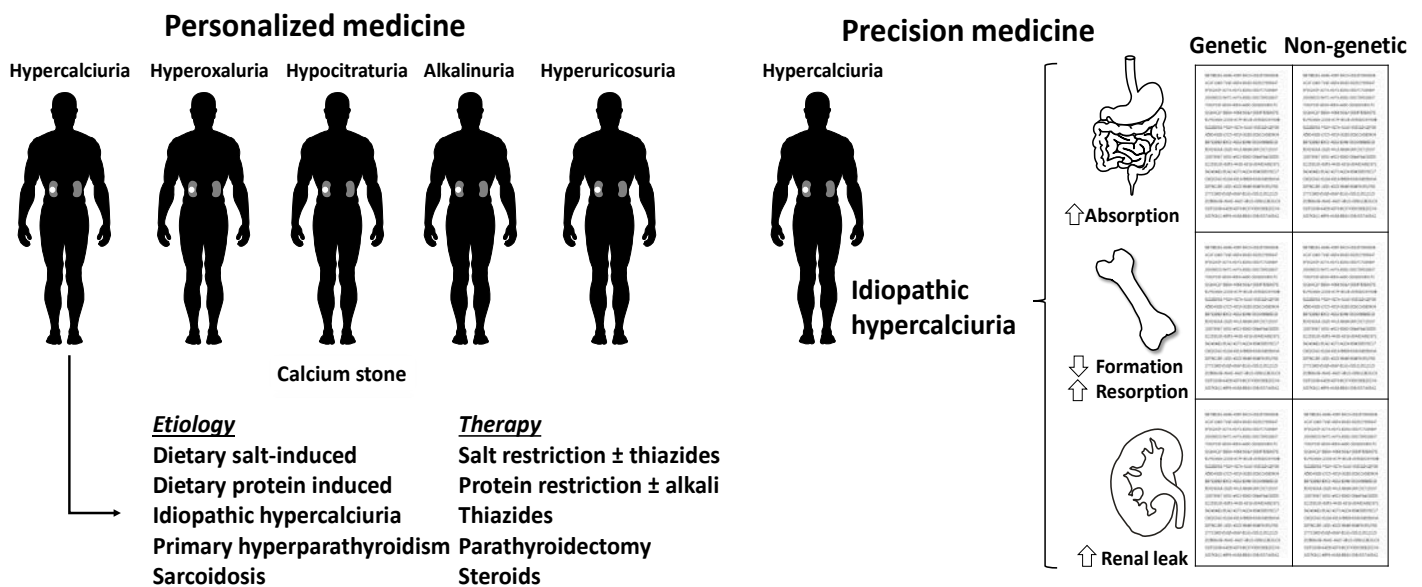
## Precision vs. Personalized Medicine



## Introduction and background.

These two terms are often used interchangeably and in fact they do overlap but there is a distinction between *personalized* medicine and *precision* medicine. Personalized medicine refers to prevention and treatment of a patient based not on a standard protocol but on the environment, lifestyle, external pathogen, and genetic disposition of that particular individual. Thus personalized medicine refers to a practice. Precision medicine begins with a scientific effort that gears towards a comprehensive understanding of the underlying molecular physiology of disease that will eventually yield targeted therapy. When this knowledge is applied to health care, *personalized* medicine can again be practice.

The first attempts to classified disease was attributed to Carolus Linnaeus, who also contributed to the taxonomic system that classify living organisms. In the 1763 *Genera Morborum*, diseases were empirically classified based on gross clinical observations into such categories as exanthematic (fever with skin eruptions), phlogistic (fever with heavy pulse and topical pain), and dolorous (painful) (Linné, 1763). This was clearly due to complete lack of cognizance of the pathobiology of disease. With ignorance of microbiology, rabies was characterized as a psychiatric disorder because of the observed neuropsychiatric symptoms in advanced cases. Even in 2019, the International Statistical Classification of Diseases and Related Health Problems 10<sup>th</sup> edition (ICD-10) is still lumping diagnoses together or splitting subgroups of diagnoses without much pathobiologic basis (Loscalzo, 2007)



## Personalized vs. precision medicine.

Personalized medicine is already in practice although not to the granular molecular details that one desires. Take the example of a patient with calcium urolithiasis. The stone can be a result of diverse underlying chemical abnormalities in the urine- namely hypercalciuria, hyperoxaluria, hypocitraturia, alkalineuria, and hyperuricosuria. If one identifies hypercalciuria, that can also result from a wide range of etiologies, which once identified will require different therapy. This is personalized medicine. The condition “idiopathic hypercalciuria” can result from a combination of increased gut absorption, decreased bone formation, increased bone resorption, and renal



leak; and all of the above can be affected by many genetic and non-genetic factors. Working out these underlying molecular mechanisms is the science of precision medicine.

## One size does not fit all.

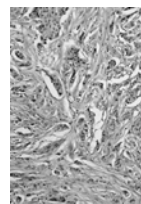
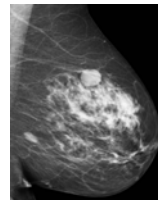
Molecular diagnosis is more advanced in oncology than a lot of specialties. While breast cancer was largely a tissue diagnosis in the 1970's subjected to standard therapy based on staging, breast cancer by itself has little meaning in 2019. The classification is based a lot more on the biology of the tumor which has important clinical correlates and implications. It also directed therapy and governs prognosis. The diagnosis and treatment of most kidney diseases have not reached this level of precision.

