Clinical Trials & Drug Development in CKD: Emerging from the Stone Age

Daniel Edmonston, MD

On behalf of Dr. Myles Wolf, Dr. Glenn Chertow, and other DCRI Think Tank stakeholders

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

Duke Nephrology
Duke University School of Medicine

DCRI **THINK TANKS**
FROM INSIGHT TO ACTION

Accelerating Drug Development for Chronic Kidney Disease and End-Stage Renal Disease

April 24-25, 2019
Washington, DC

Adapted from dcri.org/insights/think-tanks

DCRI **THINK TANKS**
FROM INSIGHT TO ACTION

Accelerating Drug Development for Chronic Kidney Disease and End-Stage Renal Disease

April 24-25, 2019
Washington, DC

Special Report AJKD

Drug Development in Kidney Disease: Proceedings From a Multistakeholder Conference

Daniel L. Edmonston, Matthew T. Roe, Geoffrey Block, Paul T. Conway, Laura M. Dember, Peter M. DiBattiste, Tom Greene, Ali Hariri, Lesley A. Inker, Tamara Isakova, Maria E. Montez-Rath, Richard Nkulikiyinka, David Polidori, Lothar Roessig, Navdeep Tangri, Christina Wyatt, Glenn M. Chertow, and Myles Wolf

Occasional bursts of discovery and innovation have appeared during the otherwise stagnant past several decades of drug development in nephrology. Among other recent drug discoveries, the unexpected kidney benefits observed with sodium/glucose cotransporter 2 inhibitors may herald a renaissance of drug development in kidney disease. This recent progress highlights the need to further promote and stimulate research and development of promising therapies that may ameliorate the morbidity and mortality associated with kidney disease. To help identify and address barriers to drug development in nephrology, the Duke Clinical Research Institute convened a conference in April 2019 that included stakeholders from academia, industry, government agencies, and patient advocacy. From these discussions, several opportunities were identified to improve every stage of drug development for kidney disease from early discovery to implementation into practice. Key topics reviewed in this article are the utility of interconnected data and site research networks, surrogate end points, pragmatic and adaptive trial designs, the promising uses of real-world data, and methods to improve the generalizability of trial results and uptake of approved drugs for kidney-related diseases.

Complete author and article information provided before references.

Am J Kidney Dis. XX(XX):1-9. published online month xx, xxxx.

doi: 10.1053/j.ajkd.2020.05.026

Introduction

Sodium/glucose cotransporter 2 (SGLT2) inhibitors represent the most significant drug development for diabetic kidney disease in the past 2 decades. Other recent drug discoveries have also improved the treatment of autosomal dominant polycystic kidney disease, hyperkalemia, and anemia. Although these discoveries herald a new era of drug development in kidney disease, numerous challenges remain. Nephrology consistently ranks among the medical subspecialties with the fewest number of published clinical trials.[1] Significant barriers impede timely drug development and uptake for patients with acute kidney injury and chronic kidney disease (CKD).

Drug development faces many challenges in both preclinical and clinical stages; in addition, even successfully approved drugs encounter barriers to clinician and patient uptake. During the past 23 years, the Duke Clinical Research Institute has facilitated "think tanks" designed to address the most pressing gaps in clinical research. In April 2019, leaders from academia, industry, patient representatives, professional societies, and government agencies, including the US Food and Drug Administration (FDA), National Institutes of Health (NIH), and Centers for Medicare & Medicaid Services (CMS), convened in Wash-

Hypothesis Generation and Drug Discovery

Although drug discovery often follows the classic "bench-to-bedside" paradigm in which laboratory data are used to identify putative therapeutic targets, investigators can also use high-quality clinical data and secondary analyses to hone hypotheses and identify new drug targets. Examples of this "reverse translation" approach include the discovery of new therapeutic targets through genome-wide association studies (GWAS) and other genetic analyses,[2] use of observational data to assess the target patient profile before the conception of clinical trials, and use of machine learning and predictive algorithms to identify patients most likely to benefit from investigational therapies.[3]

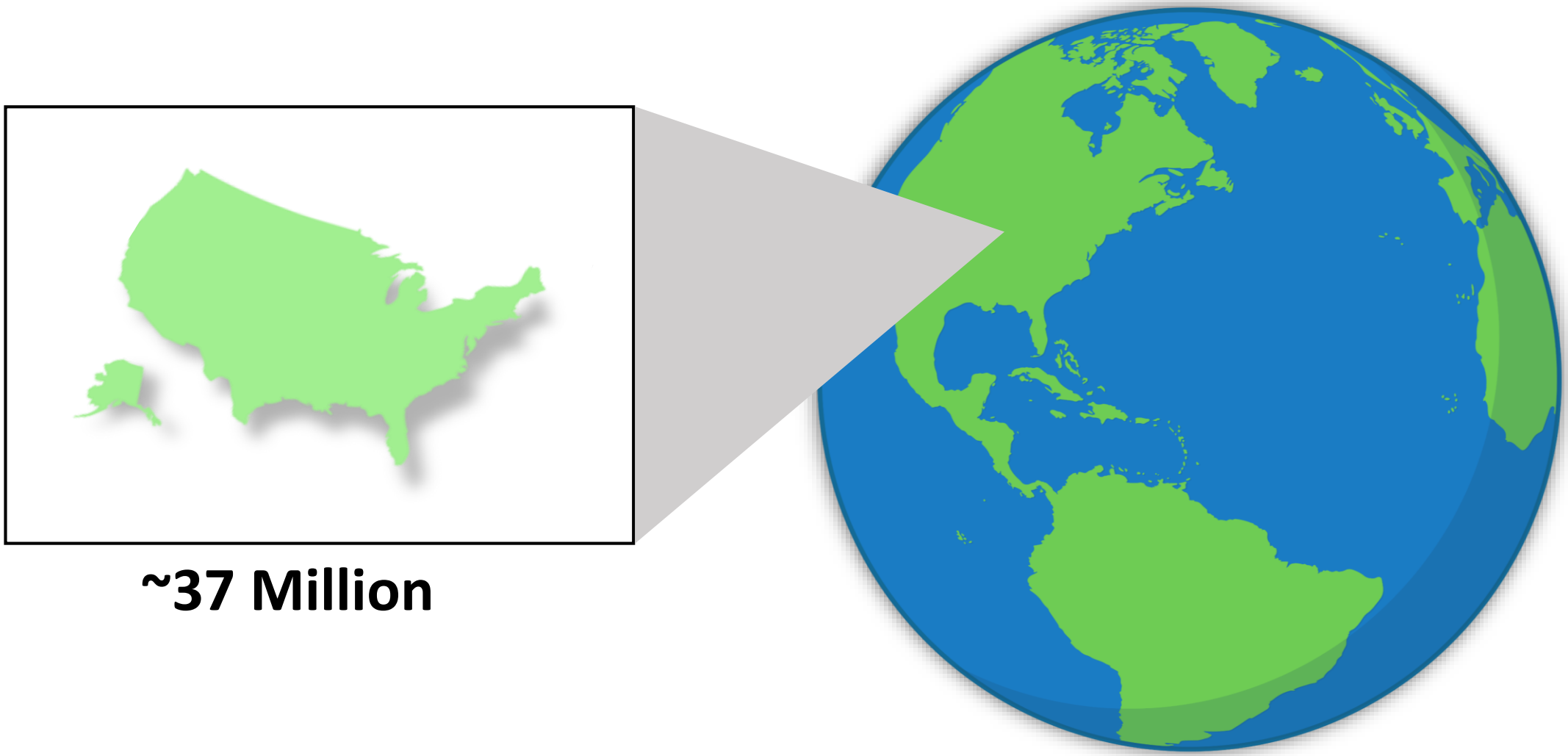
Several barriers limit the use of such data in the drug development process. These barriers include uncertain CKD cause due to a lack of kidney biopsy data for many patients with CKD; lack of standardized data collection for kidney disease end points, even in the context of clinical trials; limited access to industry-sponsored clinical trial data for secondary analyses; and fragmented data networks with inconsistent and often incompatible electronic records across different health systems data. Potential strategies to improve data access include interconnected data networks, disease-specific registries and networks, and

Edmonston et al. Am J Kidney Dis. 2020

I have no relevant financial disclosures or conflicts of interest to disclose.

~700 Million

GBD Chronic Kidney Disease Collaboration, *Lancet*, 2020



~37 Million

~700 Million

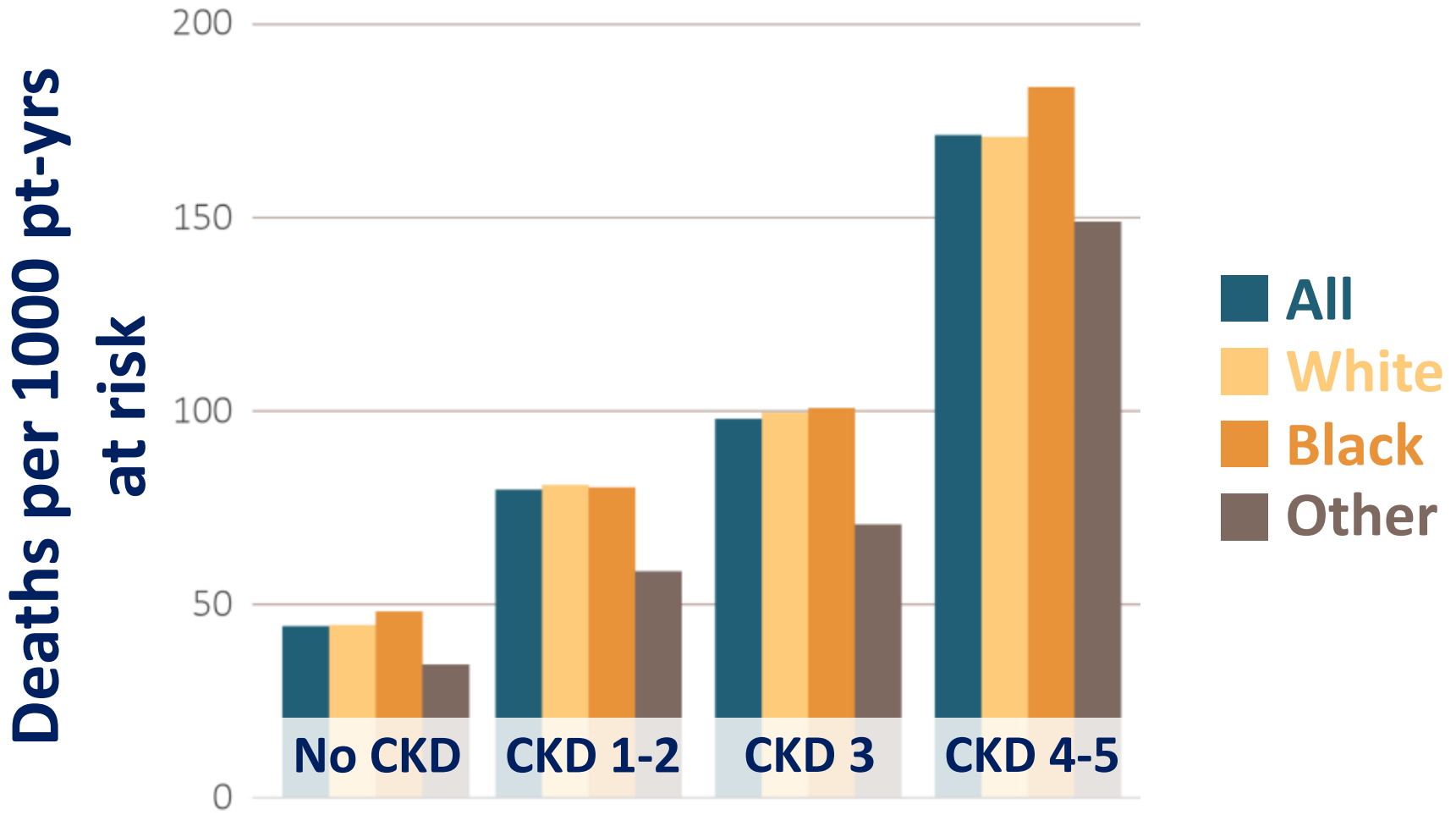
CDC, 2020

$84 billion CKD

$36 billion ESKD

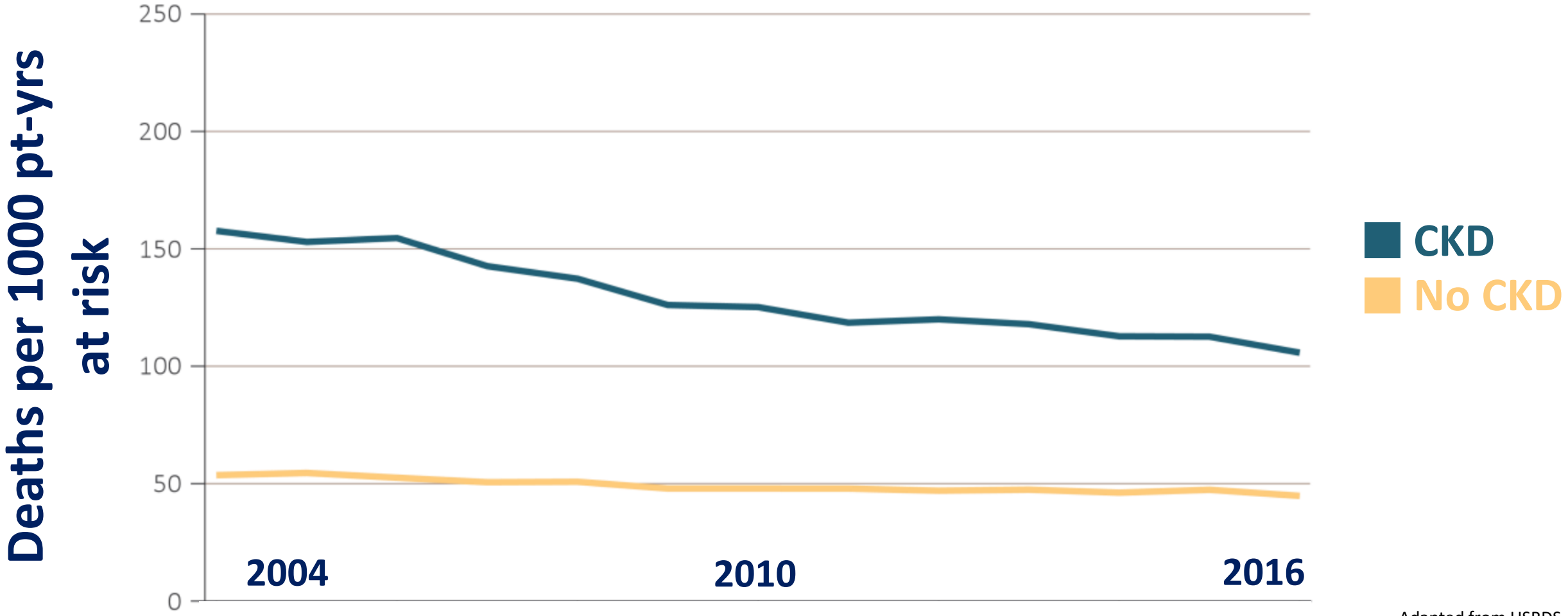
CDC, 2020

Adjusted All-Cause Mortality Among Persons with CKD Stratified by Race

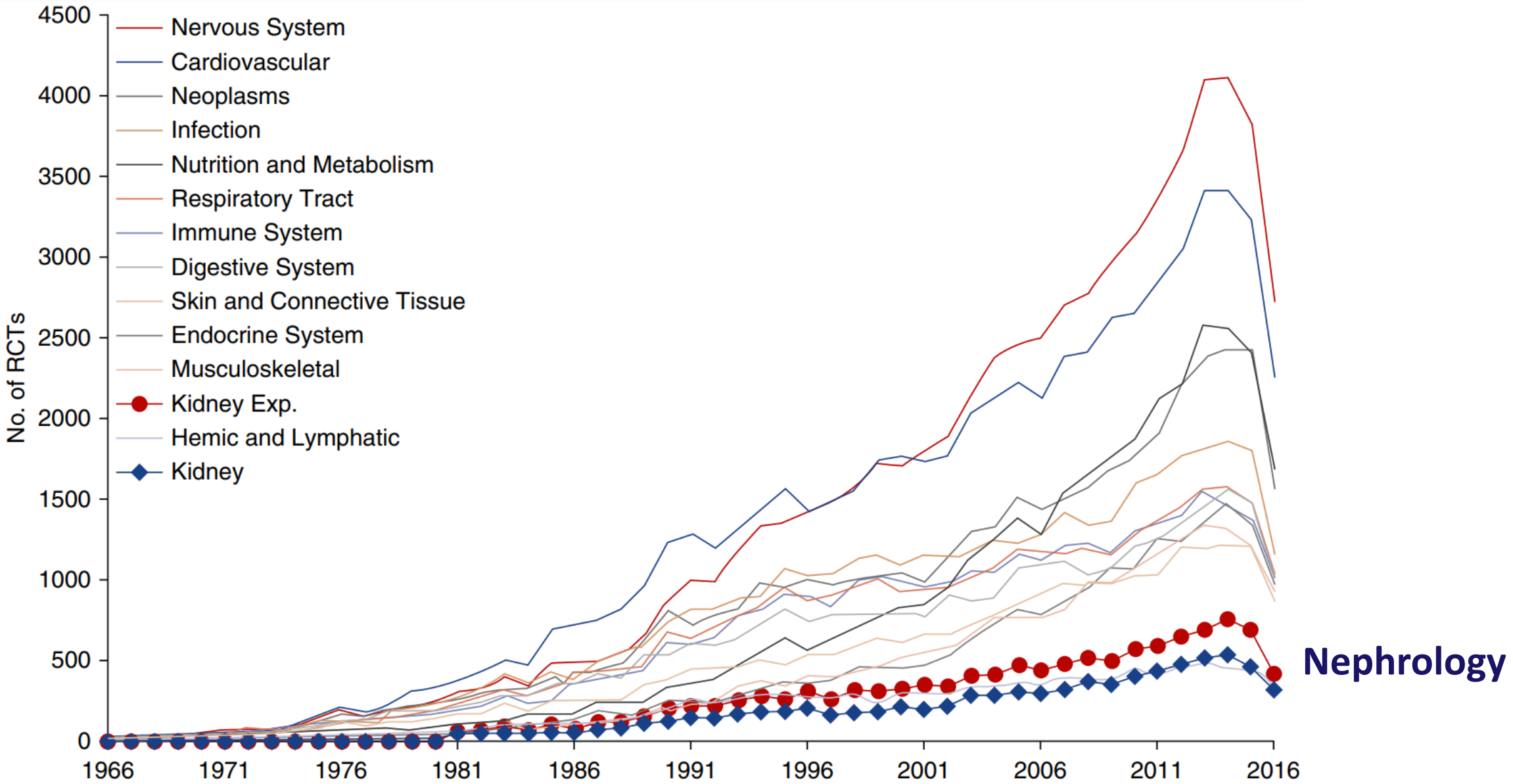


Adapted from USRDS, 2018

Adjusted All-Cause Mortality in CKD vs non-CKD

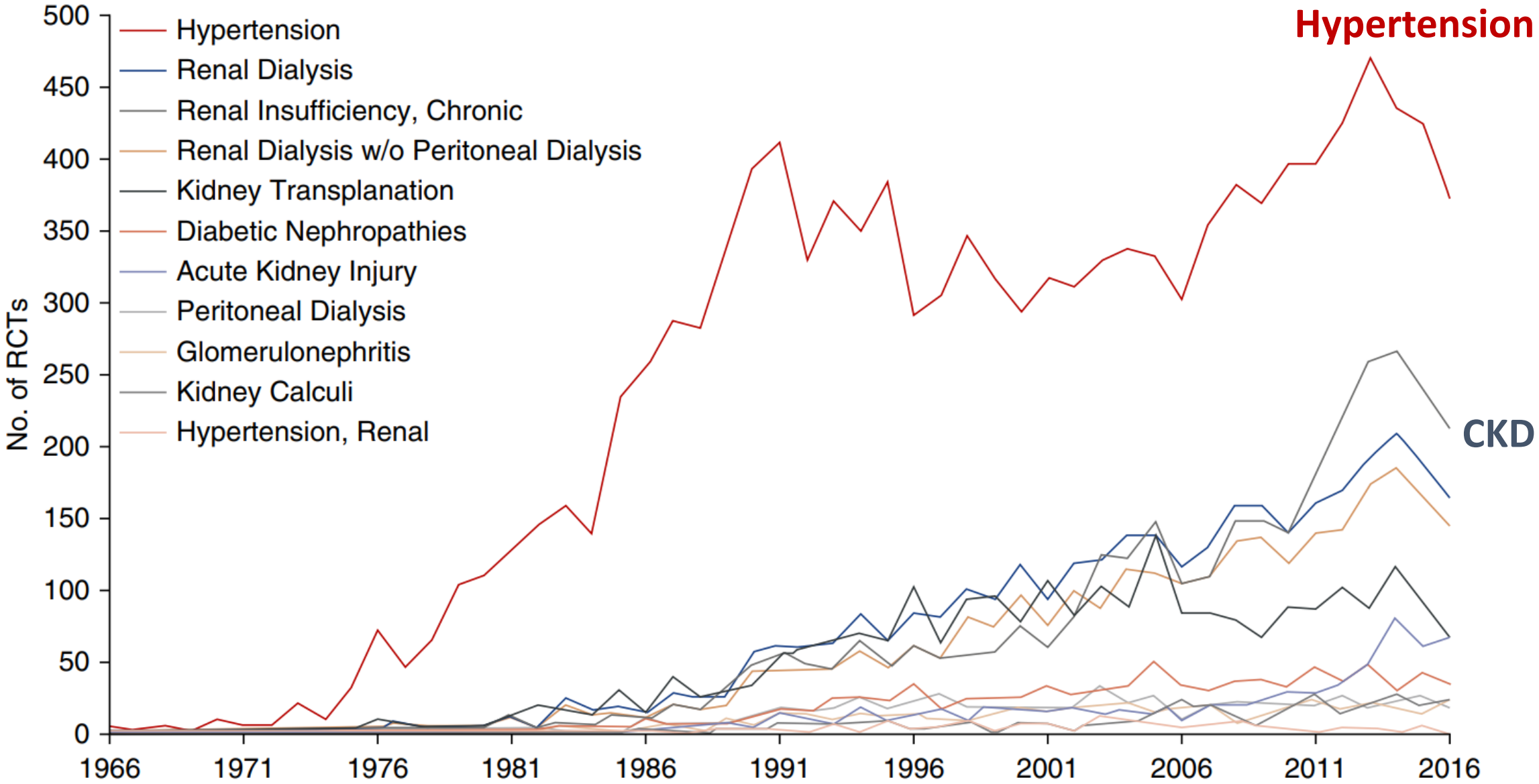


Adapted from USRDS, 2018



Nephrology

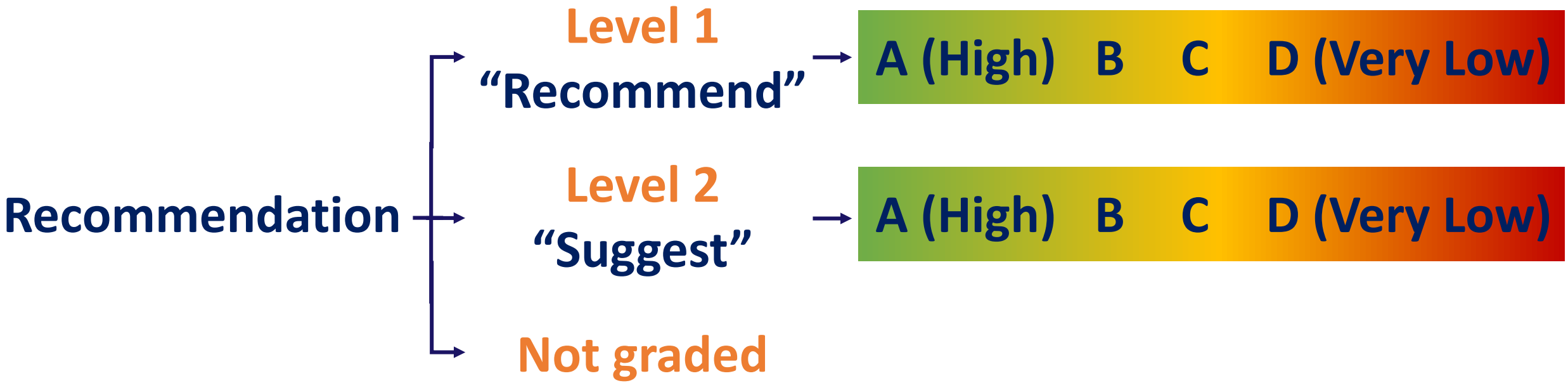
Adapted from Chatzimanouil et al. *JASN*, 2019



