Potential Opportunities to Disrupt CKD Progression:

Insights from the CRIC Study

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Outline

- Introduction to the CRIC Study
- Risk factors for CKD progression
  - Types of risk factors
  - Behavioral and lifestyle factors
  - Clinical factors
  - Biomarkers
- A look to the future

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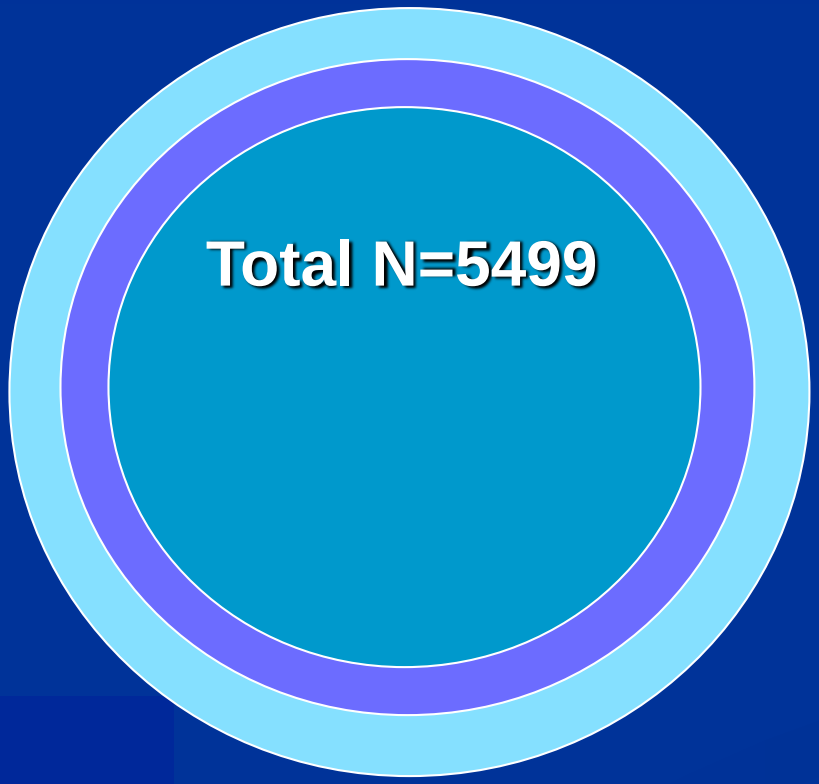
CRIC Study Design Overview

- Initial Cohort (2003-2008)
- Supplemental Hispanic Cohort (HCRIC)

- Inclusion Criteria
  - Age 21-74 years
  - eGFR
    - 20-70 ml/min (21-44 yrs)
    - 20-60 ml/min (45-64 yrs)
    - 20-50 ml/min (65-74 yrs)
  - ~ 50% DM / female, ~45% AA
  - No dx of ADPKD

CRIC Study Design Overview

- Initial Cohort (2003-2008)
- Supplemental Hispanic Cohort (HCRIC)
- New Recruitment 2013-2015 (N=1560)



- Inclusion Criteria (new recruits)
  - Age 45-79 years
  - eGFR 45-70 ml/min
  - Predominantly proteinuric CKD
  - No dx of ADPKD

Study Elements

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Types of Risk Factors

- Progressive kidney damage often arises from
  - Factors that alter the hemodynamics of the kidney
  - The tendency to create scar tissue (fibrogenesis)
- Risk factors for CKD progression are varied and may or may not be modifiable

Modifiability of Risk Factors

- *Modifiable risk factors* (e.g., behaviors, environmental exposures) *are excellent targets for interventions*
- Intervening on these factors may not reduce risk
  - In advanced disease (ex.: if eGFR < 30)
  - If multiple disease mechanisms are active
- Understanding *unmodifiable risk factors* (e.g., genetics, sex, race) *may help improve outcomes by*
  - Providing insight into disease mechanisms
  - Identifying individuals for intensive disease management
- Clinical trials are often necessary to assess the impact of interventions on any particular risk factor

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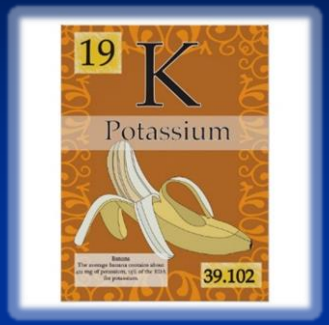
Urinary Sodium and Potassium Excretion

He J et al. *J Am Soc Nephrol* 2015

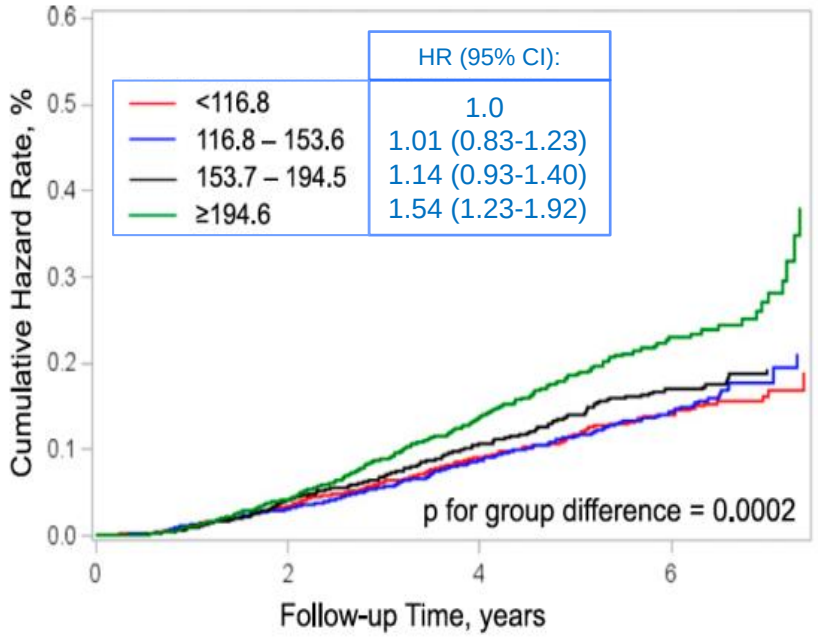


- High dietary sodium (Na) intake, and low potassium (K) intake, → higher BP
- Data on how Na & K intake affects CKD progression are sparse and inconsistent
- Dietary intake measures are unreliable, so urinary Na & K levels served as proxies

