**Title**
Examining opportunities to reduce costs and improve outcomes of vascular access during early hemodialysis dependence



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**Publication Date**
2021

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

# Examining opportunities to reduce costs and improve outcomes of vascular access during early hemodialysis dependence

A dissertation submitted in partial satisfaction

of the requirements for the degree Doctor of Philosophy

in Health Policy and Management

by

Timothy Paul Copeland

2021

ABSTRACT OF THE DISSERTATION

Examining opportunities to reduce costs and improve outcomes of vascular access during early hemodialysis dependence

By

Timothy Paul Copeland

Doctor of Philosophy in Health Policy and Management

University of California, Los Angeles, 2021

Professor James Macinko, Chair

Progression to end stage kidney disease (ESKD) is often sudden due to few symptoms during earlier stages of chronic kidney disease (CKD), and health care access barriers preventing recommended CKD screening. Due to nonrandom processes dictating selection into pre-ESKD nephrology care, permanent access versus catheter, and arteriovenous graft (AVG) versus arteriovenous fistula (AVF), measurement of outcomes subsequent to these processes must consider remedies to potential selection bias.

In paper one, a recursive bivariate probit estimated factors associated with permanent access creation prior to hemodialysis after accounting for selection into pre-ESKD nephrology care. Nearly all patient factors had small effects, whereas pre-ESKD nephrology care increased the likelihood of improved care (permanent access) more than fourfold. Polices related to health

insurance access and pre-ESKD nephrology care are therefore essential for improving rates of early permanent access creation.

Paper two examines determinates of vascular access type and infection, with some factors (e.g., pre-ESKD nephrology care) relating to infection risk indirectly, through selection into an access type. An endogenous Poisson was used to model variability in hospitalization for vascular access infection after adjusting for selection into permanent access. The results suggest ESKD patients under 30, patients with a history of intravenous drug use, and residents of nursing homes should be a focus of interventions to reduce vascular access infection among ESKD patients, as adjustment for selection into an access type substantially increased estimates of these groups' infection risks, relative to estimates from a Cox proportional hazards model that does not correct for selection bias.

In paper three, rates of filled opioid prescription did not differ by access type, and a modeling approach accounting for selection into AVF versus AVG was found to be inappropriate. However, among patients filling an opioid prescription, AVG recipients had, on average, 2 additional 5 milligram hydrocodone equivalents prescribed to them relative to AVF recipients. Federal, state, and health system policymakers, as well as members of surgical societies and research scientists, may wish to use these findings to inform methodological approaches and decisions related to the identification and care of late-stage CKD and early-stage ESKD patients.

The dissertation of Timothy Paul Copeland is approved.

Roshan Bastani

Warren Comulada

Elaine Ku

James Macinko, Committee Chair

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2021

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**Acknowledgements**

I would like to thank those who have helped me along the way, both in the preparation of this document, and throughout my academic pursuits:

My wife, Tania Reza, for too many things to list.

My parents, Sara & Philip Copeland, for their unconditional love and support.

Karen Woo, for providing me with numerous opportunities for learning and collaboration.

Benjamin Franc, for teaching me how to prepare and submit a manuscript.

T.J. McCarthy, for introducing me to Stata and connecting me with my first opportunity to use Stata outside of a classroom.

Richard Rothstein, for giving me the opportunity that sparked my interest in policy analysis.

Paul K. Miller, for his assistance with administrative barriers.

Eric Chagala and Jill Frank-Aldrich, for their perspectives.

My PhD committee, James Macinko, Elaine Ku, W. Scott Comulada, and Roshan Bastani, for their advisement in the preparation of this document.

# VITA

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**Copeland, T. P.**, Lawrence, P., & Woo, K. (2019) Outcomes of Initial Hemodialysis Vascular Access in Patients Initiating Dialysis with a Tunneled Catheter. *Journal of Vascular Surgery, 62*, 1235-1241.

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**Copeland, T.P.**, Lawrence, P., & Woo, K. "Continuity of Care in Vascular Access and Revision Procedures." Southern California Vascular Surgical Society, 38th Annual Meeting (2020).

**Copeland, T.P.**, Lawrence, P., & Woo, K. "Comparing Outcomes of Initial and Repeat Vascular Access in Hemodialysis Dependent Patients." American College of Surgeons' Scientific Forum at Clinical Congress 2020 (2020).

**Copeland, T.P.**, Lawrence, P., & Woo, K. "Provider Factors Have a Larger Effect on Vascular Access Type and Outcomes than Patient Factors." Society for Clinical Vascular Surgery Annual Symposium (2019).

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**Copeland, T.P.**, Lawrence, P., & Woo, K. "Outcomes of Initial Hemodialysis Vascular Access in Patients Initiating Dialysis with a Tunneled Catheter." Western Vascular Society Annual Meeting (2018).

## Chapter 1: Introduction

### Background

#### *Chronic and End-Stage Kidney Disease*

Chronic Kidney Disease (CKD) is defined by an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73m$^2$ (i.e. Stage 3 CKD); end-stage kidney disease (ESKD), which requires treatment with dialysis or kidney transplant, is defined by an eGFR below 15 ml/min/1.73m$^2$ (i.e. Stage 5 CKD) and dependence on dialysis.[1] Causes of CKD include diabetes mellitus; inflammation and/or damage to the glomerulus (i.e. glomerulonephritis), the capillary blood vessels that facilitate blood filtration by the kidney; genetic diseases, such as adult polycystic kidney disease; drug use (e.g., penicillins non-steroidal anti-inflammatory drugs, proton pump inhibitors, diuretics, and anti-retrovirals); urological conditions; and infection (e.g., post-infectious glomerulonephritis, HIV, hepatitis, tuberculosis, and malaria).[2] Diabetes mellitus is the most common cause of CKD; 40% of people with diabetes develop CKD at some point during their life.[2]

Approximately 750,000 people in the United States are affected by ESKD annually, and though this represents only 1% of U.S. Medicare enrollees, patients with ESKD account for approximately 7% of annual Medicare expenditures (e.g., $35 billion in 2016).[1] 80% of the total Medicare expenditures related to ESKD patients result from hemodialysis, which costs an average of 90 thousand dollars per ESKD patient-year among Medicare patients.[1]

Progression to ESKD is often sudden, with about 1 in 3 ESKD patients receiving little to no nephrology-specific care prior to their diagnosis with ERSD.[1] ESKD risk varies widely depending on race, irrespective of sex-differences.[3] Though there are also racial disparities in the diseases most frequently cited as the primary causes of ESKD, such as diabetes mellitus,

hypertension, and glomerulonephritis, these differences do not fully account for disparities in the prevalence of ESKD.[3-5] Socioeconomic factors and health behaviors are also associated with racial differences in ESKD, but irrespective of factors controlled for predicting risk of ESKD, underlying racial differences in ESKD risk persist.[3-8]

*Treatment for End-Stage Kidney Disease*

When a patient develops ESKD, their kidneys have reached a point of failure, necessitating intervention through either dialysis or kidney transplantation. The primary treatment modalities in 2016 were hemodialysis (87.3%), peritoneal dialysis (9.7%), and preemptive kidney transplant (2.8%).[1] Peritoneal dialysis involves inserting a catheter into the abdomen and using the peritoneal membrane to facilitate hemodialysis by introducing hemodialysis fluid into the peritoneal cavity through a catheter to accomplish dialysis.[9] Hemodialysis requires external filtration of a patient's blood using a dialysis machine, which requires access to patient's blood using either a tunneled hemodialysis catheter, arteriovenous fistula, or arteriovenous graft to access the circulatory system.[9]

*Vascular Access for Hemodialysis*

Among ESKD patients initiating hemodialysis in 2016, 80% initiated access with a tunneled hemodialysis catheter (THC) and at 90 days post-initiation 69% of patients were still using THC for dialysis.[1] THC is the most common access modality at hemodialysis initiation because catheter placement allows for hemodialysis immediately, whereas both arteriovenous fistula (AVF) and arteriovenous graft (AVG) are not immediately available for hemodialysis use after creation. Unlike THC, which is the placement of a tube into the vein to achieve vascular access for hemodialysis, AVF requires connecting of an artery and vein to create a vascular location of increased blood flow to facilitate efficient hemodialysis. AVG involves connecting

the artery and vein with synthetic material, rather than relying exclusively on the vein and artery to create the linkage.[9] AVF and AVG are permanent access types and are preferable to THC due to THC's greater rate of infections, malfunction leading to inadequate blood flow, and thickening and narrowing of veins' walls (i.e. vein stenosis).[9] With the notable exception of patients who are not expected to survive for more than a number of days or weeks, as well as a minority of patients who do not have veins that can support access creation, THC is never a preferred hemodialysis access type. Ideally, AVF or AVG creation should occur prior to initiation of hemodialysis or during a hospitalization resulting in an initial diagnosis of ESKD.[9] Not having a permanent access functioning or placed at hemodialysis is not necessarily representative of poor clinical decision making, and may be a potential consequence of limitations in access to care.[10-12]

*Selection of Vascular Access Type*

In 2006, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) updated their guidelines to reflect a "Fistula First" approach, in which AVF was recommended as the preferred access type for initiating hemodialysis, as opposed to AVG.[13, 14] However, approximately one-third of fistulas never mature, meaning they do not become a functional access for hemodialysis,[15] and as many as 60% do not mature within 5 months of the AVF procedure.[16] Among the fistulas that do mature, 44% require a minimum of one additional surgical intervention to facilitate successful maturation.[17] In addition to the literature on issues with fistula maturation, there have also been findings that the duration of patency (i.e., the duration a vascular access remains open and available for hemodialysis) is shorter for AVF than AVG.[18-21]

While AVFs typically require at least 4 weeks before they can be used, AVG usually only require 2 weeks to heal and be used.[13] Though some subgroups of patients have better outcomes

with AVG, the primary drawback of AVG is they typically have a higher rate of complications and trend towards more procedures to maintain patency than AVF.[22, 23]

Decisions on whether or not a patient would benefit most from AVF or AVG depends on a number of patient factors. Patients who are over 65, have peripheral vascular disease, have coronary arterial disease, or are black tend to have higher risk of fistula failure and are typically better candidates for AVG.[24, 25] Examination of physiological differences in black patients found that though black patients tended to have poorer primary and functional AVF patency than whites, this appeared to be caused by significantly narrower vein diameters among black patients; among black patients with appropriate vein diameters for AVF (i.e., veins that were not too narrow), patency rates were comparable to non-black patients.[26] As implied by the findings of the aforementioned study, "vein diameter is a major predictor of fistula maturation."[27]

If an access has previously failed and a new access location will be pursued, a change in access type may be appropriate given the specific context of the patient's previous access failure.[25] For this reason, it is easiest to study differences in index access, as opposed to subsequent access procedures.

In 2020, KDOQI published their 2019 update for vascular access guidelines, which included advisement about developing an ESRD "Life-Plan" for long-term access planning, as well as new guidance for vascular access choice.[28] The updated guidelines provide greater emphasis on using surgeons' clinical judgement, comorbidities, vessel characteristics, patient characteristics, and patient preference to select a permanent access type, whereas the 2006 "Fistula First" guidelines were much more rigid in their advisement.

*Early Vascular Access Creation*

Ideally, AVF or AVG creation should occur prior to initiation of hemodialysis or during a hospitalization resulting in an initial diagnosis of ESKD.[9] However, access to care issues aside, it is difficult for providers to estimate when a patient with CKD will enter ESKD and require dialysis, which is likely a substantial factor behind achieving high rates of permanent vascular access at hemodialysis initiation.[25, 29, 30] Whether or not patients initiate hemodialysis on a permanent vascular access is largely dependent on access to nephrology care prior to the need for dialysis. Nephrology care at least 12 months prior to the onset of ESKD is associated with 11.3 times the odds of initiating HD with a permanent vascular access (95% CI 11.0-11.5).[31] The same study also found the mortality rate of patients with pre-ESKD nephrology care was associated a 27% to 42% decrease in the hazard of death depending on whether or not patients had nephrology care less than 6 months pre-ESKD, 6 to 12 months pre-ESKD, or more than 12 months pre-ESKD.[31] Pre-ESKD nephrology visit intensity is also associated with a greater likelihood of HD initiation on a permanent vascular access (RR 3.6; 95% CI 3.4-3.8), and lower mortality.[32]

*Nonrandom Assignment of Pre-ESKD Nephrology Care and Access Type*

A major limiting factor in accurately measuring the effect of pre-ESKD nephrology care and vascular access type on patient outcomes is the nonrandom assignment of patients to nephrology care and a particular access type. For instance, if pre-ESKD nephrology care and being a non-Hispanic white patient both increase the likelihood of initiating dialysis on a permanent access, and being a non-Hispanic white patient also is associated with a greater likelihood of pre-ESKD nephrology care, then the effects size of both variables would be misrepresented without accounting for the endogenous relationship between the variables.

Without adequately accounting for the complexities of selection into pre-ESRD care, effects sizes will be biased and may misinform policy decision making regarding Medicare policy (e.g., bundled payments that encompass vascular access[33]). The studies herein evaluate the utility of applying statistical approaches that attempt to account for nonrandom assignment of pre-ESKD nephrology care and access type, and measure differences in the magnitude of outcomes by patient factors after accounting for bias in treatment assignment

**Data**

The United States Renal Data System (USRDS) has been collecting and reporting data on patients with kidney failure for 30 years. USRDS is the primary source of epidemiologic data on kidney disease in the United States and is a critical resource to researchers requiring a national-level database on kidney disease and end-stage kidney disease (ESKD).[1] In 1972, the Medicare ESKD program was established in order to provide widespread access to hemodialysis to patients with ESKD, as the cost of hemodialysis has been prohibitive for many ESKD patients since the development of dialysis.[1]

Though not all ESKD patients opt to enroll in Medicare if they have employer or other coverage they prefer, all ESKD patients are included in USRDS, irrespective of age and insurance coverage. Only Medicare enrollees have their claims submitted to USRDS, somewhat limiting investigations related to hospitalizations, costs, and clinical services to Medicare enrollees. However, the most recent data release shows 90% to 95% of patients initiating hemodialysis in the USRDS database were enrolled in Medicare, Medicare Advantage, or had applied for Medicare enrollment at the time of their first dialysis.

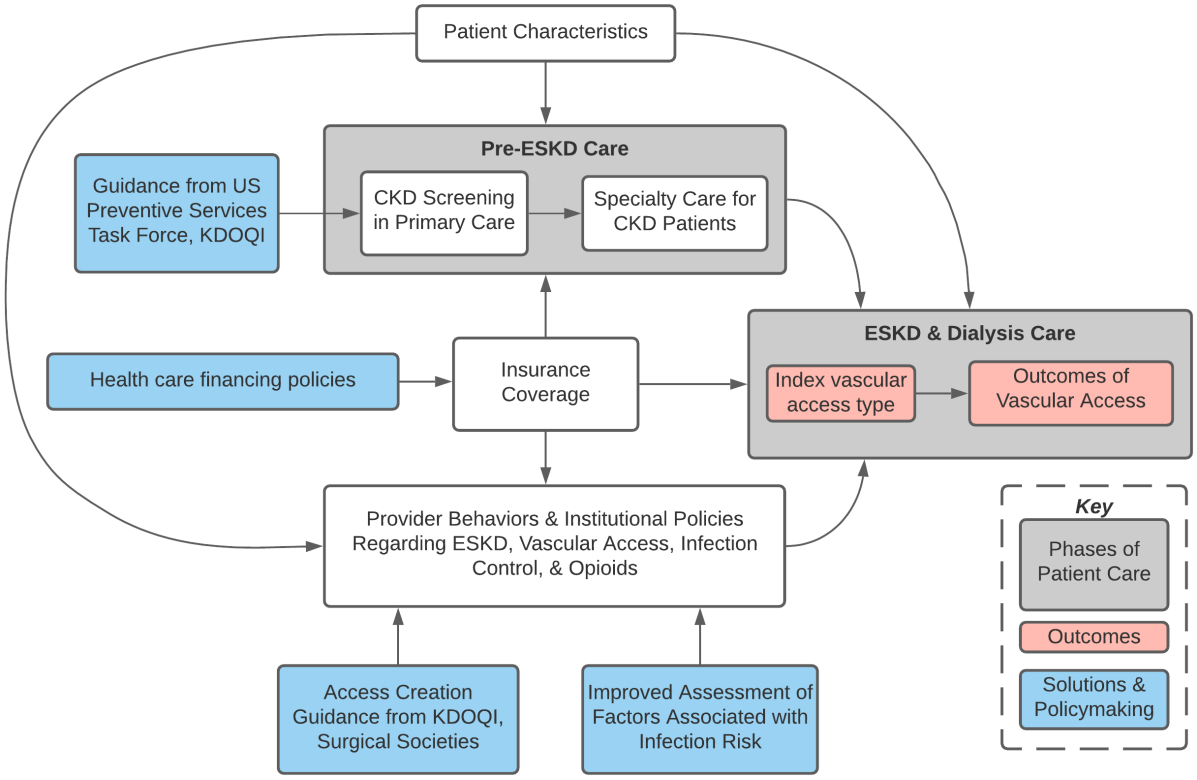
The USRDS is comprised of multiple data files, of which a subset of files will be used for this analysis: The patient file, the medical evidence file (i.e., CMS Form 2728 responses),

hospital claims, Medicare Part D claims, Medicare Part D enrollment files, and CROWNWeb hemodialysis history file. The patient file includes demographic information and geographic location, as well as dates of first ESKD service, transplant, and death. The medical evidence file contains information on comorbidities and insurance at the time of initial ESKD diagnosis. The CROWNWeb file includes information on hemodialysis visits and was used as a secondary source of information on initial hemodialysis access type between 2012 and 2017. Index access will be determined using responses to patients first recorded 2728 form. Among those who did not have initial access type recorded in their 2728 form, the initial access recorded in CROWNWeb will be assumed to be the index access type. CROWNWeb data is available beginning May 1, 2012. The hospital dataset was used to identify hospitalizations for vascular access infections during inpatient admissions. Medicare Part D files were used to identify opioid prescription using a data file from the Centers for Disease Control to identify opioids using National Drug Codes (NDCs) for linkage between the datasets.[34] Medicare Part D enrollment files were used to verify patients had Part D coverages in the months their vascular access claims occurred. The American Community Survey will be used to provide median-county level income within each year.[35] The number of internal medicine subspecialists, which includes nephrologists, and rural-urban continuum code were defined using Area Health Resource Files from 2015.[36]

Data management and analysis were conducted using Stata 17 (Stata Corp, College Station, Texas).

## Framework

**Figure 1.1. Framework of relationships underlying index vascular access type and vascular access outcomes**




The studies herein connect variations in vascular access placement and outcomes with policy implications. An adaptation of Crews & Novick's conceptual framework for understanding financing policies pertaining to dialysis, which was outlined to examine inequities in dialysis access and ESKD care.[37] The framework of Crews & Novick is expanded upon by identifying inputs into the flow of patients from primary care to vascular access outcomes. Three additional inputs are considered that may be categorized as "solutions and policy making." In Figure 1.1, the areas of potential policy changes identified during the discussion of the findings in each of these dissertation chapters, and are highlighted in blue. The patient care segments of the model (i.e., pre-ESKD sources of care, ESKD & dialysis care) are highlighted in grey. The

outcomes of the studies in this dissertation are highlighted in red, with "Outcomes of Vascular Access" referring to hospitalization for vascular access infection, filled opioid prescription for vascular access creation, and persistent opioid associated with vascular access creation.

Though the framework (Figure 1.1) incorporates elements unrelated to financing and inequities, it does so through broad categories to suit the present context. The framework reflects that patient characteristics, insurers, medical societies, providers, and institutions are the avenues through which variation in access to health care, the health care (i.e., primary and specialty care pre-ESKD), and ESKD outcomes may be most readily understood. Health care financing policies are identified as a policy solution that feeds into insurance rather than from it.

Patient characteristics, though important for understanding access to care and health care outcomes, are explored in more depth within the context of each study (Figures 2.1, 3.1, & 4.1). The characteristics may be grouped into three categories: demographic characteristics (i.e., age, sex, race), comorbidities (e.g., diabetes, hypertension), and proxies of socioeconomic status other than race (e.g., insurance status, median zip code level income). Direct indicators of access to care (e.g., pre-ESKD nephrologist and surgeon office visits) are located in the pre-ESKD care portion of these studies' framework (Figure 1.1), while patient access type is considered to be an outcome of entering ESKD rather than a patient characteristic.

Provider behaviors, both in the sense of individual providers and "providers" as health care systems, are influenced in part by recommendations from governmental bodies, such as the US Preventive Services Task Force recommendation on CKD screening;[38] clinical practice guidelines, such as those published by KDOQI;[28] and payer incentives, such as Medicare's End-Stage Renal Disease Quality Incentive Program (ESRD QIP), which assesses facility-level

performance through a Total Performance Score (TPS) and applies up to a 2% penalty on Medicare payments for a substandard TPS.[39]

Aside from financial incentives through Medicare, financial incentives may also be understood in this model as incentives originating from private payers. Commercial insurers are responsible for a minimum of 4 months of ESKD coverage, and up to 30 months, depending on patient preference. Commercial insurers already have begun using value-based payment models to incentivize improved outcomes to reduce costs, with up to 60% of a payers annual payments paid through value-based programs.[40] Though increasing reimbursement for CKD screening among high-risk patients and increasing reimbursement for nephrology care during CKD would increase up-front costs of care, the savings from reducing hospitalizations and dialysis costs due to improved CKD management would be substantial.[41] At Medicare reimbursement rates, every month in which dialysis imitation is delayed saves approximately $5,000 per patient per month.[1, 41]

One of the most leading causes of hospitalization among hemodialysis patients is access infection or complications, with hospitalization rates nearing those of the rates for cardiovascular issues (0.36 per patient year [PPY] versus 0.42 PPY, respectively).[1] Policies pertaining to infection control are generally addressed through specific practices not dictated by Medicare reimbursement, though it would be possible for Medicare to consider infection rates as a factor influencing ESRD QIP. The practical implications regarding infection control are addressed in more detail in the introduction and discussion of Chapter 3.

Opioid prescription is the only outcome of vascular access examined in this dissertation that is best not addressed through financial incentives, but rather through provider education via institutional guidelines for practice. Guidance from surgical societies is a convenient solution to

reduce opioid prescription, as the cost of implementation is trivial. Though there were state-level laws in 26 states by the end of 2017 that limited prescribing of opioid for acute pain,[42] they are not targeted in a way that pertains to encounters for creation of a permanent vascular access. Furthermore, it is not reasonable to impose restrictions on opioid prescription when the goal is to minimize opioid prescription for vascular access, rather than completely eliminate it; there will doubtlessly be circumstances where opioids are appropriate for creation of a permanent vascular access. Though prescription drug monitoring programs (PDMPs) are another potential policy option, a recent systematic review found, "little consistent evidence has yet emerged to demonstrate PDMPs' impact on outcomes of greatest importance, whether more proximal targets such as prescribing behavior or distal outcomes, such as opioid misuse, diversion, morbidity, and mortality."[43] Furthermore, PDMPs suffer from the same shortcoming as a blunt policy instrument as state-level opioid prescription laws; neither are appropriate policy solutions to reduce opioid prescription for vascular access.

**Dissertation Aims**

The first study of my dissertation is presented in Chapter 2. This study examines the relationship between pre-ESKD nephrology care and the likelihood of starting hemodialysis using a permanent vascular access. Pre-ESKD nephrology care is a key step in preparing CKD patients to begin dialysis; this study measures the effect of pre-ESKD nephrology with consideration for variability in effect by race and geographic region. A recursive bivariate probit regression model was used to estimate variability in likelihood of a permanent access after adjusting for the relationship between patient factors and endogenous health care access (i.e., pre-ESKD nephrology care).

Aim 1 (Chapter 2): Measure the impact of pre-ESKD nephrology care on the likelihood of permanent access at hemodialysis initiation.

- Sub Aim 1: Evaluate the extent to which racial and regional differences in vascular access at hemodialysis initiation are related to disparities in pre-ESKD nephrology care.
    - Hypothesis 1: The magnitude of the association between a patient's race and their likelihood of permanent access is moderated by the region of the patient.
    - Hypothesis 2: The magnitude of the association between a patient's race and their likelihood of permanent access is moderated by whether or not they had pre-ESKD nephrology care.
- Sub Aim 2: Evaluate potential biases in estimating differences in likelihood of initiating hemodialysis on a permanent access.
    - Hypothesis 1: Given the nonrandom assignment of access to health care, a recursive bivariate probit regression will demonstrate the effect of pre-ESKD nephrology care on likelihood of permanent access is underestimated by single-equation regressions.
    - Hypothesis 2: Given the nonrandom assignment of access to health care is influenced by race and geography, a recursive bivariate probit regression will demonstrate the effects of race and ESRD network region on likelihood of initiating hemodialysis on a permanent access are biased in estimates from single-equation regressions.

The second study of my dissertation is presented in Chapter 3. This study attempts to clarify the factors with the largest impact on the likelihood of hospitalization for vascular access infection, which is one of the most common causes of hospitalization among ESKD patients,

with approximately one infection occurring per every three patient years in 2018.[1] This study uses an endogenous Poisson to estimate variability in hospitalization for vascular access infection after adjusting for the relationship between patient factors and permanent access at hemodialysis initiation. A logistic regression was used to examine variability in the likelihood of an infection with a diagnosis code for Methicillin-resistant Staphylococcus aureus (MRSA).

Aim 2 (Chapter 3): Measure the impact of hemodialysis access type on hospitalization for vascular access infection.

- Sub Aim 1: Estimate the association between an access type and risk of hospitalization for a vascular access infection after accounting for the relationship that underlying whether or not patients have a tunneled catheter or permanent access.
    - Hypothesis 1: Without accounting for the relationships underlying whether or not people start their dialysis with a tunneled catheter, estimates of variation in vascular access infection will be biased.
- Sub Aim 2: Evaluate whether differences in vascular access infection by patient demographics are due to variability in access type.
    - Hypothesis 1: The effect of age will be significantly different after adjustment for nonrandom assignment to tunneled catheter.
    - Hypothesis 2: The effect of sex will be significantly different after adjustment for nonrandom assignment to tunneled catheter.
    - Hypothesis 3: The effect of race will be significantly different after adjustment for nonrandom assignment to tunneled catheter.
    - Hypothesis 4: The effect of ESRD network region will be significantly different after adjustment for nonrandom assignment to tunneled catheter.

The final study of my dissertation is presented in Chapter 4. This study describes the rate of filled opioid prescription for post-operative pain management of vascular access creation. Unnecessary opioid prescription has become a major concern in recent decades, and there is a dearth of literature addressing opioid prescription for vascular access procedures at the national level. This study uses a mixed effect logistic regression to model the likelihood of filled opioid prescription for an ESKD patients first vascular access creation. A mixed effect linear regression was used to measure variability in the dose of opioids prescribed. A Cox proportional hazards model was used to measure variability in persistent opioid use.

Aim 3 (Chapter 4): Explore variability in filled opioid prescriptions for post-operative pain control for hemodialysis access.

- Sub Aim 1: Determine if endogeneity related to vascular access type requires a two-stage modeling approach to estimate likelihood of filled opioid prescriptions for post-operative pain control.
    - Hypothesis 1: A two-stage regression model will be necessary to account for endogeneity related to selection into either a fistula or graft; access type is expected to influence access differently depending on the characteristics that lead to the access type used.
- Sub Aim 2: Determine if there are differences in prescription of opioids for index access procedures based on access type (AVF vs. AVG).
    - Hypothesis 1: AVF patients will have a greater likelihood of opioid prescription.
- Sub Aim 3: Determine if there are differences in prescription of opioids for index access procedures by surgeon type (vascular vs. general vs. thoracic vs. cardiac).

    - Hypothesis 1: Patients of general surgeons will have a greater likelihood of opioid prescription than patients of other surgical specialties.
    - Hypothesis 2: Patients of vascular surgeons will have a lower likelihood of opioid prescription than patients of other surgical specialties.
- Sub Aim 4: Determine the average dosage of opioids among filled opioid prescriptions.
    - Hypothesis 1: Dosages will vary by individual provider.
    - Hypothesis 2: General surgeons will prescribe the greatest dose of opioids.
- Sub Aim 5: Evaluate evidence of persistent opioid use associated with opioid prescription for index access.
    - Hypothesis 1: The risk of opioid use between 90- and 180-days post access will be greater among patients who filled an opioid prescription for their index access procedure.

## Chapter 2: Measuring the impact of pre-ESKD nephrology care on likelihood of permanent access at hemodialysis initiation

Sub Aims & Hypotheses

- Sub Aim 1: Evaluate the extent to which racial and regional differences in vascular access at hemodialysis initiation are related to disparities in pre-ESKD nephrology care.
    - Hypothesis 1: The magnitude of the association between a patient's race and their likelihood of permanent access is moderated by the region of the patient.
    - Hypothesis 2: The magnitude of the association between a patient's race and their likelihood of permanent access is moderated by whether or not they had pre-ESKD nephrology care.
- Sub Aim 2: Evaluate potential biases in estimating differences in likelihood of initiating hemodialysis on a permanent access
    - Hypothesis 1: Given the nonrandom assignment of access to health care, a recursive bivariate probit regression will demonstrate the effect of pre-ESKD nephrology care on likelihood of permanent access is underestimated by single-equation regressions.
    - Hypothesis 2: Given the nonrandom assignment of access to health care is influenced by race and geography, a recursive bivariate probit regression will demonstrate the effects of race and ESRD network region on likelihood of initiating hemodialysis on a permanent access are biased in estimates from single-equation regressions.

Key Findings & Implications

- After adjusting for interactions and adjusting for selection into pre-ESKD nephrology care, a recursive bivariate probit estimates ESKD patients with nephrology care at least 6 months before ESKD had a 55.8 percentage point greater probability of a permanent access than those without pre-ESKD nephrology care (95% CI 55.5-56.1). The effect of nephrology care was estimated to be 3.76 times greater using a bivariate probit versus a naive probit ($p<0.0001$).
- Adjusting for covariates and nonrandom assignment of pre-ESKD nephrology care, the permanent access rate was 72.1% (95% CI 71.8%-72.4%) among those with pre-ESKD nephrology care, 4.42 times the rate of those without pre-ESKD nephrology care (16.3%; 95% 16.1%-16.4%).
- The decrease in the regional level variability after accounting for non-random assignment to pre-ESKD nephrology care suggests the policy solutions to improve catheter use are primarily in the hands of stakeholders influencing financing policies that would facilitate earlier pre-ESKD nephrology care, rather than in the hands of physicians and health systems.
- Given variability in vascular access and optimal care delivery are heavily influenced by patients' ability to access health care, retrospective analyses should consider the non-random assignment to health care access and optimal health care delivery in their estimation of the effects of health care services and utilization.

## Introduction

Care by a nephrologist prior to end-stage kidney disease (ESKD) is associated with lower rates of adverse outcomes.[10, 11, 44, 45] Individual poverty (as determined by dual Medicare-Medicaid eligibility), zip-code level poverty, black (vs. white) race, and Hispanic ethnicity have been found to be associated with lower access to pre-ESKD nephrology care.[46, 47] Low rates of pre-ESKD nephrology care are, in part, a reflection of barriers to health care access,[48-50] defined by patients' ability to pay for care and health insurance prior to ESKD, as well as through patients' ability to search and initiate primary care,[51] which is necessary to access pre-ESKD nephrology care for the majority of patients.

Social determinants of health frameworks identify racial disparities in health and health outcomes as the consequence of social, institutional, and organizational structures that systematically disadvantage racial minorities.[52-55] Associations between race and health care access, such as pre-ESKD nephrology care, or outcomes, such as index vascular access type, are reflections of social conditions which cause variation in health access and outcomes; racial variability in outcomes is typically not a reflection of heritable biological differences between races. A study of United States Renal Data System patients initiating dialysis between 2005 and 2006 found the racial composition of a patient's zip code was associated with access to pre-ESKD care, but not the quality of nephrology care.[10, 56] This suggests that, among ESKD patients, the characteristics associated with poorer access to care measures (e.g., race, racial composition of region) have independent associations with ESKD outcomes that may be biased if adjustment is not made for "assignment" of patients to pre-ESKD nephrology care. Norris et al. address variability in dialysis access and outcomes between black and white patients through both the lenses of potential biological differences and social factors; they note that though some

racial differences in biological measurements are a result of true differences in biologic variation, there are separate social forces proxied by race which may influence the same outcomes as biologic variations.[57] Norris et al. conclude disparity-focused policy evaluations and interventions must explicitly distinguish between these potentially causal factors to appropriately conceptualize evaluations and interventions.[57]

Pre-ESKD nephrology care at least 12 months prior to ESKD is associated with 11.3 times the adjusted odds of initiating hemodialysis with a permanent vascular access (95% Confidence Interval [CI] 11.0-11.5)[12] and a pre-ESKD nephrology visit is associated with a greater likelihood of HD initiation on a permanent vascular access (Relative Risk [RR] 3.6; 95% CI 3.4-3.8), and lower mortality.[32] Other studies have also found higher rates of permanent access use and lower mortality rates associated with pre-ESKD nephrology care.[56, 58-61]

Eighty percent of ESKD patients initiate dialysis through a tunneled hemodialysis catheter (THC) and 69% are continuing to dialyze through a THC 90 days after hemodialysis initiation.[1] THC is associated with greater rates of infection, malfunctions leading to inadequate blood flow, and thickening and narrowing of vein walls.[29] A permanent access (i.e., arteriovenous fistula or arteriovenous graft) is preferable to THC due to lower infection rates and fewer complications.[62] In the most recent United States Renal Data System report, which covers data through 2016, Hispanic ESKD patients had the highest rate of hemodialysis initiation on THC only (66.1%), with modestly lower rates among whites of any ethnicity (63.2%) and blacks (61.8%), and the lowest rates among Native Americans (58.2%), and Asians (58.3%).

