1. Full Title: Screening Strategies for Chronic Kidney Disease in US Populations
   
b. Abbreviated Title (Length 26 characters): Screening for CKD

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3. Timeline:

4. Rationale:
   Screening for chronic kidney disease (CKD) has the potential to significantly decrease kidney disease-
   related morbidity and mortality via early diagnosis and initiation of evidence-based therapies. However,
   whether patients should be screened for CKD remains highly controversial, as is the optimal target population
   in whom screening should be evaluated and implemented. Large randomized trials of screening have not been
   conducted in part because we do not know which populations to target. Cost-effectiveness analyses have
examined dipstick screening for proteinuria but have not examined estimated glomerular filtration rate (eGFR) or urine albumin-to-creatinine ratio (UACR)-based methods. While the American Diabetes Association and National Kidney Foundation recommend screening for CKD in high-risk populations, the United States (US) Preventive Services Task Force has no recommendation for CKD screening due to insufficient evidence.2-4

Discordant CKD screening recommendations exist due to the lack of evidence of the impact of CKD screening. We will address this critical public health question by simulating the potential benefits of screening for CKD across different populations by developing a kidney outcomes enhanced version of the Cardiovascular Disease (CVD) Policy Model, called the CKD Policy Model. The CVD Policy Model is a validated state-transition Markov model of CVD events and mortality in US adults.5 Markov modeling is an established technique that enables us to synthesize evidence as well as simulate and quantify the expected benefits of interventions on downstream outcomes.6 We will first estimate the probabilities of health state transitions across the span of CKD stages and progression by leveraging data from pooled longitudinal cohorts comprising over 65,000 individuals followed for up to 30 years with sequential measurements of eGFR and UACR. We will then adapt and enhance the CVD Policy Model for nephrology applications by incorporating categories of eGFR and UACR to model CKD stage transitions in two dimensions. The resulting CKD Policy Model will allow us to estimate the incidence of CKD, CVD events, end-stage renal disease (ESRD), and mortality under usual care. Using the same CKD Policy Model, we will then conduct a Markov decision analysis to project the impact of CKD screening and subsequent treatment initiation/intensification (via angiotensin converting enzyme inhibitor or angiotensin receptor blocker use, statin use, and intensification of antihypertensive regimen) upon identification of CKD.

5. Main Hypothesis/Study Questions:

Aim 1. To determine individualized probabilities of incident CKD and CKD progression based on patient demographics (age, sex, and race/ethnicity) and risk factors (diabetes, hypertension, and family of history of kidney disease) and develop the CKD Policy Model

Hypothesis 1: CKD screening based on individualized Atherosclerotic Cardiovascular Disease (ASCVD) risk will have a greater yield of newly diagnosed CKD cases per number screened compared with age-based, race/ethnicity-based, or risk factor-based screening.

Aim 2. To estimate the expected impact of different selective CKD screening strategies on CVD events, incident ESRD, and cause-specific and all-cause mortality using Markov modeling

Hypothesis 2a: To prevent a single CVD event, less than 100 persons with hypertension and diabetes will need to be screened for CKD.

Hypothesis 2b: CKD screening among persons with a family history of kidney disease and diabetes will gain more health over a lifetime time horizon (measured in quality-adjusted life years) and yield more deaths averted per number screened compared with other screening populations.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Aim 1 Study Design: Pooled longitudinal cohort analysis

Study Population: We will leverage the detailed longitudinal sociodemographic, comorbidity, treatment, laboratory (including eGFR and UACR), and outcomes data in each cohort within the National Heart, Lung and Blood Institute Pooled Cohorts Study, which includes: Atherosclerosis Risk in Communities (ARIC), Coronary Artery Risk Development in Young Adults (CARDIA), Cardiovascular Health Study (CHS), Framingham Heart Study Offspring Cohort (FHS-O), Health, Aging and Body Composition Study (HABC), Hispanic Community Health Study/Study of Latinos (HCHS-SOL), Jackson Heart Study (JHS), Multi-Ethnic Study of Atherosclerosis (MESA), and the Strong Heart Study (SHS).7,8
Outcomes: 1) Newly detected CKD, as defined by creatinine-based eGFR <60 or UACR >30 mg/g on two sequential occasions; and 2) Progression of CKD stage (Figure 1)