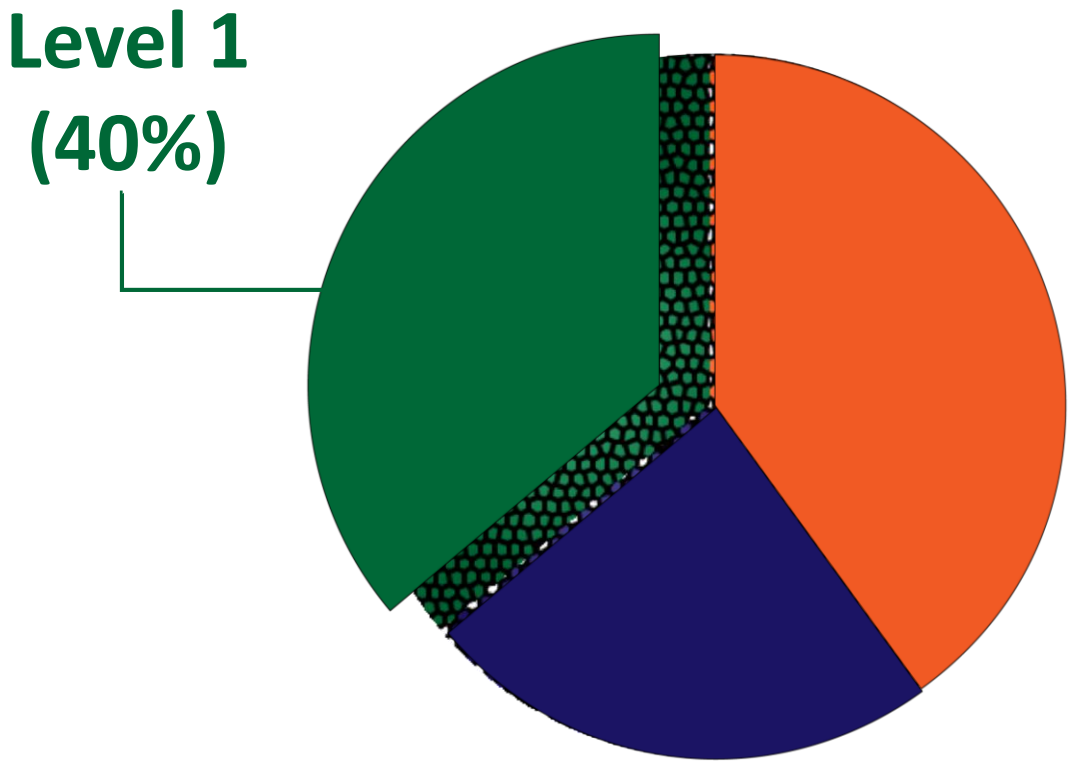
Chatzimanouil et al. *JASN*, 2019

Evidence-Based Guideline Recommendations

KDIGO: Clinical Practice Guideline for Evaluation and Management of CKD

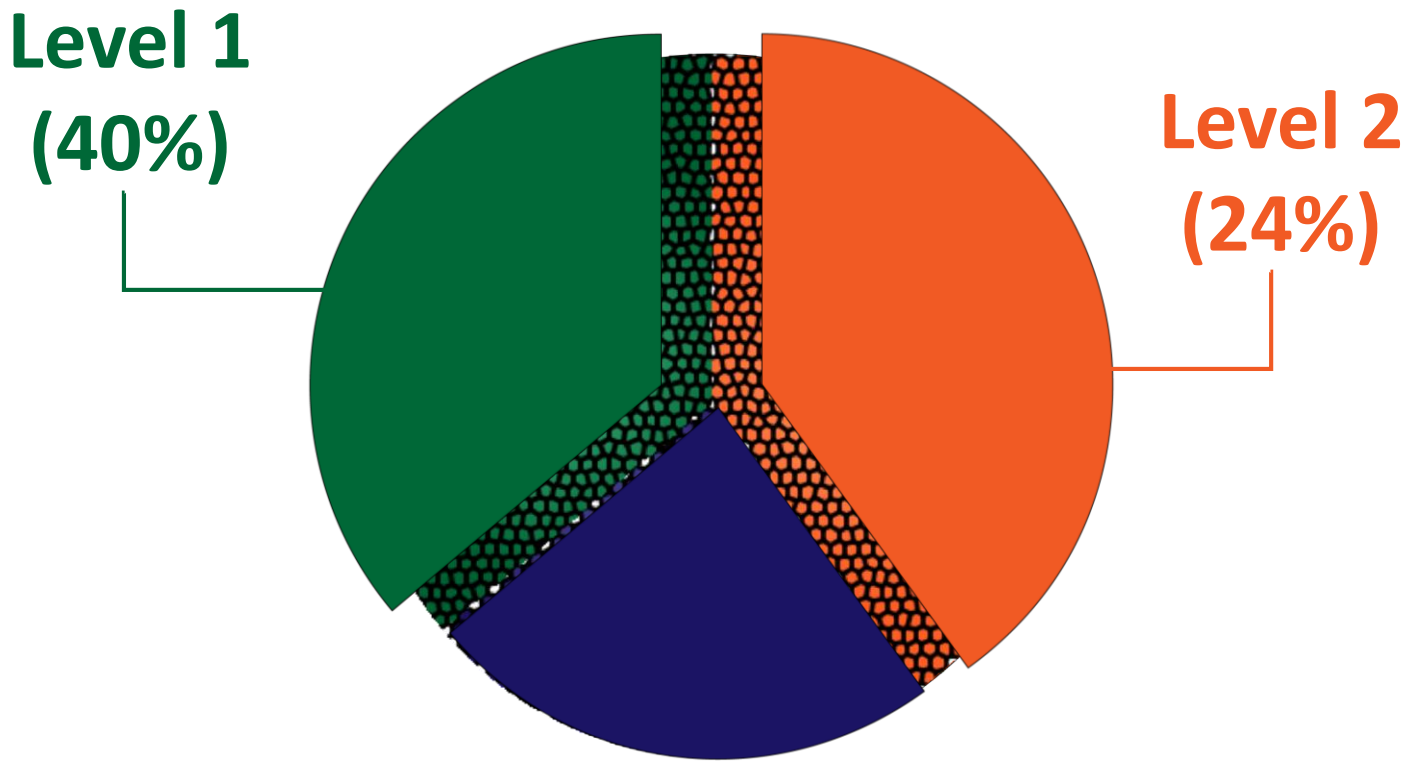


KDIGO, *KI Supplements*, 2013



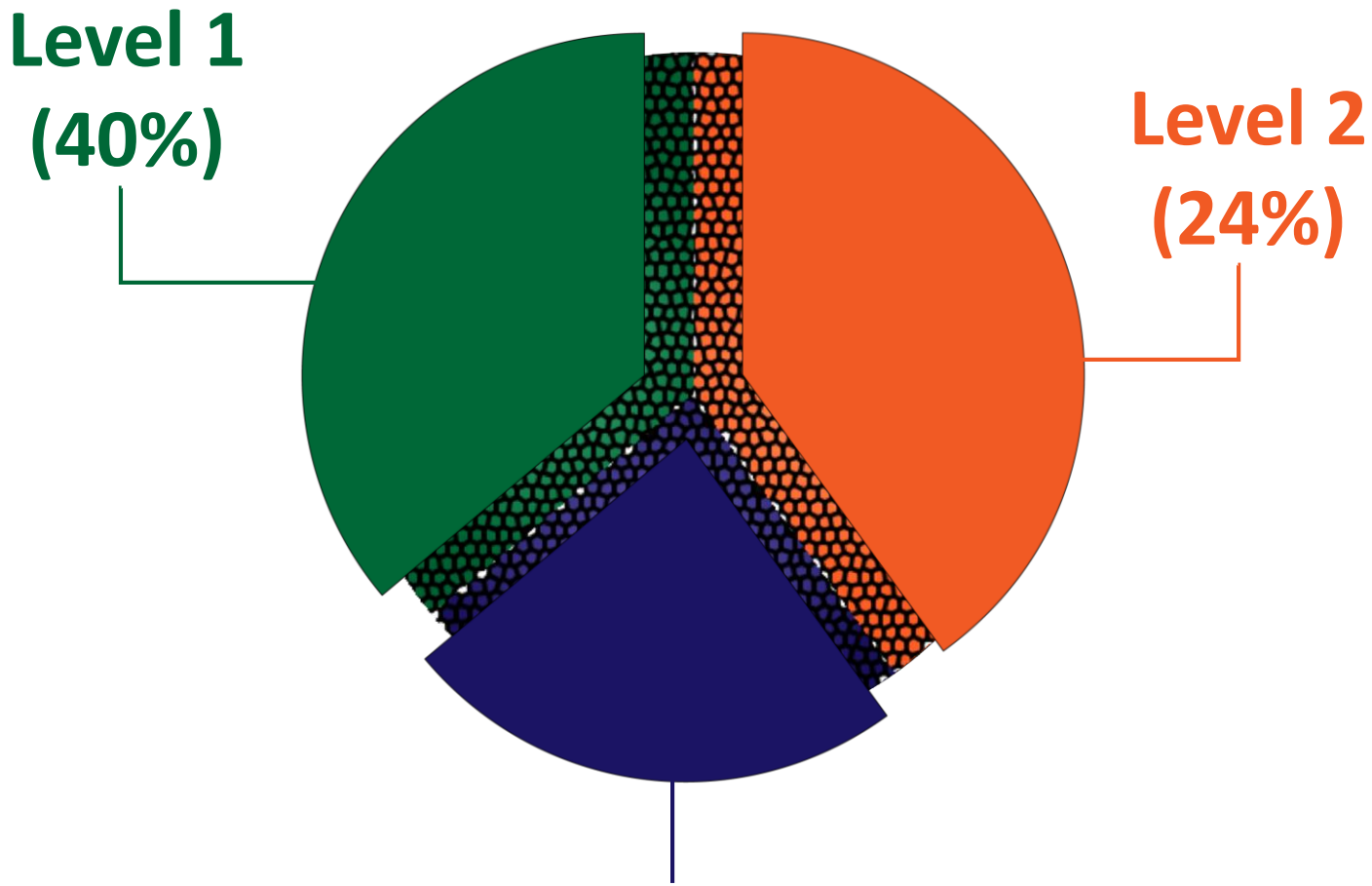
*110 total recommendations

KDIGO, *KI Supplements*, 2013



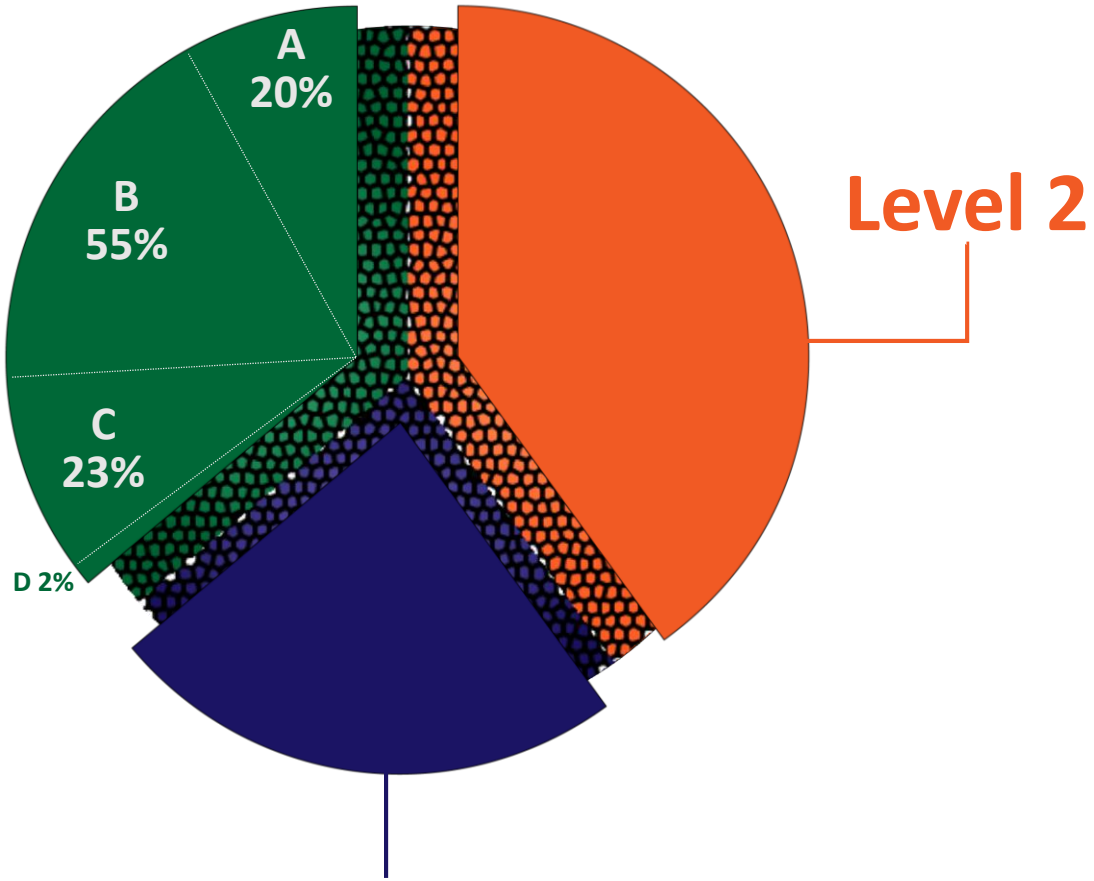
*110 total recommendations

KDIGO, *KI Supplements*, 2013



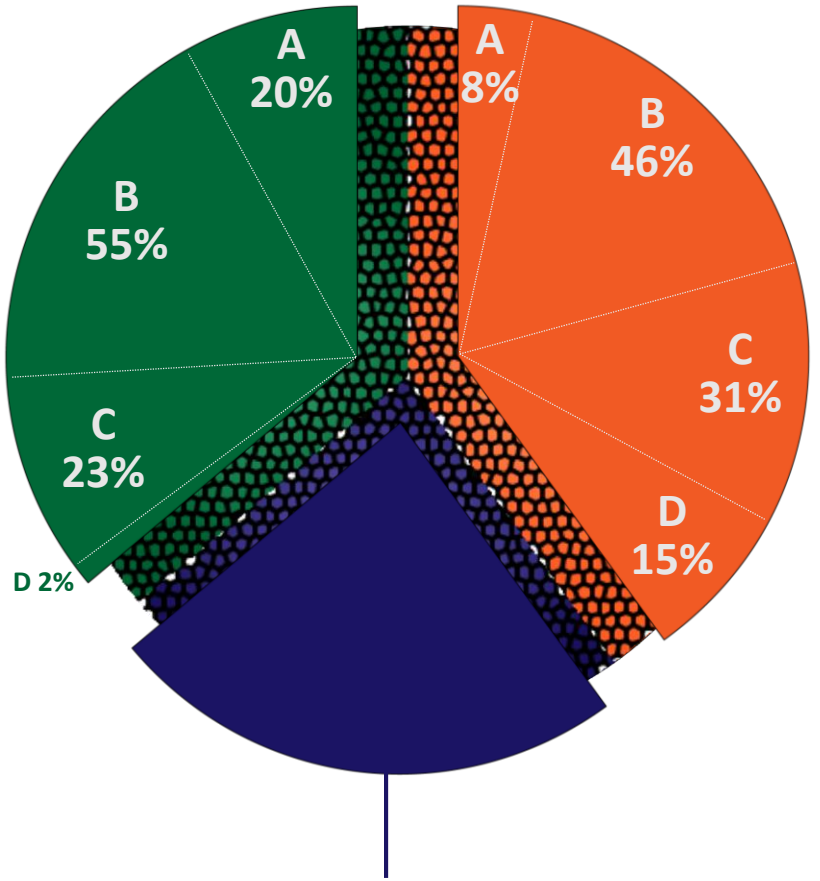
*110 total recommendations

KDIGO, *KI Supplements*, 2013



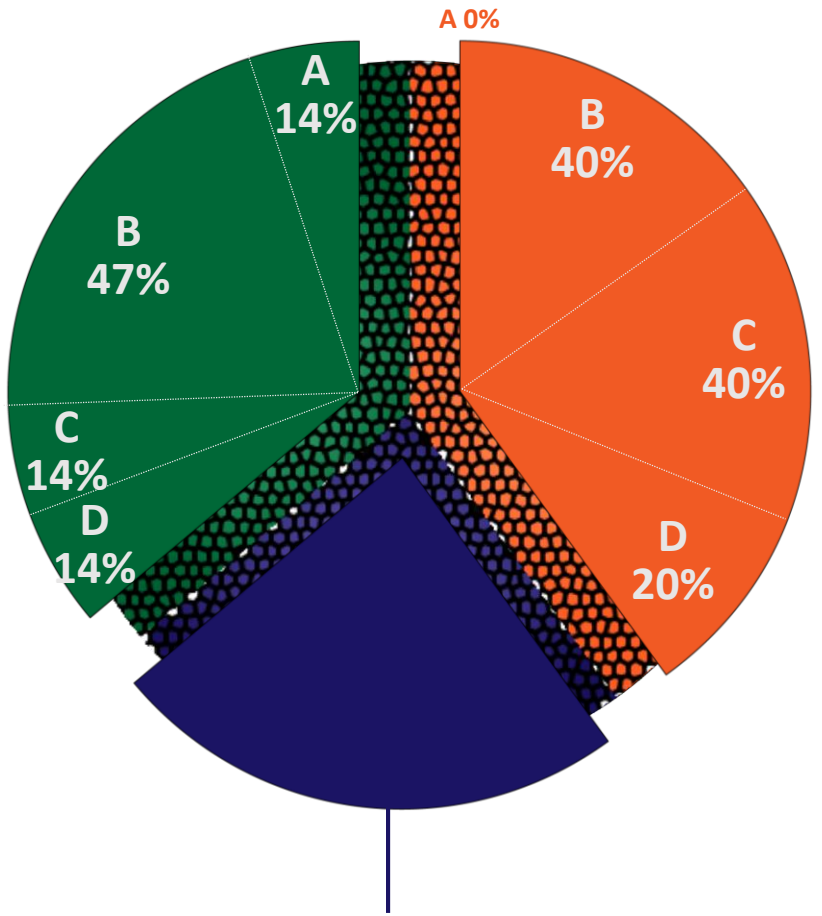
*110 total recommendations

KDIGO, *KI Supplements*, 2013



*110 total recommendations

KDIGO, *KI Supplements*, 2013



Not Graded

*21 total recommendations

KDIGO, *KI Supplements*, 2013

Only ~5% of treatment recommendations reached a "Grade A" level of evidence.

KDIGO, *KI Supplements*, 2013

Why is observational data specifically dangerous in CKD and ESRD?

*21 total recommendations

KDIGO, *KI Supplements*, 2013

CHOIR (2006)
Hb 13.5 vs 11.3
(Epo Alpha)

→ ↑CV composite (HR 1.34, 1.04-1.74)
NS QoL difference

CREATE (2006)
Hb 13-15 vs 10.5-11.5
(Epo Beta)

→ NS CKD/CV composite
↑Dialysis requirement

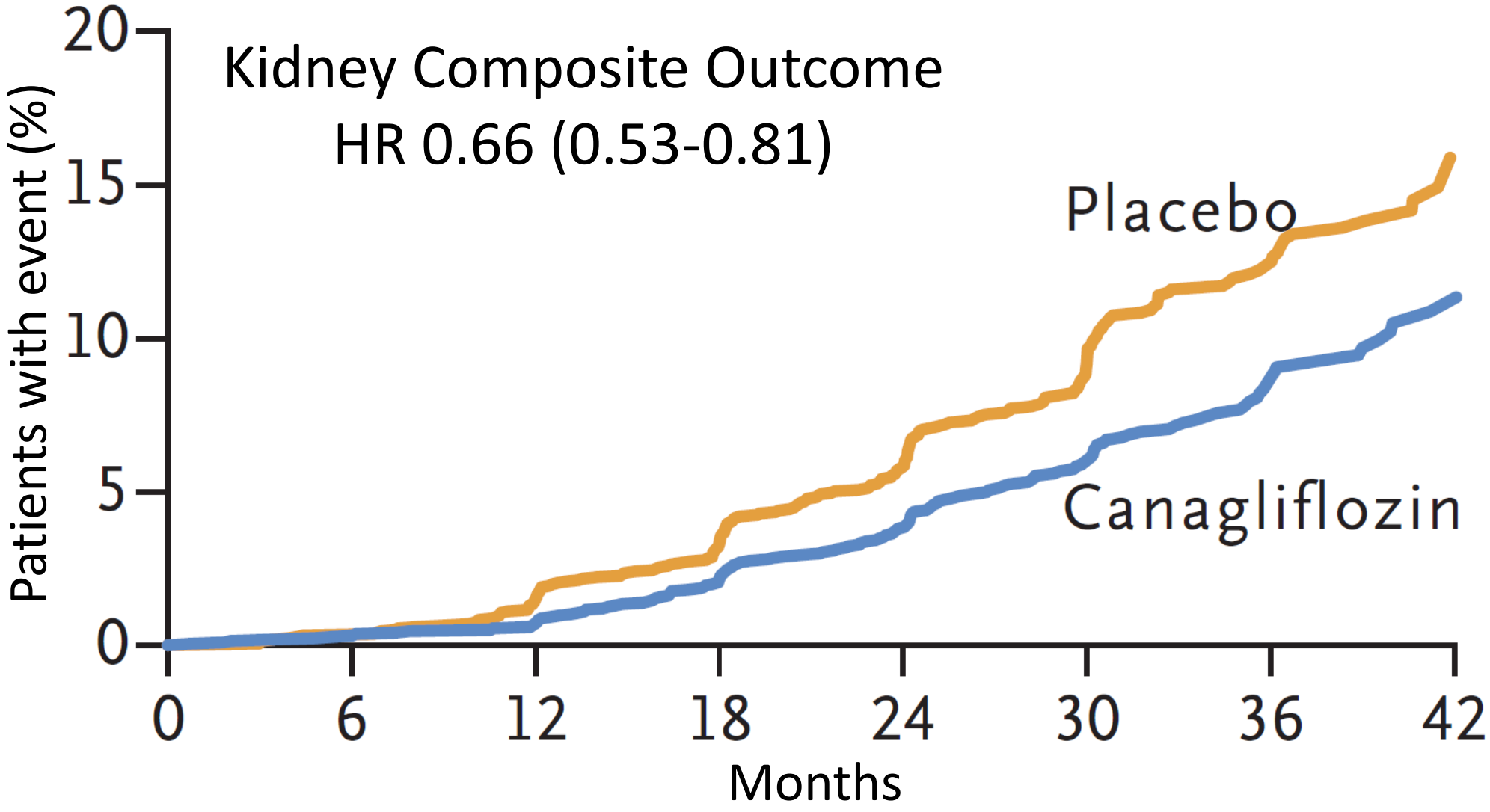
TREAT (2009)
Hb 13 vs 9
(Darbepoetin Alpha)

→ NS death/CV composite
↑Stroke (HR 1.92, 1.38-2.68)

Singh et al. *NEJM*. 2006; Drueke et al. *NEJM*. 2006; Pfeffer et al. *NEJM*. 2009

"I bet he forgot about SGLT2 inhibitors."

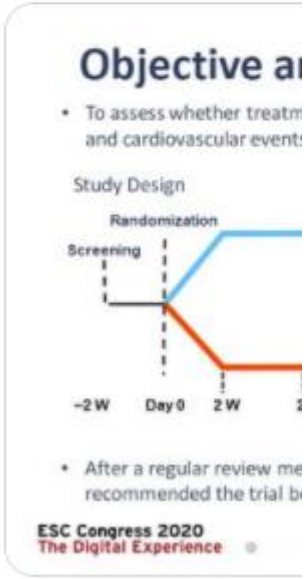
-Willy Wonka (probably)



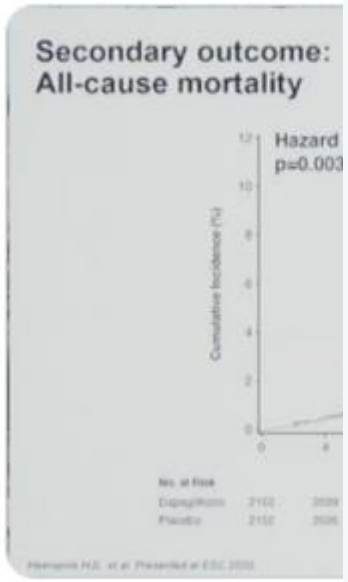
Adapted from Perkovic et al. *NEJM. 2019*

European Society of Cardiology @escardio · 23h
#DAPA-CKD trial: randomly allocated 4,304 #CKD patients with and without type 2 #diabetes to da
of 2.4 years bit.ly/3jcGl

#ESCCongress



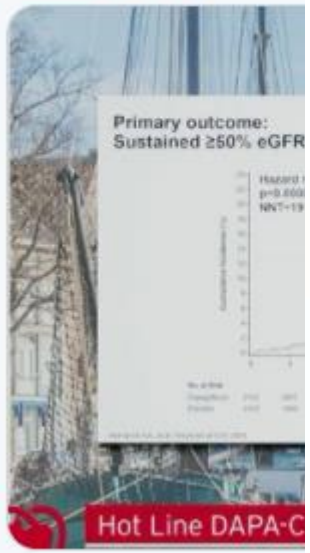
Swapnil Hiremath, MD, MPH @hswapnil · 23h
hugely impressive reduction in all-cause mortality
#DAPACKD #ESCCongress



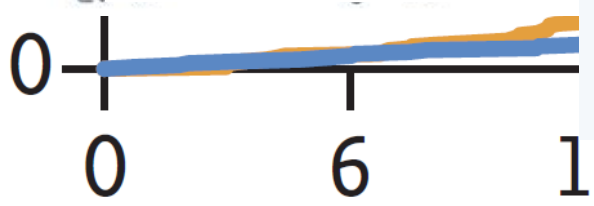
2 1

Jennie Lin, MD MTR @jenniejlin · 23h
#DAPACKD primary ou

#ESCCongress

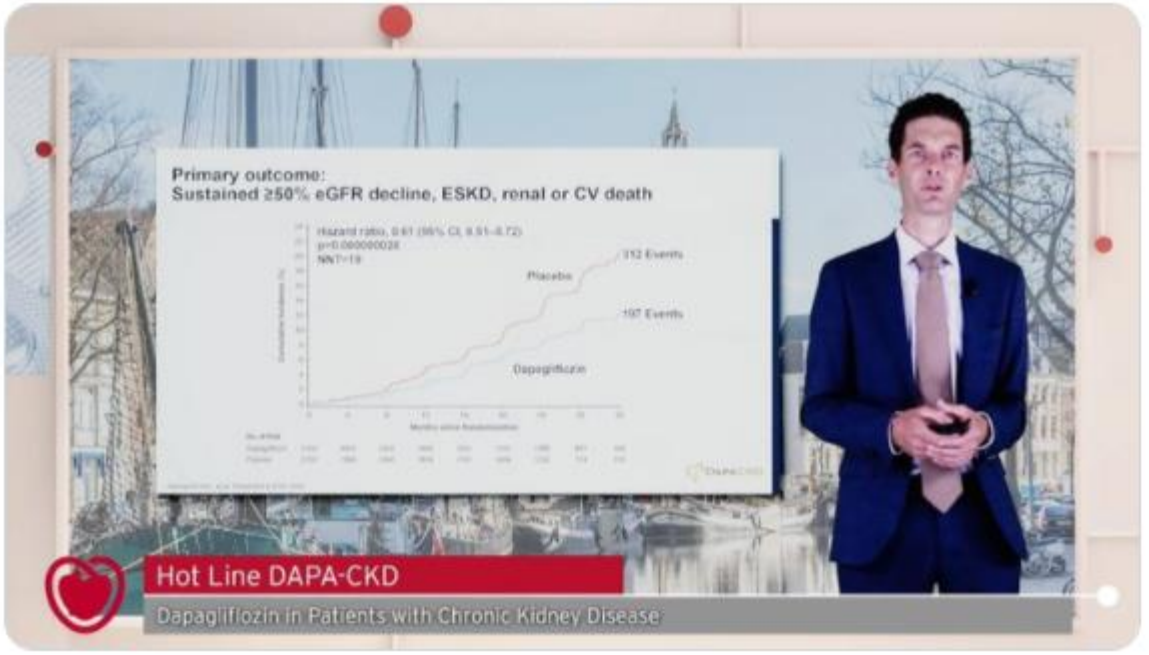


3



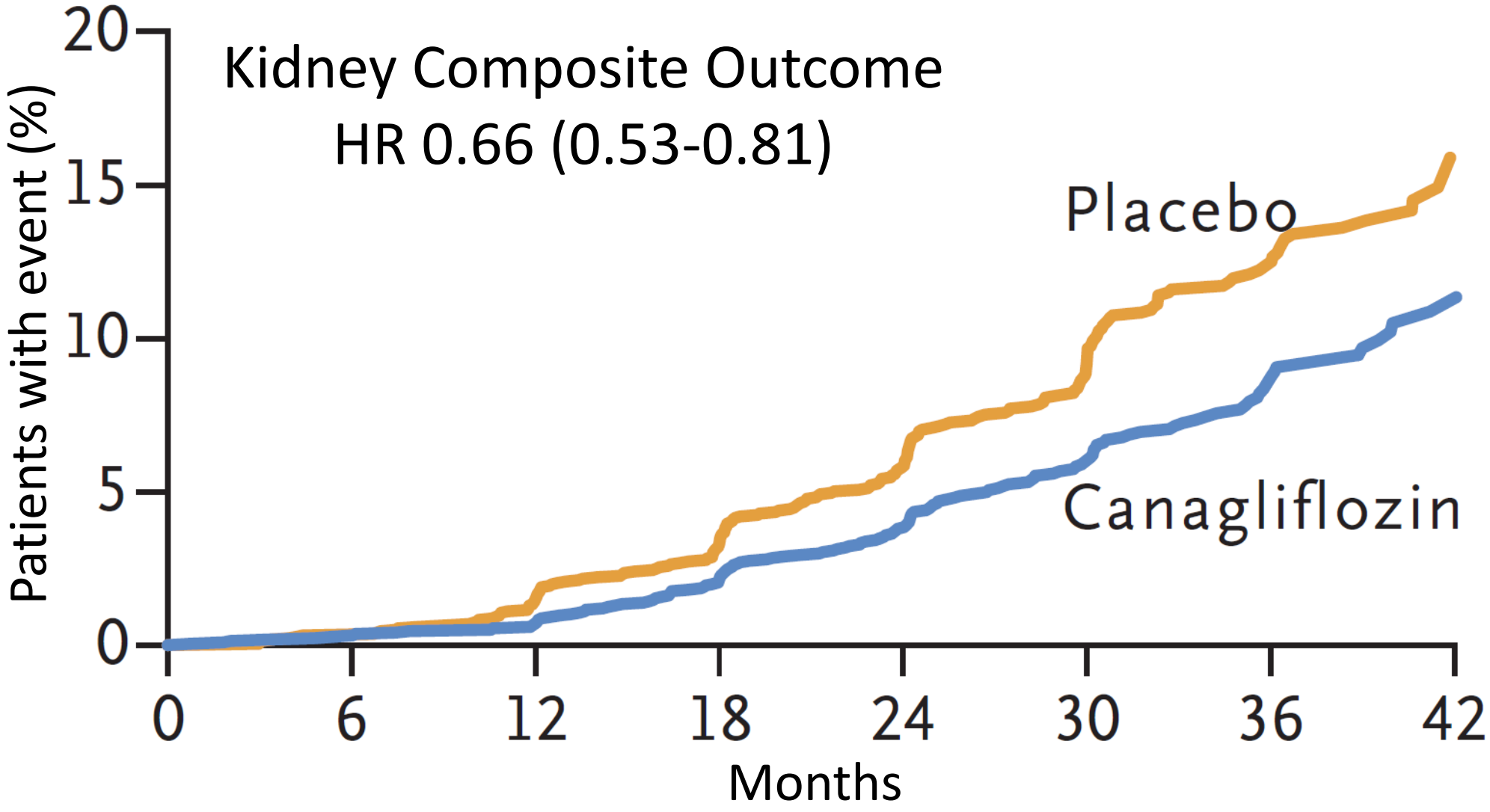
Matthew Sparks, MD, FASN, FAHA
@Nephro_Sparks