Hispanic patients in USRDS are less likely to initiate dialysis on a permanent vascular access using both unadjusted (prevalence ratio [PR] 0.85; 95% CI 0.83-0.88) and adjusted (PR 0.94; 95% CI 0.92-0.97) models.[62] In examining this disparity, Arce et al. estimated unadjusted

likelihood of permanent access; likelihood adjusted by socio-demographics; likelihood adjusted by socio-demographics, BMI, and comorbidities; likelihood adjusting for previous factors plus frailty; and likelihood adjusting for previous factors plus pre-ESKD nephrology care.[62] They noted the variability in likelihood of permanent access by Hispanic ethnicity was only significantly altered by the final inclusion of pre-ESKD nephrology care; estimates of the difference between Hispanics and non-Hispanics that were essentially identical to the unadjusted analysis (PR 0.85; 95% CI 0.83-0.88) when adjusting for all factors other than pre-ESKD nephrology care,[62] highlighting the extent to which pre-ESKD nephrology care may serve as a mediator or moderator in the relationship between Hispanic ethnicity and index vascular access.

Though prior literature has established the association between pre-ESKD nephrology care and improved ESKD outcomes,[12, 32, 58] failure to adequately account for the selection bias in pre-ESKD care access may misrepresent the magnitude and significance of the associations between patient characteristics (e.g., race, ESRD network, etc.) and vascular access at hemodialysis initiation, partially reflecting differences in access to pre-ESKD nephrology care, rather than differences in practice patterns related to index vascular access.

The 2016 analysis by Fischer et al. of patients who initiated HD from 2000 to 2001 uses a propensity score matching (PSM) approach to adjust for selection into pre-ESKD visit intensity to account for variation in ESKD outcomes.[32] However, their PSM approach assumes no unobserved systematic variation in allocation of their treatment variable, pre-ESKD nephrology care, aside from the observed variables being modeled.[44] Fischer et al. estimated that patients with high intensity pre-ESKD nephrology care had 3.6 times the likelihood of permanent vascular access at hemodialysis initiation (95% CI 3.42-3.79).

## Methods

### *Data*

This study used data from the USRDS,[1] American Community Survey,[35] and Area Health Resource Files.[36] The USRDS patient file, form 2728 file, and provider claims supplied patient demographics, comorbidities, access type, and pre-ESKD nephrology care definitions. Herein, shorthand references to "pre-ESKD nephrology care" or "pre-ESKD care" refer specifically to either (1) seeing a nephrologist at least 6 months prior to ESKD, as defined by Medicare claims, or (2) either not seeing a nephrologist prior to ESKD or not encountering one until fewer than 6 months were remaining until their ESKD. The definition of the household median income by zip code was supplied by the American Community Survey. The number of internal medicine subspecialists, which includes nephrologists, and rural-urban continuum code (2013) were defined using the Area Health Resource Files. See Appendix 1 for variable definitions and operationalizations.

### *Study Sample Selection*

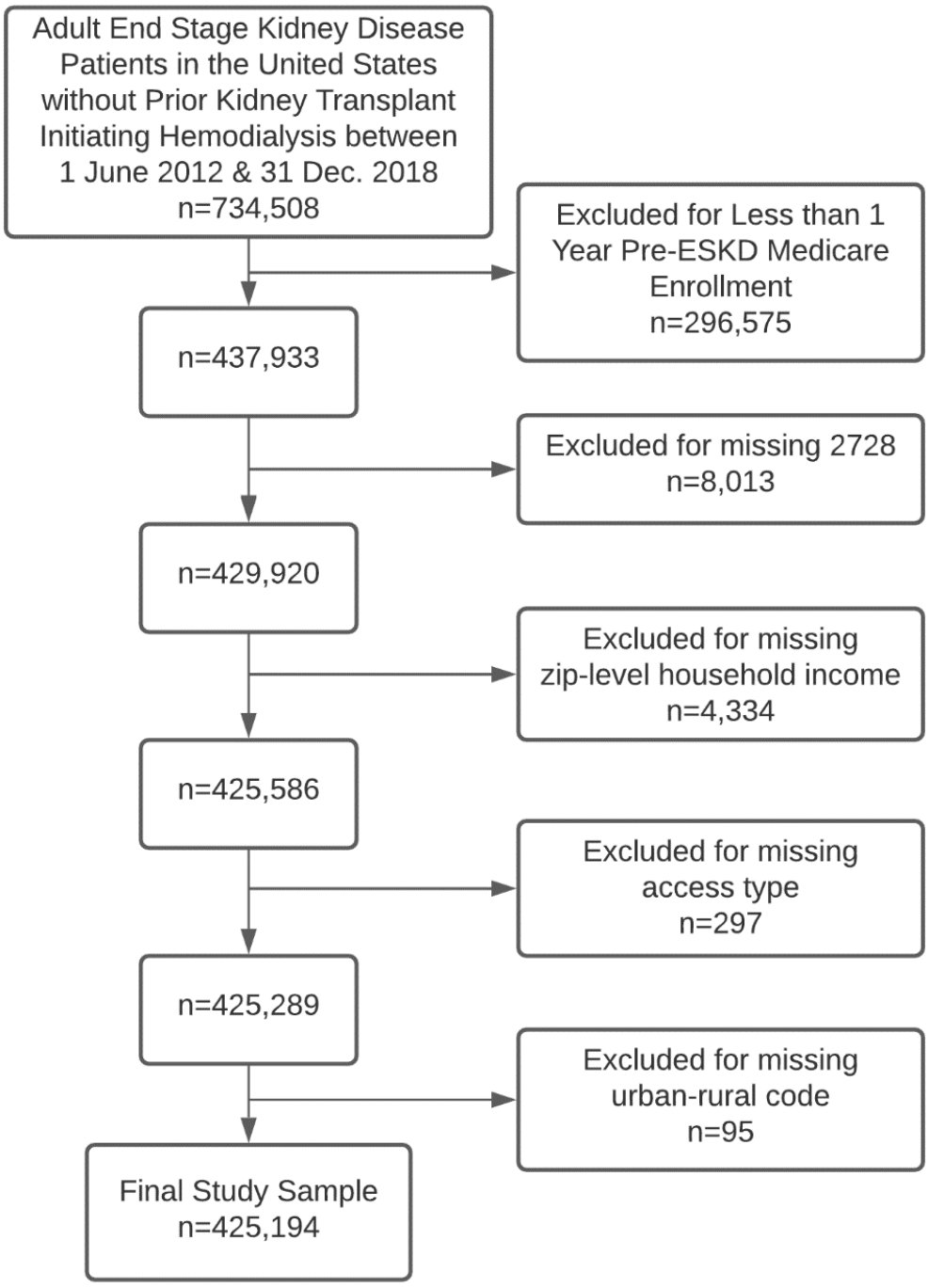
Inclusion criteria for the study population includes: (1) age 18 or older at dialysis initiation; (2) began hemodialysis at first date of end stage kidney disease without a concurrent or prior kidney transplant; (3) resident of United States, not including United States territories; and (4) initiated treatment using hemodialysis between June 1, 2012 and December 31, 2018. The study was limited to an adult population because the etiology and treatment of kidney disease among pediatric patients is not comparable, leading to very different patient populations.[63] Patients with transplants on or before the beginning of dialysis for end stage kidney disease were excluded, given they had reached their desired outcome (i.e., kidney transplant). This was done even if these patients continued dialysis since they were not expected

to remain on dialysis for a long period of time. The population was limited to residents of the United States because residents of the Virgin Islands, Guam, and Puerto Rico would be expected to differ in terms of health care access compared to residents of the 50 states and the District of Columbia.[64] These regions also fall outside of the ESRD network assignments, which will be used as a geographic fixed effect and will be interacted with race. Additionally, the American Community Survey only provides median household incomes on zip codes in the United States, District of Columbia, and Puerto Rico, excluding all other territories.

After applying the aforementioned inclusion criteria, 734,508 patients were identified for potential study inclusion. Patients were excluded from the study if: they did not have a at least 1 year of pre-ESKD Medicare enrollment (n=296,575), if they did not have 2728 form in USRDS (n=8,013); they did not match to a zip-code level median household income (n=4,334); they had an unknown index access (n=297); or they had an unknown urban-rural county code (n=95) This resulted in a study sample size of 425,194 patients. See Figure 2.1 for a diagram of exclusion criteria.

To evaluate potential bias resulting from exclusion due to missing values, missingness by place (i.e., state of residence) and time (i.e., dialysis initiation year) were evaluated for the five exclusion criteria.

**Figure 2.1. Application of exclusion criteria to the end stage kidney disease cohort identified for inclusion**



The exclusion criteria leading to the greatest number of exclusions was the requirement of Medicare Part A & B enrollment for at least 365 days prior to ESKD, which is necessary to measure pre-ESKD nephrology care. Pre-ESKD nephrology care was not imputed for these individuals. Though it would be possible to use multiple imputation for pre-ESKD nephrology care, I believe it would not be appropriate in the context of this dissertation; the differences in a population who does not have Medicare at least 1 year prior to ESKD is fundamentally too different to infer their pre-ESKD nephrology care status. Patients who do not have Medicare pre-ESKD typically include most of the younger ESKD population, who should be expected have different ESKD causes and/or etiologies, different health-risk related behaviors, and fewer chronic conditions, particularly among the younger adult population (i.e., age 18-30). Given these circumstances, using the characteristics of the 1-year pre-ESKD Medicare enrollment cohort to impute the pre-ESKD nephrology care for those without adequate Medicare enrollment may lead to additional bias. This led to the exclusion of 40.4% of the potentially eligible population.

Overall, 40.5% of the potential study population was excluded due to insufficient pre-ESKD Medicare enrollment, with the percentage missingness by state ranging from 28.1% in Vermont to 47.2% in the Nevada. By year, missingness ranged from ranged from 59.0% to 60.1%, an insubstantial amount of variability. The variability by state is likely a reflection of patient-level factors, particularly age. Due to this exclusion criterion, 93.5% of ESKD patients 18-29 were excluded, 82.6% of patients age 30 to 49, and 67% of patients age 50-64; by contract only 9.6% of patients 65-79 and 3.6% of patients age 80+ were not included (Appendix 2). Glomerulonephritis and cystic kidney disease were less likely to be represented in the study cohort relative to other ESKD etiologies. As a result, the findings of this study are generalizable

to the older population of ESKD patients; this study lacks the external validity to generalize these findings to patients between the ages of 18 to 49, in particular.

The file that resulted in the most missingness, the 2728 Form file, was missing for 1.8% of the initial cohort, with the percentage missingness by state ranging from 0.39% in Rhode Island to 4.3% in the District of Columbia. By year, missingness ranged from 2.6% in 2012 to 1.25% in 2016. Given the 2728 Form is collected to register patients for ESRD Medicare entitlement and should not be collected for people with acute kidney injury that are expected to recover within a few months (i.e., not end stage kidney disease) the variability in availability of the 2728 Form may be attributed to administrative error or misperception by administrators regarding the diagnosis of end stage kidney disease. It is unlikely this variation will cause systematic bias in this study, particularly given the similar distribution of missingness across time and location.

Median household income by zip code was missing for 1% of the sample post-exclusion for missing 2728 Form. Ohio had the lowest rates of missingness, at 0.26%, and Alaska had the highest rate of missingness, at 9.5%; the only other state to exceed 3% missingness was Wyoming at 5.3%. The relative rurality of the residences of many residents in these states suggests that household income is either not available or not reported due to small sample size. This is a potential source for bias by excluding patients from rural areas or of lower socioeconomic status. There range of missingness across years was 0.9% to 1.1%.

Index access type was missing for 0.1% of patients remaining after exclusion for missing median income. In general, the low percentage of missingness and lack of outlier missingness by place and time suggest that potential bias resulting from exclusion of these patients is not meaningful.

Urban-rural continuum codes from the Area Health Resource File was missing for 0.02% of the patients remaining after exclusion for missing index access type. Due to the low absolute number of patients with this missing variable (n=95) there is likely little bias resulting from this exclusion criteria.

*Variable Identification*

Access type (i.e., tunneled hemodialysis catheter versus mature or maturing arteriovenous fistula or graft) at hemodialysis initiation was determined using a combination of the 2728 form and CROWNWeb (See Appendix 1). Initiating dialysis with a tunneled catheter with maturing access was recorded as a permanent access, since the time until an access becomes functional will vary based on patient characteristics.[23, 65] Due to this distinction, this study is able to speak to how patient factors influence the outcome of permanent access without concern regarding how those factors also affect time to access patency.

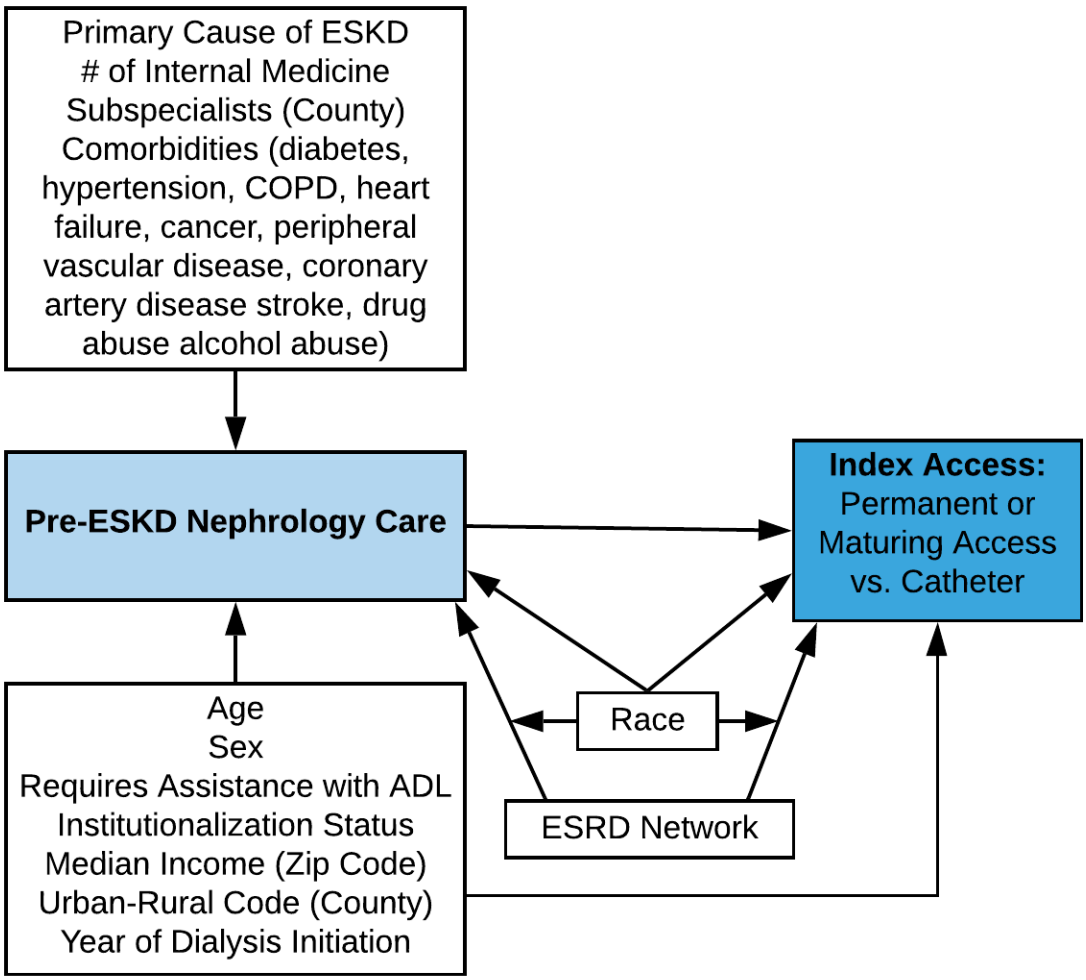
The operationalization of pre-ESKD nephrology care used in the present study was dichotomized as pre-ESKD nephrology care at least 6 months prior to ESKD versus no nephrology care or nephrology care beginning less than 6 months before ESKD, rather than using a measure of nephrology visit intensity. Nephrology visit intensity may correlate strongly with chronic kidney disease (CKD) etiology, since patients with certain kidney specific diseases would likely have both earlier and higher intensity care. Visit intensity in the year prior to ESKD is also a direct result of earlier pre-ESKD nephrology care, as more time between the first nephrologist ESKD nephrology encounter and ESKD would be positively correlated with intensity of pre-ESKD nephrology care. This led to an approach that would allow for a more straightforward conceptual relationship between variables, with a time-threshold to measure pre-ESKD nephrology care.

Pre-ESKD nephrology care at least 6 months prior to hemodialysis initiation was defined using outpatient physician Medicare claims for office visits with Nephrologists (Appendix 1). Though a 2728 form definition of pre-ESKD nephrology are is also available, the literature has found that the 2728 form definition of pre-ESKD nephrology care has 70% accuracy, with 49% sensitivity and 85% specificity when using a claims-based definition as the true measurement of pre-ESKD nephrology care.[66] Prior to proceeding with the primary analysis, the accuracy, sensitivity, and specificity of the Form 2728 defined pre-ESKD nephrology care was evaluated to ensure the precision of the Form 2728 variable has not improved over time.

Covariates include sex, age, race, ESRD network, year of access placement, median zip code-level income (from the ACS), county-level urban-rural code, the county-level number of internal medicine subspecialists in 2015, primary cause of ESKD, institutionalization status of the patient, and ability to perform activities of daily living (ADL). All covariates were used as predictors for both of the equations in the recursive bivariate probit, with the exception: the county-level number of internal medicine subspecialists in 2015, primary cause of ESKD, which will only be included in the selection equation for pre-ESKD nephrology use, and comorbidity indicators (Figure 2.2).

The number of county-level internal medicine subspecialists, which include nephrologists, was included in the regression to predict likelihood of pre-ESKD dialysis access as a proxy for the availability of nephrologists in a patient's county of residence. The availability of providers from Area Health Resource Files is the most suitable available predictor, as facility density (from the USRDS facility file) is not as representative of the availability of pre-ESKD nephrology care relative to the true count of internal medicine subspecialists.

**Figure 2.2. Permanent vascular access at hemodialysis initiation conceptual model**




Requiring assistance with ADLs and institutionalization status are indicators of severe disability that would correlate with access to nephrology care, though the direction of the relationship could be positive or negative; a positive relationship would indicate that seriously physically impaired patients are more likely to have their CKD caught earlier due to increased interaction with providers, whereas a negative relationship would indicate seriously physical impairment have difficulty accessing high quality care, despite their more frequent interactions with the health care system. The county-level number of internal medicine subspecialists and

primary cause of ESKD should not have a direct effect on index access. Though primary cause of ESKD impacts whether or not someone encounters a nephrologist prior to ESKD, it should not independently impact access type at hemodialysis initiation. If there were variability in access type by primary cause of ESKD, it would be a proxy for comorbidities rather than a factor representing socioeconomic or geographic variability, which suggests that even if this conceptual approach is incorrect, it should not dramatically alter the estimation of the socioeconomic or geographic effects.

Comorbidities were included only in an equation predicting pre-ESKD nephrology care. Comorbidities included those with the strongest conceptual link to earlier pre-ESKD nephrology referral and were common chronic conditions (i.e., diabetes, hypertension, coronary arterial disease, peripheral vascular disease, heart failure, chronic obstructive pulmonary disease [COPD], cancer, stroke, illicit drug abuse, alcohol abuse). Etiology of ESKD variable, which is necessary given the etiology of ESKD is strongly linked to whether or not a patient would have earlier referral to a nephrologist, given some causes of ESKD (e.g., diabetes mellitus and hypertension) are chronic illnesses that would be evident to providers long before ESKD, assuming a patient is having encounters with the health care system. However, the etiology of ESKD is not included in the access type equation because it should only influence access type indirectly via how ESKD etiology influenced early access to pre-ESKD nephrology care.

*Descriptive Tables and Statistics*

Wilcoxon rank sum tests and Kruskal-Wallis tests were used to compare skewed continuous variables between groups. T-tests and ANOVA were used to compare normal continuous variables between groups. Chi-square tests were used to compare binary and categorical variables between groups.

*Regression Analysis*

To describe the variation in initiation of hemodialysis on a permanent vascular access (versus THC only), a recursive bivariate probit model was used, with the first stage predicting probability of pre-ESKD nephrology care and the second stage predicting index access type. A recursive bivariate probit has several benefits: (1) pre-ESKD nephrology care, the outcome of the first equation, may be interacted with independent variables in the second equation, (2) the model allows for variation in the outcome equation based on factors in the treatment effect equation. The primary limitation of the approach is its lack of the ability to accommodate more than two treatment groups (e.g., multiple categories of pre-ESKD nephrology care as a treatment effect).

The likelihood ratio test that the null hypothesis ($\rho = 0$) was used to evaluate the recursive bivariate probit relative to a naïve probit; rejection of the null hypothesis indicates a recursive bivariate probit is a preferred to a naïve probit. Results from a naïve probit model with a single stage predicting likelihood of hemodialysis initiation on a permanent vascular access will be compared to recursive bivariate probit results to evaluate potential selection bias for Aim 1. A recursive bivariate probit was used because of its ability to capture the heterogenous nature of the treatment effect, by allowing an interaction to interact of the treatment (i.e., pre-ESKD nephrology care) with race and ESRD network; interactions between the treatment effect and other covariates are not possible in a number of standard treatment effects models.

Though the likelihood ratio test of $\rho$ determined appropriateness of the recursive bivariate probit, both models' goodness of fit will be evaluated using Hosmer-Lemeshow tests. Covariates with $p > 0.2$ and which also reduce the Akaike information criterion (AIC) by at least 5 upon exclusion were evaluated for omission from the model; these exclusion criteria are based on the

assumption that if a covariate does not have at least a confounding effect (i.e., $p < 0.2$) and improves model fit that it is likely not providing a useful measurement, and may be capturing some of the effect of correlated covariates.

An interaction between race ESRD network will be tested in both equations, as well as between pre-ESKD nephrology care in the model predicting index access type. Pre-ESKD nephrology care has already been shown to be associated with variations across geographic regions defined by the Centers for Medicare and Medicaid Services (CMS),[12] which led to the inclusion of ESRD network as a geographic indicator. Given the effect of race likely varies by geography, as racism and policies affecting racial minorities vary by geography, testing of an interaction is necessary. Testing the interaction between race and pre-ESKD nephrology care is also necessary because pre-ESKD care will likely serve as a proxy for the effect of health care access to some extent, because variation in health care access by race and ethnicity has been demonstrated, with Hispanic and Black Americans in particular having lower rates of access to health care generally,[67, 68] and lower rates of access to pre-ESKD care, specifically.[46] ESRD network is not the most granular geographic variable available, but it is the most complete. Predicted probabilities of permanent or maturing vascular access at HD initiation will be generated by combinations of race and ESRD network and combinations of race and pre-ESKD nephrology care. Predicted probabilities of pre-ESKD nephrology care will be generated by combinations of race and ESRD network.

## Results

### *Descriptive Statistics*

This study included 375,098 patients, 52.1% of which had nephrology care at least 6 months prior to ESKD, and 38.9% of which had a functional or maturing permanent vascular

access at hemodialysis initiation (Table 2.1). Differences in pre-ESKD nephrology care and permanent access rates were significant at $p<0.001$ between all groups, with except for differences in pre-ESKD nephrology care by heart failure ($p=0.049$) and stroke ($p=0.69$).

Patients with nephrology care at least 6 months prior to ESKD had a higher rate of permanent index access than those without pre-ESKD nephrology care (46.7% vs. 31.4%). Rates of pre-ESKD nephrology care and permanent access at dialysis initiation were comparable between men and women. Patients aged 18-29 and 80+ tended to have lower rates of permanent access (33% and 35%), but had comparable rates of pre-ESKD nephrology care to the other age groups (49.8% and 50.1%). The rates of permanent access and pre-ESKD nephrology care did not follow a discernable pattern between races. Native Americans had a high rate of pre-ESKD nephrology care (56.6%), but a relatively average rate of permanent access (43.1%). Hispanic patients had the lowest rate of pre-ESKD nephrology care (42.6%) and the lowest rate of permanent access (36.7%). Despite the second highest rate of pre-ESKD nephrology care (50.5%), whites had the second lowest rate of permanent access (38.4%). Patients with cystic disease had the highest rate of pre-ESKD nephrology care (63.3%) and permanent access (61.4%), while patients with ESKD caused by diabetes, hypertension, or glomerular nephropathy had both comparable rates of pre-ESKD nephrology care (approximately 50%) and permanent access (approximately 40%). Though the difference in rates of pre-ESKD nephrology care were relatively modest between those with (44.2%) and without (49.9%) ADL impairment and those who did (42.4%) or did not (49.8%) live in a nursing or assisted living facility, the differences in their rates of permanent access were much greater; Those who live in assisted living or nursing facilities had the lowest rate of permanent access of any sub-group (24.8%), followed by those with at least 1 ADL impairment (28.9%). Rates of pre-ESKD nephrology care and permanent

access did not vary meaningfully by urban-rural county code, though counties with 1+ million residents had slightly lower rates of pre-ESKD nephrology care and the most rural counties had slightly lower rates of permanent access (34.6%). There was a more pronounced relationship between rates of pre-ESKD nephrology care and county-level availability of internal medicine subspecialists within a county, with pre-ESKD nephrology care decreasing with increased specialist availability, which was the opposite direction expected; however, rates of permanent access between these groups were comparable.

The distribution of pre-ESKD nephrology care, permanent access at hemodialysis initiation, race, and rural-urban code by ESRD network region, found in Table 2.2, is sorted by rate of pre-ESKD nephrology care to attempt to make clear any monotonic relationships. Though pre-ESKD nephrology care and permanent access rates do not appear to vary together, Southern California had both the lowest rate of pre-ESKD nephrology care and the lowest rate of permanent access (34.6% and 33.1%, respectively). There seemed to be a more clearly monotonic trend related to rates of permanent access and the proportion of the population that is white, with regions with large white populations typically having the highest rates of permanent access. New England stands out in particular, as having the greatest proportion of patients who are white (80.7%), the highest rate of pre-ESKD nephrology care (59.5%), and the second highest rate of permanent access (47%). New York state, which had the highest rate of permanent access (47.4%), had the second lowest rate of pre-ESKD nephrology care (43.1%); New York also had a more racially diverse ESKD population, and the second highest rate of patients living in a metropolitan area with over one million residents (86%).

There was substantial discordance between the Medicare claims definition of pre-ESKD nephrology care and the Form 2728 definition. Though the rate of nephrology care at least 6

months pre-ESKD was very comparable between the two measures, with 52.2% by Form 2728 (not shown in Table 2.1) and 48.9% by Medicare claims definitions, sensitivity was 64.1% and specificity was 59.3%, with a correct classification rate of 61.6% (95% CI 61.5%-61.8%).

*Regression Results*

The null hypothesis that $\rho = 0$ was rejected given that $\rho = -0.88$; ($p<0.0001$, 95% CI -0.88 to -0.86), indicating the recursive bivariate probit was superior to a naïve probit. Accordingly, these results will focus on the estimations from the recursive bivariate probit, though reference will be made to the differences between the estimates from the two modeling approaches. Hosmer-Lemeshow tests found both recursive bivariate and naïve probit models achieved good model fit ($p<0.0001$). No covariates had a p-value greater than 0.2, leading no variables to be dropped from the initial modeling approach.

The probit coefficients for the naïve and bivariate probit models may be found in Appendix 2 and Appendix 3. The coefficients' effect sizes are not interpretable on their own, so the marginal predictions will be presented (Tables 2.3, 2.4, and 2.5). The following effects sizes are expressed in proportion or percentage changes in the probability of initiating hemodialysis with either a functional or maturing permanent access.

The omnibus tests of the interactions between (1) race and ESRD network region and (2) race and pre-ESKD nephrology care in the second equation of the probit predicting functional or maturing permanent access at hemodialysis initiation were both statistically significant ($\chi^2$ 1391 and 283, respectively; $p<0.0001$); these findings confirm Hypothesis 1 and 2 of Aim 1. An omnibus test of the interaction between race and ESRD network region in the first equation predicting assignment to pre-ESKD nephrology are was also significant ($\chi^2$ 970; $p<0.0001$)

After adjusting for interactions, the bivariate probit estimates indicates that ESKD patients with nephrology care at least 6 months before ESKD had a 55.8 percentage point greater probability of a permanent access than those without pre-ESKD nephrology care (Table 2.3; 95% CI 55.5-56.1). The practical impact of this is a permanent access rate of 72.1% (95% CI 71.8%-72.4%) among those with pre-ESKD nephrology care, 4.42 times (95% CI 4.41-4.46) the rate of those without pre-ESKD nephrology care at least 6 months before hemodialysis initiation (16.3%; 95% 16.1%-16.4%). A naïve probit underestimates the effects size by 41 percentage points; the effect of nephrology care is estimated to be 3.76 times greater using a bivariate probit and the difference in the outcome equation's pre-ESKD nephrology coefficients are significantly different between modeling approaches (Table 2.3; Appendix 3). At the level of the main effect of pre-ESKD nephrology care and all levels of the interaction between race and pre-ESKD care except for the interaction with Native American race, there were significant differences in the estimation from the naïve and bivariate probit models except for among Native Americans ($p<0.0001$). The main effect of race was significantly different for blacks ($p<0.0001$), Hispanics ($p<0.0001$), Asians ($p<0.0001$), but not among Pacific Islanders or Native Americans. The main effect of network was also significantly different at all levels of the variable. The significance of the levels of the network and race interaction varied widely.

When examining the bivariate probit estimations of differences by un-interacted patient characteristics, it is notable that the effect of being institutionalized is nearly eliminated relative to the naïve probit, and the effect of an ADL impairment is more than halved (Table 2.3). The effect of urban-rural code also is greater in both significance absolute magnitude at all levels in the bivariate probit.

When predicting the average probability of a permanent access at hemodialysis initiation by race and pre-ESKD nephrology care (Table 2.4), there was some variability in the relative difference between the likelihood of permanent access within races between pre-ESKD nephrology care. However, the variability was not meaningful except for among Native Americans, though this group had a wide 95% confidence interval (61% to 71%).

Adjusting for the other characteristics including pre-ESKD nephrology care, the average probability of permanent access among whites had moderate variability across ESRD network regions, ranging from 37% to 49% (Table 2.4). Among blacks, the range was 37% to 54%, with rates that were typically comparable to their white counterparts. Hispanics had greater heterogeneity in rates across regions compared to whites and blacks. Pacific Islanders and Asians had rates that were comparable to Hispanics in most regions, while Native Americans a wide range of point estimates, and very wide 95% confidence intervals due to the small number of Native Americans and many regions. The lowest rate of any ESRD network regions by race were among Native Americans in ESRD Network region 9, which contains Ohio, Illinois, and Kentucky, and region 10, which contains Indiana. Indiana had consistently low rates of permanent access for every race (approximately 37%), with higher rates for Pacific Islanders (44%), though the confidence interval for this group was very wide (30%-57%). Contrastingly, the New York region had consistently higher rates among non-white patient groups compared to both patients of the same race in other regions, and comparable rates to whites the region.

*Pre-ESKD Nephrology Care Equations*

There was significant variability in pre-ESKD nephrology care, modeled by the endogenous equation, by sex, race, cause of ESKD, all comorbidity indicators other than stroke year of ESKD, number of internal medicine subspecialists in the county, urban-rural code, and

ESRD network (Tables 2.5 & Appendix 4). The largest effects sizes were for primary cause of ESKD, alcohol dependence, drug dependence, urban-rural code, and ESRD network region.

**Discussion**

*Sub-Aim 1: Variation in Pre-ESKD Nephrology Care as a Source of Racial Differences in Permanent Access*

Sub-aim one's first and second hypotheses were confirmed: There were significant interactions between both race and pre-ESKD nephrology care, as well as between race and ESRD network region in the equation to predict permanent index access at hemodialysis initiation ($p<0.0001$).

Racism and racial segregation are cornerstones of health disparities in the United States, as the prosperity of a white American hegemony was built upon centuries of structural, cultural, and interpersonal racism.[69, 70] Federal, state, and local policies have influenced housing segregation, with racist housing policies influencing generations of educational outcomes of black Americans in the name of housing for whites[71] and infrastructure development.[70, 71] Though scholarship on the impact of housing segregation has focused on education and poverty, it is a short step to connect America's racist housing policies to health disparities. In fact, a substantial body of literature is dedicated to how structural racism, including housing segregation, are linked to disparities in health outcomes.[55, 69, 70, 72-74] However, the way in which policies are influenced by different concepts of racism (e.g., structural, interpersonal) are unlikely to be uniform across the United States, given the country's varied history of racism.[75]

*Sub-Aim 2: Improving Estimates of the Effect of Pre-ESKD Nephrology Care*

Sub-aim two's first hypothesis was confirmed: The average treatment effect of pre-ESKD nephrology care 6 months prior to ESKD is radically underestimated by a naïve probit, with the recursive bivariate probit effects size being 3.76 times greater (Table 2.3).

Sub-aim two's second hypothesis was also confirmed: The effect sizes for race and ESRD network region in likelihood of initiating hemodialysis on a permanent access was significantly different between probit and bivariate probit models.

The decrease in effect sizes for patient characteristics after accounting for non-random assignment to pre-ESKD nephrology care 6 months prior to ESKD (Tables 2.3 & Appendix 3) suggest variability in maturing or functional permanent access at hemodialysis initiation. This is due to the patient characteristics' relationship with early pre-ESKD nephrology care, rather than a direct influence of practice patterns related to patient characteristics. Further evidence to support this is found in the tables of the transformed probit coefficients, which exclude the interaction comparisons and aggregate effects for the interacted variables into the original categories (Table 2.3 & 2.4).

The reduction in effects sizes for all but the urban-rural continuum code suggests the effects of those variables in the naïve probit were actually a reflection of the effects of variability in pre-ESKD nephrology care (Table 2.3). In modeling pre-ESKD nephrology care, the largest effects sizes were between ESRD network regions and urban-rural codes, rather than among individual-level characteristics, such as age, sex, or race.

The effect of race was highly variable in predicting both likelihood of maturing or functional permanent access and likelihood of pre-ESKD nephrology care (Tables 2.3, 2.4, & 2.5), depending on patient ESRD network region. The findings regarding variation in pre-ESKD

nephrology care by race largely agree with previous findings about racial disparities,[46, 56] with non-Hispanic blacks and Hispanics having lower pre-ESKD nephrology care rates than non-Hispanic whites.

*Implications for Health Policy Analysts*

Formal cost-benefit analysis evaluates the monetary benefit of policies relative to costs.[76] However, if observational data is the only resource available, thoughtful quasi-experimental approaches, such as the use of a bivariate probit or another model that adequately accounts for nonrandomization of health care access or services, are warranted. This analysis demonstrated that the effect of pre-ESKD nephrology care and corresponding costs reductions related to nephrology care improving outcomes can easily be underestimated.