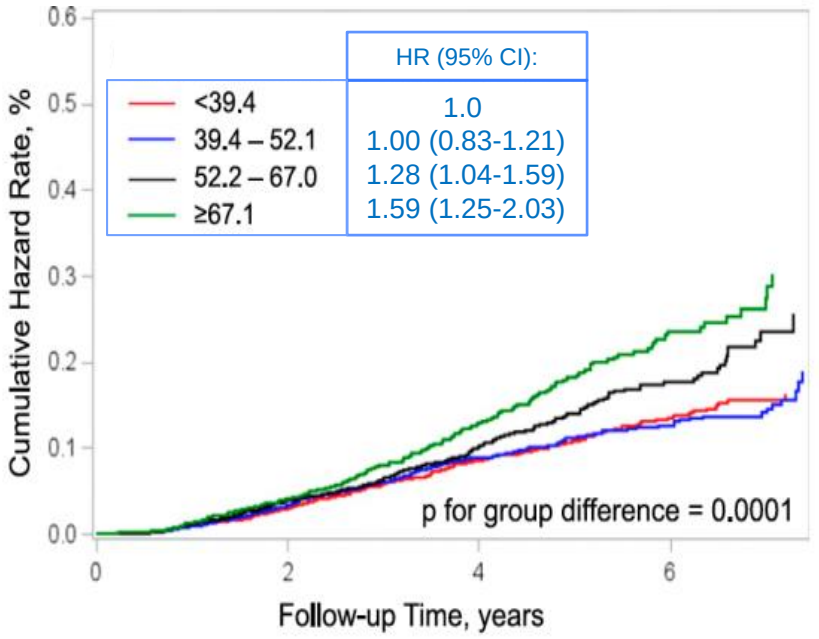
Urinary Sodium and Potassium Excretion

Hazard of CKD Progression by Quartile of Na and K Excretion

Sodium



Potassium



A significant, independent, and potentially important association of high urinary sodium and potassium excretion with CKD progression

He J et al. *J Am Soc Nephrol* 2015

Self-Management Behaviors

Schrauben S et al. *Am J Kidney Dis* 2018

- Self-management reflects patients' engagement in health-related behaviors
- Self-management behaviors have been incorporated into CKD guidelines
- Goals: Define the constellation of self-management domains and assess their relationship with clinical outcomes

Self-Management Behaviors

Using the data discovery tool of Principal Components Analysis

and information on 6 domains of self-management -

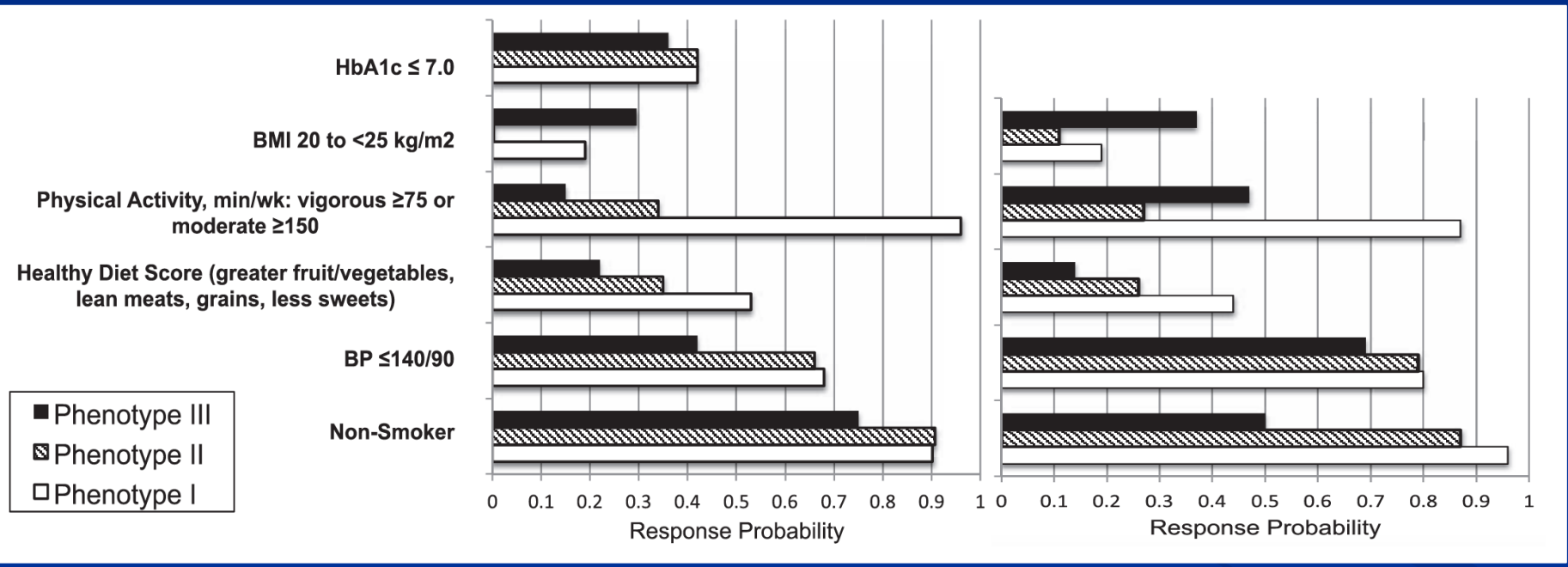
- Good glycemic control
- Ideal body weight
- Physical activity
- Healthy diet
- Controlled BP
- Not smoking