Covariates: Demographics: Age, race, sex, BMI, waist, height, weight, date of exam, time since entry of study, education, study center, geography

Comorbidities: Hypertension – SBP, DBP, History of hypertension, Hypertension medications, Hypertension status
Diabetes – Fasting and non-fasting glucose, fasting status, DM status, DM medications, DM self report, use of insulin, Hb A1c, oral glucose tolerance test
Lipidemia – total cholesterol, HDL, LDL, triglycerides, lipid medication, statin
Medical history – MI, CHD, stroke, heart failure, cancer, kidney disease
Smoking – smoking status, age started smoking, age stopped smoking, # cigarettes per day, pack-years of cigarette smoking
Medications – ACEi/ARB use, diuretics, beta-blockers

Laboratory: Serum creatinine, urine creatinine, urine albumin, UACR, eGFR CKDEpi

Outcomes: Death, CHD hard events, CHD all events, stroke (ischemic/hemorrhagic/all), CVD hard events, CVD all events, non-CVD death, heart failure, HFrEF/HFrEF, EF, time to death, time to CHD, time to stroke, time to non-CVD death, time to heart failure

Statistical Approach: These data have been previously harmonized across cohorts, and several studies have been published using this resource. We will harmonize UACR data across cohorts following the same strategy previously employed. We will use data from ARIC as well as CARDIA, CHS, FHS-O, Health ABC, HCHS-SOL, JHS, MESA, and SHS, to impute missing interim UACR measurements at each year of age, based on models including age, demographics, and other factors affecting UACR, with time-dependent factors imputed earlier in the process. To deal with the skewed distribution of UACR, we will use a two-stage procedure, first using a mixed logistic model to impute detectable UACR, and then using a linear mixed model to impute log-transformed UACR for observations with imputed detectable levels. For ARIC, sparse UACR measurements will entail substantial borrowing of information across cohorts, under the assumption that the UACR values do not depend on cohort, once available information on age, demographics, and other risk factors are taken into account. We will use descriptive statistics to evaluate the distribution of the exposures and outcomes of interest and relevant covariates using graphical displays and summary statistics. Covariates that are missing in more than 30% of participants will be excluded.

We will then model the data longitudinally using Markov incidence models. Univariable models will be constructed to determine the effect of each covariate on the risk of incident CKD. Covariates will be updated in a time-dependent fashion. At the end of Aim 1, we will have calculated probabilities of incident CKD and CKD progression for patients based on their individual demographics and risk factors, and in different candidate screening populations. For example, we will calculate the probability of incident CKD and CKD progression in populations such as: all adults above the age of 50, adults with diabetes, adults with hypertension, adults with diabetes and hypertension, and family history of kidney disease. We will determine the yield of newly diagnosed CKD cases based on varying screening strategies, such as by individualized Atherosclerotic Cardiovascular Disease (ASCVD) risk, age-based, race/ethnicity-based, or risk factor-based targeted screening. We will incorporate these probabilities supplemented with additional data from published meta-analyses, randomized trials including the Systolic Blood Pressure Intervention Trial (SPRINT), the United States Renal Data System, and National Vital Statistics into the current CVD Policy Model to develop the kidney outcomes enhanced CKD Policy Model.
**Power Calculation:** We estimate that 5% of the participants without CKD or CVD in our study will have incident CKD. We will have 80% power to detect an odds ratio of incident CKD of 1.06 or more per standard deviation increase in continuous predictors. For categorical predictors, we will have 80% power to detect an odds ratio of 1.20 or more if the prevalence of the predictor is 10%.

**Aim 2 Study Design:** The newly developed *CKD Policy Model* will be a microsimulation, Markov, state-transition model of U.S. adults programmed in TreeAge Pro software. Similar to the established CVD Policy Model, it will simulate individual lifetime exposures to CKD risk factors and annual risk CKD-related outcomes from age 20 to 89.\(^\text{15}\) It will include the health states of “well” (without CKD or CVD), incident CKD, CKD progression stages, three CVD states (coronary heart disease, heart failure, or stroke), ESRD, and mortality.