Most health outcomes contexts are conditioned on some other factor, or set of factors, typically social,[54] economic,[77] or biological[78, 79] determinants of health.[80] Because of this, reliance exclusively on ameliorating non-random assignment (e.g., propensity score matching to balance for assignment into nephrology care) or only on the immediate context (e.g., the naïve probit without accounting for variation in assignment to pre-ESKD nephrology care) to model health care outcomes may not always adequately capture the true effect of a scarce resource (e.g., health care). Herein lies a benefit of approaches using two equations (e.g., recursive bivariate probit), with one equation modeling non-random treatment assignment to health care access, and the other equation modeling an outcome. However, the recursive bivariate probit is functionally limited by its inability to accommodate a categorical treatment classification with 3 or more treatments; this makes it a somewhat blunt instrument for evaluating differences in policies or treatments. As a matter of practice, recursive bivariate probit models with large samples and random intercepts, with or without random slopes, are very computationally intensive.

Depending on one's interest in the providers, institutions, and/or regions, and nesting of these groups within the model, a recursive bivariate probit may fail to converge with no further options to achieve convergence. Though this study did not specify partially observed variables, with partially observed specification bivariate probit models are also more likely to suffer from convergence issues.[81]

*Implications for Payers and Providers*

This study sought to measure of the impact of pre-ESKD nephrology care and permanent access creation prior to dialysis initiation while accounting for variability in pre-ESKD nephrology care by race and region, without concern for bias resulting from non-random assignment to pre-ESKD nephrology care. However, a necessary step in pre-ESKD nephrology care is earlier identification of chronic kidney disease (CKD). Practice guidelines by the United States Preventive Services Task Force (USPSTF) do not currently recommend CKD screening among adult patients, due to the relatively low rate of ESKD in the general population.[38] However, specific advisement for sub-populations were not included in their 2012 recommendation. In 2019, the American Diabetes Association began recommending annual CKD screening among all patients with type II diabetes and among patients with a type I diabetes diagnosis from at least five years prior.[82] This is a much more practical approach to CKD care, ESKD prevention, and improvement of early ESKD outcomes, given the relatively low population-level rate of ESKD and the most common cause of ESKD being diabetes. When USRDS data releases include patients initiating dialysis from 2020 onward, it will be worthwhile to see if there is an increase in patients with either 2728-defined or claims-defined nephrology care at least 6 months pre-ESKD. At present, however, there are no adequate means of assessing

this. Furthermore, the COVID-19 pandemic likely will distort any trend changes due to policy changes occurring in the same time period.

National and regional nephrology and vascular surgery societies would also benefit from greater clarity regarding the role of health care access in improving a key determinant of outcomes during ESKD (i.e., index vascular access type). It would be of interest to some audiences that variability in likelihood of permanent access by region is much lower after adjusting for selection into pre-ESKD nephrology care, indicating variability in that outcomes were a result of access to pre-ESKD nephrology care rather than a direct effect of those variables. Much discussion has been had about decreasing the rate of incident and prevalent rates hemodialysis with a catheter,[14, 15, 25, 28, 29, 83] including graphs of the distribution of incident and prevalent access type by year in the annual USRDS data report.[1] However, these cited works[14, 15, 25, 83] do not explicitly address how initiating hemodialysis on a permanent access is largely an expression of variability in health care access, as opposed to a direct result of provider behaviors and practice patterns. To wit, the most recent guidelines from KDOQI on vascular discuss evidence that supports each guidelines, and clarifies when evidence is from "nonrandomized studies," but does not speak as to why the nonrandomization of vascular access type is an issue.[28] Ethier et al. examine rates of permanent index access and outcomes of vascular access and only briefly make note of the findings regarding access type's effect based on propensity score matching, and later has a single sentence remarks, "More in-depth studies of factors leading to delays and effects of health care management issues, such as impact of a VA coordinator and Fistula First program, should be initiated," without any mention of the causes for variability in the success of national-level policy initiatives, such as access to pre-ESKD nephrology care. [84] A meta-analysis of over 200 studies with over 100 citations as of August 2021 makes no mention

of potential confounding related to pre-ESKD nephrology care, access type, or nonrandom assignment of either.[65] Though meta-analyses typically are considered a greater level of evidence than single studies, if the studies systematically ignore bias related to nonrandom assignment of pre-ESKD nephrology care and access type, the evidence is at least somewhat suspect. All of the aforementioned studies focus on provider-level variation, and refer to variation in practice pattern variation in management of CKD and ESKD, but do not further interrogate the modeling implications.

With better information regarding the additional costs associated with dialysis initiation on a THC, Medicare, Medicaid, and commercial payers may see greater benefit from additional reimbursement incentive for annual CKD screening among patients with diabetes, hypertension, or a family history of CKD. Though all ESKD patients become eligible for Medicare in their fourth month of dialysis, ESKD patients can elect to keep their existing group coverage, which is the primary payer for ESKD services for the first 30 months;[85] TRICARE enrollees are required to apply for Medicare if they enter ESKD[86] with Medicare being the primary payer for these dual TRICARE/Medicare enrollees;[87] and Medicare is also the primary payer whenever a ESKD patient is also a Medicaid dual enrollee.[88] Given commercial programs are responsible for ESKD costs in the first 30 months of their enrollee's care and all other public insurance programs are funded and administered by the federal government to some degree, it would benefit all payers to provide financial incentives to ensure more aggressive CKD screening and provide the appropriate referrals to nephrologists.

*The Big Picture: Pre-ESKD Nephrology Care and Systemic Barriers to Health Care Access*

Despite the earnestness of proximate policy solutions described above (e.g., provider incentives, updating USPSTF guidelines with respect to CKD screening for those at a high-risk

for ESKD), those policies would likely have minimal impact on improving the rate of hemodialysis initiation with a functional or maturing permanent access. Given that it appears a substantial amount of variability is accounted for by acknowledging non-random assignment to pre-ESKD nephrology care, we should expect that the root causes of the disparities in functional or maturing permanent access at hemodialysis initiation are barriers to accessing care.[89]

Carrillo et al. provide a framework for understanding and addressing health care access barriers (i.e., the Health Care Access Barriers [HCAB] Model), which is useful in assessing this study's outcomes and context.[89] The HCAB approach uses barriers as the unit of analysis, identifying financial barriers (e.g., underinsured, uninsured), cognitive barriers (e.g., knowledge gaps, communication difficulties), and structural barriers (e.g., transportation to health care appointments, availability of providers) as the sources of health outcomes disparities. These three categories of barriers lead to late presentation of diseases, decreased disease prevention, and decreased care.

Regional-level differences between probit and biprobit models were substantial, with the bivariate probit tending to produce lower estimates of the variability between regions (Table 2.3), suggesting the naïve probit estimates misattributed regional variation in pre-ESKD nephrology care to be a result of the region themselves, rather than pre-ESKD nephrology care within those regions. With New England serving as the reference class, the difference in catheter use between regions in the bivariate probit was typically less than half as large (Table 2.3). It is important for stakeholders and policymakers to understand the strengths and weaknesses of particular regions, so that policy solutions target the appropriate areas; these findings suggest the avenues to improve catheter use are in the hands of those controlling financing policies that

would facilitate earlier pre-ESKD nephrology care, rather than in the hands of physician and health systems.

**Limitations**

Permanent access is defined as having either a permanent or maturing access at hemodialysis initiation. The choice was made to include maturing accesses for two reasons: (1) maturing accesses at HD initiation are similar to a functioning permanent access as a measure of optimal pre-ESKD care planning, and (2) variability in access maturation by age and other patient characteristics in the time until the access becomes functional.[83, 90] To the latter point, measuring only functioning accesses introduces additional bias to the measurement of permanent vascular access. For instance, it could be that a 60-year-old patient and a 70-year-old patient have identical access type, access creation timing, and visit intensity of pre-ESKD nephrology care, but because of differences in time to access functionality by age, only one has a functioning access at HD initiation, meaning that an index permanent access variable is measuring maturation, rather than the intended outcome of permanent access creation via optimal pre-ESKD care planning. Including the maturing accesses indicators from Form 2728 in the definition of permanent access resolves this potential shortcoming.

Though many studies use the pre-ESKD nephrology care variable from Form 2728, the definition of pre-ESKD nephrology care in the primary analysis should be expected to only have about 70% accuracy, with 49% sensitivity and 85% specificity in pre-ESKD nephrology care measurement via Form 2728.[66] In this study's analysis, sensitivity was 64.1%, specificity was 59.3%, and the correct classification rate was 61.6%; demonstrating lower correct classification and specificity than in prior literature, but higher sensitivity. This shortcoming is addressed by including a parallel analysis based on Medicare claims for the outcome variables, as provider

specialty is available in the provider Medicare claims. The findings of this study suggest that the inaccuracy in recording pre-ESKD nephrology care necessitates parallel analyses when using USRDS cohorts include non-Medicare enrollees and pre-ESKD nephrology care is variable included in the study.

As with prior studies, this study and USRDS in general do not provide information on socioeconomic status, general health knowledge, or chronic kidney disease knowledge. However, these analyses do measure health care availability and ability to access pre-ESKD nephrology care at least 6 months prior to ESKD, which is the conceptual pathway through which the effect of access to care on early hemodialysis outcomes may be measured. By not measuring socioeconomic status, general health knowledge, or chronic kidney disease knowledge, the variables in the equation predicting access to pre-ESKD nephrology care (e.g., age, race, institutionalization status) are serving as proxies for these measures to varying extents. While it is useful to know the extent to which certain characteristics are related to access to care (i.e., pre-ESKD nephrology care), our ability to understand what is truly being measured by each of those variables is somewhat limited since health knowledge and more granular indicators of socioeconomic status are lacking in the data and modeling approach. However, given the data source, the present analysis is essentially the most complete analysis possible in the United States, with respect to capturing as many incident ESKD patients as possible.

A potentially substantial criticism of my methodological approach is the use of ESRD network to account for regional variability. Zip code is available, and if my intent in interacting ESRD network with race was to account for variability in the effect of race by region, another way I could have accomplished this is to have a random intercept for zip code and random slopes for race dummies. However, I believe there would be more substantial shortcomings to this

approach. There are likely zip codes with very small sample sizes, and adjusting for such small samples would provide very wide confidence intervals around many zip-codes intercepts and race dummies' random slopes. The sample size and number of people in each race are much more substantial at the level of ESRD network region, and even then, there are very wide confidence intervals among Native Americans within some ESRD network regions, such as the Pennsylvania and Delaware region (Table 2.4; 95% CI 0% to 54%). In short, the approach taken was choosing to prioritize more narrow confidence intervals to facilitate an analysis that is making general points about variability by race and region, as opposed to wider confidence intervals and a more granular understanding of the effects of race within many, but not all, zip codes. This is a problem that will be present in all national-level analyses of ESKD patients, given the relatively small number of ESKD patients among Medicare enrollees, the majority of whom were Medicare eligible prior to their ESKD.[1]

## Tables

Table 2.1. Patient Characteristics, Rates of Pre-ESKD Nephrology Care, and Rates of Permanent Access

| Variables | Overall<br>N=375,098<br>N (Column %) | Nephrology Care 6+ Months Pre-ESKD<br>N=183,538<br>Row % | Maturing or Permanent Access<br>N=145,866<br>Row % |
|---|---|---|---|
| Pre-ESKD Nephrology Care | | | |
| None/Within 6 Months Pre-ESKD | 179,500 (47.9) | N/A | 31.4 |
| Nephrology Care 6+ Months Pre-ESKD | 195,598 (52.1) | N/A | 46.7 |
| Index Access | | | |
| THC | 229,232 (61.1) | 42.7 | N/A |
| Maturing or Permanent Access | 145,866 (38.9) | 58.8 | N/A |
| Sex | | | |
| Male | 209,719 (55.9) | 48.2 | 40.3 |
| Female | 165,379 (44.1) | 49.8 | 37.2 |
| Age at first ESKD Service | 71.1 ± 11.0 | 71.2 ± 11.1 | 70.6 ± 10.8 |
| Age at first ESKD Service | | | |
| 18-29 | 1,055 (0.3) | 49.8 | 33.0 |
| 30-49 | 15,772 (4.2) | 50.4 | 40.3 |
| 50-64 | 64,720 (17.3) | 47.9 | 40.8 |
| 65-79 | 209,434 (55.8) | 48.7 | 39.8 |
| 80+ | 84,117 (22.4) | 50.1 | 35.0 |
| Race | | | |
| Non-Hispanic White | 229,541 (61.2) | 50.5 | 38.4 |
| Non-Hispanic Black | 89,776 (23.9) | 47.6 | 40.1 |
| Hispanic | 38,390 (10.2) | 42.6 | 36.7 |
| Asian | 12,415 (3.3) | 47.6 | 43.1 |
| Pacific Islander | 2,367 (0.6) | 42.8 | 44.0 |
| Native American | 2,609 (0.7) | 56.6 | 43.1 |
| Median Income in Zip Code in $10,000s | 5.2 ± 2.0 | 5.3 ± 2.1 | 5.3 ± 2.1 |
| Primary Cause of Renal Failure | | | |
| Diabetes | 183,284 (48.9) | 50.7 | 41.9 |
| Hypertension | 119,759 (31.9) | 50.9 | 39.1 |
| Glomerulonephritis | 17,610 (4.7) | 49.3 | 40.0 |
| Cystic kidney | 4,292 (1.1) | 63.3 | 61.4 |
| Other urologic | 5,039 (1.3) | 42.8 | 34.7 |
| Other/Unknown/Missing | 45,114 (12.0) | 35.7 | 23.9 |
| Requires Assistance with ADL | | | |

| | | | |
|---|---|---|---|
| No ADL Impairment | 309,086 (82.4) | 49.9 | 41.0 |
| 1+ ADL Impairments | 66,012 (17.6) | 44.2 | 28.9 |
| Institutionalized | | | |
| Non-Institutionalized | 330,023 (88.0) | 49.8 | 40.8 |
| Assisted Living, Nursing Home | 45,075 (12.0) | 42.4 | 24.8 |
| Rural-Urban Continuum Code 2013 | | | |
| Metro, 1+ mil | 195,110 (52.0) | 46.3 | 39.0 |
| Metro, 0.25-1mil | 79,433 (21.2) | 50.0 | 39.8 |
| Metro, <0.25mil | 37,158 (9.9) | 53.4 | 38.1 |
| Urban 20k+, Metro Adj. | 18,632 (5.0) | 52.5 | 38.2 |
| Urban 20k+, Not Adj. | 6,224 (1.7) | 56.5 | 38.5 |
| Urban 2.5-19.9K, Metro Adj. | 21,742 (5.8) | 51.3 | 37.7 |
| Urban 2.5-19.9K, Not Adj. | 10,635 (2.8) | 54.7 | 38.9 |
| Completely Rural, Metro Adj. | 3,064 (0.8) | 54.4 | 37.9 |
| Completely Rural, Not Adj. | 3,100 (0.8) | 54.3 | 34.6 |
| Number of IM Subspecialists in County | | | |
| None | 42,203 (11.3) | 52.3 | 37.5 |
| 1-10 | 61,028 (16.3) | 52.2 | 38.1 |
| 11-100 | 116,637 (31.1) | 51.5 | 39.2 |
| 101-300 | 67,974 (18.1) | 47.2 | 40.6 |
| 301+ | 87,256 (23.3) | 42.9 | 38.4 |
| Diabetes Mellitus | | | |
| Absent | 144,613 (38.6) | 47.5 | 37.4 |
| Present | 230,485 (61.4) | 49.8 | 39.8 |
| Hypertension | | | |
| Absent | 44,779 (11.9) | 43.9 | 32.5 |
| Present | 330,319 (88.1) | 49.6 | 39.8 |
| COPD | | | |
| Absent | 326,243 (87.0) | 49.1 | 39.7 |
| Present | 48,855 (13.0) | 47.7 | 33.5 |
| Coronary Artery Disease | | | |
| Absent | 305,991 (81.6) | 48.4 | 38.7 |
| Present | 69,107 (18.4) | 51.4 | 39.8 |
| Peripheral Vascular Disease | | | |
| Absent | 327,299 (87.3) | 48.7 | 39.0 |
| Present | 47,799 (12.7) | 50.8 | 38.4 |
| Heart Failure | | | |
| Absent | 240,364 (64.1) | 48.8 | 41.4 |
| Present | 134,734 (35.9) | 49.1 | 34.5 |
| Malignancy | | | |
| Absent | 340,108 (90.7) | 49.0 | 39.1 |

| | | | |
|---|---|---|---|
| Present | 34,990 (9.3) | 47.9 | 36.4 |
| Stroke | | | |
| Absent | 335,029 (89.3) | 48.9 | 39.0 |
| Present | 40,069 (10.7) | 49.0 | 37.7 |
| Drug Dependence | | | |
| Absent | 372,669 (99.4) | 49.0 | 38.9 |
| Present | 2,429 (0.6) | 33.0 | 33.6 |
| Alcohol Dependence | | | |
| Absent | 370,843 (98.9) | 49.1 | 39.0 |
| Present | 4,255 (1.1) | 33.4 | 28.4 |

* All pre-ESKD nephrology care and permanent access rates significant at $p<0.001$ except for differences in pre-ESKD nephrology care by Heart Failure ($p=0.049$) and Stroke ($p=0.69$).

Table 2.2. Pre-ESKD Nephrology Care, Permanent Access, Race, and Rural-Urban Code by ESRD Network Region

| ESRD Network Region | N | Pre-ESKD Nephrology Care | Permanent Access | Race | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Non-Hispanic White | Non-Hispanic Black | Hispanic | Asian | Pacific Islander | Native American |
| 1:New England | N=13,168 | 59.5 | 47.0 | 80.7 | 11.1 | 6.0 | 1.8 | 0.2 | 0.2 |
| 5:DC/MD/VA/WV | N=21,358 | 56.0 | 35.2 | 56.4 | 39.2 | 1.7 | 2.3 | 0.3 | 0.0 |
| 3:New Jersey | N=12,688 | 55.8 | 44.7 | 63.6 | 24.6 | 8.2 | 3.0 | 0.5 | 0.0 |
| 10:Indiana | N=17,109 | 54.6 | 31.8 | 64.2 | 25.8 | 7.3 | 2.5 | 0.2 | 0.0 |
| 12:NE/KS/IA/MO | N=14,928 | 54.0 | 36.8 | 78.1 | 17.8 | 2.6 | 0.8 | 0.2 | 0.5 |
| 6:NC/SC/GA | N=33,479 | 52.6 | 41.9 | 49.2 | 48.1 | 1.4 | 0.8 | 0.1 | 0.4 |
| 13:LA/AR/OK | N=15,867 | 51.6 | 34.7 | 60.3 | 34.2 | 1.9 | 0.7 | 0.2 | 2.7 |
| 16:WA/OR/ID/MT/AK | N=11,074 | 50.4 | 49.0 | 80.3 | 4.9 | 5.8 | 5.1 | 1.6 | 2.2 |
| 9:OH/IL/KY | N=31,393 | 50.2 | 37.9 | 79.0 | 18.6 | 1.7 | 0.4 | 0.1 | 0.0 |
| 14:Texas | N=31,850 | 49.6 | 35.7 | 42.7 | 21.1 | 33.8 | 2.0 | 0.3 | 0.1 |
| 8:TN/AL/MI | N=21,837 | 48.7 | 40.0 | 57.1 | 41.3 | 0.8 | 0.5 | 0.1 | 0.2 |
| 11:MI/WI/MN/ND/SD | N=25,188 | 48.1 | 37.5 | 73.8 | 20.2 | 2.4 | 1.6 | 0.2 | 1.7 |
| 15:NV/UT/WY/CO/AZ/NM | N=16,206 | 47.6 | 40.4 | 64.3 | 7.2 | 19.3 | 2.5 | 1.0 | 5.7 |
| 7:Florida | N=26,550 | 45.8 | 35.6 | 60.4 | 23.7 | 14.3 | 1.2 | 0.3 | 0.1 |
| 4:PA/DE | N=17,541 | 44.5 | 39.2 | 76.2 | 19.6 | 3.1 | 0.9 | 0.1 | 0.0 |
| 17:NorCal/HI | N=16,224 | 44.2 | 42.8 | 45.4 | 10.6 | 17.2 | 20.8 | 5.4 | 0.5 |
| 2:New York | N=22,749 | 43.1 | 47.4 | 59.8 | 24.2 | 10.6 | 4.8 | 0.4 | 0.2 |
| 18:SoCal | N=25,889 | 34.6 | 33.1 | 42.4 | 11.1 | 32.3 | 12.3 | 1.8 | 0.2 |

| ESRD Network Region | Rural-Urban Continuum Code 2013 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Metro, 1+ mil | Metro, 0.25-1mil | Metro, <0.25mil | Urban 20k+, Metro Adj. | Urban 20k+, Not Adj. | Urban 2.5-19.9K, Metro Adj. | Urban 2.5-19.9K, Not Adj. | Completely Rural, Metro Adj. | Completely Rural, Not Adj. |
| 1:New England | 53.9 | 29.6 | 5.9 | 4.6 | 0.6 | 2.3 | 2.6 | 0.5 | 0.2 |
| 5:DC/MD/VA/WV | 62.0 | 11.2 | 11.0 | 2.8 | 1.0 | 6.7 | 2.4 | 2.0 | 1.0 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 3:New Jersey | 86.9 | 8.9 | 4.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 10:Indiana | 71.8 | 6.7 | 8.1 | 4.0 | 1.1 | 4.8 | 3.0 | 0.3 | 0.3 |
| 12:NE/KS/IA/MO | 35.3 | 20.0 | 12.0 | 5.6 | 5.5 | 9.2 | 7.6 | 1.6 | 3.2 |
| 6:NC/SC/GA | 27.8 | 30.4 | 15.2 | 10.1 | 1.3 | 10.6 | 2.2 | 1.6 | 0.8 |
| 13:LA/AR/OK | 20.6 | 33.5 | 14.1 | 6.3 | 2.3 | 13.1 | 7.7 | 0.7 | 1.7 |
| 16:WA/OR/ID/MT/AK | 39.5 | 21.5 | 18.4 | 5.9 | 5.5 | 4.4 | 3.3 | 0.6 | 0.8 |
| 9:OH/IL/KY | 42.2 | 20.8 | 9.1 | 10.0 | 2.2 | 8.9 | 4.5 | 0.9 | 1.4 |
| 14:Texas | 58.0 | 21.2 | 6.5 | 3.4 | 1.9 | 6.3 | 2.0 | 0.5 | 0.3 |
| 8:TN/AL/MI | 24.8 | 25.6 | 13.5 | 7.6 | 3.9 | 13.0 | 6.6 | 3.2 | 1.9 |
| 11:MI/WI/MN/ND/SD | 43.8 | 15.6 | 17.9 | 5.2 | 1.4 | 7.2 | 5.0 | 1.4 | 2.5 |
| 15:NV/UT/WY/CO/AZ/NM | 51.3 | 20.7 | 13.7 | 4.4 | 3.1 | 2.8 | 3.4 | 0.0 | 0.5 |
| 7:Florida | 60.2 | 28.4 | 7.7 | 1.6 | 0.0 | 2.1 | 0.0 | 0.0 | 0.0 |
| 4:PA/DE | 49.8 | 27.1 | 10.3 | 7.1 | 0.0 | 3.8 | 1.6 | 0.2 | 0.2 |
| 17:NorCal/HI | 49.2 | 36.2 | 8.0 | 2.6 | 2.3 | 1.1 | 0.4 | 0.2 | 0.0 |
| 2:New York | 78.2 | 11.5 | 3.3 | 3.9 | 0.6 | 1.8 | 0.8 | 0.0 | 0.0 |
| 18:SoCal | 86.0 | 12.1 | 1.8 | 0.0 | 0.0 | 0.0 | 0.1 | 0.0 | 0.0 |

Table 2.3. Marginal Differences and Estimates for Naïve and Recursive Bivariate Probit Modeling of Likelihood of Permanent Index Access

| | Probit, Diff. | | | Biprobit, Diff. | | | Magnitude Difference |
|---|---|---|---|---|---|---|---|
| | Prob. | 95% CI | p-value | Prob. | 95% CI | p-value | |
| Pre-ESKD Nephrology Care | | | | | | | |
| None/Within 6 Months Pre-ESKD | | Reference | | | Reference | | |
| Nephrology Care 6+ Months Pre-ESKD | 0.1487 | [0.1456, 0.1518] | <0.0001 | 0.5584 | [0.5552, 0.5616] | <0.0001 | 3.7554 |
| Race | | | | | | | |
| Non-Hispanic White | | Reference | | | Reference | | |
| Non-Hispanic Black | 0.0238 | [0.0194, 0.0281] | <0.0001 | 0.0175 | [0.0144, 0.0207] | <0.0001 | 0.7386 |
| Hispanic | 0.0011 | [-0.0081, 0.0102] | 0.8204 | 0.0042 | [-0.0024, 0.0108] | 0.2133 | 3.9559 |
| Asian | 0.0215 | [0.0072, 0.0358] | 0.0032 | -0.0072 | [-0.0174, 0.0031] | 0.1717 | -0.3324 |
| Pacific Islander | 0.0203 | [-0.0123, 0.0529] | 0.2223 | 0.0175 | [-0.0066, 0.0417] | 0.1552 | 0.8642 |
| Native American | -0.0207 | [-0.0659, 0.0245] | 0.3692 | -0.0411 | [-0.0747, -0.0075] | 0.0164 | 1.9864 |
| ESRD Network | | | | | | | |
| 1:New England | | Reference | | | Reference | | |
| 2:New York | 0.0302 | [0.0189, 0.0416] | <0.0001 | 0.0753 | [0.0675, 0.0831] | 0.0000 | 2.4892 |
| 3:New Jersey | -0.0185 | [-0.0314, -0.0056] | 0.0050 | 0.0041 | [-0.0048, 0.0130] | 0.3636 | -0.2229 |
| 4:PA/DE | -0.0492 | [-0.0619, -0.0366] | <0.0001 | 0.0225 | [0.0136, 0.0313] | 0.0000 | -0.4566 |
| 5:DC/MD/VA/WV | -0.1171 | [-0.1294, -0.1048] | <0.0001 | -0.0504 | [-0.0590, -0.0418] | 0.0000 | 0.4304 |
| 6:NC/SC/GA | -0.0523 | [-0.0640, -0.0407] | <0.0001 | -0.0077 | [-0.0157, 0.0004] | 0.0614 | 0.1468 |
| 7:Florida | -0.0890 | [-0.1001, -0.0778] | <0.0001 | -0.0080 | [-0.0158, -0.0002] | 0.0441 | 0.0900 |
| 8:TN/AL/MI | -0.0621 | [-0.0758, -0.0483] | <0.0001 | 0.0036 | [-0.0060, 0.0132] | 0.4620 | -0.0580 |
| 9:OH/IL/KY | -0.0711 | [-0.0829, -0.0594] | <0.0001 | -0.0094 | [-0.0176, -0.0012] | 0.0243 | 0.1327 |
| 10:Indiana | -0.1419 | [-0.1537, -0.1301] | <0.0001 | -0.0673 | [-0.0757, -0.0590] | 0.0000 | 0.4745 |
| 11:MI/WI/MN/ND/SD | -0.0739 | [-0.0855, -0.0623] | <0.0001 | -0.0016 | [-0.0097, 0.0065] | 0.6962 | 0.0218 |
| 12:NE/KS/IA/MO | -0.0894 | [-0.1023, -0.0764] | <0.0001 | -0.0289 | [-0.0379, -0.0198] | 0.0000 | 0.3231 |
| 13:LA/AR/OK | -0.1209 | [-0.1338, -0.1081] | <0.0001 | -0.0380 | [-0.0471, -0.0288] | 0.0000 | 0.3138 |
| 14:Texas | -0.0919 | [-0.1030, -0.0808] | <0.0001 | -0.0231 | [-0.0308, -0.0154] | 0.0000 | 0.2514 |
| 15:NV/UT/WY/CO/AZ/NM | -0.0724 | [-0.0853, -0.0596] | <0.0001 | 0.0028 | [-0.0063, 0.0118] | 0.5485 | -0.0382 |
| 16:WA/OR/ID/MT/AK | 0.0374 | [0.0219, 0.0530] | <0.0001 | 0.0570 | [0.0462, 0.0677] | 0.0000 | 1.5223 |
| 17:NorCal/HI | -0.0484 | [-0.0612, -0.0355] | <0.0001 | 0.0393 | [0.0304, 0.0483] | 0.0000 | -0.8130 |
| 18:SoCal | -0.1045 | [-0.1162, -0.0928] | <0.0001 | 0.0314 | [0.0231, 0.0398] | 0.0000 | -0.3007 |
| Sex | | | | | | | |
| Male | | Reference | | | Reference | | |
| Female | -0.0271 | [-0.0302, -0.0240] | 0.0000 | -0.0242 | [-0.0264, -0.0221] | 0.0000 | 0.8941 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Age at first ESKD Service | | | | | | | |
| 18-29 | | Reference | | | Reference | | |
| 30-49 | 0.0728 | [0.0447, 0.1010] | <0.0001 | 0.0406 | [0.0198, 0.0614] | 0.0001 | 0.5581 |
| 50-64 | 0.0892 | [0.0618, 0.1166] | <0.0001 | 0.0589 | [0.0386, 0.0792] | <0.0001 | 0.6596 |
| 65-79 | 0.0794 | [0.0522, 0.1067] | <0.0001 | 0.0517 | [0.0315, 0.0719] | <0.0001 | 0.6512 |
| 80+ | 0.0347 | [0.0074, 0.0621] | 0.0129 | 0.0193 | [-0.0010, 0.0396] | 0.0619 | 0.5559 |
| Requires Assistance with ADL | | | | | | | |
| No ADL Impairment | | Reference | | | Reference | | |
| 1+ ADL Impairments | -0.0656 | [-0.0700, -0.0612] | <0.0001 | -0.0266 | [-0.0298, -0.0234] | <0.0001 | 0.4055 |
| Institutionalized | | | | | | | |
| Non-Institutionalized | | Reference | | | Reference | | |
| Assisted Living, Nursing Home | -0.1154 | [-0.1204, -0.1104] | <0.0001 | -0.0435 | [-0.0474, -0.0395] | <0.0001 | 0.3766 |
| Median Income in Zip Code | 0.0041 | [0.0032, 0.0050] | <0.0001 | -0.0039 | [-0.0046, -0.0033] | <0.0001 | -0.9520 |
| Year of first ESRD service | | | | | | | |
| 2012 | | Reference | | | Reference | | |
| 2013 | -0.0005 | [-0.0073, 0.0062] | 0.8767 | 0.0000 | [-0.0048, 0.0047] | 0.9894 | 0.0601 |
| 2014 | -0.0171 | [-0.0238, -0.0104] | <0.0001 | -0.0075 | [-0.0122, -0.0028] | 0.0019 | 0.4360 |
| 2015 | -0.0226 | [-0.0292, -0.0159] | <0.0001 | -0.0098 | [-0.0145, -0.0051] | <0.0001 | 0.4335 |
| 2016 | -0.0299 | [-0.0365, -0.0233] | <0.0001 | -0.0124 | [-0.0170, -0.0077] | <0.0001 | 0.4137 |
| 2017 | -0.0302 | [-0.0368, -0.0236] | <0.0001 | -0.0107 | [-0.0154, -0.0060] | <0.0001 | 0.3549 |
| 2018 | -0.0285 | [-0.0352, -0.0218] | <0.0001 | 0.0234 | [0.0186, 0.0281] | <0.0001 | -0.8206 |
| Rural-Urban Continuum Code 2013 | | | | | | | |
| Metro, 1+ mil | | Reference | | | Reference | | |
| Metro, 0.25-1mil | 0.0048 | [0.0006, 0.0090] | 0.0253 | -0.0147 | [-0.0176, -0.0117] | <0.0001 | -3.0516 |
| Metro, <0.25mil | -0.0109 | [-0.0165, -0.0053] | 0.0001 | -0.0374 | [-0.0414, -0.0335] | <0.0001 | 3.4399 |
| Urban 20k+, Metro Adj. | -0.0081 | [-0.0156, -0.0006] | 0.0342 | -0.0345 | [-0.0398, -0.0292] | <0.0001 | 4.2562 |
| Urban 20k+, Not Adj. | -0.0134 | [-0.0256, -0.0012] | 0.0313 | -0.0547 | [-0.0633, -0.0462] | <0.0001 | 4.0852 |
| Urban 2.5-19.9K, Metro Adj. | -0.0018 | [-0.0089, 0.0054] | 0.6292 | -0.0259 | [-0.0310, -0.0209] | <0.0001 | 14.6862 |
| Urban 2.5-19.9K, Not Adj. | 0.0054 | [-0.0043, 0.0152] | 0.2741 | -0.0362 | [-0.0430, -0.0294] | <0.0001 | -6.6484 |
| Completely Rural, Metro Adj. | -0.0100 | [-0.0271, 0.0072] | 0.2543 | -0.0423 | [-0.0543, -0.0302] | <0.0001 | 4.2366 |
| Completely Rural, Not Adj. | -0.0352 | [-0.0522, -0.0181] | 0.0001 | -0.0596 | [-0.0717, -0.0475] | <0.0001 | 1.6957 |

| | Probit Estimates | | | Biprobit Estimates | |
|---|---|---|---|---|---|
| | Prob. | 95% CI | | Prob. | 95% CI |
| Pre-ESKD Nephrology Care | | | | | |
| None/Within 6 Months Pre-ESKD | 0.3152 | [0.3131, 0.3173] | | 0.1626 | [0.1613, 0.1639] |
| Nephrology Care 6+ Months Pre-ESKD | 0.4639 | [0.4616, 0.4662] | | 0.7210 | [0.7184, 0.7237] |

