Department of Medicine
Duke University School of Medicine
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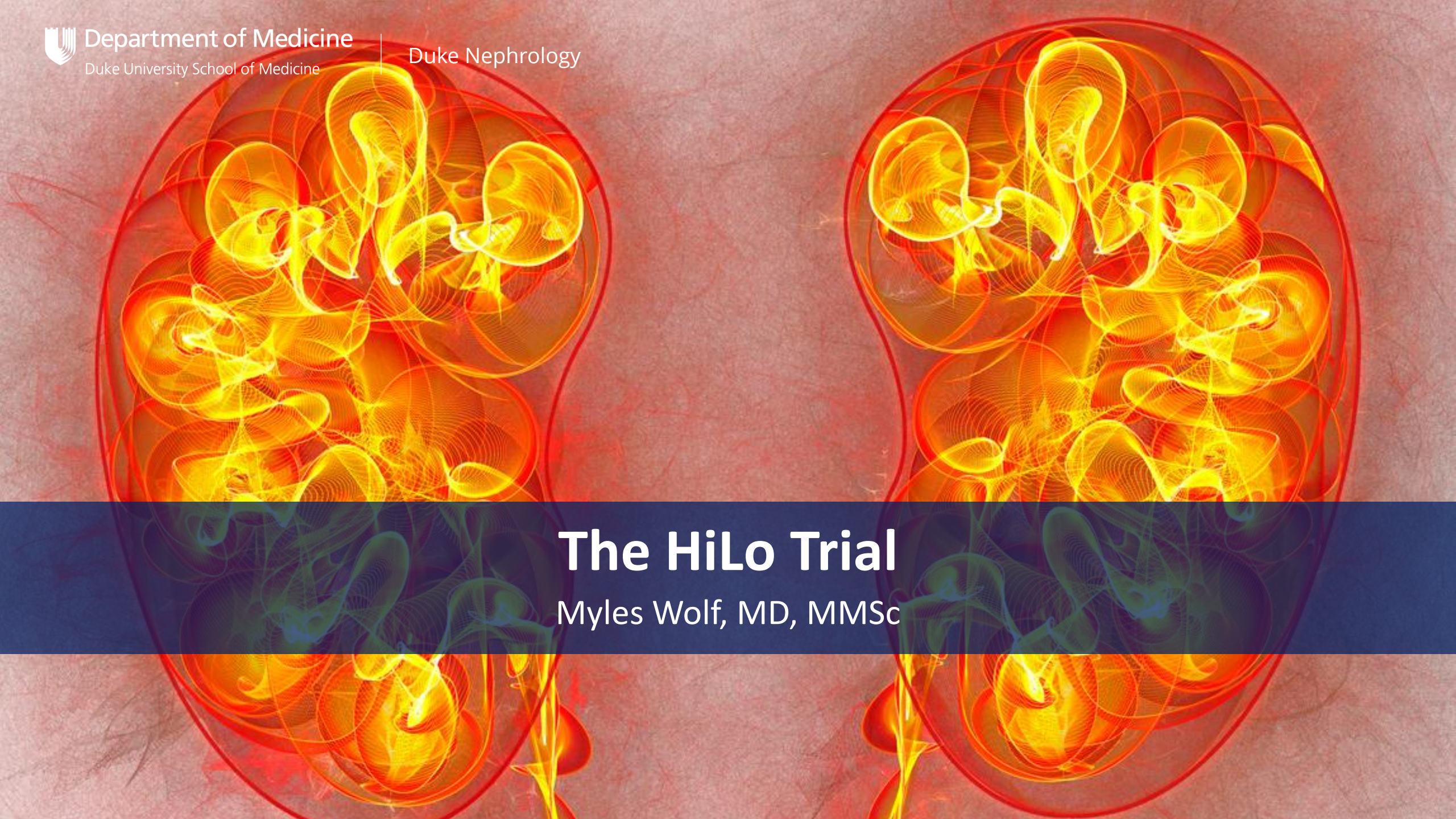

The HiLo Trial

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ESRD: Trials needed & an ideal setting for pragmatism