3 Distinct Subtypes Identified

Phenotype III: minimal recommended behaviors
Phenotype II: mixture of recommended and not recommended behaviors
Phenotype I: most recommended behaviors

Schrauben S et al. *Am J Kidney Dis* 2018

Self-Management Behaviors



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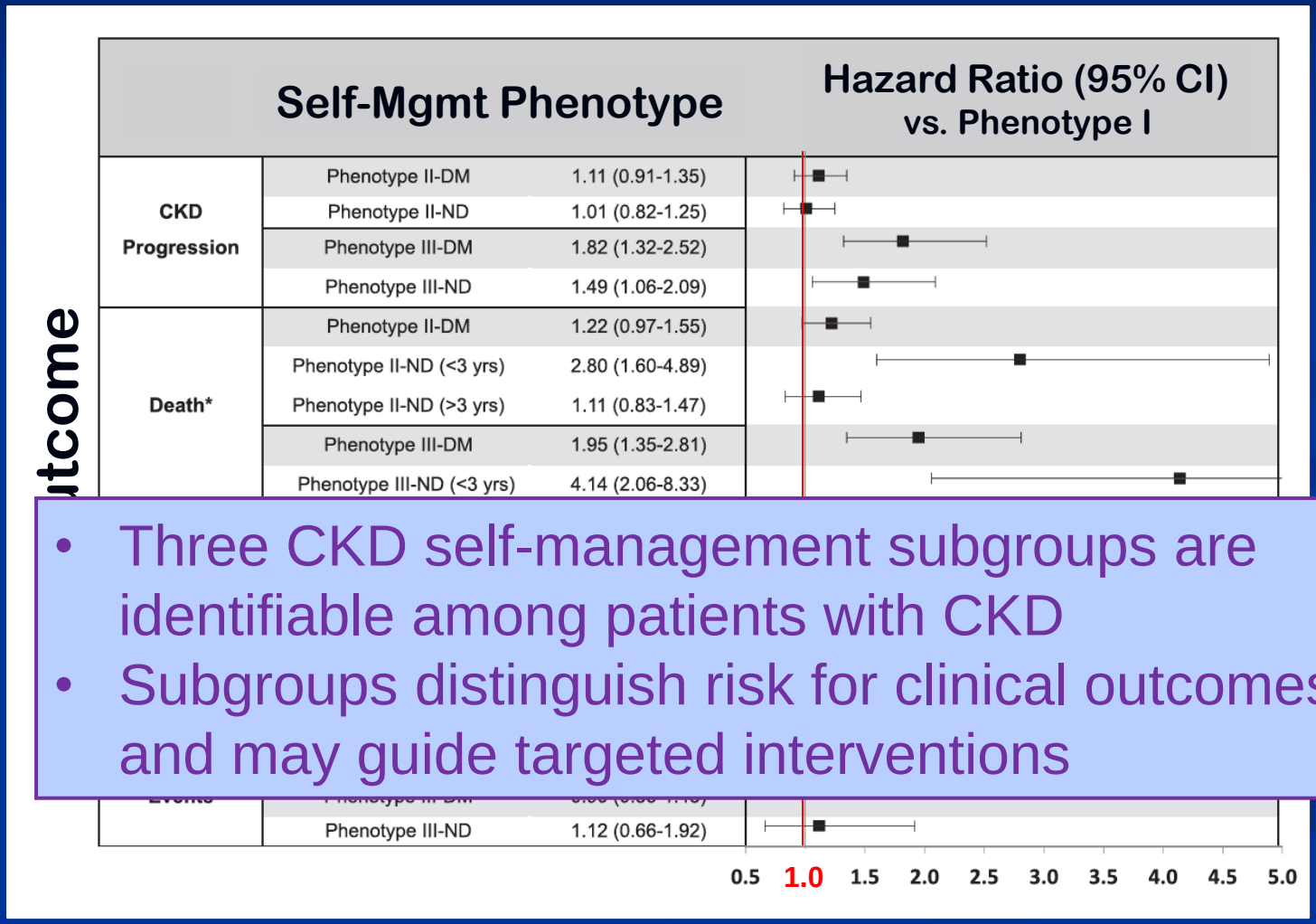
Self-Management Behaviors and Clinical Outcomes



- Three CKD self-management subgroups are identifiable among patients with CKD
- Subgroups distinguish risk for clinical outcomes and may guide targeted interventions

Schrauben S et al. *Am J Kidney Dis* 2018

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Time-Updated Systolic Blood Pressure

