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PREVALENCE AND SOCIAL DETERMINANTS OF CHRONIC KIDNEY DISEASE AMONG ACTIVE AND RETIRED MILITARY PERSONNEL AND ADULT DEPENDENTS

by

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Dissertation submitted to the Faculty of the
Doctor of Public Health Graduate Program
Uniformed Services University of the Health Sciences

UNIFORMED SERVICES UNIVERSITY, SCHOOL OF MEDICINE GRADUATE PROGRAMS
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APPROVAL FOR THE DOCTOR OF PHILOSOPHY IN PUBLIC HEALTH DISSERTATION IN THE DEPARTMENT OF PREVENTIVE MEDICINE AND BIOSTATISTICS

Title of Thesis: "Prevalence and Social Determinants of Chronic Kidney Disease among Active and Retired Military Personnel and Adult Dependents"

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December 3, 2020

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ACKNOWLEDGMENTS

First, I must acknowledge and thank my Dissertation Advisor, Dr. Tracey Koehlmoos, whose pragmatic advice and scientific guidance made this project possible. Her commitment to my project, ongoing support and wise insights enabled me to balance personal, professional and academic demands in order to accomplish this goal. I thank the entire Comparative Effectiveness and Provider Induced Demand Collaboration (EPIC) project team, especially Lindsay Grunwald, Amanda Banaag and Jessica Pope, who introduced me to the Military Health System Data Repository and whose contributions to this work were essential in many ways.

I also thank my Dissertation Committee Chair, Dr. Eric Marks, and committee members, Dr. Andrew Narva and Dr. Cara Olsen, who provided thoughtful feedback at each step of this process. Their input and insights were instrumental to the success of this project. I would particularly like to thank Dr. Andrew Narva, who has been a significant scientific and personal mentor to me. Dr. Narva encouraged me to take my current job at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), which changed the course of my career and set me on a path to pursue science. He encouraged me to return to school to seek my PhD and pointed me in the direction of USU. I quite literally would not be where I am today without his guidance, encouragement, humor and support.

I also thank my colleagues at the NIDDK, who have granted me tremendous flexibility and shown me substantial support in seeking this PhD. I am humbled by the brilliance and dedication of my NIDDK colleagues, and I continue to learn from them every day. In particular, I would like to thank Dr. Robert Star, who has fought for my

career and my scientific interests in many ways, Dr. Paul Kimmel, who has sought numerous opportunities for me to advance my skills and my career, and Dr. Tamara Bavendam, who has given me an up close view of what it looks like to shatter glass ceilings.

Finally, I thank my family, who motivate me every day to work hard. A huge thank you to my husband, Dr. Joshua Bunger, who picked up the slack at home while I was hitting the books, and to my children—Jonas and Astrid—for letting mama get her work done and for only sometimes interrupting my virtual classes. I also thank my sisters and parents, who supported me and kept me sane throughout this process. I love you all!

DEDICATION

To Jonas and Astrid. Thank you for sharing me with my studies. I hope I make you proud.

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ABSTRACT

Prevalence and Social Determinants of Kidney Diseases among Active and Retired Military Personnel and Adult Dependents

Jenna M Norton, MPH, PhD Candidate, 2020

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Abstract

Chronic kidney disease (CKD) is common and burdensome in the general U.S. population. However, little is known about CKD in the Military Health System (MHS). While clear associations exist between health-impeding social determinants of health and CKD prevalence in the general U.S. population, whether such associations persist under the universal health care coverage provided through the MHS is not clear. To better assess the burden of CKD in the MHS, this project developed and validated a laboratory-value-based electronic phenotype to improve sensitivity for detecting CKD from the electronic health record and applied it to data from the MHS Data Repository (MDR) for fiscal years 2016 to 2018. We conducted a cross-sectional analysis to determine the prevalence of CKD in adult MHS beneficiaries and to describe the relationship between health-impeding social determinants of health and CKD prevalence. Of 3,330,893 MHS

beneficiaries, 3.2% (105,504 people) had CKD identified either by ICD-10 code or the e-phenotype. Of those with CKD, only 37% had an ICD-10 code for CKD recorded in the MDR. Of note, 60% of individuals with coded CKD did not have lab values indicative of CKD recorded in the MDR. Individuals with uncoded CKD were on average younger, more likely to be female and active duty, and less likely to be of Black race or to have diabetes or hypertension. In models adjusted for suspected confounders, Black beneficiaries had 1.67 times higher odds of prevalent CKD compared to their white counterparts. Compared to senior officers, senior enlisted beneficiaries had higher 1.7 times higher odds of CKD and junior enlisted beneficiaries had 1.3 times higher odds of CKD in confounder-adjusted analyses. Unexpectedly, single beneficiaries had lower odds of CKD than married beneficiaries in confounder-adjusted analyses. Decreasing zip code level median household income was associated with increasing odds of prevalent CKD through all quintiles except the lowest. Prevalence of CKD in the MHS appears to be disproportionately high in individuals of Black race as well as in those of low socioeconomic status. However, CKD is less likely to be coded in individuals who are traditionally considered lower risk for CKD, including younger adults, females, people of non-Black race, and those without diabetes or hypertension. Research and clinical quality improvement efforts are needed to improve detection and coding of CKD in the MHS, as well as to address the racial and SES CKD disparities present in the system.

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CHAPTER 1: BACKGROUND

INTRODUCTION

Defining Chronic Kidney Disease

Chronic kidney disease (CKD) is characterized by progressive and long-term loss of kidney function. The *Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for Chronic Kidney Disease* (1) defines CKD as "abnormalities of kidney structure or function, present for >3 months, with implications for health." In clinical settings, kidney function is assessed using the estimated glomerular filtration rate (eGFR), which is calculated from serum creatinine using population-based estimating equations, including the Modification of Diet in Renal Disease (MDRD) (2) and CKD-epidemiology (CKD-EPI) (3) equations. An eGFR < 60 mL/min/1.73m^2 is indicative of CKD (1). Structural damage to the kidney may be identified through presence of albuminuria, abnormalities of urine sediment, electrolyte abnormalities due to tubular disorders, histological abnormalities, structural abnormalities detected through imaging, or a history of kidney transplantation (1). The urine albumin-to-creatinine ratio (UACR) is the preferred measure for screening, assessing, and monitoring kidney damage in the clinical setting, as it is non-invasive and—unlike the dipstick urine albumin test—controls for variation in urine concentration (4). A UACR of ≥ 30 mg/g is indicative of CKD. The duration of greater than 3 months for decreased eGFR and/or elevated UACR is specified in the CKD definition to establish chronicity of disease, distinguishing CKD from acute kidney injury (AKI). CKD often progresses toward kidney failure, typically defined as an eGFR < 15 ml mL/min/1.73m^2 (1). When

kidney failure is treated by dialysis or transplant, it is defined as end-stage renal disease (ESRD) by the Centers for Medicare and Medicaid Services (CMS), which provides Medicare coverage for eligible U.S. citizens who reach ESRD, after a 90-day waiting period (5).

Kidney Diseases in the Military Population

Very little research has been conducted to understand the incidence or prevalence of CKD in military personnel and their dependents. An interagency agreement (#16FED1604638) was established between the Centers for Disease Control and Prevention (CDC) and the Uniformed Services University of the Health Sciences (USU) to assess the burden of kidney disease within the Military Health System (MHS). This work identified for the first time the prevalence of CKD in the MHS at between 2.6% and 2.9% of the population based on diagnosis code data extracted from the Military Health System Data Repository (MDR) for the total Tricare population, and at 2.5% based on two abnormal laboratory values in the direct care population (6, 7). As expected, prevalence of CKD was lower in the active duty compared to non-active duty population and was elevated with increasing age, male (versus female) sex, and Black (versus non-Black) race. Among the active duty population, those with CKD were less likely to be officers than those without CKD (6). Consistent with studies in the general population, which suggest that use of diagnosis codes to assess prevalence of CKD may underestimate the true burden of the disease (8), diagnosis codes for CKD in the MHS had high specificity but low sensitivity for lab-defined CKD (7).

BURDEN OF CKD IN THE GENERAL POPULATION

Prevalence of CKD

The Centers for Disease Control and Prevention (CDC) estimates that more than 30 million American adults (about 15% of the US Adult population) are living with CKD based on presence of reduced eGFR or elevated albuminuria (9). These estimates are based on data from the National Health and Nutrition Examination Survey (NHANES). Due to the cross-sectional nature of NHANES, the CDC determines CKD based on a single random sample of eGFR and/or albuminuria and therefore, chronicity of disease cannot be established (9). As a result, the CDC estimates of CKD prevalence may overestimate the true population prevalence.

Racial and Ethnic Disparities in CKD

Racial and ethnic disparities have long been recognized in terms of both the prevalence of CKD and the risk for progression from CKD to ESRD. Non-Hispanic Black Americans have the highest age-adjusted prevalence of CKD at 18% compared to 13% of the non-Hispanic White population, while Hispanic Americans have an age-adjusted prevalence of CKD of 15%, based on estimates from the 2011 to 2014 NHANES sample (9). According to data from the United States Renal Data System (USRDS)—which uses data from NHANES, the Behavioral Risk Factor Surveillance System, the Optum Clinformatics™ Data Mart, the Veterans Health Administration, and Medicare to estimate rates of CKD and ESRD in the United States, the adjusted incidence of ESRD was 8.4 times higher among Native Hawaiians/Pacific Islanders, 3.0 times

greater in Black Americans, and 1.2 times greater in American Indians/Alaska Natives compared to White Americans (10). In the same year, ESRD incidence was 1.3 times greater for Hispanic Americans compared to non-Hispanic Americans (10). Among Black Americans—who account for 13% of the U.S. population but 30% of U.S. ESRD patients—the elevated incidence of ESRD is driven by a 3.5 times greater risk of progression from early CKD to ESRD compared to White Americans (10-12).

These racial and ethnic disparities likely result from interaction among poverty and associated poor social determinants of health, biologic factors, and clinical characteristics (13). The role of poverty in racial disparities in kidney outcomes are reflected in analyses of merged USRDS-Census data for 11,027 ESRD patients, which found elevated mortality rates for Black compared to White ESRD patients were attenuated in high versus low socioeconomic status (SES) neighborhoods after adjusting for baseline demographics, clinical characteristics, rurality, and access to care factors (14). Similarly, a study of 1.2 million patients (with and without CKD) from a 5% Medicare random sample found that greater poverty—measured by the proxy "buy-in" status—in Black compared to White beneficiaries fully accounted for the higher sex-and-age adjusted mortality in the Black patient group (15).

Outcomes Associated with CKD

Individuals with CKD experience substantial morbidity and mortality, including disproportionate rates of hospitalization (10). CKD is characterized by numerous serious complications, including cardiovascular disease (CVD), mineral and bone disorders, anemia, metabolic acidosis, malnutrition and AKI (10, 16-19). In general, these

complications become increasingly common as kidney function declines (16). Psychiatric illnesses—including depression, anxiety, organic disorders, dementias, substance abuse disorders, and schizophrenic disorders, among others—are common in patients with ESRD (20, 21). Less research is available on the total burden of psychiatric illnesses in non-dialysis dependent CKD; however, depression is common in this population (22-24). Patients across the spectrum of CKD and ESRD report reduced quality of life as a result of their disease (25, 26). In addition, CKD and ESRD place a substantial financial burden on the health system. In 2016, beneficiaries with CKD or ESRD cost Medicare more than $114 billion, representing 23% of total Medicare fee-for-service (FFS) spending (10).

RISK FACTORS FOR CKD AND ESRD IN THE GENERAL POPULATION

Demographic Risk Factors

Sex and Age

Data from NHANES suggest CKD is more common in women than men, with estimated prevalence rates of 16% and 13%, respectively (9). However, men progress more rapidly to ESRD compared to women (27, 28). The prevalence of CKD increases with age (10). However, the nephrology community remains divided regarding whether relatively small decreases in kidney function that tend to occur with increasing age reflect a disease state or normal aging processes (29-31).

Race and ethnicity

As discussed in the *Racial and Ethnic Disparities in CKD* section, several racial and ethnic minority groups experience elevated prevalence of CKD and higher rates of incident ESRD. Specifically, in 2015, the incidence of ESRD was 8.4 times higher

among Native Hawaiians/Pacific Islanders, 3.0 times greater in Black Americans, and 1.2 times greater in American Indians/Alaska Natives compared to White Americans (10). In the same year, ESRD incidence was 1.3 times greater for Hispanic Americans compared to non-Hispanic Americans (10). Additionally, Black Americans tend to progress to ESRD more rapidly than their White counterparts (10-12).

Clinical and Biological Risk Factors

Diabetes and Hypertension

Diabetes and hypertension have long been reported as the top two causes of ESRD in the United States; however, these conclusions have been based largely on the "primary cause of renal failure" reported to the Centers for Medicare and Medicaid Services by individual physicians (10). Because causal relationships cannot be definitively established through clinical judgement and confirmatory biopsies are rarely conducted in the clinical setting, such reports may overestimate the contribution of diabetes and hypertension to ESRD, instead reflecting ESRD patients who have co-existent—but not necessarily causal—diabetes or hypertension (10, 32). A retrospective cohort study to assess diagnostic accuracy for diabetes reported to CMS as the primary cause of ESRD found that more than 20% of cases reported as diabetic nephropathy did not meet KDOQI criteria for diagnosing diabetic nephropathy (32). For hypertension, growing evidence suggests APOL1 risk variants may account for some of the ESRD previously attributed to hypertension (33). As a result of these uncertainties, the USRDS stopped reporting data on the primary cause of ESRD beginning with its 2017 Annual Data Report, citing the unknown reliability of physician reported "primary cause of renal failure" (10).

However, causal mechanisms linking diabetes and hypertension to CKD have been identified and these conditions undoubtedly contribute to the burden of CKD. CKD is a microvascular complication of diabetes, with pathophysiology believed to stem from osmotic stress from sorbitol accumulation in cells, formation of advanced glycosylated end products in response to high blood glucose levels, oxidative stress due to free radical production from elevated blood glucose levels, and increased production of growth factors, such as vascular endothelial growth factor (34). Renal damage from hypertension is believed to result from barotrauma from the increased pressure on the renal vascular bed (35).

Glomerulonepritis Risk Factors

Glomerulonephritis (GN) has traditionally been considered the third most common cause of CKD, after diabetes and hypertension (36). GN is primarily immunologically-mediated and typically has an auto-immune basis (37). Common forms of GN include post-infectious GN (resulting from infections including Streptococcal infection, human immune deficiency virus (HIV), hepatitis and bacterial endocarditis, among others), IgA nephropathy, anti-glomerular basement membrane (GBM) antibody disease nephritis, Antineutrophil cytoplasmic antibodies (ANCA)-associated GN and lupus nephritis (37). Notably, infectious forms of GN are becoming increasingly rare in developed countries with the advent of antiretroviral treatment for HIV (37).

Genetics

The majority of CKD is likely the result of complex gene-environment interactions. The totality of genetic contributions to CKD is not fully understood, but

research is ongoing. While accounting for only a small portion of CKD, the autosomal dominant and autosomal recessive types of polycystic kidney disease have clear genetic underpinnings resulting from mutations in ciliary and cystogenes (38, 39). Further, recently identified APOL1 gene variants are believed to account for much of the increased risk of nondiabetic kidney disease in individuals of African descent (40). Presence of two APOL1 risk variants is associated with increased risk for elevated albuminuria (41), reduced eGFR (41, 42) and rapid progression of CKD (42, 43). However, even individuals with two APOL1 risk variants do not consistently develop CKD (44), suggesting APOL1 risk variants alone are not sufficient to produce disease. Instead, "second hits" (e.g., viral infections, social and environmental factors) are hypothesized to trigger development of progressive CKD in individuals with high risk APOL1 variants (45-48).

Social Determinants

The World Health Organizations defines the social determinants of health as the "conditions in which people are born, grow, live, work, and age"(49). Social determinants of health include a variety of contextual factors, such as housing quality and safety, access to transportation, proximity to healthcare centers, availability of safe places for physical activity, availability of paid leave for seeking medical care, access to grocery stores or other sources of healthful food, health insurance coverage status, level of support from social networks, and health literacy level, among others. Negative social determinants of health—or social risks—are fueled by poverty and combine and interact with clinical and biological factors to generate poor health outcomes, including CKD, by acting as barriers that affect a person's likelihood of exposure to disease-causing agents,

ability to participate in healthful behaviors and activities, exposure to stressors and resulting level of stress, and capacity for coping with stressors (13). Importantly, many social risks are exacerbated by systemic racial discrimination in the United States (13). Further, the impacts of negative social risks may span an individual's life course or even cross generations, as a result of epigenetic changes and developmental programming (50).

McLeroy's adaptation of the social ecological model to health promotion (51) provides a helpful framework for understanding the role of social determinants of health in disease. The model addresses the influence of public policy, community, organizational, interpersonal and individual domains on health, and contextualizes individual health factors as dependent on the interpersonal, organizational, community and public policy settings in which a given individual exists, which may act as barriers to or facilitators of health. For example, behaviors relating to healthy diet may depend on an individual's interest in healthy eating patterns, the dietary patterns among peers and others in the individual's social circles, the presence or absence of healthy food choices in the person's workplace, and the proximity of grocery stores and other fresh produce retailers in her or his community, which may depend on local zoning, infrastructure and economic policies.

Socioeconomic Status

Recent systematic reviews show significant associations between low socioeconomic status (SES) and increased incidence and prevalence of CKD and ESRD. In 2015, a systematic review and meta-analysis that included 35 studies with more than

800 thousand individuals with CKD and over 3.6 million total participants determined low SES is associated with both prevalent CKD—defined as presence of either reduced eGFR, elevated levels of urine albumin, or both—and incident ESRD (52). A more recent systematic review and meta-analysis published in 2018, which included 43 studies across multiple countries, showed increased incidence and prevalence of CKD, as well as progression from CKD to ESRD, were each associated with lower income and lower overall SES (53). Interestingly, however, incident CKD and progression of CKD were associated with lower occupation but not lower education, while prevalent CKD was associated with lower education but not lower occupation (53). Associations between income and CKD prevalence were stronger in the United States than in Asian, European, or Latin American countries (53). This difference in association may result from variation across these countries in provision of social support, health system structure, access to healthcare, cost of healthcare, standards of healthcare practice, cultures, lifestyles, or other potentially moderating factors.

While the association between individual SES and poor kidney outcomes are strong, relationships between area poverty and such outcomes are less clear. Results across numerous studies have been mixed, which may reflect differences in the size and diversity within the areas under study. Use of larger, less uniform regions, such as counties, may mask within area variability in terms of both availability of health promoting resources and overall wealth compared to use of smaller regions, such as census tracts. In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, incidence of ESRD among 23,314 participants was not associated with county level poverty after adjusting for age, sex, race, education and income (54).

Yet, merged data from the USRDS and U.S. Census for 1.4 million newly diagnosed ESRD patients showed individuals residing in a zip code with high (compared to low) poverty was associated with a 23% higher incidence of ESRD and faster rates of eGFR decline, after adjusting for age, sex, race/ethnicity, and time period (55). Adjusting for smoking status, alcohol intake, physical activity, BMI, hypertension, diabetes, total cholesterol, HDL cholesterol and lipid-lowering medication use attenuated the association, but it remained significant for incident ESRD (but not CKD) (56). These results suggests that such lifestyle and clinical factors may contribute to the relationships between area poverty and both CKD and ESRD, but they may not fully explain the association between area poverty and ESRD.

Similarly, risk of incident CKD and ESRD rose in a dose-response fashion with increased level of neighborhood deprivation (assessed at the zip code level) among 14,086 ARIC study participants with a baseline eGFR in the normal range, after adjustment for age, sex, race and baseline eGFR. Further, in analyses adjusting for age, gender, study site, baseline creatinine, lifestyle risk factors, diabetes, hypertension, and individual SES using data from the Cardiovascular Health Study, living in a census tract in the lowest SES quartile was associated with 50% higher risk of progressive CKD over four years, compared to living in a census tract in the highest SES quartile, among 4,735 participants aged 65 and older (57). These results indicate area poverty may increase risk of progressive CKD independently from individual poverty.

Low SES is also associated with higher mortality risk in individuals with CKD. Data from the prospective REGARDS cohort study found that among 2,761 participants with CKD, those with a baseline household income in the lowest group, defined by an

income of less than $20,000, had a higher hazard of all-cause mortality compared to those in the highest household income group, defined by an income of greater than $75,000 (58). Among 10,392 White individuals with ESRD identified through the UK Renal Registry, residents of high social deprivation areas, which were characterized by low home and car ownership, high unemployment, and overcrowding, had poorer survival than their counterparts in less deprived areas after adjustment for age, gender, and cause of renal failure (59). In an Irish tertiary center, being in the lowest compared to highest SES quartile—measured by a spatial index of deprivation—was associated with lower survival in 1,794 incident dialysis recipients, after adjusting for age, gender, and dialysis modality (60). Further, in an analysis of 589,036 individuals with ESRD using merged USRDS and Census data, those living in a higher, compared to lower, income area had increased survival, after adjusting for sex, age, race, year of dialysis initiation, smoking, comorbidities, insurance and employment status, area income inequality and area racial segregation (61).

Neighborhood Resources and Environment

As suggested by McLeroy's Social Ecological Model (51), the community context in which an individual lives can have significant influence on her or his health outcomes. The area where an individual resides will determine what health promoting resources she or he is able to access and the hazards to which she or he is exposed, with potential implications for CKD. Of particular relevance to CKD is the food environment in which an individual lives, given the complex nature of dietary recommendations in CKD and the potential influence of dietary intake of protein, sodium, potassium, phosphorus and other nutrients on kidney outcomes (62). High poverty areas are often

characterized by low availability of fresh fruits and vegetables and high availability of processed foods containing sodium and phosphorus. Diets low in fresh fruits and vegetables are associated with increased acid load, which has been associated with progression of CKD to ESRD (63), reduced eGFR (64) and increased albuminuria (64). Among Chronic Renal Insufficiency Cohort Study participants, individuals in the lowest income groups had higher serum phosphate concentrations than participants with the highest incomes (65), and elevated serum phosphorus levels are associated with mortality in people with CKD (66).

Neighborhood of residence may also influence exposures to potential nephrotoxins. Evidence is growing to support associations between low-level environmental exposure to lead, cadmium, and mercury and onset of CKD; indeed, such exposures are widely hypothesized contributors to the epidemic of CKD of unknown origin found primarily in poor, agricultural communities in South America, India and Egypt (67, 68). Compared to high income communities, low income areas have more toxic waste sites (69), poorer air quality (70, 71), elevated crime rates (72), and poorer quality of housing, including contamination with lead, molds, and other toxins (73).

Stress

Stress presents another pathway through which poverty and social risks may lead to CKD. When the body is under physiologic or psychologic stress, the body responds with increased activity in the endocrine, cardiovascular, metabolic, immune and autonomic systems to maintain allostasis—a state of physiologic homeostasis achieved when stress responses are appropriately matched to stressor demands (74). Exposure to social risk is widely acknowledged to increase stress, leading to an elevated allostatic

load, characterized by repeated and/or continuously elevated activity in stress response systems (74). During prolonged exposure to stress, an elevated allostatic load may overwhelm the body's ability to achieve allostasis, contributing to health consequences (74-76). Stress is particularly problematic in persons with CKD. Reduced kidney function in CKD impedes the ability to adequately clear and metabolize stress hormones through the kidneys, resulting in elevated hormone levels and prolonged stress responses (20). As a result of consistently high stress hormone levels, individuals with CKD are suspected to have a down regulated stress responses and disproportionate allostatic load (20).

Stress may also fuel negative coping behaviors, such as smoking and overeating, which are widely recognized to lead to poor health outcomes. Support for a pathway from social risks to increased stress to health-compromising behavior was demonstrated in a cross-sectional study of 1,010 low SES individuals receiving care at a publicly-funded sexually transmitted disease (STD) clinic (77). The study demonstrated an association between poverty and poor health that was mediated by perceived stress. Further, perceived stress fully accounted for a relationship between low SES and health-compromising behaviors (77).

While a 2009 systematic review of 26 studies that explored relationships between poverty and stress in a variety of groups concluded that existing evidence of an association between the two was weak, the authors suggested that inconsistent findings across studies were likely a result of differences in measurement methods for assessing stress (e.g., biomarkers versus self-report, weekday versus weekend, diurnal vs life-course variation) and SES (e.g., income versus education versus occupation) or differences in study populations (78). Since that study, the body of evidence showing

associations between poverty and stress has grown dramatically—with numerous studies suggesting a strong association (79-83).

Stress has been associated with reduced quality of life in adults with CKD (84), and poor quality of life is in turn associated with negative kidney outcomes (85). Individuals with CKD appear to have elevated serum cortisol levels, which increase as eGFR decreases (86, 87); however, the cross-sectional design of studies showing this relationship prohibit ability to discern whether stress contributes to reduced kidney function, worsening CKD leads to increased stress, or both. In a randomized, non-blinded trial of mindfulness-based stress reduction techniques in people with diabetes and elevated urine albumin levels, individuals in the intervention groups had lower UACR and blood pressure at one-year follow up than their counterparts in the control group; however, differences were lost at 2 and 3 years follow up (88).

Social support

Social support includes a variety of forms of help—which include emotional (e.g., empathy), informational (e.g., advice) and instrumental (e.g., transportation to health appointments) assistance—which may be provided by family, friends, neighbors, community members, and/or health care providers, among other. Social support may enable individuals to successfully access healthcare and engage in self-management activities by providing a wide array of assistance, ranging from financial help to pay for care and/or costs associated with reaching care; transportation to and from healthcare appointments, social service programs, or health promoting resources (e.g., grocery stores); advice on how and where to access care; reinforcement of positive health behaviors; and company at medical appointments, among many other forms of support. A

cross-sectional study of data on 18,980 Minnesota and Tennessee residents from the Behavioral Risk Factor Surveillance System found an association between limited social support and delay of necessary medical care, which remained after adjusting for demographics, socioeconomic status, comorbidities and access to care (89). In a cross-sectional assessment of 410 CKD patients in Taiwan with various levels of kidney function, those with greater social support were better able to manage their disease (90). Similarly, dialysis recipients with higher social support levels have improved dietary, fluid (91) and medication (92) adherence and better self-management practices (93). A systematic review of 37 studies aiming to identify potential barrier to treatment adherence in kidney transplant recipients identified an association between low social support and poorer adherence (94).

Poverty is associated with smaller, less robust social support systems. In a cross-sectional study of 410 African American and Hispanic/Latina women in Texas, neighborhood disadvantage—defined as a composite measure including low-wage jobs, joblessness, percent of professionals and managers, percent high school graduates, female headed households, and poverty—was associated with less robust peer social support (95). Another cross-sectional analysis of 4,814 middle aged, urban-dwelling adults in Germany found that low, compared to high, income and education were each associated with poor social support (96).

Social support may also provide a source of empathy or sense of being understood that may alleviate stress and mitigate its negative health consequences (20, 97), and buffer against depression in kidney disease. Depression is more common among ESRD patients with lower levels of social support (98, 99) as well as in transplant recipients

with negative perceptions of social support (100). In individuals with ESRD, social support is associated with improved quality of life (101, 102) and appears to mediate the association between depression and poor quality of life, weakening the association in those with strong social support networks (103). Robust social support networks are also associated with improved immune function (104).

Among 6,916 middle-aged adults with non-albuminuric diabetes followed prospectively for 5.5 years, a small social support system was associated with incident CKD and mortality (105), with a population-attributable fraction of 6.28% for mortality (106). Social support from less than 13 people and poor satisfaction with social support each were associated with psychological distress in a cross-sectional study of 382 adults with CKD in Sri Lanka (107). In addition, lower levels of social support have been associated with increased hospitalizations (102, 108), elevated mortality (109, 110), reduced patient satisfaction (102), and poorer psychological (111) and general well-being (112) in dialysis patients.

Healthcare Access

The ability to access and receive high quality healthcare has clear influence on health outcomes in CKD. Health insurance coverage is a common metric for access to care, and indeed, un- and under-insured individuals with CKD are less likely to access care and more likely to have poor health outcomes. In an analysis of data from 903 NHANES participants aged 18-64 who had albuminuria, lack of insurance and public insurance coverage were each associated with elevated all-cause mortality compared to coverage with private insurance (113). Lack of health insurance was associated with increased risk of ESRD incidence and death, after adjusting for age, race, ethnicity,

education level, and smoking status, in 86,588 participants of the Kidney Early Evaluation Program (114).

A systematic review of 24 studies of people with non-dialysis-dependent CKD and 34 studies of people with ESRD, which in combination assessed more than 8.9 million participants across 10 countries, found that both un- and under-insurance in both populations were associated with reduced access to necessary healthcare services, including nephrology care in CKD and cardiovascular disease care in both populations (115). Among adult kidney transplantation recipients identified through the Scientific Registry of Transplant Recipients, those covered by Medicaid were listed with more severe organ failure and shorter transplant wait times and had lower post-transplantation survival compared to their privately insured counterparts (116). In a study using USRDS data for 669,206 hemodialysis patients who initiated treatment between 2007 and 2012, ESRD patients with dual eligibility for Medicare and Medicaid—a proxy measure for poverty—were significantly less likely than individuals with Medicare alone to initiate dialysis with an arteriovenous fistula, the preferred method of vascular access in dialysis (117). These results suggest that individuals with dual coverage may receive delayed access to nephrology care. Similarly, dual Medicare/Medicaid eligibility, higher area poverty by zip code, Black race and Hispanic ethnicity were each associated with lower likelihood of pre-ESRD nephrology care in adjusted models among a cohort of more than 700,000 dialysis patients (118).