| | | | | | |
|---|---|---|---|---|---|
| Race | | | | | |
| Non-Hispanic White | 0.3808 | [0.3788, 0.3829] | | 0.4292 | [0.4276, 0.4308] |
| Non-Hispanic Black | 0.4046 | [0.4008, 0.4084] | | 0.4468 | [0.4440, 0.4496] |
| Hispanic | 0.3819 | [0.3730, 0.3908] | | 0.4334 | [0.4269, 0.4399] |
| Asian | 0.4023 | [0.3882, 0.4165] | | 0.4221 | [0.4119, 0.4322] |
| Pacific Islander | 0.4011 | [0.3686, 0.4337] | | 0.4468 | [0.4226, 0.4709] |
| Native American | 0.3601 | [0.3150, 0.4053] | | 0.3881 | [0.3545, 0.4217] |
| ESRD Network | | | | | |
| 1:New England | 0.4556 | [0.4462, 0.4649] | | 0.4353 | [0.4289, 0.4418] |
| 2:New York | 0.4858 | [0.4793, 0.4923] | | 0.5106 | [0.5061, 0.5151] |
| 3:New Jersey | 0.4371 | [0.4281, 0.4461] | | 0.4395 | [0.4333, 0.4457] |
| 4:PA/DE | 0.4063 | [0.3979, 0.4148] | | 0.4578 | [0.4517, 0.4639] |
| 5:DC/MD/VA/WV | 0.3385 | [0.3305, 0.3464] | | 0.3850 | [0.3792, 0.3907] |
| 6:NC/SC/GA | 0.4032 | [0.3963, 0.4101] | | 0.4277 | [0.4229, 0.4325] |
| 7:Florida | 0.3666 | [0.3605, 0.3726] | | 0.4273 | [0.4229, 0.4317] |
| 8:TN/AL/MI | 0.3935 | [0.3835, 0.4035] | | 0.4389 | [0.4319, 0.4460] |
| 9:OH/IL/KY | 0.3844 | [0.3774, 0.3914] | | 0.4259 | [0.4209, 0.4310] |
| 10:Indiana | 0.3137 | [0.3065, 0.3208] | | 0.3680 | [0.3626, 0.3734] |
| 11:MI/WI/MN/ND/SD | 0.3816 | [0.3748, 0.3884] | | 0.4337 | [0.4289, 0.4386] |
| 12:NE/KS/IA/MO | 0.3662 | [0.3573, 0.3751] | | 0.4065 | [0.4002, 0.4128] |
| 13:LA/AR/OK | 0.3346 | [0.3259, 0.3434] | | 0.3974 | [0.3909, 0.4039] |
| 14:Texas | 0.3637 | [0.3577, 0.3696] | | 0.4122 | [0.4080, 0.4165] |
| 15:NV/UT/WY/CO/AZ/NM | 0.3831 | [0.3743, 0.3919] | | 0.4381 | [0.4318, 0.4445] |
| 16:WA/OR/ID/MT/AK | 0.4930 | [0.4806, 0.5054] | | 0.4923 | [0.4837, 0.5009] |
| 17:NorCal/HI | 0.4072 | [0.3983, 0.4161] | | 0.4747 | [0.4684, 0.4810] |
| 18:SoCal | 0.3511 | [0.3440, 0.3582] | | 0.4668 | [0.4614, 0.4721] |
| Sex | | | | | |
| Male | 0.4008 | [0.3987, 0.4028] | | 0.4464 | [0.4448, 0.4480] |
| Female | 0.3737 | [0.3714, 0.3760] | | 0.4222 | [0.4203, 0.4240] |
| Age at first ESKD Service | | | | | |
| 18-29 | 0.3182 | [0.2910, 0.3454] | | 0.3906 | [0.3704, 0.4108] |
| 30-49 | 0.3910 | [0.3836, 0.3984] | | 0.4312 | [0.4259, 0.4365] |
| 50-64 | 0.4074 | [0.4037, 0.4111] | | 0.4495 | [0.4468, 0.4522] |
| 65-79 | 0.3976 | [0.3956, 0.3997] | | 0.4423 | [0.4407, 0.4440] |
| 80+ | 0.3529 | [0.3497, 0.3561] | | 0.4099 | [0.4074, 0.4124] |
| Requires Assistance with ADL | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| No ADL Impairment | 0.3997 | [0.3980, 0.4015] | | 0.4402 | [0.4388, 0.4416] |
| 1+ ADL Impairments | 0.3341 | [0.3302, 0.3381] | | 0.4136 | [0.4105, 0.4167] |
| Institutionalized | | | | | |
| Non-Institutionalized | 0.4020 | [0.4003, 0.4036] | | 0.4407 | [0.4393, 0.4420] |
| Assisted Living, Nursing Home | 0.2866 | [0.2819, 0.2912] | | 0.3972 | [0.3933, 0.4012] |
| Median Income in Zip Code | | | | | |
| Year of first ESRD service | | | | | |
| 2012 | 0.4089 | [0.4035, 0.4143] | | 0.4385 | [0.4347, 0.4423] |
| 2013 | 0.4084 | [0.4043, 0.4124] | | 0.4385 | [0.4356, 0.4413] |
| 2014 | 0.3918 | [0.3878, 0.3957] | | 0.4310 | [0.4282, 0.4339] |
| 2015 | 0.3863 | [0.3825, 0.3902] | | 0.4287 | [0.4259, 0.4316] |
| 2016 | 0.3790 | [0.3752, 0.3828] | | 0.4261 | [0.4233, 0.4289] |
| 2017 | 0.3787 | [0.3749, 0.3825] | | 0.4278 | [0.4250, 0.4306] |
| 2018 | 0.3804 | [0.3765, 0.3843] | | 0.4619 | [0.4589, 0.4649] |
| Rural-Urban Continuum Code 2013 | | | | | |
| Metro, 1+ mil | 0.3899 | [0.3876, 0.3922] | | 0.4485 | [0.4467, 0.4504] |
| Metro, 0.25-1mil | 0.3947 | [0.3913, 0.3981] | | 0.4339 | [0.4314, 0.4363] |
| Metro, <0.25mil | 0.3790 | [0.3741, 0.3839] | | 0.4111 | [0.4076, 0.4146] |
| Urban 20k+, Metro Adj. | 0.3817 | [0.3748, 0.3887] | | 0.4140 | [0.4090, 0.4190] |
| Urban 20k+, Not Adj. | 0.3765 | [0.3646, 0.3883] | | 0.3938 | [0.3854, 0.4021] |
| Urban 2.5-19.9K, Metro Adj. | 0.3881 | [0.3815, 0.3947] | | 0.4226 | [0.4179, 0.4273] |
| Urban 2.5-19.9K, Not Adj. | 0.3953 | [0.3860, 0.4046] | | 0.4123 | [0.4058, 0.4188] |
| Completely Rural, Metro Adj. | 0.3799 | [0.3630, 0.3968] | | 0.4062 | [0.3943, 0.4182] |
| Completely Rural, Not Adj. | 0.3547 | [0.3379, 0.3715] | | 0.3889 | [0.3770, 0.4008] |

Table 2.4. Recursive Bivariate Probit Estimates of Rates of Permanent Access by Race and Pre-ESKD Nephrology and by Race and ESRD Network Region

| Variables | White<br>Prop. [95% CI] | Black<br>Prop. [95% CI] | Hispanic<br>Prop. [95% CI] | Asian<br>Prop. [95% CI] | Pacific Islander<br>Prop. [95% CI] | Native American<br>Prop. [95% CI] |
|---|---|---|---|---|---|---|
| Pre-ESKD Nephrology Care | | | | | | |
| None/Within 6 Months Pre-ESKD | .1512 [0.1496, 0.1496] | .1805 [0.1776, 0.1776] | .1706 [0.1649, 0.1649] | .1678 [0.1586, 0.1586] | .1956 [0.1724, 0.1724] | .1308 [0.1061, 0.1061] |
| Nephrology Care 6+ Months Pre-ESKD | .7204 [0.7175, 0.7175] | .7252 [0.7210, 0.7210] | .7087 [0.7000, 0.7000] | .6882 [0.6748, 0.6748] | .7093 [0.6790, 0.6790] | .6592 [0.6119, 0.6119] |
| ESRD Network Region | | | | | | |
| 16:WA/OR/ID/MT/AK | .4906 [0.4837, 0.4837] | .4921 [0.4633, 0.4633] | .5197 [0.4934, 0.4934] | .4523 [0.4238, 0.4238] | .4503 [0.3998, 0.3998] | .4146 [0.3738, 0.3738] |
| 2:New York | .488 [0.4824, 0.4824] | .5425 [0.5334, 0.5334] | .5704 [0.5568, 0.5568] | .4961 [0.4754, 0.4754] | .5578 [0.4848, 0.4848] | .4674 [0.3764, 0.3764] |
| 18:SoCal | .4642 [0.4576, 0.4576] | .4744 [0.4612, 0.4612] | .4636 [0.4558, 0.4558] | .4578 [0.4454, 0.4454] | .4921 [0.4592, 0.4592] | .4392 [0.3552, 0.3552] |
| 17:NorCal/HI | .4629 [0.4553, 0.4553] | .5084 [0.4922, 0.4922] | .4391 [0.4264, 0.4264] | .531 [0.5192, 0.5192] | .537 [0.5138, 0.5138] | .484 [0.4129, 0.4129] |
| 4:PA/DE | .4517 [0.4460, 0.4460] | .4849 [0.4734, 0.4734] | .4733 [0.4445, 0.4445] | .3895 [0.3379, 0.3379] | .2937 [0.1366, 0.1366] | .2562 [-0.0242, -0.0242] |
| 11:MI/WI/MN/ND/SD | .4455 [0.4406, 0.4406] | .4052 [0.3957, 0.3957] | .4348 [0.4079, 0.4079] | .3997 [0.3669, 0.3669] | .4739 [0.3725, 0.3725] | .433 [0.4018, 0.4018] |
| 15:NV/UT/WY/CO/AZ/NM | .4453 [0.4389, 0.4389] | .4055 [0.3859, 0.3859] | .4585 [0.4464, 0.4464] | .456 [0.4221, 0.4221] | .4489 [0.3955, 0.3955] | .4785 [0.4572, 0.4572] |
| 8:TN/AL/MI | .4417 [0.4358, 0.4358] | .4521 [0.4449, 0.4449] | .4196 [0.3676, 0.3676] | .3602 [0.2951, 0.2951] | .416 [0.2812, 0.2812] | .366 [0.2719, 0.2719] |
| 1:New England | .4303 [0.4240, 0.4240] | .4494 [0.4320, 0.4320] | .4441 [0.4205, 0.4205] | .4337 [0.3898, 0.3898] | .3483 [0.2281, 0.2281] | .3036 [0.1827, 0.1827] |
| 6:NC/SC/GA | .4268 [0.4217, 0.4217] | .4491 [0.4438, 0.4438] | .3874 [0.3572, 0.3572] | .411 [0.3702, 0.3702] | .4414 [0.3405, 0.3405] | .3606 [0.3084, 0.3084] |
| 9:OH/IL/KY | .4246 [0.4204, 0.4204] | .4409 [0.4322, 0.4322] | .4105 [0.3820, 0.3820] | .4051 [0.3474, 0.3474] | .4644 [0.3508, 0.3508] | .2659 [0.0847, 0.0847] |
| 3:New Jersey | .4184 [0.4111, 0.4111] | .4718 [0.4598, 0.4598] | .4613 [0.4407, 0.4407] | .4929 [0.4579, 0.4579] | .4376 [0.3518, 0.3518] | .5564 [0.2751, 0.2751] |
| 14:Texas | .412 [0.4064, 0.4064] | .4214 [0.4132, 0.4132] | .3995 [0.3929, 0.3929] | .3625 [0.3363, 0.3363] | .4395 [0.3676, 0.3676] | .4581 [0.3256, 0.3256] |
| 7:Florida | .4036 [0.3985, 0.3985] | .4658 [0.4572, 0.4572] | .4638 [0.4525, 0.4525] | .457 [0.4195, 0.4195] | .4506 [0.3720, 0.3720] | .4464 [0.3035, 0.3035] |
| 12:NE/KS/IA/MO | .4022 [0.3961, 0.3961] | .4302 [0.4173, 0.4173] | .3666 [0.3339, 0.3339] | .4169 [0.3549, 0.3549] | .513 [0.3711, 0.3711] | .3426 [0.2674, 0.2674] |
| 13:LA/AR/OK | .3921 [0.3854, 0.3854] | .4252 [0.4161, 0.4161] | .3614 [0.3239, 0.3239] | .3924 [0.3265, 0.3265] | .4255 [0.2984, 0.2984] | .3666 [0.3357, 0.3357] |
| 5:DC/MD/VA/WV | .3818 [0.3759, 0.3759] | .3783 [0.3711, 0.3711] | .4158 [0.3809, 0.3809] | .4045 [0.3744, 0.3744] | .362 [0.2827, 0.2827] | .3251 [0.1191, 0.1191] |
| 10:Indiana | .3661 [0.3599, 0.3599] | .3726 [0.3625, 0.3625] | .3689 [0.3505, 0.3505] | .3669 [0.3348, 0.3348] | .4353 [0.3023, 0.3023] | .2652 [0.0537, 0.0537] |

*Proportions (Prop.) of patients initiating hemodialysis on a permanent access adjusting for covariates and nonrandom assignment into access type

Table 2.5. Marginal Differences Estimated by the Endogenous Equation of the Recursive Bivariate Probit

| Variables | Endogenous Equation | | |
|---|---|---|---|
| | Prob. | 95% CI | p-value |
| Age at first ESKD Service | | | |
| 18-29 | | Reference | |
| 30-49 | -0.0078 | [-0.0381, 0.0225] | 0.6142 |
| 50-64 | -0.0302 | [-0.0598, -0.0006] | 0.0457 |
| 65-79 | -0.0264 | [-0.0558, 0.0031] | 0.0790 |
| 80+ | -0.0077 | [-0.0373, 0.0219] | 0.6090 |
| Sex | | | |
| Male | | Reference | |
| Female | 0.0193 | [0.0162, 0.0225] | <0.0001 |
| Race | | | |
| Non-Hispanic White | | Reference | |
| Non-Hispanic Black | -0.0194 | [-0.0239, -0.0149] | <0.0001 |
| Hispanic | -0.0263 | [-0.0357, -0.0168] | <0.0001 |
| Asian | 0.0277 | [0.0131, 0.0422] | 0.0002 |
| Pacific Islander | -0.0373 | [-0.0701, -0.0044] | 0.0262 |
| Native American | 0.0538 | [0.0078, 0.0999] | 0.0220 |
| Primary Cause of ESKD | | | |
| Diabetes | | Reference | |
| Hypertension | -0.0152 | [-0.0187, -0.0117] | <0.0001 |
| Glomerulonephritis | -0.0376 | [-0.0441, -0.0312] | <0.0001 |
| Cystic kidney | 0.1390 | [0.1273, 0.1507] | <0.0001 |
| Other urologic | -0.0875 | [-0.0985, -0.0764] | <0.0001 |
| Other/Unknown/Missing | -0.1690 | [-0.1736, -0.1644] | <0.0001 |
| Diabetes Mellitus | 0.0029 | [-0.0004, 0.0062] | 0.0827 |
| Hypertension | 0.0474 | [0.0434, 0.0513] | <0.0001 |
| Coronary Artery Disease | 0.0217 | [0.0182, 0.0251] | <0.0001 |
| Peripheral Vascular Disease | 0.0062 | [0.0023, 0.0102] | 0.0020 |
| Heart Failure | -0.0313 | [-0.0341, -0.0285] | <0.0001 |
| Malignancy | 0.0048 | [0.0004, 0.0092] | 0.0321 |
| Stroke | 0.0016 | [-0.0025, 0.0058] | 0.4436 |
| Drug Dependence | -0.0751 | [-0.0917, -0.0585] | <0.0001 |
| Alcohol Dependence | -0.0984 | [-0.1110, -0.0859] | <0.0001 |
| COPD | -0.0278 | [-0.0317, -0.0240] | <0.0001 |
| Requires Assistance with ADL | -0.0231 | [-0.0277, -0.0186] | <0.0001 |
| Institutionalized | -0.0524 | [-0.0577, -0.0472] | <0.0001 |
| Median Income in Zip Code | 0.0164 | [0.0155, 0.0173] | <0.0001 |
| Year of first ESRD service | | | |
| 2012 | | Reference | |
| 2013 | -0.0017 | [-0.0085, 0.0051] | 0.6276 |
| 2014 | -0.0072 | [-0.0140, -0.0004] | 0.0384 |
| 2015 | -0.0102 | [-0.0170, -0.0035] | 0.0031 |
| 2016 | -0.0153 | [-0.0221, -0.0086] | <0.0001 |
| 2017 | -0.0209 | [-0.0277, -0.0141] | <0.0001 |
| 2018 | -0.1037 | [-0.1104, -0.0969] | <0.0001 |
| Number of IM Subspecialists in County | | | |

| | | | |
|---|---|---|---|
| None | | Reference | |
| 1-10 | -0.0027 | [-0.0083, 0.0029] | 0.3434 |
| 11-100 | -0.0010 | [-0.0070, 0.0051] | 0.7498 |
| 101-300 | -0.0078 | [-0.0146, -0.0010] | 0.0238 |
| 301+ | -0.0188 | [-0.0257, -0.0118] | <0.0001 |
| Rural-Urban Continuum Code 2013 | | | |
| Metro, 1+ mil | | Reference | |
| Metro, 0.25-1mil | 0.0378 | [0.0331, 0.0425] | <0.0001 |
| Metro, <0.25mil | 0.0727 | [0.0665, 0.0789] | <0.0001 |
| Urban 20k+, Metro Adj. | 0.0693 | [0.0609, 0.0777] | <0.0001 |
| Urban 20k+, Not Adj. | 0.1111 | [0.0983, 0.1239] | <0.0001 |
| Urban 2.5-19.9K, Metro Adj. | 0.0560 | [0.0475, 0.0645] | <0.0001 |
| Urban 2.5-19.9K, Not Adj. | 0.0918 | [0.0812, 0.1024] | <0.0001 |
| Completely Rural, Metro Adj. | 0.0853 | [0.0671, 0.1035] | <0.0001 |
| Completely Rural, Not Adj. | 0.0935 | [0.0755, 0.1116] | <0.0001 |
| ESRD Network | | | |
| 1:New England | | Reference | |
| 2:New York | -0.1432 | [-0.1544, -0.1319] | <0.0001 |
| 3:New Jersey | -0.0469 | [-0.0597, -0.0342] | <0.0001 |
| 4:PA/DE | -0.1290 | [-0.1416, -0.1164] | <0.0001 |
| 5:DC/MD/VA/WV | -0.0528 | [-0.0653, -0.0403] | <0.0001 |
| 6:NC/SC/GA | -0.0653 | [-0.0771, -0.0535] | <0.0001 |
| 7:Florida | -0.1128 | [-0.1240, -0.1017] | <0.0001 |
| 8:TN/AL/MI | -0.1116 | [-0.1256, -0.0976] | <0.0001 |
| 9:OH/IL/KY | -0.0820 | [-0.0939, -0.0702] | <0.0001 |
| 10:Indiana | -0.0396 | [-0.0516, -0.0275] | <0.0001 |
| 11:MI/WI/MN/ND/SD | -0.1006 | [-0.1122, -0.0890] | <0.0001 |
| 12:NE/KS/IA/MO | -0.0595 | [-0.0726, -0.0464] | <0.0001 |
| 13:LA/AR/OK | -0.0889 | [-0.1022, -0.0756] | <0.0001 |
| 14:Texas | -0.0853 | [-0.0965, -0.0742] | <0.0001 |
| 15:NV/UT/WY/CO/AZ/NM | -0.1158 | [-0.1288, -0.1027] | <0.0001 |
| 16:WA/OR/ID/MT/AK | -0.0928 | [-0.1083, -0.0773] | <0.0001 |
| 17:NorCal/HI | -0.1736 | [-0.1865, -0.1608] | <0.0001 |
| 18:SoCal | -0.2374 | [-0.2490, -0.2259] | <0.0001 |

## Chapter 3: Reducing Bias in Measurement of the Impact of Hemodialysis Access Type on Hospitalization for Vascular Access Infection

Sub Aims & Hypotheses

- Sub Aim 1: Estimate the association between an access type and risk of hospitalization for a vascular access infection after accounting for the relationship that underlying whether or not patients have a tunneled catheter or permanent access.
    - Hypothesis 1: Without accounting for the relationships underlying whether or not people start their dialysis with a tunneled catheter, estimates of variation in vascular access infection will be biased.
- Sub Aim 2: Evaluate whether differences in vascular access infection by patient demographics are due to variability in access type.
    - Hypothesis 1: The effect of age will be significantly different after adjustment for nonrandom assignment to tunneled catheter.
    - Hypothesis 2: The effect of sex will be significantly different after adjustment for nonrandom assignment to tunneled catheter.
    - Hypothesis 3: The effect of race will be significantly different after adjustment for nonrandom assignment to tunneled catheter.
    - Hypothesis 4: The effect of ESRD network region will be significantly different after adjustment for nonrandom assignment to tunneled catheter.

Key Findings & Implications

- The estimated difference in hospitalization for access infection between catheter and permanent access differs based on residence in a nursing home or assisted living facility; while a Cox model correctly estimates differences by access type in infection rates

among non-institutionalized patients, it misestimates the direction and magnitude of the difference between access types for patients living in nursing homes or assisted living facilities.

- The literature describes a number of infection risk factors that only impact institutional patients. Further study of the institutionalized ESKD population is required to clarify what known infection risks are impacting the ESKD population.
- After institutionalization status and age, history of drug dependence or opioid abuse had the second largest effect size (0.7 PPY; 95% CI 0.0423,0.0820), suggesting intravenous drug users with ESKD may be using their access for recreational drug use; this group's adjusted risk of access infection is 89% greater than those without a history of drug use (95% CI 1.39, 2.56).
- A mixed methods study of ESKD patients with a history of drug or opioid abuse may provide the context for development of interventions to reduce vascular access infection resulting for recreational use of catheters, and to a lesser extent, permanent access.
- Rates of methicillin-resistant Staphylococcus aureus (MRSA) have been consistently high among residents of assisted living and nursing home facilities from 2012 through 2017 (43.0% to 44.6%), but increased among community-residing patients from 2012 to 2017 (22.9% to 41.8%).
- Given variability in hemodialysis access type is influenced by patient factors, particularly patients' ability to access pre-ESKD nephrology care, retrospective analyses should consider the non-random assignment to access type in estimation of the effects of access type and patients' characteristics on early hemodialysis access outcomes, such as vascular access infection.

## Introduction

Hemodialysis vascular access infections may present with pus, redness, and/or swelling of the vascular access location, or with symptoms of blood infection and sepsis, such as fever, increased resting heart rate, low blood pressure, and disorientation.[91, 92] Laboratory cultures are required for definitive definition, and are taken either via swab at the access site, or via a blood culture.[93] Generally, patients undergoing hemodialysis have an increased risk of infection, in part due to dysfunction related to kidney failure,[94] as well as due to inherent risks of hemodialysis, including the repeated compromising of skin integrity and quality issues with the dialysis water treatment system.[94, 95] Though there are a wide range of catheter infection causes and risk-related behaviors,[26, 96, 97] infection rates are greatest among patients with hemodialysis catheters due to the practical implications of a plastic tube extending from one's body. Bacteria's adherence to synthetic materials, namely arteriovenous grafts and tunneled catheters, may also contribute to infection risk among hemodialysis dependent patients.[95] As described by Jaber, "four pathogenic pathways have been incriminated in the development of catheter-related bloodstream infections, and include, in order of descending frequency: (1) colonization of the cutaneous catheter tract and tip with skin flora; (2) intra-luminal colonization due to contamination of the catheter hub; (3) hematogenous seeding to the catheter from an-other focus of infection; and (4) very rarely, intraluminal contamination of the catheter with solvent/infusate."[94]

In the literature, staphylococcus species are the most common cause of infection among ESKD patients.[98-100] In 2014, Staphylococcus aureus (S. aureus) was the most common blood infection for hemodialysis patients (31%) with 40% of those S. aureus infections being methicillin-resistant.[101] Multi-center studies in the United States have demonstrated that dialysis facilities exhibit substantial variability in vascular access infection outcomes,[102, 103] while a

similar study of Canadian dialysis centers did not identify any center-level variability in access-related infection.[104] Variability in antibiotic resistant infection rates is due largely to variability between centers.[105] Methicillin-resistant Staphylococcus aureus (MRSA), a bacteria with increased anti-biotic resistance, was historically not acquired outside of health care facilities, but MRSA infections originating in community settings have been increasing in frequency in recent years.[95, 105, 106] More than three-quarters of bloodstream infections reported by hemodialysis facilities are vascular access related, with 70% of access related infections occurring among patients dialyzing through a catheter.[101]

Preventive strategies to reduce vascular access infections include topical antibiotics at catheter sites,[107-109] combination topical anti-biotic anti-fungal ointments,[110] and antimicrobial catheter lock solutions.[94, 111-113] An in-depth review of the literature by Lafrance et al. found strong evidence that prior episodes of bacteremia and vascular access type are risk factors for infection; moderate evidence that patient hygiene and serum albumin were risk factors for infection; and weak evidence that a variety of other factors may be related to risk of vascular access infection.[95]

Management of access infection includes the use of one or more antimicrobial agent, typically an antibiotic, with the specific agent and dosage depending on the severity of the infection and the specific type of bacteremia or fungal infection.[93] Vancomycin is the a commonly recommended therapy for MRSA infection,[91, 93] but the recommended agents vary more widely among the non-antibiotic resistant gram-negative and gram-positive types of bacteremia.[93] If a patient with an access infection was dialyzing through a catheter or is discontinuing permanent access use to dialyze through a catheter, an antimicrobial locking

solution is also recommended.[91-93, 113, 114] In the event a bloodstream or access infection results in sepsis, endocarditis, or osteomyelitis, additional therapeutic planning is necessary.[92, 93]

According to the most recent USRDS annual report, which used 2016 data, all cause hospitalization was 1.7 hospitalizations per patient year; infection hospitalizations are 0.44 per patient year, of which 0.13 (30%) are vascular access infections.[1] Hospitalization for access infection has fallen 54.6% since 2007.[1] Among patients hospitalized for vascular access infection, within 30 days of discharge 3.5% die, 2.7% are re- hospitalized and die, and 30.2% are re-hospitalized and survive, with all three rates being generally comparable to rates among patients discharged after hospitalizations for infections unrelated to vascular access.[1] Among patients discharged for a vascular access infection hospitalization, 6% are re-admitted for avascular access infection and 8% are re-admitted for an infection unrelated to vascular access.[1]

A meta-analysis of outcomes of vascular access reported that annual infection rates are lowest among patients with AVFs (0.02; 95% CI 0.01-0.04), followed by patients with AVGs (0.13; 95% CI 0.10-0.17), followed by patients with THCs (0.16; 95% CI 0.08-0.34);[65] this is consistent with the literature, which consistently identifies THC as the access type with substantially greater risk of vascular access infection, followed by AVG.[96, 115-117] However, the extent to which THC results in greater risk of infection varies widely by study context, due in part to varied definitions of vascular access infection.

In a study of ESKD septic shock survival, roughly half of non-survivors were dialyzing through THCs, whereas only 28% of survivors were using THCs.[116] However, this association is likely spurious, and an example of how characteristics associated with selection into access type are independently associated with vascular access outcomes. In the septic shock study, THC status is likely serving as a proxy for ability to access health care and/or individual-level health

measures, given the rate of vascular access infection was 11% among both survivors and non-survivors.[116] If the rates of infection are comparable, but patients with THC are less likely to have had adequate access to care prior to hospitalization for access infection, it's more likely comorbidities, nth order effects of socioeconomic position, and corresponding variations in health care access impacted the likelihood of dialyzing through THC. This study seeks demonstrates the necessity of adjusting for non-random assignment of access type when attempting to estimate associations between patient characteristics and vascular access infection risk.

## Methods

### *Data*

This study used data from the USRDS and Area Health Resource File.[36] The USRDS patient file, form 2728 file, the hospitalization file, provider claims, and CROWNWeb supplied patient demographics, comorbidities, access type, a change in access type, pre-ESKD nephrology care, and hospitalization for vascular access infection. Herein, shorthand references in the results and discussion to "infection" or "vascular access infection" as an outcome are all references to hospitalization with a primary diagnosis of vascular access infection. As in the sub-group analysis of Chapter 2, "pre-ESKD nephrology care" or "pre-ESKD care" refer specifically to seeing a nephrologist at least 6 months prior to ESKD, as defined by Medicare claims. The definition of the household median income by zip code was supplied by the American Community Survey. Rural-urban continuum code (2013) were defined using the Area Health Resource Files. See Appendix 5 for variable definitions and operationalizations.

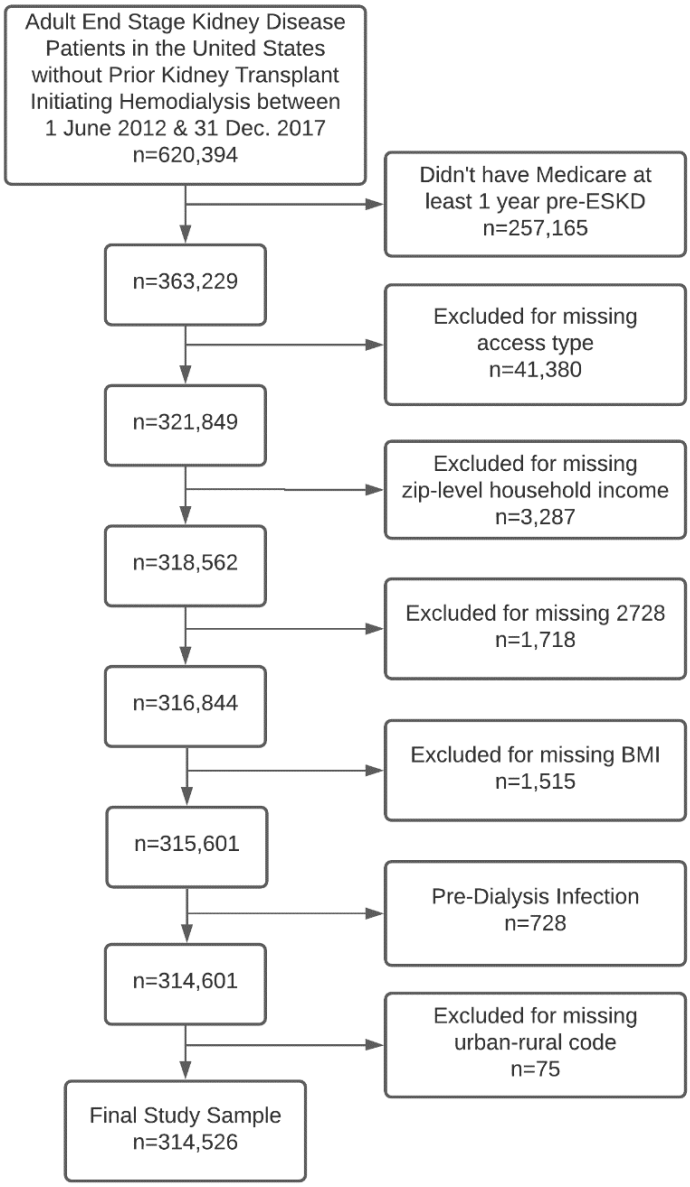
*Study Sample Selection*

Inclusion criteria for the study population will include: (1) age 18 or older at dialysis initiation; (2) began hemodialysis at first date of end stage kidney disease without a concurrent or prior kidney transplant; (3) resident of United States, not including United States territories; and (4) initiated treatment using hemodialysis between June 1, 2012 and December 31, 2017. The study was limited to an adult population because the etiology and treatment of kidney disease among pediatric patients is not comparable, leading to very different patient populations.[25] Patients with transplants on or before the beginning of dialysis for end stage kidney disease were excluded, given they had reached their desired outcome (i.e., kidney transplant). This was done even if these patients continued dialysis since they were not expected to remain on dialysis for a long period of time. The population was limited to residents of the United States because residents of the Virgin Islands, Guam, and Puerto Rico would be expected to have different health disparities and health care access disparities compared to residents of the 50 states and the District of Columbia.[26] Additionally, the American Community Survey only provides median household incomes on zip codes in the United States, District of Columbia, and Puerto Rico, excluding all other territories. One year of follow up was required for a clear definition of the outcome (i.e., rate of hospitalization for vascular access infection); given USRDS observation currently ends on December 31, 2018, all patients with hemodialysis start dates prior to January 1, 2017 were not included.

After applying the aforementioned inclusion criteria, 620,394 patients were identified for potential study inclusion. Patients were excluded from the study if: they were not enrolled in Medicare Part A at least 365 days before hemodialysis initiation (n=257,165); they had indeterminate access type in CROWNWeb (n=41,380); they did not have zip-code level median

household income (n=3,287); they did not have a 2728 form in USRDS (n=1,718); their BMI was missing from their 2728 form (n=1,515); they had a vascular access infection recorded before hemodialysis initiation (n=728); or they had an unknown urban-rural county code (n=75). This resulted in a study sample size of 314,526 patients. See Figure 3.1 for a diagram of exclusion criteria.

**Figure 3.1 Application of exclusion criteria to the end stage kidney disease cohort identified for inclusion**



To evaluate potential bias resulting from exclusion due to missing values, missingness by place (i.e., state of residence) and time (i.e., dialysis initiation year) was evaluated for the six exclusion criteria resulting in more than 100 exclusions. The exclusion criteria for at least 1 year of pre-ESKD Medicare Part A enrollment resulted in the largest number of exclusions; missingness ranged from 30% in Vermont to 54% in the District of Columbia. Missingness was between 58% and 59% from 2012 to 2017. Though the variation over time is inconsequential, the variation by place suggests there is uneven distribution of age cohorts across geography, as age is the primary reason for ESKD patients to be enrolled in Medicare at least 365 days prior to ESKD.

Access type was missing between 4% (Rhode Island) and 23% (Washington DC) of patients across States. Missingness did not appear to follow a geographic pattern. However, the most recent years (2016-2017) had a much lower rate of missing access (~6%) than previous years, which had ranged from 12% to 17% between 2012 and 2014. Temporal variation in reported access type is likely a consequence of improvement of reporting to CROWNWeb.