An example from the laboratory bench can be cited from a paper by Ferré and coworkers who examined the role of the unfolded protein response (UPR) in acute kidney injury (AKI) (Ferré, 2019). UPR is an evolutionarily conserved cell response reactive to endoplasmic reticulum stress. UPR is activated in response to an accumulation of unfolded or misfolded proteins in the endoplasmic reticulum lumen. UPR contributes to restoring normal cellular function by stopping unnecessary protein translation, destroying improperly folded proteins, and activating pathways that increase molecular chaperones to aid protein folding. UPR can protect the cell but can also harm the cell if excessively activated. Abnormal UPR has been implicated in many human diseases.

## Breast cancer

1970's

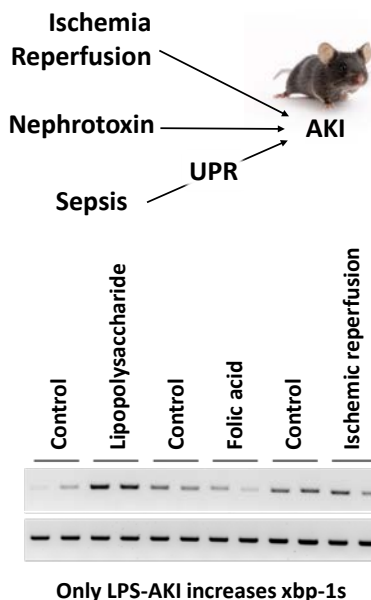
Mass → Histology → Treatment



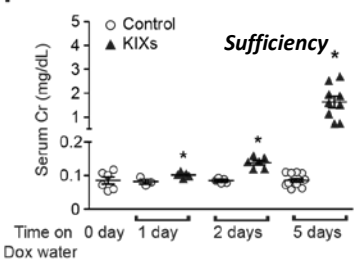
Surgery  
Radio Rx  
Chemo Rx

2019

Subtypes of breast cancer	Er Pr	Her-2	Ki67
Luminal a	Er + and/or Pr +	Her-2-	Ki67<14%
Luminal b Her-2-	Er+ and/or Pr+	Her-2-	Ki-67≥14%
Luminal b Her-2+	Er + and/or Pr +	Her-2 +	Any Ki67
Her-2 enriched	Er-, Pr-	Her-2 +	Any Ki67
Basal-like (triple negative)	Er-, Pr-	Her-2-	Ck5/6 + and/or EGFR+

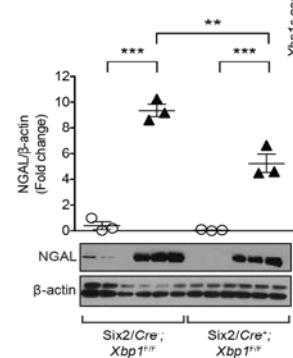


Not all AKI involve the Unfolded protein response (UPR)  
Xbp1-s is a major player in UPR



Induction of xbp-1s → AKI

Necessity



Deletion of xbp-1s ameliorates LPS-AKI

Ferré and coworkers examined one of the main players of UPR called Xbp-1s, and its role in AKI. AKI is a disease caused by a myriad of etiologies. Xbp1s is increased only in a septic model of AKI mimicked by injection of lipopolysaccharide (LPS). To examine beyond association and test for causality of these changes, Xbp-1s was either overexpressed (test for sufficiency) or deleted (test for necessity) in the renal tubules. Xbp-1s



overexpression was sufficient to induce AKI and Xbp-1s deletion reduced the LPS-induced renal damage to half demonstrating necessity. This data places Xbp-1s in the intermediate pathway between sepsis and AKI. However, if one were to proceed and test an Xbp-1s inhibitor in *all patients with AKI*, the effect would have been buried and the efficacy of the compound would have been lost. A negative trial will be declared which will obliterate the prospect of a new therapy. Therefore, cognizance of the specific activation of UPR in sepsis is critical in the design and testing of a UPR-modifying agent.

Human disease

Clinical

Pathologic

Molecular

Edema

Creatinine

Proteinuria

Genome

Epigenome

Transcriptome

Proteome

Interactome

Phosphoproteome

Microbiome

Molecular diagnoses.

Our clinical encounter has been complemented with anatomic histology since the early years of medicine. The histologic classification of disease while valid is very far from the details required to obtain molecular taxonomy. The emergence of “omic” technology enables one to catalogue and characterize all copies of the genome, epigenome, transcripts, proteins, covalently modified proteins, interacting clusters, lipids, symbiotic microbial cohabitants, and many others. Coupled with powerful bioinformatics, these techniques can furnish a comprehensive “fingerprint” of a specific biologic state including disease. The field is in dire need to move the classification of disease from structural to molecular.