However, health insurance is a necessary but insufficient resource to ensure access to care. In the Medicare population, where coverage is universal, low income is associated with lower use of services (119). Similarly, studies in countries with universal

healthcare coverage, including the UK, Denmark and Australia, have found that low SES is associated with increased CKD prevalence, elevated ESRD incidence, and reduced dialysis survival – indicating that presence of health insurance alone is not sufficient to mitigate the effects of poverty on CKD (59, 120-124). Universal healthcare coverage through the Veteran's Health Administration (VHA) has been shown to reduce racial disparities in some but not all health outcomes. A systematic review of 25 studies assessing racial disparities in mortality within the VHA found that mortality among black beneficiaries was similar to or lower than for white beneficiaries despite disproportionate mortality rates in black Americans in the general population; however, mortality rates in black compared to white beneficiaries remained modestly elevated for specific conditions including CKD, diabetes, HIV, and stroke, among others (125). Further, in a sample of 56,767 veterans with stage 3 or 4 CKD, black veterans were more likely than their white counterparts to progress to ESRD despite universal access to care and higher rates of nephrology referral for black compared to white veterans (126).

Andersen's Behavioral Model of Health Services Use provides a framework allowing us to consider an individual's ability to access healthcare from a broader perspective (127, 128). The model suggests that healthcare access is determined by individual and contextual factors that predispose (e.g., demographics, education, community composition, cultural norms), enable (e.g., income, insurance status, transportation access, proximity to care), and generate real or perceived need for (e.g., functional state, occupation-/traffic-/crime-related injury) healthcare (127, 128). Barriers to care identified under Andersen's model include co-payment and out-of-pocket costs, limited availability of transportation to/from healthcare appointments, lack of paid sick

leave from work, absence of child care, poor health literacy or numeracy, and lack of a social support network.

Individuals with health insurance coverage have cited such issues in accessing care. Among publicly insured adults enrolled in Minnesota Health Care Programs, reported barriers to care included inability to cover out-of-pocket costs, transportation limitations, clinic hours that conflicted with other responsibilities, and lack of childcare (129). A population of majority low income, African American "safety net" CKD patients who were receiving primary care in Buffalo, NY reported similar barriers despite insurance coverage; these included transportation difficulties, financial challenges and lack of work leave (130).

Both health literacy and numeracy are important skills in making optimal health decisions and contribute to an individual's ability to access and use healthcare resources. Health literacy is defined as the degree to which individuals have the capacity to "obtain, process, and understand basic information and services," (131) and health numeracy is defined as the ability to "access, process, interpret, communicate, and act on numerical, quantitative, biostatistical, and probabilistic health information" (132). Poor health literacy is associated with limited education, lack of insurance and public rather than private insurance (133). The dearth of plain language information on CKD and the high prevalence of low health literacy and numeracy in the CKD population have been recognized as major barriers to successful patient education and self-management (134).

Individuals with poor health literacy are more likely to have lower levels of CKD knowledge (135), reduced kidney function (136, 137) and lower capacity for self-management (90) and are less likely to receive a kidney transplant than individuals with

higher literacy levels (138). In the UK, individuals with kidney failure who had poor health literacy were more likely to be of low socioeconomic status and were less likely to be placed on the transplantation waiting list or to receive pre-emptive or live donor transplantation (139). Low health literacy has also been associated with poor blood pressure control (140), reduced self-management ability (141, 142), increased hospitalizations (142), and elevated mortality in individuals with ESRD (143). In 187 late stage CKD or ESRD patients followed prospectively, higher health numeracy was positively associated with receipt of a transplant and active waiting list status (144). Barriers to accessing health information may be exacerbated by reduced access to health information via digital channels, particularly as the healthcare system increasingly transitions to electronic health records (EHR). Among more than 2,000 nephrology clinic patients, EHR portal users were less likely to be Black, single, privately insured, and wealthy (145).

Developmental Programming

Developmental programming has been defined as "the ability of the normal developing organism to undergo durable changes in response to environmental conditions without change in DNA sequence" (50). Both epidemiologic and animal data suggest developmental programming may contribute to CKD as a result of maternal-fetal undernutrition (MFUN), maternal-fetal energy excess (MFEE), and maternal-fetal psychosocial stress (MFPS) (50). In animal studies, MFUN has been associated with low birth weight, poor postnatal growth, and heightened risk of hypertension later in life (146). Poor nutritional status in pregnant women is associated with low birth weight (147, 148), which in turn is associated with increased risk of obesity, hypertension, diabetes,

cardiovascular disease and CKD in adulthood (149-156). MFUN, MFEE and MFPS may contribute to CKD through multiple pathways, including 1) altered epigenetic regulation of gene expression that results in low nephron number, creating a mismatch between kidney capacity and excretory demand 2) perturbed postnatal energy homeostasis, contributing to increased growth and excretory load, and 3) elevated risk for diabetes and hypertension—the leading cause of CKD—in progeny (50, 157-161). Because all three of these mechanisms elevate stress on the kidneys, they may interact additively or synergistically, furthering risk for CKD (50).

MFUN, MFEE and MFPS and their effects on birthweight in offspring occur more frequently among women living in poverty compared to their wealthier counterparts (50). In fact, the severe socioeconomic disparities that occurred during the Industrial Revolution in England and Wales—and the disproportionate rates of coronary death experienced later in life by children born during that time period—first led researchers to recognize the phenomenon of developmental programming (162). More recently, a study analyzing nationally representative data sets from the United States, the United Kingdom, Canada and Australia—which included data for 37,620 singleton births—showed a dose-response relationship between income and birth weight, wherein prevalence of births of less than 2500 grams increased with decreasing income quintiles (163). These associations were stronger in the U.S., which—of the countries studied—has the scantest social support systems (163). A Canadian longitudinal cohort of 2,068 maternal-infant pairs found lower neighborhood SES increased the risk of high pre-pregnancy BMI in the mothers, and in turn, increased rates of macrosomia and large for gestational age (LGA) infants (164). Among 1,498 women with gestational diabetes, presence of maternal

psychosocial vulnerability—which was assessed through material and monetary assets, social networks, healthcare access and leisure time—was associated with LGA offspring (165).

Lifestyle and Behavioral Risk Factors

Several behavioral factors—including limited physical activity, poor dietary habits, and smoking—may increase risk for CKD and poor CKD outcomes, either directly or by increasing the risk for conditions such as diabetes and obesity that in turn increase the risk of CKD. However, it is important to understand and address these behaviors with consideration of an individual's social and environmental context. As discussed by McLeroy in his work developing the social ecological model of health promotion, "…use of terms like 'lifestyle' and 'health behavior' may focus attention on changing individuals, rather than changing the social and physical environment which serves to maintain and reinforce unhealthy behaviors"(51). The area where a person lives largely determines the availability or absence of health-promoting resources (e.g., sidewalks, grocery stores carrying fresh produce) as well as the relative saturation of health limiting factors (e.g., fast food restaurants, air and water pollution). Low income communities are less likely to have walkable areas, safe places for physical activity, and sources of healthy food (166-170), but are more likely to have fast food restaurants and convenience stores (171), compared to high income areas. Therefore, while evidence suggests these behaviors do contribute to CKD—as discussed below, focusing health promotion and CKD prevention efforts on these health risk or promoting behaviors

without addressing the contextual barriers and facilitators that encourage or inhibit such behaviors is likely an ineffective strategy.

Physical Activity

A cross-sectional analysis of 20,740 NHANES participants found that higher levels of physical activity—measured using an accelerometer—was associated with higher kidney function levels (172). A systematic review and meta-analysis of ten studies including 505 participants that assessed the effect of physical activity on blood pressure in CKD found significant improvements in blood pressure in the short term (up to 26 weeks); however, differences were lost with longer term follow-up in the range of 48 to 52 weeks (173). A systematic review of the impact of physical activity on mortality in CKD found a consistent association between increased physical activity and reduced mortality risk in CKD (174). The efficacy of physical activity in management of diabetes (175) and hypertension (176) has been clearly demonstrated; therefore, physical activity may play a role in preventing onset and progression of CKD by improving control of blood pressure and blood sugar.

Diet

A variety of dietary factors—such as high animal and total protein intake, low fruit and vegetable intake, high dietary acid load, and low fiber intake—are associated with poor CKD-related outcomes, including increased risk of CKD incidence and more rapid progression of CKD to ESRD. In 3,071 women from the Nurses' Health Study, those in the highest quartile for Western diet pattern—which is characterized by higher intake of red and processed meats, saturated fats, and sweets—were more likely to have incident albuminuria and rapid eGFR decline compared to those in the lowest quartile

(177). In the ARIC cohort study, a Dietary Approaches to Stop Hypertension (DASH) diet pattern was associated with reduced risk of incident CKD, after adjusting for demographic characteristics, established kidney risk factors, and baseline kidney function (178). Specifically, high red and processed meat intake was associated with increased risk of CKD, while high consumption of nuts, legumes, and low-fat dairy products was associated with reduced CKD risk (178). In a cohort study of 2,255 post-myocardial infarction patients—for whom dietary data were collected via a biomarker-validated food frequency questionnaire—incremental increases in dietary protein intake were associated with corresponding decrements in eGFR, after adjusting for age, sex, total energy intake, smoking, diabetes, systolic blood pressure, renin-angiotensin system blocking drugs and fat intake (179). Diets low in fresh fruits and vegetables and high in animal proteins contribute to increased acid load, which has been associated with progression of CKD to ESRD (63), reduced eGFR (64) and increased albuminuria (64). Further, interventions to reduce acid load using either increased fruit and vegetable intake or serum bicarbonate supplementation have demonstrated reductions in urine albumin levels (180) and preserved eGFR (181). In an analysis of 14,543 NHANES participants, increased dietary fiber intake was associated with reduced markers of inflammation regardless of CKD status and reduced mortality in those with CKD (182).

Smoking

Smoking has been linked to both incidence and progression of CKD. A systematic review and meta-analysis of 15 prospective cohort studies found statistically significant elevated summary relative risks for incident CKD of 1.27 for ever-smokers, 1.34 for current smokers and 1.15 for former smokers as compared to never smokers and for

incident ESRD of 1.51 for ever-smokers, 1.91 for current smokers, and 1.44 for former smokers as compared to never smokers (183). However, no summary associations were found between smoking status and incident albuminuria (183). Based on data from human and animal studies, chemicals introduced through smoking—including nicotine—are believed to exacerbate kidney damage through creation of reactive oxygen species, activation of pro-fibrotic pathways, and transient increases in blood pressure (184). In addition, smoking appears to increase cardiovascular events in the already high-risk, CKD population. A pooled analysis of nearly 35 thousand adult men and women enrolled in 8 cohort studies showed increased risk of cardiovascular and all-cause mortality in current or former smokers with CKD compared to never smokers with CKD (185). Similarly, risk of cardiovascular mortality was elevated in current (compared to never) smokers with CKD in the Study of Heart and Renal Protection (186).

IDENTIFYING KIDNEY DISEASES FROM THE ELECTRONIC HEALTH RECORD

Benefits of Early Identification of CKD

CKD is asymptomatic in its early stages, and often goes undiagnosed until the disease is very advanced. Such poor recognition of CKD in its early stages limits the ability to properly treat and educate patients with CKD in order to slow progression of the disease, reduce its complications, and prepare the patient for renal replacement therapy. Optimal renal replacement therapy requires advance planning, such as patient education and training, surgical placement of a permanent vascular access for hemodialysis, surgical placement of an abdominal catheter for peritoneal dialysis, and/or evaluation and wait-listing for transplantation. When a patient reaches kidney failure without sufficient preparation, the patient may be left with only one option for renal

replacement therapy: hemodialysis via a temporary central venous catheter. Such "crash" dialysis starts are common in the United States. In 2015, 80% of new dialysis patients initiated treatment with a central venous catheter (36). Use of central venous catheters is associated with higher risk of death, fatal infections, and cardiovascular events (187).

In addition to the benefits of early CKD identification to clinical management of individual patients with the disease, such identification of patents with CKD may facilitate population health programs, disease surveillance, and recruitment of patients for research (188). Implementation of a population health approach to management of CKD that was supported by health information technology systems and which integrated CKD care into an existing, community and primary care-based diabetes program within the Indian Health Service has been associated with a 54% decrease in the incidence of kidney failure among American Indian and Alaska Native people with diabetes (189). Development of CKD registries within a variety of health systems have been integral to implementation of population health approaches to the management of CKD (190-193). Further, organizations such as the Alberta Kidney Disease Network and Institute for Clinical Evaluation Science, Kidney, Dialysis, and Transplant Program have leveraged data available from the EHR to create regional CKD registries that have supported research on the disease (194, 195).

Use of Diagnosis Codes to Identify CKD

International Classification of Disease (ICD) codes are typically inadequate for identifying patients with CKD given low diagnosis rates. A systematic review of various studies validating prevalence of CKD assessed by ICD codes against either eGFR value or medical record review found that use of ICD codes vastly underestimated true CKD

prevalence, with sensitivity ranging from 8% to 83% (8). A separate systematic review of 19 observational studies that validated diagnostic and procedural codes for CKD found poor sensitivity with a median of 41% and a range from 3% to 81% (196).

Use of Laboratory Data to Identify CKD

Because CKD is defined by objective laboratory measures, use of a laboratory-value based electronic (e-) phenotype for CKD has the potential to more accurately identify cases of CKD using the EHR (188), facilitating population health management quality improvement initiatives, disease surveillance and research. In 2014, the electronic medical records and genomics (eMERGE) Network published an automated phenotyping algorithm for identification of diabetic or hypertensive CKD cases from the EHR using laboratory results, in combination with diagnostic codes, medication and blood pressure records, and textual information culled from notes (197). Validation of the eMERGE algorithm demonstrated a sensitivity of 93.43% and a specificity of 95.84%—compared to 40.06% sensitivity and 75.04% specificity for ICD, Ninth Revision (ICD-9) codes alone (197). By design, the eMERGE phenotype identifies only the subset of individuals with CKD whose disease was caused by diabetes or hypertension, excluding those with primary glomerular diseases and other potential secondary CKD, such as sickle cell and HIV associated nephropathy. A simple e-phenotype based on laboratory measures alone may enable identification of all individuals with CKD.

THE TRICARE PROGRAM AND THE MILITARY HEALTH SYSTEM DATA REPOSITORY (MDR)

TRICARE

TRICARE, a health care program managed by the Defense Health Agency, provides care to nearly 9.5 million eligible beneficiaries of the MHS including uniformed service members, retirees, and their families around the world (198). In 2018, this included 4.8 million beneficiaries on the TRICARE Prime managed care program, 2.1 million beneficiaries on TRICARE Select—an enrollment-based, self-managed preferred provider network plan—and 2.1 million beneficiaries on TRICARE For Life—a Medicare-wraparound coverage for eligible beneficiaries who have Medicare Part A and B—with the remaining beneficiaries on a variety of less-utilized programs (e.g., TRICARE PLUS) (198). TRICARE does not include treatment for soldiers in combat zones or care administered though Veterans Administration facilities. Only about 20% of TRICARE beneficiaries are active duty personnel. Specifically, TRICARE beneficiaries are comprised of approximately 1.38 million active duty services members, 1.72 million active duty family members, 170,000 Guard and Reserve Members, 740,000 Guard/Reserve family members, 3.18 million retirees and family members under age 65, and 2.24 million retirees and family members age 65 and over (198). TRICARE provides for healthcare services through "direct care" services provided via military treatment facilities (MTF) including military hospitals and clinics across the globe, as well as through "purchased care" from both network and non-network TRICARE-authorized civilian health care professionals, institutions, pharmacies, and suppliers (198). Purchased care accounts for slightly more Military Health System expenditures than direct care at approximately 54% in fiscal year (FY) 2018 (198).

Considerations of Healthcare Access for the Military Population

While access to healthcare is a major social determinant of health in the general U.S. population, eligibility for TRICARE for uniformed service members, retirees, and their families provides every member of this population with at least some level of healthcare access. Between 82% and 84% of patients in the MHS who completed an outpatient survey reported they were able to see their provider when needed in FY2018 (198). Racial and ethnic disparities in health outcomes present in the general population appear to be absent in some (199-202)—but not all (203)—conditions in the MHS, suggesting potential reductions in racial/ethnic variation in access to care in the MHS compared to the general U.S. healthcare system. Additionally, in a sample of 200 active duty army soldiers and family members surveyed on access to care, satisfaction with care, physical health status, and mental health status, no disparities were identified across race, gender, and sponsor rank (204).

However, despite recent efforts to streamline care with the MHS under the National Defense Authorization Act for Fiscal Year 2017 (198, 205), ease of access to care—such as wait times, proximity to facilities, and out-of-pocket cost of care—and utilization of care may vary based on whether an individual receives direct or purchased care, the type of TRICARE plan in which she or he is enrolled, and where she or he receives care (i.e., region, individual MTF) within the MHS (198, 206). Among TRICARE Prime enrollees, 85% reported at least one out-patient visit during FY2018 and 89% had administrative data evidencing at least one visit in FY2018 (198). Results were similarly high for direct care enrollees, with administrative data suggesting at least one primary care visit in FY2017 for 89% of direct care enrollees, but slightly lower for

purchased care enrollees at 80% (198). A study assessing variation in per capita costs and utilization rates for back surgery and Cesarean sections for TRICARE Prime and Plus enrollees between FY2007 and 2010 found variation comparable to external U.S. health systems (206).

The Military Health System Data Repository

The MDR captures, archives, validates, and merges data for the approximately 9.4 million beneficiaries of the MHS including all in- and outpatient visits in Department of Defense and/or civilian facilities where the TRICARE Health Plan was the payer. The Defense Health Agency, which manages the MDR, conducts significant steps to clean the raw data pulled from the EHR before it is made available through the MDR, including identification of likely coding errors, assessing for data not missing at random, and imputation of missing values (207). For all direct care visits within military treatment facilities, data include vital signs, body mass index, tobacco usage, medications, and laboratory results, among other variables (207). However, data from purchased care interactions are limited to the contents of the claim for billing purposes and lack details on outcomes or results of the clinical encounter (e.g., laboratory findings). As required for all covered entities under the Health Insurance Portability and Accountability Act (HIPAA), the MHS transitioned coding of medical diagnosis and procedure coding from ICD-9 to ICD, Tenth Revision (ICD-10) (208).

DETAILED PROJECT DESCRIPTION

Overview of the Proposed Project

The proposed project aims to improve the understanding of the burden of CKD in adult MHS beneficiaries receiving direct care at MTFs and the potential role of social determinants of health in that burden. While CKD is common in the general U.S. population, little is known about rates of CKD among active duty and retired military personnel and their adult dependents—despite the substantial human and financial costs associated with this condition. Additionally, clear associations have been identified between various social determinants of health and CKD risk and progression in the general U.S. population; however, it is unclear whether such associations will occur under the universal health care coverage provided through the MHS. Since CKD is not readily captured from the EHR using diagnosis codes alone, this project will develop and leverage a laboratory-based e-phenotype to identify cases of CKD in order to provide a complete picture of CKD in the MHS. The project will consider both "coded CKD" (i.e., CKD identified by a diagnosis code) as well as "phenotyped CKD" (i.e., CKD identified by laboratory values prescribed by an e-phenotype).

The proposed study will leverage data from the Military Healthcare Data Repository (MDR) under the Comparative Effectiveness and Provider Induced Demand Collaboration (EPIC) project, an ongoing research collaboration between the Uniformed Services University and the Brigham and Women's Hospital Center for Surgery and Public Health (209). The EPIC Project database provides MHS patient data from direct and purchased care settings (209). The proposed project aims to accomplish the specific aims and test the associated hypotheses described below:

Specific Aims and Hypotheses

Specific Aim 1

Develop an e-phenotype to identify CKD from the EHR using laboratory values of eGFR and UACR (or dipstick UA) and implement and validate the e-phenotype in multiple clinical settings using a blinded chart review. *(Previously completed at NIH.)*

Objective 1a: Assess how dipstick UA values correlate with same-day UACR values to determine whether dipstick values may be used as a proxy for UACR in detecting CKD when UACR values are unavailable.

Objective 1b: Assess the sensitivity, specificity, ROC area, positive predictive value and negative predictive value of a laboratory measure-based e-phenotype to detect CKD from the EHR.

Objective 1c: Assess the diagnostics accuracy of the laboratory measure-based e-phenotype to detect CKD stage based on GFR.

Specific Aim 2

To determine the prevalence of coded, phenotyped and uncoded CKD among adult MHS direct care beneficiaries, as well as the characteristics of populations with coded and uncoded CKD, through a cross-sectional analysis using data available in the MDR during fiscal years 2016 - 2018.

Hypothesis 2a: Individuals with uncoded CKD will have a younger mean age compared to individuals with coded CKD.

Hypothesis 2b: Individuals with uncoded CKD will have a higher mean eGFR compared to individuals with coded CKD.

Hypothesis 2c: Individuals with uncoded CKD will have a lower mean UACR compared to individuals with coded CKD.

Hypothesis 2d: Individuals with uncoded CKD will have fewer eGFR and proteinuria measurements (UACR, UA, and UPCR) recorded in the MDR compared to individuals with coded CKD.

Hypothesis 2e: Individuals with uncoded CKD will be more likely to be of Black race compared to individuals with coded CKD.

Hypothesis 2f: Individuals with uncded CKD will be more likely to be female compared to individuals with coded CKD.

Hypothesis 2g: Individuals with uncoded CKD will be more likely to be active duty compared to individuals with coded CKD.

Hypothesis 2h: Individuals with uncoded CKD will be less likely to have diabetes compared to individuals with coded CKD.

Hypothesis 2i: Individuals with uncoded CKD will be less likely to have hypertension compared to individuals with coded CKD.

Specific Aim 3

To determine the social determinants of health associated with "any CKD" prevalence (phenotyped and/or coded) compared to no CKD among military personnel and adult dependents by comparing sociodemographic factors (e.g., race, rank, zip code, marital status) in individuals with and without "any CKD" through a cross sectional analysis using data from the MDR during Fiscal Year 2016.

Hypothesis 3a. Individuals of Black race will be more likely to have CKD compared to individuals of White race.

Hypothesis 3b. Individuals with sponsors of lower rank—a proxy for SES (income & education)—will be more likely to have CKD compared to individuals with sponsors of higher rank.

Hypothesis 3c. Individuals living in low income zip codes will be more likely to have CKD compared to individuals in high income zip codes.

Hypothesis 3d. Unmarried individuals will be more likely to have CKD compared to married individuals and this association will be modified by sex.

CHAPTER 2: METHODS

STUDY DESIGN AND OVERVIEW

Aim 1 of the study included development of a consensus-based e-phenotype definition for CKD, implementation of the CKD e-phenotype in multiple clinical settings, and validation of the sensitivity, specificity, area under the receiver operating characteristic (ROC) curve, positive predictive value, negative predictive value, and diagnostic accuracy of the e-phenotype through a blinded chart review for a random sample of patients across settings.

Aims 2 and 3 of the study involved a cross sectional analysis of adult MHS beneficiaries receiving direct care at MTFs during the 3-year period from October 1, 2015 to September 30, 2018 to determine 1) prevalence of coded CKD identified based on presence of a diagnosis code in the EHR, 2) prevalence of "phenotyped" CKD identified based on presence of laboratory values indicative of CKD, 3) prevalence of un-coded CKD identified based on presence of laboratory values indicative of CKD without any diagnosis code in the EHR, and 4) social determinants associated with prevalence of any (coded and/or phenotyped) CKD. The study was considered exempt by the USUHS IRB.

DETAILED METHODS AIM 1 (COMPLETED AT NIH)

Study Population

The CKD e-phenotype was applied to EHR data for all "active" patients age 18 years or older as of the index date of January 1, 2017 at five clinical settings: University of Minnesota; University of California, San Francisco; Columbia University; University

of Utah; and Christiana Care Health System. Active patients include all individuals who interacted with the health system (i.e., vital sign, lab value, clinic visit, hospitalization) during the 18 months leading up to the index date.

Inclusion criteria

1. Individual was aged 18 years or older at the time of data extraction.
2. Individual interacted with one of the five health systems between August 1, 2015 and January 1, 2017.
3. Individual was alive as of the January 1, 2017 index date.

Exclusion criteria

1. Individual was under the age of 18 at the time of data extraction.
2. Individual died prior to the January 1, 2017 index date.

Variables

Race

Patient race was identified from the EHR and was categorized as Black, non-Black or missing.

Age

Patient age was calculated from the date of birth identified from the EHR and treated as a continuous variable.

Sex

Patient sex was identified from the EHR and categorized as male, female or unknown.

Estimated glomerular filtration rate (eGFR)

The eGFR was defined from the most recent laboratory value available in the EHR at each site—including eGFRs calculated via the Modification of Diet in Renal Disease (MDRD) or CKD-Epidemiology (CKD-EPI) formulas—using the LOINC codes outlined in **Table 1**. eGFR was categorized as missing, normal (at or above 60 mL/min/1.73m^2), slightly decreased (45-59 mL/min/1.73m^2), moderately decreased (30-44 mL/min/1.73m^2), substantially decreased (15-29 mL/min/1.73m2) or severely decreased (< 15 mL/min/1.73m^2).

Number of eGFR measurements

The number of eGFR measurements recorded in the EHR for each patient was counted and treated as a discrete variable.

Days to Most Recent eGFR

The number of days between the index date and the date of the most recent eGFR measurement recorded in the EHR for each patient was counted and treated as a discrete variable.

Prior eGFR < 60

For patients with at least one eGFR < 60, presence or absence of an earlier eGFR measurement < 60 was determined.

Prior eGFR < 60 More than 90 Days Prior

For patients with at least one eGFR < 60, presence or absence of an eGFR measurement < 60 more than 90 days before the most recent measurement was determined.

Urine albumin-to-creatinine ratio (UACR)

UACR was identified from the most recent laboratory value available in the MDR using the LOINC codes outlined in **Table 2**. UACR was categorized as normal (< 30 mg/g), moderately increased (30 -300 mg/g), or severely increased (> 300 mg/g).

Number of UACR measurements

The number of UACR measurements recorded in the EHR for each patient was counted and treated as a discrete variable.

Urine albumin (UA)

UA was identified from the most recent laboratory value available in the EHR using the LOINC codes outlined in **Table 3**. UA was categorized as negative, trace, (1+), (2+), or (3+).

Number of UA measurements

The number of UA measurements recorded in the EHR for each patient was counted and treated as a discrete variable.

Urine protein-to-creatinine ratio (UPCR)

UPCR was defined from the most recent laboratory value available in the EHR using the LOINC codes outlined in **Table 4**. UPCR was categorized as normal (<150mg/g), moderately increased (150 to 500mg/g), or severely increased (>500mg/g).

Number of UPCR measurements

The number of UPCR measurements recorded in the EHR for each patient was counted and treated as a discrete variable.

Any Proteinuria Measurement

Presence or absence of data in the EHR for any measure of proteinuria (UACR, UA or UPCR) was determined for each patient.

UACR Measurement

Presence or absence of data in the EHR for a UACR measurement was determined for each patient.

Dialysis recipient

Dialysis was defined as presence in the EHR of a Current Procedural Terminology (CPT) or ICD-10 code indicative of dialysis (**Tables 5 and 6**).

Transplant recipient

Transplant was defined as presence in the EHR of a CPT or ICD-10 code indicative of transplant (**Tables 7 and 8**).

Defining the CKD e-Phenotype

The National Kidney Disease Education Program convened a working group including nephrologists, informaticists, public health practitioners, people with CKD and others involved in care of people with CKD to develop a pragmatic e-phenotype to identify individuals likely to have CKD from the EHR that could be implemented across a variety of settings. The CKD e-phenotype definition evolved through iterative working group discussions, which involved determining (1) the e-phenotype definition of CKD, (2) clinical variables integral to the definition, (3) Logical Observation Identifiers Names and Codes (LOINC) for each clinical variable, (4) billing and procedure codes for important related diagnoses (e.g., kidney transplantation and dialysis), and (5) critical implementation considerations (e.g., handling missing data).

The e-phenotype aligned with the KDIGO (1) definition, defining CKD as based on presence of values for the most recent laboratory results of:

- **eGFR < 60 mL/min/1.73 m^2** with 1 or more values < 60 at least 90 days prior

  -- AND/OR --

- **UACR ≥ 30 mg/g** with 1 or more values ≥ 30 at least 90 days prior

Because UACR was not universally measured—even for individuals at high risk of CKD—the e-phenotype working group also explored cut-off values for dipstick urine albumin for use in the e-phenotype when UACR values are unavailable.

LOINC codes for eGFR and UACR are shown in **Tables 1 and 2**, respectively, and CPT and ICD-10 codes for dialysis and transplant are shown in **Tables 5 - 8**. The e-phenotype allows for use of eGFR as reported by the laboratory, regardless of estimating

equation used, or recalculation of eGFR from serum creatinine, race, age, and sex using the CKD-EPI equation. If race is missing from the EHR, the e-phenotype recommends assuming race based on the overall demographics of the population, acknowledging that assuming the missing race is black will yield less sensitive, more specific results, while assuming the missing race is non-black will yield more sensitive, less specific results.

Data Analytic Plan

Objective 1a

To determine how urine albumin results correspond with UACR, patients with simultaneous UACR and UA results were identified from the EHR at each site, and the distribution of their UACR results was compared across urine albumin result categories of negative, trace, 30 (1+), 100 (2+) and 300 (3+) and > 300 (4+). In secondary analyses, patients with simultaneous urine protein-to-creatinine ratio (UPCR) and UACR results were identified from the EHR at each site, and the distribution of UACR results was compared across UPCR result categories of < 0.15, 0.15-0.50, and > 0.50. For both primary and secondary analyses, box and whisker plots were created using the minimum, first quartile, median, third quartile, and maximum UACR results within each dipstick urine albumin category. For each category, the proportion of UACR results that fell below 30 mg/g and above 300 mg/g were noted.

Objectives 1b and 1c

At each site, the following information was recorded from the EHR: age, sex, race, most recent lab results (eGFR, UACR, UPCR, and UA); number of lab results, prior lab results, transplant status and dialysis status. Means and standard deviations were

calculated for continuous variables (age, eGFR, UACR, number of lab measures) and population proportions were calculated for categorical variables (sex, race, UA, transplant status, dialysis status). Means and proportions were calculated for the population as a whole, as well as for subgroups stratified by eGFR result (missing, ≥ 60, 45-59, 30-44, 15-29, < 15). The NKDEP e-phenotype was implemented at each site. At four of the sites—Columbia, Minnesota, Christiana Care, and UCSF—patients were selected at random within each of the following strata for manual validation through a blinded chart review:

- 7-10 patients per stage of CKD (by eGFR) at each site (stages: 1/2, 3, 4, 5)
- 5-10 patients who have received a transplant at each site
- 5-10 patients on dialysis at each site
- ~20 patients without CKD at each site.