WHOA #DAPACKD #ESCCongress #ESC2020

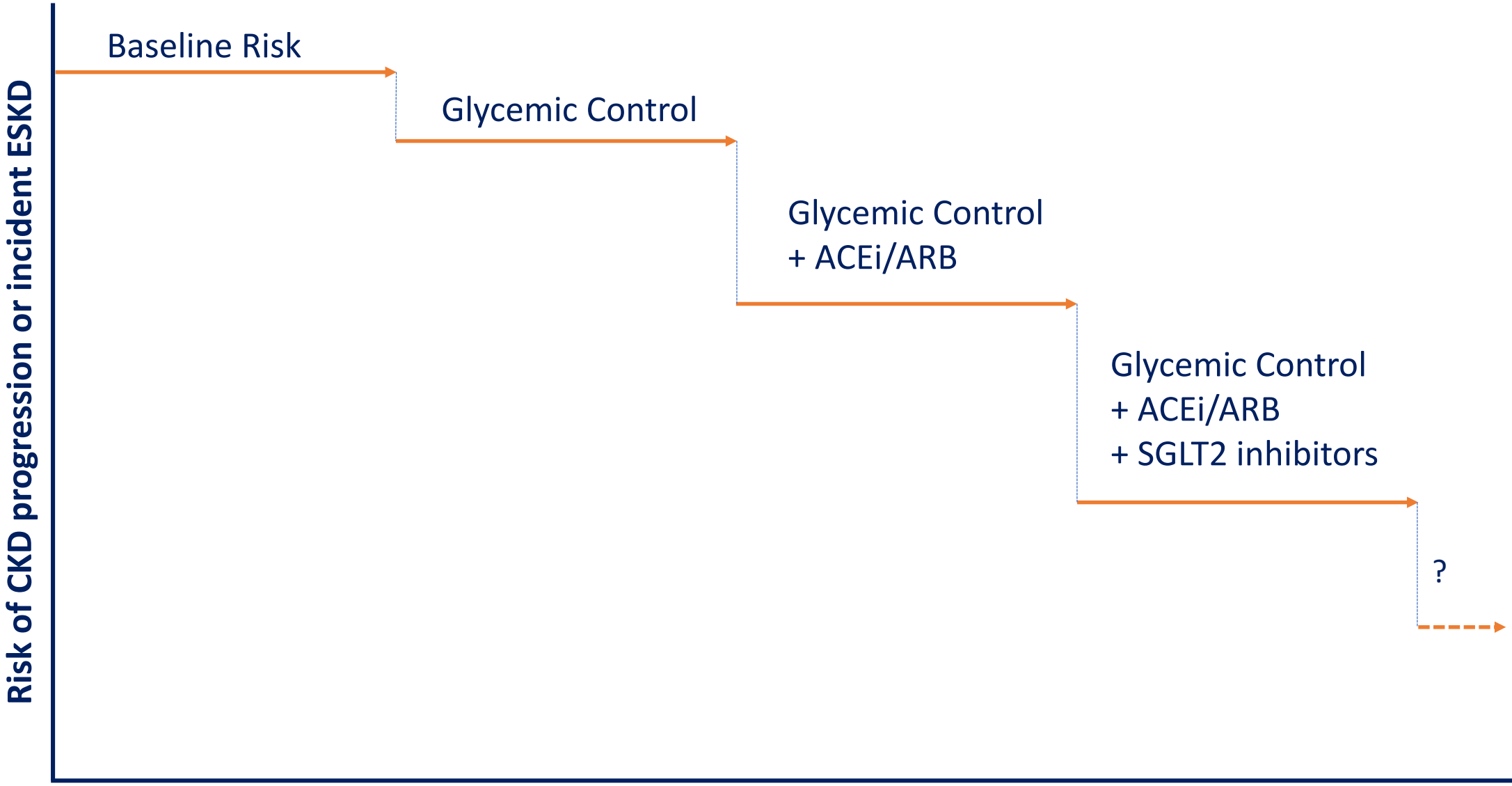


11:05 AM · Aug 30, 2020 · Twitter Web App

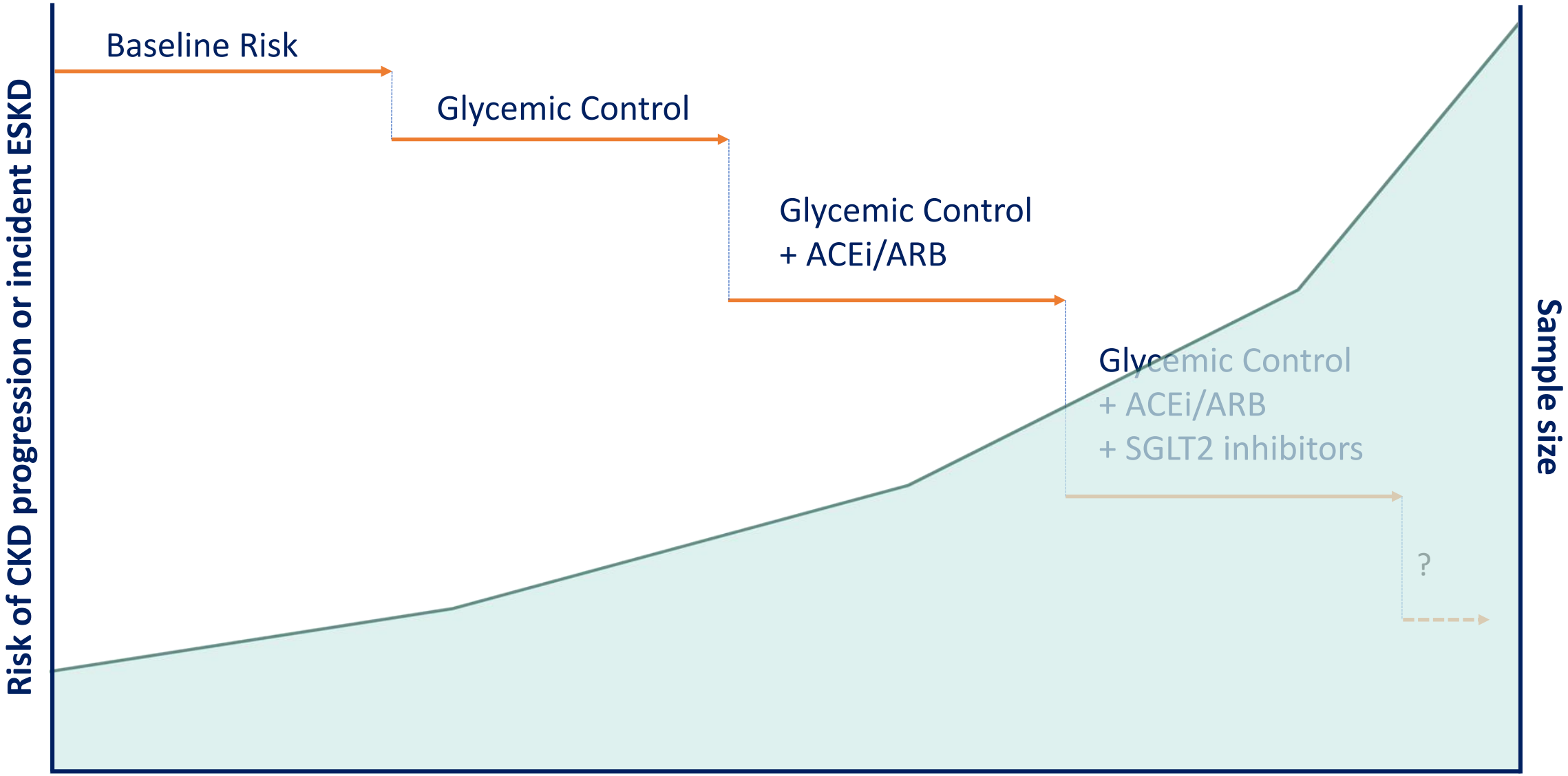
Heerspink et al. *NEJM. 2020*



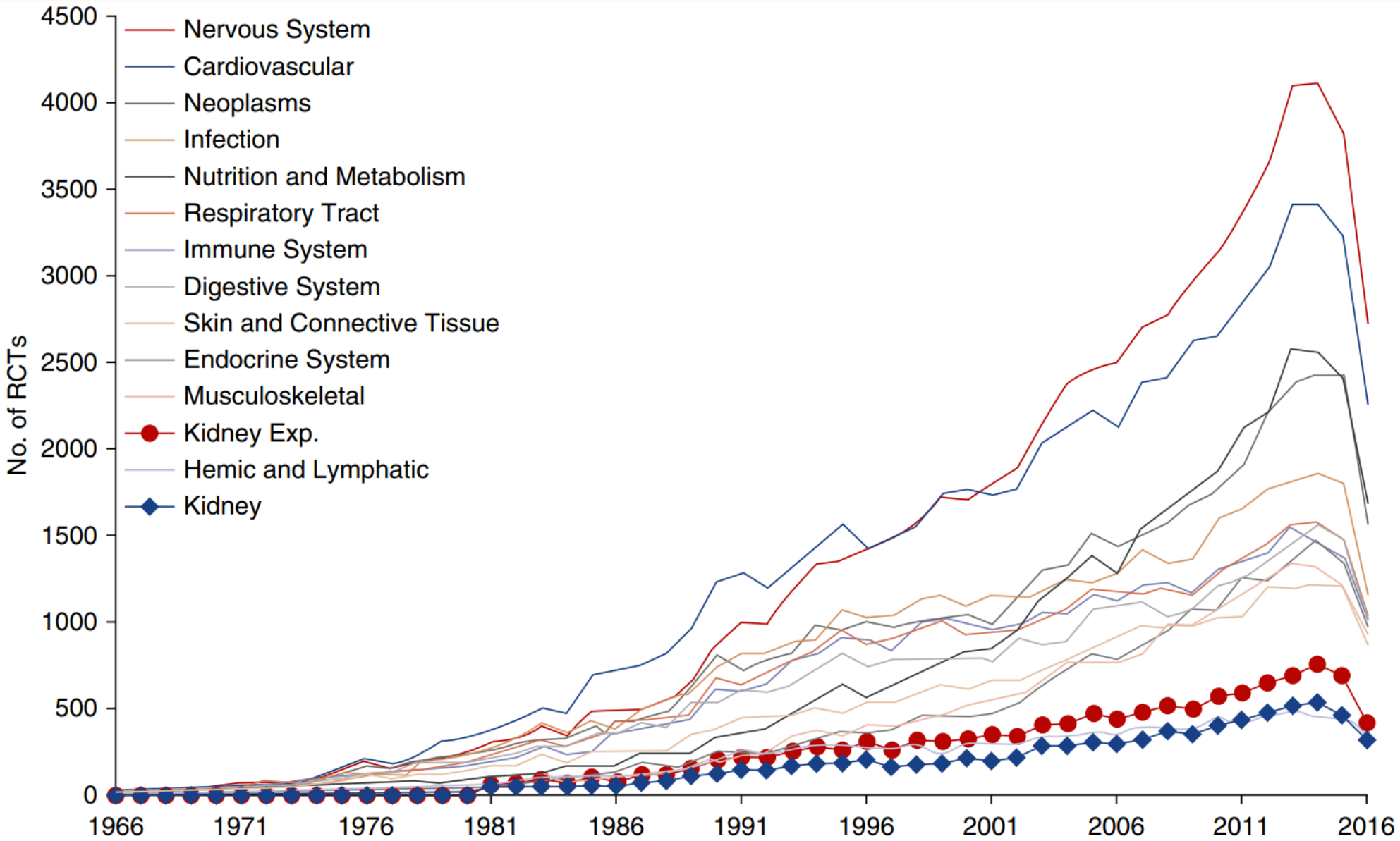
Adapted from Perkovic et al. *NEJM. 2019*



UKPDS Group, *Lancet*. 1998; Brenner et al. *NEJM*. 2001; Perkovic et al. *NEJM. 2019*



UKPDS Group, *Lancet*. 1998; Brenner et al. *NEJM*. 2001; Perkovic et al. *NEJM. 2019*



Chatzimanouil et al. *JASN*, 2019


Dark Ages
Golden Era


↓Drug Discovery
↑Trial Costs
↑Extrapolation
Golden Era

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

Duke Nephrology
Duke University School of Medicine

DCRI **THINK TANKS**
FROM INSIGHT TO ACTION

Accelerating Drug Development for Chronic Kidney Disease and End-Stage Renal Disease

April 24-25, 2019
Washington, DC

Adapted from dcri.org/insights/think-tanks

Myles Wolf, MD MMSc
Chief of Nephrology
Professor of Medicine
Duke University

Glenn Chertow, MD MPH
Chief of Nephrology
Professor of Medicine
Stanford University

Matthew Roe, MD MHS
CMO, Verana Health
Adjunct Professor, Duke

Carolyn Arias, MPH
Assoc Dir, Think Tanks
DCRI

Stakeholders

American Association of Kidney Patients
aakp.org

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

FDA

NIH National Institute of Diabetes and Digestive and Kidney Diseases

ASN
American Society of Nephrology

KHI KIDNEY HEALTH INITIATIVE

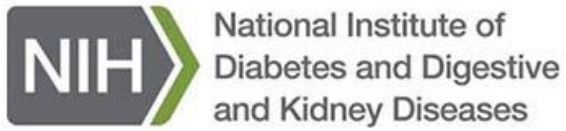
DukeHealth

Stanford MEDICINE

Northwestern Medicine

University of Manitoba

HEALTH UNIVERSITY OF UTAH



Regulatory & Government

Kidney Societies

ASN
American Society of Nephrology

KHI
KIDNEY HEALTH INITIATIVE

Academia

DukeHealth
University of Manitoba
Stanford Medicine
HEALTH University of Utah
Northwestern Medicine