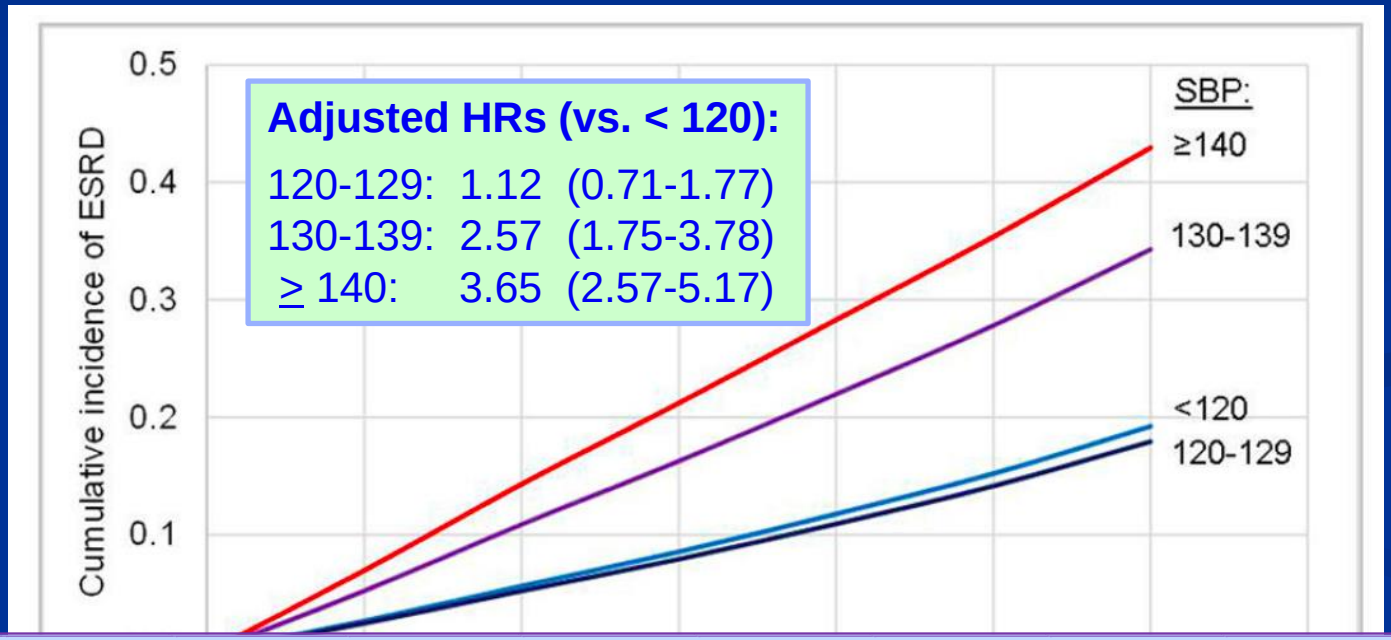
Anderson AH et al. *Ann Intern Med* 2015

- High blood pressure (BP) → CKD progression in previous studies
- Proper target BP for people with CKD unclear

- CRIC measures BP annually, so we were able to use time-updated BP

Time-Updated Systolic Blood Pressure

Estimated ESRD Incidence at Different Levels of Time-Updated SBP



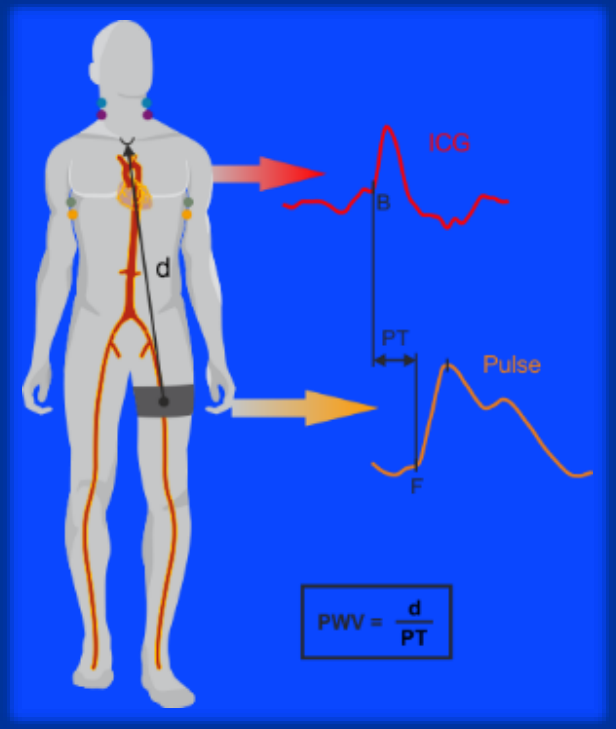
Achieved BP level of 130-139 mmHg, a level that would meet current clinical targets, is associated with marked elevations in the risk of CKD progression

Results for baseline BP (not shown) were similar, but not as strong.