Serum antibody	Glomerular antigen	Molecular diagnosis
Anti-PLA2R positive	PLA2R enhanced	PLA2R-mediated active pMN
Anti-PLA2R negative	PLA2R enhanced	PLA2R-mediated inactive pMN
Anti-THSD7A positive	THSD7A enhanced	THSD7A-mediated active pMN
Anti-THSD7A negative	THSD7A enhanced	THSD7A-mediated inactive pMN
Anti-PLA2R/THSD7A positive	PLA2R/THSD7A enhanced	Double PLA2R/THSD7A-mediated active pMN
Anti-PLA2R/THSD7A negative	PLA2R/THSD7A enhanced	Double PLA2R/THSD7A-mediated inactive pMN
Anti-NEP positive	NEP positive	NEP-mediated active pMN (fetomaternal alloimmunization), in new-borns
Anti-NEP negative	NEP positive	NEP-mediated inactive pMN(fetomaternal alloimmunization), in new-borns
Anti-BSA positive	BSA positive	BSA-mediated active pMN, in young children
Anti-BSA negative	BSA positive	BSA-mediated inactive pMN in young children
Anti-PLA2R/THSD7A/NEP/BSA/anti-aryl sulphatase negative	PLA2R/THSD7A/NEP normal BSA/anti-aryl sulphatase absent	pMN-mediated by other unknown anti-podocytes antigens

Anti-PLA2R (IIFA)

+

Anti-PLA2R (ELISA)

≥ 2 RU/mL

Primary MGN

Avoid Kidney Bx if preserved GFR

-

Kidney Bx

≤ 2 RU/mL

Kidney Bx

Couser CJASN 20217

Pozdzik Curr Opin Nephrol 2019

It is not entirely true that there have been no attempts to move kidney disease from the histologic into the molecular realm. This is being attempt for several glomerulonephritides. The advancement of molecular diagnosis of focal segmental glomerulosclerosis by the Nephrotic Syndrome Study Network (NEPTUNE) is an example of a successful attempt. This will be covered in more detail in a subsequent section. Another condition is membranous glomerulopathy or membranous glomerulonephritis (MGN). A number of biomarkers were identified that can potentially reclassify MGN into molecular categories (Couser 2017). One such biomarker-antibodies against phospholipase A receptor- has been approved to be used clinically to sub-classify MGN. Practice has changed since the availability of this test (Pozdzik 2019).

### III. KPMP GOALS AND ORGANIZATION

**KPMP Background and Goals.** KPMP (Kidney Personalized Medicine Project) is an NIH-funded national consortium designed to change our understanding and treatment of kidney disease. As described by Bob Toto and Orson Moe, Nephrology needs mechanism-based diagnostic methods and diagnoses that provide therapeutic information. Other fields such as Hematology-Oncology, Hepatology, and Dermatology have advanced because sufficient tissue was available to perform biochemical studies and identify molecular pathways in diseases. Understanding of these pathways led to mechanism-based treatment in many cases (Perou 2000). Nephrology lagged behind other fields because of the small amount of tissue available from

biopsies and the structural complexity of kidneys. Over the past 20 years, clinicians reduced the number of biopsies that performed because 1) The results usually did not inform treatment, 2) Kidney biopsies are riskier than biopsies of other tissues, and 3) kidney biopsies are not cost-efficient for nephrologists. Over that time, new methods have been developed including laser capture microscopy (LCM) that allows isolation of parts of tissues such as glomeruli, arterioles, or specific segments of tubules, RNA-Seq

#### Goals of the Kidney Precision Medicine Project - KPMP

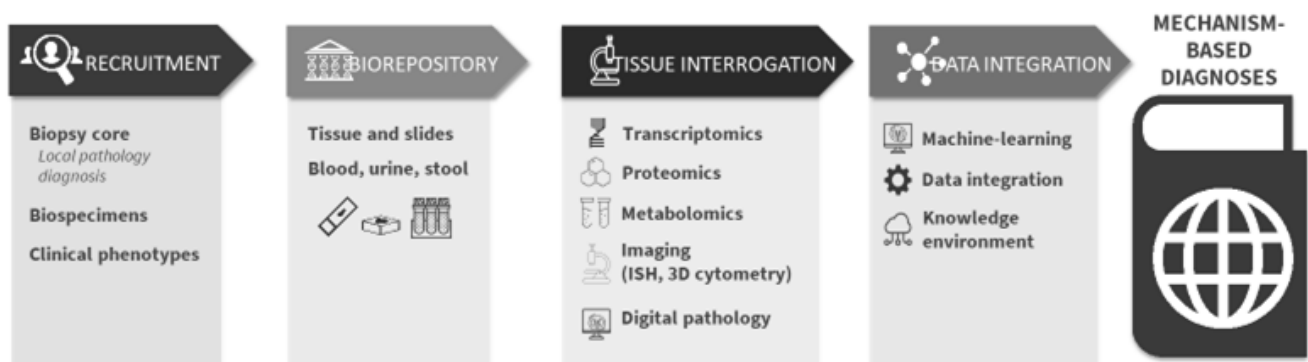
- Obtain **kidney biopsies** from patients with AKI or CKD
- Define kidney cell and molecular biology
- Identify **cells, pathways, and targets** for new therapies
- Find disease subgroups to devise **individualized Rx**
- Improve diagnostic and therapeutic pipeline



that allows identification of mRNAs that are being transcribed in LCM specimens, small groups of cells, or single cells and individual nuclei. These new methods make it possible for people studying kidney disease to perform the sorts of studies that have been common in Hematology-Oncology and GI (Perou 2000).