Median income was missing for 1% overall, though all but Alaska (10%) and Wyoming (5%) had more than 3% missingness. Considering this exclusion only resulted in 1% of patients, this is not likely to be a major limitation. Form 2728 missingness, body mass index, and missing urban-rural code accounted for less than 0.5% of missingness at the application of each exclusion criteria. A total of 435 patients were excluded from the analysis due to exclusion for a vascular access infection prior to initiation of hemodialysis. Infections prior to ESKD are a consequence of either pre-ESKD permanent access creation, or a hemodialysis catheter infection for acute kidney injury. This is the most likely source of bias, as these people were likely pre-disposed for infection and may have had their infection after hemodialysis start for ESKD.

*Variable Identification*

Vascular access infection was defined using International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes (Appendix 5) as the primary diagnosis for hospitalization in the hospitalization file for Medicare enrollees. The list of codes was derived from the list of vascular access infection codes used in USRDS's annual reports.[118] ICD-10 codes for catheter infections were only counted among patients with catheters, as there is a potential for catheters related to non-ESKD treatments.

ICD-9 vascular access codes descriptions:

- Infection and inflammatory reaction due to other vascular device, implant, and graft
- Other and unspecified infection due to central venous catheter
- Bloodstream infection due to central venous catheter
- Local infection due to central venous catheter

ICD-10 vascular access infection code descriptions:

- Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts, initial encounter
- Other infection due to central venous catheter, initial encounter
- Unspecified infection due to central venous catheter, initial encounter
- Bloodstream infection due to central venous catheter, initial encounter
- Local infection due to central venous catheter, initial encounter

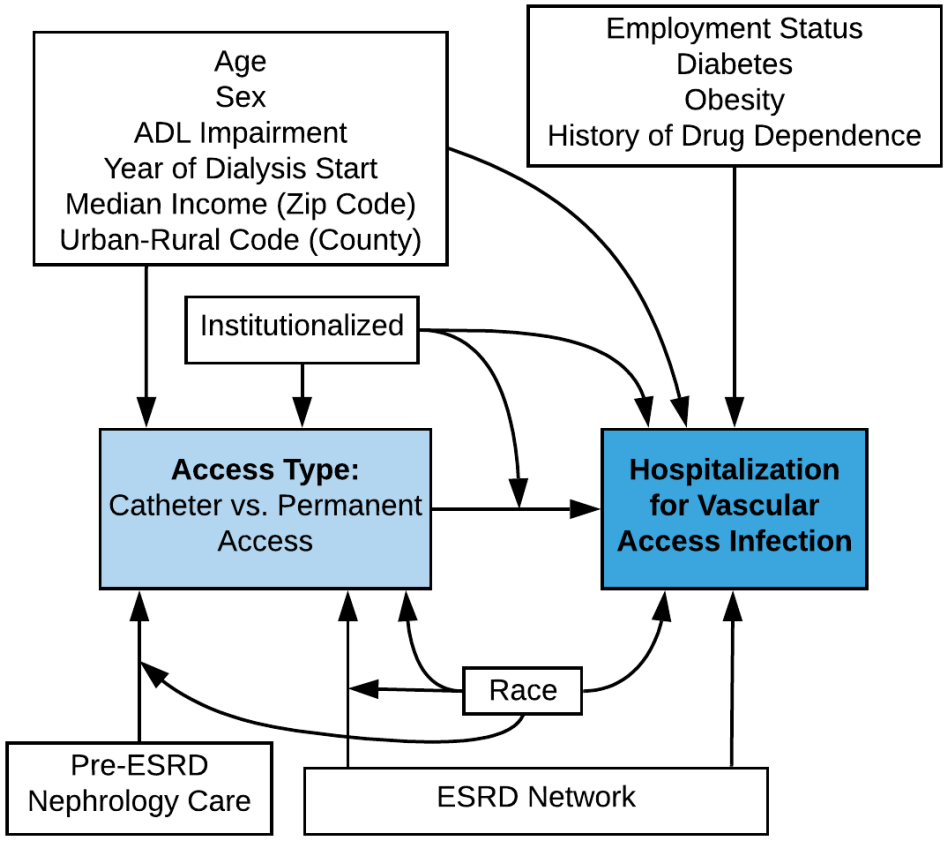
Access type (i.e., tunneled hemodialysis catheter versus arteriovenous fistula or graft), was determined using CROWNWeb. CROWNWeb was used to define access because censoring for change in access type was defined using CROWNWeb; exclusively using CROWNWeb to define access type reduces uncertainty related to measurement error. Given access type is the

outcome of one of the equations in the primary regression approach, it is critical that access type is correctly defined. Though there is some uncertainty related to dates, CROWNWeb is the best longitudinal source of information on what access is being used to dialyze ESKD patients over the course of their renal replacement therapy.

Independent variables included sex, age, race, ESRD network, year of dialysis initiation, median zip code-level income (from the American Community Survey), county-level urban-rural code, institutionalization status of the patient (i.e., resides in an assisted or skilled living facility), ability to perform activities of daily living (ADL), pre-ESKD nephrology care at least 6 months prior to ESKD, diabetes, obesity, history of illicit drug dependence, and employment status.

All covariates were used as predictors for both of the equations in endogenous Poisson described below, with the exception of one exclusion variable in the access equation (i.e., pre-ESKD nephrology care at least 6 months prior to ESKD) and four variables that were only in the infection equation (i.e., diabetes, obesity, history of illicit drug dependence, employment status). Given the findings of Chapter 2, age, sex, race, ADL impairment, year of dialysis initiation, median zip-code level income, rural-urban code and institutionalization status. In addition to the aforementioned variables, diabetes, obesity, and a history of illicit drug dependence have been found to be associated with increased risk of hospitalization for infection, and are included in the infection equation. History of illicit drug dependence from the 2728 form was combined with ICD indicators for a history of opioid abuse in Medicare claims prior to the first access procedure (Appendix 5).

**Figure 3.2. Hospitalization for vascular access infection conceptual model**




An interaction between race and ESRD network, and an interaction between race and pre-ESKD nephrology care will be used in the model predicting index access type. Chapter 2 previously describes the reasoning behind interactions between pre-ESKD nephrology care and race, as well as between ESRD network and race. Institutionalization status was interacted with access type in the equation modeling vascular access infection because the risk of infection associated with a tunneled catheter likely vary depending on the patient's residential environment. Living in an assisted living facility or nursing home puts patients at a higher risk of infection.[119, 120] Institutionalized patients living in nursing homes or assisted living facilities are generally elderly, and their immune systems may be weaker and increase infection risk.[121]

Residence in a facility may also increase the risk for health care facility-related transmission of infections to other institutionalized patients with greater infection risk. During the preliminary analysis for this study, an omnibus test of the interaction between race and ESRD network in the equation modeling likelihood of access infection was not significant, leading to the exclusion of this previously planned interaction.

*Descriptive Tables and Statistics*

Wilcoxon rank sum tests and Kruskal-Wallis tests were used to compare skewed continuous variables between groups. T-tests and ANOVA were used to compare normal continuous variables between groups. Chi-square tests were used to compare binary and categorical variables between groups.

*Regression Analysis*

The primary outcome of the regression models will be hospitalization for vascular access infection. An endogenous Poisson model[122] will be used to model the average difference in time to initial vascular access infection, using access type (i.e., permanent access versus tunneled hemodialysis catheter) as the endogenous treatment variable. The Poisson is intended to approximate a Cox model, with the Poisson treating the event as the dependent variable and time to event as an exposure variable.[123, 124] Only the initial case of vascular access infection will be modeled. Patients will be censored at death; first kidney transplant; change in access type, as defined by CROWNWeb; any hospitalization other than vascular access infection; and ending of Medicare Part A enrollment. Censoring at hospitalizations is a conservative approach, but it is undertaken because hospitalization is a risk factor for vascular access infection, and risk of other hospitalization is the result of a separate function that should be appropriately modeled, if hospitalization is included as an independent variable. Change in access type is given by month,

rather than by date. Accordingly, all access changes will be assumed to be on the 15th of each month. Choosing the 15th ensures that the maximum number of days between the true date of access change and estimated date of access change is minimized. In other words, the greatest number of days off the estimate can be is 15, whereas if the 1st day of each month was assumed, the maximum possible error in the estimate is 29 days. Though the model does not distinguish between graft and fistula in measuring permanent access versus catheter, a change between these access types will also be treated as a censoring event. An administrative censoring date of 365 days post-dialysis initiation will be used for patients who have not been censored and have not had a vascular access infection. To evaluate the magnitude of the adjustment provided by the access type equation, a Cox model will also be modeled.

Patients were censored at access change rather than treating access type as a time-varying variable due to the conceptual approach of the endogenous equation. Pre-ESKD nephrology care has been shown to be incredibly important in adjusting for selection into index access in Chapter 2 and is included in the endogenous equation used in this Chapter 2's primary modeling approach. However, pre-ESKD nephrology care should only have an effect on the index access, not subsequent accesses. To accommodate this, a separate equation predicting access that doesn't include pre-ESKD nephrology care would be necessary for subsequent accesses only, which is not feasible

The Wald test of independent equations, testing the null hypothesis that there is no correlation between treatment and outcome errors ($\rho = 0$), was used to evaluate the endogenous Poisson relative to a naïve Poisson (i.e., an approximation of a Cox proportional hazards model); rejection of the null hypothesis indicates an endogenous Poisson has good model fit and is superior to a naïve Poisson. Results from a Cox proportional hazards model with a single stage

predicting hospitalization for vascular access infection will be compared to an endogenous Poisson's results to evaluate potential selection bias for sub-aims 1 and 2. Though the Wald test of independent equations determined appropriateness of the endogenous Poisson, both models' goodness of fit will be evaluated using Wald tests. Covariates with $p > 0.2$ and which also reduce the Akaike information criterion (AIC) by at least 5 upon exclusion were evaluated for omission from the model; this exclusion criteria are based on the assumption that if a covariate does not have at least a confounding effect (i.e., $p < 0.2$) and improves model fit that it is likely not providing a useful measurement, and may be capturing some of the effect of correlated covariates. Seemingly unrelated estimation will be used to compare the exponentiated coefficients between naïve and endogenous Poisson models.

Among patients who were hospitalized for vascular access infection, a logistic regression will be used to evaluate variability in MRSA infection (ICD-9 038.12, 041.12; ICD-10 A49.02, B95.62, A49.02, A41.01, and A41.02) by age, sex, race, institutionalization status, year of hospitalization, and ESRD network region. An interaction between institutionalization status and year of hospitalization was included in the model to account for variability in the impact of institutionalization status across years. A sensitivity analysis was conducted to evaluate inclusion of dialysis facility as a random-effect.

**Results**

*Descriptive Statistics: Primary Analysis*

The study cohort consisted of 314,526 patients with ESKD, 2.9% (n=9,156) of whom had a hospitalization for a vascular access infection during their first year of hemodialysis (Table 3.1; all THC rate p-values except for diabetes $<0.001$; all vascular access infection rate p-values except for pre-ESKD nephrology care significant at $p<0.001$). Overall, 74.3% of patients-

initiated hemodialysis on a tunneled hemodialysis catheter (n=233,693). Patients living in assisted living or nursing facilities had the highest rate of catheter use (86.4%) and the highest hospitalization for vascular access infection rates outside of age (0.11 PPY) at nearly double the rate of access infection for those who did not live in an assisted living or nursing facility (0.06 PPY). The unadjusted rate of THC infections was nearly five times greater than the rate among patients with a permanent access (0.09 vs. 0.02 PPY).

Differences by sex in rates of THC or infection were not clinically meaningful. Access infection appears to be independent of catheter rates when stratifying by age; older (age 80+) and younger (18-29) patients had the highest rates of catheter use, but infection risk was lowest among those 50 and older, and much higher among those 18 to 29 (0.17 per person year [PPY]) and 30 to 49 (0.11 PPY). Age was strongly related to risk of access infection, with an infection rate of 0.17 PPY among those age 18-29, and decreasing infection rates by age group through those age 65-79 and 80+, both of which had an infection rate of 0.06. The infection rate was somewhat greater among Black, Hispanic, and Native American patients. Those with a history of opioid or drug dependence had the greatest unadjusted infection rate of any sub-group outside of differences by age (0.13 vs. 0.06 PPY ). By rural-urban continuum code, counties with greater population densities had greater infection rate, with an infection rate of 0.07 PPY among counties with metropolitan areas of 1 million or more residents, and an infection rate of 0.05 PPY among completely rural counties that are not metropolitan adjacent.

By ERSD region, Florida had the greatest infection rate at 0.09 PPY (Table 3.2). West Coast regions had the lowest rates of infection, and locations in the Northeastern regions had the highest rates, after Florida. Most regions have infection rates between 0.04 and 0.06 PPY. There did not appear to be a systematic pattern between time-adjusted rates of vascular access and

tunneled catheter. However, states with greater infection rates also tended to have greater rates of patients who lived in nursing homes or assisted living facilities.

The infection rate for non-institutionalized patients with a permanent access was 0.016 PPY, and the PPY for non-institutionalized patients with a catheter was 0.050 PPY (Table 3.3). The infection rate for institutionalized patients with a permanent access was 0.084 PPY the RI for institutionalized patients with a catheter was 0.124 PPY.

Among patients initiating hemodialysis via catheter, 29.8% switched to a permanent access prior to vascular access infection, transplant, hospitalization, or end of Medicare enrollment (Appendix 6). Among patients initiating hemodialysis through a permanent access, 13.1% switched to either a catheter or another permanent access type (i.e., fistula to graft; graft to fistula). Transplant as a censoring event was more common among younger age groups than among older age groups.

*Regression Results: Primary Analysis*

The null hypothesis that $\rho = 0$ was rejected given $\rho = 0.35$ ($p<0.0001$, 95% CI 0.29 to 0.42), indicating the endogenous Poisson was superior to a naïve Poisson (Appendix 7). Accordingly, these results will focus on the estimations from the endogenous Poisson, though reference will be made to the differences between the estimates from the two modeling approaches to address Sub-Aim 1 and 2. Wald tests found both naïve and endogenous Poisson models achieved good model fit ($p<0.0001$). No covariates had a p-value greater 0.2, leading no variables to be dropped from the initial modeling approach. When comparing the effects of the naïve and endogenous Poisson models (Appendix 7), the main effect of THC was 0.33 times as large ($p<0.0001$), the main effect of institutionalized living was 1.52 times as large ($p<0.0001$), and the interaction effect was 1.44 times as large ($p<0.0001$). Age; sex; Black race, Hispanic

ethnicity, and Native American race (versus non-Hispanic white); and all but one ESRD network region had significantly different magnitudes of effect between the models. With the exception of access type, all significantly different coefficients underestimated their respective effects sizes, though no effects changed direction.

Given the coefficients in Appendix 7 are not interpretable on their own, the marginal differences are presented in Tables 3.3 & 3.4. The following effects sizes are expressed as adjusted rates of hospitalization for vascular access infection per person year. The marginal effects without the stratification by levels of the interacted access type and institutionalization status are given in Table 3.4 (i.e., no interaction terms are expressed, but rather the marginal differences after accounting for the interaction). Table 3.3 presents average rates of infection by access type and institutionalization status to fully examine the interaction. The estimated difference in vascular access infection rates between THC and permanent access among non-institutionalized patients is nearly identical when estimated by a Cox model versus an endogenous Poisson (0.3% relative change in effects size). Contrastingly, the absolute effect size for THC is nearly doubled among patients in nursing homes or assisted living facilities, with the effect in the opposite direction estimated by the Cox model.

The adjusted infection rate was 0.02 greater (95% CI 0.00-0.04) among patients initiating hemodialysis through a catheter versus the reference class of permanent access (Table 3.3). Institutionalized (i.e., assisted or skilled living facility) patients adjusted infection rate was 0.09 greater (95% CI 0.06-0.12) than those who were not institutionalized. When estimating outcomes by access type and institutionalization status, among non-institutionalized patients, catheter was associated with an infection rate 0.03 PPY (95% CI 0.03-0.4) greater than those with permanent

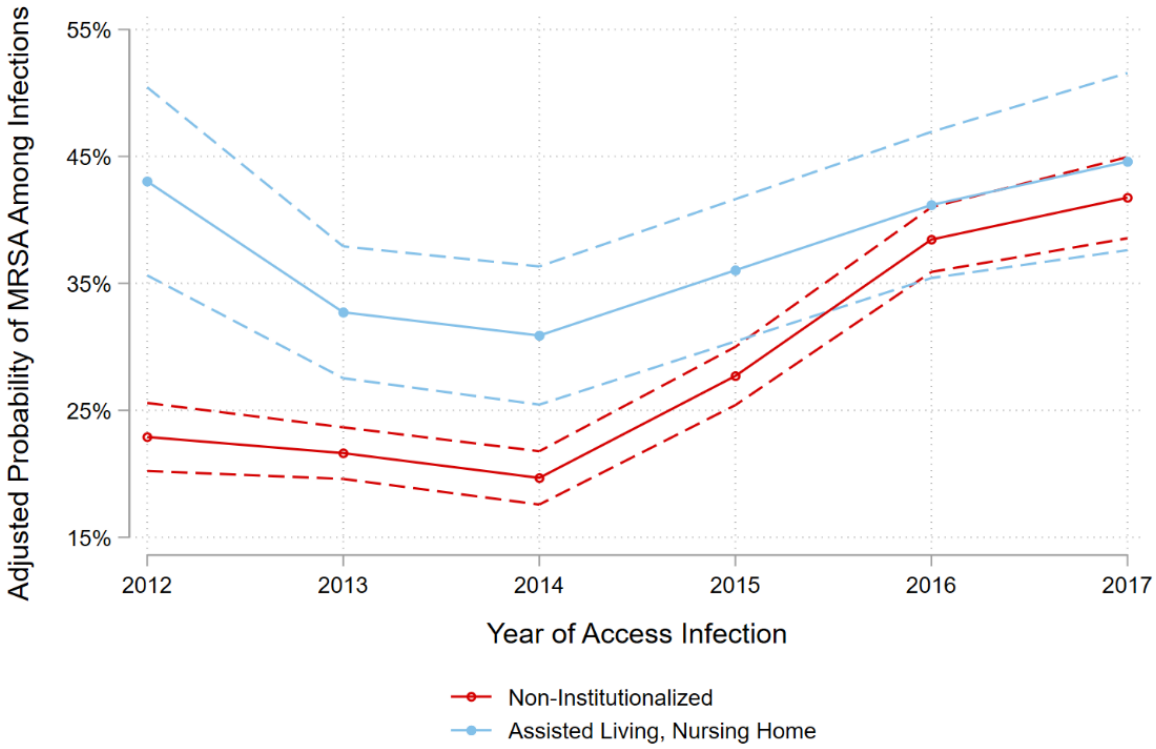
access. Contrastingly, among institutionalized patients, catheter was associated with an infection rate 0.07 lower (95% CI -0.14,-0.01.) than those with a permanent access.

Older age was associated with lower infection rate, as was being male, white, and employed part- or full-time (Table 3.4). Variation by ESRD network region was comparable between most regions, though Florida has the greatest adjusted infection rate relative to any other region (0.08 greater than the reference region, ESRD network region 16, which had the lowest rate). The Pacific Northwest, northern California and Hawaii, and Southern California (ESRD regions 16, 17, & 18) had the lowest infection rate by region. There has been a temporal trend towards lower infection rates in recent years, with rates rapidly decreasing in 2017 relative to 2015 to 2016. Aside from access type and institutionalization status, the largest magnitude effect among patient factors was a history of illicit drug or opioid abuse.

*Secondary Analysis: MRSA*

The probability of a vascular access infection admissions also including a code for MRSA varied significantly by sex, race, ESRD network region, institutionalization status, and year of hospitalization, with a significant interaction between institutionalization and hospitalization (Table 3.5). There was not significant variation between age groups. The interaction between institutionalization and year of access infection showed that until 2016 institutionalized patients consistently had greater rates of MRSA infection (Figure 3.3). The sensitivity analysis including primary dialysis facility as a random effect was not adopted, as center accounted for less than 1% of the variability in the likelihood of MRSA among infections and a likelihood ratio test comparing a mixed effect model to a logistic model was not significant ($p=0.3193$).

**Figure 3.3 Adjusted probability of access infection including MRSA diagnosis by year and institutionalization status**




## Discussion

*Sub-Aim 1: Association between access type and hospitalization for a vascular access infection*

Sub-aim one's hypothesis that a Cox proportional hazards model underestimates the effect of access type on hospitalization for vascular access infection was confirmed. Though the seemingly unrelated estimation is useful for directly comparing coefficients between models (Appendix 7), it is necessary to calculate the average treatment effects of access type, institutionalization, and the combination of access type and institutionalization (Table 3.3 and Table 3.4). Regardless of if the average treatment effect is calculated by access type, institutionalization status, or by the interaction between the two, the Cox model is shown to underestimate the absolute rate of vascular access infection hospitalization, as well as the

difference in hospitalization between groups. However, the net impact of the Cox model's underestimation is almost entirely borne by the institutionalized population; the difference between THC and permanent access isn't changed by the endogenous Poisson among the non-institutionalized population.

The findings pertaining to this sub-aim suggest that the benefits of permanent access, both in terms of the rate of access infection hospitalization and the corresponding costs of care, are not the same between institutionalized and non-institutionalized populations. Since tunneled catheter should inherently carry more risk of vascular access infection and complication, this suggests closer attention is required to the process of undergoing hemodialysis for institutionalized patients and institutionalized patients with an AVF or AVG are cared for. Along with the generally high rate of access infection among institutionalized patients, these findings suggest vascular infection risk is very sensitive to the residential and patient care contexts. Further exploration of variability in access infection and institutionalization status by ESRD network region and a more granular definition of access types may prove to be instructive in identifying the contexts in which institutionalized patients with permanent access may derive their greater risk from.

Future studies should use this methodological framework to assess variability in access infection between patients with arteriovenous fistula and arteriovenous graft. The literature has described variation by patients and provider factors in selection of fistula versus graft.[83, 90, 125] An endogenous Poisson with fistula versus graft as the endogenous variable would build upon the present study and clarify the extent to which differences in infection in graft versus fistula are due to non-random assignment to access type.

*Sub-Aim 2: Evaluating whether differences in vascular access infection by patient characteristics are due to variability in access type*

Sub-aim two's two hypotheses were confirmed: There was a significant difference in the coefficients for all age groups, sex. all but one ESRD network region, and among black race, Hispanic ethnicity, and Native American race between the Cox and endogenous Poisson models (Table 3.6). All coefficients except for black race were underestimated by the Cox model. In both models, age appeared to have the largest effect size on risk of access infection. Vascular access infection risk being greater among younger cohorts of patients is consistent with existing literature with respect to catheter-related bloodstream infections.[97] Employment status was added post hoc, after considering its potential to confound the effects of age and institutionalization status on infection risk. It's reasonable to expect that employment impacts one's exposure to opportunities for infection, which is in part a reflection of risk related to age and institutionalization status.

The change in infection risk between models for black, Hispanic, and Native American patients, but not Asians or Pacific Islanders, may suggest differences due to race are due to differences in infection risk, rather than proxies for health care access or differences in hemodialysis access type. However, estimation of the marginal differences of rate of access infection PPY show that Black, Hispanic, and Native American patients all had approximately 3 times the infection rate PPY when estimated using the endogenous Poisson, versus a Cox model.

Relative to the region with the lowest rate of access infection, Florida consistently had the greatest rate of access infection, both unadjusted (Table 3.2) and using both modeling approaches (Table 3.4). Florida's patients had generally greater rates of catheter use, in addition to one of the lowest rates of pre-ESKD nephrology care (Table 3.2); even so, living in Florida

still substantially increase the risk of vascular access infection. From a policy perspective, it is worth investigating whether this variability is due to variation in modifiable risk factors, such as infection control practices at hemodialysis centers to reduce the rate of access infection. Patients with common CKD etiologies that would have been treated pre-ESKD, such as diabetes or hypertension, may be of particular interest when considering how to improve rates of pre-ESKD nephrology care. For instance, if the aforementioned patient groups were treated at large Floridian health systems, it would be useful to understand their referral rate to nephrologists when patients present with low glomerular filtration rates, indicating advanced CKD. This demonstrates how approaches that address nonrandom assignment to treatment or proxies of health care access, such as an endogenous Poisson, are useful in clarifying what additional questions need to be addressed to develop effective policies. These approaches are particularly salient when access to care may be biasing variability between different patient groups within different regions.

*Methicillin-resistant Staphylococcus aureus (MRSA)*

The analysis of likelihood of MRSA among access infection patients (Table 3.5) showed a substantially increased risk of access infection among institutionalized patients (i.e., patients residing in a nursing home or assisted living facility) from 2012 through 2015, 2016 and 2017 patients with community infections had comparable rates to institutionalized patients. Notably, rates did not decrease meaningfully among institutionalized patients over the study period, while the national MRSA infection trends during this time period steadily declined.[126, 127] Given age-adjusted emergency department visits range from 0.38 to 0.58 PPY among the general population versus 2.6 to 3.0 PPY among the ESKD hemodialysis population,[1] one would expect the increased risk of MRSA may be due to increased inpatient encounters. However, in this study

the access infections were censored if they came after a hospitalization for reason other than vascular access infection, so the access infections among the institutionalized patients are more likely to have resulted from their nursing home or skilled living facility than from an inpatient encounter. As seen in Figure 3.3, MRSA infections among non-institutionalized patients has become comparable to institutionalized patients as of 2016, with institutionalized patients' rate of MRSA remaining fairly constant from 2012 through 2017. Further investigation is warranted to evaluate which infection control practices may be lacking in hemodialysis patients' care at nursing homes and assisted living facilities.

*Implications for Policy Making*

This study reinforces the notions set forth in Chapter 2 regarding the benefit of evaluating variation in health care outcomes with consideration of nonrandom assignment to past health care and current treatments. The present study further advances the case that estimates of the benefit of specialty care, health insurance coverage, and different treatment options may be underestimated, or overestimated, depending on the relevant health care access context.

This study also demonstrates the value of improving risk assessment through modeling approaches that address endogeneity. One of the primary takeaways of this study was that after from age, access type has the second largest impact of access infection, but only among institutionalized patients. However, this insight was not evident in a single-equation approach with a Cox model. Because of the high rate of tunneled catheter use among institutionalized patient populations and nonrandom assignment to tunneled catheter versus permanent access, which partially depends on pre-ESKD nephrology care, single equation estimations of the impact of institutionalization on vascular access infection mistake variation in selection into THC as a result of factors that are associated with both access type and vascular access infection.

Despite patients with a drug abuse history accounting for less than 1% of the patient population, after institutionalization status and age, history of drug dependence or opioid abuse had the second largest effect size (0.07 PPY, 95% CI 0.0423,0.0820; HR 1.89, 95% CI 1.39, 2.56), suggesting intravenous drug users with ESKD may be using their access for recreational use. Further investigation revealed the unadjusted catheter infection was 0.17 PPY among illicit drug users (n=1,443) versus 0.09 PPY among non-illicit drug users (n=232,250); whereas when using a permanent access, the difference between the groups was 0.03 PPY among illicit drug users (n=369) and 0.02 PPT among non-illicit drug users (n=80,464). This suggests that it's catheters in particular that are of greater infection risk for illicit drug users. However, it is likely that either because of the existing interaction in the outcome equation or the very small size of the drug using cohort, there was no interaction between drug use and access type (p= 0.741). Despite the lack of interaction, the unadjusted rates clearly suggest that it's a catheter rather than permanent access that increases the risk of access infection for drug users. This is may be because the catheter is very easy to inject drugs with. ESKD drug users have likely observed that a substantial amount of pressure is required to control bleeding from a permanent access if they were to use it outside of hemodialysis; if one were injecting heroin, it would be somewhat more dangerous to use recreationally versus a catheter. It is more likely injecting recreational drugs into a permanent access would lead to uncontrolled bleeding while impaired by opioids or other substances, leaving the patient unable to appropriately respond.

Though the literature does discuss the potential for issues related to vascular access creation among patients with a history of intravenous drug use,[128-132] there are not any studies addressing the use of catheters and permanent access for recreational intravenous drug use. In a personal discussion with a vascular surgeon practicing in southern California, the surgeon

anecdotally reported that the use of hemodialysis access for recreational drug use with nonsterile implements was a common cause of vascular access infection among their patients.[133] Considering the substantial literature on the benefits of harm reduction policies related to intravenous drug use,[134-137] these findings suggest it may be beneficial to consider advising patients with a documented history of opioid or illicit drug abuse regarding best practices if they were to use their catheter or permanent access for recreational drug use.

Though Native Americans had the greatest unadjusted (Table 3.2) and adjusted (Table 3.4) rates of vascular access infection, they had the lowest unadjusted and adjusted likelihoods of vascular access infections being related to MRSA (Table 3.6). Though intuition may suggest this is related to where Native Americans may live, namely on reservations, there are reasons why this may not be the case: (1) only 22% of Native Americans live on reservations,[138] (2) the regressions have some degree of adjustment region via ESRD network, and (3) the regressions have adjustment for rurality. However, Indian Health Services treat nearly half (45%) of Native Americans.[138, 139] The difference directions of rates of infection and MRSA relative to other races suggest that Native Americans in their first year of ESKD experience differences in exposure, rather than behaviors (e.g., hygiene practices). This difference requires more directed exploration using Indian Health Services retrospective institutional data to clarify how the etiology of vascular access infections and infection risk may differ among Native Americans with ESKD.

*Institutionalized Living, Infection Risk, and Potential Solutions*

One of the key takeaways from this study was the substantially increased risk ESKD patients have for vascular access infection if they reside in a skilled nursing facility or nursing home (Table 3.3 and Table 3.4), with a greater than expected risk of access infection for patients with a permanent access. This study's purpose and framing was not focused on an

institutionalized population, which generally makes up a smaller portion of ESKD patients, only making up 11.5% (n=36,268) of this study's population. However, the findings strongly suggest that this population is in particular need of policy interventions to reduce access infections. It's not necessarily appropriate to attempt to increase the rate of catheter use since catheters typically carry increased risks of infection and complication, meaning policy interventions to improve access outcomes for institutionalized patients should focus directly on infection prevention and early identification of potential complication and/or infection risk.

Aside from evaluation of expected infection control practices, some important questions to explore regarding the role of facility-level factors in vascular access infection include: Where are institutionalized patients receiving their dialysis? Which comorbidities have a stronger causal relationship with infection among institutionalized patients (e.g., nursing home patients requiring feeding tube are at a much greater risk for pneumonia, local infections, and soft tissue infections[119])? What are the average number of staff members per resident during the day and during the night? What are the median weekly hours worked by registered nurses (as opposed to lower-level technicians) at the nursing home during a given year?

Though the aforementioned research questions are suitable for retrospective analysis, a prospective analysis would be best served by focusing on what infection control practices exist at each residential nursing facility and evaluate the quality of care received by hemodialysis patients in residential facilities. A narrative review of 327 publications that studied omissions of care in long-term care settings identified 46 articles that identified omissions of care that increased the incidence of infections;[140] among these articles, omissions that contributed to risk of infection included, "Lack of infection preventionist on staff; Lack of vaccination among staff and residents; Lack of routine assessment; Lack of implementation of infection control practices

due to boundaries related to daily workflow, collaboration, and technological infrastructure; Lack of supplementation to address low levels of zinc and vitamins E and D; Poor hygiene practices; [and] Lack of environmental infection control practices (surface cleaning)."[140] The omissions of care identified by Ogletree et al. would be an appropriate starting point for developing an evaluation or implementation study to determine which of the common care omissions pose the greatest risk to ESKD patients.

*Temporal Variability in Hospitalization for Access Infection*

A trend worth noting is the decrease in the absolute and adjusted rates of vascular access infection across years (Table 3.1, Table 3.4, & Appendix 6). Potential new vascular access codes were reviewed as a reason for the decline, as well as evaluation of bias due to exclusion criteria, or bias due to exclusion of catheter infections among those without a hemodialysis catheter. None of these issues proved to be a factor. However, Appendix 6 reveals that in recent years there is a much higher rate of change in access type during the first year, as well as a decrease in the proportion of patients censored for no hospitalization or competing events in their first year of hemodialysis. This suggests the decrease in access infection is at least partially due to censoring due to changes in access. The USRDS annual data report indicates rates of hospitalization for vascular access infection are stable across this time, but are not censoring for potentially competing events.[141] This suggests that there isn't a temporal trend in infection rate, but rather a change in how early in their ESKD people are changing access type. However, since the majority of patients initiate hemodialysis with a catheter and the majority of ESKD population is on permanent access,[141] this is a favorable outcome, because it suggests in recent years, Medicare patients on tunneled catheters have been switching to permanent access earlier than in previous years.

**Limitations**

This study's variables and exclusion criteria have been defined such that the limitations, as described below, would generally underestimate the true rate of vascular access infection, rather than overestimate the true rate of vascular access infections at the population level. The benefit of this more conservative approach is the findings can be used to define the minimum expected benefit from policies to reduce access infection that target different patient groups or geographic regions.

The primary limitation of this study is the exclusion of Medicare patients with at less than 1 year of pre-ESKD enrollment. The pre-ESKD enrollment was necessary to identify both pre-ESKD nephrology care and any access creation procedures. This limits the generalizability of these findings somewhat, with the population biased towards ESKD patients who obtained their Medicare entitlement via age (65+) or disability (i.e., received Social Security Disability Insurance for at least 24 months), rather than ESKD. Though most United States studies of hospitalization outcomes among ESKD patients also have a similar limitation, the present study does introduce some additional bias from requiring a year of enrollment to properly capture pre-ESKD nephrology care. Access creation doesn't require a full year of prior enrollment, but given the importance of correctly defining pre-ESKD nephrology care that was highlighted in Chapter 2, it is reasonable to choose an approach that uses more accurate data at the cost of external validity of the findings. Gaining greater insight into the relationships underlying vascular access infection was a greater priority for this study than ensuring the findings were generalizable to all United States ESKD patients.

This study only focuses on the first access and analysis time stops after the first access infection (i.e., there are no repeated events) and after changes in access type. As mentioned in the

methodology section, pre-ESKD nephrology care is one of the most important variables in predicting first access type, but it should only have an effect on the index access, not subsequent accesses. To accommodate changes in access, a separate equation predicting access that doesn't include pre-ESKD nephrology care would be necessary for subsequent accesses only, which is not feasible. During a vascular access infection hospitalization, irrespective of if the access is a catheter or permanent access, many patients will have a new catheter placed at a different site to continue dialysis, complicating the measurement of access type's influence on access infection after the first access infection hospitalization. If these shortcomings regarding censoring time resulted in bias, it's more likely that infection rates are overestimated rather than underestimated, due to premature censoring and the end of observation at 365 days post-dialysis initiation.