Industry

AAKP
American Association of Kidney Patients
aakp.org

Patients & Advocates

Hypothesis Generation & Pre-Clinical Studies

Interconnected Data Networks

Genomics and GWAS

Observational Studies & Secondary Analyses

Standardized Kidney Data Collection

Disease-Specific Networks

Phase 1 Studies

Pharamacokinetic Studies Across the Spectrum of CKD and Dialysis Modalities

Phase 2 & 3 Studies

Pragmatic Trial Features

Surrogate & Intermediate Endpoints

Adapative Trial Designs

Patient-Centered Endpoints

Post-Marketing Studies

Real-World Evidence

Cardiovascular & Other Non-Kidney Endpoints

Dissemination & Uptake

Generalizability of Trial Design

Quality Clinical Guidelines

Edmonston et al, *AJKD*, 2020

Hypothesis Generation & Pre-Clinical Studies

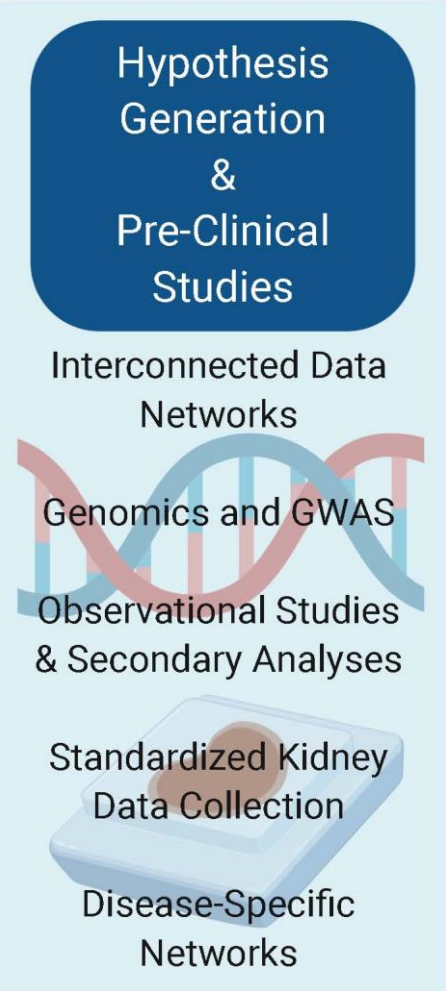
Interconnected Data Networks

Genomics and GWAS

Observational Studies & Secondary Analyses

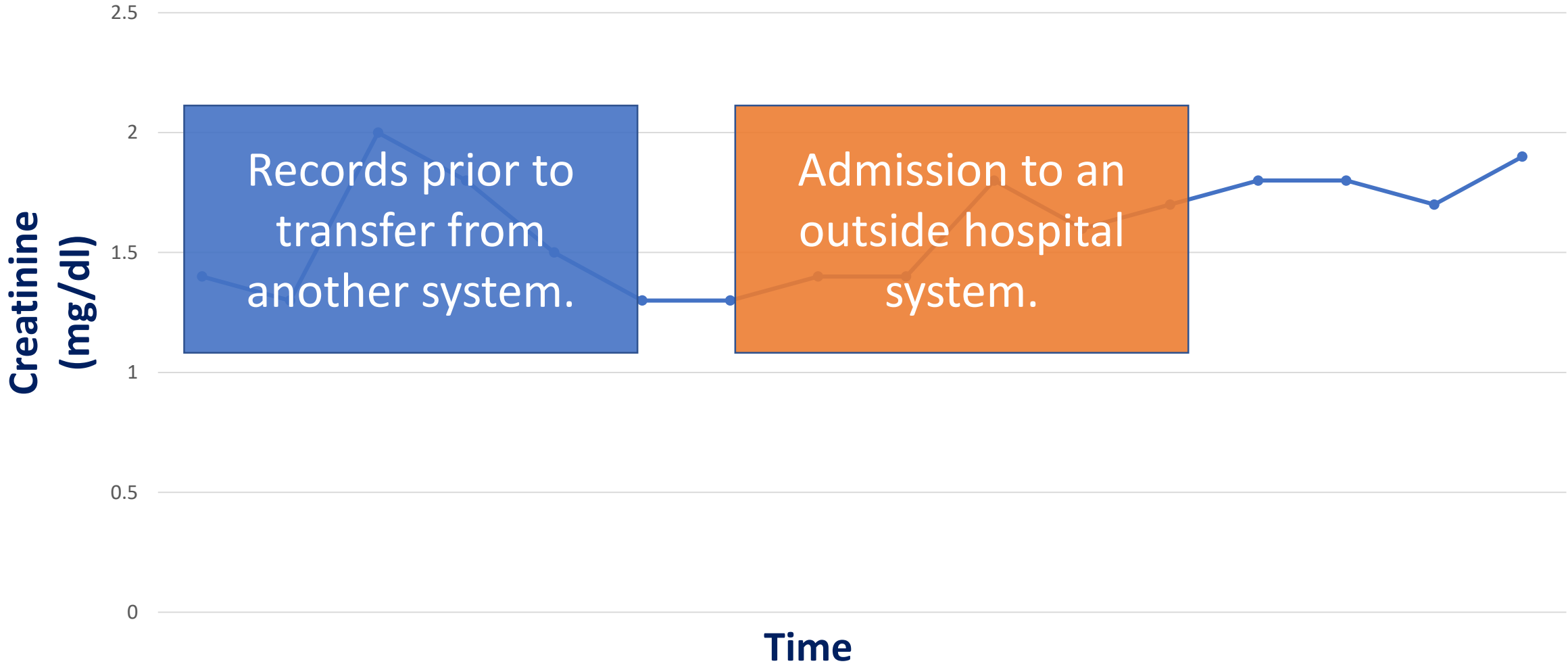
Standardized Kidney Data Collection

Disease-Specific Networks

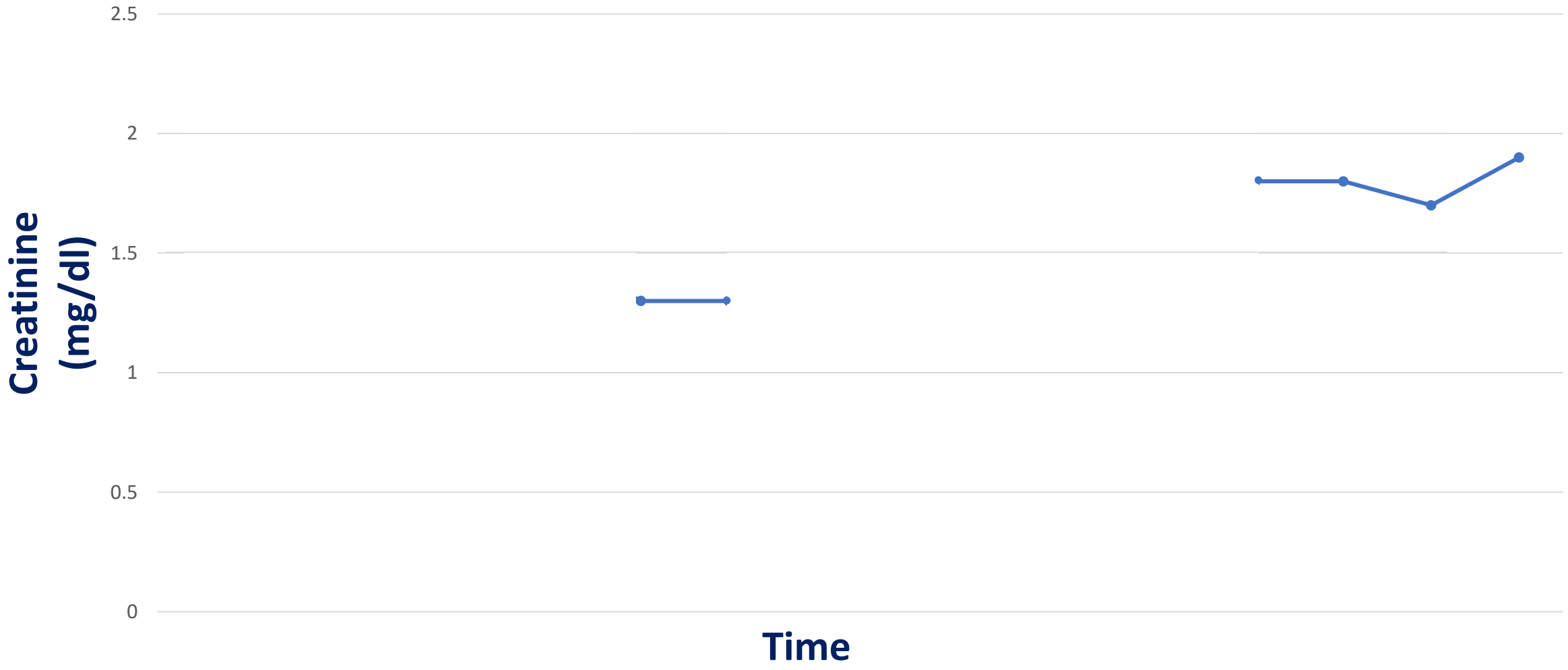


Interconnected Data Networks

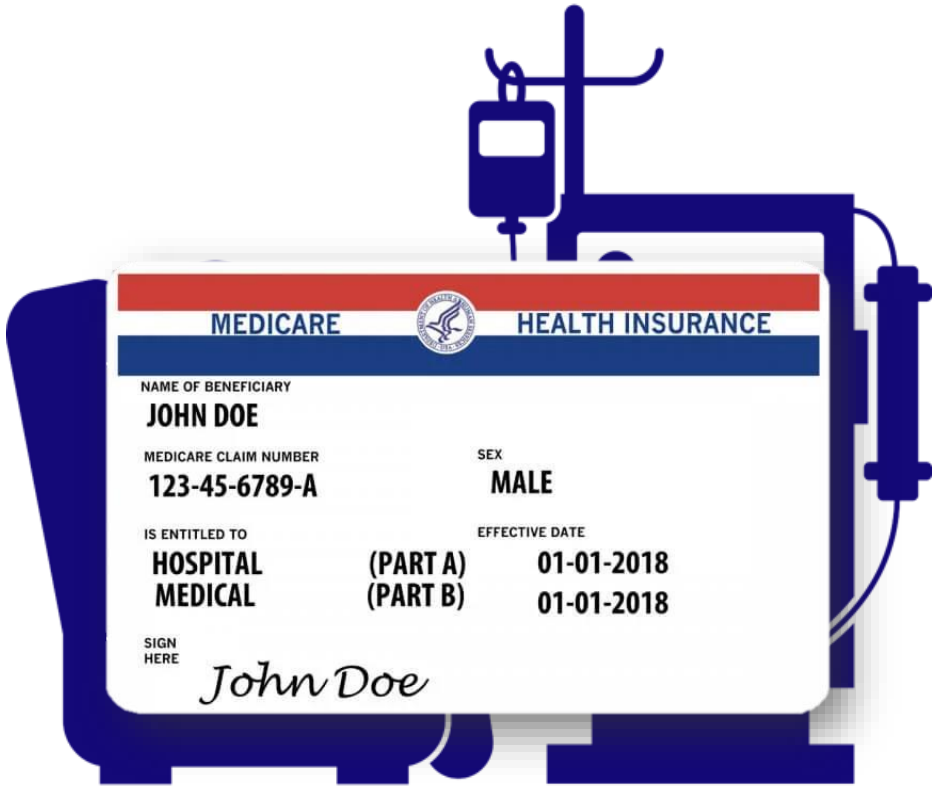
Fragmented, Privatized System



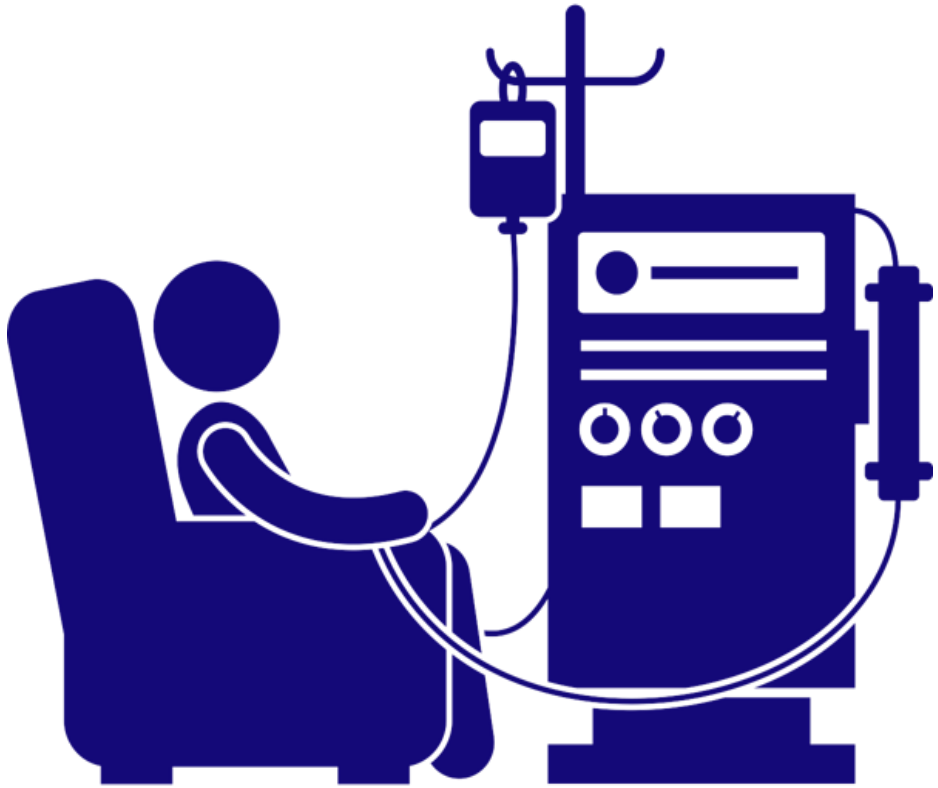
Fragmented, Privatized System



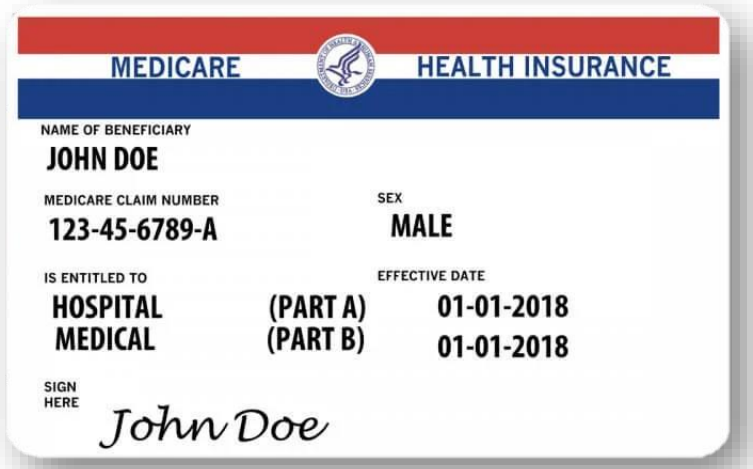
Fragmented, Privatized System



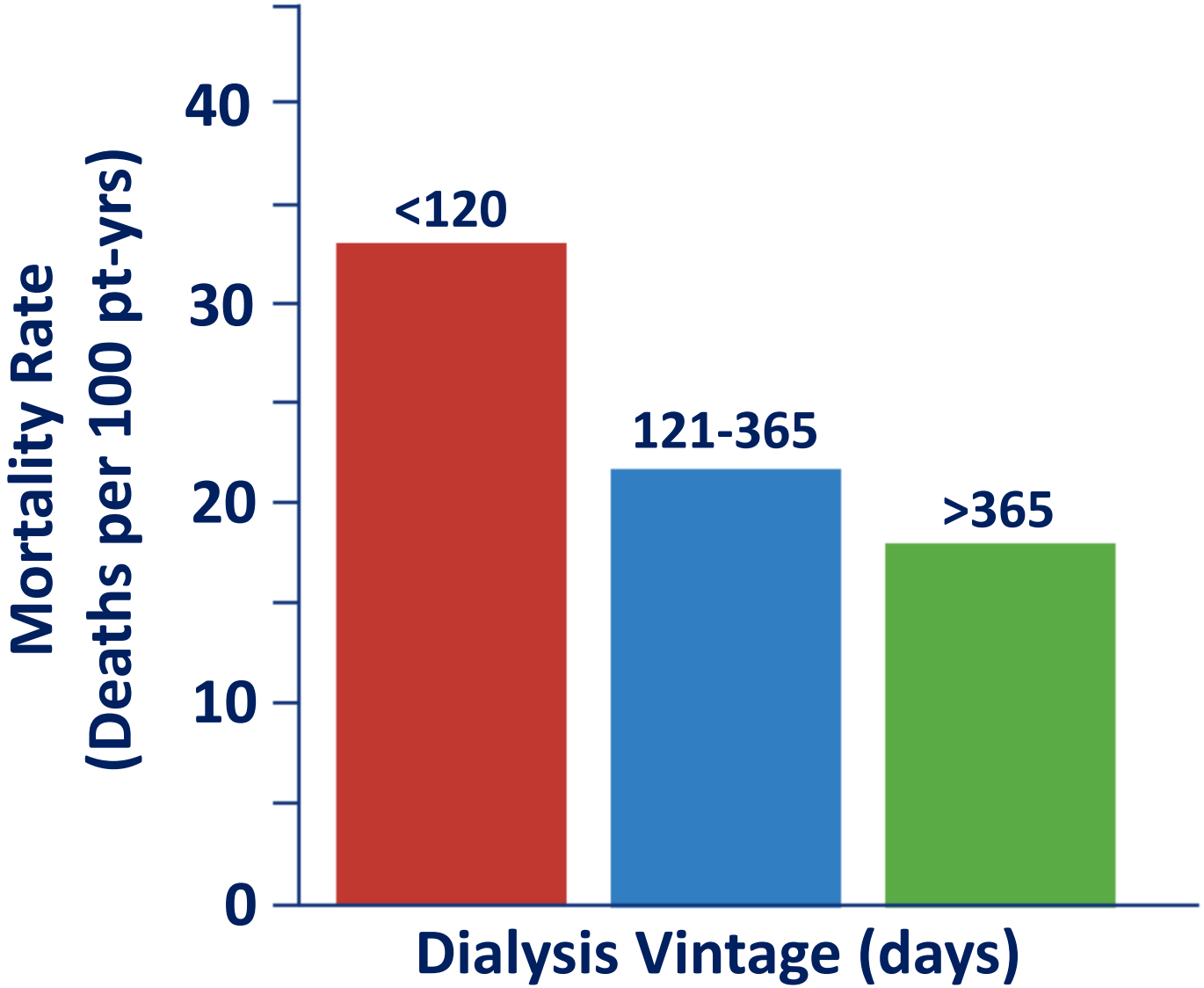
Fragmented, Privatized System



← 90 Days →



Mortality Risk by Dialysis Vintage



Adapted from Robinson et al. *KI*. 2014

NIH Collaboratory

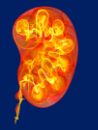
Health Care Systems Research Collaboratory

Rethinking Clinical Trials®

pcornet

The National Patient-Centered Clinical Research Network

Sentinel



NIH Collaboratory

Health Care Systems Research Collaboratory

Rethinking Clinical Trials®

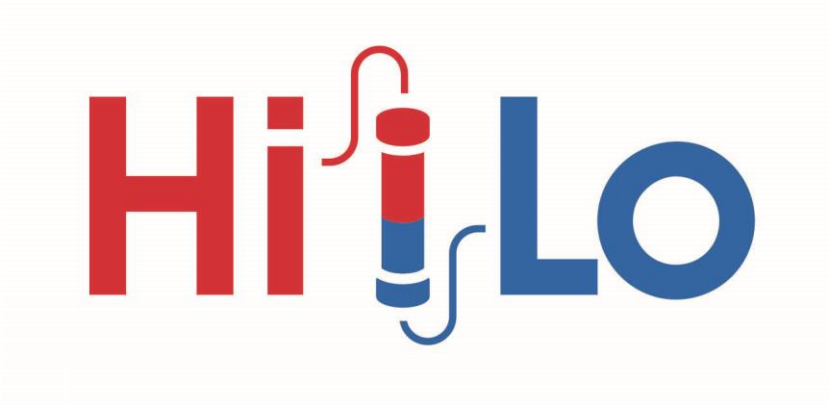
pcornet

The National Patient-Centered Clinical Research Network

Sentinel

https://rethinkingclinicaltrials.org/

TiME

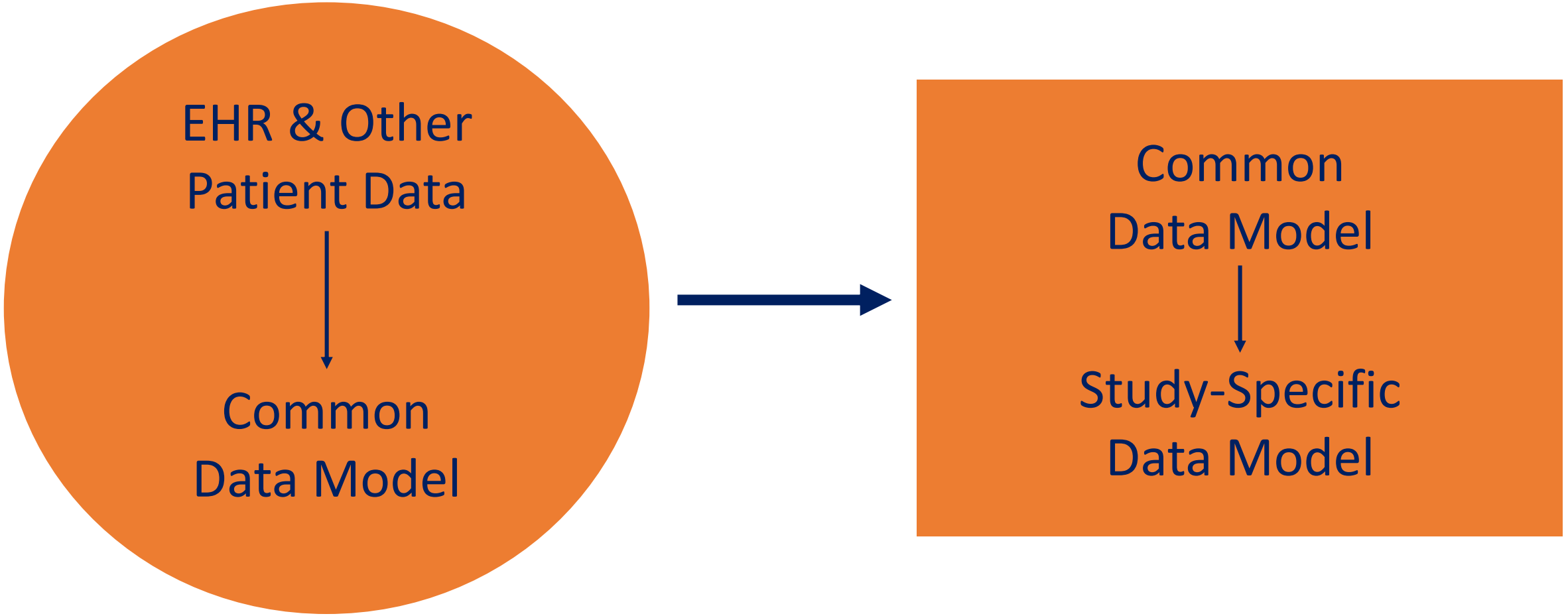


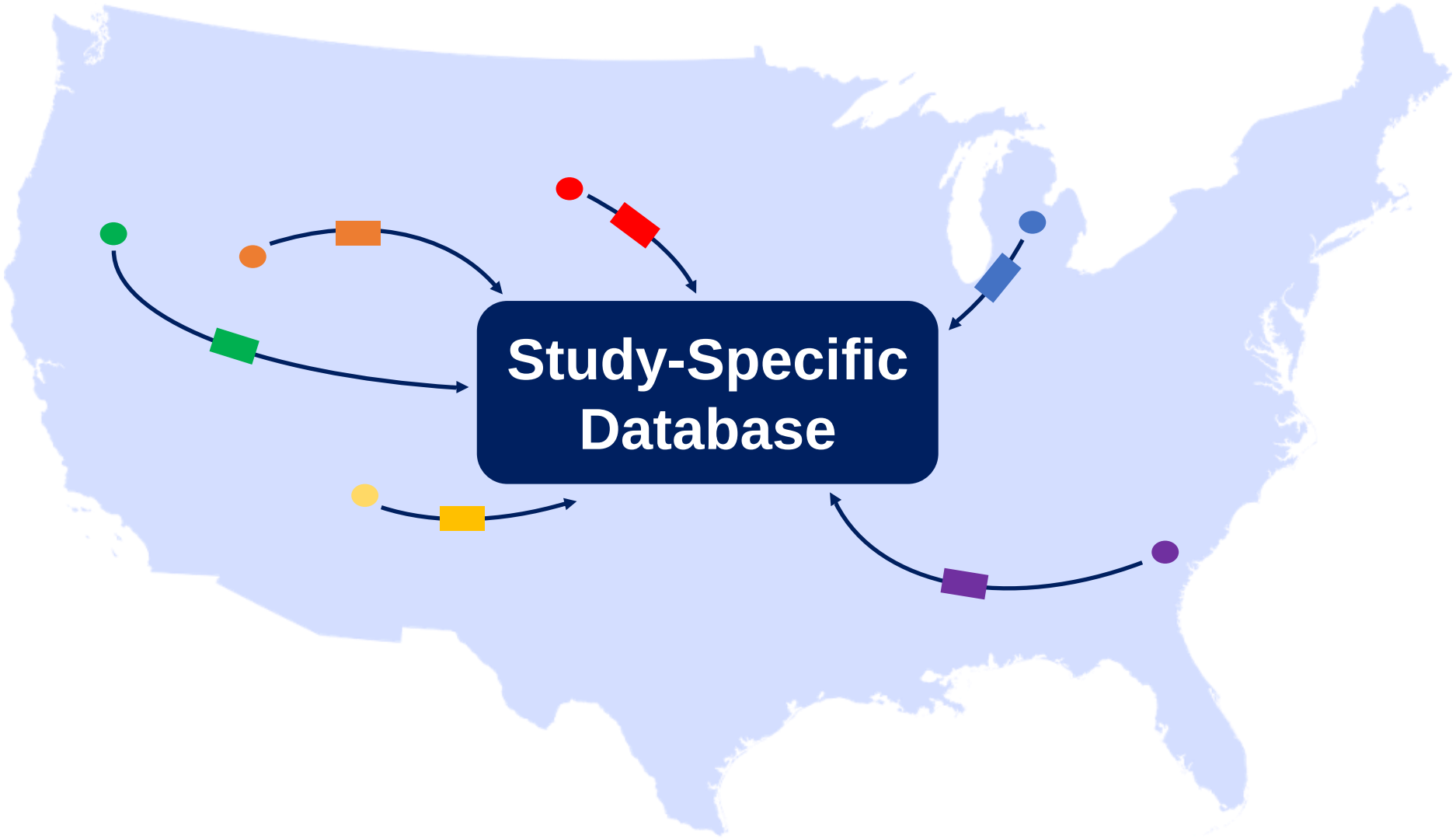
Dember et al, *JASN*, 2019; Edmonston et al, AJKD, 2020

NIH Collaboratory
Health Care Systems Research Collaboratory
Rethinking Clinical Trials®

pcornet
The National Patient-Centered Clinical Research Network

Sentinel


EHR & Other Patient Data
Common Data Model
Common Data Model
Study-Specific Data Model


Study-Specific Database

The ADAPTABLE Aspirin Study

pcornet® | The National Patient-Centered Clinical Research Network

THE QUESTION

Clinicians often prescribe aspirin to prevent strokes and heart attacks in people living with heart disease. Research has yet to determine the best dose to use, since aspirin can cause serious side effects – like bleeding – in some people.

THE PROBLEM

Heart disease is the No. 1 killer in the U.S.

611,000
people in 2013, one death in 4; accounting for 1 in every 6 healthcare dollars.

Cardiovascular disease (heart attack and stroke) is the most common form of heart disease.

Heart disease strikes someone in the U.S. about once every
43 seconds.

Aspirin is widely prescribed to prevent heart attacks and strokes in people living with heart disease.

60%
of patients with heart disease take a 325 milligram dose each day while 36% take 81 milligrams (or baby aspirin).

THE STUDY

The ADAPTABLE trial will compare two common aspirin dosages.

The study will be large and will involve patients across the U.S.

15,000
patients living with heart disease will use a daily aspirin dose of either 81 mg or 325 mg.

ADAPTABLE will use PCORnet to conduct the study and disseminate results. Patients will be partners at every stage of the trial, which will collect data using tools with state-of-the-art security.

ANSWERS FOR BETTER CARE

Results of this study will help patients and their caregivers answer questions like:

- How much aspirin should I take each day to reduce my risk of another heart attack or stroke?
- Do the benefits of taking aspirin every day differ based on the dose?
- Do the risks differ based on the dose?
- Based on my health, age, and other circumstances, what's the best dose to protect my health?

This study will use the power of PCORnet to seek answers to these questions and improve patient care and outcomes.

Identifying the aspirin dose that works best could prevent as many as **88,800** deaths per year worldwide

pcori

PCORnet is an initiative of the Patient-Centered Outcomes Research Institute.

Theaspirinstudy.org

NIH Collaboratory
Health Care Systems Research Collaboratory
Rethinking Clinical Trials®

pcornet
The National Patient-Centered Clinical Research Network

Sentinel

https://www.sentinelinitiative.org/

Hypothesis Generation & Pre-Clinical Studies

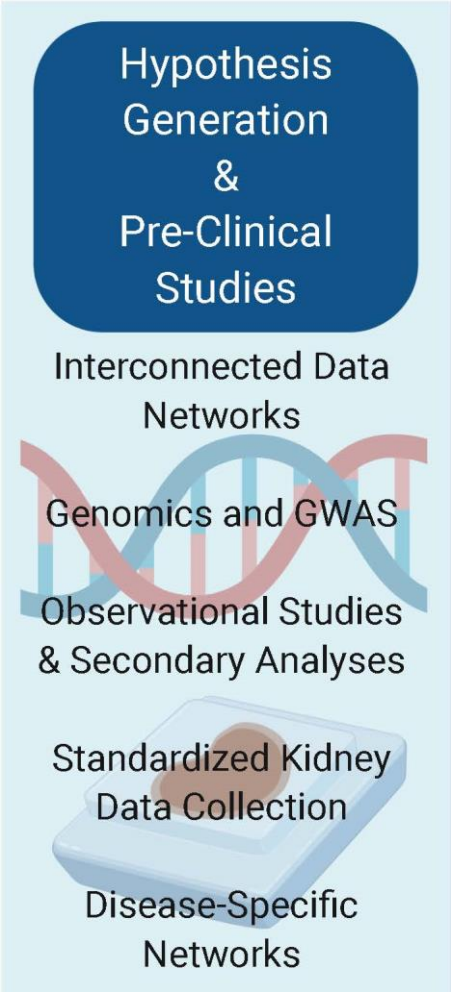
Interconnected Data Networks

Genomics and GWAS

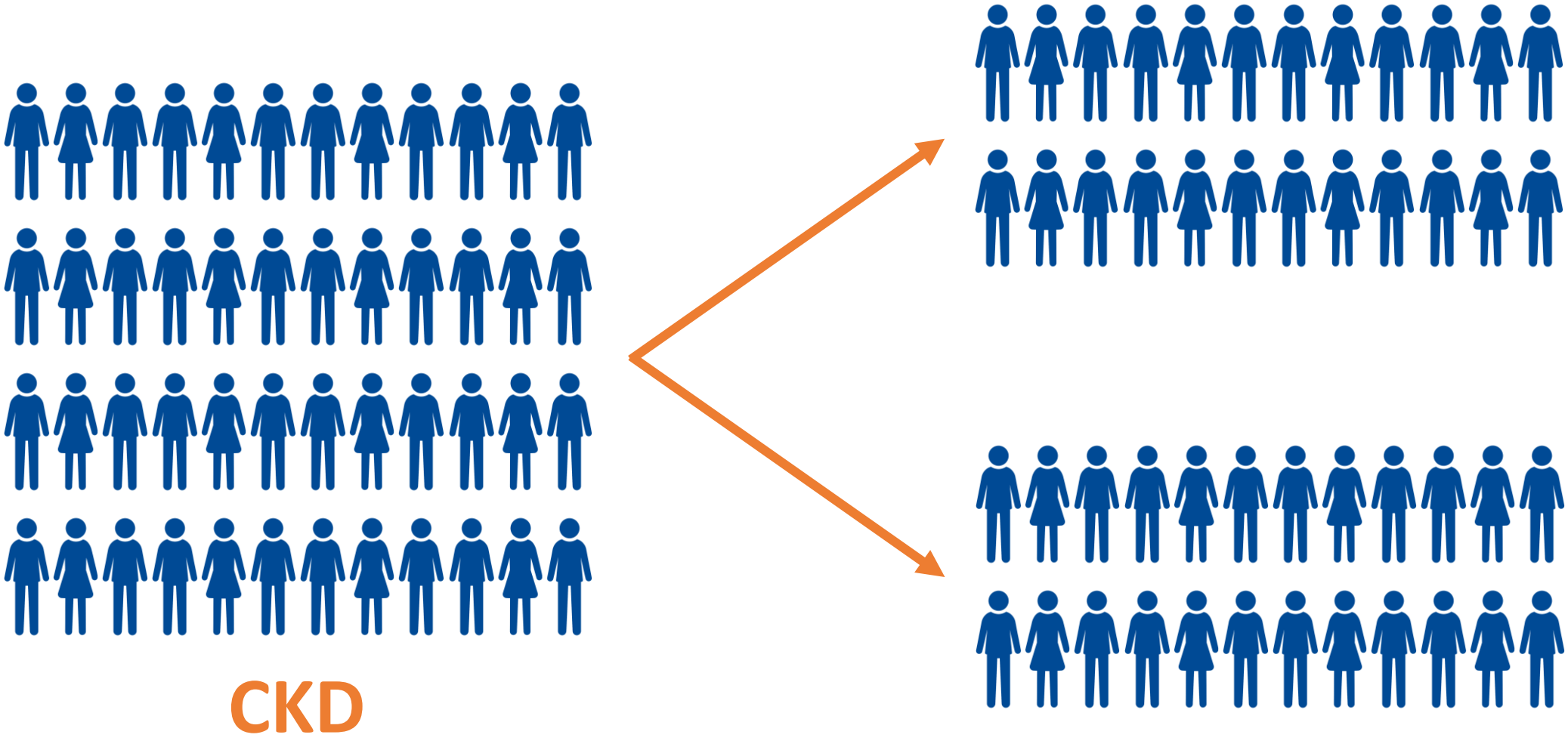
Observational Studies & Secondary Analyses