- ESRD population is desperately in need of clinical innovation
  - High event rates
  - Few, if any therapies proven by RCT
- Highly accessible study population with 3 x weekly clinical encounters
- Highly granular, regular, uniform data collected in routine clinical care → EHR
  - Remote biochemical monitoring
  - Pragmatic ascertainment of outcomes, covariates
- Centralized infrastructure of dialysis provider organizations allows for
  - Centralized implementation
  - Inclusion of large number of facilities with broad geographic distribution
  - Facility-level randomization

Hypotheses

1. **Primary:** Compared to the current standard approach of targeting serum phosphate levels of <5.0 mg/dl, less stringent control of serum phosphate to target levels of 6–7 mg/dl will yield non-inferior rates of all-cause hospitalization among patients with ESRD undergoing hemodialysis.

2. **Main secondary:** Compared to strict phosphate control, less stringent control will reduce risk of all-cause mortality, enhance markers of diet and nutrition, and improve quality of life.

Overview of study design: An 'A' vs. 'B' trial in dialysis

Pragmatic, multicenter, cluster-randomized, open-label, non-inferiority, outcomes trial

- Compare effects of two different phosphate management strategies
  - Liberal P control, targeting 6–7 mg/dl, or
  - Strict P control, targeting <5.0 mg/dl
  - Facility-level cluster randomization: simplify trial execution, prevent within-facility "bleeding" of intervention arms, support remote study monitoring
- N = ~4400 patients being treated with hemodialysis at >100 facilities
- Partners
  1. Large national for-profit dialysis corporation: DaVita, Inc.
  2. Mid-sized national non-profit dialysis corporation: DCI, Inc.
  3. Small regional academic program: University of Utah
- Build on lessons learned from the TIME trial

DaVita®

DCI® Dialysis Clinic, Inc. A Non-Profit Corporation

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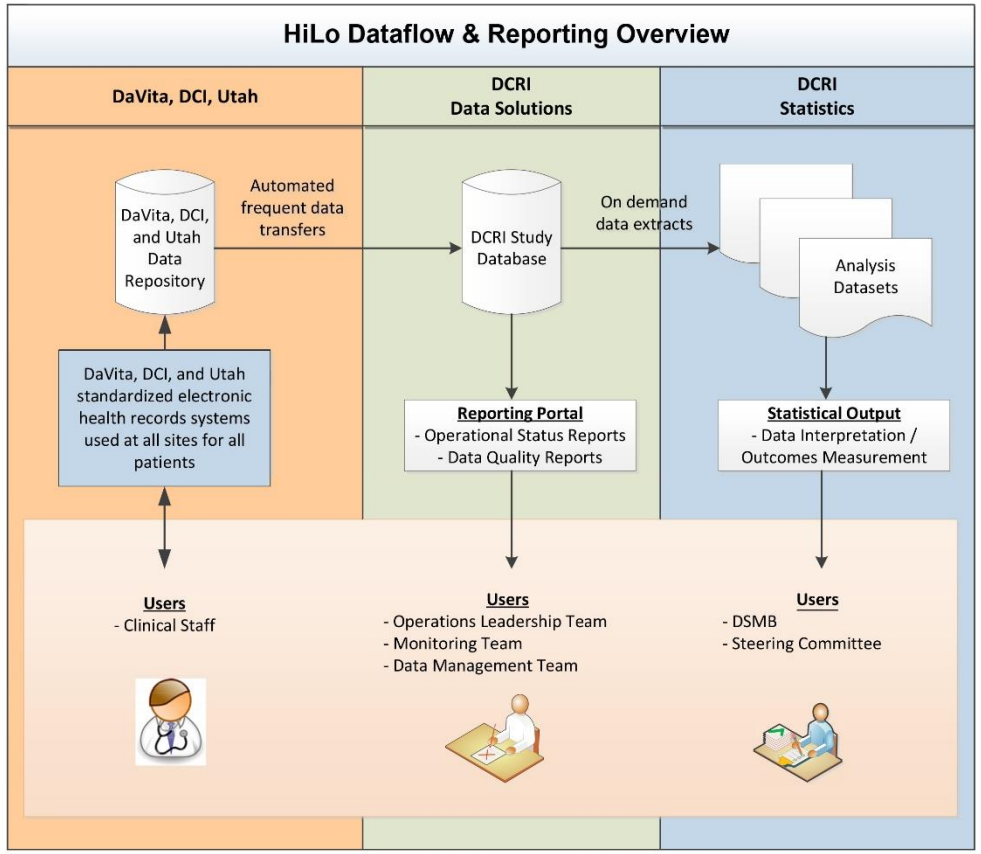
Outcomes