Charts were reviewed by at least one nephrologist at all sites. At Minnesota and UCSF, two reviewers assessed each chart, and a third reviewer adjudicated disagreements. Sensitivity, specificity, and positive and negative predictive values were calculated using binom.test in R version 3.4.1. Diagnostic accuracy was calculated by dividing the total number of patients the e-phenotype correctly categorized by stage by the total number of charts reviewed. The study was approved by the institutional review board at each site.

DETAILED METHODS AIMS 2 & 3

Study Population

The study cohort was identified using de-identified data from the MDR, provided through the Comparative Effectiveness and Provider Induced Demand Collaboration (EPIC) Project. The total population was identified using the Defense Enrollment Eligibility Reporting System (DEERS) to capture all active and retired military personnel and their adult dependents who received healthcare at MTFs during the 3-year period from October 1, 2015 to September 30, 2018.

Inclusion criteria

1. Individual was an MHS beneficiary, including active duty military, retired military, adult dependents, and dependent survivors.
2. Beneficiary was aged 18 to 64 years
3. Beneficiary received care in the MHS between October 1, 2015 to September 30, 2018.

Exclusion criteria

1. Beneficiary was categorized as inactive guard/reserve, active guard/reserve (if not included as active duty) and dependents of inactive and active guard/reserve.

Dependent Variables

Coded CKD

Coded CKD was defined as presence in the MDR of an ICD-10 code indicative of CKD (listed below), including dialysis and transplant recipients (**Tables 6 and 8**):

ICD-10 Codes: CKD (N18.1, N18.2, N18.3, N18.4, N18.5, N18.6, N18.9), polycystic kidney disease (Q61.2, Q61.3), glomerulonephritis/nephritis/nephrotic syndrome (N01.3, N08, N03.0, N03.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N03.8, N03.9), diabetic

nephropathy (E08.22, E09.22, E10.21, E10.22, E10.29, E11.21, E11.22, E11.29, E13.22), hypertensive nephrosclerosis (I12.0, I12.9, I13.0, I13.1, I13.2, I13.9).

Dialysis recipient

Dialysis was defined as presence in the MDR of a CPT or ICD-10 code indicative of dialysis (**Tables 5 and 6**), as identified by the NKDEP CKD e-phenotype (210).

Transplant recipient

Transplant was defined as presence in the MDR of a CPT or ICD-10 code indicative of dialysis (**Tables 7 and 8**), as identified by the NKDEP CKD e-phenotype (210).

Phenotyped CKD

Phenotyped CKD was defined using the validated NKDEP CKD e-phenotype (210) applied to laboratory values available in the MDR, developed through Specific Aim 1. This analysis used the more specific but less sensitive version of the NKDEP phenotype wherein a urine albumin result of 1+ or greater or a UPCR result of 150mg/g or greater was indicative of CKD. Individuals with missing serum creatinine (to calculate eGFR), UACR, UPCR and dipstick UA values (i.e., none of the 4 values present) were categorized as no phenotyped CKD. Since the NKDEP e-phenotype uses Logical Observation Identifiers Names and Codes (LOINC) to specify lab values from the EHR, and LOINC are not used by MTFs, specified tests were identified based on test name and specimen type by cross-walking from the provided LOINC codes. eGFR was pulled directly from the EHR as reported and recalculated using the CKD-EPI formula based on serum creatinine, age, sex and race, as recommended by the CKD phenotype. For missing

race, this analysis used the more specific phenotype approach of assuming missing race is black.

Uncoded CKD

Individuals identified as having phenotyped CKD but who did not have an ICD-10 diagnosis codes noted above present in the MDR was categorized as having uncoded CKD.

Reported Estimated glomerular filtration rate (eGFR)

The eGFR was identified from lab oratory values available in the MDR—including eGFRs calculated via the Modification of Diet in Renal Disease (MDRD) or CKD-Epidemiology (CKD-EPI) formulas. eGFR was categorized as normal (at or above 60 mL/min/1.73m2), moderately decreased (30-59 mL/min/1.73m2), or substantially decreased (15-29 mL/min/1.73m2) or severely decreased (< 15 mL/min/1.73m2).

Recalculated Estimated glomerular filtration rate (eGFR)

The eGFR was calculated using the CKD-EPI formula (3) based on serum creatinine, age, sex and race values available in the MDR. Serum creatinine results were identified by test name and result name + specimen type. eGFR was categorized as normal (at or above 60 mL/min/1.73m^2), moderately decreased (30-59 mL/min/1.73m^2), substantially decreased (15-29 mL/min/1.73m2) or severely decreased (< 15 mL/min/1.73m^2).

Number of eGFR measurements

The number of eGFR measurements recorded in the MDR for each patient were counted and treated as a discrete variable.

Urine albumin-to-creatinine ratio (UACR)

UACR was identified from laboratory values available in the MDR. Since LOINC codes are not used in the MHS, UACR results were identified by test name and result name + specimen type, cross-walking to the LOINC codes outlined in **Table 2**. UACR was categorized as normal (< 30 mg/g), moderately increased (30 -300 mg/g), or severely increased (> 300 mg/g).

Number of UACR measurements

The number of UACR measurements recorded in the MDR for each patient were counted and treated as a discrete variable.

Urine albumin

Dipstick urine albumin was identified from laboratory values available in the MDR. Since LOINC codes are not used in the MHS, UA results were identified by test name and result name + specimen type, cross-walking to the LOINC codes outlined in **Table 3**. UA was categorized as negative, trace, (1+), (2+), or (3+).

Number of UA measurements

The number of UA measurements recorded in the MDR for each patient was counted and treated as a discrete variable.

Urine protein-to-creatinine ratio (UPCR)

UPCR was identified from laboratory values available in the MDR. Since LOINC codes are not used in the MHS, UPCR results were identified by test name and result name + specimen type, cross-walking to the LOINC codes outlined in **Table 4**. UPCR was categorized as normal (<150mg/g), moderately increased (150 to 500mg/g), or severely increased (>500mg/g).

Number of UPCR measurements

The number of UPCR measurements recorded in the MDR for each patient were counted and treated as a discrete variable.

Independent Variables

Race

Race was defined as it is defined in the MDR: White, Black, Asian, Native American/Alaskan Native, Other or unknown based on the sponsor's self-reported race.

Sponsor's Military Rank

The sponsor's military rank was defined as it is defined in the MDR: "Officer," including Junior Officers (O-1 to O-4), Senior Officers (O-5 to O-10) and Warrant Officers (WO-1 to WO4), or "Enlisted," including Junior Enlisted (E-1 to E-4) and Senior Enlisted (E-5 to E-9).

Area Income Level

For each individual, the sponsor's home zip code was identified from the MDR. Using data from the US Census Bureau, the median household income (MHI) for each zip code was determined using the corresponding US Census Bureau Zip Code

Tabulation Area (ZCTA)—a generalized areal representation of the US Postal Service ZIP Code service area defined by the most frequently occurring ZIP Code in that area. ZCTAs were categorized into quintiles of area-level MHI corresponding to areas with very low, low, medium, high and very high income.

Marital Status

For each individual, the marital status was defined as it is defined in the MDR: married, single, other or unknown.

Potential Confounding, Mediating or Moderating Variables

Diagnosed Diabetes Mellitus (Type 1 or Type 2)

Diagnosed diabetes was defined as presence in the patient's record in the MDR of one or more of the ICD-10 codes outlined in **Table 9**. The ICD-10 codes were pulled from a value set developed by the National Committee for Quality Assurance (NCQA) available from the National Library of Medicine's (NLM) Value Set Authority Center (VSAC).

Diagnosed Hypertension

Diagnosed hypertension was defined as presence in the patient's record in the MDR of one or more of the ICD-10 codes outlined in **Tables 10**. The ICD-10 codes were pulled from a value set developed by the NCQA available from the NLM's VSAC.

BMI

BMI was calculated based on height and weight (weight in kilograms divided by height in meters squared) and was treated as a continuous variable. Biologically implausible values for height and weight (height <111.8 cm [<44 inches] or >228.6 cm

[>90 inches] and weight <24.9 kg [>55 pounds] or >453.6 kg [>1,000 pounds]) were excluded (211).

Diagnosed Major Depression

Diagnosed major depression was defined as presence in the patient's record in the MDR of one or more of the ICD-10 codes outlined in **Table 11**. The ICD-10 codes were pulled from a value set developed by the NCQA available from the NLM's VSAC.

Diagnosed Human Immunodeficiency Virus (HIV)

Diagnosed HIV was defined as presence in the patient's record in the MDR of one or more of the ICD-10 codes outlined in **Table 12**. The ICD-10 codes were pulled from a value set developed by the NCQA available from the NLM's VSAC.

Age

Beneficiary age was calculated from the date of birth identified from the MDR and treated as a continuous variable.

Sex

Beneficiary sex was identified from the MDR and categorized as male, female or unknown.

Benefits category

Benefits category was identified from the MDR and defined as active duty, dependent, retired or dependent survivor. Inactive guard/reserve, active guard/reserve (if

not included as active duty) and dependents of inactive and active guard/reserve were excluded.

Sponsor's branch of service

Sponsor's branch of service was identified from the MDR and categorized as Army, Air Force, Coast Guard, Marine Corps, Navy, other or unknown.

Data Analytic Plan

EPIC Project data, which includes de-identified data from MDR and DEERS, was queried to identify the study population: all active and retired military personnel and their adult dependents who received direct care from TRICARE during the 3-year period from October 1, 2015 to September 30, 2018. When values are missing from the MDR, analyses for each variable were based on the observed values only. Analyses were conducted using SAS, Version 9.4.

The total study population was counted and served as the denominator for all prevalence analyses. Individuals with coded CKD, phenotyped CKD, and uncoded CKD were each counted and the proportions of the total study population with coded CKD, phenotyped CKD, and uncoded CKD were calculated. Characteristics of each population were described using means with standard deviations or medians and interquartile ranges for continuous/discrete variables: age, number of eGFR measurements, number of UACR measurements, number of UA measurements, and number of UPCR measurements. Frequency distributions with percentages were used for categorical variables: race, sex, diabetes status, hypertension status, dialysis status, transplant status, eGFR, UACR, UPCR and UA.

Hypotheses 2a–d: Unadjusted means for age, eGFR, UACR and the number of eGFR, UACR, UA and UPCR tests were calculated for individuals with uncoded CKD and for individuals with coded CKD. Unadjusted means were used in analyses to enable identification of groups at higher risk for having missed CKD diagnoses. The means were compared across the two populations using two-tailed t tests. A $P \leq 0.05$ was considered statistically significant.

***Hypothesis 2e-i*:** Frequency distributions of individuals with each of the variables of interest were calculated among those with uncoded CKD and among those with coded CKD. The frequencies were compared between the two populations using Pearson's Chi Square test for independence. A $P \leq 0.05$ was considered statistically significant.

Hypotheses 3a-d: Crude odds ratios were calculated for phenotyped CKD versus no CKD using univariate logistic regression models for each of the potential explanatory variables: race, rank, area income level and marital status. Because sex has been shown to modify the association between marital status and health, the univariate logistic regression model for marital status was repeated in the population stratified by sex. Adjusted odds ratios were calculated for phenotyped CKD using a series of multivariate logistic regression models: model 1 controlling for potential confounders (age, sex, benefits category, and branch of service, depression) and model 2 controlling for potential confounders + potential mediators (hypertension, diabetes, BMI and HIV). Model fit was tested using the Hosmer-Lemeshow test.

Power Analyses

Specific Aim 2

Estimated required sample sizes for comparing means and frequency distributions by CKD status with an alpha of $p < 0.05$ and a power of $1\text{-}\beta = 0.80$ are shown in **Tables 13 and 14**. The population of coded CKD in the MDR is estimated to be approximately 86,954, the number of people with CKD identified using ICD-9 codes from the MDR by Oliver, et al for 2015 (6). The population of people with uncoded CKD in the MDR is estimated to be at least 17,809, assuming a high sensitivity of ICD-9 codes for identifying CKD of 83%. The 2010 systematic review that assessed accuracy of using ICD codes to identify CKD found sensitivity ranged from 9 to 83% (8). Therefore, for **Table 13**, a minimum sample size of at least 17,442 is assumed, which would enable detectable differences in means ranging from 1.5 (at a standard deviation of 50) to 0.15 (at a standard deviation of 5). For **Table 14**, population proportions for each variable of interest in the 2015 CKD population, reported by Oliver et al. (6), are used to determine the absolute difference detectable assuming a per group minimum sample size approaching the expected number of cases of uncoded CKD in the MDR of 17,809. Based on the anticipated sample size, we will be able to detect absolute differences in population proportions ranging from 1.0 to 1.5 percentage points.

Specific Aim 3

Estimated required sample sizes for conducting one-tailed univariable and multivariable logistic regression with an event proportion of 3%, a minimum detectable odd ratio of 1.1, alphas of $p < 0.05$ or $p < 0.01$ and powers of $1\text{-}\beta = 0.80, 0.90$ or 0.95 are shown in **Table 15**, based on sample size estimates provided by Hsieh (212). While this

project proposed two-tailed analyses, the high power levels included in these tables should provide a sufficiently large sample size for two-tailed tests at a lower power of 1-$\beta = 0.80$. Assuming an extremely large multiple correlation coefficient of 0.8, the largest required sample size is estimated at 170,250, which will be easily achieved given the large size of the MDR database.

CHAPTER 3: DEVELOPMENT AND VALIDATION OF A PRAGMATIC ELECTRONIC PHENOTYPE FOR CKD (Aim 1)

This chapter is comprised of a manuscript that summarizes the background, methods, and results of ***Aim 1***. Aim 1 was executed as proposed, with no changes to the hypotheses or methods.

Manuscript citation:

Norton JM, Ali K, Jurkovitz CT, Kiryluk K, Park M, Kawamoto K, Shang N, Navaneethan SD, Narva AS, Drawz P. Development and Validation of a Pragmatic Electronic Phenotype for CKD. Clin J Am Soc Nephrol. 2019 Sep 6;14(9):1306-1314. doi: 10.2215/CJN.00360119. Epub 2019 Aug 12. PMID: 31405830; PMCID: PMC6730512.

Abstract

Background and objectives: Poor identification of individuals with CKD is a major barrier to research and appropriate clinical management of the disease. We aimed to develop and validate a pragmatic electronic (e-) phenotype to identify patients likely to have CKD.

Design, setting, participants, & measurements: The e-phenotype was developed by an expert working group and implemented among adults receiving in- or outpatient care at five healthcare organizations. To determine urine albumin (UA) dipstick cutoffs for CKD to enable use in the e-phenotype when lacking urine albumin-to-creatinine ratio (UACR), we compared same day UACR and UA results at four sites. A sample of patients, spanning no CKD to ESKD, was randomly selected at four sites for validation via blinded chart review.

Results: The CKD e-phenotype was defined as most recent eGFR <60 ml/min per 1.73 m^2 with at least one value <60 ml/min per 1.73 m^2 >90 days prior and/or a UACR of ≥30 mg/g in the most recent test with at least one positive value >90 days prior. Dialysis and transplant were identified using diagnosis codes. In absence of UACR, a sensitive CKD definition would consider negative UA results as normal to mildly increased (KDIGO A1), trace to 1+ as moderately increased (KDIGO A2), and ≥2+ as severely increased (KDIGO A3). Sensitivity, specificity, and diagnostic accuracy of the CKD e-phenotype were 99%, 99%, and 98%, respectively. For dialysis sensitivity was 94% and specificity was 89%. For transplant, sensitivity was 97% and specificity was 91%.

Conclusions: The CKD e-phenotype provides a pragmatic and accurate method for EHR-based identification of patients likely to have CKD.

Introduction

CKD is associated with increased morbidity, mortality, and health care costs (36) as well as decreased quality of life (25). An estimated 30 million American adults—nearly 15% of the population—have CKD, and millions more are at risk for the disease (9). CKD is progressive, often resulting in ESKD or death from cardiovascular disease (36). Treatments exist to slow progression and manage complications of CKD; yet, many with the disease do not receive such treatments (213). For example, in 2015, serum creatinine, lipids levels, and albuminuria were assessed in only about one third of Medicare recipients with CKD, and just under two thirds were prescribed recommended renin-angiotensin-aldosterone system blockers (213). Limited progress has been made in reducing the burden of CKD in the United States, despite published clinical guidelines and efforts to raise awareness of the disease and improve patient care.

A major barrier to appropriate CKD management is delayed identification of individuals with the disease. National estimates indicate that only 8% of people with CKD are aware of their condition (214). Although recent studies suggest that questions used to evaluate CKD awareness in national samples may underestimate actual awareness, such studies still find low CKD awareness at about 30%–40% (215). Because CKD is often asymptomatic in early stages, it frequently goes undiagnosed until the disease is very advanced. Therefore, diagnostic codes are inadequate to identify individuals with CKD for population management, surveillance, and research (8, 197).

An electronic (e-) CKD phenotype using data widely available in the electronic health record (EHR) could facilitate identification of patients likely to have CKD (188). CKD is typically detected by objective laboratory data, including serum creatinine used

to estimate the GFR (eGFR) and urine albumin-to-creatinine ratio (UACR) to detect albuminuria (188). Although e-phenotypes for CKD exist (197), they are complex and require substantial information technology (IT) infrastructure and support that many health systems lack. The National Kidney Disease Education Program (NKDEP) established a working group to develop a pragmatic CKD e-phenotype to help health care organizations, providers, and researchers identify patients likely to have CKD to facilitate population health management, surveillance, and research. The NKDEP CKD e-Phenotype working group functions under the NKDEP Health IT working group, which was established in October 2012 to "enable and support the widespread interoperability of data related to kidney health among health care software applications to optimize CKD detection and management." This manuscript describes the development, implementation, and validation of the pragmatic CKD e-phenotype across multiple health systems.

Materials and Methods

Development of the NKDEP CKD e-Phenotype

The NKDEP CKD e-phenotype was iteratively developed by the working group over a series of conference calls. The working group aimed to keep the phenotype as simple as possible to enable broad implementation. The steps in the development of the e-phenotype were to (*1*) determine a definition of CKD, (*2*) identify clinical variables integral to the definition, (*3*) identify Logical Observation Identifiers Names and Codes (LOINC) for each clinical variable, and (*4*) identify billing and procedure codes for important related diagnoses (*e.g.*, kidney transplantation and dialysis).

Determining Cutoffs for Urine Albumin

Prior experience with EHR data suggested that UACR would only be available in a small proportion of patients, but urinalyses (urine albumin [UA]) would be more widely available. However, the appropriate cutoffs for determining CKD on the basis of UA have not been well established. Therefore, in order to determine UA results corresponding with the accepted definition of CKD on the basis of UACR, four sites—the Cleveland Clinic, Columbia University, the University of Minnesota, and the Veteran's Health Administration—identified patients with simultaneous UACR and UA results using data available from the EHR. The distribution of UACR results was compared across UA result categories at each site. In secondary analyses, three of the sites also identified simultaneous urine protein-to-creatinine ratio (UPCR) and UA results and compared the distribution of UPCR results across UA result categories.

Phenotype Implementation and Validation

After developing the NKDEP e-phenotype, the working group validated the implementation feasibility and precision of the e-phenotype, including an electronic validation and a manual chart review to determine its sensitivity, specificity, and accuracy. The e-phenotype was implemented among adult patients (ages ≥18 years old) receiving in- or outpatient care at five health care organizations using EHR data. Unique health systems with varying population demographics, distinct EHR systems, and diverse levels of health IT infrastructure were selected to mitigate selection bias and enhance generalizability of findings. Assumptions and considerations for implementing the NKDEP e-phenotype varied across sites (**Table 16**).

Patients were considered active if they had any of the following in the last 18 months: vital signs, laboratory value, clinic visit, or hospitalization. Patients were excluded if they had died before the data extraction date. Each site collected the following information from the EHR and calculated means and SDs or proportions (as appropriate): age, sex, race (black versus nonblack), eGFR, UACR, UPCR, UA, transplant status, and ESKD status. For each of the laboratory values, the sites determined the number of results per patient and whether a value that would qualify a patient as having CKD (*e.g.*, eGFR<60 ml/min per 1.73 m^2 or UACR≥30 mg/g) existed at least 90 days before the most recent value. The NKDEP e-phenotype was used to identify patients for the manual validation at four of the five sites. Patients were randomly selected for manual validation across stages of CKD to reduce spectrum bias, wherein the phenotype may be more likely to capture individuals with advanced disease. Patient selection targeted (*1*) seven to ten patients within each of CKD stages 3A, 3B, 4, and 5; (*2*) five to ten patients who had received a transplant; (*3*) five to ten patients on hemodialysis or peritoneal dialysis; and (*4*) 20 patients without phenotyped CKD; however, numbers varied across sites. Reviewers were blind to the e-phenotype—except for five "no CKD" charts reviewed at the University of California, San Francisco (UCSF) due to a protocol error. At the University of Minnesota and UCSF, two reviewers assessed each chart, and a third reviewer adjudicated disagreements. At Columbia University and Christiana Care Health System (Christiana Care), one reviewer performed all chart reviews. Reviewers recorded the following EHR data: (*1*) most recent eGFR, UACR, UPCR, and UA before data extraction; (*2*) dialysis status; (*3*) transplant status; and (*4*) race. Sensitivity,

specificity, and positive and negative predictive values were calculated using binom.test in R version 3.4.1.

The study was approved by the institutional review board at each site.

Results

The NKDEP e-Phenotype

The working group adhered to its guiding principle of simplicity by focusing primarily on CKD. However, the group acknowledges that organizations may expand on the NKDEP e-phenotype to include important CKD-related data, such as relevant conditions (*e.g.*, hypertension and diabetes), medications, and interventions (*e.g.*, vascular access and nephrology consults). The working group defined the CKD e-phenotype as follows: most recent eGFR <60 ml/min per 1.73 m^2 with at least one value <60 ml/min per 1.73 m^2 >90 days prior and/or proteinuria presenting as a UACR≥30 mg/g in the most recent test with at least one positive value >90 days prior (**Figure 1**). The NKDEP e-phenotype uses LOINC to identify laboratory values from the EHR (**Tables 1-4**). To determine eGFR, implementers may need to make assumptions about race when race data are unavailable in the EHR, which often is the case. The NKDEP e-phenotype will be less sensitive and more specific if patients are assumed to be black, and it will be more sensitive and less specific if patients are assumed to be nonblack. Similarly, because UACR is frequently unavailable in the EHR, the e-phenotype allows sites to use the most recent result among all proteinuria measures (UACR, UPCR, or UA) for more specific results or any positive result among the most recent UACR, UPCR, or UA for more sensitive results. To facilitate implementation at sites with a variety of

technical capabilities, the e-phenotype allows for implementers to use eGFR as reported by the laboratory (regardless of eGFR equation used). Given the small differences between performance of the Modification of Diet in Renal Disease and the Kidney Disease Epidemiology Collaboration (CKD-EPI) estimating equations relative to measured GFR—especially for individuals with an eGFR≥60 ml/min per 1.73 m^2—any differences in e-phenotype from using one equation or the other are unlikely to be clinically meaningful (3, 216). However, for more consistent results, implementors may choose to recalculate the eGFR from the reported serum creatinine value using the CKD-EPI equation (3). The NKDEP e-phenotype also identifies transplant or dialysis recipients using billing/encounter data using International Classification of Diseases (ICD), Ninth or Tenth Revision and Current Procedural Terminology codes (**Tables 5-8**).

UA Cutoffs

Four sites identified patients with same-day UACR and UA results: University of Minnesota (n=47,940), Cleveland Clinic (n=10,809), Columbia University (n=12,185), and the Veterans Health Administration (n=344,498) (Figure 2). Across the sites, the majority of patients with negative UA result had a same-day UACR <30 mg/g (76%–83%). Approximately one half (50%–53%) of patients with a trace UA result had a UACR<30 mg/g. The majority of patients with a 1+ UA result had a UACR≥30 mg/g (65%–84%), and virtually all patients with 2+, 3+, or 4+ UA results had a UACR≥30 mg/g (97%+). On the basis of these findings, the working group concluded that—in the absence of a UACR result—a sensitive definition of CKD would consider a negative UA result as normal to mildly increased (Kidney Disease Improving Global Outcomes [KDIGO] A1 category), UA results in the trace to 1+ range as moderately increased

(KDIGO A2 category), and UA results of 2+ or greater as severely increased (KDIGO A3 category). However, shifting the UA cutoffs to include negative/trace as A1 would yield more specific results. Three sites assessed values from patients with same-day UPCR/UACR and UPCR/UA laboratory results: University of Minnesota (n=9193 and 37,865, respectively), Cleveland Clinic (n=539 and 6403, respectively), and Columbia University (n=4642 and 29,438, respectively). Results are shown in **Figures 2 and 3**.

Population Characteristics

Table 17 shows the characteristics of the total implementation population from all five sites overall and across eGFR levels. **Tables 18–22** show the population characteristics by site. The implementation population totaled 2,082,017 patients. Average age was 50±19 years old. Of these patients, 58% were women, 9% were black, 55% had at least one eGFR, and 39% had a proteinuria measurement. The proportion of patients with proteinuria measurements varied across sites from 20% to 52% and increased as eGFR decreased.

Table 23 shows population characteristics from the four validation sites overall and across eGFR levels. The validation population totaled 1,680,334 patients, with similar characteristics to the implementation population (average age =50±19 years old, 59% women, 10% black, 60% with at least one eGFR, and 41% with a proteinuria measurement).

Implementation

All sites successfully implemented the NKDEP e-phenotype. The time investment for implementation varied considerably across sites, ranging from 20 to 223 hours (**Table 16**). However, four sites completed implementation in <50 hours. The considerable time

investment by site 5 involved efforts to match and merge data across two distinct EHR systems used for in- and outpatient care. Time investment depended on existing infrastructure, personnel involved, use of data standards (*e.g.*, LOINC), and IT support. Both nephrologist input and informaticist (or other information technologist) input were instrumental to efficient implementation. Both were involved at four of five sites. The site lacking nephrologist input—the University of Utah—received nephrology guidance from the working group.

Validation

Table 24 shows results of the NKDEP e-phenotype validation for CKD, dialysis, and transplantation. For CKD, 207 charts were reviewed: 71 at Christiana Care, 60 at Columbia University, 58 at the University of Minnesota, and 18 at UCSF. Sensitivity for identification of patients with CKD was 99%, with a 95% confidence interval (95% CI) of 96% to 100%. Three sites achieved perfect sensitivity. The remaining site achieved 93% sensitivity (95% CI, 66% to 100%). Specificity was 99% (95% CI, 92% to 100%). Three sites achieved perfect specificity. The remaining site achieved 96% specificity (95% CI, 79% to 100%). **Table 25** shows the adjudication for CKD stage overall and across the validation sites. Of 207 charts analyzed, 202 were correctly categorized by CKD stage, suggesting a diagnostic accuracy of 98%. The five misclassifications resulted from (*1*) outside laboratory values not captured by the e-phenotype, (*2*) delayed transfer of a laboratory result to the corporate data warehouse, (*3*) an eGFR value just at the cutoff (14.8 by e-phenotype versus 15 by chart review), (*4*) a case of IgA nephropathy where laboratory values did not indicate CKD, and (*5*) a case where the most recent recorded eGFR for a patient on dialysis was 39 ml/min per 1.73 m^2.

The two approaches to defining proteinuria were evaluated at the University of Minnesota. Using the sensitive definition (any positive result from among the last UACR, last UPCR, or last UA), 34,271 patients were identified as having CKD. Of these, 26,897 patients were positive on the last available UACR, UPCR, or UA. The 7374 patients identified by the sensitive definition were more likely to have mild to moderate increased proteinuria.

To evaluate the NKDEP e-phenotype for identification of patients on dialysis, 231 charts were reviewed: 80 at Columbia University, 72 at Christiana Care, 58 at the University of Minnesota, and 21 at UCSF. Sensitivity was 94% (95% CI, 87% to 98%) overall, ranging from 86% (95% CI, 65% to 97%) to 100% (95% CI, 72% to 100%). Overall specificity was 89% (95% CI, 83% to 94%), ranging from 40% (95% CI, 12% to 74%) to 95% (95% CI, 85% to 99%).

To evaluate the NKDEP e-phenotype for identification of patients with transplants, 160 charts were reviewed: 80 at Columbia University, 72 at Christiana Care, 58 at the University of Minnesota, and ten at UCSF. Sensitivity was 97% (95% CI, 86% to 100%), ranging from 94% (95% CI, 71% to 100%) to 100% (95% CI, 69% to 100%). Specificity was 91% (95% CI, 84% to 95%), ranging from 50% (95% CI, 12% to 88%) to 98% (95% CI, 92% to 100%).

Discussion

Identification of patients likely to have CKD using laboratory data available in the EHR provides an opportunity to facilitate quality improvement, disease surveillance, health systems research, and clinical trial recruitment. To advance automatic, EHR-based identification of patients with CKD, the NKDEP CKD e-phenotype working group

developed a laboratory value–based e-phenotype, implemented the e-phenotype across five sites with diverse informatics infrastructure and capabilities, and validated the e-phenotype at four sites. The NKDEP CKD e-phenotype performed well in identifying patients with CKD, yielding a sensitivity and specificity of 99%. The ICD code–based identification of maintenance dialysis and transplant recipients had slightly lower accuracy: at 94% sensitivity and 89% specificity for dialysis and 97% sensitivity and 91% specificity for transplant.

The performance of the NKDEP e-phenotype for CKD was slightly better than an algorithm developed as part of the Electronic Medical Records and Genomics (**eMERGE**) Network (sensitivity of 93% and specificity of 96%) (197). Key differences between the two phenotypes—regarding the criteria specified both for identifying CKD and in the validation populations—should be noted. Whereas the NKDEP e-phenotype relied on laboratory values only, the eMERGE algorithm used diagnostic codes, procedure codes, laboratory results, and physician observation reports to identify patients with CKD. The eMERGE algorithm was designed to include only those with hypertensive and diabetic kidney disease, excluding those with primary glomerular diseases and other potential secondary CKD, such as sickle cell and HIV-associated nephropathy. The eMERGE algorithm also does not include proteinuria in the definition. Additionally, the eMERGE group did not calculate sensitivity and specificity on the basis of the entire active clinical population at each site but rather, on the specified patient and control populations, which were characterized by specific exclusion criteria. Selection of the NKDEP e-phenotype versus the eMERGE algorithm will depend on the intended purpose. The NKDEP e-phenotype was specifically designed for ease of implementation

to identify a group of patients likely to have CKD; the eMERGE algorithm was designed to identify patients with hypertensive or diabetic kidney disease for research.