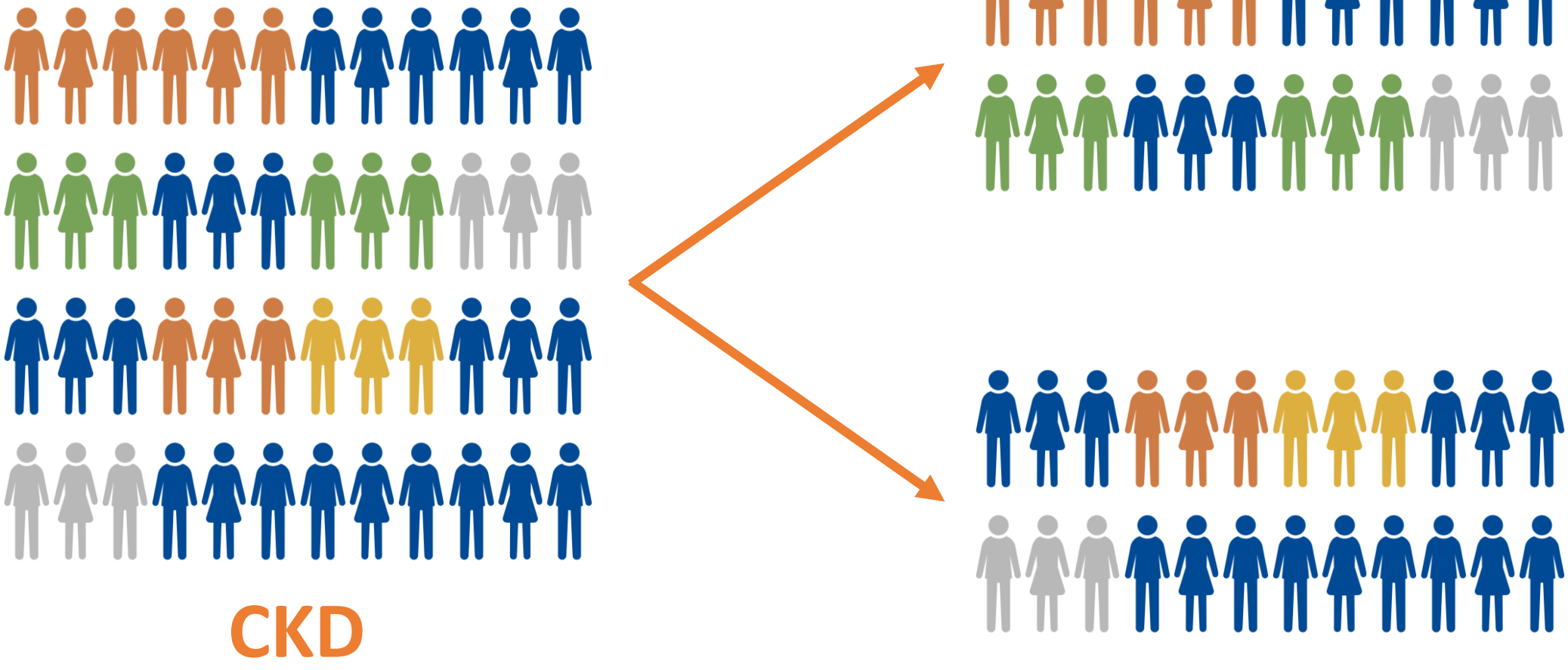
Standardized Kidney Data Collection

Disease-Specific Networks



Subphenotyping in CKD


CKD


CKD

neptune

KIDNEY PRECISION MEDICINE PROJECT

https://www.neptune-study.org; https://www.kpmp.org

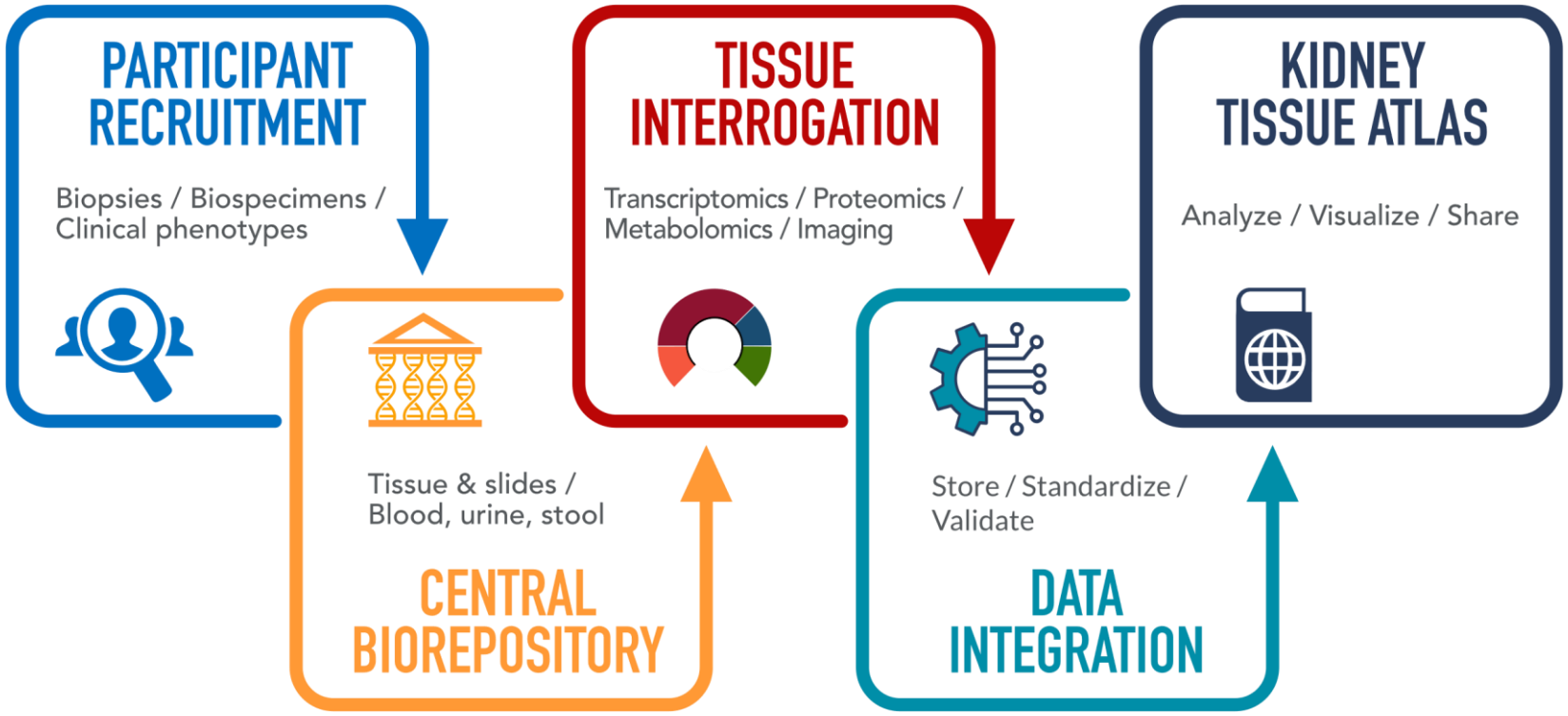
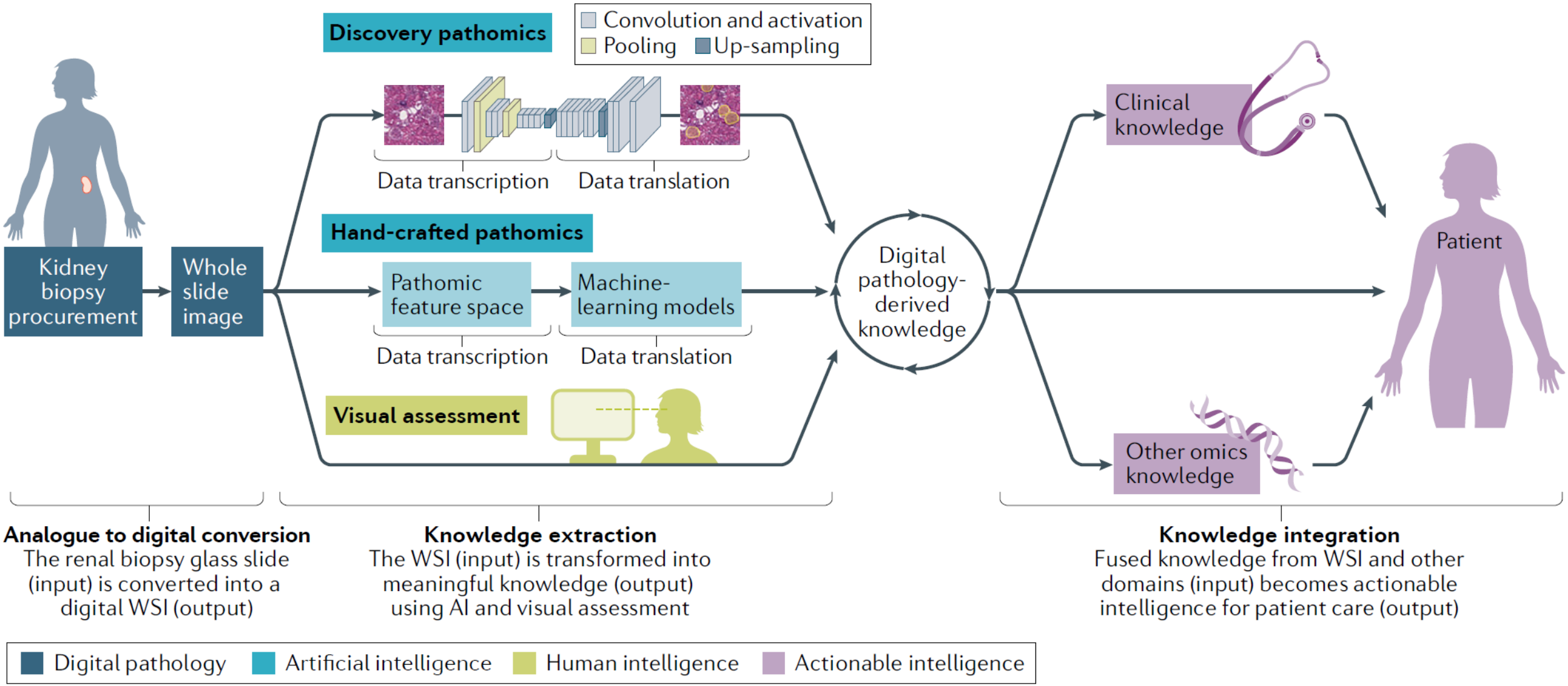


Image credit: https://www.kpmp.org



Adapted from Barisoni et al. *Nat Rev Nephrol.* 2020

Hypothesis Generation & Pre-Clinical Studies

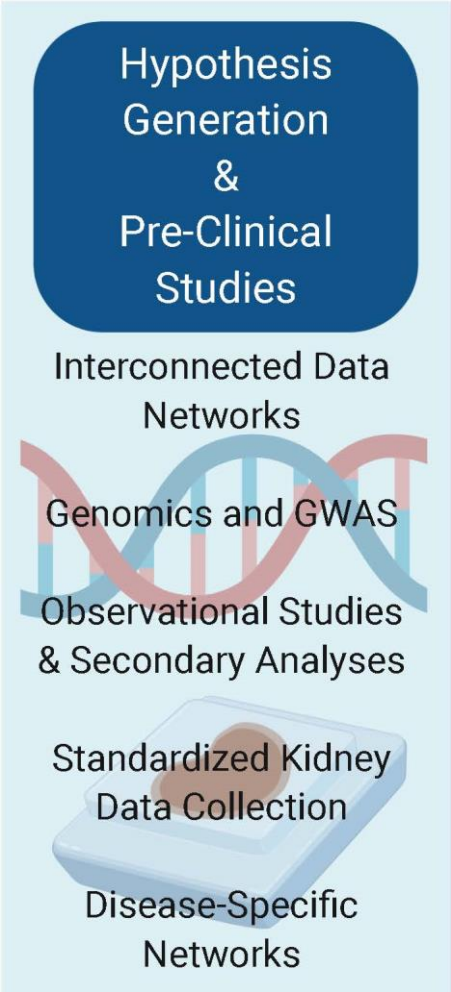
Interconnected Data Networks

Genomics and GWAS

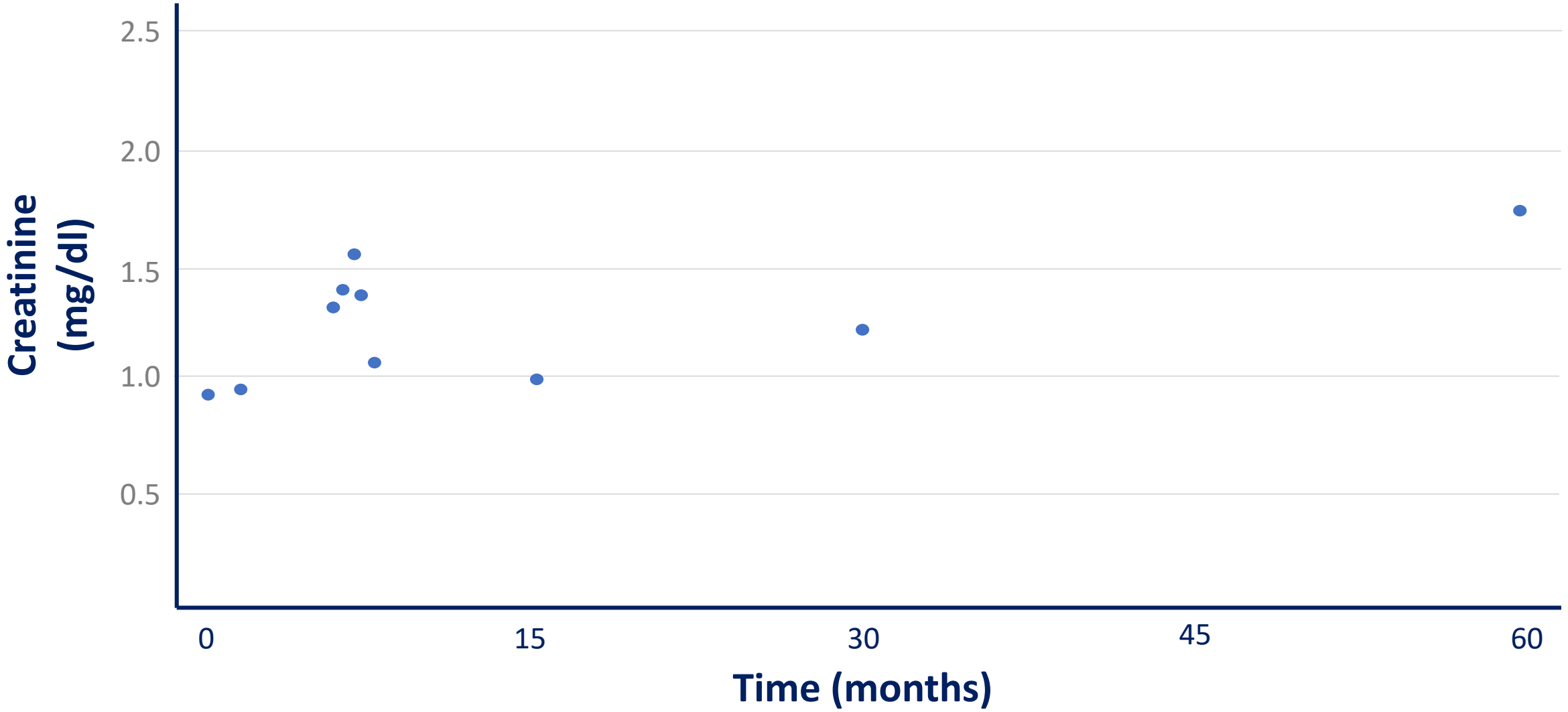
Observational Studies & Secondary Analyses

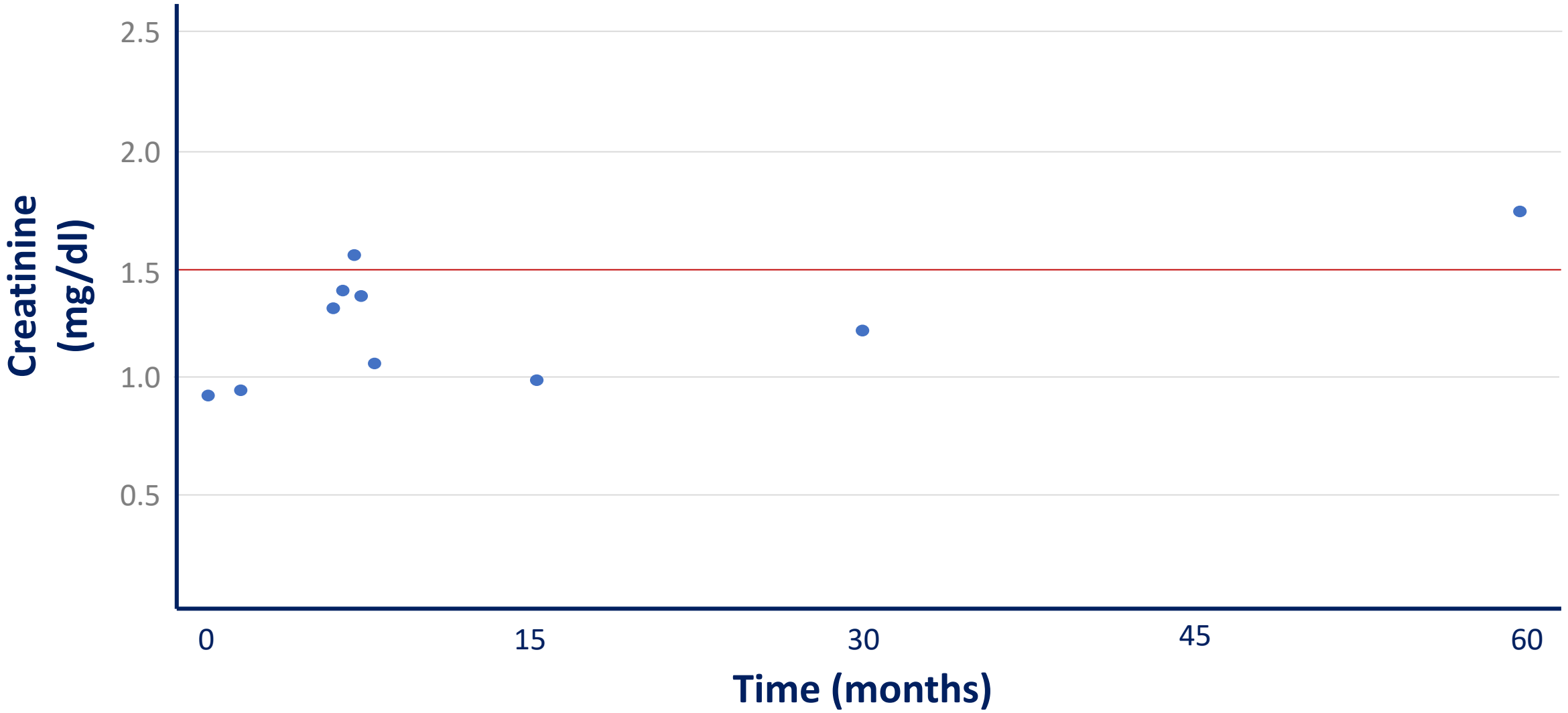
Standardized Kidney Data Collection

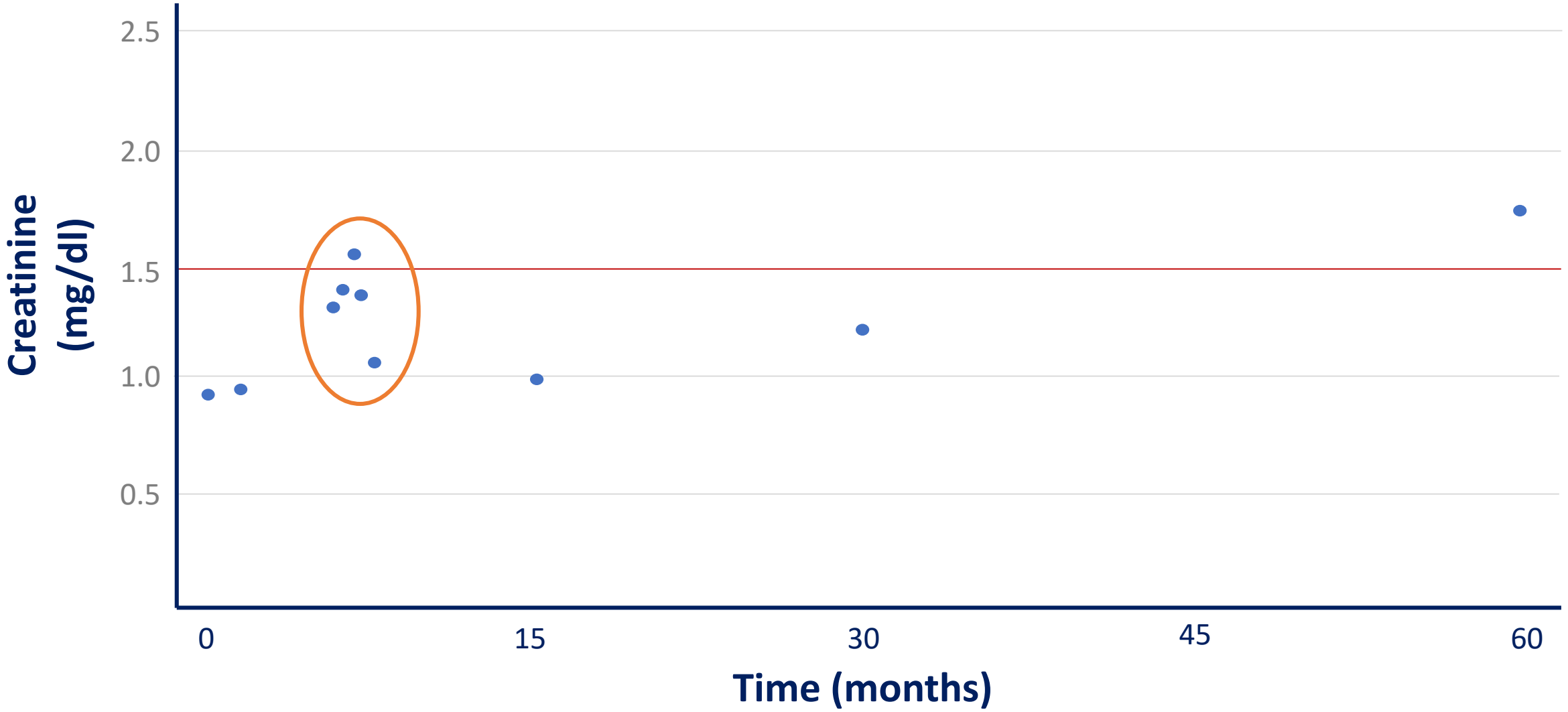
Disease-Specific Networks

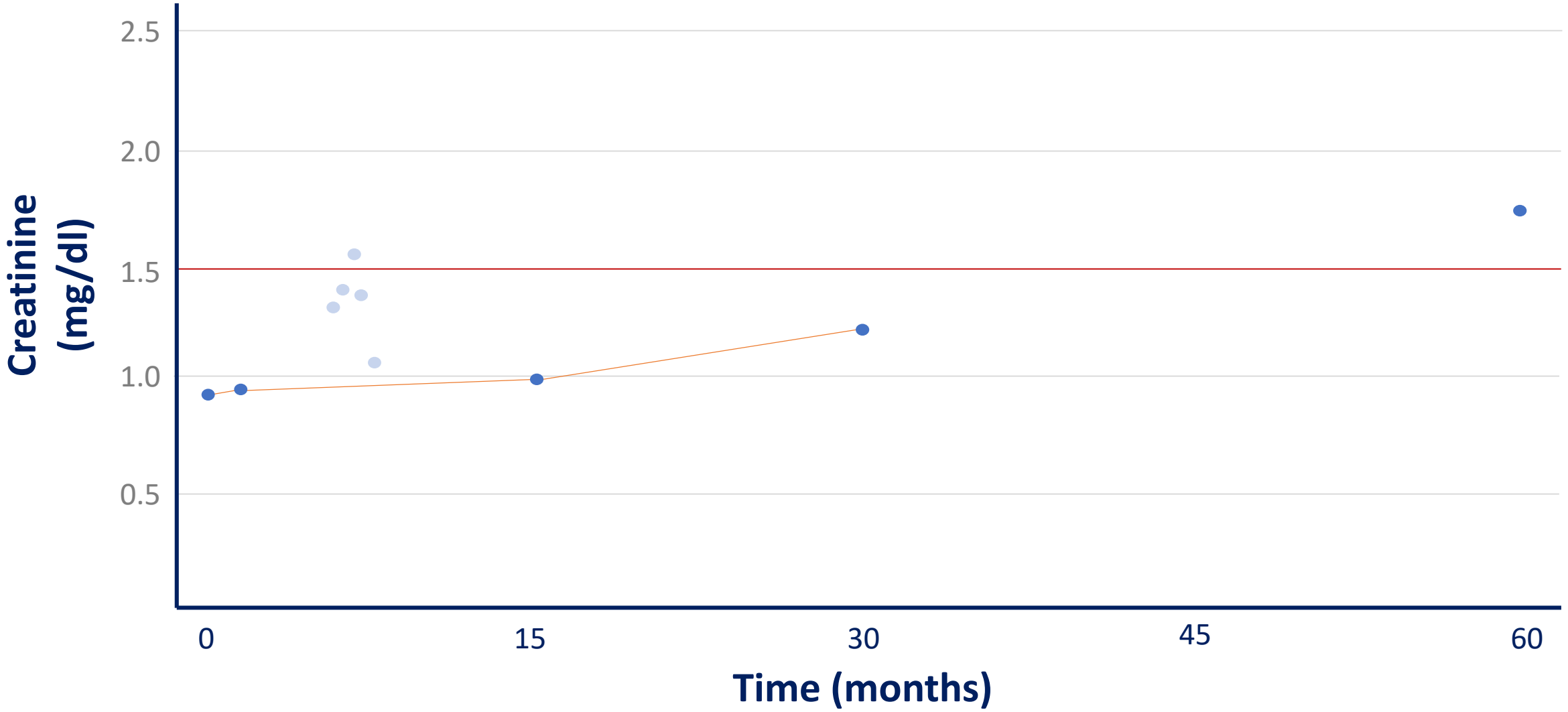


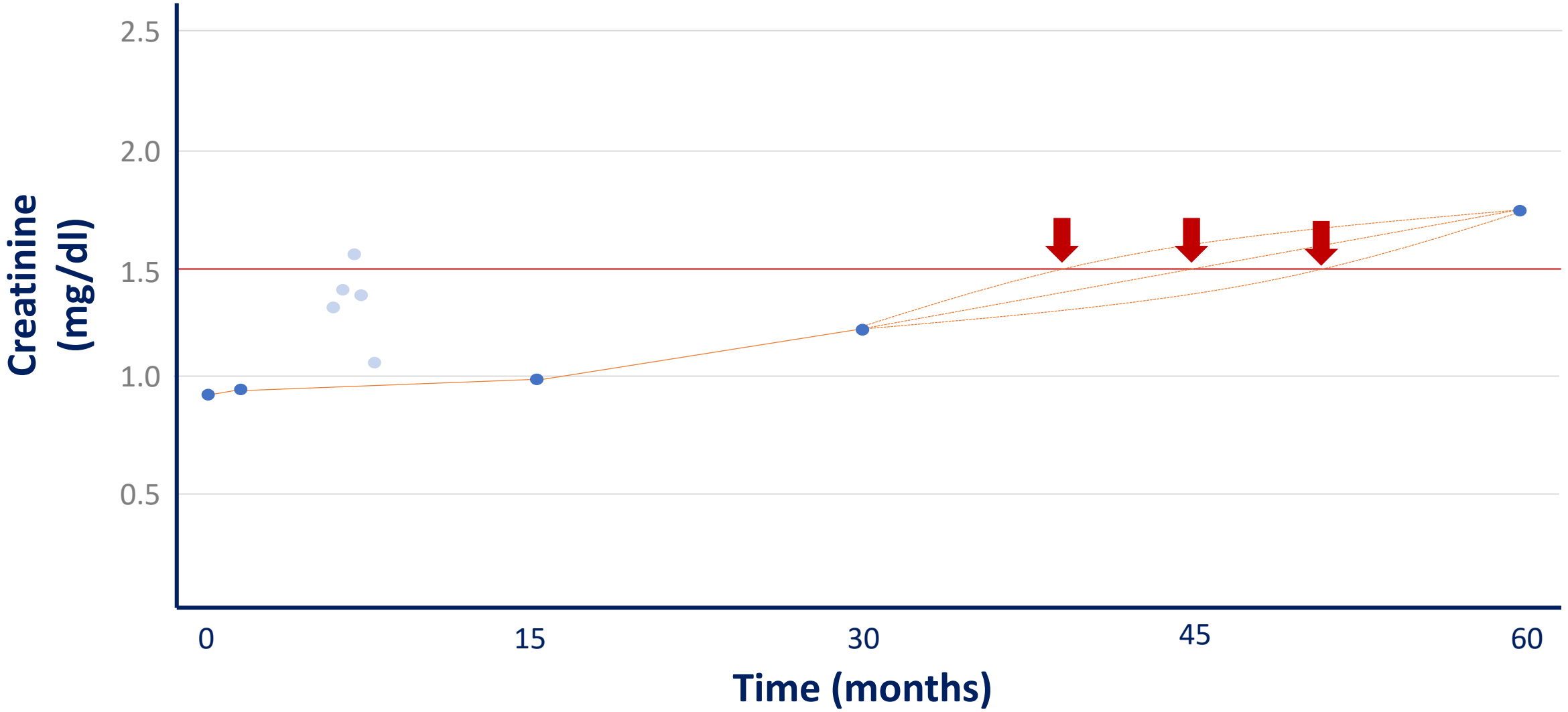
Standardized Kidney Data Collection

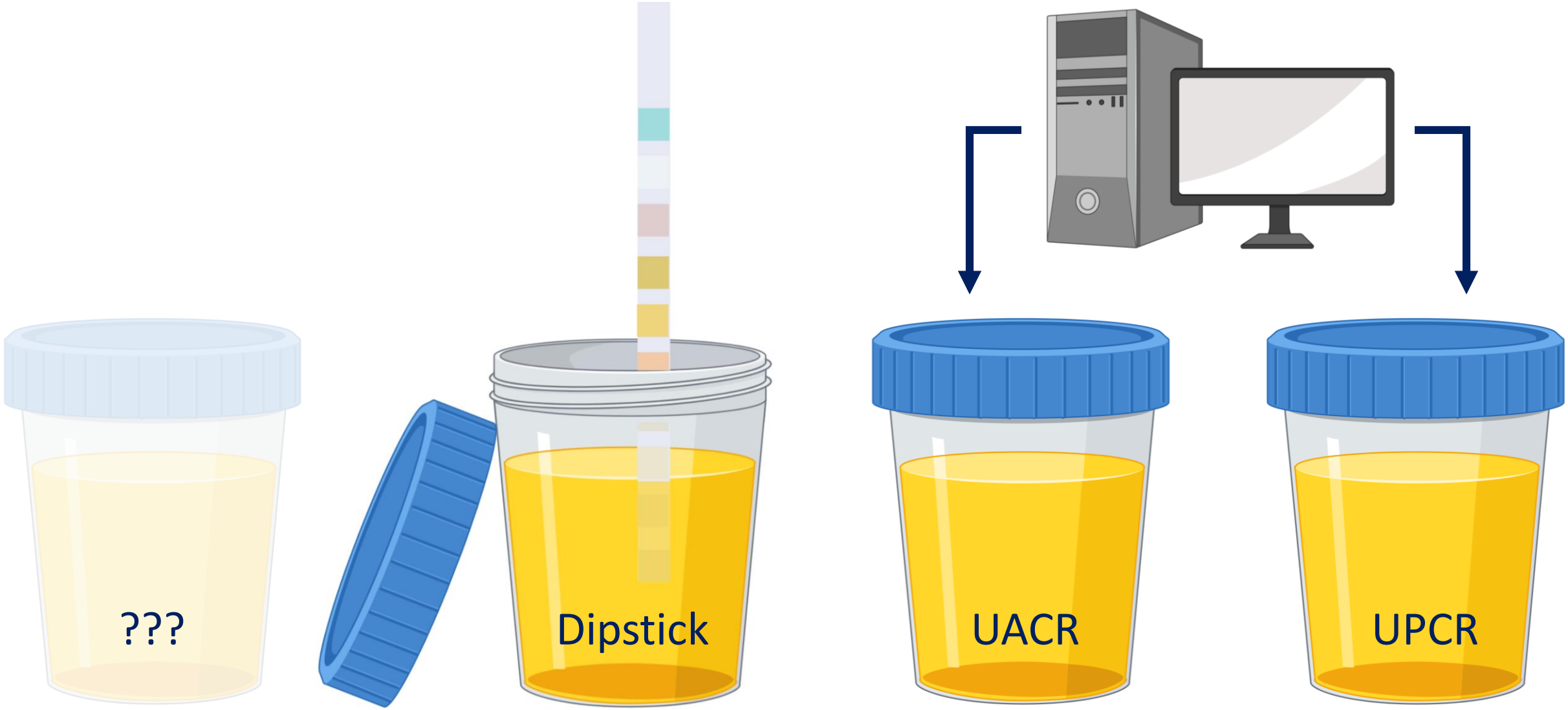

Creatinine (mg/dl)
2.5
2.0
1.5
1.0
0.5
0
15
30
45
60
Time (months)