1. **Primary**
   - All-cause hospitalization rate: total counts per person-years of follow-up (continuous)
2. **Secondary**
   - All-cause mortality, time-to-event
   - Total inpatient hospital days per person-years of follow-up
   - Cause-specific hospitalizations in Medicare beneficiaries based on merging clinical data from HiLo with claims data from the CMS Virtual Research Data Center as in PROVEN
   - Diet & nutrition: serum albumin, protein catabolic rate (PCR)
   - Quality of life: F36-SF
   - Customized dialysis-phosphate Patient-reported outcomes (PROs) TBD during UG3 phase

Pragmatic features

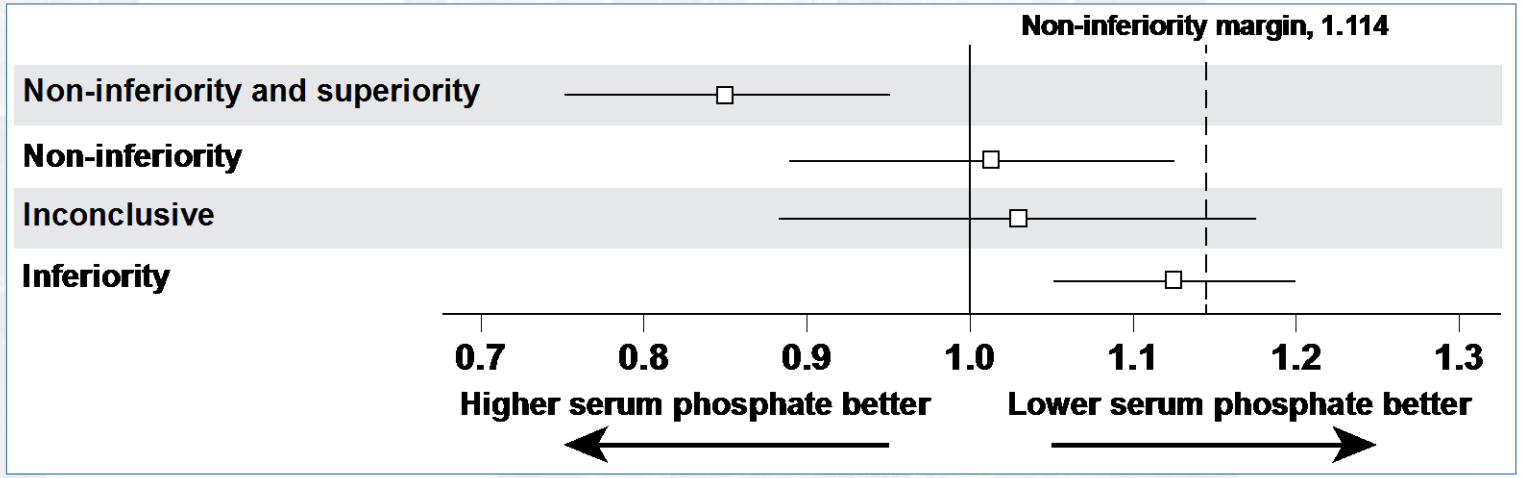
- Liberal eligibility criteria
- Internet/tablet-based eConsent for individual patient-level informed consent
- In-center dietitians implement the intervention
- Develop P management protocols with “look and feel” as in clinical practice
- Implementation of intervention using approved medications
- Use of EHR data to remotely & continuously monitor fidelity of interventions
- Use of EHRs to extract clinical data, outcomes
- Merge with Medicare claims for 2’ analyses