KPMP Is patterned after the NEPTUNE study (Nephrotic Syndrome Study Network) and the two studies share

### KPMP Biospecimen Analysis and Data Flow



many sites, personnel, and general approaches (Barisoni 2013; Bhavnani 2009; Gadegbeku 2013; Lindenmeyer 2010; Sampson 2015). In NEPTUNE, patients with nephrotic syndrome (minimal change disease (MCD), focal and segmental glomerulosclerosis (FSGS) and membranous nephropathy (MGN) are biopsied. LCM and transcriptomic and proteomic approaches are used to analyze and reclassify patients based on molecular pathways. NEPTUNE is less complex than KPMP and the analyses are more limited, but the basic approach of KPMP has a solid precedent in the success of NEPTUNE. The consortium is working with people in other fields

including neuroscience, oncology, pathology, informatics, and basic sciences to adopt new approaches as they are developed.

KPMP investigators will study patients with CKD and AKI. For the CKD component, patients with the two most common causes of ESRD, Diabetic Nephropathy (DN, as described in part 1), and Hypertensive Nephrosclerosis (also a clinical syndrome with descriptive pathology and no molecular definition, a common reason for ESRD, particularly in African Americans) will be recruited in the three CKD recruiting sites. KPMP will also study AKI in the other three recruitment sites because it is a common factor leading to CKD and ESRD. Participants in KPMP will perform kidney biopsies on more patients and earlier in disease than is common practice now.

KPMP will obtain kidney biopsy specimens along with urine, blood, stool, clinical, and demographic information. The consortium is using existing methodology and developing new methodology to study the biology of kidney disease. These approaches involving single cell transcriptomics will permit identification of unanticipated injury pathways in known renal cells and inflammatory cells and allow identification of kidney cell types that might be unknown at this time. Methods are being developed to visualize transcriptomic, proteomic, and metabolomic data in situ in the kidney biopsy specimens. Methods are also being developed to integrate the different areas of KPMP using artificial intelligence. Ultimately KPMP investigators, referring nephrologists, and patients will

have access to KPMP data and its analysis. The goal is to develop a database that can be used first to redefine/reclassify kidney diseases in mechanistic terms, and then to develop molecular markers (serum or urine) that will allow stratification of patients based on simpler analysis of biopsy specimens.

## Who Does This? – KPMP Personnel, Sites and Organization



### Central Hub

- University of Washington
- University of Michigan
- Icahn School of Medicine Mount Sinai
- Duke University
- Princeton University

### Tissue Interrogation Sites

- UCSD-Wash U
- UM-Broad-Princeton
- Indiana U - OHSU
- UTHSA-PNNL-EMBL
- UCSF

### Recruitment Sites

- Columbia
- Pittsburgh
- Brigham & Women's
- Joslin Diabetes
- Cleveland
- UT Southwestern
- John Hopkins
- Vale

## Questions About Research Kidney Biopsies

### Patient and Investigator collaboration

#### • Ethics

- Limited benefit and some risk to patient, large benefit to society
- Informed consent – patient input

**Goal → Perform routine clinical biopsy early in disease that guides care (change in culture)**

#### • Safety

- Discomfort, bleeding; small risk of death

#### • Costs

- Biopsy Procedure
- Complications
- Insurance



**KPMP Structure.** KPMP is a national consortium with six university Recruitment Sites (three CKD, three AKI), five Tissue Interrogation (TI) Sites (multiple molecular and pathology assays with overlapping and complementary expertise), and a Central Hub that coordinates the activities of the other groups. The Central Hub also supports the informatics and data visualization efforts of the study and is composed of five sites that offer complementary expertise. The Recruitment Sites will recruit patients, perform biopsies, and obtain biologic specimens and demographic data. They will supply specimens to the TISs, and supply other data (e.g. demographic, clinical) to the Central Hub. KPMP has one international TI site, EMBL in Heidelberg, Germany.

The fact that kidney biopsies are performed less commonly than in the past means that standard of practice has changed. For KPMP to be successful, we need to biopsy people earlier and in situations where many clinicians would not perform biopsies. This situation created a debate about the ethics of doing kidney biopsies for a

research project. The scientific/medical community understood that to make progress, we needed tissue, and this view is supported by the KPMP patient group.

**Patient Involvement is Integral to KPMP.** A unique feature of KPMP is the involvement of patients from the beginning of the study. Shown in the picture are many of the patients who attend meetings in Washington regularly along with several NIH staff members who organize the meetings. The patients are from each of the study sites and members of national kidney disease patient advocacy groups (American Association of Kidney Patients), AAKP. Some have transplants, and some are progressing toward dialysis or transplantation. The patients all support early biopsies once the analyses and specimen handling are assured and safety is maximized. The patient group worked with investigators to write the consent form. On member of the patient group led the effort to obtain insurance for complications of biopsies.