The NKDEP CKD e-phenotype has limitations. It relies on availability and accuracy of EHR data, including eGFR, UACR (or UA/UPCR), and race. Among the study's implementation patient sample, only about 55% had an eGFR, and <7% had a UACR in the EHR (**Table 17**). Of those with at least one eGFR indicative of CKD, the proportion with no prior eGFR <60 ml/min per 1.73 m^2 was high: ranging from 50% in those with a most recent eGFR of 45 ml/min per 1.73 m^2 to 60%–31% in those with a most recent eGFR of 15–29 ml/min per 1.73 m^2 (**Table 17).** Furthermore, spot UA measurements used in calculating the UACR have not been standardized, and results from commercially available UA measurement procedures showed positive and negative biases in the range of 40% compared with an isotope dilution mass spectrometry procedure (217). The NKDEP e-phenotype allows use of UA in place of UACR, but UA was only available in the EHR for 36% of patients at implementation sites (**Table 17**). The NKDEP e-phenotype uses both inpatient and outpatient laboratory values and may misclassify some patients with AKI as having CKD. Race is often absent in the EHR, requiring assumptions to implement the NKDEP e-phenotype. Sensitivity and specificity of the NKDEP e-phenotype may vary depending on the degree of missingness of these data elements in the EHR. In addition, the e-phenotype relies on use of LOINC to identify laboratory data from the EHR. LOINC is widely but not universally implemented, and some sites may need to crosswalk an internal coding system to LOINC to implement the e-phenotype, which will increase time for implementation, as was the case for several sites in this study. Finally, despite the intended pragmatic nature of the e-

phenotype and its successful implementation across five unique sites, implementation time varied significantly across sites, with one site requiring significant time and resource investment due to use of different EHRs for in- and outpatient settings.

Despite these limitations, the NKDEP CKD e-phenotype advances existing methods for identifying patients with CKD from the EHR. The NKDEP e-phenotype performed better compared with previous reported use of diagnosis codes in identifying patients with CKD (8). Additionally, the NKDEP e-phenotype has unique characteristics that distinguish it from the eMERGE e-phenotype (197)—including use of proteinuria measures and less complex requirements—which may make it more appropriate in certain settings, particularly small health centers with less robust informatics infrastructure.

Key strengths and limitations of the study design should also be noted. The study was implemented and validated at numerous sites with distinct patient populations and diverse informatics capabilities. However, the sites were primarily large, research-based institutions, which may not reflect implementation barriers and facilitators or level of accuracy that may occur in smaller settings. The overall validation population was large, approaching 1.7 million patients, with record reviews of >200 patients. Yet, the number of record reviews varied across sites and was small for certain sites. In addition, a protocol deviation leading to a nonblinded review of some patient charts may have affected results. However, this deviation affected only five charts: <3% of the charts assessed. Furthermore, lack of laboratory data for some patients in the EHR may subject the results of the sensitivity and specificity analyses to what may be best described as confounding by indication; patients with multiple eGFR and UA laboratory results are

more likely to be detected by the e-phenotype and identified as having CKD in the manual chart review. This may lead to overestimation of the sensitivity of the e-phenotype in identifying patients with CKD, because neither the e-phenotype nor the manual chart review would detect those with only a single or fewer eGFR and/or UA measures.

Individuals with CKD cannot be accurately identified from the EHR using diagnosis codes alone. Using laboratory data available in the EHR to automate identification of patients with CKD may facilitate population health management, surveillance, and research. The NKDEP CKD e-phenotype provides a pragmatic and accurate method for EHR-based identification of patients likely to have CKD.

CHAPTER 4: PREVALENCE OF CODED AND UN-CODED CHRONIC KIDNEY DISEASE IN THE MILITARY HEALTH SYSTEM (AIM 2)

This chapter is comprised of a manuscript that summarizes the background, methods, and results of ***Aim 2***. Aim 2 was executed primarily as proposed, with no changes to the hypotheses and minor changes to the methods. Specifically, we discovered that laboratory reported eGFR is available in the MDR, and thus we included both recalculated and reported eGFR in the analyses.

Manuscript citation:

Norton JM, Grunwald L, Olsen C, Narva AS, Marks E, Koehlmoos TP. Prevalence of Coded and Un-coded Chronic Kidney Disease in the Military Health System. *Kidney Medicine* (***submitted***)

Abstract

Rationale & Objective: Chronic kidney disease (CKD) is common but often goes unrecorded. We identify prevalence of coded and uncoded CKD in the Military Health System (MHS) and populations at risk for uncoded CKD.

Study Design: Cross-sectional

Setting & Participants: MHS beneficiaries aged 18 to 64 who received care during fiscal years 2016-2018.

Predictors: Age, sex, active duty status, race, diabetes, hypertension, and numbers of kidney test results.

Outcomes: We defined CKD using a validated laboratory value-based electronic phenotype and/or ICD-10 codes. We defined coded CKD by presence of an ICD-10 code. We defined uncoded CKD by a positive e-phenotype result without an ICD-10 code.

Analytical Approach: We compared coded and uncoded populations using two-tailed t tests (continuous variables) and Pearson's Chi Square test for independence (categorical variables).

Results: The MHS population included 3,330,893 beneficiaries. Prevalence of CKD was 3.2%. Of those identified with CKD, 63% were uncoded. Compared to beneficiaries with coded CKD, those with uncoded CKD were younger (age 45 +/- 13 vs 52 +/- 11), more often female (54.4% vs 37.6%) and active duty (20.2% vs. 12.5%), and less often of Black race (18.5% vs 31.5%) or with diabetes (23.5% vs 43.5%) or hypertension (46.6% vs 77.1%) ($p < .0001$). Beneficiaries with coded (versus uncoded) CKD had greater numbers of kidney test results ($p < .0001$).

Limitations: This analysis used cross-sectional administrative data, thus causality cannot be inferred. The CKD e-phenotype may fail to capture CKD in individuals with missing laboratory data, and thus may underestimate CKD.

Conclusions: We found, for the first time, prevalence of CKD in the MHS is 3.2%. Beneficiaries with well-known CKD risk factors (e.g., older age, male sex, black race, diabetes, hypertension) were more likely to be coded, suggesting clinicians may be missing CKD in groups traditionally considered lower risk, resulting in suboptimal care.

Introduction

More than 30 million American adults (about 15% of the US adult population) are estimated to have chronic kidney disease (CKD) (9), which is characterized by progressive and long-term loss of kidney function that may lead to end-stage kidney disease (ESKD). Individuals with CKD experience substantial morbidity and mortality, including disproportionate rates of hospitalization, cardiovascular disease, mineral and bone disorders, anemia, metabolic acidosis, malnutrition, acute kidney injury, psychiatric illnesses and reduced quality of life (10, 16-19). In addition, CKD imposes a substantial financial burden. In 2016, care for Medicare beneficiaries with CKD or ESKD cost more than $114 billion, representing 23% of total Medicare fee-for-service spending despite only accounting for approximately 13% of the Medicare population (10). In ESKD, the disproportionate costs are even more extreme, as people with ESKD reflect less than 1% of the Medicare population but account for 7% of spending (10). These significant costs are potentially modifiable, as effective strategies exist to slow progression of CKD and reduce potential complications (1).

Despite the substantial human and financial costs associated with CKD and the high prevalence of CKD in the general population, little is known about CKD in the nearly 9.5 million beneficiaries of the Military Health System (MHS). While the active duty population is notably healthier than the general population, only about 20% of MHS beneficiaries are active duty personnel, with the remaining beneficiaries comprised of retirees and service members' families (198). Recent analyses on rates of diabetes mellitus and hypertension, the primary causes of ESKD, in the MHS are limited.

However, available data suggest the prevalence of these CKD risk factors may be considerable (218, 219).

The MHS Data Repository (MDR) contains health data for MHS beneficiaries, including laboratory results for beneficiaries who receive direct care at Military Treatment Centers (MTF), making assessment of CKD in the MHS possible. International Classification of Disease (ICD) codes are typically inadequate for identifying patients with CKD, given low diagnosis rates based solely on ICD coding. A systematic review of various studies validating prevalence of CKD assessed by ICD codes against either eGFR value or medical record review found that use of ICD codes vastly underestimated true CKD prevalence, with sensitivity ranging from 8% to 83% (8). A separate systematic review of 19 observational studies that validated diagnostic and procedural codes for CKD found poor sensitivity with a median of 41% and a range from 3% to 81% (196).

Because CKD is defined by objective laboratory measures, a laboratory-data based electronic (e-) phenotype for CKD has the potential to more accurately identify cases of CKD using electronic health record (EHR) data such as is available through the MDR (188). Application of CKD e-phenotypes inclusive of laboratory measures to EHR data has demonstrated ability to identify cases of CKD with high accuracy (197, 210), outperforming ICD codes alone (197). A National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) working group recently developed a CKD e-phenotype based on estimated glomerular filtration rate (eGFR) and measures of proteinuria, including urine albumin-to-creatinine ratio (UACR), urine protein-to-creatinine ratio

(UPCR), and dipstick urine albumin, that identified CKD from the EHR across four healthcare settings with 99% sensitivity and 99% specificity (210).

To understand the prevalence of CKD in adult MHS beneficiaries, we used ICD-10 codes to identify previously diagnosed cases of CKD, as well as the NIDDK CKD e-phenotype to identify probable, but uncoded cases of CKD. We compared prevalence of coded and uncoded CKD, and explored factors associated with uncoded CKD.

Methods

Data Source

The cross sectional study used data from the MDR under the Comparative Effectiveness and Provider Induced Demand Collaboration (EPIC) project, which has been previously described.(209) The MDR captures, archives, validates, and merges data for the approximately 9.5 million beneficiaries of the MHS, including all in- and outpatient visits in Department of Defense (DoD) facilities (direct care) and/or civilian facilities where the Military's TRICARE Health Plan was the payer (purchased care). Before data are made available through the MDR, they are thoroughly cleaned, including identification of likely coding errors, assessment for data not missing at random, and imputation of missing values (207). For all direct care visits (i.e., care provided within military treatment facilities), data include vital signs, body mass index, self-reported tobacco usage, medications, and laboratory results, among other variables (207). However, data from the civilian fee-for-service (purchased care) environment are limited to the contents of the claim for billing purposes and lack details on outcomes or results of the clinical encounter (e.g., laboratory findings). The MDR does not include treatment for service members in combat zones or care administered though Veterans Administration

facilities. Further, the MDR has previously been employed in studies designed to evaluate epidemiology and quality of healthcare delivery in a variety of clinical contexts including surgical care, women's health and pediatrics (220-222).

Study Population

We identified all active duty and retired military personnel and their adult dependents or dependent survivors who received healthcare through the MHS during the 3-year period from October 1, 2015 to September 30, 2018. Adults aged 18 to 64 were included in the sample. Adults aged 65 and over were excluded, as Medicare rather than TRICARE, is the primary payer in this population. Inactive guard/reserve, active guard/reserve (if not included as active duty) and dependents of inactive and active guard/reserve were excluded due to the infrequency with which this population accesses TRICARE services.

Variables of Interest

Coded CKD was defined by ICD-10 code (**Table 26**). Any CKD was defined by presence of an ICD-10 code for CKD and/or laboratory markers of CKD, as defined by the NIDDK CKD e-phenotype.(210) This analysis applied the more specific, less sensitive version of the e-phenotype, wherein missing race is assumed Black, dipstick urine albumin cut-off for CKD is 1+ or greater, and UPCR cut-off for CKD is 150mg/g or greater. Individuals with missing eGFR, serum creatinine (sCr), UACR, UPCR and dipstick UA values (i.e., none of the 5 values present) were categorized negative for phenotyped CKD. Importantly, the NIDDK e-phenotype could not be applied to beneficiaries who receive care through purchased care, as lab data are not available for

this population. Individuals identified as phenotype positive for CKD who did not have an ICD-10 diagnosis code for CKD were categorized as having uncoded CKD.

Dialysis and transplant recipients were identified by presence of indicative ICD-10 or CPT codes (**Tables 5-8**). Diabetes, hypertension, depression and HIV positive status were identified by ICD-10 code using National Committee for Quality Assurance value sets available from the National Library of Medicine's Value Set Authority Center (**Tables 9-12**) (223). BMI was calculated based on height and weight, excluding biologically implausible values for height and weight (height <111.8 cm [<44 inches] or >228.6 cm [>90 inches] and weight <24.9 kg [<55 pounds] or >453.6 kg [>1,000 pounds]) (211), and was categorized as obese (≥ 30), overweight (≥ 25, < 30), or normal/underweight (< 25).

For each beneficiary, sex, race, birth year, benefits category, marital status, and the number of serum creatinine, eGFR, UACR, UPCR and dipstick urine albumin measurements were recorded from the MDR. Benefits category was defined as active duty, dependent, retired or dependent survivor. In addition, for each beneficiary, the sponsor's military rank, branch of service, and home zip code were captured. Sponsor's military rank, a commonly used proxy for socioeconomic status (224, 225), was defined as Senior Officers (O-5 to O-10), including Warrant Officers (WO-1 to WO4), Junior Officers (O-1 to O-4), Senior Enlisted (E-5 to E-9), and Junior Enlisted (E-1 to E-4). Branch of service was categorized as Army, Air Force, Marine Corps, Navy, or other.

Data Analysis

We identified the total study population, which served as the denominator for all prevalence analyses. We calculated proportions of the population with any CKD, coded

CKD, and uncoded CKD. Characteristics of the any CKD, coded CKD and uncoded CKD populations were described using means with standard deviations and/or medians with interquartile ranges for continuous or discrete variables (age and number of laboratory measurements) and frequency distributions with percentages for categorical variables (race, sex, benefits category, rank, branch of service, BMI, income and comorbidities). To enable identification of groups at higher risk for having uncoded CKD, unadjusted means and frequency distributions were compared across the coded and uncoded CKD populations using two-tailed t tests and Pearson's Chi Square test for independence, respectively. For each t-test, the equality of variances assumption was checked, and the Satterthwaite method was used when we could not assume equal variances. A $P \leq 0.05$ was considered statistically significant. Analyses for each variable were based on the observed values only, with missing values excluded from analysis. Analyses were conducted using SAS, Version 9.4. This study was found exempt by the Uniformed Services University of the Health Sciences Institutional Review Board.

Results

The total study population consisted of 3,330,893 MHS beneficiaries. We found that 3.2% of the MHS population had CKD identified either by ICD-10 code or laboratory values indicative of CKD, accounting for 105,504 people. Of those with CKD, 38,688 (37%) had an ICD-10 code for CKD recorded in the MDR, while 66,816 (63%) were uncoded and identified by laboratory values alone. Of note, 53% of the total population had no kidney test results (sCr, eGFR, UACR, UPCR or dipstick urine album) recorded in the MDR. Interestingly, 60% of individuals with coded CKD did not have lab values indicative of CKD recorded in the MDR. **Table 27** shows the characteristics of the

total, coded and uncoded CKD populations within the MHS. The total CKD population was 48 years of age on average, 48% female, predominantly of White (47%) or Black (23%) race and predominantly senior enlisted (75%). Of the total CKD population, 39% were retired, 30% were dependents of non-active duty beneficiaries (e.g., retirees, survivors), 17% were active duty and 14% were dependents of active duty. Both hypertension (57.8%) and diabetes (30.8%) were common in the total CKD population. Approximately half (49%) of the CKD population had at least 1 proteinuria measurement (UACR, UPCR or dipstick urine albumin) recorded in the MDR, with only 36% having the preferred UACR test. Virtually all (99.2%) had a kidney function test (sCr or eGFR).

Those with coded CKD were 52 years of age on average, 37.6% female, 41.8% of White race, and 31.5% of Black race, whereas and those with uncoded CKD were 45 years of age on average, 54.4% female, 50.2% of White race, and 18.5% of Black race. About half (50.6%) of the coded CKD population was retired and 12.5% were active duty, compared to 32.1% and 20.2%, respectively, of the uncoded CKD population. Among those with coded CKD, 77.1% had hypertension and 43.5% had diabetes, whereas in the uncoded CKD population, only 46.6% had hypertension and 23.5 had diabetes. Finally, 71.1% of the coded CKD population had at least one proteinuria measurement, whereas only 37.7% of the uncoded CKD population had a proteinuria measurement.

Table 28 provides crude comparisons between the coded and uncoded CKD populations. Individuals with coded CKD were aged 52 on average, significantly older than those with uncoded CKD, aged 45 on average ($p < .0001$). Those with coded

compared to uncoded CKD were less likely to be female and active duty, but more likely to be of Black race and to have diabetes or hypertension (all p <.0001). Among those with test results recorded in the MHS, those with coded CKD had greater numbers of urine albumin, UACR, UPCR, sCr, and eGFR results (all p <.0001).

Discussion

To date, little published data are available on the burden of CKD in the MHS. This analysis suggests that 3.2% of the MHS population—105,504 MHS beneficiaries—may have CKD, based on data from federal fiscal years 2016 through 2018. Prior, unpublished estimates of CKD prevalence in the MHS by Oliver and colleagues have been lower. An analysis using diagnosis codes in the full TRICARE population estimated the 2015 prevalence of CKD at between 2.6% and 2.9% (6). A separate study in the sub-population of MHS beneficiaries who receive exclusive direct care from Military Treatment Centers estimated the 2015 prevalence of CKD at 2.5%, based on presence of at least two abnormal laboratory values indicative of CKD (i.e., eGFR, UACR or UPCR) separated by 90 or more days (226). Given the incomplete overlap of diagnosed and phenotyped CKD, the higher prevalence identified in this analysis likely results from the combined use of diagnosis codes and/or laboratory values to capture CKD. In addition, the NIDDK e-phenotype for CKD used in this analysis includes dipstick urine albumin as a measure of proteinuria, with CKD indicated in individuals with two or more results of 1+ or greater separated by at least 90 days, whereas the prior analysis by Oliver and colleagues did not use dipstick urine albumin to identify CKD. As in other healthcare settings (210), dipstick urine albumin is more commonly available than other measures of

proteinuria in the MHS, and therefore, addition of this lab result likely increased sensitivity for identifying CKD.

Importantly, the 3.2% prevalence of CKD found in this analysis likely underestimates the true prevalence of CKD in the MHS population. Diagnosis codes have been demonstrated to under capture cases of CKD.(8, 226) While use of the NIDDK e-phenotype to capture probable cases of CKD by laboratory values will increase the sensitivity of CKD detection, the less sensitive, more specific versions of the NIDDK e-phenotype was used in the analysis, and therefore, the phenotype may have failed to capture some cases of CKD. In addition, kidney test results must be available in order to apply the e-phenotype. However, 53% of the included MHS population did not have any sCr, eGFR, UACR, UPCR or dipstick urine albumin results recorded in the MDR on which to apply the e-phenotype. This may, to a large degree, result from the lack of laboratory data in the MDR for any purchased care interactions received from both network and non-network TRICARE-authorized civilian health care professionals, institutions, pharmacies, and suppliers. Just over half (~54%) of TRICARE expenditures are for purchased care services (198). Therefore, phenotype positive labs may exist for MHS beneficiaries who were tested through purchased care interactions, which we were unable to include in this analysis. This may also explain the finding that 60% of individuals coded as having CKD had no laboratory data to support this diagnosis available in the MDR.

Uncoded CKD was more common in groups traditionally considered to be of lower risk for progressive CKD: younger adults, females, people of non-Black race, and those without diabetes or hypertension (10). These findings are largely consistent with

studies conducted in primary care practices in the United Kingdom, which found CKD was more frequently coded in men, individuals of older age, and those with relevant comorbidities (227, 228). Contrary to our findings in the MHS, the studied U.K. primary care practices had higher rates of uncoded CKD in practices with predominantly minority patients (228). However, differences in demographic, social and contextual factors between the U.K. primary care population and the MHS population must be acknowledged. In an analysis of data from the U.S. National Health and Nutrition Examination Survey, Black Americans were twice as likely to have undiagnosed kidney disease (based on self-reported diagnosis and a single eGFR measure) compared to white Americans; however, due to use of self-reported diagnosis, differential awareness of CKD may also contribute to the disparity (229). The high rates of CKD coding in Black MHS beneficiaries is perhaps unsurprising, given that many black-white healthcare disparities that persist in the U.S. are absent in the MHS (199-202), perhaps due to the universal healthcare coverage provided through the MHS, the high rate of employment for MHS beneficiaries (or their sponsors), and/or differences in clinical cultures and practices.

Lack of CKD coding in these traditionally low CKD risk groups suggests clinicians may be missing CKD diagnoses—despite available laboratory data indicative of CKD. As a result, these individuals with uncoded CKD may not be receiving appropriate management to slow progression of the disease and address potential complications. Prior research has shown associations between lack of clinical coding for CKD and guideline discordant care (227). In addition, presence of coded CKD is associated with a greater likelihood of patient awareness of their CKD diagnosis (230).

As expected, beneficiaries with uncoded CKD had fewer numbers of urine albumin, UACR, UPCR, sCr, and eGFR results, suggesting kidney function and damage is not monitored as closely in this patient population. Application of the NIDDK CKD e-phenotype(210) in population health management initiatives in the clinical setting could potentially help identify these individuals likely to have CKD, thereby enabling improved disease management.

This analysis is a novel first attempt to identify all cases of CKD in the MHS population using both ICD-10 codes and laboratory values indicative of CKD. Additional strengths include the large sample size and the application of a validated, laboratory value-based e-phenotype to improve sensitivity of CKD detection. However, important limitations must be acknowledged. Data used in this analysis are administrative, and thus are intended for use in claims adjudication and not research. Due to the cross-sectional nature of the data, causality cannot be inferred. More than half of the total MHS population lacked kidney test results on which to apply the CKD e-phenotype. As a result, the CKD e-phenotype may fail to capture CKD in individuals who have laboratory values indicative of CKD acquired through purchased care. The phenotype also cannot be applied to any individual who has simply not received any kidney tests. As a result, we may underestimate the true burden of CKD in the MHS.

Conclusion

This novel study, for the first time, identified the prevalence of CKD in the MHS at 3.2%. Of MHS beneficiaries with probable CKD, 63% lacked an ICD-10 code for CKD, suggesting they may not be receiving appropriate management to slow progression and address complications. Beneficiaries with well-known risk factors for CKD (e.g.,

older age, male sex, black race, diagnosed diabetes, diagnosed hypertension) were more likely to have a CKD ICD-10 code, suggesting clinicians may be missing CKD in groups traditionally considered lower risk—despite available laboratory data to asses CKD status.

CHAPTER 5: RACIAL AND SOCIOECONOMIC DISPARITIES IN CKD IN THE CONTEXT OF UNIVERSAL HEALTHCARE PROVIDED BY THE MILITARY HEALTH SYSTEM (AIM 3)

This chapter is comprised of a manuscript that summarizes the background, methods, and results of ***Aim 3***. Aim 3 was executed primarily as proposed, with no changes to the hypotheses and minor changes to the methods. Specifically, we discovered that laboratory reported eGFR is available in the MDR, and thus we included both recalculated and reported eGFR in the analyses.

Manuscript citation:

Norton JM, Grunwald L, Olsen C, Narva AS, Marks E, Koehlmoos TP. Racial and Socioeconomic Disparities in CKD in the Context of Universal Healthcare Provided by the Military Health System. *JASN* (***submitted***)

Abstract

Background: Health-impeding social determinants of health contribute to racial and socioeconomic disparities in chronic kidney disease (CKD). Reduced access to healthcare may contribute to these relationships. The Military Health System (MHS) provides an opportunity to assess a large, diverse population for racial and socioeconomic disparities in CKD in the context of universal healthcare.

Methods: We identified MHS beneficiaries aged 18 to 64 who received care between October 1, 2015 and September 30, 2018. CKD was defined by ICD-10 codes and/or a validated, laboratory value-based electronic phenotype. We developed directed acyclic graphs to determine potential confounding or mediating covariates. We used multivariable logistic regression to compare CKD prevalence by race, rank (a proxy for socioeconomic status), median household income (MHI) by sponsor's zip code, and marital status, controlling separately for suspected confounders (age, sex, active duty status, sponsor's service branch, and depression) and mediators (hypertension, diabetes, HIV and BMI).

Results: Of 3,330,893 included beneficiaries, 105,504 (3.2%) had CKD. In confounder-adjusted models, CKD prevalence was elevated in beneficiaries of black vs white race, lower vs higher rank, lower vs higher MHI, and married vs single status ($p < .0001$). Associations were partially or fully attenuated when further adjusting for suspected mediators.

Conclusions: Racial and socioeconomic CKD disparities exist in the MHS despite universal healthcare coverage. While underlying genetic differences may contribute to racial disparities in CKD, the existence of disparities by rank and MHI suggest social

risks may contribute to both racial and socioeconomic disparities despite access to universal healthcare coverage.

Introduction

Chronic kidney disease (CKD) is common and burdensome, often leading to kidney failure and dialysis. Health-impeding social determinants of health—or social risks—have strong and well-documented associations with CKD incidence, prevalence and progression, as well as with the substantial racial and socioeconomic disparities that characterize the disease (13, 48). Social risks are fueled by poverty and combine and interact with clinical and biological factors to generate poor health outcomes, including CKD. They appear to act by affecting a person's likelihood of exposure to disease-causing agents, ability to participate in healthful behaviors and activities, exposure to stressors and resulting level of stress, and capacity for coping with stressors (13, 48).

Inadequate access to healthcare is an important social risk in the general U.S. population, particularly among low-income individuals. In 2017, 7.4% of the total U.S. Population—and 16.2% of those living below the Federal poverty line—delayed or missed necessary medical care due to cost (231). Un- and under-insurance, common proxies for inadequate healthcare access, are associated with poor outcomes in CKD (113, 114).

Universal healthcare coverage appears to mitigate racial and socioeconomic disparities across numerous health conditions (125, 200). Racial disparities in CKD often persist despite universal access to care (125, 126), and have been attributed to underlying genetic risk factors (126). However, socioeconomic disparities in CKD—which cannot be explained by genetic differences—are also apparent in settings with universal healthcare coverage, including the United Kingdom, Denmark and Australia (59, 122, 124). To better understand the role of healthcare access in racial and socioeconomic disparities in

CKD, this analysis explores the extent to which socioeconomic factors and race are associated with CKD prevalence in context of the universal healthcare coverage provided within the Military Health System (MHS).

Methods

Data Source

This analysis employed data from the MHS Data Repository (MDR) via the Comparative Effectiveness and Provider Induced Demand Collaboration (EPIC) project.(209) The MDR includes data for all in- and outpatient visits for the approximately 9.5 million MHS beneficiaries who receive "**direct care**" from a Department of Defense military treatment facility (MTF) and/or "**purchased care**" from a civilian facility when the Military's TRICARE Health Plan is the primary payer. Approximately half of TRICARE expenditures are for purchased care services.(198) The MDR does not contain data on care provided for soldiers in combat zones or in Veterans Health Administration facilities. Data from **direct care** visits (within an MTF) include vital signs, body mass index, self-reported tobacco use, medications, and laboratory results, among other variables (207). However, data from **purchased care** visits (in civilian facilities, paid by TRICARE) are limited to claims data for billing and do not include outcomes or results of the clinical encounter (e.g., laboratory findings). Before being made available for research, MDR data are thoroughly cleaned, including correction of likely coding errors, identification of data not missing at random, and imputation for missing values (207).

Study Population

All adults aged 18 to 64, including active duty military personnel and their dependents, retired military personal and their dependents, and dependent survivors, who received direct or purchased healthcare through the MHS between October 1, 2015 and September 30, 2018 were included in the sample. Because Medicare, rather than TRICARE, becomes the primary payer for adults at 65, we excluded beneficiaries aged 65 and older. In addition, we excluded inactive guard/reserve, active guard/reserve (if not active duty) and their dependents, as this population infrequently accesses TRICARE services.

Variables of Interest

CKD, the primary outcome of interest, was defined by presence of an ICD-10 code for CKD (**Table 26**) and/or laboratory indicators of CKD delineated by the NIDDK CKD e-phenotype (210). In this analysis, we used the more specific, less sensitive e-phenotype version; we set CKD cut-offs at 1+ or greater for urine albumin and 150mg/g or greater for UPCR and, when calculating eGFR, we assumed missing race was Black. When CKD lab data were unavailable for an individual (i.e., no eGFR, serum creatinine, UACR, UPCR or dipstick urine albumin results), that individual was categorized as phenotype negative. Notably, laboratory results acquired through purchased care (outside an MTF) are not available in the MDR, and thus cannot be assessed by the e-phenotype.

Primary explanatory variables included race, sponsor's rank (a common proxy for SES and social class) (224, 225), median household income (MHI) by zip code, and marital status. For each beneficiary, race, marital status, sponsor's military rank, and home zip code were recorded, as available, from the MDR. Sponsor's military rank was

categorized as Senior Officer (O-5 to O-10; WO-1 to WO4), Junior Officer (O-1 to O-4), Senior Enlisted (E-5 to E-9), and Junior Enlisted (E-1 to E-4). Sponsor's home zip code was mapped to US Census Bureau data for MHI, where available, and categorized into quintiles of zip code-level MHI corresponding to areas with very low, low, medium, high and very high income. Individuals missing zip codes and those from zip codes lacking MHI data were categorized as missing MHI.