Creatinine (mg/dl)
2.5
2.0
1.5
1.0
0.5
0
15
30
45
60
Time (months)


Creatinine (mg/dl)
2.5
2.0
1.5
1.0
0.5
0
15
30
45
60
Time (months)


Creatinine (mg/dl)
2.5
2.0
1.5
1.0
0.5
0
15
30
45
60
Time (months)


Creatinine (mg/dl)
2.5
2.0
1.5
1.0
0.5
0
15
30
45
60
Time (months)



Absent **Semi-Quantitative** **Quantitative**

Hypothesis Generation & Pre-Clinical Studies

Interconnected Data Networks

Genomics and GWAS

Observational Studies & Secondary Analyses

Standardized Kidney Data Collection

Disease-Specific Networks

Phase 1 Studies

Pharamacokinetic Studies Across the Spectrum of CKD and Dialysis Modalities

Phase 2 & 3 Studies

Pragmatic Trial Features

Surrogate & Intermediate Endpoints

Adapative Trial Designs

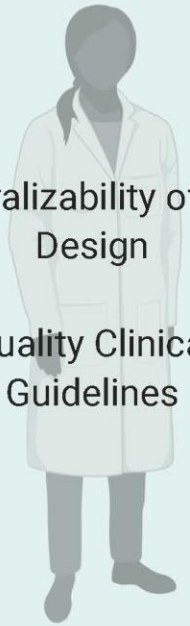
Patient-Centered Endpoints

Post-Marketing Studies

Real-World Evidence

Cardiovascular & Other Non-Kidney Endpoints

Dissemination & Uptake



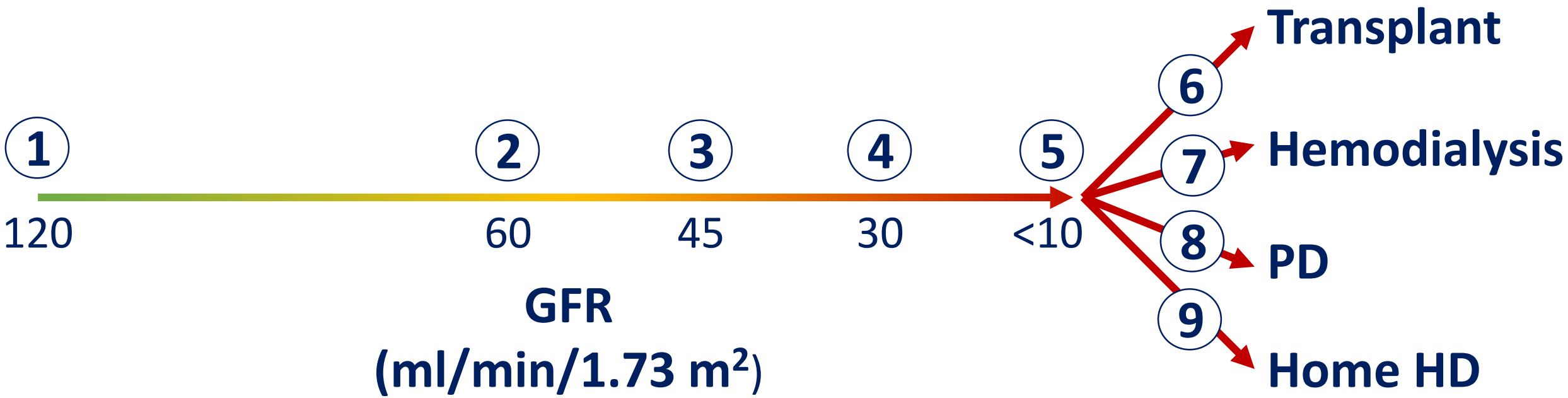
Generalizability of Trial Design

Quality Clinical Guidelines

Phase 1 Studies

Phase 1 Studies

Pharmacokinetics


1
2
3
4
5
6
7
8
9
120
60
45
30
<10
GFR
(ml/min/1.73 m²)
Transplant
Hemodialysis
PD
Home HD

Hypothesis Generation & Pre-Clinical Studies

Interconnected Data Networks

Genomics and GWAS

Observational Studies & Secondary Analyses

Standardized Kidney Data Collection

Disease-Specific Networks

Phase 1 Studies

Pharamacokinetic Studies Across the Spectrum of CKD and Dialysis Modalities

Phase 2 & 3 Studies

Pragmatic Trial Features

Surrogate & Intermediate Endpoints

Adapative Trial Designs

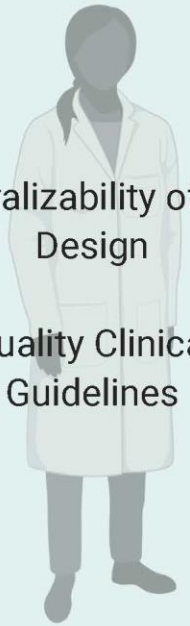
Patient-Centered Endpoints

Post-Marketing Studies

Real-World Evidence

Cardiovascular & Other Non-Kidney Endpoints

Dissemination & Uptake



Generalizability of Trial Design

Quality Clinical Guidelines

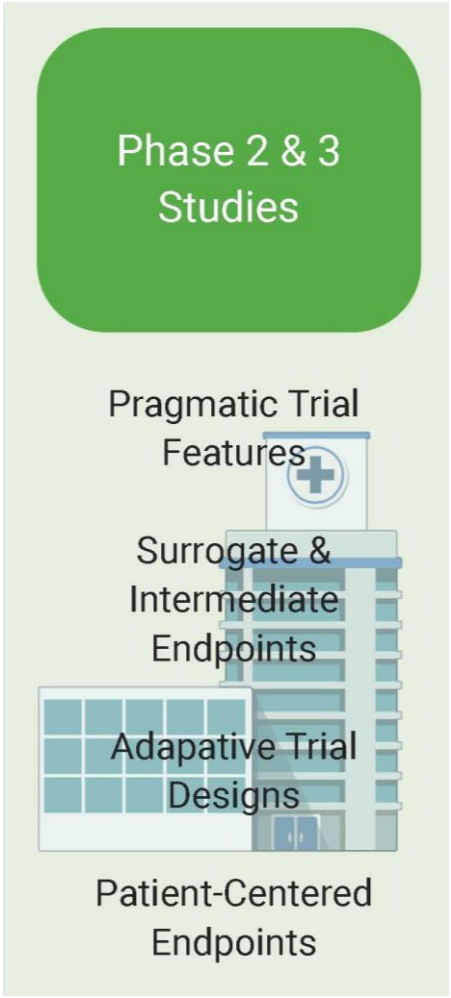
Phase 2 & 3 Studies

Pragmatic Trial Features

Surrogate & Intermediate Endpoints

Adapative Trial Designs

Patient-Centered Endpoints



Pragmatic Trials

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

Duke Nephrology
Duke University School of Medicine

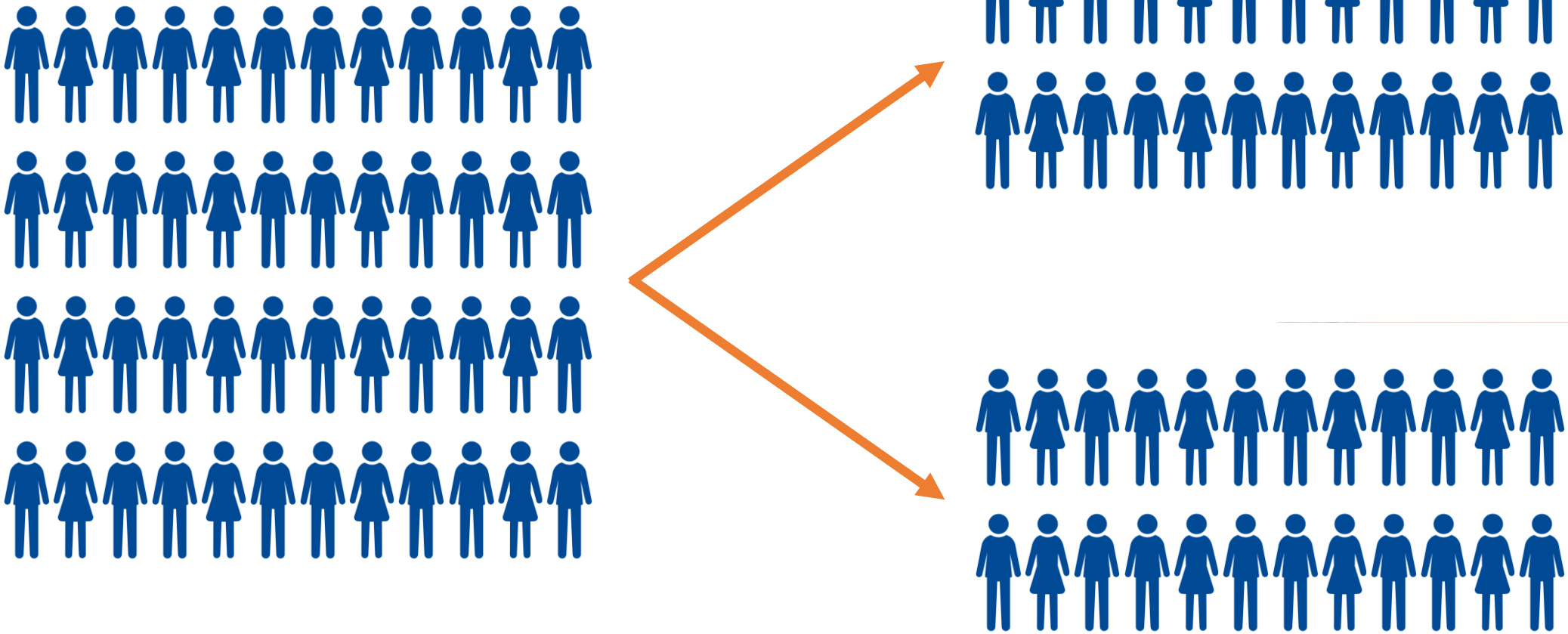
HiLo

A Pragmatic Trial Sponsored by the National Institutes of Health

Adapted from hilostudy.org

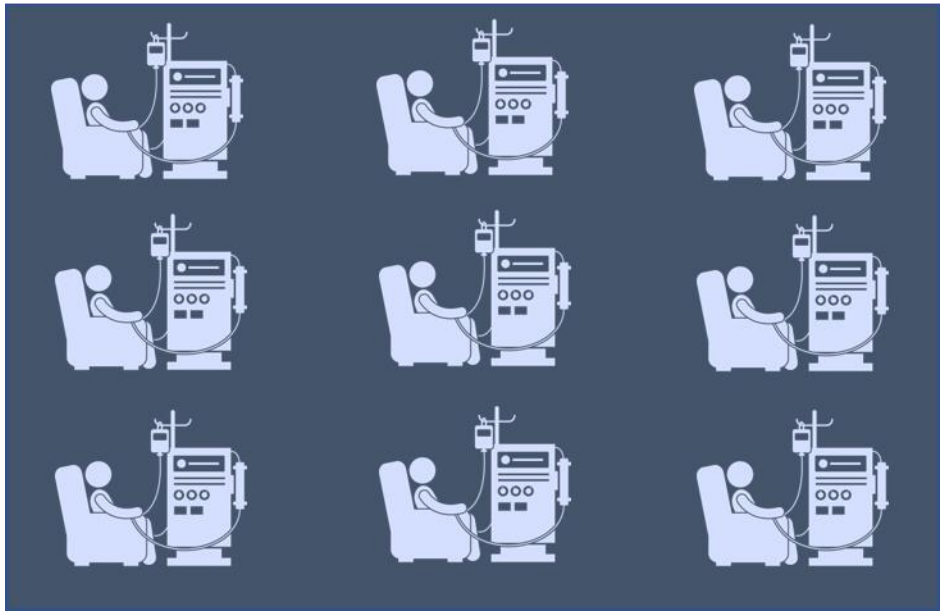
HiLo

A Pragmatic Trial Sponsored by the National Institutes of Health



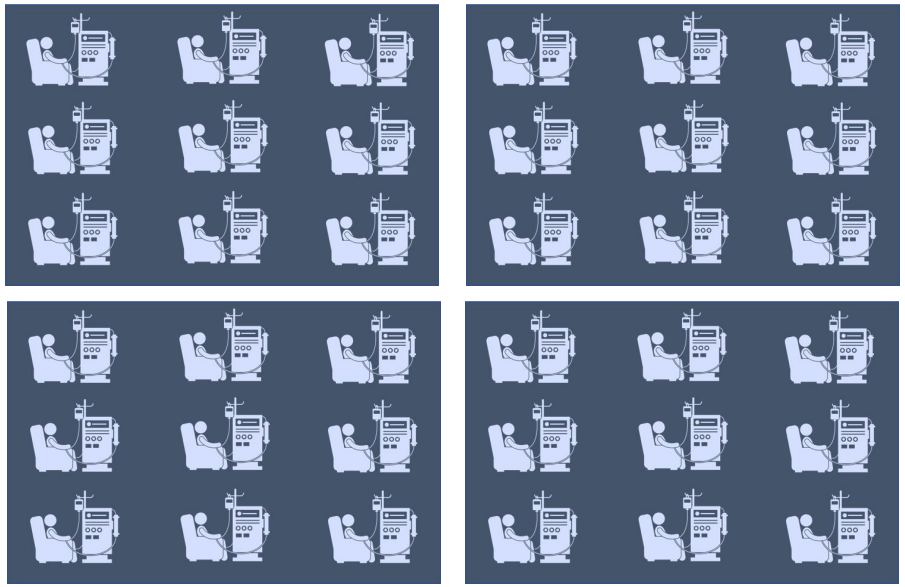
HiLo

A Pragmatic Trial Sponsored by the National Institutes of Health



HiLo

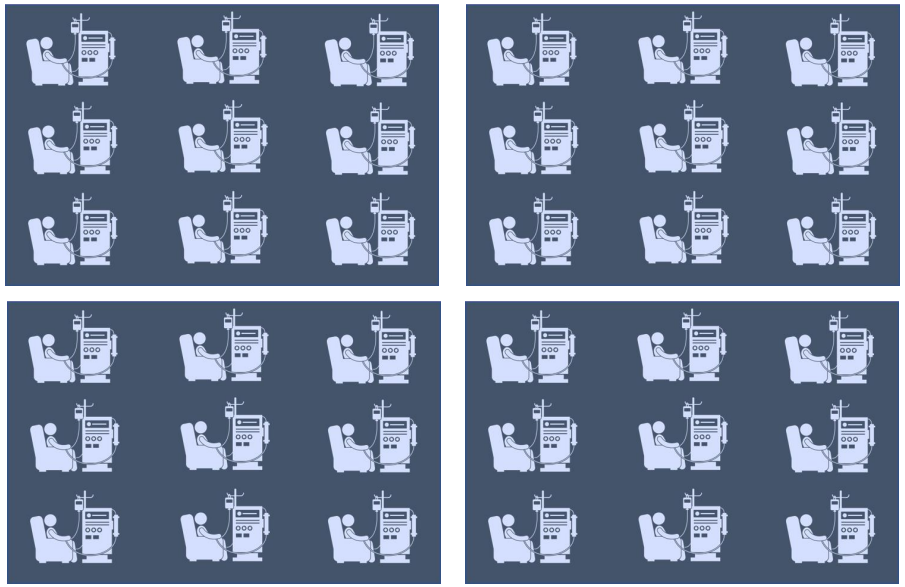
A Pragmatic Trial Sponsored by the National Institutes of Health



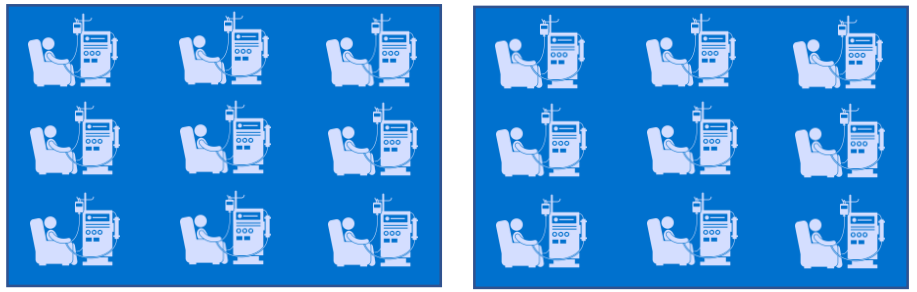
4400 patients, 80-120 facilities

HiLo

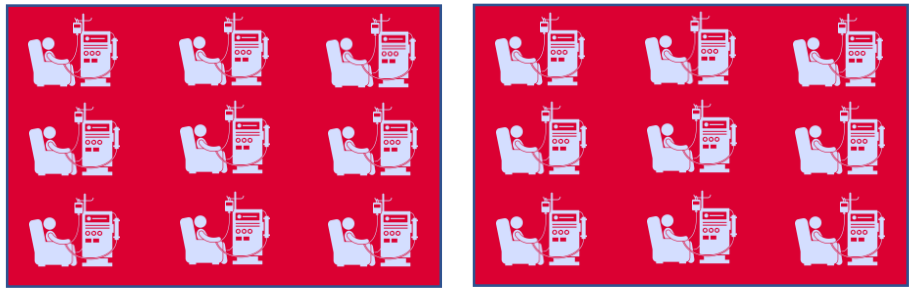
A Pragmatic Trial Sponsored by the National Institutes of Health



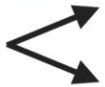
~4400 patients, 80-120 facilities



'Lo' Arm: Phosphate <5.5 mg/dl



'Hi' Arm: Phosphate ≥6.5 mg/dl

Explanatory Trial		Pragmatic Trial
Strict eligibility criteria based on prior phosphate control		Liberal eligibility criteria irrespective of prior phosphate control
Individual randomization		Cluster randomization
Dedicated study visits outside usual dialysis		Study activities occur during usual dialysis care
Protocolized phosphate interventions led by site investigators		How to reach phosphate targets at discretion of clinical team
Onsite study staff and monitors		No onsite study staff, remote monitors
Informed consent obtained by local study staff		eConsent obtained by central study leadership
Trial-specific data collection via case report forms		Real-world data collection via EHR
Endpoints that require adjudication		Endpoints extracted from EHR without adjudication
Formal adverse event reporting		No formal adverse event reporting
High cost		Lower cost
Extrapolation required for patients that would not meet strict eligibility criteria		Maximize generalizability to US standard in-center hemodialysis population