## Nice Idea, But Can It Work?

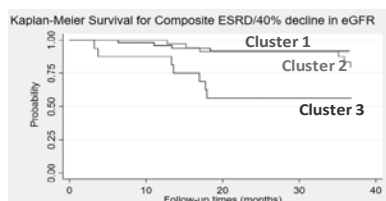
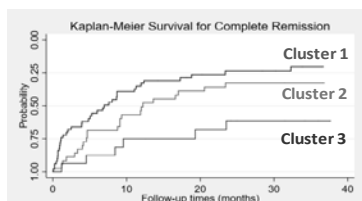
### Nephrotic Syndrome - MCD vs FSGS, NEPTUNE Study

	Minimal Change Disease (MCD)	Focal Sclerosis (FSGS)
Cause	?	Multiple, genetic, acquired
Age	Pediatric >> Adult	Adult >> Pediatric
Presentation	Nephrotic Syndrome	Nephrotic Syndrome
Diagnosis	Clin Synd/Descriptive Pathology	Clin Synd/Descriptive Pathology
Treatment	Steroids +/- Other Immune Supp	Steroids usually + Other Immune Supp.
Response to Treatment	Better Young than Old	Variable
Progression to ESRD	Remissions Common in Ped Pop	Common

**Descriptive pathology does not distinguish between those who will progress to ESRD or those who will respond to treatment**

Disease (MCD) and Focal Segmental Glomerulosclerosis (FSGS). These two disease have common features and are diagnosed based on clinical syndrome (nephrotic syndrome) and descriptive pathology of biopsies. The behavior of these two diseases is heterogenous and some investigators feel that there is overlap between the two. Patients with MCD can have second biopsies that show FSGS. Patients with MCD generally respond to steroids or additional immunosuppressive therapy, while patients with FSGS have a much lower response rate. Although the presenting clinical syndromes are similar, the courses vary, and the pathologic diagnoses are descriptive not helping with molecular mechanism, guiding treatment, or prognosis (Rosenberg 2017; Sampson 2015; Tune 1997; Vivarelli 2017; Waldman 2007). Mariani and coworkers with the NEPTUNE consortium analyzed the transcriptomes of 123 patients with MCD or FSGS and found that the patients clustered into three groups based on differential expression of mRNAs. Cluster 3 that had the highest levels of mRNA divergence had a greater risk of failing to achieve remission or progressing to ESRD.

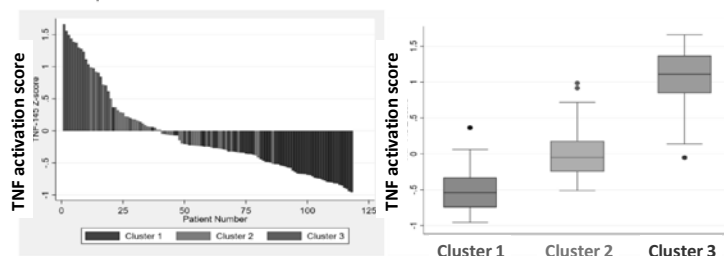
### Cluster Analysis of Differentially Expressed mRNAs Identifies a Sub-group of Patients At Increased Risk for ESRD or Rapid Loss of GFR



- Clusters based on number and magnitude of differentially expressed mRNAs from kidney biopsies
- All clusters contained patients with MCD and FSGS
- Cluster 3 had a worse prognosis with fewer remissions and more disease progression

This analysis did not involve identifying specific genes or networks, but only considered number and magnitude of differentially expressed genes.

## Transcriptomic Profiles of Patients in Cluster 3 vs 1 and 2 Identifies TNF Pathway Activation in Cluster 3



- The TNF pathway was identified using transcripts for TNF signaling proteins, and down-stream targets
- A TNF activation score was calculated based on 145 mRNAs related to TNF signaling
- Down-stream TNF targets (CCL2, TIMP1) were measured in urine and correlated with clusters

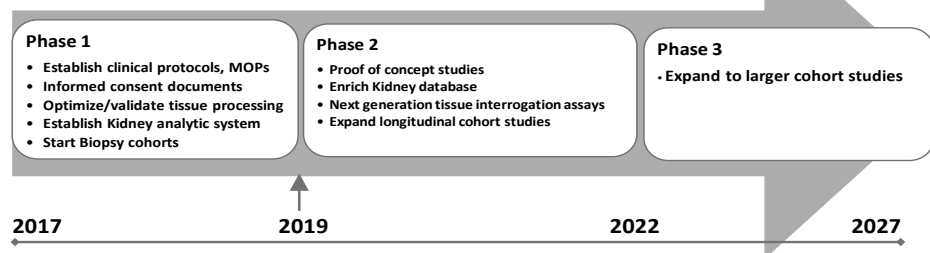
In this analysis, clusters 1 (n=62) and 2 (n=42) behaved in a similar manner. Patients in cluster 3 (n=19) had a reduced probability of achieving complete remission and greater probability of progressing to ESRD or losing 40% of their GFR over the study period. All clusters had patients with MCD and FSGS (conventional light and EM diagnosis), and there was no difference in race, sex, or duration of disease across the clusters. Cluster 3 had older patients with more FSGS and lower eGFR and higher UPCr values at baseline.