**Study Population:** Simulated nationally representative US population of adults from the National Health and Nutrition Examination Survey (NHANES). We will assemble a hypothetical cohort of 10,000 simulated individuals by taking repeated random draws, with replacement.

**Primary Interventions Modeled in Decision Tree Analysis:** 1) ACEi/ARB use; 2) statin use; and 3) blood pressure regimen intensification to the ACC/AHA 2017 hypertension guideline goal for CKD (<130/80 mmHg).

**Primary Outcomes:** Quality-adjusted life years (QALYs) gained from reduction in: 1) CVD Events: 2) Incident ESRD: and 3) Mortality. Secondary outcomes will be the number of CKD cases identified and deaths averted per 1,000 persons screened, which can be converted into a “number needed to screen.”

**Statistical Approach:** We will simulate a Markov decision analysis using the *CKD Policy Model* developed in Aim 1. Based on Aim 1 analyses, each simulation cohort member will be assigned to an eGFR lifetime trajectory, depending on their demographic characteristics and risk factors. Random effects will account for inter- and intra-individual eGFR variability over time. Modifiable components of the model will include population distributions, risk factor levels and distributions, risk factor (beta) coefficients, disease event rates, and mortality rates. Simulated individuals will receive interventions based on current guideline recommendations, accounting for baseline medication use.\(^\text{16-19}\) Beta coefficients of the association of risk factors with ESRD and mortality rates will be assumed to have a normal probability distribution. We will assume that effects of the covariates on outcomes are independent.

Parameters will be explored simultaneously, resulting in a range of parameter combinations that vary based on feasibility, available resources, choice of outcome, and the expected efficacy of the intervention. Standard methods will be used to simulate placebo effects and potential decay in treatment effect over time (declining medication adherence or informative drop-out).

**Exploratory and sensitivity analyses** will be performed using Monte Carlo simulations, varying key assumptions and estimates. Sensitivity analyses will compare new CKD cases and CVD events, ESRD incidence, and deaths averted; QALYs gained; changes in time-to-CKD progression and time-to-ESRD; and lifetime chronic treatment and acute event costs over a range of the following parameters: age at screening initiation, frequency of screening, treatment uptake, and a range of treatment efficacy.

**Methodologic Limitations**
Due to the cohorts’ initial enrollment criteria, there may be “healthy participant bias” and “survivor bias” among the oldest participants. However, many of the cohorts have accrued >10 years of follow-up, and we will be able to capture disease onset on a lifetime horizon. We will also consider using inverse probability weighting to address these potential biases.

**Summary/conclusion:** The overall goal of this proposal is to establish an evidence-based framework for developing potential CKD screening strategies, and ultimately inform the design of a future pragmatic CKD screening trial. To achieve this goal, Aim 1 will answer the initial critical question in CKD screening – How many new cases of CKD would screening yield in a given target population? Aim 1 will determine the
probabilities of incident CKD and CKD progression in various candidate screening populations over a multi-
decade period; these results will serve as inputs for our Markov decision analysis in Aim 2. Aim 2 will quantify
the impact of CKD screening on downstream outcomes of CVD events, incident ESRD, and mortality. The
results of this research will identify the optimal age and risk characteristics to guide patient selection for first
CKD screening and the optimal repeat screening frequency in at-risk patients.

7.a. Will the data be used for non-CVD analysis in this manuscript?  _X_ Yes  ____ No

    b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value
       RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD
       Research” would be used?  _X_ Yes  ____ No
       (This file ICTDER has been distributed to ARIC PIs, and contains
       the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?  ____ Yes  _X_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be
    used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage
    DNA”?  ____ Yes  _--_ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript
    proposals and has found no overlap between this proposal and previously approved manuscript
    proposals either published or still in active status. ARIC Investigators have access to the publications
    lists under the Study Members Area of the web site at:
    http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

    _X_ Yes  ______ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead
    authors of these proposals for comments on the new proposal or collaboration)?

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study
    data?  ____ Yes  _X_ No

11.b. If yes, is the proposal
    A. primarily the result of an ancillary study (list number* __________)
    _X_ B. primarily based on ARIC data with ancillary data playing a minor role (usually control
    variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at https://www2.cscc.unc.edu/aric/approved-ancillary-studies

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not
    submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript
    proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the
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