Edmonston et al. AJKD. 2020

Pragmatic ≠ Panacea

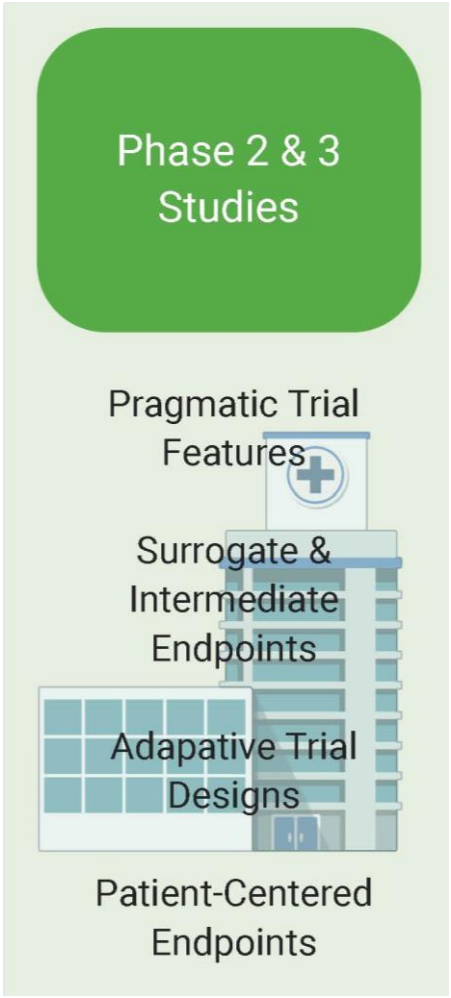
Phase 2 & 3 Studies

Pragmatic Trial Features

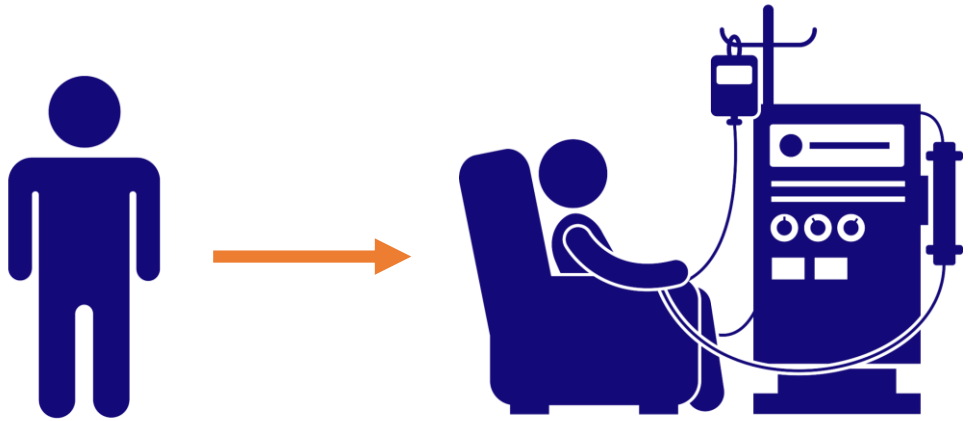
Surrogate & Intermediate Endpoints

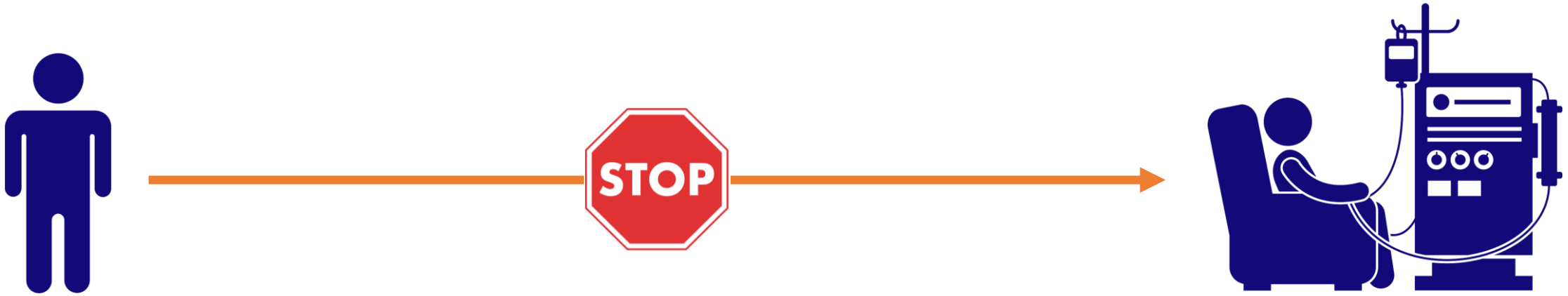
Adapative Trial Designs

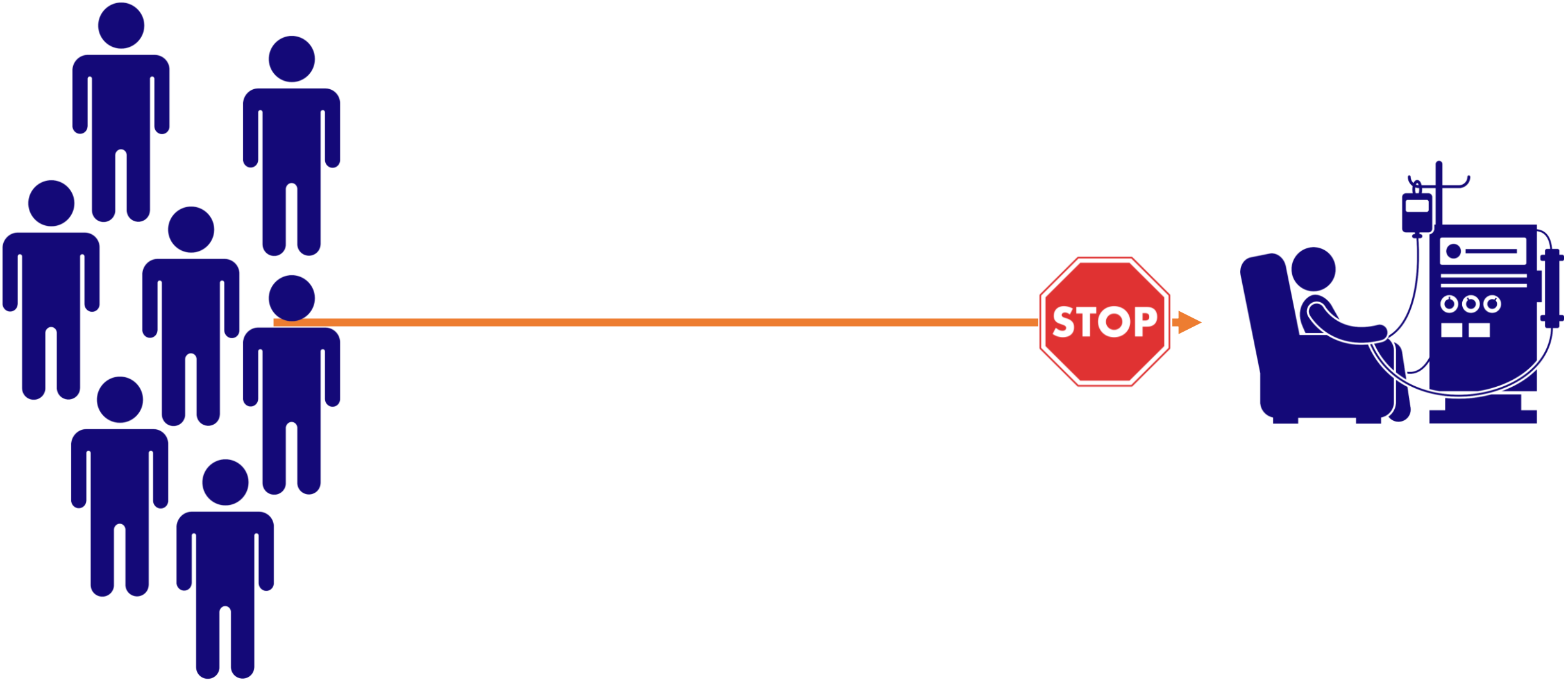
Patient-Centered Endpoints

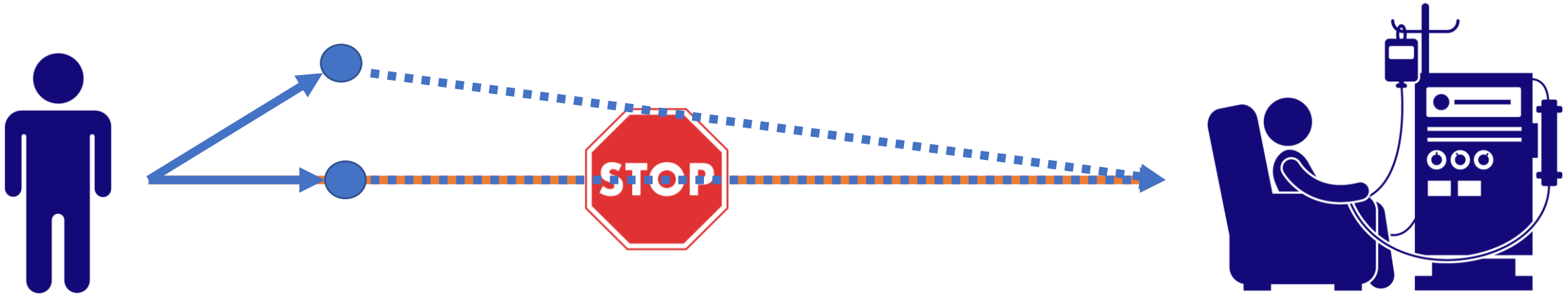


Surrogate & Intermediate Endpoints




STOP

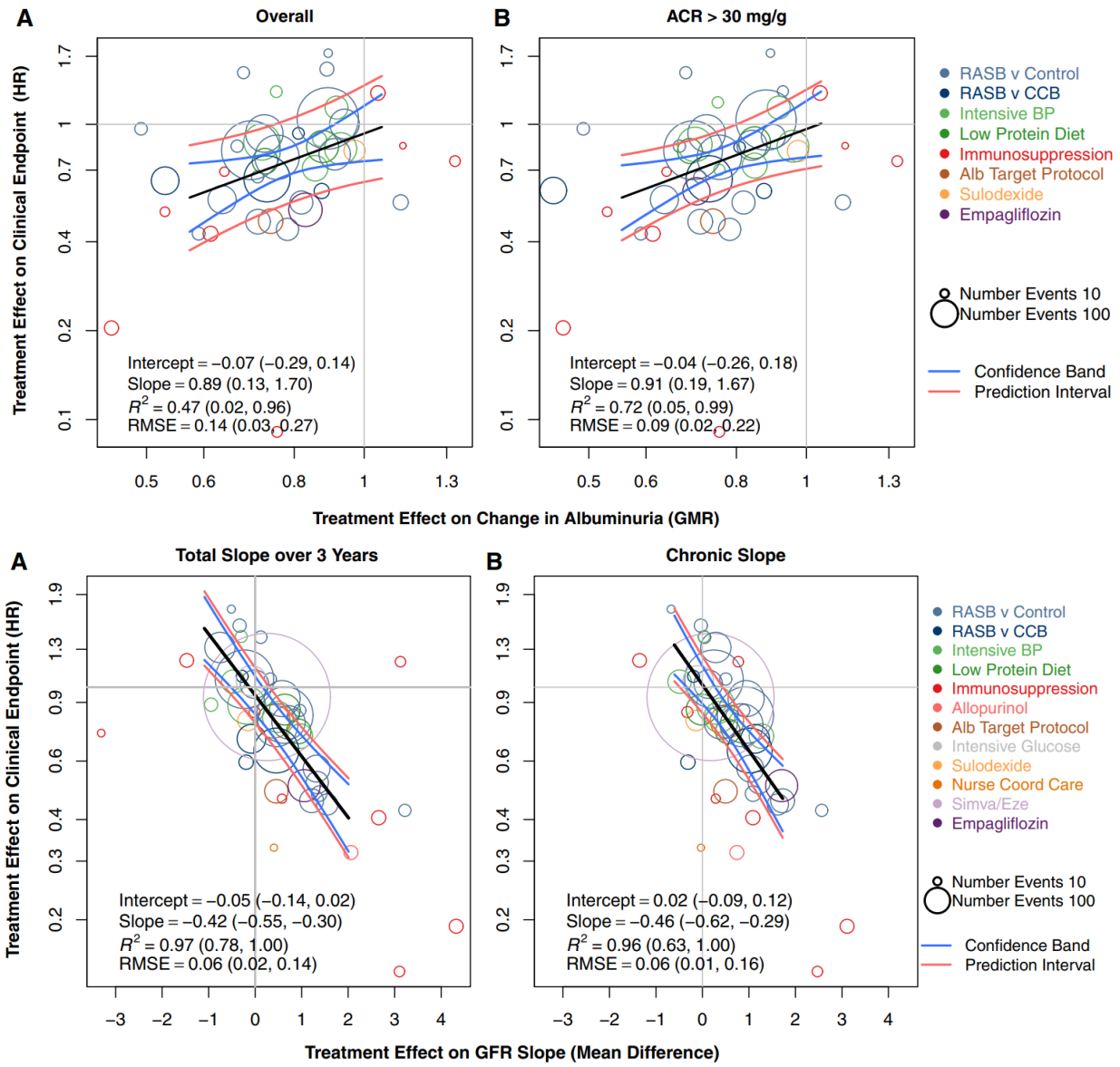

STOP


STOP

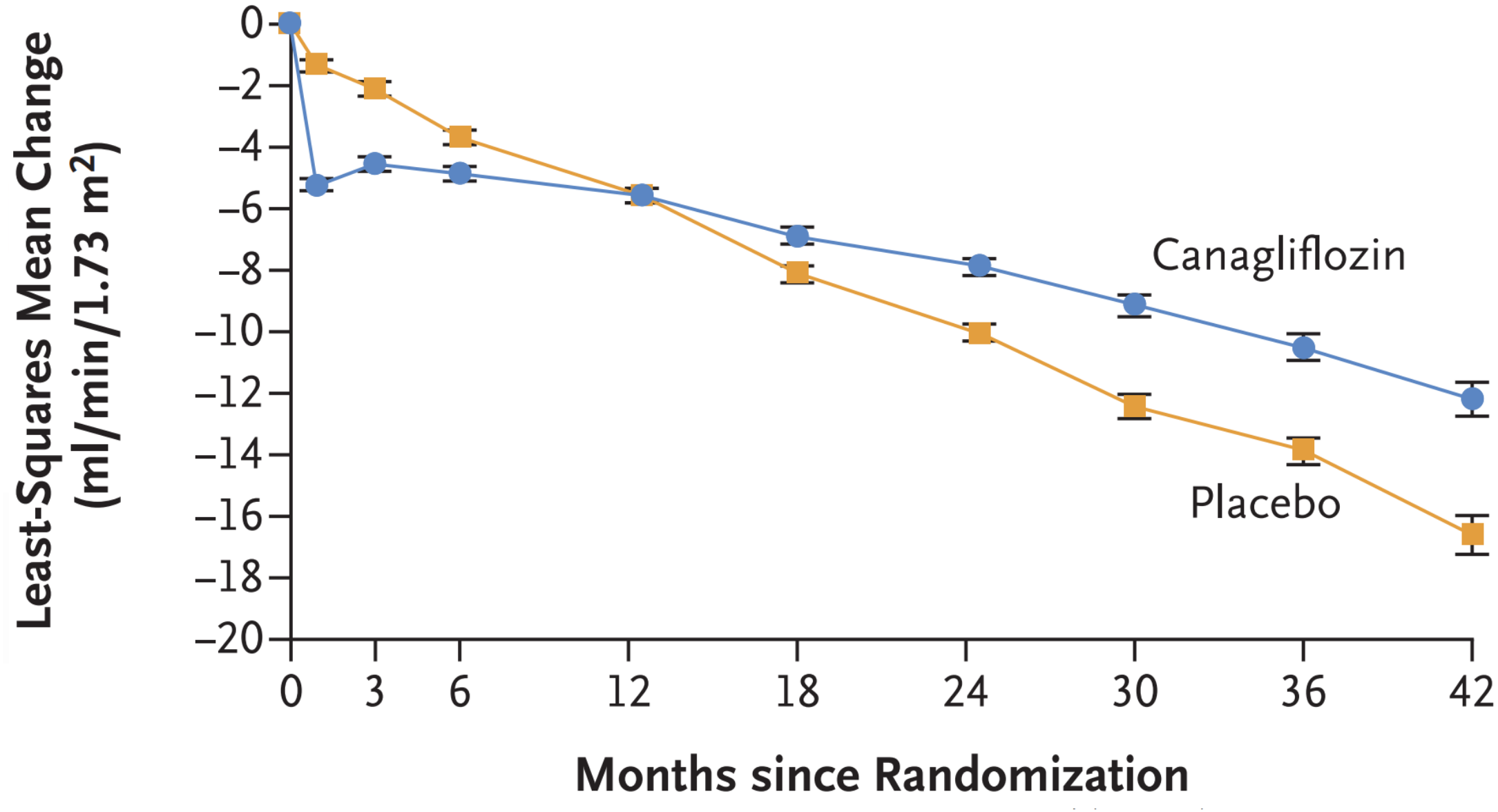
National Kidney Foundation™

FDA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



Levey et al. *AJKD.* 2019

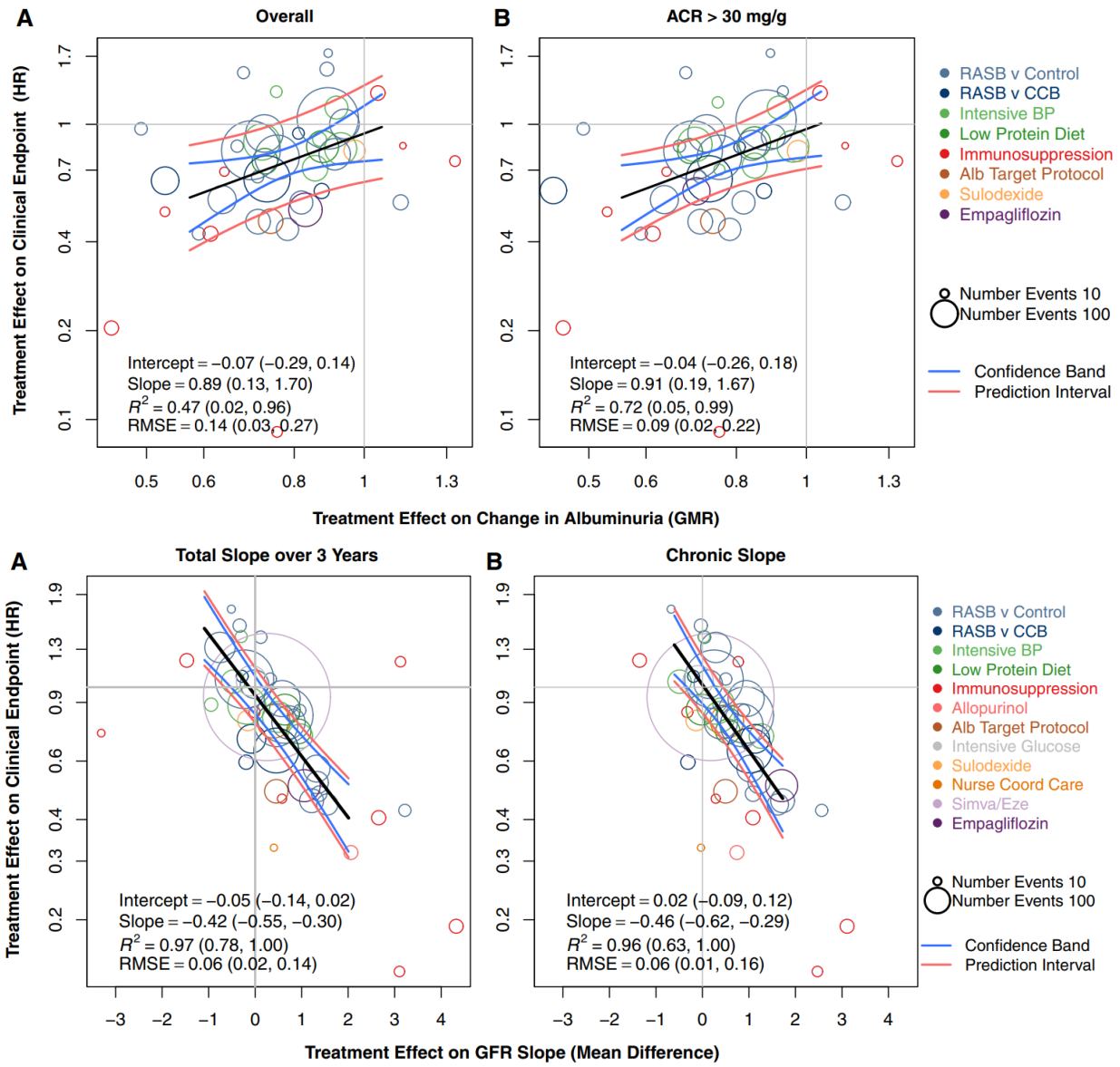


Perkovic et al. *NEJM.* 2019

National Kidney Foundation™

FDA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



Levey et al. *AJKD.* 2019

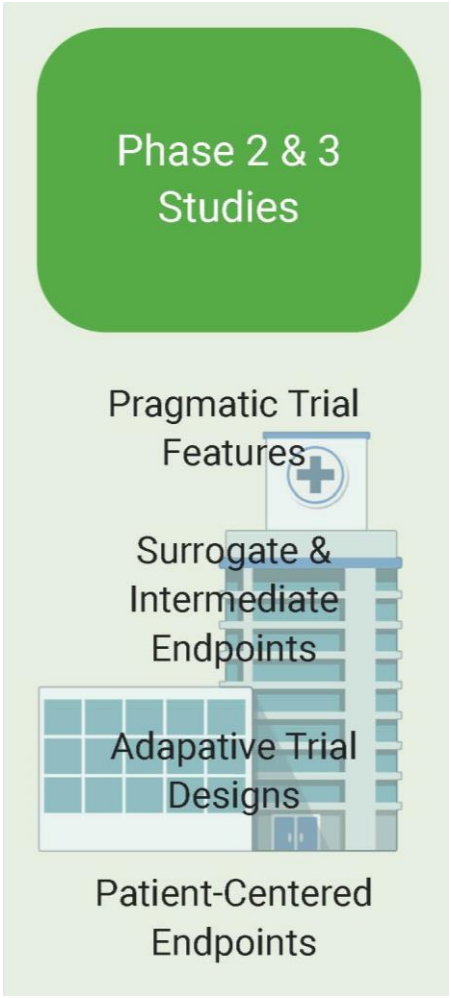
Phase 2 & 3 Studies

Pragmatic Trial Features

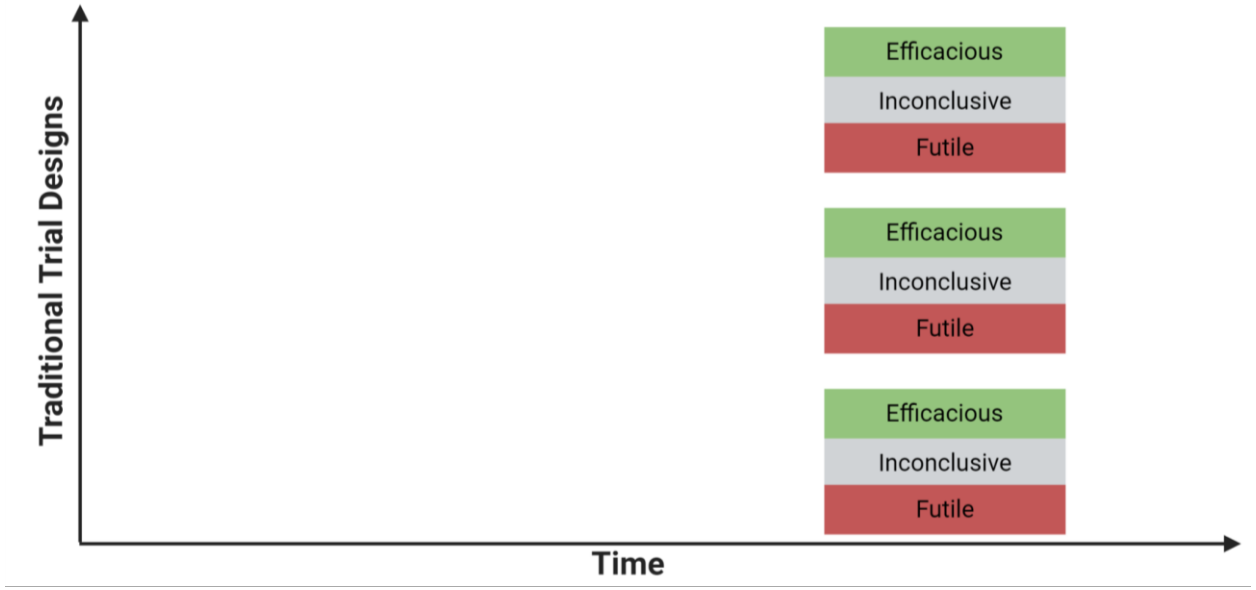
Surrogate & Intermediate Endpoints

Adapative Trial Designs

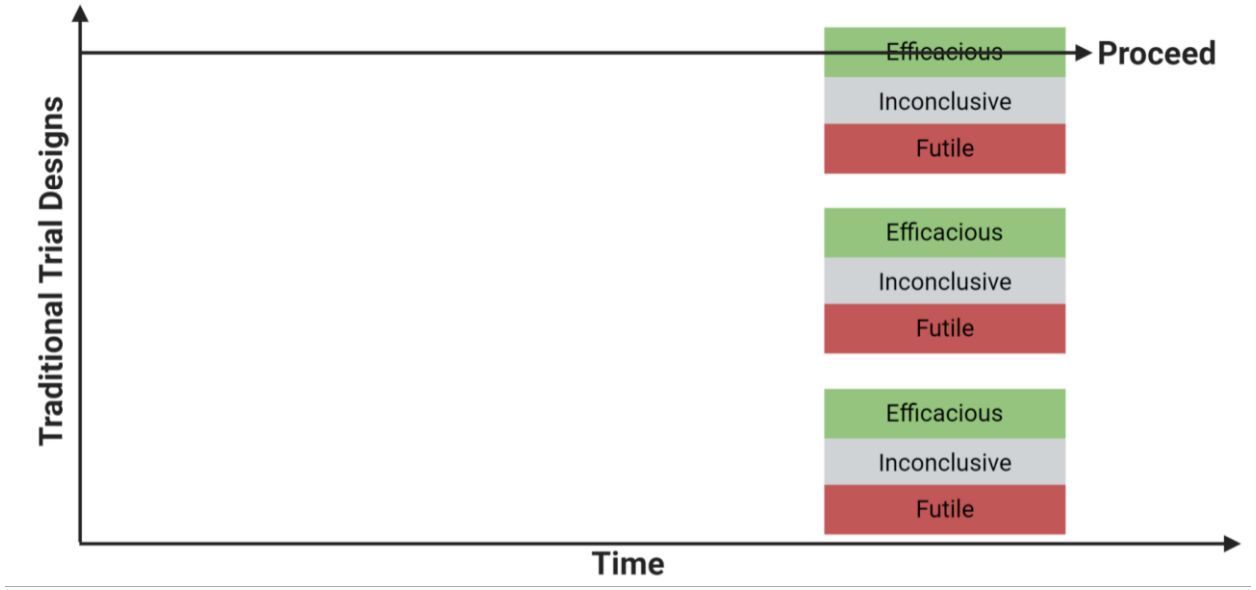
Patient-Centered Endpoints



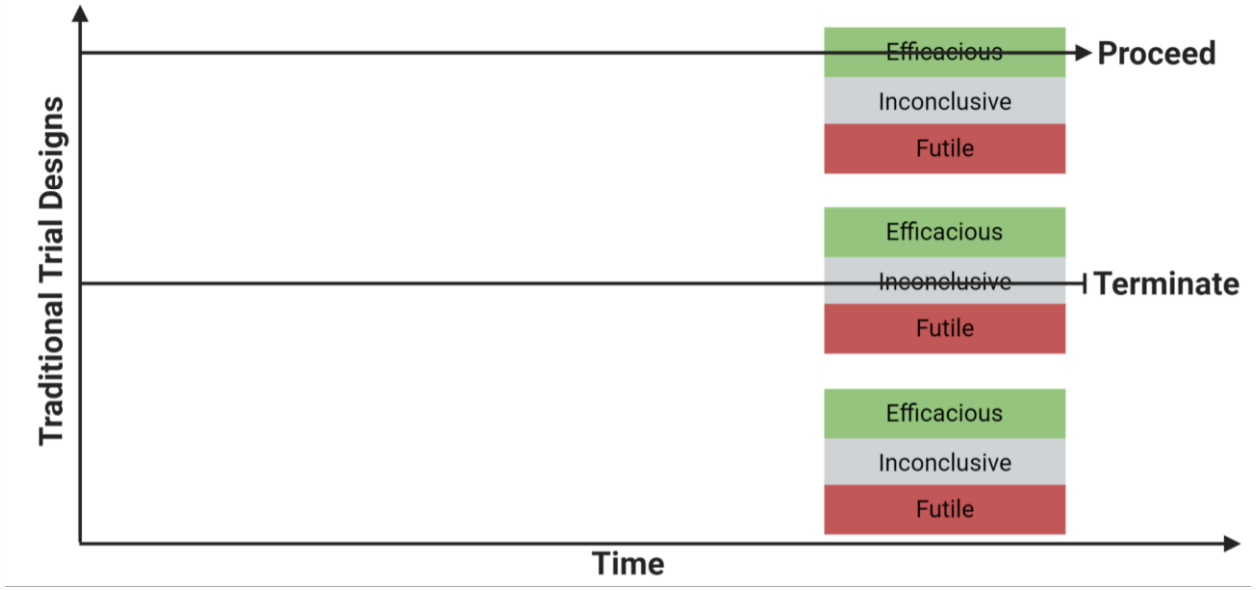
Adaptive Trial Designs



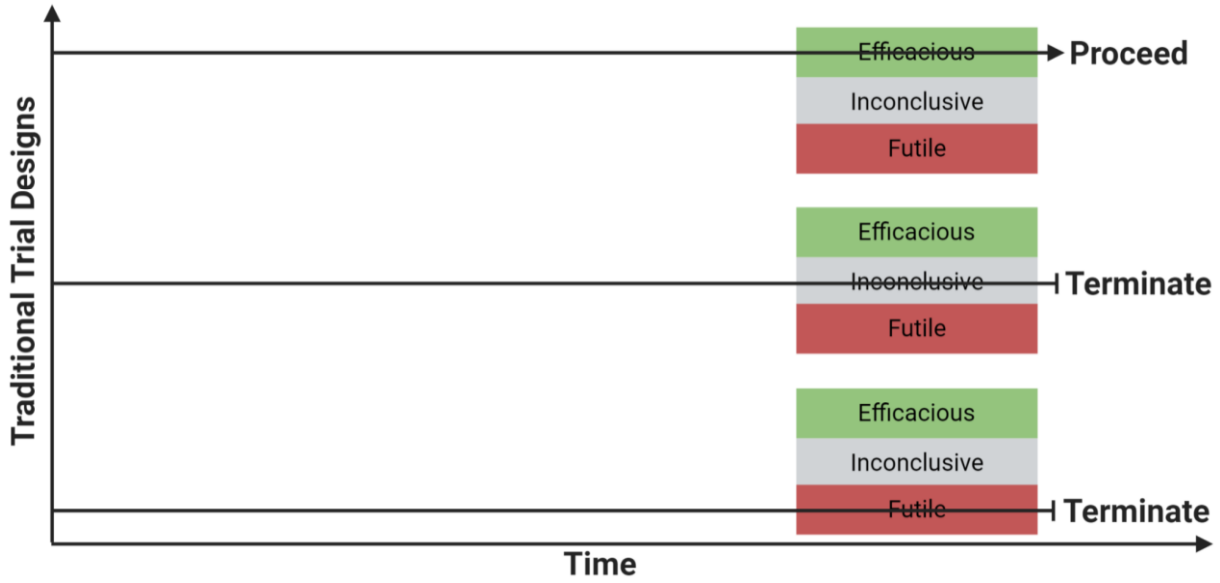
Adapted from Edmonston et al. *AJKD.* 2020



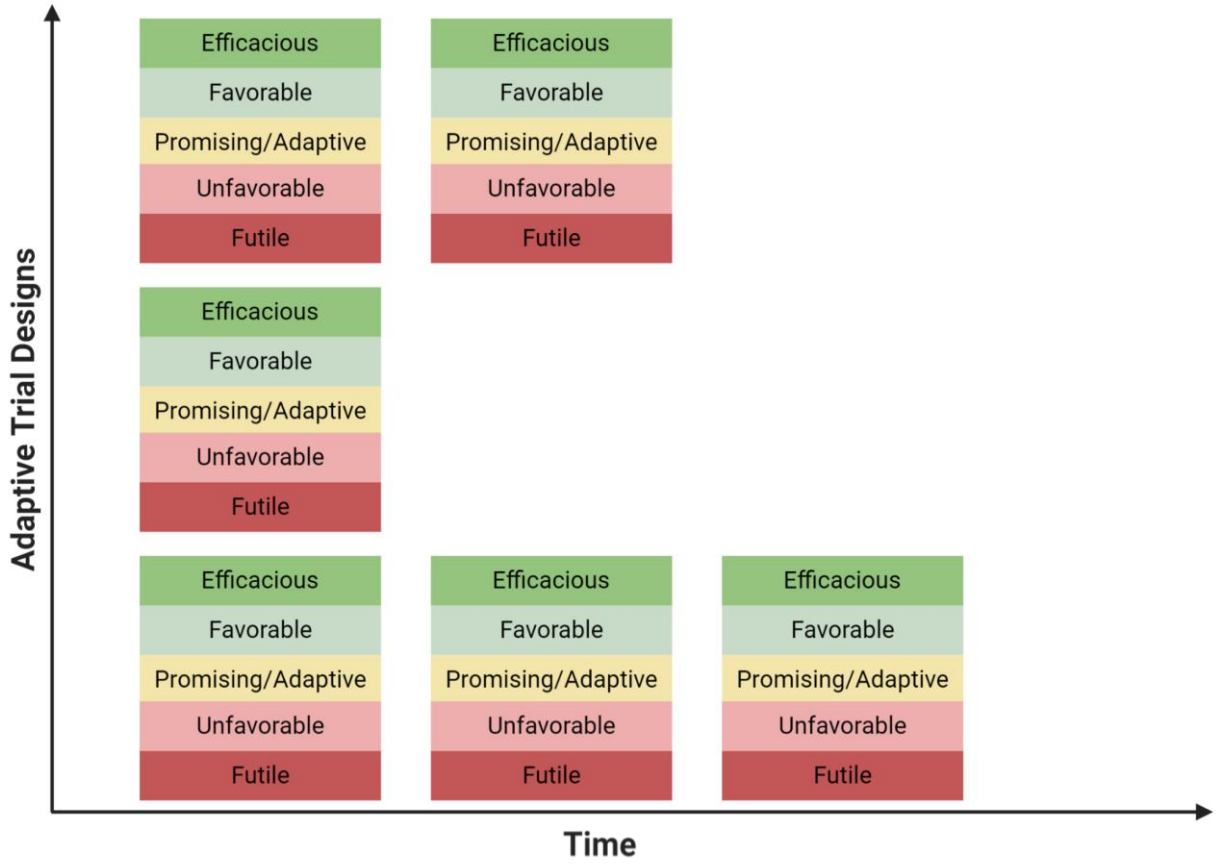
Adapted from Edmonston et al. *AJKD.* 2020