Anderson AH et al. *Ann I*

Pulse Wave Velocity and CKD Progression

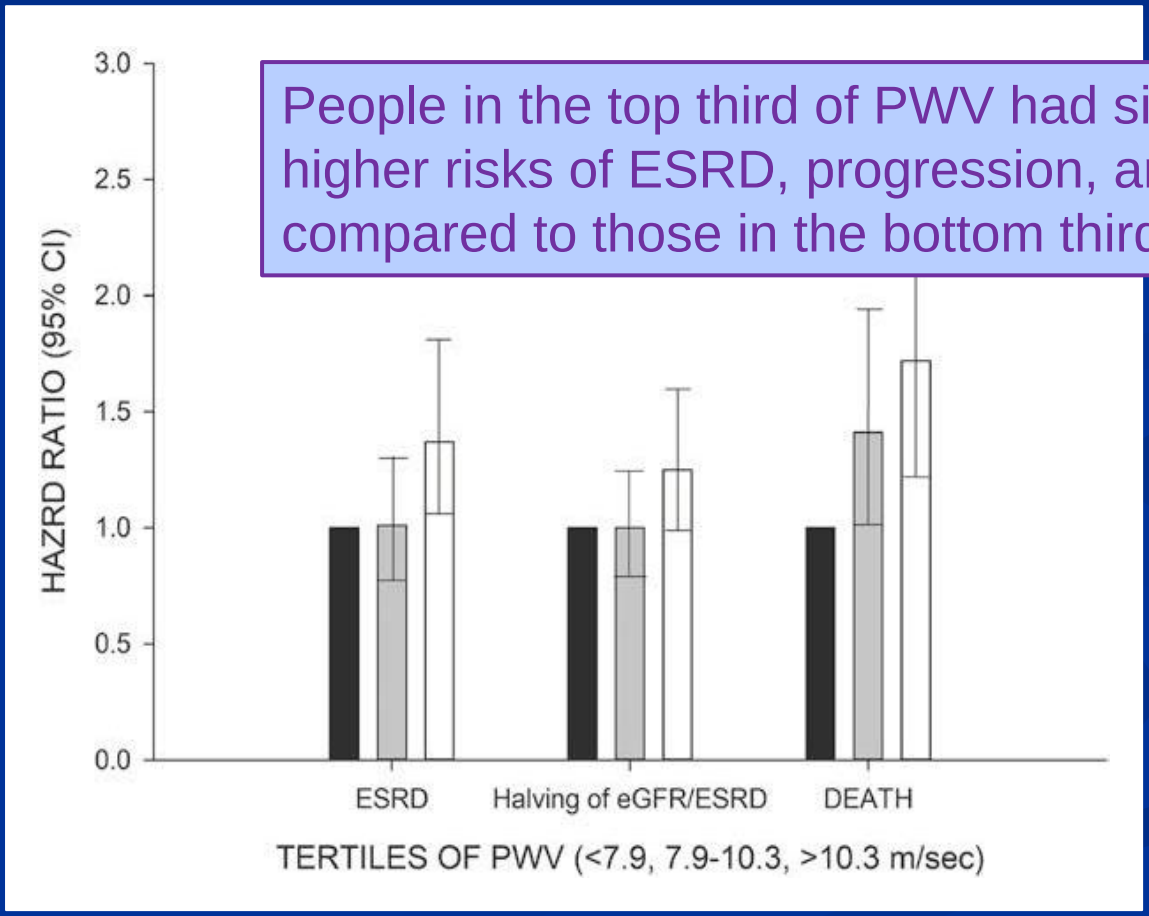
Townsend RR et al. *Hypertens* 2018



- Pulse wave velocity (PWV) is a measure of arterial stiffness
- In CKD, arterial stiffness → increased risk of CV events independently of high BP
- Drug interventions may reduce arterial stiffness
- The goal of this study was to examine the role of PWV in CKD progression

Pulse Wave Velocity and CKD Progression

Adjusted Associations of Pulse Wave Velocity with ESRD, CKD Progression, and Death



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Inflammatory Biomarkers

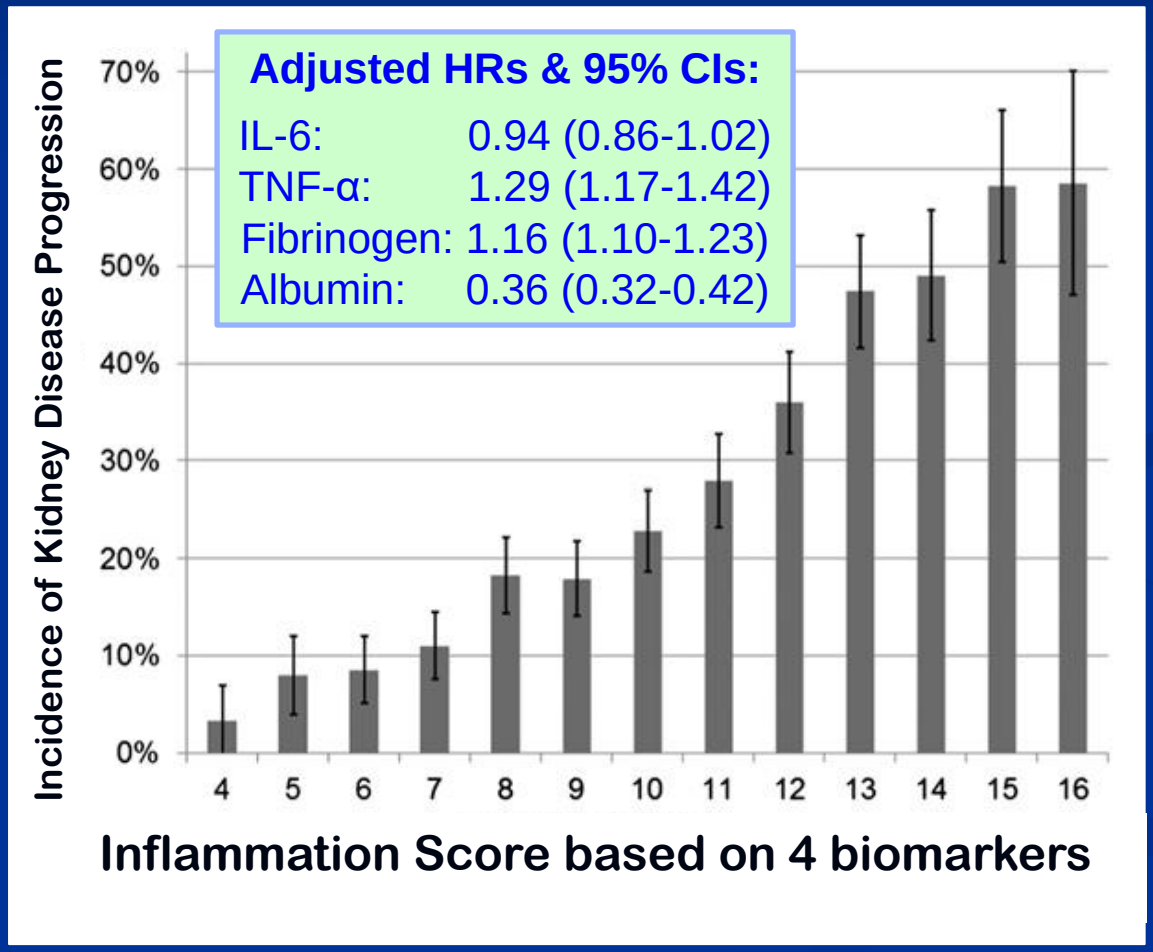
Amdur RL et al. *Clin J Am Soc Nephrol* 2016

- CKD is characterized by persistent low-grade inflammation (part of the wound healing process)
- This study evaluated the association of CKD progression with blood levels of a set of biomarkers of inflammation:

- TNF-α
- TGF-β
- Fibrinogen
- Serum albumin
- High-sensitivity C-reactive protein
- IL-1 and IL-1 receptor antagonist
- IL-6