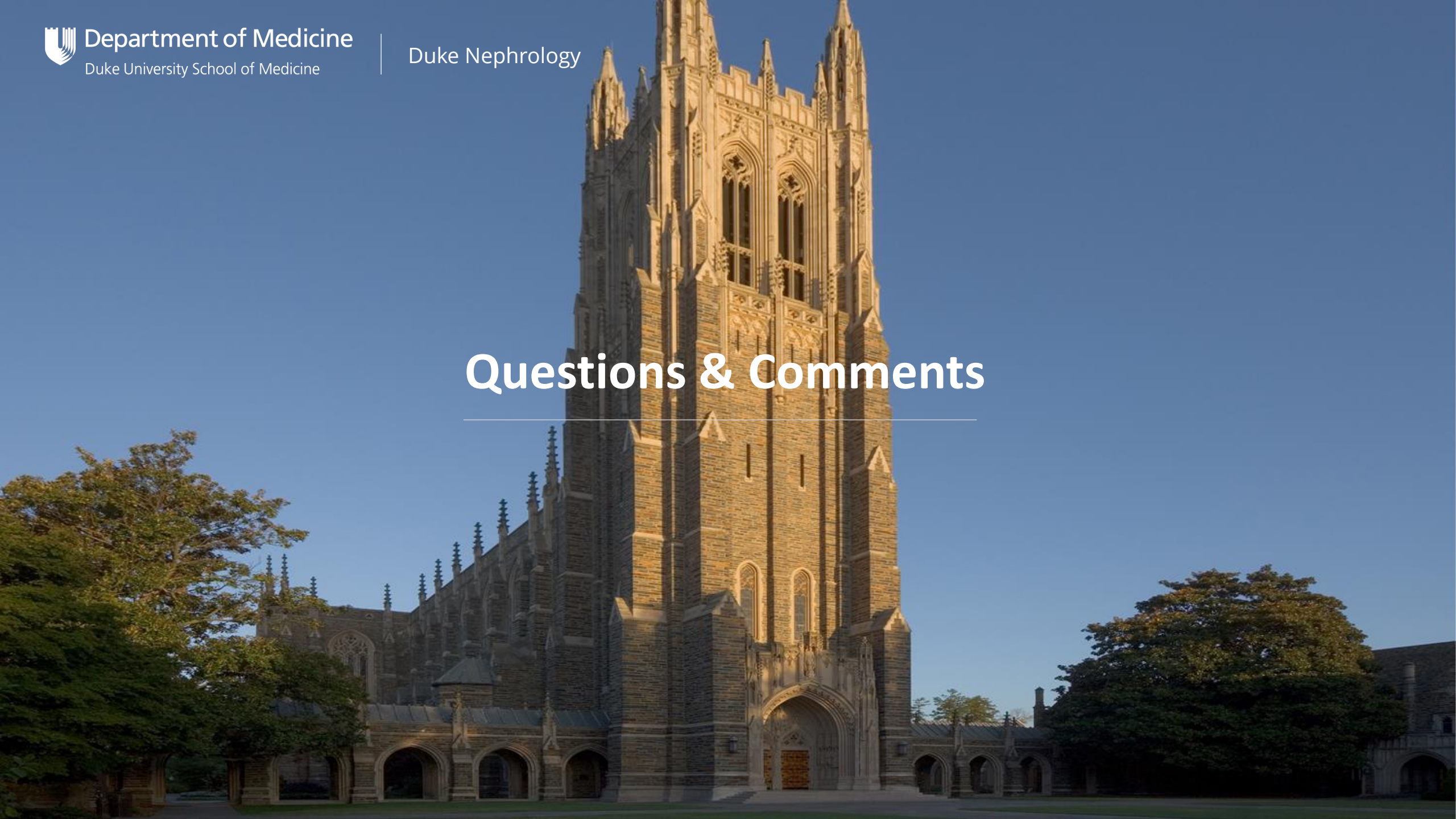
Bioinformatics platform



Possible HiLo results: Would rapidly influence ESRD practice

1. **Higher P target non-inferior:**
   - Contradicts guidelines
   - Relax P target, dietary restrictions
   - Reallocate dialysis resources
   - Reduce burden on patients
2. **Higher P target superior:**
   - Contradicts guidelines
   - Relax P target, dietary restrictions
3. **Higher P target inferior = low P target superior:**
   - Fail to reject null hypothesis
   - First definitive clinical trial-grade evidence for opinion-based guidelines for P management
   - For CMS: justify P as a validated dialysis quality-of-care measure
   - Support additional trials of P control in earlier stages of CKD





Questions & Comments