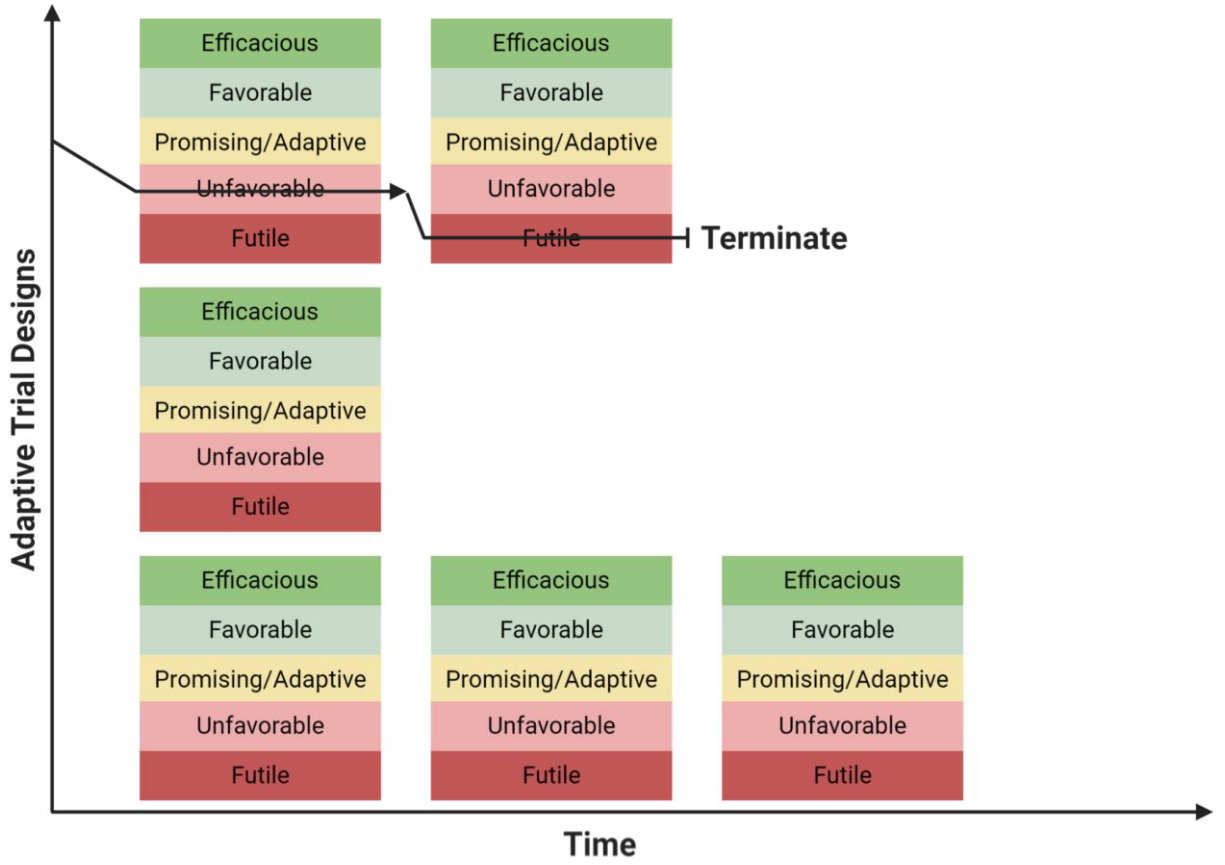
Adapted from Edmonston et al. *AJKD.* 2020



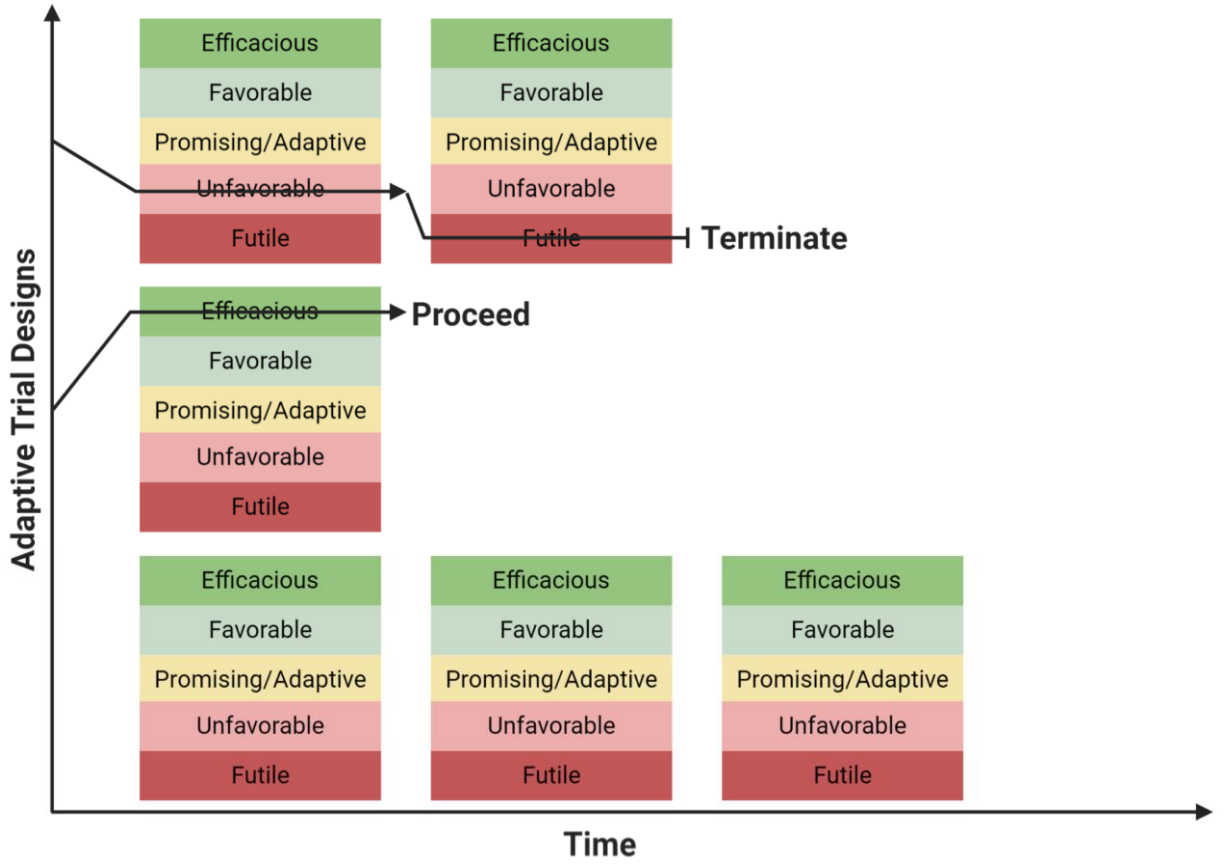
Adapted from Edmonston et al. *AJKD.* 2020



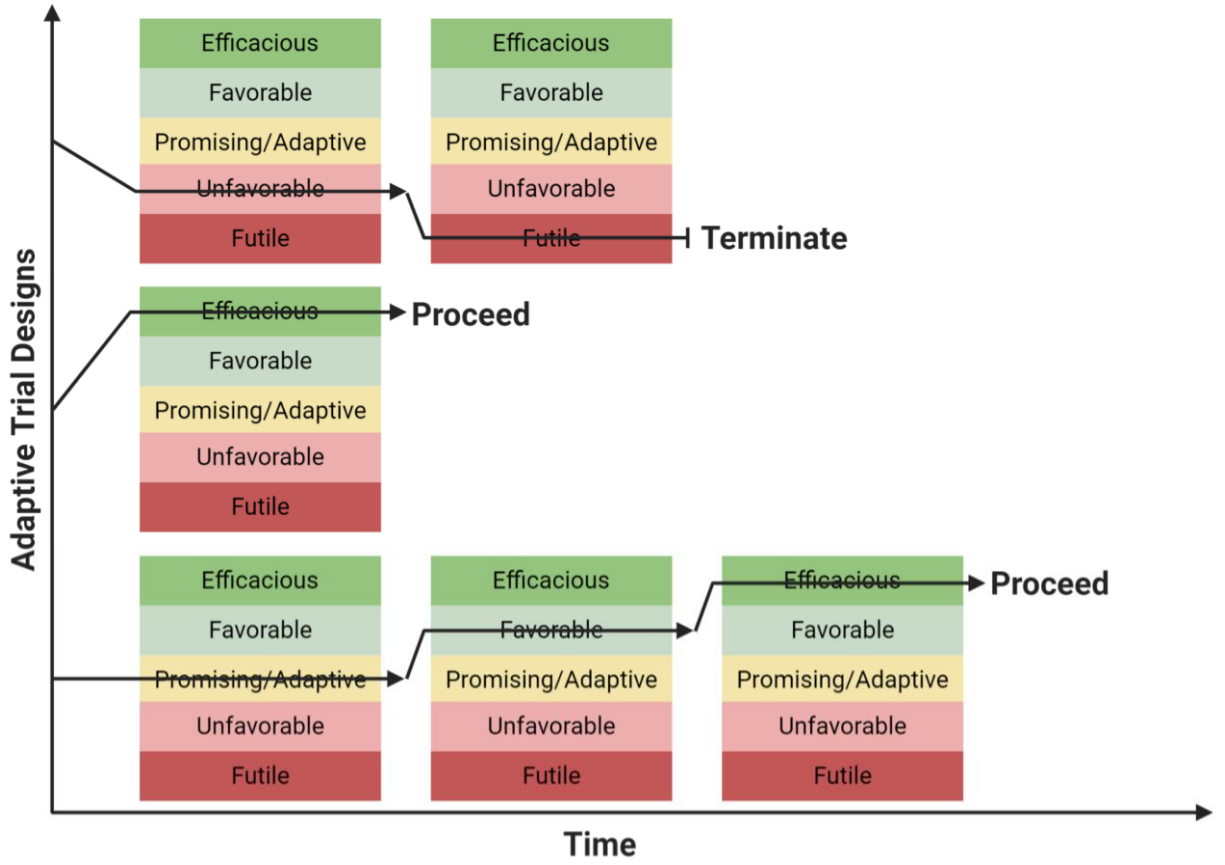
Adapted from Edmonston et al. *AJKD.* 2020



Adapted from Edmonston et al. *AJKD.* 2020



Adapted from Edmonston et al. *AJKD.* 2020



Adapted from Edmonston et al. *AJKD.* 2020

Hypothesis Generation & Pre-Clinical Studies

Interconnected Data Networks

Genomics and GWAS

Observational Studies & Secondary Analyses

Standardized Kidney Data Collection

Disease-Specific Networks

Phase 1 Studies

Pharamacokinetic Studies Across the Spectrum of CKD and Dialysis Modalities

Phase 2 & 3 Studies

Pragmatic Trial Features

Surrogate & Intermediate Endpoints

Adapative Trial Designs

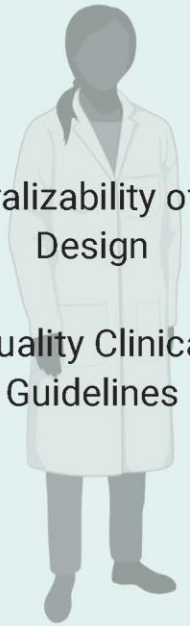
Patient-Centered Endpoints

Post-Marketing Studies

Real-World Evidence

Cardiovascular & Other Non-Kidney Endpoints

Dissemination & Uptake



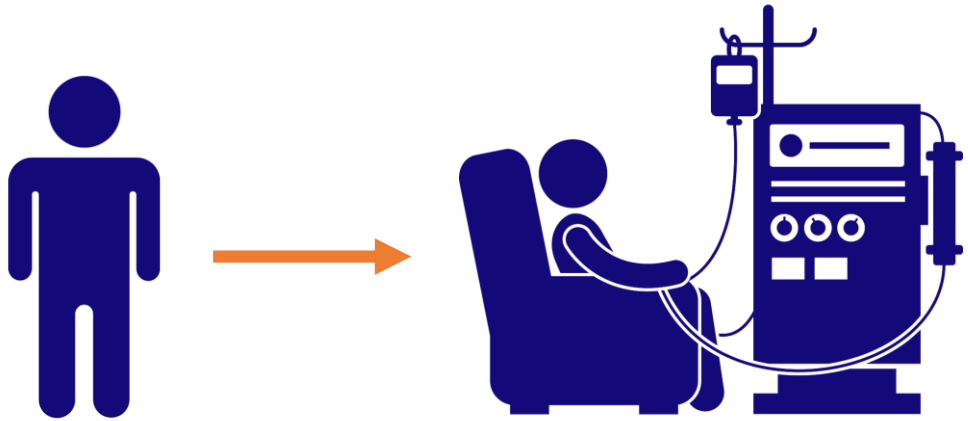
Generalizability of Trial Design

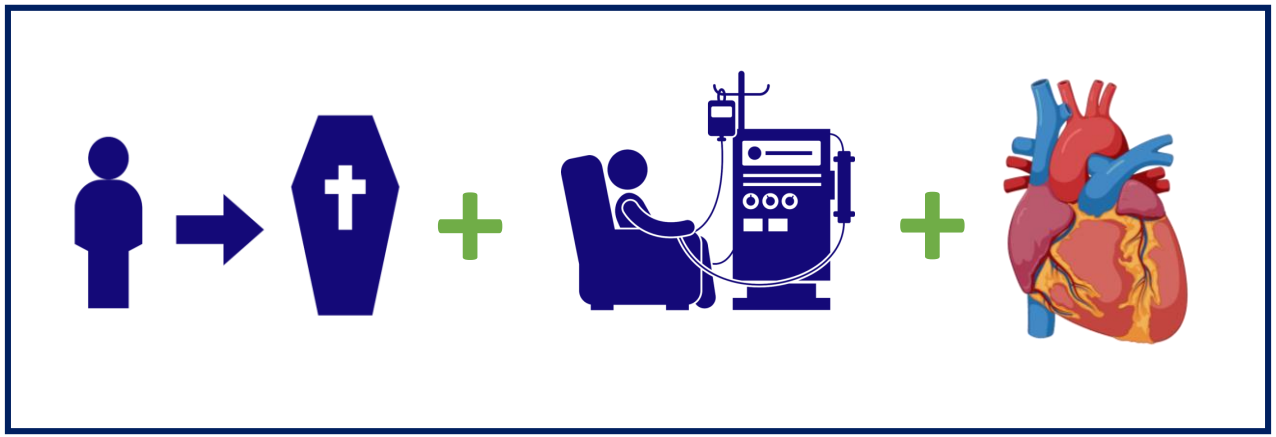
Quality Clinical Guidelines

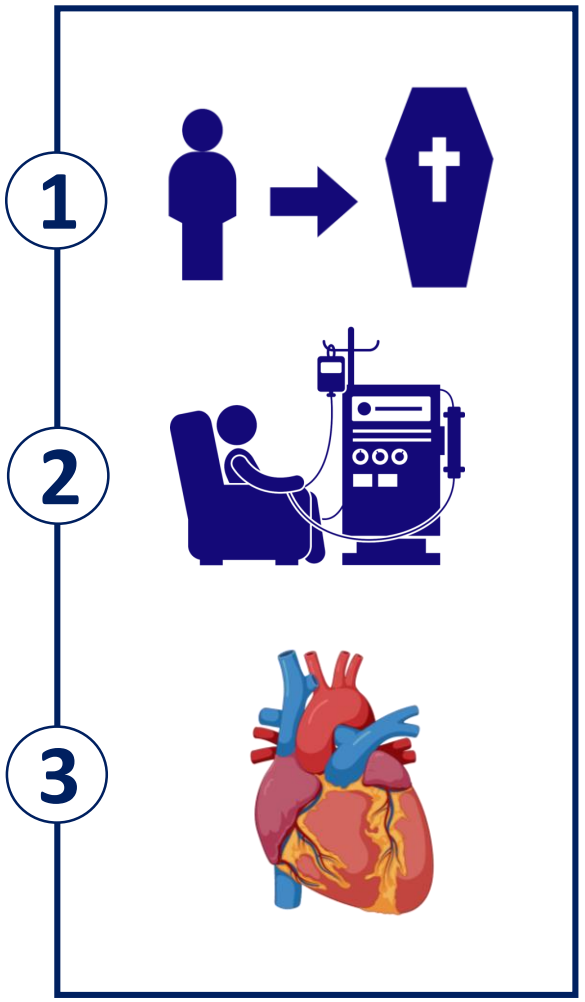
Post-Marketing Studies

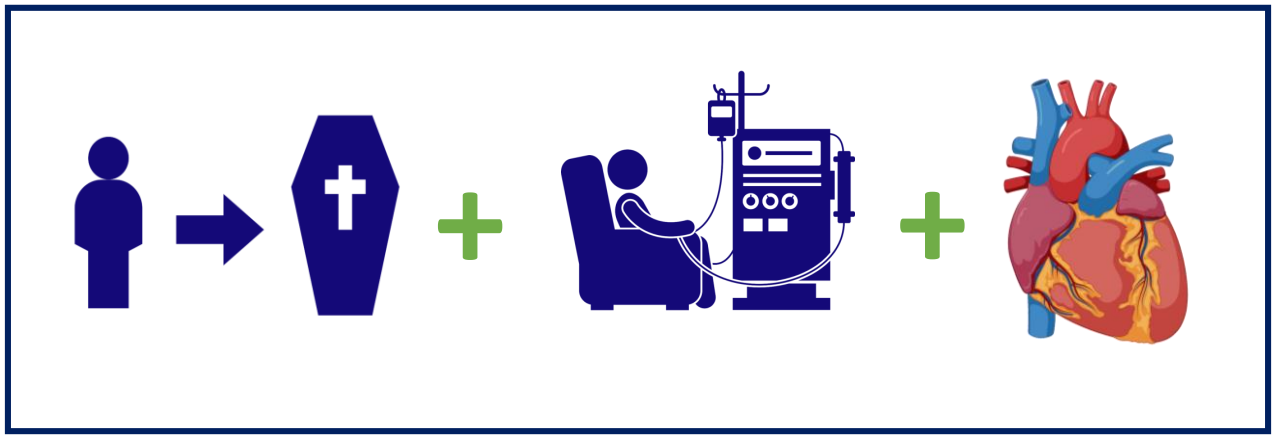
Post-Marketing Studies

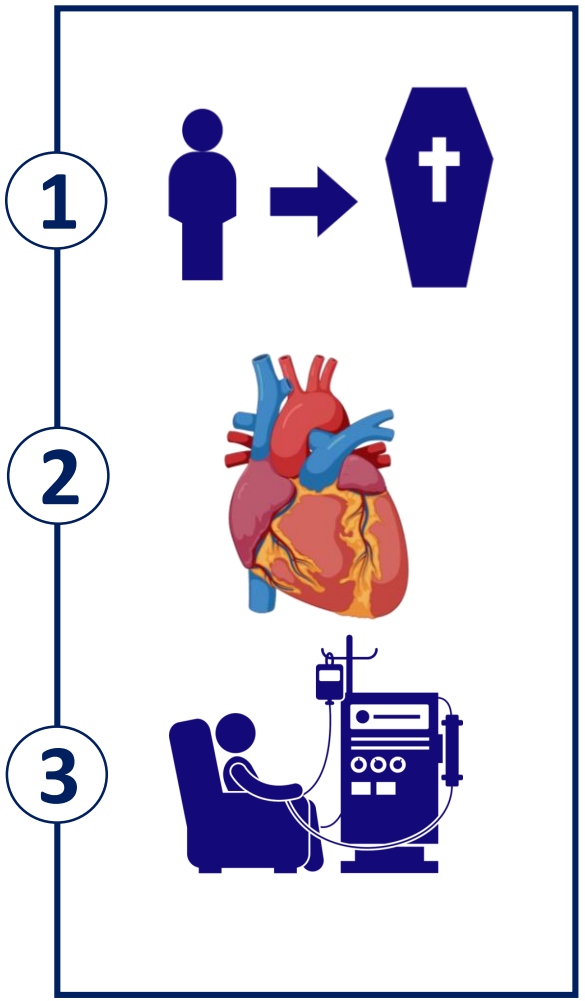
Non-Kidney Endpoints






1
2
3




1
2
3

Hypothesis Generation & Pre-Clinical Studies

Interconnected Data Networks

Genomics and GWAS

Observational Studies & Secondary Analyses

Standardized Kidney Data Collection

Disease-Specific Networks

Phase 1 Studies

Pharamacokinetic Studies Across the Spectrum of CKD and Dialysis Modalities

Phase 2 & 3 Studies

Pragmatic Trial Features

Surrogate & Intermediate Endpoints

Adapative Trial Designs

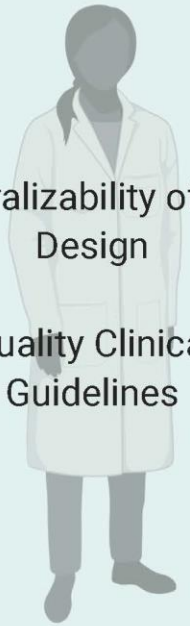
Patient-Centered Endpoints

Post-Marketing Studies

Real-World Evidence

Cardiovascular & Other Non-Kidney Endpoints

Dissemination & Uptake



Generalizability of Trial Design

Quality Clinical Guidelines

Dissemination & Uptake

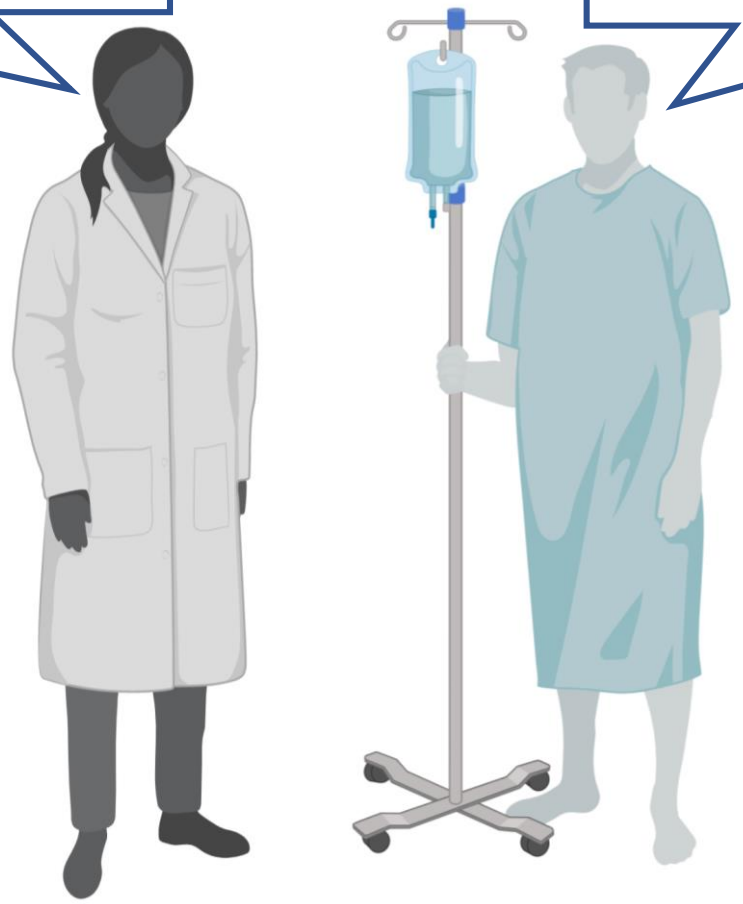
Generalizability of Trial Design

Quality Clinical Guidelines

Dissemination & Uptake

Doesn't apply to my patients.
Not feasible for my practice.
Not in the guidelines.

Will it make me feel better or keep me out of the hospital?




Dark Ages
Golden Era

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

Duke Nephrology
Duke University School of Medicine

DCRI THINK TANKS
FROM INSIGHT TO ACTION

Accelerating Drug Development for Chronic Kidney Disease and End-Stage Renal Disease




Special Report AJKD

Drug Development in Kidney Disease: Proceedings From a Multistakeholder Conference

Daniel L. Edmonston, Matthew T. Roe, Geoffrey Block, Paul T. Conway, Laura M. Dember, Peter M. DiBattiste, Tom Greene, Ali Hariri, Lesley A. Inker, Tamara Isakova, Maria E. Montez-Rath, Richard Nkulikiyinka, David Polidori, Lothar Roessig, Navdeep Tangri, Christina Wyatt, Glenn M. Chertow, and Myles Wolf

Occasional bursts of discovery and innovation have appeared during the otherwise stagnant past several decades of drug development in nephrology. Among other recent drug discoveries, the unexpected kidney benefits observed with sodium/glucose cotransporter 2 inhibitors may herald a renaissance of drug development in kidney disease. This recent progress highlights the need to further promote and stimulate research and development of promising therapies that may ameliorate the morbidity and mortality associated with kidney disease. To help identify and address barriers to drug development in nephrology, the Duke Clinical Research Institute convened a conference in April 2019 that included stakeholders from academia, industry, government agencies, and patient advocacy. From these discussions, several opportunities were identified to improve every stage of drug development for kidney disease from early discovery to implementation into practice. Key topics reviewed in this article are the utility of interconnected data and site research networks, surrogate end points, pragmatic and adaptive trial designs, the promising uses of real-world data, and methods to improve the generalizability of trial results and uptake of approved drugs for kidney-related diseases.

Complete author and article information provided before references.

Am J Kidney Dis. XX(XX):1-9. published online month xx, xxxx.

doi: 10.1053/j.ajkd.2020.05.026

Introduction

Sodium/glucose cotransporter 2 (SGLT2) inhibitors represent the most significant drug development for diabetic kidney disease in the past 2 decades. Other recent drug discoveries have also improved the treatment of autosomal dominant polycystic kidney disease, hyperkalemia, and anemia. Although these discoveries herald a new era of drug development in kidney disease, numerous challenges remain. Nephrology consistently ranks among the medical subspecialties with the fewest number of published clinical trials.[1] Significant barriers impede timely drug development and uptake for patients with acute kidney injury and chronic kidney disease (CKD).

Drug development faces many challenges in both preclinical and clinical stages; in addition, even successfully approved drugs encounter barriers to clinician and patient uptake. During the past 23 years, the Duke Clinical Research Institute has facilitated "think tanks" designed to address the most pressing gaps in clinical research. In April 2019, leaders from academia, industry, patient representatives, professional societies, and government agencies, including the US Food and Drug Administration (FDA), National Institutes of Health (NIH), and Centers for Medicare & Medicaid Services (CMS), convened in Wash-

Hypothesis Generation and Drug Discovery

Although drug discovery often follows the classic "bench-to-bedside" paradigm in which laboratory data are used to identify putative therapeutic targets, investigators can also use high-quality clinical data and secondary analyses to hone hypotheses and identify new drug targets. Examples of this "reverse translation" approach include the discovery of new therapeutic targets through genome-wide association studies (GWAS) and other genetic analyses,[2] use of observational data to assess the target patient profile before the conception of clinical trials, and use of machine learning and predictive algorithms to identify patients most likely to benefit from investigational therapies.[3]

Several barriers limit the use of such data in the drug development process. These barriers include uncertain CKD cause due to a lack of kidney biopsy data for many patients with CKD; lack of standardized data collection for kidney disease end points, even in the context of clinical trials; limited access to industry-sponsored clinical trial data for secondary analyses; and fragmented data networks with inconsistent and often incompatible electronic records across different health systems data. Potential strategies to improve data access include interconnected data networks, disease-specific registries and networks, and