Other variables of interest included potential confounders and mediators of the association between the explanatory variables and CKD. Date of birth, sex, and benefits category (active duty, retired, active duty dependent, or other dependent [including retired dependents and dependent survivors]) were recorded from the MDR for each beneficiary. In addition, the sponsor's branch of service was also captured from the MDR for each beneficiary and was categorized as Army, Air Force, Coast Guard, Marine Corps, Navy, other or unknown. Transplant recipients and dialysis patients were defined by presence of relevant ICD-10 and/or CPT codes (**Tables 5-8**). ICD-10 codes using value sets authored by the National Committee for Quality Assurance and published in the National Library of Medicine's Value Set Authority Center were used to identify cases of diabetes, hypertension, depression and HIV positive status (**Tables 9-12**). Height and weight were used to calculate body mass index (BMI), with biologically implausible values for height and weight excluded (height <111.8 cm [<44 inches] or >228.6 cm [>90 inches] and weight <24.9 kg [<55 pounds] or >453.6 kg [>1,000 pounds]) (211).

Data Analysis

Crude odds ratios were calculated for presence vs absence of CKD using univariate logistic regression models for each of the potential explanatory variables: race,

rank, area MHI and marital status. Directed acyclic graphs (**Figure 4**) were developed to understand potential confounding or mediating roles of covariates. Age, sex, benefits category, branch of service, and depression were identified as likely confounders, as they have known or hypothesized associations with both explanatory variables and CKD but are not likely on the pathway from social risks to CKD. Hypertension, diabetes, BMI (for overweight/obesity) and HIV were identified as likely mediators, as social risks contribute to the burden of these conditions and, in turn, these conditions increase the risk of CKD (10, 232-235). Adjusted odds ratios were calculated for CKD using a series of multivariate logistic regression models: model 1 controlling for potential confounders (age, sex, benefits category, branch of service, and depression) and model 2 controlling for potential confounders + potential mediators (hypertension, diabetes, BMI and HIV). Given known challenges using goodness of fit tests for logistic regression on large populations (236), we ran the Hosmer Lemeshow test, as well as logistic regression covariate pattern diagnostics (i.e., residuals, influence measures, delta chi-square, "Cook's Distance"), on a random subsample of 10,000 individuals, showing good fit. Analyses were conducted using SAS, Version 9.4. This study was found exempt by the Uniformed Services University of the Health Sciences Institutional Review Board.

Results

The total study population included 3,330,893 MHS beneficiaries, with mean age of 33 years and mean BMI of 28 (**Table 29**). The total population was racially diverse, including 55% White, 15% Black, 10% other race, 5% Asian American/Pacific Islander (AAPI), and 0.6% American Indian/Alaska Native (AIAN) beneficiaries. However, 16% of the population had missing or unknown race. Just over half of the population (52%)

was active duty, while 36% were dependents and 12% were retired. The majority of the population (49%) was senior enlisted, followed by junior enlisted at 31%, senior officer at 10% and junior officer at 9%. Hypertension, depression and diabetes were relatively common in the population at 13%, 6% and 5% respectively; whereas HIV, dialysis and transplant were extremely rare or absent. Area MHI was relatively high for the population, with a median zip code level MHI of $58,121 and the interquartile range between $48,377 and $73,966. Less than half of the total population (47%) had a kidney test result (eGFR, serum creatinine, dipstick urine albumin, UACR or UPCR) recorded in the MDR.

Of the total population, 105,504 people, or 3.2%, had CKD identified by ICD-10 code and/or laboratory values indicative of CKD (**Table 29**). Compared to beneficiaries without CKD, those with CKD were on average older, less likely to be active duty, more likely to be retired, more likely to be Black, more likely to be senior enlisted or senior officer and more likely to be married. Beneficiaries with CKD also had higher average BMI and were more likely to have hypertension, diabetes and depression compared to those without CKD. Almost all individuals with CKD (99%) had at least one measure of eGFR recorded in the MDR, but only half (50%) had a measure of proteinuria.

Table 30 provides crude, confounder-adjusted and confounder-mediator-adjusted odds ratios for the associations between sociodemographic factors and CKD. In crude analyses, both AAPI (OR = 1.18 95% CI: 1.15, 1.22) and Black (OR = 1.87 95% CI: 1.84, 1.90) beneficiaries had elevated prevalence of CKD compared to whites; however, statistical significance was lost for AAPI beneficiaries after adjusting for confounders. In confounder adjusted models, we found that Black beneficiaries had 1.67 times higher

odds of prevalent CKD compared to their white counterparts. As expected, when additionally adjusting for suspected mediators, the association between Black race and CKD was partially but not completely mitigated (OR = 1.30, 95% CI: 1.28, 1.32).

Compared to senior officers, senior enlisted beneficiaries had higher odds of CKD in crude analyses (OR = 1.34, 95% CI: 1.31,1.36), whereas junior officers (OR = 0.48, 95% CI: 0.46, 0.49) and junior enlisted beneficiaries had lower odds of CKD (OR = 0.20, 95% CI: 0.20, 0.21). However, after adjusting for suspected confounders, all ranks below senior officers had elevated odds of prevalent CKD. After further adjusting for suspected mediators, statistical significance was lost for both junior officer and junior enlisted beneficiaries, while the odds of CKD remained statistically significant for senior enlisted beneficiaries (OR = 1.33, 95% CI: 1.30, 1.35).

Compared to married beneficiaries, those who were single had lower odds of CKD in crude and adjusted analyses; however, the magnitude of the protective effect of single status dropped from an OR of 0.41 (95% CI: 0.41, 0.42) in the crude analysis, to 0.77 (95% CI: 0.76, 0.79) in the confounder adjusted model, to 0.82 (95% CI: 0.81, 0.83) in the confounder- and mediator-adjusted models.

In crude, confounder and mediator adjusted models, decreasing zip code level MHI was associated with increasing odds of prevalent CKD through all quintiles except the lowest. Of note, 13% of the total sample were missing MHI data. After adjusting for confounders, the magnitude of the association increased across all MHI quintiles. Compared to the very high MHI quintile, the high quintile had 1.40 (95% CI: 1.37, 1.44) times greater odds of CKD, the medium quintile had 1.98 (95% CI: 1.94, 2.02) times greater odds of CKD, the low quintile had 2.76 (95% CI: 2.70, 2.82) times greater odds

of CKD, and the very low quintile had 2.58 (95% CI: 2.52, 2.64) times greater odds of CKD. After further adjusting for suspected mediators, the magnitude of the association was attenuated but remained significant for all MHI levels.

Discussion

This analysis found racial and socioeconomic disparities exist in the MHS despite universal healthcare coverage. In confounder-adjusted models, Black MHS beneficiaries had 1.67 times higher odds of prevalent CKD compared to their White counterparts, which is consistent with the elevated odds of CKD among Black Americans recently reported by the USRDS.(10) Individuals of lower compared to higher SES and social class in the MHS experience higher prevalence of CKD, with odds ratios ranging from 1.32 (junior enlisted compared to senior officer) to 2.76 (fourth compared to first quintile of MHI). This increased odds of CKD is consistent with a recent meta-analysis of US studies, which found a pooled odds of prevalent CKD in low compared to high income groups of 1.55 (53).

Genetic differences, such as the elevated prevalence of high risk APOL1 risk variants in Black Americans, may partially account for racial disparities in CKD found within the MHS (126). However, race is increasingly recognized as a poor proxy for underlying genetics (237, 238). While certain genetic variants, such as APOL1, are associated with black race, the social construct of race does not accurately reflect or completely align with genetic differences resulting from ancestral origin.(238) Among Americans who identify as Black, roughly one quarter of ancestry informative genetic markers suggest non-African origin—likely in part a result of European colonization and the forced enslavement of Africans in America (239, 240). Instead, race reflects a

complex mixture of social, cultural, and biological factors (237). Further, the COVID 19 pandemic has highlighted the substantial role that systemic racism plays in health outcomes for Americans of color.

The presence of SES disparities in CKD within the MHS supports a role for social factors in black-white CKD disparities. The role of low SES in racial disparities in kidney mortality has been demonstrated in analyses of merged United States Renal Data System (USRDS)-Census data for 11,027 ESRD patients, which found elevated mortality rates for Black compared to White ESRD patients were attenuated in high versus low SES neighborhoods after adjusting for baseline demographics, clinical characteristics, rurality, and access to care factors (14). Similarly, in participants of the Americans' Changing Lives study followed over 25 years, adjusting for SES fully attenuated the increased risk of death in black compared to white individuals with CKD (241).

The presence of SES disparities in CKD within the MHS further suggests that presence of healthcare coverage alone is not sufficient to mitigate the effects of low SES on CKD. Social risks that are disproportionately prevalent in both low-income and minority populations may contribute to both racial and SES disparities in CKD found in the MHS. Social risks, such as lack of transportation, lack of childcare, and competing time and resource priorities, may impede access to healthcare services despite universal healthcare coverage (129, 130). Among publicly insured adults enrolled in Minnesota Health Care Programs, reported barriers to care included inability to cover out-of-pocket costs, transportation limitations, clinic hours that conflicted with other responsibilities, and lack of childcare (129). A population of majority low income, African American

"safety net" CKD patients reported similar barriers despite insurance coverage, including transportation difficulties, financial challenges and lack of work leave (130).

Social risks may also contribute to the racial and SES disparities in CKD seen in the MHS through numerous pathways outside of the healthcare system. These include increased stress and allostatic load, increased risk behaviors (e.g., smoking), barriers to health-promoting behaviors, reduced health literacy and knowledge, reduced social support, and increased risk of environmental exposures (13). However, data are limited to assess the relevance of these pathways in the MHS. Enlisted rank, high psychosocial stress, and low levels of social support were each associated with increased prevalence of overweight/obesity in Army spouses (242). Smoking is more common among enlisted military personnel compared to officers (243), suggesting this risk behavior could contribute to increased CKD risk among lower rank individuals.

Our findings are consistent with prior findings relating to both racial and SES disparities in CKD in populations with universal healthcare coverage. Studies in countries that provide universal healthcare coverage, including the UK, Denmark and Australia, have found that low SES is associated with increased CKD prevalence, elevated ESRD incidence, and reduced dialysis survival (59, 122, 124). A systematic review of 25 studies assessing racial disparities in mortality within the VHA found that mortality among Black beneficiaries was similar to or lower than white beneficiaries; however, when narrowed to individuals with CKD, mortality rates in Black compared to white beneficiaries were modestly elevated (125). Further, in a sample of 56,767 veterans with stage 3 or 4 CKD, Black veterans were more likely than their white counterparts to progress to ESRD

despite universal access to care and higher rates of nephrology referral for Black compared to white veterans (126).

Of note, the MHS population has several unique aspects that distinguish it from the general U.S. population, which may limit generalizability of our findings. Since access to the MHS system is achieved through employment in (or retirement from) the military, the MHS population may be more economically stable than the general U.S. population. In addition, military service members often have access to benefits that are not typically available in the general U.S. population, such as subsidized childcare, savings on food expenses through commissaries, and educational support. However, these subsidies are not universally available, do not address all social risks, and their health benefits may be countered by the negative health effects of increased stress and demands associated with individual and family military service (e.g., deployment, combat, separations).

This analysis is among the first studies assessing the burden of CKD in the MHS and provides additional context for understanding the role of universal healthcare coverage in racial and SES disparities in CKD. Strengths of the study include the large sample size and the use of a validated, laboratory value-based e-phenotype—in combination with diagnosis codes—to improve sensitivity of CKD detection. However, we must acknowledge important limitations. The administrative data used in this analysis are intended for use in claims adjudication and not research, and thus have inherent shortcomings. Because the data are cross-sectional, causal links between race or SES and CKD prevalence cannot be inferred. Because we lack laboratory data for purchased care interactions, our analysis may have missed laboratory results indicative of CKD, and thus

we may underestimate the true prevalence of CKD. Particularly if purchased and direct care use varies by race, such misclassification may introduce bias. In addition, because race was assumed to be black in calculating eGFR for those with missing or unknown race (to provide a more specific measure of CKD), GFR estimates in this population were inflated, and we may underestimate prevalence of CKD. Given the recently identified disparity in CKD among Pacific Islanders (10), the combined AAPI race category available from the MDR may mask CKD disparities in the MHS Pacific Islander population. While rank is commonly used to represent SES (224, 225), it does not perfectly align with the three traditional components of SES (income, education, and occupation) and may also reflect differences in social standing in context of military hierarchy, as well as differences in health knowledge, attitudes and beliefs, which may influence health and care seeking behaviors as well as quality of care and, ultimately, CKD outcomes. The transient nature of the MHS population may limit accuracy and usefulness of the zip code level MHI data, as a beneficiary's most recent zip code may not accurately reflect long term exposure to area deprivation.

Despite universal healthcare coverage provided through the MHS, racial and socioeconomic CKD disparities exist in this population. Our findings are consistent with racial and socioeconomic CKD disparities identified in other domestic and international settings that provide universal healthcare coverage. Genetic differences may partially account for the racial disparities in CKD in insured populations. However, the existence of disparities by rank and zip code level MHI suggest that SES and associated social risks may increase risk for CKD despite access to universal healthcare coverage. Therefore, access to healthcare coverage alone may not be sufficient, and broader interventions to

address social risk factors may be necessary to significantly mitigate racial and socioeconomic CKD disparities.

CHAPTER 6: SUMMARY AND DISCUSSION

Despite the burden of chronic kidney disease (CKD) in the general United States (US) population, little research has been conducted to understand the prevalence and determinants of CKD in the Military Health System (MHS). This study is among the first to assess the burden of CKD in the MHS, and the first to explore relationships between CKD and social determinants of health (SDH) in the MHS. In the general US population, increasing evidence supports a causal link between health-impeding SDH—or social risks—and the incidence, prevalence and progression of CKD, as well as the racial and socioeconomic disparities that characterize the disease (13, 52, 53). Social risks that are associated with increased risk for CKD in the general population are linked closely with poverty and include limited access to healthcare, exposure to pollutants, food and housing insecurity, reduced social support, and experiences of discrimination, among others (13). The MHS—where all beneficiaries have access to healthcare coverage—provides a rare opportunity to assess the role of SDH in CKD in context of universal healthcare coverage in the United States.

This study developed and validated a novel laboratory value based electronic phenotype to more accurately detect CKD from the electronic health record (EHR) and applied it to the MHS to determine, for the first time, the prevalence of CKD in adults MHS beneficiaries. In addition, we determined the prevalence of coded and uncoded CKD in the MHS and identified groups more likely to have uncoded CKD. Finally, we identified associations between SDH—including race, rank (a proxy for socioeconomic status and class), zip code level median household income (MHI), and marital status—

and prevalence of CKD. Specifically, we identified the following results across three aims:

AIM 1: LABORATORY VALUE-BASED E-PHENOTYPE TO IDENTIFY CKD FROM THE EHR

CKD often goes unrecorded in the EHR, and thus use of diagnosis codes to identify CKD often has poor sensitivity. Aim 1 developed a consensus-based e-phenotype for CKD to improve detection of CKD from the EHR using laboratory values indicative of CKD. We implemented the CKD e-phenotype in multiple clinical settings and validated the accuracy of the e-phenotype for detecting CKD through a blinded chart review for a random sample of patients across settings.

The CKD e-phenotype was determined by a working group with expertise in nephrology and clinical terminology and defined as: most recent eGFR < 60 ml/min per 1.73 m2 with at least one value <60 ml/min per 1.73 m2 >90 days prior and/or proteinuria presenting as a UACR ≥ 30 mg/g in the most recent test with at least one positive value >90 days prior. The e-phenotype includes several pragmatic elements to accommodate missing data in the EHR. Specifically, the e-phenotype allows for assumptions about race based on population demographics when—as is often the case—individual level data on race are unavailable in the EHR. If patients are assumed to be black, the e-phenotype will be less sensitive and more specific. If patients are assumed to be non-black, the e-phenotype will be more sensitive and less specific.

Similarly, because UACR is frequently unavailable in the EHR, the e-phenotype allows for use of other proteinuria measures (i.e., UPCR or UA). Based on correlation analyses of same-day UACR and UPCR or same day UACR and urine albumin results,

the working group concluded that—in the absence of a UACR result—a sensitive definition of CKD would consider a negative urine albumin result as normal to mildly increased (Kidney Disease Improving Global Outcomes [KDIGO] A1 category), urine albumin results in the trace to 1+ range as moderately increased (KDIGO A2 category), and urine albumin results of 2+ or greater as severely increased (KDIGO A3 category). However, shifting the UA cutoffs to include negative/trace as A1 would yield more specific results.

The e-phenotype was implemented and validated across 4 distinct clinical settings in a population totaling 1,680,334. After review of 207 randomly selected charts, sensitivity for identification of patients with CKD was 99% and specificity was 99%. In addition, 202 of 207 charts were correctly categorized by CKD stage, suggesting a diagnostic accuracy of 98%.

AIM 2: PREVALENCE OF CODED AND UNCODED CKD IN ADULT MHS BENEFICIARIES

Aim 2 examined the prevalence of coded and uncoded CKD among adult MHS beneficiaries and compared the characteristics of populations with coded and uncoded CKD through a cross-sectional analysis of MDR data from fiscal years 2016 to 2018. Of 3,330,893 MHS beneficiaries included in the study, 3.2% (105,504 people) had CKD identified either by ICD-10 code or laboratory values indicative of CKD. Of those with CKD, only 37% had an ICD-10 code for CKD recorded in the MDR. Of note, 60% of individuals with coded CKD did not have lab values indicative of CKD recorded in the MDR. Individuals with uncoded CKD were on average younger, more likely to be female and active duty, and less likely to be of Black race or to have diabetes or hypertension.

Among those with laboratory test results recorded in the MHS, those with uncoded CKD had fewer numbers of urine albumin, UACR, UPCR, sCr, and eGFR results.

AIM 3: SOCIAL DETERMINANTS OF HEALTH ASSOCIATED WITH PREVALENT CKD

Aim 3 examined associations between SDH (race, rank, zip code MHI, and marrital status) and CKD prevalence through a cross sectional analysis of MDR data from fiscal years 2016 to 2018. Compared to beneficiaries without CKD, the 3.2% of the population with CKD were on average older, less likely to be active duty, more likely to be retired, more likely to be Black, more likely to be senior enlisted or senior officer and more likely to be married. Beneficiaries with CKD also had higher average BMI and were more likely to have hypertension, diabetes and depression compared to those without CKD.

In models adjusted for suspected confounders, Black beneficiaries had 1.67 times higher odds of prevalent CKD compared to their white counterparts. Compared to senior officers, senior enlisted beneficiaries had higher 1.7 times higher odds of CKD and junior enlisted beneficiaries had 1.3 times higher odds of CKD in confounder-adjusted analyses. Unexpectedly, single beneficiaries had lower odds of CKD than married beneficiaries in confounder-adjusted analyses, suggesting any social support provided by married is not protective in this context. Decreasing zip code level MHI was associated with increasing odds of prevalent CKD through all quintiles except the lowest. Compared to the very high MHI quintile, the high quintile had 1.40 times greater odds of CKD, the medium quintile had 1.98 times greater odds of CKD, the low quintile had 2.76 times greater odds of CKD, and the very low quintile had 2.58 times greater odds of CKD.

STRENGTHS AND LIMITATIONS

Strengths

This study developed and leveraged a novel phenotype for detecting CKD from the EHR with improved accuracy compared to diagnosis codes. The e-phenotype was implemented and validated at multiple clinical sites with distinct patient populations and varied health IT infrastructure. The overall e-phenotype validation population was large, at nearly 1.7 million patients, and included chart reviews for more than 200 patients. Through application of the e-phenotype to the MHS, we provide a first attempt to identify all cases of CKD in the MHS population. This work also provides a novel effort to understand how social risks influence CKD outcomes in the MHS population, yielding additional context for understanding the role of universal healthcare coverage in racial and SES disparities in CKD in a large population. In addition, we successfully applied zip code level MHI data as a marker of poverty and area deprivation for the first time in the MHS population.

In addition, this study highlighted key challenges in leveraging the MDR—and other clinical data sets—for use in research, as well as challenges relating to the lack of interoperability of clinical and social data for use in the clinical management of chronic disease both within and beyond the MHS. Specifically, this study highlights clinical care, population health management, and research challenges resulting from the lack of access to laboratory data from purchased care settings. Currently, the results of laboratory tests performed in the purchased care setting are not available in the MHS for either research or clinical management. Thus, any attempts to systematically identify people with CKD—or other laboratory defined chronic condition—for research or population health efforts are substantially inhibited, as without complete access to laboratory data, we will

fail to identify some people with the disease of interest. Further, clinicians may not be able to identify laboratory defined chronic conditions, such as CKD, in routine care at the individual patient level, as even individual clinicians cannot access purchased care laboratory information that is critical to the detection, monitoring and management of disease. Similarly, poor availability of data on social risks in the MHS (and many other health settings) represents a challenge to the integration of social and medical care, as well as to SDH research leveraging clinical data. Many of the data available in the EHR are poor proxies for the social risks we hope to measure. For example, race as a variable reflects a complex mix of social, cultural and biological information that cannot easily be parsed out. Similarly, rank reflects not only income and education level but also social status within the Military and thus the implications of findings relating to rank are not clear. Availability of more accurate social risk data in the EHR could support both social risk-informed (e.g., not prescribing a medication that requires refrigeration to a person who is homeless and this has no access to a refrigerator) and social need targeted care (e.g., referring a person suffering from food insecurity to a food bank to improve dietary disease management) (244), as well as better assessment of the influence of these factors on a variety of health outcomes.

Limitations

Data used in these analyses are administrative, and thus are intended for use in claims adjudication and not research. Due to the cross-sectional nature of the data, causality cannot be inferred. The e-phenotype used in this study relies on availability and accuracy of EHR data, including eGFR, UACR (or urine albumin/UPCR), and race—which are frequently missing from the EHR. More than half of the total MHS population

lacked results for these laboratory tests, and test results acquired through purchased care are not available in the MDR. Thus, the CKD e-phenotype may have failed to capture CKD in individuals who acquired laboratory results through purchased care or who simply had never received any kidney tests. As a result, we may underestimate the true burden of CKD in the MHS. In addition, race was assumed to be black in calculating eGFR for those with missing or unknown race (to provide a more specific measure of CKD), and therefore, GFR estimates in this population were inflated, potentially further underestimating prevalence of CKD. Because the e-phenotype uses both inpatient and outpatient laboratory values, it may misclassify some patients who had recurrent AKI as having CKD; however, this did not occur in the validation study.

In addition, the variables available through the MDR may carry certain measurement biases. For example, the combined AAPI race category available from the MDR may mask CKD disparities in the MHS Pacific Islander population, as disproportionate rates of ESRD were recently identified for the Pacific Islander population using USRDS data (10). While rank is commonly used to represent SES,(224, 225) it does not perfectly align with the three traditional components of SES (income, education, and occupation) and may also reflect differences in social standing in context of military hierarchy, as well as differences in health knowledge, attitudes and beliefs. The transient nature of the MHS population may limit accuracy and usefulness of the zip code level MHI data, as a beneficiary's most recent zip code may not accurately reflect long term exposure to area deprivation. Finally, the MHS population has several unique aspects that distinguish it from the general U.S. population, which may limit generalizability of our findings.

IMPLICATIONS

This work provides a novel and well validated method for detecting CKD from the EHR with improved sensitivity compared to diagnosis codes. The pragmatic, CKD e-phenotype has many potential uses across research and clinical care. In the research context, the e-phenotype provides a tool to more accurately identify CKD populations for epidemiologic and health services research, as demonstrated by aims 2 and 3 of this project. In addition, it may provide a means to identify a broader sample of potentially eligible patients for recruitment into clinical trials. In the context of clinical care, the e-phenotype may be used to generate population health panels of patients likely to have CKD for further follow up, including diagnosis of CKD in individuals who do in fact have CKD but have not been diagnosed, as well as quality improvement efforts to increase the proportion of people with CKD receiving guideline-based care (e.g., prescription of renin-angiotensin aldosterone system blockers).

The prevalence of CKD in MHS beneficiaries may be higher than previously recognized, as a large number of beneficiaries have laboratory values indicative of CKD but lack diagnosis codes for the disease. Uncoded CKD was more common in groups traditionally considered to be of lower risk for progressive CKD: younger adults, women, people of non-Black race, and those without diabetes or hypertension.(10) Lack of CKD coding in these traditionally low CKD risk groups suggests clinicians may be missing CKD diagnoses—despite available laboratory data indicative of CKD. These individuals with uncoded CKD may receive suboptimal care, as prior research has shown that lack of clinical coding for CKD is associated with guideline discordant care(227) and a lower likelihood that the patient is aware of their CKD diagnosis.(230)

Despite access to universal healthcare coverage provided by the MHS, and the mitigation of racial disparities within the MHS in other disease areas (199-204), the prevalence of CKD in the MHS is disproportionately high in individuals of Black race, as well as in individuals of low socioeconomic status. While Genetic differences, such as the elevated prevalence of high risk APOL1 risk variants in Black Americans, may partially account for these racial disparities,(126) race is increasingly recognized as a social rather than biological construct, providing a poor proxy for ancestral differences in genetics and instead, reflecting a complex mixture of social, cultural, and biological factors (237, 238).

The presence of SES disparities in CKD within the MHS suggests that access to healthcare coverage alone is not sufficient to mitigate the effects of low SES on CKD. Social risks that are disproportionately prevalent in both low-income and under-represented populations, such as lack of transportation and childcare, may impede access to healthcare services despite universal healthcare coverage,(129, 130) thereby contributing to racial and SES disparities. In addition, social risks may contribute to increased prevalence of CKD through social risks that impede health via mechanisms outside of the healthcare system (e.g., barriers to health promoting behaviors, increase stress and allostatic load).

FUTURE DIRECTIONS

This project serves as a starting point for understanding the burden of CKD in the MHS, and further research is needed to understand CKD in this population. For example, longitudinal studies should be leveraged to better understand incidence of CKD and

ESRD in this population, as well as to identify risk factors, mediators and moderators that contribute to disease onset and progression. Specific areas of interest to the MHS population may include exploration of high protein intake and/or protein supplementation and exposures to high exertion activities in high temperature areas during deployment activities—both of which may be commonly experienced in the active duty population. In addition, further exploration of acute kidney injury rates in the MHS is warranted.

Efforts are needed within the MHS to improve CKD care and outcomes, specifically relating to better detection and coding of CKD and addressing racial and socioeconomic disparities in the prevalence of the disease. Application of the CKD e-phenotype (210) in population health management initiatives in the MHS and other clinical settings could potentially help identify individuals likely to have CKD, thereby enabling improved disease management (i.e., ensuring all cases of CKD are coded in the EHR, increasing the proportion of beneficiaries with CKD who receive guideline based care).

However, such work would have greater impact if complemented by policy efforts to ensure access to purchased care laboratory data, as the phenotype cannot be applied accurately in the absence of laboratory data. As discussed above, this work highlights a clear need for the MHS to pursue access to laboratory data acquired in the purchased care setting—not only for healthcare and research relating to CKD, but for all of the many chronic conditions that rely on laboratory data for optimal detection and management. While poor interoperability of such data is not unique to the MHS, the MHS does have a unique opportunity in its role as a payor, to require that purchased care laboratory results data be reported back to the MHS in order for reimbursements to be

received by purchased care providers, as is the case in similar health systems, such as the Indian Health Service. Improving access to purchased care laboratory data within the MHS represents a significant opportunity to improve both clinical care and research relating to numerous chronic conditions.

Given the associations between social risks and CKD in both the MHS and general population, addressing racial and SES CKD disparities in the MHS may require re-evaluation of a broader set of social support services provided to the Military population and their beneficiaries. However, further research is needed to understand how to best to address these challenges – both within the MHS and in the general population. Specifically, research is needed to inform integration of social and medical care, including capturing social risks and social needs in clinical contexts, as well as providing social risk-informed and social need-targeted care (244). Such work will not only require strengthening of the health IT infrastructure to improve exchange of social risk data across social and healthcare settings, as well as improved understanding of optimal methods for capturing and reviewing social risk data in clinical contexts that will be realistic and which can be aligned with clinical workflows. Such efforts are underway, through initiatives including the Gravity project (https://www.hl7.org/gravity/) and the e-Care Plan Project for People with Multiple Chronic Conditions (https://ecareplan.ahrq.gov/collaborate/), among many others.

CONCLUSIONS

The prevalence of CKD in the MHS may be higher than previously recognized. Prevalence of CKD in the MHS appears to be disproportionately high in individuals of Black race as well as in those of low socioeconomic status. However, CKD

is less likely to be coded in individuals who are traditionally considered lower risk for CKD, including younger adults, females, people of non-Black race, and those without diabetes or hypertension. Research and clinical quality improvement efforts are needed to improve detection and coding of CKD in the MHS, as well as to address the racial and SES CKD disparities present in the system.