Expression of 2517 genes that were differentially regulated between cluster 3 and clusters 1 and 2 was analyzed and showed increased TNF levels and found to center on a TNF interaction network. Increasing activation of the TNF signaling across clusters 1 – 3 with cluster 3 having the highest level. Activation of the TNF pathway explained 26% of the differentially activated genes (660/2517). A TNF activation score was calculated for each individual using 145 genes. The L panel in the figure shows the TNF activation scores for each patient. Cluster 3 is red, cluster 2 is green, and cluster 1 is blue. The Y axis is TNF activation score and the X axis is patient number ordered from the highest (Left) to the lowest (Right) TNF activation score. The panel on the R shows the TNF activation score for each cluster (mean +/- SD). A 1 unit greater TNF activation score was associated with a 12 mL/min/1.73 m<sup>2</sup> lower eGFR during follow-up.

TNF inhibition has been used in patients with steroid-unresponsive MCD and FSGS with little success. A minority of patients benefitted (clear benefit) but the majority did not (Ito 2010; Peyser 2010; Raveh, 2004). Without a method to determine who will benefit, TNF pathway inhibition is not useful in MCD or FSGS. Down-stream TNF target gene products, CCL2 and TIMP1 were measured in the urine of study participants and found to correlate

with the TNF activation index. Studies are under way to determine if TNF pathway activity as assessed by urine markers will be valuable in guiding anti-TNF therapy in MCD and FSGS.

## 10 Year KPMP Timeline

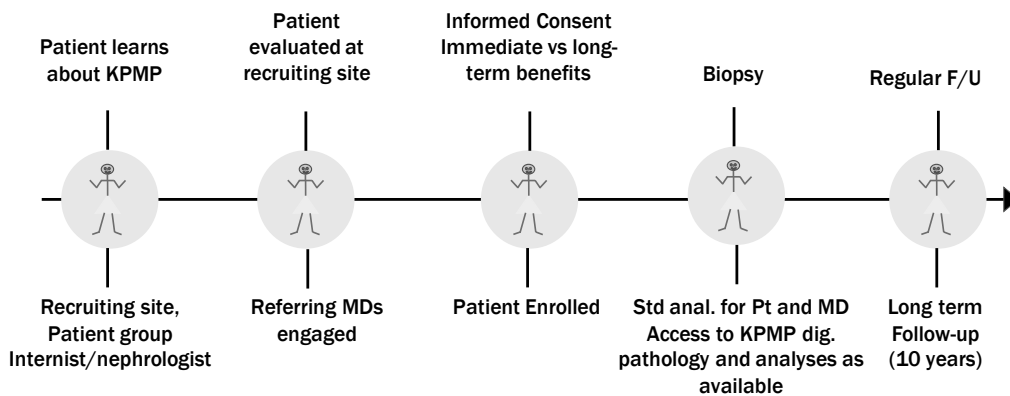


## The KPMP 10 Year Timeline.

KPMP began in 2017 with organizational meetings involving NIH staff, investigators from the Recruitment and Tissue Interrogation sites, the Central Hub, and patients. Clinical protocols, operating procedures,

decisions on what analyses were to be used, consents, methods for handling and sharing samples, analytics, and data visualization protocols were developed. At this time, 2019, we are preparing to do our first biopsies and test the system. With time, the number of recruitment sites and patients will increase, so that by 2022, KPMP should have enough patient samples and data to begin to perform analyses and develop initial approaches to understanding “Diabetic Nephropathy”, “Hypertensive Nephrosclerosis”, and Acute Kidney Injury.

## Our Patient Meets KPMP 2019



**If Our Patient Came to KPMP today.** Our patient would come into contact with KPMP through one of the centers involved in the project. She would be screened for study criteria, and if appropriate for the study would have her protocol biopsy. Biopsy issue would also be sent for standard of care pathologic analysis and KPMP studies. Blood, urine, stool, clinical, and demographic data would also be sent to KPMP sites for analysis. At this point, it is unlikely that she would derive direct benefit from

participation because understanding her data will require combining it with data from many more patients and validating it. At this time, KPMP is predicted to continue through 2027, but it may continue longer. The NIH and KIDDK strongly support this project because it is essential for changing the way nephrology is practiced and improving care through mechanism-based diagnoses and treatments.

## IV. USING KPMP

Many factors have come together to support the launching of the KPMP effort. As noted in the prior discussion there is a clear scientific rationale to leverage new methods for studying human kidney disease and characterizing patients. Advances in basic research including genomics, proteomics and metabolomics have been matched with the development of bioinformatics and computational tools to collect and analyze large amounts of data and generate knowledge applicable to health and disease. (Collins, 2015; Califf, 2018) Advances in medicine and science do occur in the context of support from initiatives in specific times, settings and a supportive collaborative environment.

### Timing KPMP

From a nephrology perspective, there have been several milestones in the long journey to treat kidney disease. Notably, the first successful kidney transplant was performed in 1954 and long-term dialysis became a reality for a small number of patients with kidney failure in 1960. One decade later in 1972 dialysis treatments became possible for thousands more with the extension of Medicare coverage.