There are also other potential sources of bias that could reduce the estimated rate of access infections due to shortcomings in the definition of access infection. For instance, it may be that the vascular access infection diagnosis code was not coded as the primary diagnosis, but rather sepsis was coded as the primary definition and vascular access infection was coded as a secondary definition. Relatedly, it could also be the case that the infection type is misidentified in the primary diagnosis, but is correctly identified as an access infection in subsequent diagnostic code positions (i.e., DX1 through DX26; with primary diagnosis being a separate variable). However, any bias due to this error in definition is unlikely to systematically bias the coefficients, though the potentially for this bias would cause underreporting of vascular access infections in com circumstances where sepsis was the primary diagnosis.

This study defines changes in access type using CROWNWeb, which has time measurement at the level of month, but not date. As discussed in the methods, there should generally be a uniform distribution of access change dates across the 28 to 30 days that make up

every month. This means error would be most evenly distributed if the 15th of each month was the assumed date of access change. Medicare claims were explored as alternate sources of access type changes, but several assumptions about claim meanings regarding access creation, catheter placement, and catheter removal would be required, which would also create uncertainty. This study chose to pursue an access change definition that introduced a single source of uncertainty, rather than multiple sources.

The limitation that would be the most beneficial to pursue in subsequent studies is regarding variability related to patients' dialysis facilities. In the context of this study, it would be necessary to use a structural equation model to accommodate a random effect only at the level of access infection, with no random effect for access type (i.e., tunneled catheter versus permanent access).

The primary methodological reason a structural equation model was not undertaken was the underlying goal of these studies is to demonstrate the issues related to endogenous independent variables, which is an especially salient issue within health care outcomes research. Adding an additional layer of complexity (e.g., a 3-category endogenous variable, an endogenous variable in the equation estimating the endogenous variable) may improve estimates, but it does not increase replicability of the findings or methodological approach.

To briefly explore the effect of dialysis facility on access infection, which is not used in the primary analysis, a single-equation Weibull model was calculated with the last dialysis facility listed in CROWNWeb before censoring or an event used as the random-effect. Though we can expect the fixed effects to be biased in this model due to the endogeneity related to access type, the intraclass correlation of dialysis facility would probably not be substantially impacted by this biased modeling approach. The intraclass correlation indicated 3.7% of the variation in

risk of access infection is attributable to hemodialysis care facility. This indicates further analysis focusing on characteristics of dialysis facilities may be appropriate.

## Tables

Table 3.1. Patient Characteristics, Rates of Tunneled Catheter, and Rates of Hospitalization for Vascular Access Infection

| | Study Sample N=314,526 | THC Rate | Hospitalization for VA Infection | |
|---|---|---|---|---|
| Variable | Column % | Row % | Rate Per Patient Year | 95% CI |
| Index Access | | | | |
| AV[F/G] | 80,833 (25.7) | N/A | 0.0176 | [0.0165-0.0188] |
| THC | 233,693 (74.3) | N/A | 0.0889 | [0.087-0.0909] |
| Hospitalized for VA Infection | | | | |
| No Hospitalizations | 305,370 (97.1) | 73.8 | N/A | |
| Hospitalized for VA Infection | 9,156 (2.9) | 90.2 | N/A | |
| Sex | | | | |
| Male | 177,572 (56.5) | 73.0 | 0.0598 | [0.0582-0.0615] |
| Female | 136,954 (43.5) | 75.9 | 0.0690 | [0.067-0.0712] |
| Age at first ESKD Service | | | | |
| 18-29 | 856 (0.3) | 77.9 | 0.1673 | [0.1293-0.2164] |
| 30-49 | 12,621 (4.0) | 74.4 | 0.1142 | [0.1056-0.1235] |
| 50-64 | 53,413 (17.0) | 73.9 | 0.0760 | [0.0726-0.0795] |
| 65-79 | 177,994 (56.6) | 73.7 | 0.0570 | [0.0554-0.0587] |
| 80+ | 69,642 (22.1) | 76.2 | 0.0614 | [0.0587-0.0643] |
| Race | | | | |
| Non-Hispanic White | 193,207 (61.4) | 74.4 | 0.0601 | [0.0585-0.0618] |
| Non-Hispanic Black | 74,042 (23.5) | 73.4 | 0.0699 | [0.0671-0.0727] |
| Hispanic | 32,736 (10.4) | 76.6 | 0.0729 | [0.0688-0.0773] |
| Asian | 10,350 (3.3) | 71.1 | 0.0553 | [0.0492-0.0621] |
| Pacific Islander | 2,011 (0.6) | 71.1 | 0.0476 | [0.0358-0.0631] |
| Native American | 2,180 (0.7) | 74.4 | 0.0760 | [0.0608-0.095] |
| Employment Status | | | | |
| Retired, Disabled, Medical Leave | 262,306 (83.4) | 74.2 | 0.0625 | [0.0611-0.0639] |
| Unemployed | 43,935 (14.0) | 76.1 | 0.0768 | [0.073-0.0807] |
| Full-Time Employment | 4,396 (1.4) | 70.3 | 0.0339 | [0.0274-0.0419] |
| Part-Time Employment | 3,671 (1.2) | 66.9 | 0.0413 | [0.0333-0.0513] |
| Student | 218 (0.1) | 77.1 | 0.0691 | [0.0329-0.1449] |
| Requires Assistance with ADL | | | | |
| No ADL Impairment | 261,711 (83.2) | 72.5 | 0.0586 | [0.0573-0.06] |
| 1+ ADL Impairments | 52,815 (16.8) | 83.2 | 0.0938 | [0.0897-0.0981] |
| Institutionalized | | | | |
| Non-Institutionalized | 278,258 (88.5) | 72.7 | 0.0587 | [0.0574-0.06] |
| Assisted Living, Nursing Home | 36,268 (11.5) | 86.4 | 0.1113 | [0.1058-0.117] |
| Obese | | | | |
| Not Obese | 190,528 (60.6) | 74.6 | 0.0582 | [0.0566-0.0598] |
| Obese | 123,998 (39.4) | 73.8 | 0.0720 | [0.0698-0.0742] |
| Diabetes Mellitus | | | | |
| No Diabetes | 122,226 (38.9) | 74.2 | 0.0594 | [0.0575-0.0615] |
| Diabetic | 192,300 (61.1) | 74.4 | 0.0664 | [0.0647-0.0682] |
| Drug Dependence | | | | |

| | | | | |
|---|---|---|---|---|
| No Drug History | 312,714 (99.4) | 74.3 | 0.0620 | [0.0646-0] |
| History of Drug or Opioid Abuse | 1,812 (0.6) | 79.6 | 0.1293 | [0.1061-0.1576] |
| Pre-ESKD Nephrology Care | | | | |
| None/Within 6 Months Pre-ESKD | 169,250 (53.8) | 80.1 | 0.0612 | [0.0595-0.0629] |
| Nephrology Care 6+ Months Pre-ESKD | 145,276 (46.2) | 67.6 | 0.0669 | [0.0649-0.0689] |
| Rural-Urban Continuum Code 2013 | | | | <0.001 |
| Metro, 1+ mil | 164,371 (52.3) | 74.3 | 0.0678 | [0.0659-0.0697] |
| Metro, 0.25-1mil | 67,120 (21.3) | 73.3 | 0.0599 | [0.0573-0.0627] |
| Metro, <0.25mil | 30,650 (9.7) | 75.0 | 0.0609 | [0.0569-0.0651] |
| Urban 20k+, Metro Adj. | 15,618 (5.0) | 75.0 | 0.0578 | [0.0525-0.0637] |
| Urban 20k+, Not Adj. | 5,112 (1.6) | 72.9 | 0.0546 | [0.046-0.0649] |
| Urban 2.5-19.9K, Metro Adj. | 17,920 (5.7) | 75.1 | 0.0630 | [0.0578-0.0687] |
| Urban 2.5-19.9K, Not Adj. | 8,713 (2.8) | 74.9 | 0.0506 | [0.0441-0.058] |
| Completely Rural, Metro Adj. | 2,505 (0.8) | 75.9 | 0.0537 | [0.0419-0.0689] |
| Completely Rural, Not Adj. | 2,517 (0.8) | 78.3 | 0.0471 | [0.0359-0.0616] |
| Year of first ESRD service | | | | |
| 2012 | 28,942 (9.2) | 69.9 | 0.0925 | [0.0873-0.0982] |
| 2013 | 51,309 (16.3) | 69.7 | 0.0865 | [0.0827-0.0905] |
| 2014 | 52,520 (16.7) | 74.1 | 0.0724 | [0.069-0.076] |
| 2015 | 57,759 (18.4) | 75.8 | 0.0688 | [0.0656-0.0721] |
| 2016 | 62,459 (19.9) | 76.7 | 0.0588 | [0.056-0.0617] |
| 2017 | 61,537 (19.6) | 76.4 | 0.0328 | [0.031-0.0348] |

Table 3.2. Hospitalization for Vascular Access Infection, Index Tunneled Catheter, Institutionalization, and pre-ESKD nephrology rates by ESRD Network Region

| | | VA Infection PPY | Index THC | Institutionalized | Pre-ESKD Nephrology |
|---|---|---|---|---|---|
| 7:Florida | N=22,593 | 0.091 | 77.7 | 12.4 | 42.7 |
| 3:New Jersey | N=10,787 | 0.077 | 75.4 | 14.0 | 53.3 |
| 10:Indiana | N=13,901 | 0.074 | 77.3 | 16.5 | 53.6 |
| 5:DC/MD/VA/WV | N=17,246 | 0.073 | 75.8 | 10.5 | 52.7 |
| 2:New York | N=20,220 | 0.071 | 74.4 | 13.8 | 38.5 |
| 4:PA/DE | N=15,441 | 0.069 | 73.1 | 13.0 | 39.9 |
| 11:MI/WI/MN/ND/SD | N=21,013 | 0.068 | 74.8 | 13.8 | 46.8 |
| 9:OH/IL/KY | N=26,247 | 0.067 | 75.1 | 15.4 | 47.4 |
| 13:LA/AR/OK | N=12,886 | 0.063 | 75.7 | 9.8 | 49.8 |
| 14:Texas | N=26,412 | 0.063 | 76.8 | 9.5 | 46.9 |
| 1:New England | N=11,031 | 0.062 | 68.0 | 11.9 | 56.2 |
| 6:NC/SC/GA | N=27,396 | 0.058 | 72.4 | 9.8 | 50.8 |
| 8:TN/AL/MI | N=18,527 | 0.057 | 72.8 | 9.0 | 46.8 |
| 15:NV/UT/WY/CO/AZ/NM | N=14,055 | 0.055 | 71.2 | 7.1 | 43.6 |
| 18:SoCal | N=21,891 | 0.053 | 75.6 | 11.1 | 32.4 |
| 12:NE/KS/IA/MO | N=12,294 | 0.052 | 76.9 | 13.5 | 51.9 |
| 17:NorCal/HI | N=13,128 | 0.044 | 70.2 | 6.1 | 41.5 |
| 16:WA/OR/ID/MT/AK | N=9,458 | 0.040 | 67.1 | 8.1 | 47.0 |

Table 3.3. Rate of Hospitalization for Vascular Access Infection Per Person-Year by Access Type and Institutionalization Status

| | | Unadjusted | | Cox Model | | | |
|---|---|---|---|---|---|---|---|
| | Sample Size | VA Infection Hosp/PPY | Marginal Diff. | VA Infection Hosp/PPY | 95% CI | Marginal Diff. | 95% CI |
| Effect By Access Type | | | | | | | |
| AV[F/G] | N=80,833 | 0.0176 | Ref. | 0.0086 | [0.0080,0.0092] | Ref. | |
| THC | N=233,693 | 0.0889 | 0.0713 | 0.0407 | [0.0398,0.0415] | 0.0321 | [0.0310,0.0332] |
| Effect By Institutionalization Status | | | | | | | |
| Non-Institutionalized | N=278,358 | 0.0587 | Ref. | 0.0277 | [0.0271,0.0283] | Ref. | |
| Assisted Living, Nursing Home | N=36,268 | 0.1113 | 0.0526 | 0.0415 | [0.0389,0.0440] | 0.0138 | [0.0111,0.0165] |
| Effect By Access Type & Institutionalization | | | | | | | |
| AV[F/G] & Non-Institutionalized | N=75,895 | 0.0161 | Ref. | 0.0073 | [0.0068,0.0078] | Ref. | |
| THC & Non-Institutionalized | N=202,363 | 0.0499 | 0.0338 | 0.0392 | [0.0383,0.0401] | 0.0319 | [0.0315,0.0323] |
| AV[F/G] & Assisted Living, Nursing Home | N=4,938 | 0.0841 | Ref. | 0.0201 | [0.0163,0.0238] | Ref. | |
| THC & Assisted Living, Nursing Home | N=31,330 | 0.1238 | 0.0397 | 0.0536 | [0.0503,0.0568] | 0.0335 | [0.0330,0.0340] |

| | | Unadjusted | | Endogenous Poisson | | | | Cox vs. E. Poisson |
|---|---|---|---|---|---|---|---|---|
| | Sample Size | VA Infection Hosp/PPY | Marginal Diff. | VA Infection Hosp/PPY | 95% CI | Marginal Diff. | 95% CI | Relative Diff. b/w Models |
| Effect By Access Type | | | | | | | | |
| AV[F/G] | N=80,833 | 0.0176 | Ref. | 0.0603 | [0.0424,0.0782] | Ref. | | - |
| THC | N=233,693 | 0.0889 | 0.0713 | 0.0808 | [0.0761,0.0855] | 0.0205 | [0.0015,0.0394] | 0.6386 |
| Effect By Institutionalization Status | | | | | | | | |
| Non-Institutionalized | N=278,358 | 0.0587 | Ref. | 0.0636 | [0.0588,0.0684] | Ref. | | - |
| Assisted Living, Nursing Home | N=36,268 | 0.1113 | 0.0526 | 0.1543 | [0.1242,0.1845] | 0.0907 | [0.0632,0.1183] | 6.5725 |
| Effect By Access Type & Institutionalization | | | | | | | | |
| AV[F/G] & Non-Institutionalized | N=75,895 | 0.0161 | Ref. | 0.0430 | [0.0313,0.0547] | Ref. | | - |
| THC & Non-Institutionalized | N=202,363 | 0.0499 | 0.0338 | 0.0750 | [0.0705,0.0796] | 0.0320 | [0.0249,0.0392] | 1.0031 |
| AV[F/G] & Assisted Living, Nursing Home | N=4,938 | 0.0841 | Ref. | 0.2022 | [0.1222,0.2822] | Ref. | | - |
| THC & Assisted Living, Nursing Home | N=31,330 | 0.1238 | 0.0397 | 0.1278 | [0.1153,0.1402] | -0.0744 | [-0.142,-0.0069] | -2.2209 |

Table 3.4. Marginal Differences in Rate of Vascular Access Infection Per Person Year by Modeling Approach

| | Cox Model | | | Endogenous Poisson | | |
|---|---|---|---|---|---|---|
| | Infection Rate | 95% CI | p-value | Infection Rate | 95% CI | p-value |
| THC (vs. AV[F/G]) | 0.0321 | [0.0310,0.0332] | <0.001 | 0.0205 | [0.0015,0.0394] | 0.0342 |
| Assisted Living, Nursing Home (vs Not) | 0.0138 | [0.0111,0.0165] | <0.001 | 0.0907 | [0.0632,0.1183] | <0.001 |
| Age | | | | | | |
| 18-29 | | Reference | | | Reference | |
| 30-49 | -0.022 | [-0.0420,-0.0020] | 0.0312 | -0.1303 | [-0.2437,-0.0169] | 0.0243 |
| 50-64 | -0.0387 | [-0.0584,-0.0190] | <0.001 | -0.1955 | [-0.3087,-0.0824] | <0.001 |
| 65-79 | -0.0453 | [-0.0650,-0.0256] | <0.001 | -0.2177 | [-0.3311,-0.1043] | <0.001 |
| 80+ | -0.0452 | [-0.0650,-0.0255] | <0.001 | -0.2159 | [-0.3294,-0.1025] | <0.001 |
| Female (vs Male) | 0.0017 | [0.0005,0.0030] | 0.006 | 0.007 | [0.0027,0.0113] | 0.0013 |
| Race | | | | | | |
| Non-Hispanic White | | Reference | | | Reference | |
| Non-Hispanic Black | 0.0013 | [-0.0002,0.0029] | 0.0922 | 0.0014 | [-0.0037,0.0065] | 0.595 |
| Hispanic | 0.006 | [0.0036,0.0085] | <0.001 | 0.0212 | [0.0124,0.0301] | <0.001 |
| Asian | 0.0056 | [0.0013,0.0098] | 0.0099 | 0.0163 | [0.0018,0.0307] | 0.0271 |
| Pacific Islander | 0 | [-0.0081,0.0080] | 0.9918 | -0.0046 | [-0.0293,0.0202] | 0.7168 |
| Native American | 0.0091 | [0.0004,0.0177] | 0.0392 | 0.0353 | [0.0009,0.0697] | 0.0441 |
| Employment Status | | | | | | |
| Retired, Disabled, Medical Leave | | Reference | | | Reference | |
| Unemployed | 0.0021 | [0.0003,0.0039] | 0.0226 | 0.0078 | [0.0015,0.0142] | 0.0159 |
| Full-Time Employment | -0.0118 | [-0.0156,-0.0080] | <0.001 | -0.033 | [-0.0443,-0.0217] | <0.001 |
| Part-Time Employment | -0.0074 | [-0.0122,-0.0026] | 0.0023 | -0.0225 | [-0.0368,-0.0081] | 0.0021 |
| Student | -0.0031 | [-0.0225,0.0163] | 0.7551 | -0.0128 | [-0.0745,0.0490] | 0.6857 |
| ESRD Network Region | | | | | | |
| 1:New England | 0.0112 | [0.0063,0.0161] | <0.001 | 0.032 | [0.0176,0.0464] | <0.001 |
| 2:New York | 0.0103 | [0.0062,0.0143] | <0.001 | 0.0361 | [0.0237,0.0485] | <0.001 |
| 3:New Jersey | 0.0126 | [0.0077,0.0174] | <0.001 | 0.0441 | [0.0282,0.0600] | <0.001 |
| 4:PA/DE | 0.0104 | [0.0062,0.0147] | <0.001 | 0.0354 | [0.0223,0.0484] | <0.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 5:DC/MD/VA/WV | 0.0115 | [0.0073,0.0156] | <0.001 | 0.0433 | [0.0296,0.0570] | <0.001 |
| 6:NC/SC/GA | 0.0062 | [0.0025,0.0099] | 0.0012 | 0.022 | [0.0113,0.0327] | <0.001 |
| 7:Florida | 0.0172 | [0.0131,0.0213] | <0.001 | 0.0671 | [0.0523,0.0820] | <0.001 |
| 8:TN/AL/MI | 0.0056 | [0.0016,0.0096] | 0.006 | 0.0216 | [0.0098,0.0333] | <0.001 |
| 9:OH/IL/KY | 0.0088 | [0.0051,0.0126] | <0.001 | 0.0321 | [0.0207,0.0436] | <0.001 |
| 10:Indiana | 0.01 | [0.0056,0.0143] | <0.001 | 0.0387 | [0.0246,0.0528] | <0.001 |
| 11:MI/WI/MN/ND/SD | 0.0102 | [0.0062,0.0142] | <0.001 | 0.0353 | [0.0231,0.0476] | <0.001 |
| 12:NE/KS/IA/MO | 0.0021 | [-0.0021,0.0062] | 0.3245 | 0.0122 | [0.0001,0.0243] | 0.0481 |
| 13:LA/AR/OK | 0.0079 | [0.0035,0.0123] | <0.001 | 0.0303 | [0.0166,0.0440] | <0.001 |
| 14:Texas | 0.0044 | [0.0007,0.0081] | 0.0184 | 0.019 | [0.0084,0.0296] | <0.001 |
| 15:NV/UT/WY/CO/AZ/NM | 0.0051 | [0.0010,0.0092] | 0.0158 | 0.0184 | [0.0065,0.0304] | 0.0025 |
| 16:WA/OR/ID/MT/AK | | Reference | | | Reference | |
| 17:NorCal/HI | 0.0001 | [-0.0040,0.0041] | 0.9697 | 0.0032 | [-0.0078,0.0142] | 0.567 |
| 18:SoCal | 0.0006 | [-0.0031,0.0043] | 0.7511 | 0.0077 | [-0.0026,0.0179] | 0.144 |
| Year | | | | | | |
| 2012 | | Reference | | | Reference | |
| 2013 | -0.0026 | [-0.0060,0.0007] | 0.1265 | -0.0096 | [-0.0218,0.0027] | 0.1264 |
| 2014 | -0.012 | [-0.0152,-0.0088] | <0.001 | -0.0375 | [-0.0492,-0.0258] | <0.001 |
| 2015 | -0.0144 | [-0.0175,-0.0113] | <0.001 | -0.0436 | [-0.0551,-0.0321] | <0.001 |
| 2016 | -0.0193 | [-0.0223,-0.0162] | <0.001 | -0.0566 | [-0.0680,-0.0452] | <0.001 |
| 2017 | -0.0314 | [-0.0342,-0.0285] | <0.001 | -0.0902 | [-0.1021,-0.0783] | <0.001 |
| Median Income in Zip Code | -0.0005 | [-0.0009,-0.0002] | 0.0056 | -0.0019 | [-0.0031,-0.0006] | 0.003 |
| Diabetic (vs not) | 0.0014 | [0.0001,0.0027] | 0.0324 | 0.0033 | [-0.0011,0.0076] | 0.1391 |
| Obese (vs not) | 0.0055 | [0.0041,0.0068] | <0.001 | 0.0194 | [0.0146,0.0241] | <0.001 |
| 1+ ADL Impairments (vs No Impairment) | 0.0054 | [0.0035,0.0074] | <0.001 | 0.0257 | [0.0181,0.0333] | <0.001 |
| History of Drug or Opioid Abuse (vs None) | 0.0153 | [0.0062,0.0245] | 0.001 | 0.063 | [0.0222,0.1037] | 0.0024 |
| County Urban-Rural Code | | | | | | |
| Metro, 1+ mil | | Reference | | | Reference | |
| Metro, 0.25-1mil | -0.0037 | [-0.0054,-0.0021] | <0.001 | -0.0136 | [-0.0192,-0.0080] | <0.001 |
| Metro, <0.25mil | -0.0043 | [-0.0065,-0.0021] | <0.001 | -0.0132 | [-0.0205,-0.0058] | <0.001 |
| Urban 20k+, Metro Adj. | -0.0061 | [-0.0089,-0.0034] | <0.001 | -0.0199 | [-0.0289,-0.0109] | <0.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Urban 20k+, Not Adj. | -0.0045 | [-0.0094,0.0004] | 0.0691 | -0.0147 | [-0.0307,0.0014] | 0.073 |
| Urban 2.5-19.9K, Metro Adj. | -0.0042 | [-0.0069,-0.0014] | 0.0027 | -0.012 | [-0.0213,-0.0027] | 0.0111 |
| Urban 2.5-19.9K, Not Adj. | -0.0094 | [-0.0127,-0.0060] | <0.001 | -0.0289 | [-0.0396,-0.0183] | <0.001 |
| Completely Rural, Metro Adj. | -0.0084 | [-0.0144,-0.0025] | 0.0056 | -0.0258 | [-0.0446,-0.0070] | 0.0071 |
| Completely Rural, Not Adj. | -0.0121 | [-0.0175,-0.0067] | <0.001 | -0.0382 | [-0.0538,-0.0227] | <0.001 |

Table 3.5. Proportion of MRSA Infections Among Patients with Vascular Access Infection by Patient Characteristics

| | **Unadjusted** | **Adjusted Estimated Difference** | | |
|---|---|---|---|---|
| | Probability | Prob. Diff. | 95% CI | P-value |
| Institutionalized*** | | | | |
| Non-Institutionalized | 0.281 | | Reference | |
| Assisted Living, Nursing Home | 0.369 | 0.092 | [0.065,0.118] | 0 |
| Year of Access Infection*** | | | | |
| 2012 | 0.261 | | Reference | |
| 2013 | 0.234 | -0.028 | [-0.060,0.004] | 0.0875 |
| 2014 | 0.215 | -0.047 | [-0.079,-0.015] | 0.0042 |
| 2015 | 0.29 | 0.028 | [-0.005,0.062] | 0.093 |
| 2016 | 0.388 | 0.127 | [0.092,0.161] | 0 |
| 2017 | 0.426 | 0.16 | [0.121,0.199] | 0 |
| Age at first ESKD Service* | | | | |
| 18-29 | 0.379 | | Reference | |
| 30-49 | 0.328 | -0.055 | [-0.185,0.075] | 0.4046 |
| 50-64 | 0.286 | -0.109 | [-0.235,0.018] | 0.0921 |
| 65-79 | 0.29 | -0.11 | [-0.236,0.015] | 0.085 |
| 80+ | 0.308 | -0.089 | [-0.216,0.038] | 0.1683 |
| Sex*** | | | | |
| Male | 0.305 | | Reference | |
| Female | 0.285 | -0.021 | [-0.040,-0.003] | 0.0238 |
| Race*** | | | | |
| Non-Hispanic White | 0.309 | | Reference | |
| Non-Hispanic Black | 0.3 | -0.003 | [-0.026,0.020] | 0.7742 |
| Hispanic | 0.248 | -0.058 | [-0.088,-0.029] | 0.0001 |
| Asian | 0.244 | -0.073 | [-0.124,-0.022] | 0.0051 |
| Pacific Islander | 0.208 | -0.121 | [-0.227,-0.015] | 0.0249 |
| Native American | 0.195 | -0.135 | [-0.217,-0.053] | 0.0013 |
| ESRD Network | | | | |
| 1:New England | 0.355 | | Reference | |
| 2:New York | 0.287 | -0.061 | [-0.124,0.002] | 0.058 |
| 3:New Jersey | 0.261 | -0.088 | [-0.157,-0.019] | 0.012 |
| 4:PA/DE | 0.237 | -0.108 | [-0.172,-0.043] | 0.001 |
| 5:DC/MD/VA/WV | 0.336 | -0.018 | [-0.083,0.047] | 0.5923 |
| 6:NC/SC/GA | 0.301 | -0.051 | [-0.113,0.011] | 0.1057 |
| 7:Florida | 0.273 | -0.066 | [-0.126,-0.006] | 0.0308 |
| 8:TN/AL/MI | 0.308 | -0.041 | [-0.107,0.025] | 0.2236 |
| 9:OH/IL/KY | 0.295 | -0.06 | [-0.121,0.001] | 0.0547 |
| 10:Indiana | 0.255 | -0.102 | [-0.167,-0.037] | 0.0022 |
| 11:MI/WI/MN/ND/SD | 0.301 | -0.06 | [-0.122,0.003] | 0.0626 |

| | | | | |
|---|---|---|---|---|
| 12:NE/KS/IA/MO | 0.298 | -0.051 | [-0.125,0.022] | 0.1729 |
| 13:LA/AR/OK | 0.329 | -0.027 | [-0.097,0.043] | 0.4493 |
| 14:Texas | 0.289 | -0.041 | [-0.103,0.022] | 0.2007 |
| 15:NV/UT/WY/CO/AZ/NM | 0.313 | -0.013 | [-0.085,0.058] | 0.7135 |
| 16:WA/OR/ID/MT/AK | 0.332 | -0.005 | [-0.090,0.079] | 0.9044 |
| 17:NorCal/HI | 0.323 | -0.005 | [-0.081,0.071] | 0.8952 |
| 18:SoCal | 0.3 | -0.031 | [-0.096,0.035] | 0.356 |

Unadjusted Difference: * $p<0.05$ ** $p<0.01$ ***$p<0.001$

**Chapter 4: Opioid Use for Pain Control After Hemodialysis Access Procedures**

Sub Aims & Hypotheses

- Sub Aim 1: Determine if endogeneity related to vascular access type requires a two-stage modeling approach to estimate likelihood of filled opioid prescriptions for post-operative pain control.
    - Hypothesis 1: A two-stage regression model will be necessary to account for endogeneity related to selection into either a fistula or graft; access type is expected to influence access differently depending on the characteristics that lead to the access type used.
- Sub Aim 2: Determine if there are differences in prescription of opioids for index access procedures based on access type (arteriovenous fistula [AVF] vs. arteriovenous graft [AVG]).
    - Hypothesis 1: AVF patients will have a greater likelihood of opioid prescription.
- Sub Aim 3: Determine if there are differences in prescription of opioids for index access procedures by surgeon type (vascular vs. general vs. thoracic vs. cardiac).
    - Hypothesis 1: Patients of general surgeons will have a greater likelihood of opioid prescription than patients of other surgical specialties.
    - Hypothesis 2: Patients of vascular surgeons will have a lower likelihood of opioid prescription than patients of other surgical specialties.
- Sub Aim 4: Determine the average dosage of opioids among filled opioid prescriptions.
    - Hypothesis 1: Dosages will vary by individual provider.
    - Hypothesis 2: General surgeons will prescribe the greatest dose of opioids.
- Sub Aim 5: Evaluate evidence of persistent opioid use associated with opioid prescription for index access

- Hypothesis 1: The risk of opioid use between 90- and 180-days post access will be greater among patients who filled an opioid prescription for their index access procedure.

Key Findings & Implications

- Rates of filled opioid prescription do not vary between arteriovenous graft and arteriovenous fistula (p=0.2151), and adjustment for nonrandom assignment to access type did not produce a more efficient model.
- Patients of general surgeons had 8% greater odds (95% CI 1.01,1.15) of opioid prescription relative to vascular access patients; patients of thoracic surgeons had 28% lower odds (95% CI 0.62,0.82) of opioid prescription relative to vascular access patients; and patients of cardiac surgeons had 33% lower odds (95% CI 0.53,0.80) of opioid prescription relative to vascular access patients. However, opioid dosage did not vary by surgical specialty.
- Individual surgeons account for 14% of the variability in opioid prescription and 39% of the variability in opioid dosage.
- Receiving an opioid dose of less than 30 5 milligram hydrocodone equivalents or between 30 and 59 5 milligram equivalents was not associated with an increased risk of persistent opioid use (Table 4.8). Receiving an opioid dose equivalent to 60 to 89 5 milligram hydrocodone equivalents was associated with a 23% increase in the risk of persistent opioid use (95% CI 1.03,1.47) compared to those who did not receive an opioid at access creation. Receiving an opioid dose equivalent to 90 or more 5 milligram hydrocodone equivalents was associated with a 78% increase in the risk of persistent

opioid use (95% CI 1.18,2.68) compared to those who did not receive an opioid at access creation.

- Patients with opioid or drug dependence are less likely to have an opioid prescription (OR 0.73; 95% CI 0.64,0.84), and do not have more opioids prescribed to them than those with not history of drug dependence (p=0.14). However, they have a greater risk of persistent opioid at a rate that is moderated by age; a 10-year increase in age was associated with a with a 4% decrease in the risk of persistent opioid use (95% CI 0.93,0.99) among those without a history of opioid abuse, and an increase of 22% (95% CI 1.04,1.43) for every 10 years among those with a history of opioid abuse.
- Given there are no guidelines for opioid prescription for vascular access creation and there is no conceptual reason why graft or fistula patients should receive a lower or higher dose of opioids, the variability in opioid outcomes by individual surgeon, surgeon specialty, and among patients with a history of drug or opioid dependence suggests a clear and present need for organized discussions among surgeons about appropriate opioid usage for vascular access creation.

## Introduction

Opioids are analgesic (i.e., pain relieving) medications derived from opium, having been used by humans for much of recorded history, with references to opium as far back as the Sumerian era, approximately 5,000 years ago.[142] Sumerians included opium among their crops, giving opium a name synonymous with "joy," and the poppy the name, "plant of joy."[142] Exogenous opioids act on receptors from the G protein-coupled receptor family,[143] which are typically activated by endogenous opioids for the purpose of adjusting rate of respiration in response to low oxygen levels or high carbon dioxide levels in blood.[144, 145] The binding of exogenous opioids to opioid receptors provides pain relief, as well as euphoria; however, opioids may cause nausea, vomiting, constipation, cognitive impairment, and abnormal sensitivity to painful stimuli, among other potential side effects, including depressed respiration, which is the typical cause of deaths from opioid overdose.[143, 146] Given the risk of death due to depressed respiration, the most salient side effects of opioids are the risk of abuse and addiction.[143, 147-149]

Prior to the changes in the study of pain and prescription of late opioids in the 1990s and 2000s, practices around pain management grew out of the dramatic increase in pain from injuries resulting in wars, from the United States Civil War through the Vietnam War era.[150, 151] In the 1990s, pain began to be highlighted as an important measure of patient health and wellbeing, with researchers going so far as to refer to pain as "the fifth vital sign."[152] During this era, both acute and chronic pain management guidelines developed during this time focused on pharmaceutical management of both acute and chronic pain, with the clinical groups developing guidelines often influenced by opioid manufactures, most notably, Purdue Pharma.[150, 151, 153]

Though there were circumstances in which opioids were deemed medically necessary, opioid use, particularly recreational use, was historically discouraged; the first United States law

addressing opioids, the Harrison Narcotic Control Act of 1914, being passed as a consequence of the advent of widespread recreational use of cocaine and opioids.[149, 154] Even through the 1950s, cancer patients were discouraged from opioid use until their final weeks of life.[149, 155] Beginning in the 1980s, there was a growing misconception that opioid use for pain management had a very low risk of addiction,[149, 156, 157] to the extent that the lead from an 1990 article in Scientific American, "The Tragedy of Needless Pain," extoled that, "Contrary to popular belief, the author says, morphine taken solely to control pain is not addictive. Yet patients worldwide continue to be undertreated and to suffer unnecessary agony."[158]

The enormities of many opioid-producing pharmaceutical companies and the lobbyists employed by them aside,[153] Bernard et al.'s historical review of the opioid epidemic identifies four regulatory interventions by the United States government, as well as by medical organizations and institutions, that made opioid use outside of chronic pain for oncology patients (*the following list is a direct quote from Bernard et al.*):[150]

1. "The introduction of the fifth vital sign, by the American Pain Society in 1995, the Veteran's Health Administration in 1999, and then in 2001, by the Joint Commission (responsible for certifying hospitals to receive Medicare payments) in 2001 overemphasized pain as a quantifiable measure. Subsequently, the use of pain as a vital sign was shown to not be helpful in pain control.[159]"
2. "The release of a document from the Institute of Medicine that called for high-quality medicine in which patient satisfaction was a proxy for patient experience. Achieving satisfied patients required relief of pain, even if the overall experience was acceptable. The discordance between patient satisfaction and pain relief was not fully acknowledged.[160, 161]"

3. “The creation by the Agency for Healthcare Research and Quality of the Hospital Consumer of Healthcare Providers and Systems (HCAHPS) Survey that incorporated patient satisfaction data as a proxy for quality with 3 questions related to pain in inpatients.”
4. “The requirement in 2005 by the Deficit Reduction Act for hospitals to submit the results of these surveys or incur a penalty in their reimbursement by Medicare.”