Table 1. LOINC Codes to Identify eGFR from the MDR

Code	Description
33914-3	Glomerular filtration rate/1.73 sq M.predicted [Volume Rate/Area] in Serum or Plasma by Creatinine-based formula (MDRD)
48642-3	Glomerular filtration rate/1.73 sq M predicted among non-blacks [Volume Rate/Area] in Serum or Plasma by Creatinine-based formula (MDRD)
48643-1	Glomerular filtration rate/1.73 sq M predicted among blacks [Volume Rate/Area] in Serum or Plasma by Creatinine-based formula (MDRD)
50044-7	Glomerular filtration rate/1.73 sq M predicted among females [Volume Rate/Area] in Serum or Plasma by Creatinine-based formula (MDRD)
50210-4	Glomerular filtration rate/1.73 sq M.predicted [Volume Rate/Area] in Serum or Plasma by Cystatin-based formula
62238-1	Glomerular filtration rate/1.73 sq M.predicted [Volume Rate/Area] in Serum or Plasma by Creatinine-based formula (CKD-EPI)
69405-9	Glomerular filtration rate/1.73 sq M.predicted [Volume Rate/Area] in Serum or Plasma
70969-1	Glomerular filtration rate/1.73 sq M predicted among males [Volume Rate/Area] in Serum or Plasma by Creatinine-based formula (MDRD)
76633-7	Glomerular filtration rate/1.73 sq M. predicted by Creatinine-based formula (MDRD) in Blood
77147-7	Glomerular filtration rate/1.73 sq M.predicted [Volume Rate/Area] in Serum, Plasma or Blood by Creatinine-based formula (MDRD)

Table 2. LOINC Codes for UACR Mapped to MDR Laboratory Tests

Code	Description	MDR Test
44292-1	Microalbumin/Creatinine [Mass Ratio] in 12 hour Urine	
14958-3	Microalbumin/Creatinine [Mass Ratio] in 24 hour Urine	
14959-1	Microalbumin/Creatinine [Mass Ratio] in Urine	
77254-1	Microalbumin/Creatinine [Ratio] in 24 hour Urine by Detection limit <= 1.0 mg/L	
59159-4	Microalbumin/Creatinine [Ratio] in 24 hour Urine	
77253-3	Microalbumin/Creatinine [Ratio] in Urine by Detection limit <= 1.0 mg/L	
30000-4	Microalbumin/Creatinine [Ratio] in Urine	
30001-2	Microalbumin/Creatinine [Ratio] in Urine by Test strip	
14585-4	Albumin/Creatinine [Molar ratio] in Urine	
13705-9	Albumin/Creatinine [Mass Ratio] in 24 hour Urine	
9318-7	Albumin/Creatinine [Mass Ratio] in Urine	
14585-4	Albumin/Creatinine [Molar ratio] in Urine	
76401-9	Albumin/Creatinine [Ratio] in 24 hour Urine	
32294-1	Albumin/Creatinine [Ratio] in Urine	

Table 3. LOINC Codes for UA Mapped to MDR Laboratory Tests

Code	Description	MDR Test
50949-7	Albumin [Presence] in Urine by Test strip	
20621-9	Albumin/Creatinine [Presence] in Urine by Test strip	
11218-5	Microalbumin [Mass/volume] in Urine by Test strip	
30001-2	Microalbumin/Creatinine [Ratio] in Urine by Test strip	

Table 4. LOINC Codes for UPCR Mapped to MDR Laboratory Tests

Code	Description	MDR Test
60678-0	Protein/Creatinine [Mass Ratio] in 12 hour Urine	
13801-6	Protein/Creatinine [Mass Ratio] in 24 hour Urine	
2890-2	Protein/Creatinine [Mass Ratio] in Urine	
40486-3	Protein/Creatinine [Ratio] in 24 hour Urine	
34366-5	Protein/Creatinine [Ratio] in Urine	

Table 5. CPT Codes to Identify Dialysis Recipients from the MDR (210)

Code	Description
3066F	Documentation of treatment for nephropathy
36800, 36810, 36815	Insertion of cannula for hemodialysis, other purpose…
36818 - 36820	Arteriovenous anastomosis, open…
36821, 36831	Thrombectomy, open, arteriovenous fistula…
36832, 36833	Revision, open, arteriovenous fistula…
90935, 90937	Hemodialysis procedure with single evaluation…
90940	Hemodialysis access flow study to determine blood flow…
90945, 90947	Dialysis procedure other than hemodialysis…
90951 - 90962	ESRD related services monthly…
90963 - 90966	ESRD related services for home dialysis per full month…
90967 - 90970	ESRD related services for dialysis less than a full month…
90989, 90993	Dialysis training, patient, including helper…
90997	Hemoperfusion
90999, 99512	Unlisted dialysis procedure, inpatient or outpatient…
G0257	Unscheduled or emergency dialysis treatment for an ESRD…
G9231	Documentation of ESRD, dialysis, renal transplant…
S2065	Simultaneous pancreas kidney transplantation…
S9339	Home therapy; peritoneal dialysis, administrative…
36145	Introduction of needle or intracatheter; arteriovenous shunt created for dialysis…
36147	Introduction of needle and/or catheter, arteriovenous shunt created for dialysis…
90918 - 90921	ESRD related services per full month…
90925	ESRD related services (less than full month)…
G0308 – G0319	ESRD related services during the course of treatment…
G0320 – G0323	ESRD related services for home dialysis patients per full month…
G0324 – G0327	ESRD related services for home dialysis (less than full month)…
G0392, G0393	Transluminal balloon angioplasty, percutaneous; for maintenance of hemodialysis access…

Table 6. ICD-10 Codes to Identify Dialysis Recipients from the MDR (210)

Code	Description
N18.6	End stage renal disease
Z49	Encounter for care involving renal dialysis
Z91.15	Patient's noncompliance with renal dialysis
Z99.2	Dependence on renal dialysis

Table 7. CPT Codes to Identify Transplant Recipients from the MDR (210)

Code	Description
00868	Anesthesia for extraperitoneal procedures in lower abdomen, including urinary tract; renal transplant (recipient) (units: 10)
50340	Recipient nephrectomy (separate procedure)
50360, 50365	Renal allotransplantation; implantation of graft…
50380	Renal autotransplantation, reimplantation of kidney

Table 8. ICD-10 Codes to Identify Transplant Recipients from the MDR

Code	Description
Z94.0	Kidney transplant status

Table 9. ICD-10 Codes to Identify Diagnosed Diabetes from the MDR

Code	Description
E10.10	Type 1 diabetes mellitus with ketoacidosis without coma
E10.11	Type 1 diabetes mellitus with ketoacidosis with coma
E10.21	Type 1 diabetes mellitus with diabetic nephropathy
E10.22	Type 1 diabetes mellitus with diabetic chronic kidney disease
E10.29	Type 1 diabetes mellitus with other diabetic kidney complication
E10.311	Type 1 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E10.319	Type 1 diabetes mellitus with unspecified diabetic retinopathy without macular edema
E10.321	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E10.3211	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, right eye
E10.3212	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, left eye
E10.3213	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, bilateral
E10.3219	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, unspecified eye
E10.329	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema
E10.3291	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, right eye
E10.3292	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, left eye
E10.3293	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, bilateral
E10.3299	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, unspecified eye
E10.331	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E10.3311	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, right eye
E10.3312	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, left eye
E10.3313	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, bilateral
E10.3319	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, unspecified eye
E10.339	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema

E10.3391	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, right eye
E10.3392	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, left eye
E10.3393	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, bilateral
E10.3399	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, unspecified eye
E10.341	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E10.3411	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, right eye
E10.3412	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, left eye
E10.3413	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E10.3419	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, unspecified eye
E10.349	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema
E10.3491	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, right eye
E10.3492	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, left eye
E10.3493	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, bilateral
E10.3499	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, unspecified eye
E10.351	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema
E10.3511	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye
E10.3512	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye
E10.3513	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral
E10.3519	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye
E10.3521	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye
E10.3522	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye
E10.3523	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral

E10.3529	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye
E10.3531	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye
E10.3532	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye
E10.3533	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral
E10.3539	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye
E10.3541	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye
E10.3542	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye
E10.3543	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral
E10.3549	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye
E10.3551	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, right eye
E10.3552	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, left eye
E10.3553	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, bilateral
E10.3559	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye
E10.359	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema
E10.3591	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye
E10.3592	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye
E10.3593	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral
E10.3599	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye
E10.36	Type 1 diabetes mellitus with diabetic cataract
E10.37X1	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, right eye
E10.37X2	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, left eye

E10.37X3	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral
E10.37X9	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye
E10.39	Type 1 diabetes mellitus with other diabetic ophthalmic complication
E10.40	Type 1 diabetes mellitus with diabetic neuropathy, unspecified
E10.41	Type 1 diabetes mellitus with diabetic mononeuropathy
E10.42	Type 1 diabetes mellitus with diabetic polyneuropathy
E10.43	Type 1 diabetes mellitus with diabetic autonomic (poly)neuropathy
E10.44	Type 1 diabetes mellitus with diabetic amyotrophy
E10.49	Type 1 diabetes mellitus with other diabetic neurological complication
E10.51	Type 1 diabetes mellitus with diabetic peripheral angiopathy without gangrene
E10.52	Type 1 diabetes mellitus with diabetic peripheral angiopathy with gangrene
E10.59	Type 1 diabetes mellitus with other circulatory complications
E10.610	Type 1 diabetes mellitus with diabetic neuropathic arthropathy
E10.618	Type 1 diabetes mellitus with other diabetic arthropathy
E10.620	Type 1 diabetes mellitus with diabetic dermatitis
E10.621	Type 1 diabetes mellitus with foot ulcer
E10.622	Type 1 diabetes mellitus with other skin ulcer
E10.628	Type 1 diabetes mellitus with other skin complications
E10.630	Type 1 diabetes mellitus with periodontal disease
E10.638	Type 1 diabetes mellitus with other oral complications
E10.641	Type 1 diabetes mellitus with hypoglycemia with coma
E10.649	Type 1 diabetes mellitus with hypoglycemia without coma
E10.65	Type 1 diabetes mellitus with hyperglycemia
E10.69	Type 1 diabetes mellitus with other specified complication
E10.8	Type 1 diabetes mellitus with unspecified complications
E10.9	Type 1 diabetes mellitus without complications
E11.00	Type 2 diabetes mellitus with hyperosmolarity without nonketotic hyperglycemic-hyperosmolar coma (NKHHC)
E11.01	Type 2 diabetes mellitus with hyperosmolarity with coma
E11.10	Type 2 diabetes mellitus with ketoacidosis without coma
E11.11	Type 2 diabetes mellitus with ketoacidosis with coma
E11.21	Type 2 diabetes mellitus with diabetic nephropathy
E11.22	Type 2 diabetes mellitus with diabetic chronic kidney disease
E11.29	Type 2 diabetes mellitus with other diabetic kidney complication
E11.311	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E11.319	Type 2 diabetes mellitus with unspecified diabetic retinopathy without macular edema

E11.321	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E11.3211	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, right eye
E11.3212	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, left eye
E11.3213	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, bilateral
E11.3219	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, unspecified eye
E11.329	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema
E11.3291	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, right eye
E11.3292	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, left eye
E11.3293	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, bilateral
E11.3299	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, unspecified eye
E11.331	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E11.3311	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, right eye
E11.3312	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, left eye
E11.3313	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, bilateral
E11.3319	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, unspecified eye
E11.339	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema
E11.3391	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, right eye
E11.3392	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, left eye
E11.3393	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, bilateral
E11.3399	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, unspecified eye

E11.341	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E11.3411	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, right eye
E11.3412	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, left eye
E11.3413	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E11.3419	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, unspecified eye
E11.349	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema
E11.3491	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, right eye
E11.3492	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, left eye
E11.3493	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, bilateral
E11.3499	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, unspecified eye
E11.351	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema
E11.3511	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye
E11.3512	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye
E11.3513	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral
E11.3519	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye
E11.3521	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye
E11.3522	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye
E11.3523	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral
E11.3529	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye
E11.3531	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye

E11.3532	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye
E11.3533	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral
E11.3539	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye
E11.3541	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye
E11.3542	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye
E11.3543	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral
E11.3549	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye
E11.3551	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, right eye
E11.3552	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, left eye
E11.3553	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, bilateral
E11.3559	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye
E11.359	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema
E11.3591	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye
E11.3592	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye
E11.3593	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral
E11.3599	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye
E11.36	Type 2 diabetes mellitus with diabetic cataract
E11.37X1	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, right eye
E11.37X2	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, left eye
E11.37X3	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral

E11.37X9	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye
E11.39	Type 2 diabetes mellitus with other diabetic ophthalmic complication
E11.40	Type 2 diabetes mellitus with diabetic neuropathy, unspecified
E11.41	Type 2 diabetes mellitus with diabetic mononeuropathy
E11.42	Type 2 diabetes mellitus with diabetic polyneuropathy
E11.43	Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy
E11.44	Type 2 diabetes mellitus with diabetic amyotrophy
E11.49	Type 2 diabetes mellitus with other diabetic neurological complication
E11.51	Type 2 diabetes mellitus with diabetic peripheral angiopathy without gangrene
E11.52	Type 2 diabetes mellitus with diabetic peripheral angiopathy with gangrene
E11.59	Type 2 diabetes mellitus with other circulatory complications
E11.610	Type 2 diabetes mellitus with diabetic neuropathic arthropathy
E11.618	Type 2 diabetes mellitus with other diabetic arthropathy
E11.620	Type 2 diabetes mellitus with diabetic dermatitis
E11.621	Type 2 diabetes mellitus with foot ulcer
E11.622	Type 2 diabetes mellitus with other skin ulcer
E11.628	Type 2 diabetes mellitus with other skin complications
E11.630	Type 2 diabetes mellitus with periodontal disease
E11.638	Type 2 diabetes mellitus with other oral complications
E11.641	Type 2 diabetes mellitus with hypoglycemia with coma
E11.649	Type 2 diabetes mellitus with hypoglycemia without coma
E11.65	Type 2 diabetes mellitus with hyperglycemia
E11.69	Type 2 diabetes mellitus with other specified complication
E11.8	Type 2 diabetes mellitus with unspecified complications
E11.9	Type 2 diabetes mellitus without complications
E13.00	Other specified diabetes mellitus with hyperosmolarity without nonketotic hyperglycemic-hyperosmolar coma (NKHHC)
E13.01	Other specified diabetes mellitus with hyperosmolarity with coma
E13.10	Other specified diabetes mellitus with ketoacidosis without coma
E13.11	Other specified diabetes mellitus with ketoacidosis with coma
E13.21	Other specified diabetes mellitus with diabetic nephropathy
E13.22	Other specified diabetes mellitus with diabetic chronic kidney disease
E13.29	Other specified diabetes mellitus with other diabetic kidney complication
E13.311	Other specified diabetes mellitus with unspecified diabetic retinopathy with macular edema
E13.319	Other specified diabetes mellitus with unspecified diabetic retinopathy without macular edema

E13.321	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E13.3211	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, right eye
E13.3212	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, left eye
E13.3213	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, bilateral
E13.3219	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, unspecified eye
E13.329	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema
E13.3291	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, right eye
E13.3292	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, left eye
E13.3293	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, bilateral
E13.3299	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, unspecified eye
E13.331	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E13.3311	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, right eye
E13.3312	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, left eye
E13.3313	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, bilateral
E13.3319	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, unspecified eye
E13.339	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema
E13.3391	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, right eye
E13.3392	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, left eye
E13.3393	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, bilateral
E13.3399	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, unspecified eye

E13.341	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E13.3411	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, right eye
E13.3412	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, left eye
E13.3413	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E13.3419	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, unspecified eye
E13.349	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema
E13.3491	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, right eye
E13.3492	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, left eye
E13.3493	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, bilateral
E13.3499	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, unspecified eye
E13.351	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema
E13.3511	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye
E13.3512	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye
E13.3513	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral
E13.3519	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye
E13.3521	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye
E13.3522	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye
E13.3523	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral
E13.3529	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye
E13.3531	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye

E13.3532	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye
E13.3533	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral
E13.3539	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye
E13.3541	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye
E13.3542	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye
E13.3543	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral
E13.3549	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye
E13.3551	Other specified diabetes mellitus with stable proliferative diabetic retinopathy, right eye
E13.3552	Other specified diabetes mellitus with stable proliferative diabetic retinopathy, left eye
E13.3553	Other specified diabetes mellitus with stable proliferative diabetic retinopathy, bilateral
E13.3559	Other specified diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye
E13.359	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema
E13.3591	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye
E13.3592	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye
E13.3593	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral
E13.3599	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye
E13.36	Other specified diabetes mellitus with diabetic cataract
E13.37X1	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment, right eye
E13.37X2	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment, left eye

E13.37X3	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral
E13.37X9	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye
E13.39	Other specified diabetes mellitus with other diabetic ophthalmic complication
E13.40	Other specified diabetes mellitus with diabetic neuropathy, unspecified
E13.41	Other specified diabetes mellitus with diabetic mononeuropathy
E13.42	Other specified diabetes mellitus with diabetic polyneuropathy
E13.43	Other specified diabetes mellitus with diabetic autonomic (poly)neuropathy
E13.44	Other specified diabetes mellitus with diabetic amyotrophy
E13.49	Other specified diabetes mellitus with other diabetic neurological complication
E13.51	Other specified diabetes mellitus with diabetic peripheral angiopathy without gangrene
E13.52	Other specified diabetes mellitus with diabetic peripheral angiopathy with gangrene
E13.59	Other specified diabetes mellitus with other circulatory complications
E13.610	Other specified diabetes mellitus with diabetic neuropathic arthropathy
E13.618	Other specified diabetes mellitus with other diabetic arthropathy
E13.620	Other specified diabetes mellitus with diabetic dermatitis
E13.621	Other specified diabetes mellitus with foot ulcer
E13.622	Other specified diabetes mellitus with other skin ulcer
E13.628	Other specified diabetes mellitus with other skin complications
E13.630	Other specified diabetes mellitus with periodontal disease
E13.638	Other specified diabetes mellitus with other oral complications
E13.641	Other specified diabetes mellitus with hypoglycemia with coma
E13.649	Other specified diabetes mellitus with hypoglycemia without coma
E13.65	Other specified diabetes mellitus with hyperglycemia
E13.69	Other specified diabetes mellitus with other specified complication
E13.8	Other specified diabetes mellitus with unspecified complications
E13.9	Other specified diabetes mellitus without complications
O24.011	Pre-existing type 1 diabetes mellitus, in pregnancy, first trimester
O24.012	Pre-existing type 1 diabetes mellitus, in pregnancy, second trimester
O24.013	Pre-existing type 1 diabetes mellitus, in pregnancy, third trimester
O24.019	Pre-existing type 1 diabetes mellitus, in pregnancy, unspecified trimester
O24.02	Pre-existing type 1 diabetes mellitus, in childbirth
O24.03	Pre-existing type 1 diabetes mellitus, in the puerperium
O24.111	Pre-existing type 2 diabetes mellitus, in pregnancy, first trimester

O24.112	Pre-existing type 2 diabetes mellitus, in pregnancy, second trimester
O24.113	Pre-existing type 2 diabetes mellitus, in pregnancy, third trimester
O24.119	Pre-existing type 2 diabetes mellitus, in pregnancy, unspecified trimester
O24.12	Pre-existing type 2 diabetes mellitus, in childbirth
O24.13	Pre-existing type 2 diabetes mellitus, in the puerperium
O24.311	Unspecified pre-existing diabetes mellitus in pregnancy, first trimester
O24.312	Unspecified pre-existing diabetes mellitus in pregnancy, second trimester
O24.313	Unspecified pre-existing diabetes mellitus in pregnancy, third trimester
O24.319	Unspecified pre-existing diabetes mellitus in pregnancy, unspecified trimester
O24.32	Unspecified pre-existing diabetes mellitus in childbirth
O24.33	Unspecified pre-existing diabetes mellitus in the puerperium
O24.811	Other pre-existing diabetes mellitus in pregnancy, first trimester
O24.812	Other pre-existing diabetes mellitus in pregnancy, second trimester
O24.813	Other pre-existing diabetes mellitus in pregnancy, third trimester
O24.819	Other pre-existing diabetes mellitus in pregnancy, unspecified trimester
O24.82	Other pre-existing diabetes mellitus in childbirth
O24.83	Other pre-existing diabetes mellitus in the puerperium

Table 10. ICD-10 Codes to Identify Diagnosed Hypertension from the MDR

Code	Description
I10	Essential (primary) hypertension
I11.0	Hypertensive heart disease with heart failure
I11.9	Hypertensive heart disease without heart failure
I12.0	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease
I12.9	Hypertensive chronic kidney disease with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease
I13.0	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease
I13.10	Hypertensive heart and chronic kidney disease without heart failure, with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease
I13.11	Hypertensive heart and chronic kidney disease without heart failure, with stage 5 chronic kidney disease, or end stage renal disease
I13.2	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease
I15.0	Renovascular hypertension
I15.1	Hypertension secondary to other renal disorders
I15.2	Hypertension secondary to endocrine disorders
I15.8	Other secondary hypertension
I15.9	Secondary hypertension, unspecified

Table 11. ICD-10 Codes to Identify Diagnosed Major Depression from the MDR

Code	Description
F32.0	Major depressive disorder, single episode, mild
F32.1	Major depressive disorder, single episode, moderate
F32.2	Major depressive disorder, single episode, severe without psychotic features
F32.3	Major depressive disorder, single episode, severe with psychotic features
F32.4	Major depressive disorder, single episode, in partial remission
F32.9	Major depressive disorder, single episode, unspecified
F33.0	Major depressive disorder, recurrent, mild
F33.1	Major depressive disorder, recurrent, moderate
F33.2	Major depressive disorder, recurrent severe without psychotic features
F33.3	Major depressive disorder, recurrent, severe with psychotic symptoms
F33.41	Major depressive disorder, recurrent, in partial remission
F33.9	Major depressive disorder, recurrent, unspecified

Table 12. ICD-10 Codes to Identify Diagnosed HIV from the MDR

Code	Description
B20	Human immunodeficiency virus [HIV] disease
B97.35	Human immunodeficiency virus, type 2 [HIV 2] as the cause of diseases classified elsewhere
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status

Table 13: Sample Size Estimates Required for Specific Aim 2, Hypotheses 2a-d

Standard Deviation	Sample size (per group)	Detectable Difference in Mean
5	17,442	0.15
10	17,442	0.30
15	17,442	0.45
20	17,442	0.60
25	17,442	0.75
30	17,442	0.90
35	17,442	1.05
40	17,442	1.20
45	17,442	1.35
50	17,442	1.50

** Assumes a two-sided alpha of $p < 0.05$ and a power of $1-\beta = 0.80$*

Table 14: Sample Size Estimates Required for Specific Aim 2, Hypotheses 2e-i

Variable	Proportion in Coded CKD Population (2015)	Sample size (per group)	Estimated Proportion in Uncoded CKD	Detectable difference (absolute)
Black Race	14.7%	16,764	15.8%	> 1.1
Female Sex	53.8%	17,294	55.3%	> 1.5
Active Duty	10.5%	15,365	11.5%	> 1.0
Diabetes	24.2%	16,720	22.9%	> 1.3
Hypertension	42.4%	16,952	40.9%	> 1.5

** Assumes a two-sided alpha of $p < 0.05$ and a power of $1-\beta = 0.80$*

Table 15: Sample Size Estimates Required for Specific Aim 3

Alpha	Power	Univariable Sample Size	Multivariable Sample Size ($\rho = 0.8$)
0.05	80	24,037	66,769
0.05	90	33,279	92,442
0.05	95	42,033	116,758
0.01	95	61,290	170,250

** Assuming an event proportion of 3% and a minimum detectable odd ratio of 1.1*

Table 16: Assumptions and considerations for electronic phenotype implementation by site

Site	Determination of eGFR	Race Assumption	Personnel Involved	Estimated Time Investment	Challenges/ Barriers	Facilitators
Christiana Care	From lab (multiple equations)	All patients had a race and GFR was checked against race	1 nephrologist 1 information technologist 1 student 1 resident	**223 hours** Communication: 13 Data extraction: 79 Data merging & cleaning: 131	Separate EHRs used for in- and out-patient care during the study period; required matching and merging multiple warehouses, data marts and pulls directly from the EHRs to produce the dataset	None
Columbia	Recalculated from serum creatinine (CKD-EPI)	Assumed non-black if race not available	1 nephrologist 1 informaticist 1 research coordinator	**20 hours** Communication: 5 Data extraction: 10 Data cleaning: 5	None	Existing clinical data warehouse; eMERGE site with adequate infrastructure and IT support
Minnesota	Recalculated from serum creatinine (MDRD)	Assumed non-black if race not available	1 nephrologist 1 IT person	**44 hours** Communication: 4 Data extraction: 20 Data cleaning: 20	eGFR was less available than serum creatinine	Leveraged data extraction completed for an ongoing project
UCSF	From lab (CKD-EPI)	Assumed non-black if race not available	1 nephrologist 1 informaticist 1 IT person 1 statistician	**49 hours** Communication: 5 Data extraction: 20 Data cleaning: 24	LOINC codes not used at UCSF; no existing cross-walk to Clarity codes	Leveraged personal relationships

Utah	From lab (multiple equations)	Assumed non-black if race not available	1 informaticist	**40 hours** Communication: 0 Data extraction: 10 Data cleaning: 10 Data analysis: 20	Identifying relevant laboratory codes	None

Table 17: Characteristics of the e-Phenotype Implementation Population

	Total Population		Group 1: No eGFR		Group 2: eGFR >= 60		Group 3: eGFR 45-59		Group 4: eGFR 30-44		Group 5: eGFR 15-29		Group 6: eGFR < 15	
	N	% / SD	N	% / SD	N	% / SD	N	% / SD	N	% / SD	N	% / SD	N	% / SD
Number	2,082,017		940,223		1,001,213		84,348		34,045		13,009		9,170	
Age, years	49.5	18.7	44.9	18.3	50.8	17.2	70.3	13.8	73.6	13.8	71.2	15.3	61.5	15.8
Female	1,209,280	58.1%	549,534	58.4%	581,798	58.1%	47,886	56.8%	19,154	56.3%	6,854	52.7%	4,049	44.2%
Black	181,742	8.7%	65,481	7.0%	104,267	10.4%	5,567	6.6%	2,768	8.1%	1,603	12.3%	2,055	22.4%
Num eGFR measurements	6.0	16.9	N/A	N/A	6.9	15.1	15.5	29.4	24.0	44.4	31.3	54.0	34.8	67.7
Days to most recent eGFR	603.6	815.5	N/A	N/A	648.7	870.4	455.6	704.3	355.2	561.3	354.5	550.0	481.7	690.7
Prior eGFR <60	178,099	8.6%	N/A	N/A	79,812	8.0%	52,214	61.9%	27,905	82.0%	10,960	84.2%	7,199	78.5%
Prior GFR <60 90+d prior	143,487	6.9%	N/A	N/A	63,949	6.4%	42,343	50.2%	22,389	65.8%	8,941	68.7%	5,864	63.9%
Any UACR, UPCR, or UA	811,462	39.0%	128,244	13.6%	585,936	58.5%	56,305	66.8%	24,789	72.8%	9,877	75.9%	6,305	68.8%
Any UACR	140,256	6.7%	2,251	0.2%	102,858	10.3%	18,758	22.2%	10,224	30.0%	4,073	31.3%	2,090	22.8%
Num UACR measurements	2.0	2.9	0.9	1.2	2.0	2.6	2.5	3.2	2.7	3.6	2.9	4.2	2.3	3.9
Most recent UACR:														
a <30mg/g	101,137	72.1%	1,773	78.8%	81,015	78.8%	12,139	64.7%	5,033	49.2%	1,030	25.3%	146	7.0%
b 30 to 300mg/g	28,637	20.4%	357	15.9%	18,105	12.9%	4,963	26.5%	3,420	33.5%	1,380	33.9%	412	19.7%
c >300mg/g	10,482	7.5%	121	5.4%	3,738	2.7%	1,656	8.8%	1,771	17.3%	1,663	40.8%	1,532	73.3%
Any UPCR	68,131	3.3%	1,910	0.2%	41,646	4.2%	9,245	11.0%	7,658	22.5%	4,673	35.9%	2,998	32.7%
Num UPCR measurements	2.3	5.2	1.1	3.0	1.9	4.3	3.0	6.4	3.5	7.7	3.7	6.6	3.6	7.3
Most recent UPCR:														
a <150mg/g	30,932	45.4%	838	43.9%	21,755	52.2%	4,600	49.8%	2,820	36.8%	780	16.7%	138	4.6%
b 150 to 500mg/g	21,952	32.2%	638	33.4%	14,027	33.7%	2,907	31.4%	2,639	34.5%	1,398	29.9%	343	11.4%
c >500mg/g	15,247	22.4%	434	22.7%	5,864	14.1%	1,738	18.8%	2,199	28.7%	2,495	53.4%	2,517	84.0%
Any UA	754,379	36.2%	125,792	13.4%	541,761	54.1%	50,852	60.3%	21,967	64.5%	8,461	65.0%	5,541	60.4%
Num UA measurements	2.8	5.2	1.4	2.6	3.3	5.4	4.2	7.0	5.1	8.3	5.7	9.6	5.8	11.5
Most recent UA:														
a Neg	589,612	78.2%	97,753	77.7%	436,605	80.6%	37,424	73.6%	13,717	62.4%	3,516	41.6%	594	10.7%
b Trace to 30 (Trace, 1+)	118,870	15.8%	20,951	16.7%	80,438	14.8%	9,226	18.1%	4,977	22.7%	2,206	26.1%	1,071	19.3%
c 100 to >300 (2+, 3+, 4+)	45,608	6.0%	7,072	5.6%	24,545	4.5%	4,174	8.2%	3,244	14.8%	2,712	32.1%	3,860	69.7%
Dialysis	26,766	1.3%	4,562	0.5%	5,696	0.6%	3,518	4.2%	3,258	9.6%	3,059	23.5%	6,672	72.8%
Transplant	12,765	0.6%	810	0.1%	4,818	0.5%	2,699	3.2%	2,166	6.4%	1,182	9.1%	1,089	11.9%

Table 18: Characteristics of the Christiana Health Care System e-Phenotype Implementation/Validation Population