#### Milestones Kidney Initiatives

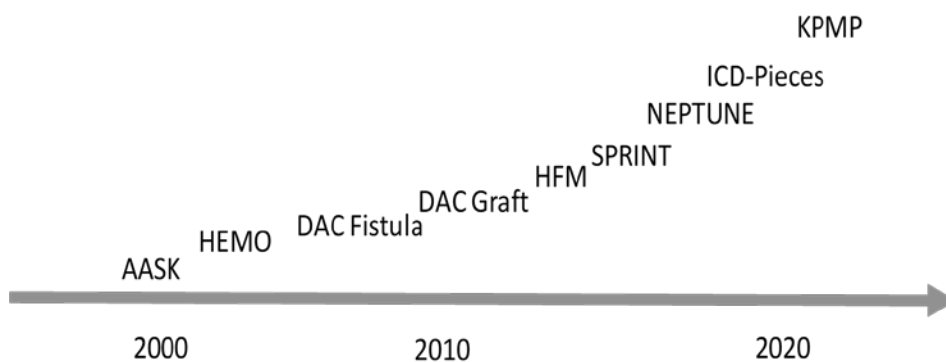
- 1954: First successful Kidney Transplant
- 1960: First patients start long-term dialysis
- 1972: Kidney disease coverage extended by Medicare
- 2015: Precision Medicine Initiative
- 2019 (July 10): American Kidney Health Initiative

The Precision Medicine Initiative was unveiled in 2015 and the Kidney Precision Medicine Project (KPMP) was funded in 2017. Just two weeks ago the Department of Health and Human Services unveiled the Advancing American Kidney Health Initiative. Among the main goals of this new federal initiative is reducing the risk of kidney failure and KPMP is one of the key components of this effort. (U.S. Department of HHS, 2019).

### Recruitment for KPMP at UT Southwestern

KPMP is a collaborative effort among many institutions. This effort is uniquely informed by patients and supported by the federal government. Recruitment Sites will play a major role as entry sites for the patients who will make this effort possible. UT Southwestern will be one of the initial three recruitment sites for chronic kidney disease (CKD) in KPMP. Our institution has been a key contributor to some of the most important NIH-sponsored clinical studies in nephrology. AASK, HEMO, DAC Fistula, DAC Graft, HFM, and SPRINT have informed the practice of nephrology in the last three decades (Wright 2002; Eknoyan 2002; Dember 2008; Dixon

#### UT Southwestern NIH – Sponosred Major Clinical Nephrology Studies



2009; Dember 2014; Wright 2015). NEPTUNE has provided some of the foundation for many of the studies in KPMP. (Gadegbeku 2013). ICD-Pieces is still in progress and is the largest embedded pragmatic clinical trial to date aimed at improving clinical outcomes for CKD. Tools developed and refined in ICD-Pieces will be used to facilitate recruitment in KPMP and subsequently guide implementation of care based on study findings. (ClinicalTrials.gov 2019)



Participants for KPMP at UT Southwestern will initially come from CUH, Parkland, North Texas VA Health Care System and Texas Health. Based on initial review these health systems provide care to more than 14,000 patients with CKD related to diabetes and/ or hypertension who could fit criteria for participation in KPMP.

### Users of KPMP

A key to the success of KPMP is that participation and use of resources and knowledge gained will be available to multiple users. Patients are at the center of KPMP and have been involved in its development from the very beginning. They will have access to use KPMP directly or via their clinicians. Nephrologists, other clinicians and pathologists will also access KPMP regularly to query for information to guide them to care for individual patients. Investigators from basic scientists to data analysts and other data miners will also find valuable information in KPMP.

### Potential Participants – KPMP

Health Care System	No. of Patients CKD, Diabetes, Hypertension
Parkland (PHHS)	10,388
UT Southwestern	5,505
VA North Texas	2,800
Texas Health (THR)	14,323

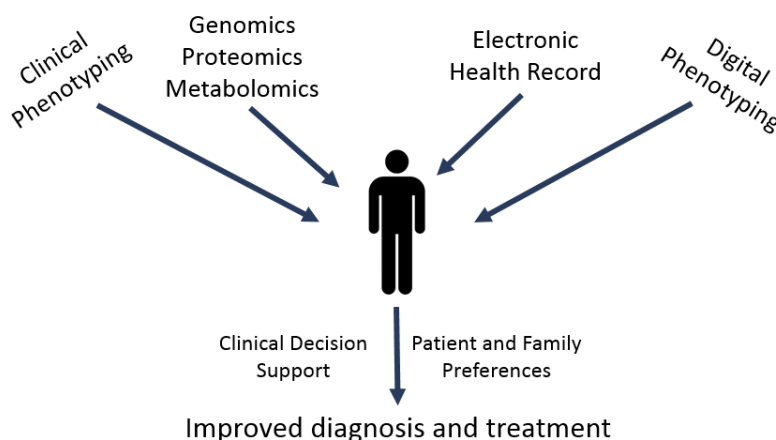
### Applications KPMP

Using KPMP will require integration of data from multiple sources including clinical data, genomics, proteomics and metabolomics as well as social determinants of health, EHR sets, and administrative claims data. (Califf 2018, Collins 2015). Application of decision support within the context of patient and family preferences will guide use of this rich data to improve diagnosis and treatments of patients with CKD



Recruitment efforts will initially focus on patients with diabetic kidney disease and hypertension-associated chronic kidney disease. Patients will be initially identified from clinic panels and registries. At Parkland and the VA there is availability of Pieces, a novel technology tool developed by co-investigators from the Parkland Center for Clinical Innovation, to identify patients meeting the inclusion criteria for KPMP. The team has experience using Pieces to identify and facilitate management of patients with CKD as part of the ongoing study, ICD-Pieces.