The increasing focus on pain over the 1990s and 2000s led to a dramatic increase in the prescription of opioids for pain relief, with opioid use roughly doubling both worldwide and within the United States between 2001 and 2013.[162] However, the increase in opioid prescription has risen to a level where overprescribing is a concern.[147] Even in the early stages of the opioid prescription boom, between 1999 and 2002 the increase in prescriptions ranged from 50% for oxycodone to 150% for fentanyl.[163] From 2004 to 2011 emergency room visits for oxycodone overdose have increased 220%, and overall opioid overdose emergency room visits have increased 153%.[164] By 2013, the total economic burden of prescription opioid overdose, abuse, and dependence in the United States was estimated at $78.5 billion, with approximately a third of that cost ($28.9 billion) resulting from increased health care utilization.[165]

Post-surgical pain management using opioids has come under particular scrutiny, and has been identified as a substantial source of excessive opioid prescribing.[166, 167] Within the past several years, United States Centers for Disease Control and Prevention has produced guidelines recommended conservative use of opioids and encouraged use of non-opioid analgesics.[148] A recent 2020 retrospective study of common vascular surgery procedures suggested no opioids should recommended for vascular access creation,[168] but discussion of guidelines specifically for vascular access creation is not evident in the literature.

Opioid use for major and minor surgeries have been explored, and surgery has been postulated as a mechanism that pre-disposes persistent opioid use.[166] A study of opioid use from 2009 to 2013 using commercial claims found that following 59% of upper extremity surgery procedures, patients filled an opioid prescription, with 8.8% of patients having potentially inappropriately prescribed opioids.[169] Opioid prescriptions have not been limited to major surgery; 80% were used for minor surgeries among a national cohort of commercially insured patients between 2004-2012.[170]

Studies of persistent opioid use among previously opioid naïve patients clearly convey the for potential addiction.[171-175] Among a 2013-2014 commercial claims cohort of 29,068 opioid naïve minor surgery patients and 7,109 opioid naïve major surgery patients, persistent opioid use (i.e., filled opioid prescription 90 to 180 days after surgery) was 5.9% after minor surgery and 6.4% after major surgery.[176]

In the most recent USRDS annual data report for 2016, opioid prescription among Medicare Part D enrollees with ESKD was 49.0% nationally, ranging from 36.6% to 58.6% between states.[1] Prior literature regarding opioid prescription among Medicare Part D enrollees in USRDS between 2006 and 2010 showed that more than 60% of dialysis patients had at least one opioid prescription annually, with 20% having a 90-day supply or more of opioids annually.[177] Though there isn't any causality attributed to the association, opioid prescription was associated with increased mortality, hospitalization, and withdrawal from dialysis.[177]

The literature addressing opioid use for vascular access creation is limited to four single-center studies in the United States, with no identifiable national studies of opioid use for vascular access. Janek et al.'s retrospective analysis of 86 patients undergoing vascular access procedures at a single institution found that 85% of patients received a prescription for opioids, 71% used

opioids for 2 or fewer days, and 53% reported receiving a greater number of opioid tablets than they needed to adequately control their postoperative pain.[178] Santos-Parker et al.'s retrospective analysis of 76 vascular access patients found 83% of patients received a prescription for opioids, 51% reported not using opioids, and AVG patients reported receiving a median of 15mg more total opioids than AVG patients.[179] Phair et al.'s retrospective analysis of 165 vascular access patients found much higher opioid prescription rates among inpatient vascular access patients (72% AVF & 62% AVG) than among ambulatory patients (19% AVF vs. 25% AVG).[180] Phair et al. also reported use of higher dosages in inpatients for both AVF (28 vs. 1 oral morphine equivalent) and AVG (22 oral morphine equivalents versus 2 oral morphine equivalents).[180] A brief abstract by Carnevale et al. indicated that in a single-center cohort of 85 patients, opioid prescription was compared between vascular surgeons and internal medicine physicians, stratifying by access type; vascular surgeons had lower rates of prescribing postoperative opioids among both AVF (18% vs. 66%; p=0.0001) and AVG (34% vs. 58%; p=0.0451) patients, and vascular surgeons also prescribed lower doses of opioids.[181]

The prior literature is useful for evaluating the necessity of opioids following vascular access creation, but none of the studies have strong external validity, as they were conducted within single centers. While recent literature has addressed opioid use among ESKD patients nationally and among ESKD patients among several institutions, there have been no national studies of opioid use within the context of vascular access procedures, and there are no vascular access-specific guidelines for opioid prescriptions issued by any medical organization or government body. This study seeks to explore the nature of opioid prescription for vascular access procedures among the USRDS Medicare population.

## Methods

### *Data*

This study used data from the USRDS,[1] the American Community Survey,[35] Area Health Resource Files,[36] and the Centers for Disease Control's Oral Morphine Milligram Equivalents file.[34] The USRDS patient file, Form 2728 file, provider claims, and Medicare Part D pharmaceutical claims provide patient demographics, comorbidities, access type, surgeon type, surgeon identifier, and filled opioid prescription data. Opioid codes were defined using all National Drug Code numbers for opioids given by the Centers for Disease Control's Oral Morphine Milligram Equivalents file. The definition of the household median income by zip code was supplied by the American Community Survey. Rural-urban continuum code (2013) were defined using the Area Health Resource Files. Herein, shorthand references in the results and discussion to "opioid prescription" refers specifically to filled opioid prescriptions, as prescribed but unfilled prescriptions for opioids are unmeasured by Medicare Part D claims. See Appendix 9 for variable definitions and operationalizations.

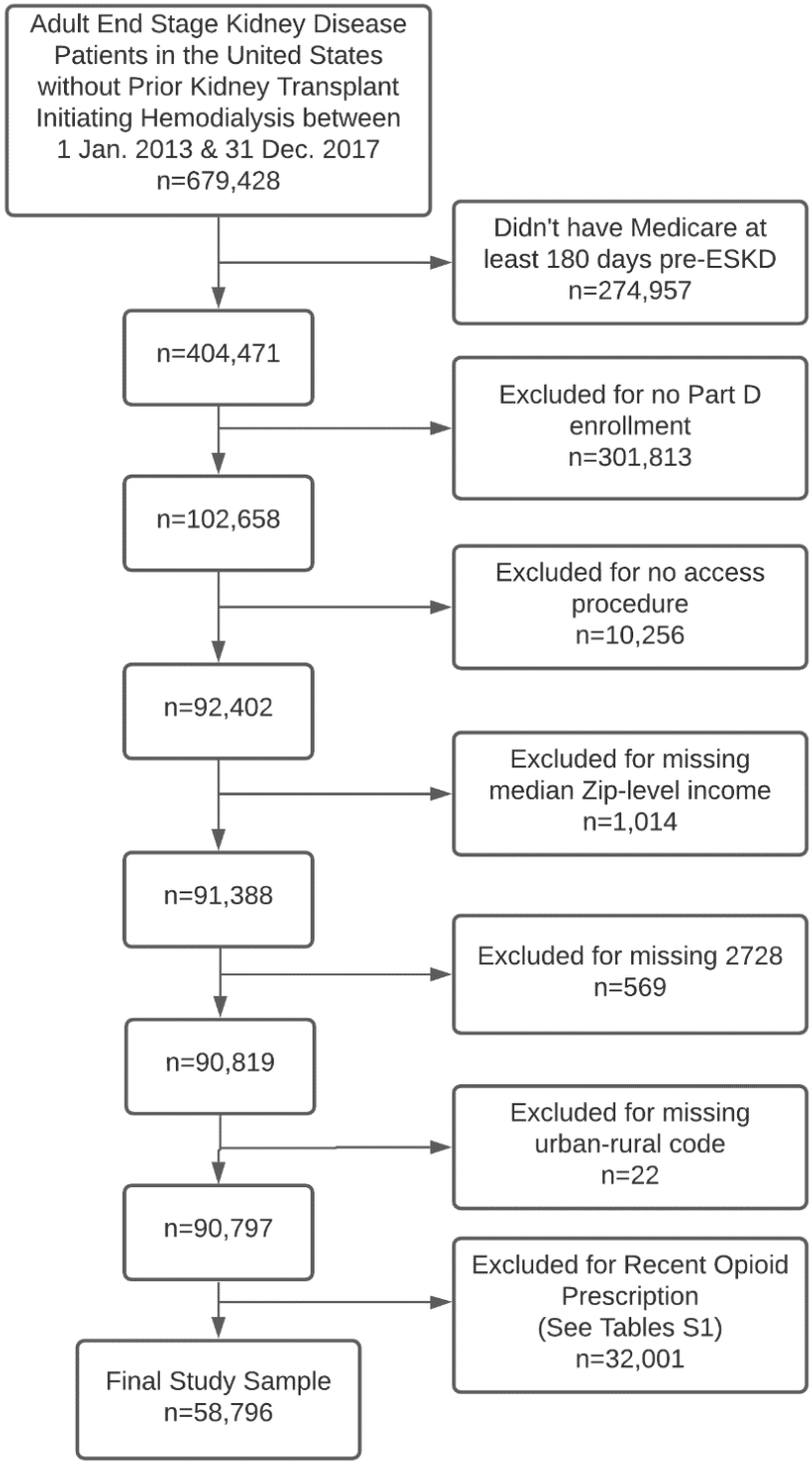
### *Study Sample Selection*

Inclusion criteria for the study population will include: (1) age 18 or older at dialysis initiation; (2) began hemodialysis at first date of end stage kidney disease without a concurrent or prior kidney transplant; (3) resident of the US, not including United States territories; and (4) initiated treatment using hemodialysis after January 1, 2013 and had an access creation surgery no later than December 31, 2017. The study was limited to an adult population for two reasons: (1) dosages are likely to vary between pediatric and adult population due to weight, and (2) the etiology and treatment of kidney disease among pediatric patients is not comparable.[25] Patients with transplants on or before the beginning of dialysis for end stage kidney disease were

excluded, given they had reached their desired outcome (i.e., kidney transplant). The population was limited to residents of the United States because residents of the Virgin Islands, Guam, and Puerto Rico would be expected to have different health disparities and health care access disparities compared to residents of the 50 states and the District of Columbia.[26] Additionally, the American Community Survey only provides median household incomes on zip codes in the United States, District of Columbia, and Puerto Rico, excluding all other territories. Since 2011 claims did not include provider specialties and the prior year's physician claims are required for patients initiating hemodialysis in 2012, January 1, 2013 was chosen as the study start date. Physician identifiers are not currently available for 2018, limiting access creation procedures to no later than December 31, 2017. However, 6 month follow up for persistent opioid use was possible given the availability of Part D pharmaceutical claims through 2018.

After applying the aforementioned inclusion criteria, 679,428 patients were identified for potential study inclusion. Patients were excluded from the study if: they were not enrolled in Medicare Parts A & B at least 180 days before hemodialysis initiation (n=274,957); they were not enrolled in Medicare Part D for the 180 days before hemodialysis initiation (n=301,813); lacking an arteriovenous graft or arteriovenous fistula procedure (n=10,256); they did not have zip-code level median household income (n=1,014); they did not have a 2728 form in USRDS (n=569); they had an unknown urban-rural county code (n=22);; or they had an opioid prescription filled in the 90 days prior to vascular access creation (n=32,001).

**Figure 4.1. Application of exclusion criteria to the end stage kidney disease cohort identified for inclusion**



To evaluate potential bias resulting from exclusion due to missing values, missingness by place (i.e., state of residence) and time (i.e., dialysis initiation year) was evaluated for the 5 exclusion criteria resulting in more than 20 exclusions. To clarify the difference between the study cohort of opioid naïve patients and recent opioid users, descriptive statistics (Appendix 10) was used to compare the two groups. This resulted in a study sample size of 58,796 patients. See Figure 4.1 for a diagram of exclusion criteria.

The exclusion criteria for at least 180 days of pre-ESKD Medicare Part A enrollment resulted in the largest number of exclusions; missingness ranged from 69% in West Virginia to 46% in the District of Columbia. Missingness was between 59% and 60% from 2013 to 2017. Though the variation over time is inconsequential, the variation by place suggests there is substantial variability in age by geography, as age is the primary reason for ESKD patients to be enrolled in Medicare at least 90 days prior to ESKD.

The exclusion criteria for at least 90 days of pre-ESKD Medicare Part D enrollment pre-ESKD and 180 days post access creation resulted in the largest number of exclusions; missingness ranged from 77% in Wisconsin to 66% in the Wyoming. Missingness was between 69% and 85% from 2013 to 2017. The variation over time suggests there may be some sampling bias in recent years, the variation by place suggests there is substantial variability in age by geography, as age is the primary reason for ESKD patients to be enrolled in Medicare Part D at least 90 days prior to ESKD.

Access type was missing for between 7% (Minnesota) and 16% (Wyoming) of patients across States. Missingness did not appear to follow a regional geographic pattern. However, the most recent years (2017) had a lower rate of access availability (80%) than previous years which had ranged from 2% to 3% between 2013 and 2016. This is due to the majority of patients

having their access creation after initiating dialysis on a catheter. The incident rate of permanent access at dialysis initiation is typically 20%, while the prevalent rate of permanent access use is about 80%.[1]

Median income, Form 2728 missingness, and urban-rural code were each missing for half a percent or less of the remaining sample. This minor amount of missingness is unlikely to cause any systemic bias.

The final exclusion criteria applied was a filled opioid prescription within 90 days prior to the first access creation. Patients with recent opioid use were excluded in order to reduce bias in opioid prescription related to the possibility the opioid was a refill. Recent opioid use was the final exclusion criteria applied. Variability in patient characteristics by recent opioid prescription is recorded in Supplemental Table 1. Patients with a history of recent opioid were more likely to have a history of drug or opioid dependence than the opioid naïve study sample (8.2% vs. 1.9%; $p<0.0001$). Women, younger patients, and less urban areas tended to have higher rates of recent opioid use. Asian patients had the lowest rate of recent opioid usage.

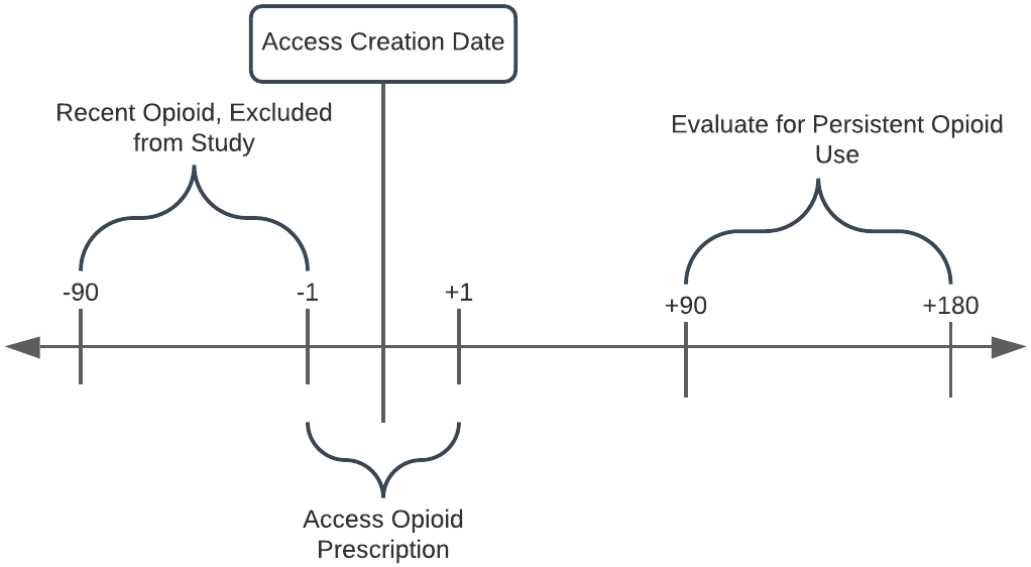
*Variable Identification*

The Centers for Disease Control's Oral Morphine Milligram Equivalents file[34] was used to identify opioid claims in the Medicare Part D files. 14,550 unique National Drug Codes were used to identify opioids. The file also provided information on drug type (e.g., hydrocodone, oxycodone, codeine, tramadol), DEA class code, and Oral Morphine Equivalence. The Medicare Part D files included the quantity dispensed, both as an absolute count and the number of days' supply. Due to the use of Medicare Part D claims to identify opioid prescriptions, this study uses prescription fill as a marker of opioid use; in other words, since Part D claims are only generated if the prescription is filled, this study cannot make statements about rates of opioid prescription,

but rather filled opioid prescriptions. Herein, any reference to this study's outcome of opioid prescription refers exclusively to filled prescriptions. Opioid dosages were converted into oral morphine equivalents per prescription to describe variability in dosage. To improve clinical understandings of dosage, dosages are expressed in the equivalent number of 5 milligrams of hydrocodone, which was the most commonly prescribed opioid.

To identify access claims, their dates of service, and surgeon type the physician line-item claims files (2012-2017) were used to identify arteriovenous fistula (AVF; 36818, 36819, 36820, 36821) and arteriovenous graft (AVG; 36830). In this analysis, AVF and AVG were defined exclusively from physician claims; access types from CROWNWeb and the 2728 forms were not considered. Each line item had a physician specialty code. Vascular surgeons (specialty code 77), general surgeons (02), thoracic surgeons (33), and cardiac surgeons (78) were identified, as they were the four most frequent provider types associated with access claims. Individual surgeons were identified as a vascular surgeon if at least one of the access claims included a vascular surgeon code; as a general surgeon if they had at least one general surgeon code but no vascular surgeon code; as a thoracic surgeon if they had at least one thoracic surgeon code but no vascular or general surgeon codes; and as a cardiac surgeon if they had at least one cardiac surgeon code but no other surgeon codes. This approach was used to account for any potential discordance in surgeon specialty within physician IDs, as 7% of surgeons had discordant specialties between their access claims prior to applying exclusion criteria.

**Figure 4.2. Opioid measurement periods for study exclusion and opioid outcomes**




To account for potential claim lag, both for hemodialysis access and opioid prescription, opioid prescriptions ranging from one day before the access procedure to one day after the access procedure were considered opioid prescriptions associated with the vascular access procedure (See Figure 4.2). Recent opioid use was defined as prescription of an opioid in the 90 days prior to the 1-day access-related opioid prescription window.

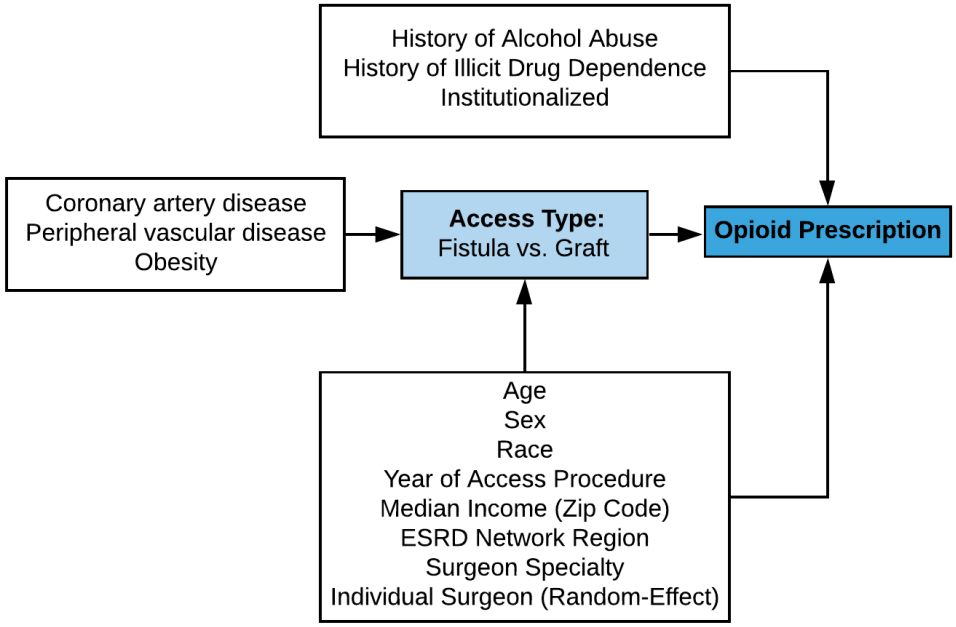
Independent variables also included sex, age, race, ESRD network region, year of access creation, median zip code-level income (from the American Community Survey), county-level urban-rural code, institutionalization status of the patient, history of illicit drug dependence, and history of alcohol dependence. History of illicit drug dependence from the 2728 form was combined with ICD indicators for a history of opioid abuse in Medicare claims prior to the first access procedure (see Appendix 9); history of alcohol dependence was similarly supplemented with history of alcohol abuse diagnostic code from claims. ESRD network region was chosen over state as the regional random effect based on AIC minimization, in which ESRD network

region proved to be superior (110,583.3 vs 110,642.7). See Appendix 9 for detailed variable definitions.

*Descriptive Tables and Statistics*

Wilcoxon rank sum tests and Kruskal-Wallis tests were used to compare skewed continuous variables between groups. T-tests and ANOVA were used to compare normal continuous variables between groups. Chi-square tests were used to compare binary and categorical variables between groups.

**Figure 4.3. Opioid prescription conceptual model: Bivariate Probit**



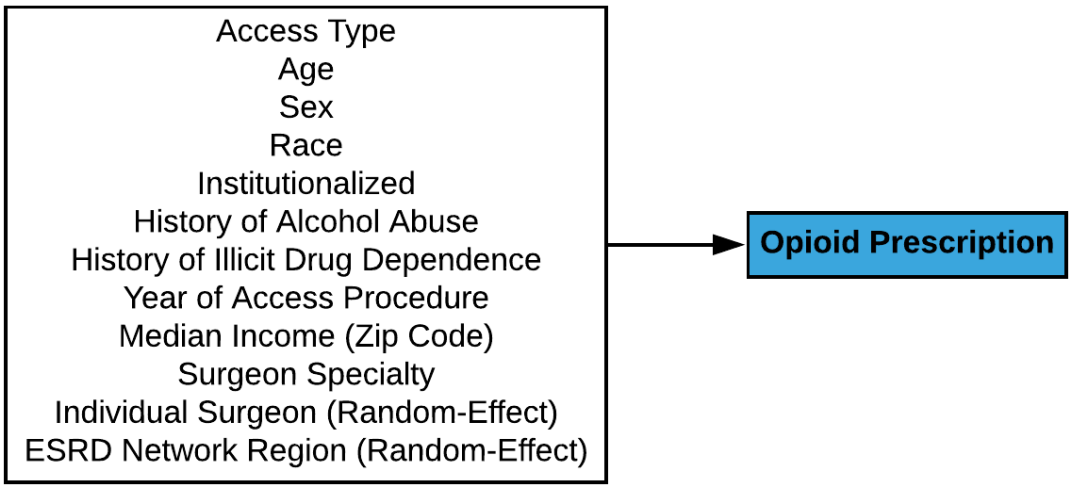

*Regression Analysis*

A recursive bivariate probit model was initially used evaluate the potential for bias related to non-random assignment of access type in estimating the adjusted likelihood of opioid prescription (Figure 4.3). The first stage, the endogenous access type equation, predicted likelihood of graft (versus fistula), and the second stage predicted the outcome, likelihood of

opioid prescription. However, the likelihood ratio test that rho ρ=0 was rejected, indicating that the endogenous equation did not produce a superior model. As described in the results and discussion, this is likely because there was not significant variation in opioid prescription by access type.

Given it was not necessary to account for non-random assignment to access type in modeling likelihood of opioid prescription, a mixed-effect logistic regression was used to model likelihood of opioid assignment, with a surgeon random effect nested within ESRD network region random effects (Figure 4.4). Without accounting for the surgeon with a random-effect, an assumption is being made that provider decision making does not play a substantial role in opioid prescription and access type, when there is evidence to the contrary for both opioid prescription[166, 177] and access type selection.[125] Intraclass correlation was used to measure the percentage of the variation in opioid prescription accounted for by ESRD network region and individual surgeons. Median odds ratios were used to describe the difference in random intercepts for individual surgeons and ESRD network regions. The random-effects' effect sizes are reported as a median odds ratio (MOR) for likelihood of filled opioid prescription for vascular access. The individual surgeon MOR may be interpreted as the median ratio of odds of opioid prescription between otherwise equivalent patients of two random surgeons.

**Figure 4.4. Opioid prescription conceptual model: Mixed Effect Logistic**




A linear mixed effects model with robust standard errors was used to explore the variability in opioid prescriptions among those who received an opioid prescription after vascular surgery. The dependent variable was number of 5 milligram tablets of opioid per prescription. ESRD network region and surgeon identifier served as random effects, with surgeon nested with ESRD network. Fixed-effects were eliminated using backward selection when $p>0.2$, starting with elimination of the coefficient with the greatest p-value. This resulted in inclusion of fixed effects for access type, sex, age, race, history of drug or opioid dependence, and institutionalization status.

A Cox proportional hazards model was used to measure the risk of persistent filled opioid use (i.e., a filled opioid prescription between 90- and 180-days post-access procedure) among those who received opioid prescription. The equation used to predict access opioid was used, with two modifications: (1) the physician identifier was not included as a random effect, and (2) the network effect was included as a fixed effect, rather than a random-effect. Observation time

was limited to 180 days post-access and was censored for any hospitalization, access procedures, kidney transplant, death, or end of Medicare Part D enrollment.

**Results**

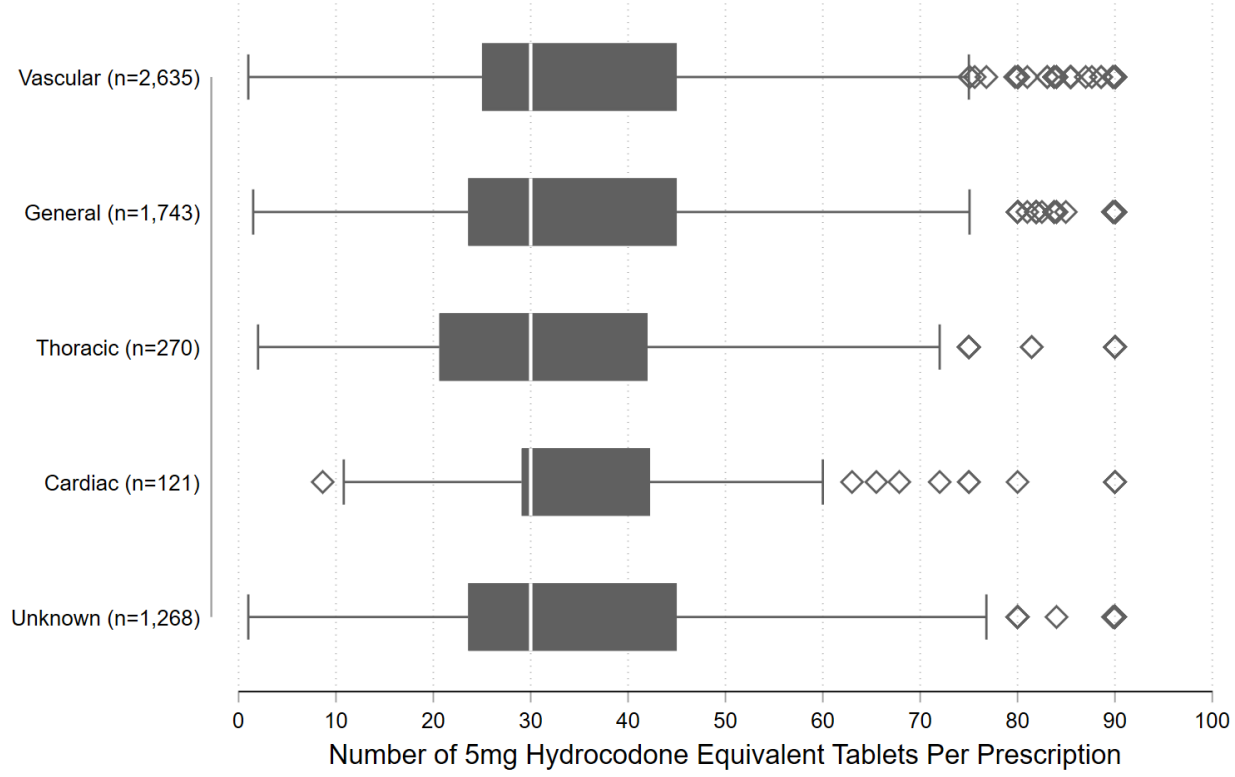
*Descriptive Statistics: Primary Analysis*

The study cohort consisted of 58,796 patients with ESKD, 38.6% (n=22,680) of whom had an opioid prescription at their first access creation (Table 4.1). The majority of patients had an AVF versus an AVG (76.4% vs. 23.6%), with the rate of opioid use being comparable between the two groups (38.5% vs 39.0%; p=0.27). The rate of opioid prescription varied significantly between surgical specialties (p<0.001), with the highest among patients of general surgeons (41.4%), followed by vascular surgeons (37.4%), thoracic surgeons (31.6%), and cardiac surgeons (30.5%). Female patients had a higher rate of opioid prescription than men (39.8% vs. 39.8%; p<0.001). Rates varied significantly by age category, with rates of 39% to 44% among patients age 18 to 49, and a lower rate of 34.8% among those 80 years of age or older (p<0.001). Rates of opioid prescription varied significantly by race (p<0.001); rates were lowest among Native Americans (36.5%) and greatest among black patients (39.4%), followed by white patients (38.7%), Hispanic patients (37%), Asians (36.8%), and Pacific Islanders (36.8%). Rates of opioid prescription were greater among patients who did not live in a nursing home or assisted living facility (40.5% vs 25.7%; p<0.001). Rates were comparable between those with and without alcohol dependence, but were significantly lower among those with a history of drug or opioid dependence versus those without (32.8% vs 38.7%; p<0.001).

A total of 6,037 surgeons treated the patient cohort (Table 4.2), of which 2,635 were vascular surgeons (55.4%), 1,743 were general surgeons (30.4%), 270 were thoracic surgeons (4.2%), 121 were cardiac surgeons (2%), and 1,258 of which were unknown (8.2%). There was a

mean of 9.7 patients per surgeon, ranging from 12 patients per surgeon among vascular surgeons to 8.7 patients per surgeon among cardiac surgeons; surgeons with an unknown type had an average of 3.8 patients per surgeon. Across all specialties and overall, the median opioid prescription was equivalent to 30 5 milligram hydrocodone tables, with little variation in the IQRs between specialties. Short acting hydrocodone medications were the most common type of opioid used across all specialties. Short acting tramadol was more common among thoracic and cardiac surgeons. See Figure 4.5 for box plots of opioid dosages by surgeon specialty. Outlier, denoted by diamonds, are all a minimum of 1.5 IQRs from the median within the surgical specialty.

**Figure 4.5. Box plot of Opioid Dosage by Surgeon Specialty**




ESRD network region 13 (Louisiana, Arkansas, Oklahoma) had the highest rate of access opioid prescription (Table 4.3; 48.5% vs. 38.6% overall); the highest rate of prescription of 60 or

more 5 milligram hydrocodone equivalents (18.5% 60-89 vs. 8.7% overall); the second highest rate of the persistent opioid use, censoring for potentially confounding events (6.6% vs. 4.8% overall); and the highest rate of persistent opioid use without censoring for potentially confounding events (28.6% vs. 15.3%). ESRD regions 16, 11, 8,17, and 12 had opioid prescription, dosage, and persistent opioid use statistics that were also relatively high compared to the overall rates. Southern California, New Jersey, and New Yorks ESRD regions had substantially lower rates of opioid use, lower dosage, and lower rates of persistent opioid use relative to all other ESRD regions. New York and New Jersey had access opioid rates of approximately 22%, and the two lowest rates of persistent opioid use censoring for potential confounding events, at 2.5% and 3.7%, respectively.

Excluding opioids that may be due to hospitalization, transplant, and vascular access creation and maintenance procedures, unadjusted persistent opioid use between 90- and 180-days post-access creation was 4.5% among those who did not receive an opioid, 5.1% among those who were prescribed 59 or fewer 5 milligram hydrocodone equivalents, 6.2% among those who were prescribed 60 to 89 hydrocodone equivalents, and 8.1% among those who were prescribed 90 or more 5 milligram hydrocodone equivalents (Table 4.4; $p<0.001$).

Persistent opioid use did not vary consistently by age, but rather declined with age among those who did not have a history of opioid or drug dependence, and increased with age among those with a history of opioid or drug dependence (Table 4.5).

*Regression Results*

In evaluating the appropriateness of a recursive bivariate probit with random-effects to account for variability in access type, the null hypothesis that $\rho = 0$ was not rejected given

p=0.6656 (ρ= -0.05; 95% CI -0.26 to 0.17); this indicates a naïve probit is superior to a recursive bivariate probit.

When fitting the mixed-effect logistic regression (Table 4.6), no covariates (or omnibus tests of significance for categorical covariates) had a p-value greater 0.2, leading to only history of alcohol dependence being dropped from the initial modeling approach. There was no significant difference in opioid prescription between graft and fistula patients (p=0.2151). Patients of general surgeons had 8% greater odds (95% CI 1.01,1.15) of opioid prescription relative to vascular access patients; patients of thoracic surgeons had 28% lower odds (95% CI 0.62,0.82) of opioid prescription relative to vascular access patients; and patients of cardiac surgeons had 35% lower odds (95% CI 0.53,0.80) of opioid prescription relative to vascular access patients.