	Total Population		Group 1: No eGFR		Group 2: eGFR >= 60		Group 3: eGFR 45-60		Group 4: eGFR 30-45		Group 5: eGFR 15-30		Group 6: eGFR < 15	
	N	% /SD	N	% /SD	N	% /SD	N	% /SD	N	% /SD	N	% / SD	N	% /SD
Number	380,190		152,954		198,087		16,429		7,279		3,327		2,114	
Age, years	50.3	18.8	44.0	18.3	52.0	17.05	71.0	14.61	74.0	13.8	73.0	14.8	65	15.23
Female	228,815	60.2 %	93382	61.1 %	118,826	60.0 %	9,534	58.0 %	4,299	59.1 %	1,818	54.6%	956	45.2 %
Black	87,976	23.1 %	31917	20.9 %	50,002	25.2 %	2,893	17.6 %	1,408	19.3 %	818	24.6%	938	44.4 %
Num eGFR measurements	4.8	7.0	N/A	N/A	4.3	6.1	7.1	8.9	9.02	10.87	10.4	12.43	12.26	16.5
Days to most recent eGFR	537.0	549.2	N/A	N/A	554.1	554.4	434.5	521.7	391.21	463.3	415.4	463.29	424.74	466.3
Prior eGFR <60	22,604	5.9%	N/A	N/A	6,051	3.1%	7,413	45.1 %	5,009	68.8 %	2,480	74.5%	1,651	78.1 %
Prior GFR <60 90+d prior	20,349	5.4%	N/A	N/A	5,446	2.7%	6,658	40.5 %	4,496	61.8 %	2,229	67.0%	1,520	71.9 %
Any UACR, UPCR, or UA	122,696	32.3 %	20,899	13.7 %	88,006	44.4 %	7,312	44.5 %	3,661	50.3 %	1,806	54.3%	1,012	47.9 %
Any UACR	30,911	8.1%	111	0.1%	24,700	12.5 %	3,318	20.2 %	1,722	23.7 %	733	22.0%	327	15.5 %
Num UACR measurements	2.8	2.3	1.21	0.75	2.7	2.24	3.3	2.6	3.38	2.9	2.9	2.6	2.4	2.3
Most recent UACR:														
a <30mg/g	22,958	76.1 %	85	76.6 %	19,793	80.1 %	2,079	62.7 %	804	46.7 %	172	23.5%	25	7.6%
b 30 to 300mg/g	5,892	19.5 %	22	19.8 %	4,121	16.7 %	896	27.0 %	572	33.2 %	219	29.9%	62	19.0 %
c >300mg/g	2,061	6.8%	4	3.6%	786	3.2%	343	10.3 %	346	20.1 %	342	46.7%	240	73.4 %
Any UPCR	6,218	1.6%	122	0.1%	4,010	2.0%	633	3.9%	645	8.9%	538	16.2%	270	12.8 %
Num UPCR measurements	3.0	6.6	1.3	0.6	2.3	5.0	4.7	9.9	5.0	9.4	4.0	7.2	4.3	8.2
Most recent UPCR:														

a <150mg/g	2,833	45.6 %	61	50.0 %	2,111	52.6 %	322	50.9 %	234	36.3 %	88	16.4%	17	6.3%
b 150 to 500mg/g	1,711	27.5 %	31	25.4 %	1,177	29.4 %	144	22.7 %	195	30.2 %	135	25.1%	29	10.7 %
c >500mg/g	1,674	26.9 %	30	24.6 %	722	18.0 %	167	26.4 %	216	33.5 %	315	58.6%	224	83.0 %
Any UA	94,260	24.8 %	20156	13.2 %	66,319	33.5 %	4,499	27.4 %	2,016	27.7 %	836	25.1%	434	20.5 %
Num UA measurements	2.5	3.2	2.4	3.0	2.6	3.2	2.4	3.0	2.27	2.7	2.1	2.2	1.97	1.92
Most recent UA:														
a Neg	62,342	66.1 %	13864	68.8 %	44,598	67.2 %	2,621	58.3 %	940	46.6 %	263	31.5%	56	12.9 %
b Trace to 30 (Trace, 1+)	22,234	23.6 %	4691	23.3 %	15,583	23.5 %	1,159	25.8 %	554	27.5 %	192	23.0%	55	12.7 %
c 100 to >300 (2+, 3+, 4+)	9,395	10.0 %	1585	7.9%	5,965	9.0%	691	15.4 %	493	24.5 %	354	42.3%	307	70.7 %
Dialysis	2,716	0.7%	131	0.1%	357	0.2%	159	1.0%	213	2.9%	459	13.8%	1,397	66.1 %
Transplant	635	0.2%	25	0.02 %	216	0.1%	101	0.6%	115	1.6%	80	2.4%	98	4.6%

Table 19: Characteristics of the Columbia University e-Phenotype Implementation/Validation Population

	Total Population		Group 1: No eGFR		Group 2: eGFR >= 60		Group 3: eGFR 45-60		Group 4: eGFR 30-45		Group 5: eGFR 15-30		Group 6: eGFR < 15	
	N	% / SD	N	% /SD	N	% / SD	N	% /SD	N	% /SD	N	% /SD	N	% /SD
Number	338,868		107,977		196,364		18,902		8,819		3,760		3,046	
Age, years	49.2	19.5	40.3	17.7	50.2	17.9	71.5	13	74.1	13.4	71.9	15.2	61.6	15.6
Female	202,289	59.7%	65,274	60.5%	119,481	60.8%	9,860	52.2%	4,456	50.5%	1,873	49.8%	1,345	44.2%
Black	27,687	8.2%	7,595	7.0%	17,035	8.7%	1,326	7.0%	751	8.5%	427	11.4%	553	18.2%
Num eGFR measurements	9.4	28.0	N/A	N/A	10.1	23.0	24.9	43.7	40.3	65.7	55.1	76.9	58.9	95.3
Days to most recent eGFR	664.6	1151.5	N/A	N/A	720.2	1208.7	387.9	753.1	285.9	528.8	261.5	484.1	388.8	591.4
Prior eGFR <60	28,120	8.3%	N/A	N/A	4,923	2.5%	10,109	53.5%	7,386	83.8%	3,323	88.4%	2,379	78.1%
Prior GFR <60 at least 90d prior	16,656	4.9%	N/A	N/A	2,671	1.4%	5,573	29.5%	4,306	48.8%	2,332	62.0%	1,774	58.2%
Any UACR, UPCR, or UA	176,656	52.1%	17,876	16.6%	132,779	67.6%	13,734	72.7%	6,846	77.6%	3,116	82.9%	2,305	75.7%
Any UACR	18,139	5.4%	101	0.1%	11,810	6.0%	2,811	14.9%	1,818	20.6%	987	26.3%	612	20.1%
Num UACR measurements	0.2	1.2	0.0	0.0	0.2	1.2	0.6	2.3	0.9	3.0	1.0	3.2	0.6	2.2
Most recent UACR:														
a <30mg/g	12,121	66.8%	63	62.4%	9,119	77.2%	1,786	63.5%	854	47.0%	247	25.0%	52	8.5%
b 30 to 300mg/g	4,068	22.4%	26	25.7%	2,184	18.5%	763	27.1%	628	34.5%	338	34.2%	129	21.1%
c >300mg/g	1,950	10.8%	12	11.9%	507	4.3%	262	9.3%	336	18.5%	402	40.7%	431	70.4%
Any UPCR	21,375	6.3%	289	0.3%	12,617	6.4%	2,975	15.7%	2,614	29.6%	1,682	44.7%	1,198	39.3%
Num UPCR measurements	0.2	1.7	0.0	0.1	0.2	1.6	0.5	2.5	1.1	3.9	2.0	5.4	2.0	5.8
Most recent UPCR:														
a <150mg/g	10,270	48.0%	207	71.6%	7,238	57.4%	1,496	50.3%	995	38.1%	290	17.2%	44	3.7%
b 150 to 500mg/g	6,122	28.6%	44.0	15.2%	3650	28.9%	896	30.1%	869	33.2%	520	30.9%	143	11.9%
c >500mg/g	4,983	23.3%	38	13.1%	1,729	13.7%	583	19.6%	750	28.7%	872	51.8%	1,011	84.4%
Any UA	173,419	51.2%	17,659	16.4%	130,353	66.4%	13,420	71.0%	6,691	75.9%	3,025	80.5%	2,271	74.6%
Num UA measurements	2.5	6.2	0.3	1.0	3.2	6.6	4.7	8.8	6.2	10.2	7.7	12.4	6.9	12.6
Most recent UA:														
a Neg	133,323	76.9%	14,188	80.3%	103,959	79.8%	9,733	72.5%	4,096	61.2%	1,157	38.2%	190	8.4%
b Trace to 30 (Trace, 1+)	27,620	15.9%	2,745	15.5%	20,003	15.3%	2,395	17.8%	1,405	21.0%	736	24.3%	336	14.8%
c 100 to >300 (2+, 3+, 4+)	12,476	7.2%	726	4.1%	6,391	4.9%	1,292	9.6%	1,190	17.8%	1,132	37.4%	1,745	76.8%
Dialysis	4,575	1.4%	58	0.1%	715	0.4%	596	3.2%	672	7.6%	644	17.1%	1,890	62.0%
Transplant	2,942	0.9%	6	0.0%	851	0.4%	670	3.5%	684	7.8%	389	10.3%	342	11.2%
Diabetes	29,614	8.7%	1,159	1.1%	20,413	10.4%	3,499	18.5%	2,391	27.1%	1,255	33.4%	897	29.4%
Hypertension	47,658	14.1%	397	0.4%	33,054	16.8%	7,522	39.8%	4,064	46.1%	1,658	44.1%	963	31.6%

Table 20: Characteristics of the University of California, San Francisco e-Phenotype Implementation/Validation Population

	Total Population		Group 1: No eGFR		Group 2: eGFR >= 60		Group 3: eGFR 45-60		Group 4: eGFR 30-45		Group 5: eGFR 15-30		Group 6: eGFR < 15	
	N	% /SD	N	% /SD	N	% /SD	N	% /SD	N	% /SD	N	% /SD	N	% /SD
Number	311,122		184,317		112,237		8,411		3,497		1,474		1,186	
Age, years	50.5 (n=311,087)	18.0	47.5 (n=184,291)	17.9	52.9 (n=112231)	16.8	70.1	13.7	71.2 (n=3495)	14.6	67.8	16.1	59.4	16
Female	179,455	57.7 %	109,822	59.6 %	62,429	55.6 %	4,173	49.6 %	1,786	51.1 %	735	49.9 %	510	43.0 %
Black	16,181	5.2%	7,195	3.9%	7,730	6.9%	560	6.7%	294	8.4%	165	11.2 %	237	20.0 %
Num eGFR measurements	4.1	14.5	N/A	N/A	8.6	18.6	17.3	28.60	24.7	38.2	28.8	38.8	31.7	44.3
Days to most recent eGFR	572.3	696.1	N/A	N/A	585.2	700.6	510.8	684.7	435.2	621.5	387.4	575.6	420.3	558.8
Prior eGFR <60	23,902	7.7%	N/A	N/A	12,550	11.2 %	6,035	71.8 %	2,993	85.6 %	1,301	88.3 %	1,023	86.3 %
Prior GFR <60 at least 90d prior	11,840	4.8%	N/A	N/A	4,520	4.0%	3,730	44.3 %	2,061	58.9 %	870	59.0 %	659	55.6 %
Any UACR, UPCR, or UA	62,850	20.2 %	7,294	3.96 %	46,416	41.4 %	4,980	59.2 %	2,384	68.2 %	1,064	72.2 %	712	60.0 %
Any UACR	8,966	2.9%	392	0.21 %	6,208	5.5%	1,145	13.6 %	681	19.5 %	337	22.9 %	203	17.1 %
Num UACR measurements	3.5	4.3	2.0	1.5	3.2	3.6	4.1	5.0	4.7	5.4	6.5	7.7	5.4	6.6
Most recent UACR:														
a <30mg/g	6,293	70.2 %	338	86.2 %	4,833	77.9 %	720	62.9 %	312	45.8 %	77	22.8 %	13	6.4%
b 30 to 300mg/g	1,817	20.3 %	38	9.7%	1,073	17.3 %	315	27.5 %	233	34.2 %	117	34.7 %	41	20.2 %
c >300mg/g	856	9.6%	16	4.1%	302	4.9%	110	9.6%	136	20.0 %	143	42.4 %	149	73.4 %
Any UPCR	11,716	3.8%	228	0.12 %	7,484	6.7%	1,635	19.4 %	1,212	34.7 %	720	48.9 %	437	36.9 %

Num UPCR measurements	3.7	5.2	2.7	6.3	3.2	4.9	4.1	5.2	4.6	5.5	5.6	6.3	5.3	5.8
Most recent UPCR:														
a <150mg/g	4,878	41.6%	122	53.5%	3,623	48.4%	684	41.8%	364	30.0%	74	10.3%	11	2.5%
b 150 to 500mg/g	4,211	35.9%	62	27.2%	2,822	37.7%	617	37.7%	451	37.2%	204	28.3%	55	12.6%
c >500mg/g	2,627	22.4%	44	19.3%	1,039	13.9%	334	20.4%	397	32.8%	442	61.4%	371	84.9%
Any UA	57,547	18.5%	6,984	3.8%	42,256	37.7%	4,572	54.4%	2,164	61.9%	932	63.2%	639	53.9%
Num UA measurements	3.3	5.7	1.8	2.7	3.1	5.3	4.4	6.8	5.5	8.5	6.5	9.2	9.0	14.7
Most recent UA:														
a Neg	48,173	83.7%	6,036	86.4%	36,723	86.9%	3,454	75.6%	1,390	64.2%	432	46.4%	138	21.6%
b Trace to 30 (Trace, 1+)	8,396	14.6%	841	12.0%	5,117	12.1%	1,004	22.0%	690	31.9%	410	44.0%	334	52.3%
c 100 to >300 (2+, 3+, 4+)	978	1.7%	107	1.5%	416	1.0%	114	2.5%	84	3.9%	90	9.7%	167	26.1%
Dialysis	11,517	3.7%	3,316	1.80%	2,766	2.5%	1,773	21.1%	1,525	43.6%	1,020	69.2%	1,117	94.2%
Transplant	4,646	1.5%	541	0.29%	2,105	1.9%	865	10.3%	574	16.4%	304	20.6%	257	21.7%

Table 21: Characteristics of the University of Minnesota e-Phenotype Implementation/Validation Population

	TOTAL POPULATION		Group 1: No eGFR		Group 2: eGFR >= 60		Group 3: eGFR 45-60		Group 4: eGFR 30-45		Group 5: eGFR 15-30		Group 6: eGFR < 15	
	N	% /SD	N	% /SD	N	% /SD	N	% /SD	N	% /SD	N	% /SD	N	% / SD
Number	650,154		238,989		367,115		29,705		9,498		2,845		2,002	
Age, years	49.4	18.1	44.2	17.3	50.3	17.0	69.5	14.3	74	14.4	70.1	15.6	59.6	16.0
Female	375,510	57.8%	140,669	58.9%	208,504	56.8%	18,070	60.8%	5,811	61.2%	1,569	55.1%	887	44.3%
Black	43,371	6.7%	14,972	6.3%	26,969	7.3%	697	2.3%	264	2.8%	171	6.0%	297	14.8%
Num eGFR measurements	8.5	18.1	N/A	N/A	7	13.6	16.7	28.0	27.6	42.5	36.6	54.2	33.8	62.8
Days to most recent eGFR	716.1	907	N/A	N/A	741	915.4	526.4	821.7	410.7	692.7	461.6	741.8	769.9	1011.7
Prior eGFR <60	80,610	12.4%	N/A	N/A	46102	12.6%	21954	73.9%	8509	89.6%	2512	88.3%	1533	76.6%
Prior GFR <60 at least 90d prior	73,634	11.3%	N/A	N/A	41979	11.4%	20222	68.1%	7828	82.4%	2267	79.7%	1338	66.8%
Any UACR, UPCR, or UA	320,068	49.2%	37,952	15.9%	247,014	67.3%	23,008	77.5%	8,023	84.5%	2,494	87.7%	1,577	78.8%
Any UACR	61,080	9.4%	277	0.1%	45,918	12.5%	8,888	29.9%	4,049	42.6%	1,273	44.7%	675	33.7%
Num UACR measurements	3	2.7	1.4	1.1	2.9	2.5	3.4	2.9	3.9	3.3	4	3.6	3.3	4.3
Most recent UACR:														
a <30mg/g	44,515	72.9%	221	79.8%	36,082	78.6%	5,827	65.6%	2,027	50.1%	322	25.3%	36	5.3%
b 30 to 300mg/g	12,561	20.6%	42	15.2%	8,250	18.0%	2,329	26.2%	1,361	33.6%	452	35.5%	127	18.8%
c >300mg/g	4,004	6.6%	14	5.1%	1,586	3.5%	732	8.2%	661	16.3%	499	39.2%	512	75.9%
Any UPCR	18,092	2.8%	258	0.1%	11,232	3.1%	2,717	9.1%	2,012	21.2%	1,109	39.0%	764	38.2%
Num UPCR measurements	3.7	6.2	1.4	1.0	2.9	4.9	4.4	6.3	5.4	10.0	5.8	7.7	4.9	6.7
Most recent UPCR:														
a <150mg/g	8,197	45.3%	108	41.9%	5,789	51.5%	1,388	51.1%	713	35.4%	168	15.1%	31	4.1%
b 150 to 500mg/g	5,984	33.1%	108	41.9%	3,888	34.6%	860	31.7%	713	35.4%	340	30.7%	75	9.8%
c >500mg/g	3,911	21.6%	42	16.3%	1,555	13.8%	469	17.3%	586	29.1%	601	54.2%	658	86.1%
Any UA	307,324	47.3%	37,732	15.8%	236,288	64.4%	21,767	73.3%	7,625	80.3%	2,385	83.8%	1,527	76.3%
Num UA measurements	4	5.7	2.3	3.2	4.1	5.7	5.1	6.8	6.3	7.8	7.1	9.4	5.9	9.9
Most recent UA:														
a Neg	251,592	81.9%	30,861	81.8%	197,657	83.7%	16,768	77.0%	5,062	66.4%	1,093	45.8%	151	9.9%
b Trace to 30 (Trace, 1+)	41,182	13.4%	5,091	13.5%	30,159	12.8%	3,502	16.1%	1,602	21.0%	568	23.8%	260	17.0%
c 100 to >300 (2+, 3+, 4+)	14,550	4.7%	1,780	4.7%	8,472	3.6%	1,497	6.9%	961	12.6%	724	30.4%	1,116	73.1%
Dialysis	4,217	0.6%	183	0.1%	780	0.2%	556	1.9%	454	4.8%	614	21.6%	1,630	81.4%
Transplant	2,973	0.5%	94	0.04%	919	0.3%	723	2.4%	574	6.0%	331	11.6%	332	16.6%
Diabetes	58,224	9.0%	4,343	1.8%	41,273	11.2%	6,848	23.1%	3,439	36.2%	1,330	46.7%	991	49.5%
Hypertension	163,280	25.1%	9,675	4.0%	121,556	33.1%	20,075	67.6%	7,781	81.9%	2,464	86.6%	1,729	86.4%

Table 22: Characteristics of the University of Utah e-Phenotype Implementation Population

	TOTAL POPULATION		Group 1: No eGFR		Group 2: eGFR >= 60		Group 3: eGFR 45-60		Group 4: eGFR 30-45		Group 5: eGFR 15-30		Group 6: eGFR < 15	
	N	% /SD	N	% /SD	N	% /SD	N	% /SD	N	% /SD	N	% /SD	N	% /SD
Number	401,683		255,986		127,410		10,901		4,952		1,603		822	
Age, years	48.4	19	46.3	19.4	49.4	16.6	69.7	12.6	73.3	12.6	71.1	15	60	15.3
Female	223,211	55.6%	140,387	54.8%	72,558	56.9%	6,249	57.3%	2,802	56.6%	859	53.6%	351	42.7%
Black	6,527	1.6%	3,802	1.5%	2,531	2.0%	91	0.8%	51	1.0%	22	1.4%	30	3.6%
Num eGFR measurements	1.6	5.3	0	0	4	6.8	7.1	11.7	9.5	13.5	11.4	15	10.5	17.2
Days to most recent eGFR	457.4	535.3	NA	NA	475.9	545.7	369.3	459.5	262.4	361	225.6	337.1	359.1	511.8
Prior eGFR <60	22,863	5.7%	NA	NA	10186	8.0%	6703	61.5%	4008	80.9%	1344	83.8%	613	74.6%
Prior GFR <60 at least 90d prior	21,008	5.2%	NA	NA	9333	7.3%	6160	56.5%	3698	74.7%	1243	77.5%	573	69.7%
Any UACR, UPCR, or UA	129,192	32.2%	44,223	17.3%	71,721	56.3%	7,271	66.7%	3,875	78.3%	1,397	87.1%	699	85.0%
Any UACR	21,160	5.3%	1,370	0.5%	14,222	11.2%	2,596	23.8%	1,954	39.5%	743	46.4%	273	33.2%
Num UACR measurements	0.1	0.8	0	0.2	0.3	1.1	0.7	1.8	1.4	2.3	1.7	2.7	1	2.1
Most recent UACR:														
a <30mg/g	15,250	72.1%	1,066	77.8%	11,188	78.7%	1,727	66.5%	1,036	53.0%	212	28.5%	20	7.3%
b 30 to 300mg/g	4,299	20.3%	229	16.7%	2,477	17.4%	660	25.4%	626	32.0%	254	34.2%	53	19.4%
c >300mg/g	1,611	7.6%	75	5.5%	557	3.9%	209	8.1%	292	14.9%	277	37.3%	200	73.3%
Any UPCR	10,730	2.7%	1,013	0.4%	6,303	4.9%	1,285	11.8%	1,175	23.7%	624	38.9%	329	40.0%
Num UPCR measurements	0.1	1.0	0.0	0.1	0.1	1.0	0.4	2.1	0.9	3.0	1.5	3.8	2.3	11.0
Most recent UPCR:														
a <150mg/g	4,754	44.3%	340	33.6%	2,994	47.5%	710	55.3%	514	43.7%	160	25.6%	35	10.6%
b 150 to 500mg/g	3,924	36.6%	393	38.8%	2,490	39.5%	390	30.4%	411	35.0%	199	31.9%	41	12.5%
c >500mg/g	2,052	19.1%	280	27.6%	819	13.0%	185	14.4%	250	21.3%	265	42.5%	253	76.9%
Any UA	121,829	30.3%	43,261	16.9%	66,545	52.2%	6,594	60.5%	3,471	70.1%	1,283	80.0%	670	81.5%
Num UA measurements	1	3.6	0.3	1.2	2	4.8	3.3	7.8	4.5	9.6	5.6	10.5	6.8	16.5
Most recent UA:														
a Neg	94,182	77.3%	32,804	75.8%	53,668	80.6%	4,848	73.5%	2,229	64.2%	571	44.5%	59	8.8%
b Trace to 30 (Trace, 1+)	19,438	16.0%	7,583	17.5%	9,576	14.4%	1,166	17.7%	726	20.9%	300	23.4%	86	12.8%
c 100 to >300 (2+, 3+, 4+)	8,209	6.7%	2,874	6.6%	3,301	5.0%	580	8.8%	516	14.9%	412	32.1%	525	78.4%
Dialysis	3,741	0.9%	874	0.3%	1,078	0.8%	434	4.0%	394	8.0%	322	20.1%	638	77.6%
Transplant	1,569	0.4%	144	0.10%	727	0.6%	340	3.1%	219	4.4%	78	4.9%	60	7.3%
Diabetes	43,122	10.7%	15,724	6.1%	20,599	16.2%	3,241	29.7%	2,206	44.5%	845	52.7%	506	61.6%
Hypertension	93,805	23.4%	33,301	13.0%	46,166	36.2%	7,782	71.4%	4,328	87.4%	1,461	91.1%	1,461	91.1%

Table 23: Characteristics of the e-Phenotype Validation Population

	Total Population		Group 1: No eGFR		Group 2: eGFR >= 60		Group 3: eGFR 45-60		Group 4: eGFR 30-45		Group 5: eGFR 15-30		Group 6: eGFR < 15	
	N	% / SD	N	% / SD	N	% / SD	N	% / SD	N	% / SD	N	% / SD	N	% / SD
Number	**1,680,334**		684,237		873,803		73,447		29,093		11,406		8,348	
Age, years	**49.8**	**18.5**	44.4	17.9	51.0	17.2	70.4	14.0	73.7	14.0	71.2	15.4	61.7	15.8
Female	**986,069**	**58.7%**	409,147	59.8%	509,240	58.3%	41,637	56.7%	16,352	56.2%	5,995	52.6%	3,698	44.3%
Black	**175,215**	**10.4%**	61,679	9.0%	101,736	11.6%	5,476	7.5%	2,717	9.3%	1,581	13.9%	2,025	24.3%
Num eGFR measurements	**7.0**	**18.4**	N/A	N/A	7.3	15.9	16.7	30.9	26.5	47.3	34.0	56.9	37.2	70.3
Days to most recent eGFR	**638.6**	**865.6**	N/A	N/A	673.9	905.4	468.4	732.9	370.9	587.2	372.6	571.4	493.8	642.1
Prior eGFR <60	**155,236**	**9.2%**	N/A	N/A	69,626	8.0%	45,511	62.0%	23,897	82.1%	9,616	84.3%	6,586	78.9%
Prior GFR <60 90+d prior	**122,479**	**7.3%**	N/A	N/A	54,616	6.3%	36,183	49.3%	18,691	64.2%	7,698	67.5%	5,291	63.4%
Any UACR, UPCR, or UA	**682,270**	**40.6%**	84,021	12.3%	514,215	58.8%	49,034	66.8%	20,914	71.9%	8,480	74.3%	5,606	67.2%
Any UACR	**118,363**	**7.0%**	881	0.1%	88,636	10.1%	16,162	22.0%	8,270	28.4%	3,330	29.2%	1,817	21.8%
Num UACR measurements	**2.5**	**3.0**	1.3	1.2	2.3	2.7	2.7	3.3	3.0	3.7	3.0	4.4	2.4	4.0
Most recent UACR:														
a <30mg/g	**85,887**	**72.6%**	707	80.2%	69,827	78.8%	10,412	64.4%	3,997	48.3%	818	24.6%	126	2.7%
b 30 to 300mg/g	**24,338**	**20.6%**	128	14.5%	15,628	17.6%	4,303	26.6%	2,794	33.8%	1,126	33.8%	359	7.8%
c >300mg/g	**8,871**	**7.5%**	46	5.2%	3,181	3.6%	1,447	9.0%	1,479	17.9%	1,386	41.6%	1,332	29.0%
Any UPCR	**57,401**	**3.4%**	897	0.1%	35,343	4.0%	7,960	10.8%	6,483	22.3%	4,049	35.5%	2,669	32.0%
Num UPCR measurements	**2.8**	**5.7**	1.3	3.4	2.2	4.5	3.4	6.7	3.9	8.2	4.0	6.9	3.7	6.8
Most recent UPCR:														
a <150mg/g	**26,178**	**45.6%**	498	55.5%	18,761	53.1%	3,890	48.9%	2,306	35.6%	620	15.3%	103	3.9%
b 150 to 500mg/g	**18,028**	**31.4%**	245	27.3%	11,537	32.6%	2,517	31.6%	2,228	34.4%	1,199	29.6%	302	11.3%
c >500mg/g	**13,195**	**23.0%**	154	17.2%	5,045	14.3%	1,553	19.5%	1,949	30.1%	2,230	55.1%	2,264	84.8%
Any UA	**632,550**	**37.6%**	82,531	12.1%	475,216	54.4%	44,258	60.3%	18,496	63.6%	7,178	62.9%	4,871	58.3%
Num UA measurements	**3.2**	**5.4**			3.4	5.5	4.3	6.9	5.2	8.0	5.8	9.5	5.7	10.9
Most recent UA:														
a Neg	**495,430**	**78.3%**	64,949	78.7%	382,937	80.6%	32,576	73.6%	11,488	62.1%	2,945	41.0%	535	11.0%
b Trace to 30 (Trace, 1+)	**99,432**	**15.7%**	13,368	16.2%	70,862	14.9%	8,060	18.2%	4,251	23.0%	1,906	26.6%	985	20.2%
c 100 to >300 (2+, 3+, 4+)	**37,399**	**5.9%**	4,198	5.1%	21,244	4.5%	3,594	8.1%	2,728	14.7%	2,300	32.0%	3,335	68.5%
Dialysis	**23,025**	**1.4%**	3,688	0.5%	4,618	0.5%	3,084	4.2%	2,864	9.8%	2,737	24.0%	6,034	72.3%
Transplant	**11,196**	**0.7%**	666	0.1%	4,091	0.5%	2,359	3.2%	1,947	6.7%	1,104	9.7%	1,029	12.3%

Table 24: Accuracy of the e-phenotype for CKD, dialysis and transplant across validation sites

Population	TP	FN	FP	TN	Total	Sensitivity (95% CI)	Specificity (95% CI)	ROC Area (95% CI)	PPV (95% CI)	NPV (95% CI)
CKD										
Total	**137**	**1**	**1**	**67**	**206**	**99.3% (96%, 100%)**	**98.5% (92.1%, 100%)**	**0.989 (0.973, 1)**	**99.3% (96%, 100%)**	**98.5% (92.1%, 100%)**
Minnesota	34	0	1	23	58	100% (89.7%, 100%)	95.8% (78.9%, 99.9%)	0.979 (0.938, 1)	97.1% (85.1%, 99.9%)	100% (85.2%, 100%)
Christiana Care	50	0	0	20	70	100% (92.9%, 100%)	100% (83.2%, 100%)	1	100% (92.9%, 100%)	100% (83.2%, 100%)
Columbia	40	0	0	20	60	100% (91.2%, 100%)	100% (83.2%, 100%)	1	100% (91.2%, 100%)	100% (83.2%, 100%)
UCSF	13	1	0	4	18	92.9% (66.1%, 99.8%)	100% (39.8%, 100%)	0.964 (0.894, 1)	100% (75.3%, 100%)	80% (28.4%, 99.5%)
Dialysis										
Total	**86**	**5**	**13**	**127**	**231**	**94.5% (87.6%, 98.2%)**	**90.7% (84.6%, 95.0%)**	**0.926 (0.892, 0.96)**	**86.9% (78.6%, 92.8%)**	**96.2% (91.4%, 98.8%)**
Minnesota	44	1	1	12	58	97.8% (88.2%, 99.9%)	92.3% (64%, 99.8%)	0.95 (0.872, 1)	97.8% (88.2%, 99.9%)	92.3% (64%, 99.8%)
Christiana Care	12	1	1	58	72	92.3% (64%0, 99.8%)	98.3% (90.9%, 100%)	0.953 (0.876, 1)	92.3% (64%, 99.8%)	98.3% (90.9%, 100%)
Columbia	19	3	5	53	80	86.4% (65.1%, 97.1%)	91.4% (81.0%, 97.1%)	0.889 (0.807, 0.971)	79.2% (57.8%, 92.9%)	94.6% (85.1%, 98.9%)
UCSF	11	0	6	4	21	100% (71.5%, 100%)	40% (12.2%, 73.8%)	0.7 (0.54, 0.86)	64.7% (38.3%, 85.8%)	100% (39.8%, 100%)
Transplant										
Total	**36**	**1**	**11**	**112**	**160**	**97.3% (85.8%, 99.9%)**	**91.1% (84.6%, 95.5%)**	**0.942 (0.905, 0.978)**	**76.6% (62.0%, 87.7%)**	**99.1% (95.2%, 100%)**
Minnesota	10	0	1	47	58	100% (69.2%, 100%)	97.9% (88.9%, 99.9%)	97.9% (88.9%, 99.9%)	90.9% (58.7%, 99.8%)	100% (92.5%, 100%)