Clinicians will be notified if a patient is potentially eligible for participation. The Informed Consent Process will focus on providing comprehensive patient education about the study and include opportunities to ask questions about KPMP and review concerns. There is also a Patient Engagement Group available to provide additional education and perspective to potential participants about the study. Patients who consent to participate in KPMP will then proceed to continue study visit(s) with collection of detailed data for deep phenotyping (clinical, digital



Modified from Califf, 2019 and Collins

and molecular) including, bio-specimens and completion of KPMP research biopsy. Patients will then continue research visits with the RS with plans to follow patients for at least 10 years



#### I want to know...

- What I have
- What will happen to me
- What I can do

Patients want to know about their kidney disease and will be able to have a resource that can help them find information about key questions including what they have, what can be expected to happen and what can be done about it. They will be able to see their biopsy slides and see the information in clear terms without having to depend on complex scientific language.

Clinicians will have access to link individual patients with best treatments. Ideally, clinicians will be able to understand the causality of disease for their patients, disease

categories and available and emerging therapies. EHR data will be readily integrated for application of decision support and selection of appropriate treatment algorithms.

In the case of a patient with CKD, diabetes and hypertension, for example, the clinician will be able to enter clinical, pathology and/ or molecular data into KPMP.

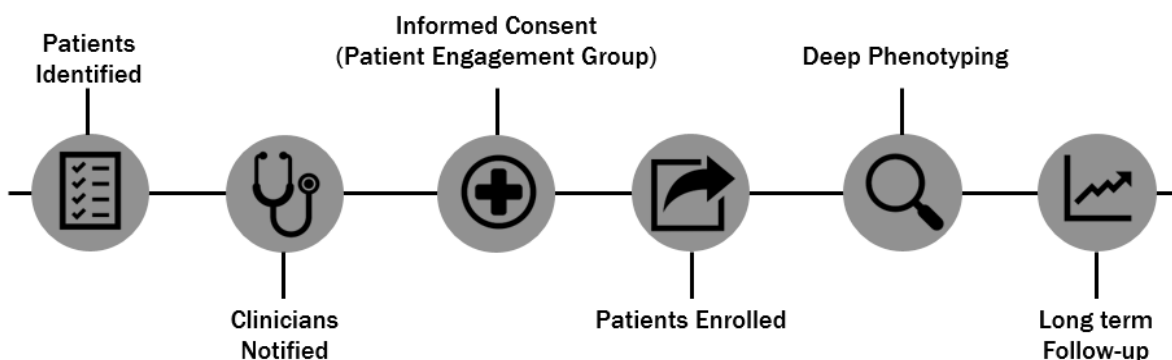
The clinician can then find the appropriate disease group, review expected outcomes, assign to a molecular subgroup and select the most appropriate therapy.



#### I want ...

- Clear diagnostic categories
- A tool for clinical decision support,
- Link my patients disease to targeted therapies

### Study Conduct





**Question:** What information can I learn that could change the management?

Atlas Point of Entry: Clinical Data



The user performs a search for clinical terms of interest:

- 68 yo with **diabetes** and HTN
- creatinine **1.47** mg/dl
- Urine: 2 + **proteinuria**

## Summary

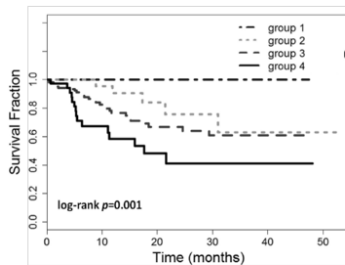
Kidney disease is a major health problem, often unrecognized and with major implications for health and survival. Patients with CKD are not only at risk for kidney failure but also have a disproportionately higher risk of premature death. Treatments for kidney disease are limited in effectiveness in large part due to lack of in-depth studies of kidney tissue.

Precision medicine has provided the scientific foundation for recent progress in patient care in other fields in

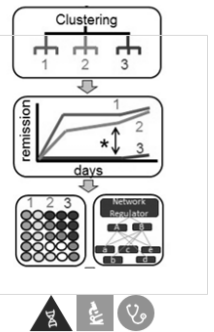
medicine. Application of precision medicine to kidney disease holds great promise. The KPMP is a national effort to understand and treat human kidney disease. KPMP aims to create a new paradigm of care in kidney disease. KPMP will use deep clinical phenotyping and novel molecular assays from bio-samples and renal tissue to elucidate pathogenic mechanisms, identify disease subgroups, develop clinical assays, and identify targets for new therapies. KPMP ultimately aims to improve outcomes for patients with kidney disease by making it possible to apply the right intervention for the right patient at the right time.



## Integrated Results



- Find Subgroup
- Review Spectrum Outcomes
- Assigns Patients to Molecular Subgroup
- Select Therapies



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