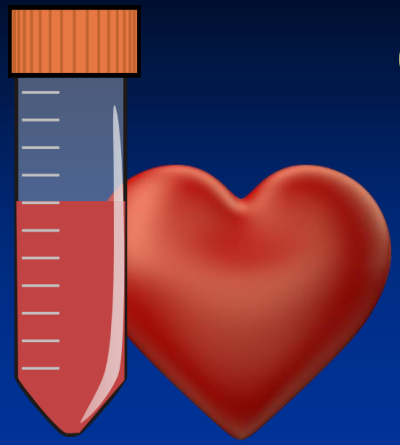
Inflammation and CKD Progression

Incidence of CKD Progression by Inflammation Score



Greater levels of inflammation were associated with higher risk of CKD progression

Amdur RL et al. *Clin J Am Soc Nephrol* 2016



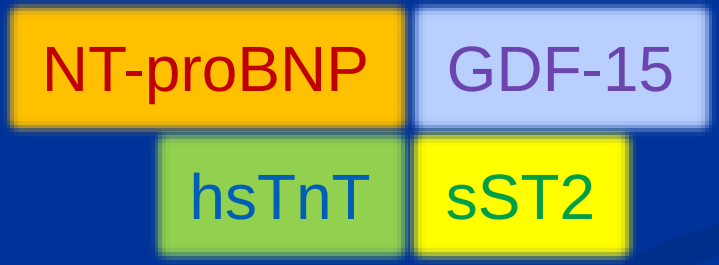
Cardiac Biomarkers

Bansal N et al. *AJKD* 2019

- Cardiovascular disease (CVD) is strongly associated with CKD progression
- This may be true even for early CVD, which is not easily detected clinically
- Biomarkers can serve as indicators of early subclinical CVD

Cardiac Biomarkers

- In the setting of CKD, 4 markers of cardiac injury have been found to predict CVD:

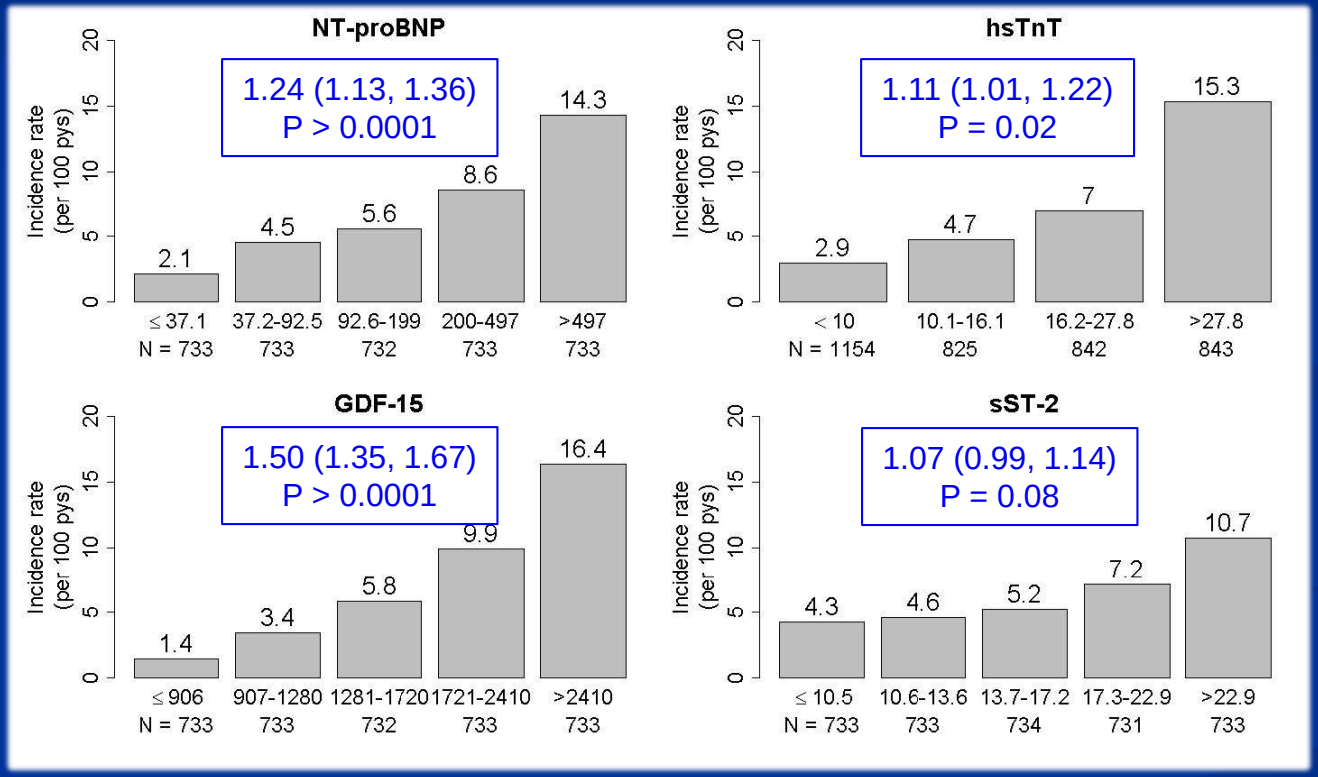


- There are few data on the association of these biomarkers with CKD progression

Bansal N et al. *AJKD* 2019

Cardiac Biomarkers

Rates of CKD Progression by Levels of Cardiac Biomarkers



Higher levels of NT-proBNP, hsTnT, and GDF-15 were associated with higher rates of CKD progression

HRs are for 1 SD increase in log-transformed level of the given biomarker.