Christiana Care	6	0	1	65	72	100% (54.1%, 100%)	98.5% (91.8%, 100%)	0.992 (0.978, 1)	85.7% (42.1%, 99.6%)	100% (94.5%, 100%)
Columbia	16	1	6	57	80	94.1% (71.3%, 99.9%)	90.5% (80.4%, 96.4%)	0.923 (0.855, 0.991)	72.7% (49.8%, 89.3%)	98.3% (90.8%, 100%)
UCSF	4	0	3	3	10	100% (39.8%, 100%)	50% (11.8%, 88.2%)	0.75 (0.531, 0.969)	57.1% (18.4%, 90.1%)	100% (29.2%, 100%)

TP: true positive, FN: false negative, FP: false positive, TN: true negative, ROC: Receiver Operating Characteristic, PPV: positive predictive value, NPV: negative predictive value; sensitivity, specifiticity, ROC area, PPV and NPV were calculated using diagti command in STATA 15.1

Table 25: Cumulative adjudication by CKD stage based on eGFR overall and across sites

		Adjudicated				
		No CKD	Stage 1/2	Stage 3	Stage 4	Stage 5
Electronic phenotype	No CKD	67 (23, 20, 20, 4)	1 (0, 0, 0, 1)			
	Stage 1/2		33 (10, 10, 10, 3)			
	Stage 3			33 (8, 12, 9, 4)	1 (1, 0, 0, 0)	1 (0, 0, 1, 0)
	Stage 4	1 (1, 0, 0, 0)			32 (6, 13, 10, 3)	
	Stage 5				1 (1, 0, 0, 0)	36 (8, 15, 10, 3)

Results displayed as: 4 Site Total (Minnesota, Christiana Care, Columbia, UCSF)

Table 26: ICD-10 Codes to Identify CKD from the MDR

Code(s)	Description
N18.1, N18.2, N18.3, N18.4, N18.5, N18.6, N18.9	Chronic kidney disease
Q61.2, Q61.3	Polycystic kidney disease
N01.3, N08, N03.0, N03.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N03.8, N03.9	Glomerulonephritis/nephritis/nephrotic syndrome
E08.22, E09.22, E10.21, E10.22, E10.29, E11.21, E11.22, E11.29, E13.22	Diabetic nephropathy
I12.0, I12.9, I13.0, I13.1, I13.2, I13.9	Hypertensive nephrosclerosis

Table 27: Characteristics of Populations with Any, Coded and Uncoded CKD in the MHS

		Any CKD	Coded CKD	Uncoded CKD
Number	N (%)	105,504 (100)	38,688 (35)	66,816 (65)
Age	mean (SD)	47.5 (12.9)	51.5 (10.6)	45.2 (13.5)
	median (IQR)	51 (39,58)	54 (46,60)	48 (34,57)
Female n (%)		50,867 (48.2)	14,547 (37.6)	36,320 (54.4)
Beneficiary Category N (%)	Active Duty Dependent	14,513 (13.8)	3,103 (8.0)	11,410 (17.1)
	Retired	41,044 (38.9)	19,581 (50.6)	21,463 (32.1)
	Other Dependent	31,616 (30.0)	11,160 (28.9)	20,456 (30.6)
	Active Duty	18,331 (17.4)	4,844 (12.5)	13,487 (20.2)
Race N (%)	White	49,697 (47.1)	16,153 (41.8)	33,544 (50.2)
	Black	24,551 (23.3)	12,197 (31.5)	12,354 (18.5)
	AAPI	4,790 (4.5)	2,163 (5.6)	2,627 (3.9)
	AIAN	372 (0.4)	111 (0.3)	261 (0.4)
	Other	13,171 (12.5)	4,547 (11.8)	8,624 (12.9)
	Unknown	2,996 (2.8)	735 (1.9)	2,261 (3.4)
	Missing	13,171 (9.4)	2,782 (7.2)	7,145 (10.7)
Rank N (%)	Junior Enlisted	7,952 (7.5)	1,329 (3.4)	6,623 (9.9)
	Senior Enlisted	79,506 (75.4)	30,257 (78.2)	49,249 (73.7)
	Junior Officer	5,333 (5.1)	1,727 (4.5)	3,606 (5.4)
	Senior Officer	12,712 (12.1)	5,374 (13.9)	7,338 (11.0)
Married N (%)		74,393 (70.5)	28,518 (73.7)	45,875 (68.7)
Branch of Service N (%)	Army	39,998 (37.9)	15,827 (40.9)	24,161 (36.2)
	Air Force	26,094 (24.7)	11,881 (30.7)	14,213 (21.3)
	Marine Corps	4,317 (4.1)	1,902 (4.9)	2,415 (3.6)
	Navy	33,456 (31.7)	8,513 (22.0)	24,952 (37.3)
Diabetes N (%)		32,503 (30.8)	16,809 (43.5)	15,694 (23.5)
Hypertension N (%)		60,955 (57.8)	29,836 (77.1)	31,119 (46.6)
Depression N (%)		12,362 (11.7)	4,831 (12.5)	7,531 (11.3)
HIV N (%)		465 (0.4)	359 (0.9)	106 (0.2)
Dialysis N (%)		1,772 (1.7)	1,772 (4.6)	0.0 (0)
Transplant N (%)		1,065 (1.0)	1,065 (2.8)	0.0 (0)
BMI N (%)	Obese	51,561 (48.9)	20,940 (54.1)	30,621 (45.8)
missing = 292,246	Overweight	35,689 (33.8)	12,568 (32.5)	23,121 (34.6)
	Normal/Under	18,254 (17.3)	5,180 (13.4)	13,074 (19.6)
Zip Code MHI	mean (SD)	$60145 (19089)	$65910 (22152)	$56825 (16171)
missing = 427,864	median (IQR)	$55251 (47737, 67344)	$60936 (50206, 77114)	$52856 (47141, 62747)
UA Measures		1.1 (1.6)	1.6 (1.9)	0.8 (1.4)
UACR Measures		0.9 (1.5)	1.3 (1.8)	0.6 (1.2)

UPCR Measures	mean (SD) number of tests <u>among those who had any test</u>	0.3 (1.5)	0.8 (2.3)	0.1 (0.5)
sCr Measures		6.1 (9.5)	9.1 (14.2)	4.3 (4.2)
eGFR Measures		10.5 (18.3)	16.9 (27.3)	6.9 (8.0)
Phenotype Positive N (%)		82,294 (78.0)	15,476 (40.0)	66,816 (100)
UA Test Result N (%)		47,477 (45.0)	24,373 (63.0)	23,118 (34.6)
UACR Test Result N (%)		38,403 (36.4)	20,040 (51.8)	18,374 (27.5)
UPCR Test Result N (%)		12,555 (11.9)	9,865 (25.5)	2,739 (4.1)
Any Proteinuria N (%)		52,682 (49.9)	27,507 (71.1)	25,190 (37.7)
Any Kidney Test N (%)		104,602 (99.2)	37,828 (97.8)	66,816 (100)

Table 28: Crude Comparisons of Characteristics Between the Coded and Uncoded CKD Populations

	Coded CKD	Uncoded CKD	P Value
Age	51.5 (10.6)	45.2 (13.5)	<.0001
Female N (%)	14,547 (37.6)	36,320 (54.4)	<.0001
Active Duty N (%)	4,844 (12.5)	13,487 (20.2)	<.0001
Black Race N (%)	12,197 (31.5)	12,354 (18.5)	<.0001
Diabetes N (%)	16,809 (43.5)	15,694 (23.5)	<.0001
Hypertension N (%)	29,836 (77.1)	31,119 (46.6)	<.0001
UA Measures*	1.6 (1.9)	0.8 (1.4)	<.0001
UACR Measures*	1.3 (1.8)	0.6 (1.2)	<.0001
UPCR Measures*	0.8 (2.3)	0.1 (0.5)	<.0001
sCr Measures*	9.1 (14.2)	4.3 (4.2)	<.0001
eGFR Measures*	16.9 (27.3)	6.9 (8.0)	<.0001

*mean number (SD) of tests among those with at least one test

Table 29: Characteristic of the MHS Population with and without CKD

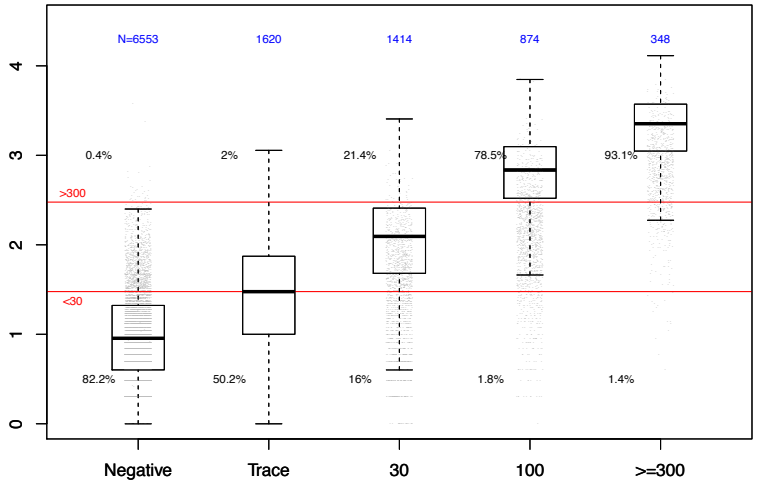
		Total	Any CKD	No CKD
n		3,330,893	105,504	3,225,389
Age	mean (SD)	33.0 (13.1)	47.5 (12.9)	32.5 (12.8)
	median (IQR)	29 (22,42)	51 (39,58)	29 (22,41)
Female		41.1	48.2	40.9
Beneficiary Category (%)	Active Duty Dependent	20.5	13.8	20.7
	Retired	12.1	38.9	11.3
	Other Dependent	15.0	30.0	14.5
	Active Duty	52.4	17.4	53.5
Race (%)	White	54.9	47.1	55.1
	Black	14.8	23.3	14.5
	AAPI	4.5	4.5	4.5
	AIAN	0.6	0.4	0.7
	Other	9.5	12.5	9.4
	Unknown	4.7	2.8	4.8
	Missing	11.0	9.4	11.1
Rank (%)	Junior Enlisted	31.4	7.5	32.2
	Senior Enlisted	49.2	75.4	48.4
	Junior Officer	8.9	5.1	9.1
	Senior Officer	10.4	12.1	10.3
Married		50.3	70.5	49.6
Branch of Service (%)	Army	39.0	37.9	39.1
	Air Force	25.5	24.7	25.6
	Marine Corps	11.5	4.1	11.8
	Navy	22.0	31.7	21.7
	Other	1.9	1.6	1.9
Diabetes (%)		4.5	30.8	3.7
Hypertension (%)		13.0	57.8	11.5
Depression (%)		6.2	11.7	6.1
HIV (%)		0.1	0.4	0.1
Dialysis (%)		0.1	1.7	0.0
Transplant (%)		0.0	1.0	0.0
BMI missing = 292,246	mean (SD)	27.5 (5.1)	30.5 (6.1)	27.4 (5.0)
	median (IQR)	26.8 (24.0, 31.1)	29.4 (26.4,33.9)	26.7 (24.0,30.0)
Zip Code MHI missing = 427,864	mean (SD)	$63789 (22216)	$60145 (19089)	$63922 (22310)
	median (IQR)	$58121 (48377, 73966)	$55251 (47737, 67344)	$58237 (48377, 74002)
Any Proteinuria (%)		8.1	49.9	6.8
GFR (%)		46.8	99.2	45.1
Any Kidney Test (%)		46.9	99.2	45.2

Table 30: Crude, Confounder and Confounder-Mediator-adjusted Associations between Sociodemographic Factors and CKD in the Adult MHS Population, FY 2016 – FY 2018

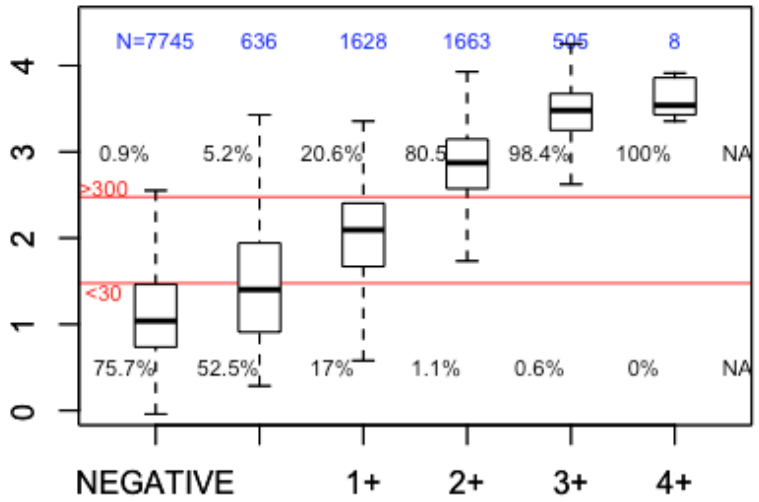
Var	Effect	Crude OR	95% Wald Confidence Limits		Confounder-adjusted OR	95% Wald Confidence Limits		Confounder & Mediator-adjusted OR	95% Wald Confidence Limits	
Race	White	1.0			1.0			1.0		
	AAPI	1.181*	1.146	1.218	0.977	0.947	1.008	0.866*	0.838	0.895
	Black	1.873*	1.844	1.903	1.667*	1.64	1.695	1.299*	1.277	1.321
	AIAN	0.631*	0.569	0.699	0.938	0.844	1.041	0.883*	0.794	0.982
	Other	1.563*	1.532	1.594	1.298*	1.271	1.324	1.171*	1.146	1.196
	Unknown	0.698*	0.672	0.724	0.732*	0.704	0.761	0.772*	0.742	0.803
Rank	Senior Officer	1.0			1.0			1.0		
	Junior Officer	0.478*	0.463	0.494	1.091*	1.055	1.128	0.998	0.965	1.033
	Senior Enlisted	1.337*	1.311	1.362	1.725*	1.691	1.759	1.326*	1.3	1.354
	Junior Enlisted	0.201*	0.195	0.207	1.323*	1.281	1.366	1.024	0.991	1.058
Marital Status	Married	1.0			1.0			1.0		
	Single	0.412*	0.407	0.418	0.774*	0.763	0.785	0.82*	0.808	0.832
Income 427,864 missing	Very High Quintile	1.0			1.0			1.0		
	High Quintile	1.228*	1.201	1.255	1.403*	1.372	1.435	1.323*	1.293	1.353
	Middle Quintile	1.539*	1.507	1.572	1.979*	1.936	2.022	1.853*	1.812	1.894
	Low Quintile	1.743*	1.707	1.779	2.759*	2.701	2.818	2.586*	2.530	2.644
	Very Low Quintile	1.431*	1.401	1.462	2.577*	2.521	2.635	2.376*	2.322	2.431
	Missing	0.287*	0.277	0.299	0.924*	0.889	0.961	0.912*	0.877	0.95

Figure 1: Correlation between Same-day UA and UACR Results at Four Sites

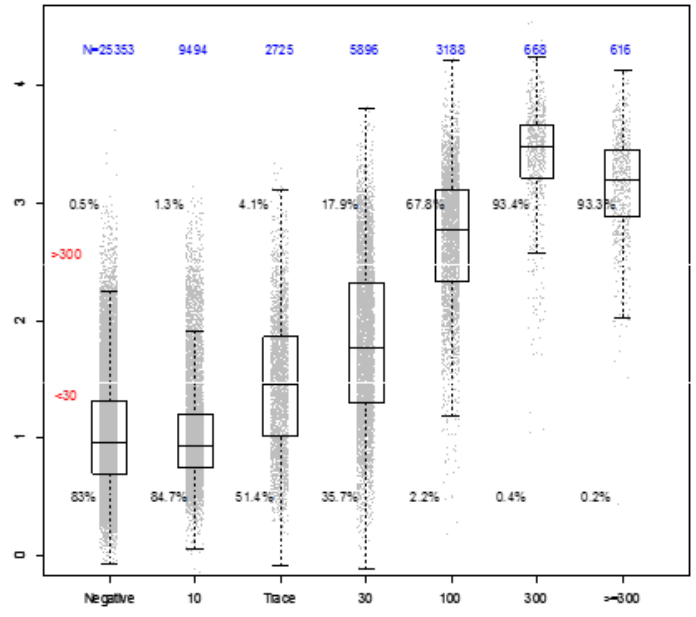
Cleveland Clinic



Columbia



Minnesota



Veterans Health Administration

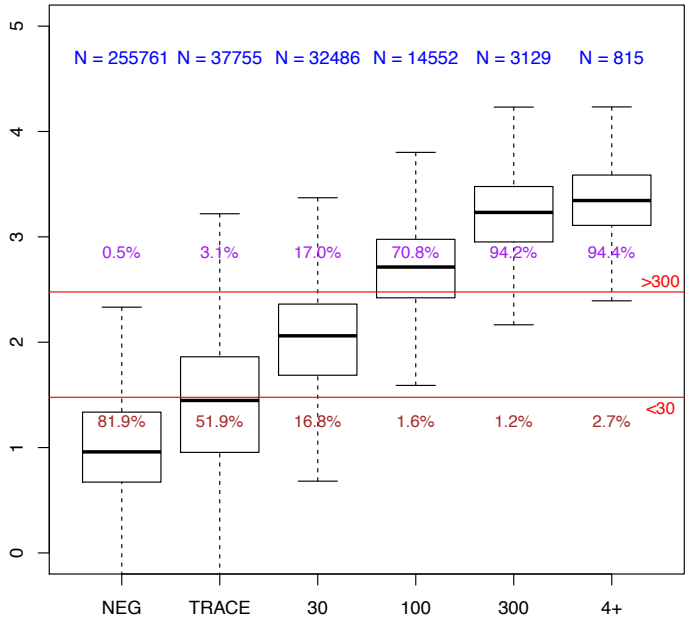
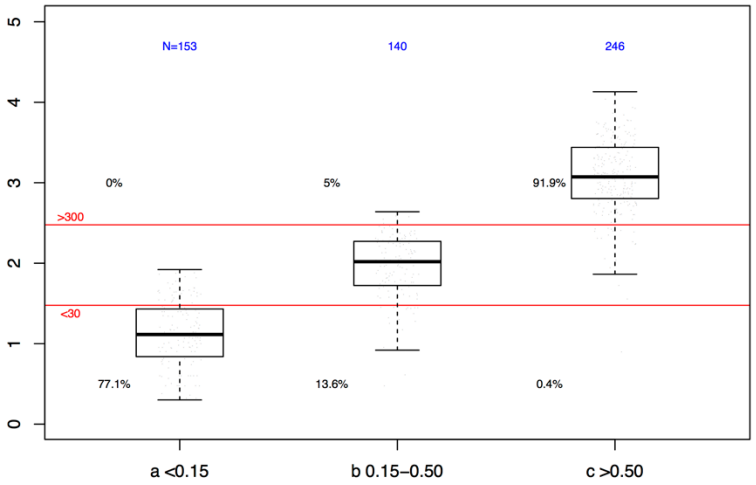


Figure 2: Correlation between Same-day UACR and UPCR Results at Three Sites

Cleveland Clinic



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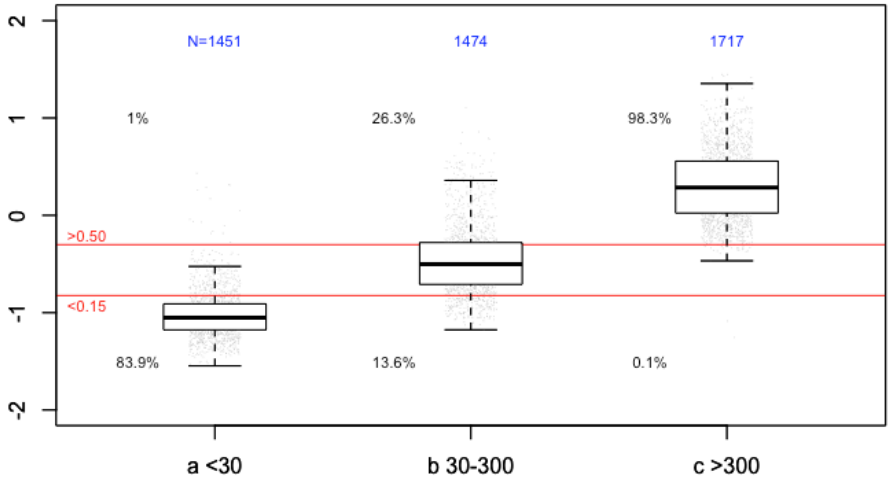

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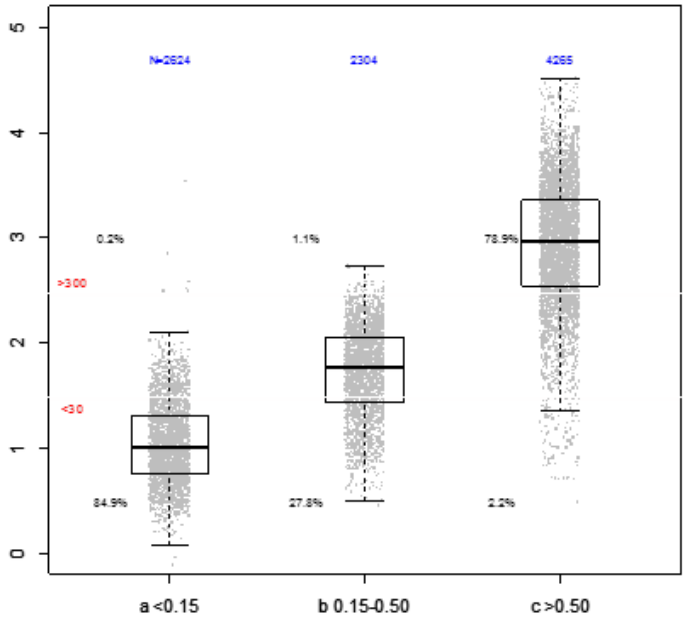
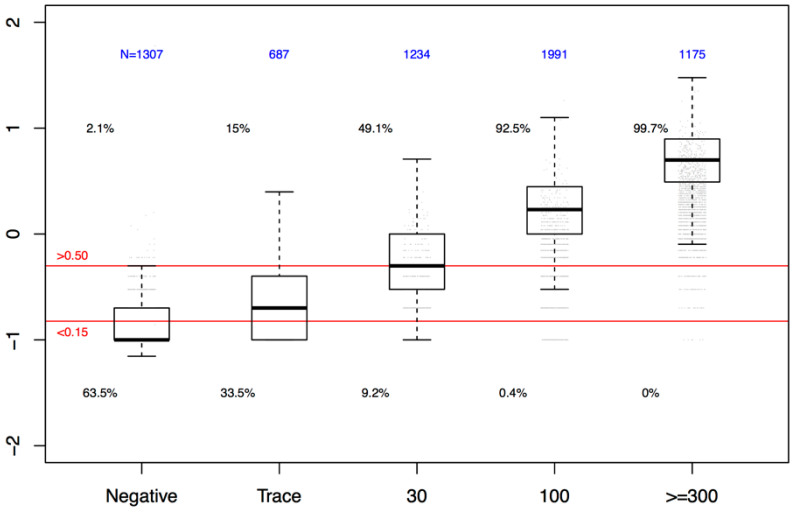


Figure 3: Correlation between Same-day UPCR and UA Results at Three Sites

Cleveland Clinic



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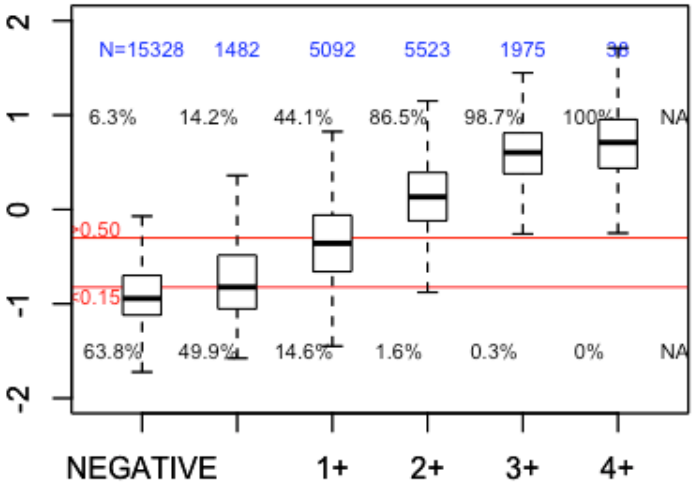

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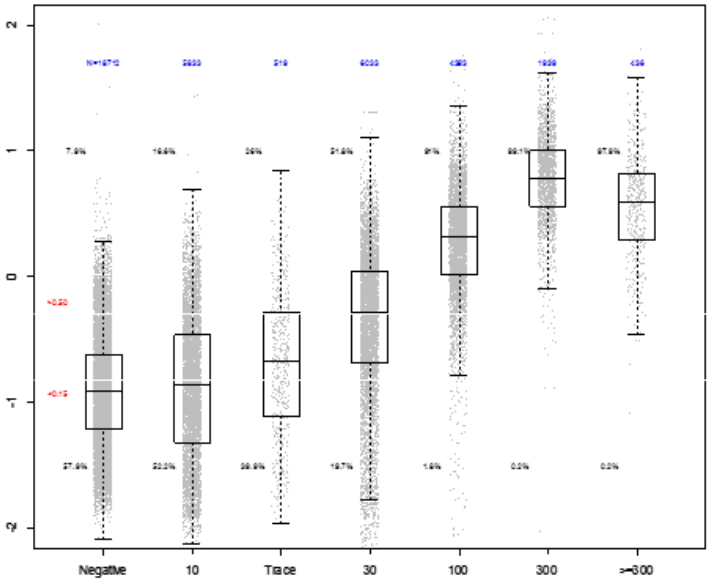
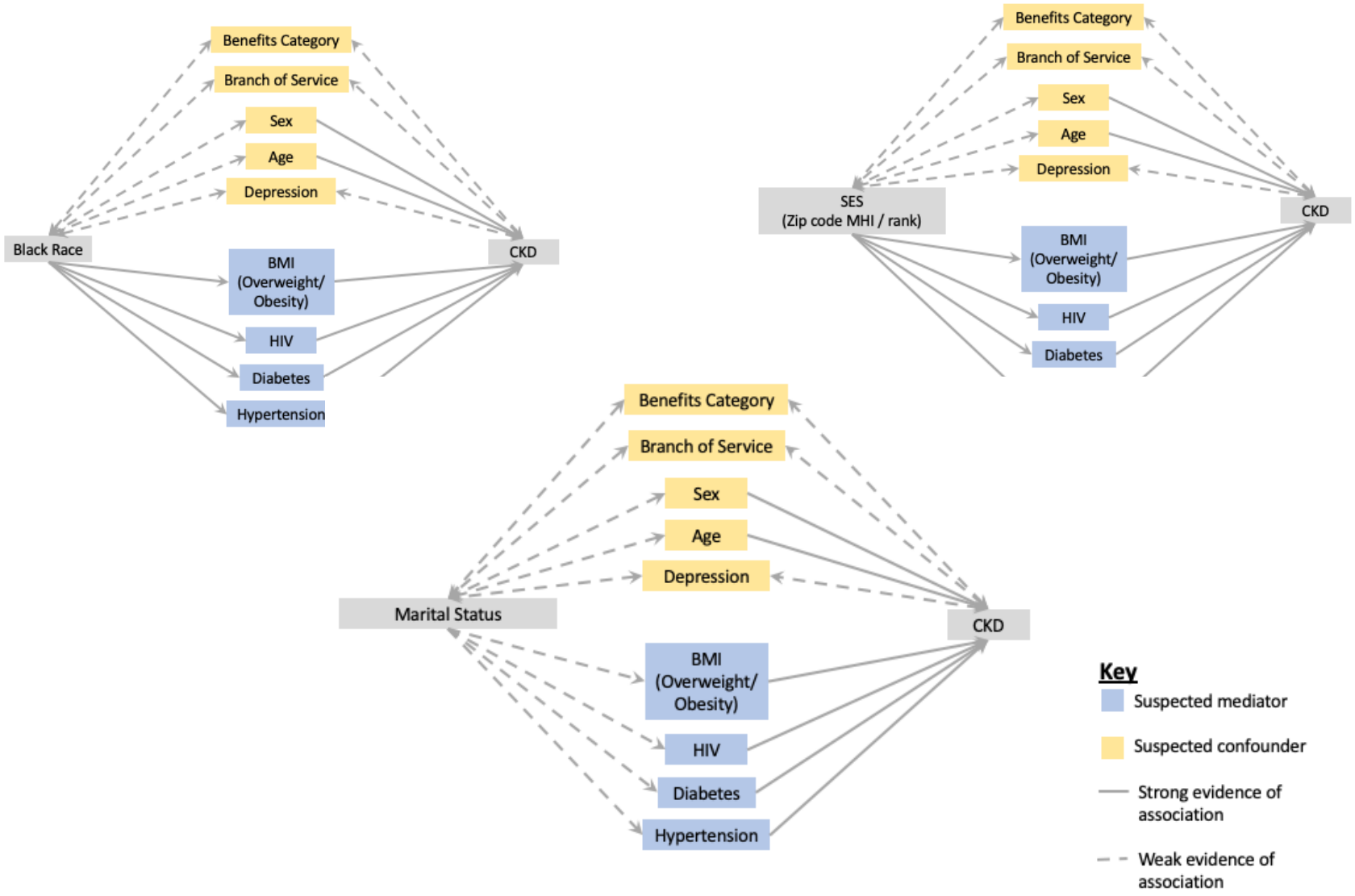


Figure 4: Directed Acyclic Graphs Showing Suspected Mediators and Confounders between Sociodemographic Risk Variables and CKD



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