Bansal N et al. *AJKD* 2019

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A Look to the Future

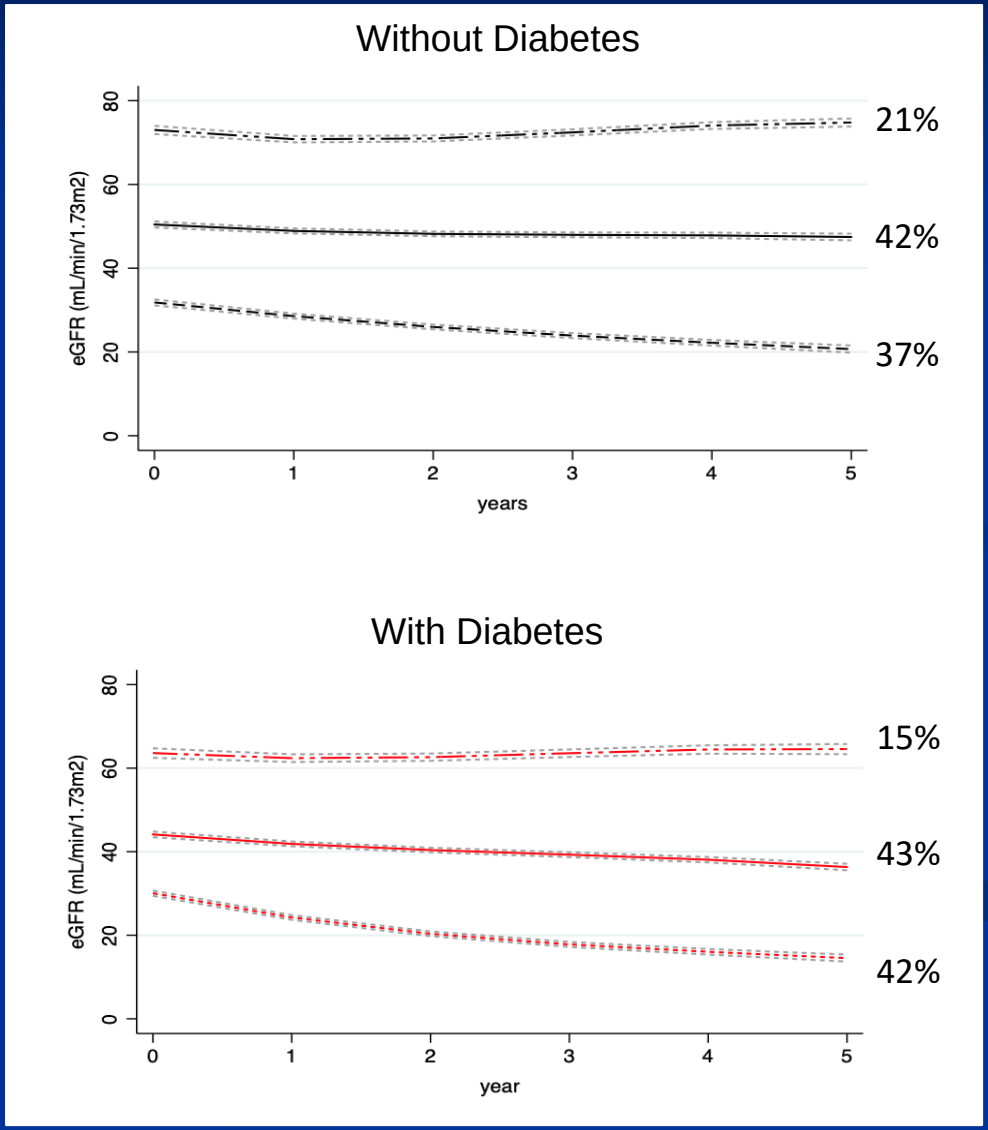
2018 - 2023

- Develop more nuanced characterizations of the trajectories of CKD progression

Novel Approaches to Subclassify Kidney Disease Outcomes

Group-Based Trajectory Modeling

Identifies clusters of individuals following similar longitudinal eGFR patterns



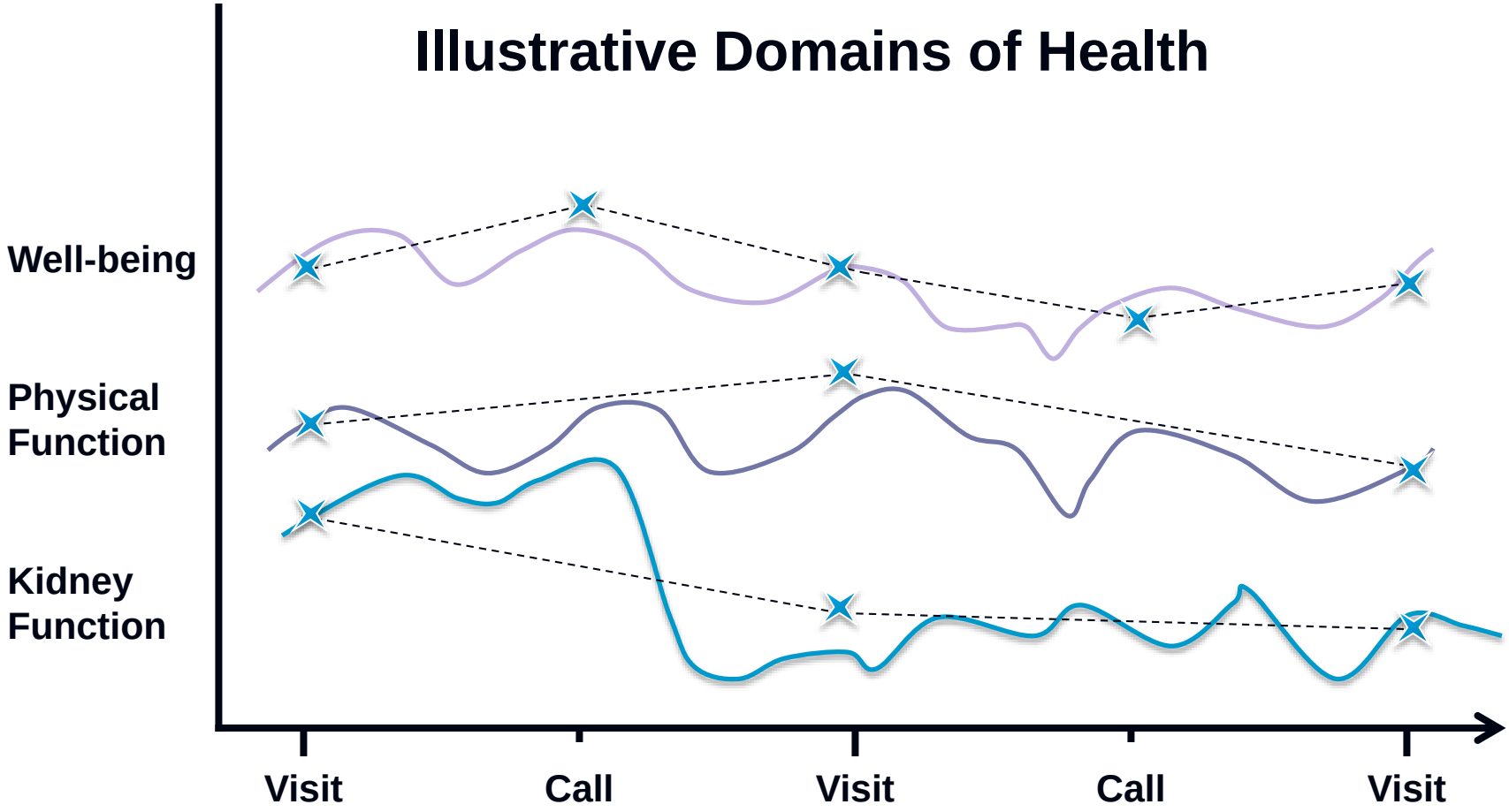
Unpublished Data

A Look to the Future

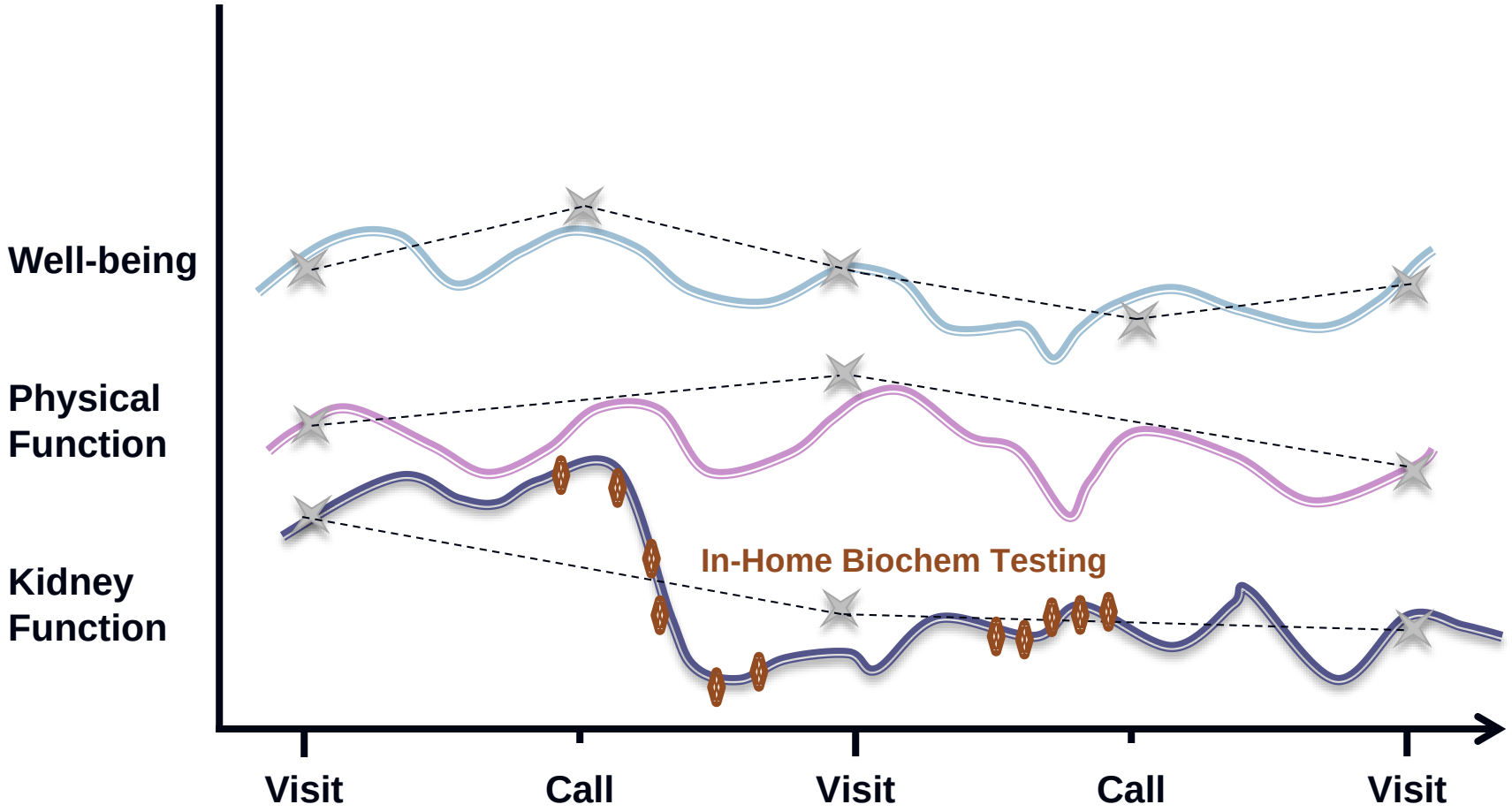
2018 - 2023

- Develop more nuanced characterizations of the trajectories of CKD progression
- Make use of mobile and wearable devices to characterize health

CRIC 2018-23
Expanding the Depth and Breadth of Phenotyping



CRIC 2018-23
Expanding the Depth and Breadth of Phenotyping



CRIC 2018-23


clinic


Community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Creatinine Monitoring System
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OWNER'S GUIDE
nova biomedical


Zephyr
Zephyr
BioHarness

With Deep Appreciation!

CRIC Study Participants
CRIC Investigators and Collaborators
CRIC Study Coordinators
NIH-NIDDK


thank
you