Female patients had 1.12 times the odds of opioid prescription (95% CI 1.08,1.16) relative to males. Likelihood of opioid prescription did not vary significantly between age group. Hispanic and Asian patients had greater odds of opioid prescriptions than non-Hispanic whites, while Native Americans had lower odds of opioid prescription (OR 0.70; 95% CI 0.56,0.87), with black and Pacific Islanders having comparable likelihoods to non-Hispanic whites. Patients with a history of drug or opioid dependence has 27% lower odds of opioid prescription (95% CI 0.56,0.87). Patients in assisted living or nursing homes had about half the odds of opioid prescription, (OR 0.49; 95% CI 0.47,0.52), and had the second lowest predicted probability of opioid use of the patient subgroups (26.3% of institutionalized patients) . Patients were more likely to receive opioids counties with fewer than 1 million people versus in metropolitan counties with 1 or more million residents, with the exception of patients in completely rural counties that were not metropolitan adjacent.

The ESRD network region median odds ratio was 1.35 (95% CI 1.24,1.52) and the intraclass correlation was 0.02 (95% CI 0.01,0.05). Adjusted network-level variability is given in Figure 4.6. The surgeon median odds ratio was 1.88 (95% CI 1.82,1.94) and the intraclass correlation was 0.14 (95% CI 0.12,0.16). Adjusted surgeon-level variability is given in Figure 4.7. The c-statistic was 0.7440, indicating acceptable model discrimination.

**Figure 4.6. Adjusted probability of opioid prescription by ESRD network region**

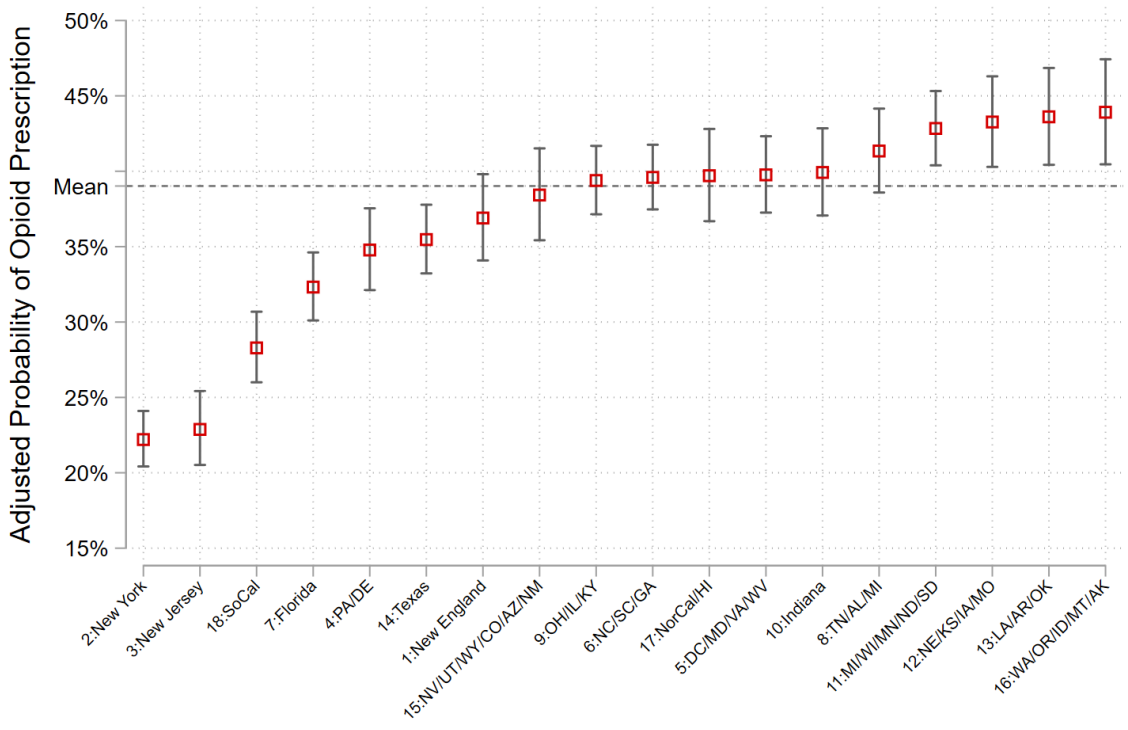
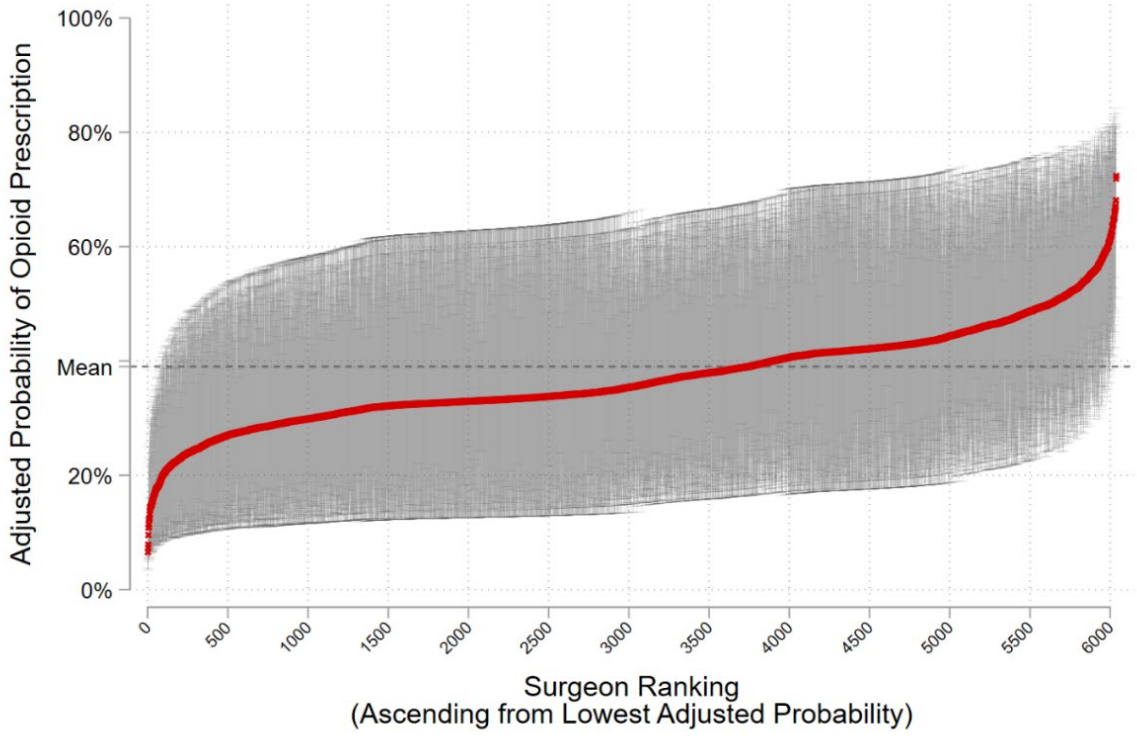


**Figure 4.7. Adjusted probability of opioid prescription by individual surgeon**




When fitting a mixed model for opioid dosage in 5 milligram hydrocodone equivalents, several variables were eliminated via backward selection due to p-values less than 0.2 and changes in AIC of at least 5. Excluded variables were median zip code level income, year, and urban-rural code. On average, graft patients had 2.05 (95% CI 1.64,2.47) more 5 milligram hydrocodone equivalents than fistula patients (Table 4.7). Patients with a history of drug or opioid dependence did not receive significantly different dose of opioids compared to those without a history of drug dependence (p=0.14). ESRD network region accounted for only 3% of the variability in opioid dosage (Figure 4.8), whereas the individual surgeon accounted for 39% of the variability in opioid dosage (Figure 4.9).

**Figure 4.8. Adjusted number of 5mg hydrocodone tablets per access opioid prescription by ESRD network region**

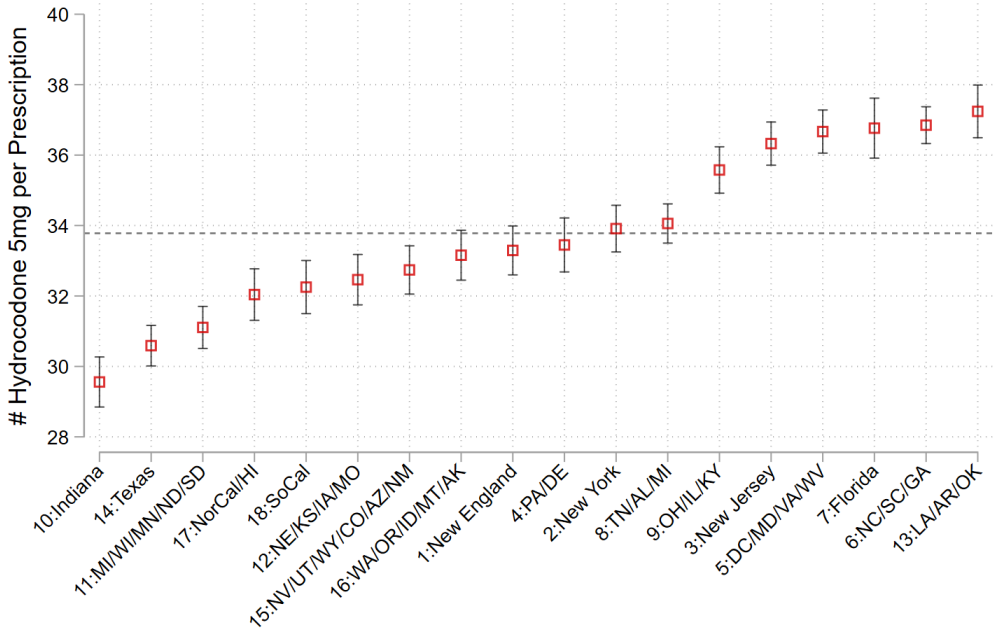
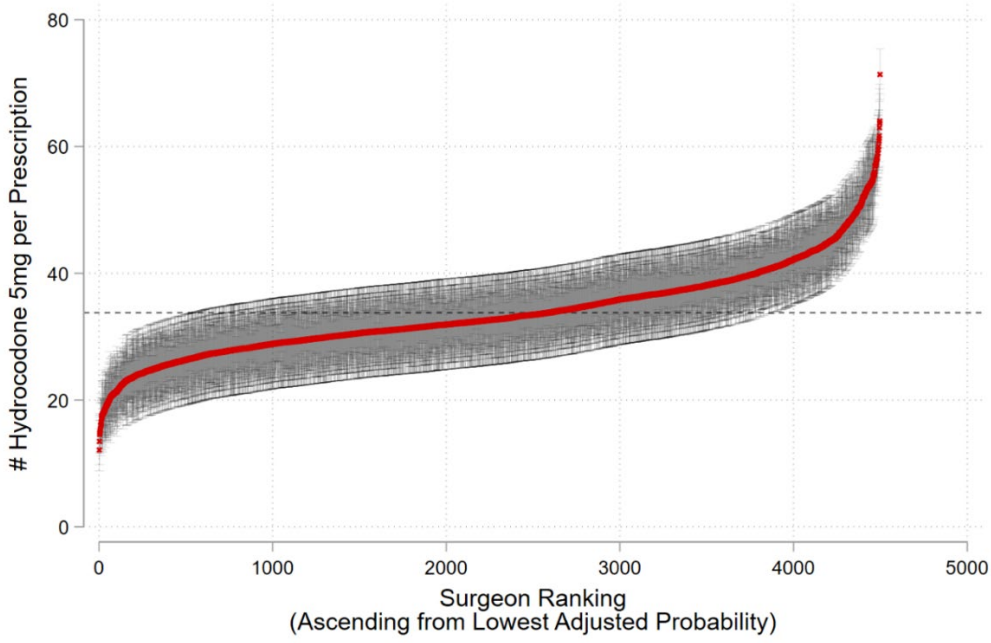



**Figure 4.9. Adjusted number of 5mg hydrocodone tablets per access opioid prescription by individual surgeon**

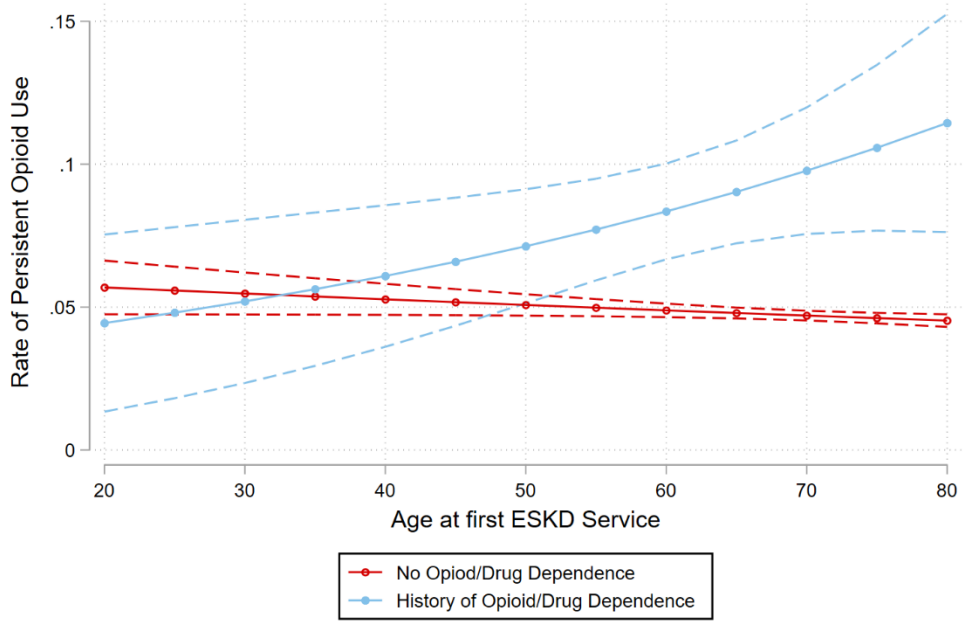


Receiving an opioid dose of fewer than thirty 5 milligram hydrocodone equivalents or between 30 and 59 5mg equivalents was not associated with an increased risk of persistent opioid use (Table 4.8). Receiving an opioid dose equivalent to 60 to 89 5 milligram hydrocodone equivalents was associated with a 23% increase in the risk of persistent opioid use (95% CI 1.03,1.47) compared to those who did not receive an opioid at access creation. Receiving an opioid dose equivalent to 90 or more 5 milligram hydrocodone equivalents was associated with a 78% increase in the risk of persistent opioid use (95% CI 1.18,2.68) compared to those who did not receive an opioid at access creation. The adjusted rate of persistent opioid use was 4.7% among those did not receive an opioid, or received an opioid dose equivalent to 59 5 milligram hydrocodone or fewer; the rate was 0.058 among those receiving a dosage of equivalent to 60 to 89 hydrocodone, and 0.083 among those who received a dosage of 90+ 5 milligram hydrocodone. Risk persistent opioid use was 1.26 times greater among those with a history of alcohol dependence (95% CI 1.11,1.44). Persistence lower among Asians (HR 0.61; 95% CI 0.48,0.77) and Pacific Islanders (HR 0.55; 95% CI 0.32,0.94) relative to non-Hispanic whites.

There was an interaction between age and history of drug or opioid abuse (Figure 4.10). While there was no difference in level between those with and without a history of drug abuse (p=0.2217), every 10-year increase in age among those with no history of drug or opioid use was associated with a 4% decrease in the risk of persistent opioid use (95% CI 0.93,0.99), while every 10-year increase in age among those with a no history of drug or opioid use increase the risk of persistent opioid use by 22% (95% CI 1.04,1.43). As seen in Figure 4.10, there is a divergence in risk between those with and without a history of opioid abuse between the ages of 45 and 55; relative to those without a history of opioid or drug abuse, those with a history have

about 50% greater risk at age 55 (~7.5% vs ~5%) and have double the risk at age 70 (~10% vs. ~5%).

**Figure 4.10. Adjusted probability of persistent opioid use by age and drug abuse history**




## Discussion

*Sub-Aim 1: Bias resulting from nonrandom assignment of access type*

Sub-aim one's hypothesis that a model adjusting for nonrandom assignment to access type would be superior to a model without an endogenous equation for access type was rejected in full. Though it is known that there is nonrandom assignment to access type,[83, 90, 125] that variation likely did not matter in this circumstance, because opioid prescription did not vary significantly by access type (Tables 4.1 & 4.6). It is reasonable that if there isn't variation by a given factor, assignment to that factor is not important for producing an efficient regression model.

*Sub-Aim 2: Likelihood of prescription by access type*

Sub-aim two's hypothesis was disproven. AVF patients were no more likely to receive an opioid prescription than AVG patients (Table 4.3; p=0.2151). On its face, this is unremarkable; there is no clinical reason why one access type should be more painful than the other. The initial hypothesis was based on an assumption that without clear guidance surgeon perceptions about differences in pain by access type would produce significant variation in one direction or the other.

However, the dose of opioids given does vary by access type, with graft patients receiving 2.05 additional 5 milligram hydrocodone tablet-equivalents (Table 4.7), which suggests that surgeons do in fact perceive pain related to access type differently, but this perception may only be among those who prescribe opioids for vascular access creation. These findings suggest the decision-making processes for whether or not an opioid is prescribed (Table 4.6) and how much is prescribed (Table 4.7) are separate processes; whether or not they are independent or conditional is a topic for future research.

*Sub-Aim 3: Likelihood of prescription by surgeon type*

Sub-aim three's first hypothesis was confirmed; patients of general surgeons had significantly greater likelihoods of opioid prescription relative to patients of other specialties (Table 4.6). The assumption behind this hypothesis was based on literature demonstrating high rates of leftover opioids among general surgery patients,[182-184] indicating at the very least that patients in general surgery contexts receive more opioids than they need. These findings suggest that any policies implemented to reduce opioid prescription for vascular access should ensure general surgeons are targeted by the policies. In this study, general surgeons created nearly 1 out

of every 3 vascular accesses (Table 4.2), highlighting their important role in implementing effective policies for outcomes related to vascular access creation.

Sub-aim three's second hypothesis was disproven; patients of vascular surgeons had the second highest adjusted probability of receiving an opioid at access creation. Considering vascular surgeons' patients frequently include limb salvage and amputation, my expectation was vascular access creation would be viewed as a less painful procedure for vascular surgeons. This was clearly not the case, as the adjusted rate of opioid prescription was 38% among vascular surgeons (Table 4.6).

*Sub-Aim 4: Surgeon-related variability in opioid dosage*

Sub-aim four's first hypothesis was confirmed; 39% of the variation in opioid dosage was due to the individual surgeon prescribing the opioids (Table 4.7). This indicates that while it is important for policy initiatives to highlight the necessity of ensuring judicious prescription of opioids to different patient populations, specifically patients with a history of drug dependence, addressing individual surgeons' decision-making framework for opioid prescription is absolutely essential for minimizing the number of opioid tablets prescribed to patients for vascular access creation.

*Sub-Aim 5: Persistent opioid use 90 to 180 days post access procedure*

Sub-aim five's hypothesis was rejected because a dichotomized indicator for access opioid was not significant in predicting persistent opioid use ($p=0.25$), which lead to testing several operationalizations of opioid prescription that incorporated dosage; the categorical operationalization used in Table 4.8 best represented the underlying relationship, and provided greater model efficiency than continuous or transformed operationalizations, while also providing clearer dose ranges. The definition of persistent opioid use was reached based on

recent literature on rates of opioid prescription for minor and major opioid prescription, which used a cohort of opioid naïve patients who received at least one opioid prescription at their surgery date.[176] The aforementioned study's rates of persistent opioid prescription was 5.9% for minor surgeries and 6.5% for major surgeries,[176] which is comparable to the adjusted rate of persistent opioid use among those receiving higher dosages at access creation (Table 4.8). However, in this cohort of ESKD patients, an appropriate rate of opioid prescription may be greater, due to their advanced age and greater number of comorbidities.

The increased risk of persistent opioid use associated with prescription for vascular access creation was identified using a time to event model that both adjusting for nonrandom assignment of access opioids, as well as censoring of patients for: hospitalization, further access procedures by surgeons, kidney transplant, death, and end of Medicare enrollment. Though there is some slight ambiguity as to whether or not the surgeon prescribed the opioid for these patients, given the patients had at least 90 days without opioid prior to access creation, it is extremely unlikely the access creation surgeons were not the prescribing physicians. As a retrospective analysis among a Medicare subpopulation of ESKD patients, one cannot ascribe causality to the findings of this study, despite adjustment for nonrandom assignment to opioid prescription at vascular access. However, the methods behind this finding strongly suggest opioid prescription for vascular access carries a risk of causing opioid seeking behavior, and potentially opioid addiction.

*Implications for Policymaking*

Unlike the prior findings of Sekhri et al.,[172] persistent opioid varied by the initial dosage of opioids (Table 4.8). This suggests interventions should not only focus on reducing opioid use, but to also make clear the potential consequences of prescribing larger doses. Medical education

is a critical element in opioid decision making; Schnell & Currie found physicians' medical school ranking had a monotonic relationship with likelihood of opioid prescription, with physicians at the top-ranking school (i.e., Harvard) having the lowest rate of opioid prescription.[185] In fact, students at higher ranking medical schools were less likely to write any (i.e., at least one) opioid prescription in a given year, and even among the conditional population of physicians with at least one opioid prescription per year, physicians from higher ranked medical schools had lower rates of opioid prescription.[185] Though this may appear to suggest continuing medical education is an avenue for altering opioid decision making, as noted by Schnell & Currie, opioid decision making patterns appear to be set early in a physician's year of practice.[186] A qualitative study of physician behavior in interacting with residents suggest that discussing appropriateness of opioid prescribing is not a priority, or at the very least is not a topic that typically arises organically.[187]

In addition to the potential difficulty in altering established opioid decision-making practices among surgeons, the literature on changing physician opioid prescription patterns is typically at the institutional level and approach the measurement of opioid prescription as a measure of the total amount prescribed, both per patient and within time periods.[188-190] This approach addresses the extreme variety of patients encountered in the clinical context by looking at the total amount prescribed, which may be appropriate given the risk of persistent opioid use identified in this study depends on initial opioid dosage (Table 4.8). A study of a comprehensive multi-specialty intervention establishing opioid prescribing guidelines for 42 procedures spanning 11 physician specialties reported an increase in the rate of inpatient discharges without opioid prescription from 35% to 53%.[191] This seems to suggest that, despite weak evidence from

other studies, initiatives to change physicians' opioid decision making practices can be effective at the health system level.

Irrespective of opioid prescription guidelines in other context, the literature addressing the appropriateness of opioid prescription for vascular access creation is limited.[168] Given the hazard of addiction and abuse associated with opioids, to say nothing of the substantial economic costs associated with opioid over prescription and persistent opioid use,[192] awareness of a surgical procedure that may benefit from explicit guidelines regarding opioid decision making is critical to reducing the risk of opioid addiction and abuse among the ESKD population, particularly ESKD patients without an existing prescription for opioids. The next revision of KDOQI's vascular access guidelines would be the most relevant guidelines that could benefit from inclusion of advisement on opioid prescription for vascular access creation. Currently, CMS strategy focuses on primary care opioid prescription[193] and CDC's guidelines to reduce opioid use focus exclusively on opioid prescription for chronic pain,[148] leaving KDOQI as the largest institutional body that would have the ability to influence clinical practice as early as possible.

Unfortunately, effective policy options to reduce potential opioid over prescription are limited to institutional policies and clinical guidelines. More aggressive policies to reduce opioid use are generally not applicable in single-encounter circumstances. Though there were state-level laws in 26 states by the end of 2017 that limited prescribing of opioid for acute pain,[42] they are not targeted in a way that pertains to encounters for creation of a permanent vascular access. Furthermore, it is not reasonable to impose restrictions on opioid prescription when the goal is to minimize opioid prescription for vascular access, rather than completely eliminate it; there will doubtlessly be circumstances where opioids are appropriate for creation of a permanent vascular

access. Though prescription drug monitoring programs (PDMPs) are another potential policy option, a recent systematic review found, "little consistent evidence has yet emerged to demonstrate PDMPs' impact on outcomes of greatest importance, whether more proximal targets such as prescribing behavior or distal outcomes, such as opioid misuse, diversion, morbidity, and mortality."[43] PDMPs also suffer from the same shortcoming as a blunt policy instrument as state-level opioid prescription laws; neither are appropriate policy solutions to reduce opioid prescription for vascular access.

Variability in opioid outcomes and dosage by ESRD network region provides a clean roadmap as to where discussions among surgeons about the appropriateness of opioid prescription may have the greatest impact (Table 4.3). The South, Pacific Northwest, and the Midwest in particular appear to have greater rates of opioid use, while New York, New Jersey, and Southern California may be models for what is a more appropriate rate of opioid use. Discussions at regional surgical societies conferences would be a potentially fruitful starting point for addressing high rates of opioid use in some regions.

Limitations

This analysis has several limitations. The primary limitation was measurement of filled opioid prescriptions, rather than the actual opioid prescriptions, which include unfilled prescriptions. This means we are measuring patient behavior and surgeon behavior simultaneously when interpreting variability by different factors. This results in some uncertainty as to the extent that variability in likelihood of access opioid and dosage among those receiving an access opioid are a result of provider beliefs and perceptions, as opposed to patient behaviors and reporting of their pain. This is an unavoidable limitation for a study of this scale, which must rely on claims rather than prescription orders. However, given most prescriptions are digital,

future analysis may benefit from using prescription data from pharmacies or pharmacy benefit managers, who are able to capture filled versus unfilled prescriptions.

Since only opioid prescriptions can only be identified from Medicare Part D claims, the analysis can only evaluate Medicare enrollees who are also enrolled in a Part D plan. This has two implications: (1) patients with access procedures prior to their first hemodialysis will only be comprised of patients older than 65 who were already enrolled in Medicare prior to hemodialysis initiation, and (2) patients with access procedures after hemodialysis initiation will be skewed towards older ages, as younger ESKD patients have a greater number of insurance options available to them. However, since the ESKD population skews towards older patients, this limitation is acceptable and likely has a minimal impact on the internal validity of this study.

This analysis is also limited by the source of the access and opioid prescription dates. Though the dates of access procedure and opioid prescription are ostensibly the dates of service and prescription, respectively, dates from claims data are not always entirely reliable. To evaluate the extent to which this may be an issue, this study's methodology includes sensitivity analyses that uses wider date ranges for date of opioid prescription relative to the date of access procedure.

Though this study evaluates variation in opioid prescription related to the surgeon, I cannot definitively determine whether or not it was the surgeon that prescribe the opioid. Though surgeons are identified for the access procedures claims, the opioid claims do not identify the prescribing provider. It could sometimes be the case that within a day of the access procedure a patient's nephrologist or general practitioner could prescribe an opioid for pain. However, this is unlikely to be the case unless the patient was already being prescribed opioids by other providers

prior to the access procedure, and the analysis takes opioid prescription in the 90 days prior to the access procedure into account to mitigate this potential bias.

This paper focuses solely on opioid prescription for index access procedure. Including subsequent procedures and opioid prescriptions in the model would cause computational challenges that would likely keep the model from running. A crossed random effect would use surgeon identifier and patient identifier as random effects, which would account for patients seeing the same or different surgeons for subsequent access procedure. However, the narrow range of total access procedures (likely no more than 5, with most people having only 1) makes modeling the outcome of subsequent procedures computationally challenging. Including subsequent access procedures without using the patient identifier would probably interfere with the estimation of the surgeon median odds ratio and the intraclass correlation. It's also reasonable to assume that subsequent access procedures are also influenced by unmeasured variation related to the progression of ESKD after initiating hemodialysis, particularly changes in comorbidity status, which is derived from the 2728 forms, which are not a regular part of longitudinal data collection in USRDS. This makes a model that focuses on the index access procedure, which is always the closest procedure to the date of the patients initial 2728, preferable to a model that includes subsequent access procedures.

As mentioned previously, it was not conceptually feasible to correctly account for the role of the individual surgeon in likelihood of persistent opioid use. Individual surgeons influence persistent opioid use through opioid prescription, so it would not be appropriate to include them as a random-effect in an outcome equation for persistent opioid use. However, including surgeon random-effect only in the endogenous equation cannot be adequately integrated with the fixed effects in the outcome equation. Using a panel regression

implementation of an endogenous Poisson where the random effects influence both equations is both not technically correct, nor is it computationally expeditious, even with substantial computational resources.

## Tables

Table 4.1. Patients Characteristics by Filled Opioid Prescription for First Access Procedure

| Variables | No Opioid N=36,116 Row % | Filled Opioid Prescription N=22,680 Row % | Total N=58,796 Column % (n) | p-value |
|---|---|---|---|---|
| Access Type | | | | 0.27 |
| Fistula | 61.5 | 38.5 | 76.4 (44,915) | |
| Graft | 61.0 | 39.0 | 23.6 (13,881) | |
| Surgeon Type | | | | <0.001 |
| Vascular | 62.6 | 37.4 | 55.4 (32,595) | |
| General | 58.6 | 41.4 | 30.4 (17,892) | |
| Thoracic | 68.4 | 31.6 | 4.2 (2,441) | |
| Cardiac | 69.5 | 30.5 | 1.8 (1,051) | |
| Unknown | 58.5 | 41.5 | 8.2 (4,817) | |
| Sex | | | | <0.001 |
| Male | 62.4 | 37.6 | 54.4 (31,978) | |
| Female | 60.2 | 39.8 | 45.6 (26,818) | |
| Age at access | | | | <0.001 |
| 18-29 | 57.4 | 42.6 | 0.4 (235) | |
| 30-49 | 56.0 | 44.0 | 4.9 (2,864) | |
| 50-64 | 59.6 | 40.4 | 17.3 (10,167) | |
| 65-79 | 61.0 | 39.0 | 55.4 (32,568) | |
| 80+ | 65.2 | 34.8 | 22.0 (12,962) | |
| Race | | | | 0.005 |
| Non-Hispanic White | 61.3 | 38.7 | 57.1 (33,577) | |
| Non-Hispanic Black | 60.6 | 39.4 | 25.2 (14,840) | |
| Hispanic | 63.0 | 37.0 | 11.8 (6,914) | |
| Asian | 63.2 | 36.8 | 4.3 (2,550) | |
| Pacific Islander | 63.2 | 36.8 | 0.7 (419) | |
| Native American | 63.5 | 36.5 | 0.8 (496) | |
| Institutionalized | | | | <0.001 |
| Non-Institutionalized | 59.5 | 40.5 | 86.8 (51,006) | |
| Assisted Living, Nursing Home | 74.3 | 25.7 | 13.2 (7,790) | |
| Alcohol Dependence | | | | 0.53 |
| No Alcohol Dependence | 61.4 | 38.6 | 92.7 (54,487) | |
| Alcohol Dependence | 61.9 | 38.1 | 7.3 (4,309) | |
| History of Opioid/Drug Dependence | | | | <0.001 |
| No Opioid/Drug Dependence | 61.3 | 38.7 | 98.1 (57,670) | |
| History of Opioid/Drug Dependence | 67.2 | 32.8 | 1.9 (1,126) | |
| Rural-Urban Continuum Code 2013 | | | | <0.001 |
| Metro, 1+ mil | 65.5 | 34.5 | 52.5 (30,846) | |
| Metro, 0.25-1mil | 57.5 | 42.5 | 20.1 (11,793) | |
| Metro, <0.25mil | 57.2 | 42.8 | 9.8 (5,743) | |
| Urban 20k+, Metro Adj. | 56.7 | 43.3 | 5.1 (3,009) | |
| Urban 20k+, Not Adj. | 54.7 | 45.3 | 1.7 (991) | |
| Urban 2.5-19.9K, Metro Adj. | 55.1 | 44.9 | 6.1 (3,581) | |
| Urban 2.5-19.9K, Not Adj. | 58.0 | 42.0 | 3.1 (1,846) | |

| | | | | |
|---|---|---|---|---|
| Completely Rural, Metro Adj. | 54.5 | 45.5 | 0.8 (484) | |
| Completely Rural, Not Adj. | 58.6 | 41.4 | 0.9 (503) | |
| Year | | | | <0.001 |
| 2012 | 65.2 | 34.8 | 7.0 (4,101) | |
| 2013 | 62.2 | 37.8 | 15.9 (9,366) | |
| 2014 | 67.8 | 32.2 | 17.7 (10,417) | |
| 2015 | 59.8 | 40.2 | 21.8 (12,791) | |
| 2016 | 58.9 | 41.1 | 22.6 (13,310) | |
| 2017 | 57.6 | 42.4 | 15.0 (8,811) | |

Table 4.2. Opioid Statistics at the Surgeon and Patient Level by Surgeon Specialty

| | | Vascular | General | Thoracic | Cardiac | Unknown | Overall |
|---|---|---|---|---|---|---|---|
| Surgeon-Level Characteristics | Number of Surgeons | 2,635 | 1,743 | 270 | 121 | 1,268 | 6,037 |
| | % of Surgeons in Sample | 55.4 | 30.4 | 4.2 | 1.8 | 8.2 | 100 |
| | Mean Patients per Surgeon (SD) | 12 ± 16 | 10 ± 15 | 9 ± 11 | 8.7 ± 12 | 3.8 ± 6.3 | 9.7 ± 14 |
| | % Patients with Filled Opioid Prescription | 37.4 | 41.4 | 31.6 | 30.5 | 41.5 | 38.6 |
| | % Surgeons Never Prescribed Opioid | 18.1 | 24.4 | 29.6 | 35.5 | 40.6 | 25.5 |
| | Median % of Specialist-Level Prescription (IQR) | 36 (17, 52) | 38 (0, 59) | 25 (0, 5) | 25 (0, 5) | 33 (0, 71) | 35 (0, 56) |
| Patient Level Characteristics | Number of Patients | 32,595 | 17,892 | 2,441 | 1,051 | 4,817 | 58,796 |
| | Mean Morphine Equivalent in MG (SD) | 172.6 ± 74.4 | 170.3 ± 77.4 | 166.7 ± 80.2 | 179.6 ± 67.1 | 172.4 ± 78.9 | 171.8 ± 75.9 |
| | Mean # of 5mg Hydrocodone Tablets (SD) | 34.5 ± 14.9 | 34.1 ± 15.5 | 33.3 ± 16.0 | 35.9 ± 13.4 | 34.5 ± 15.8 | 34.4 ± 15.2 |
| | Median # of 5mg Hydrocodone Tablets (IQR) | 30.0 (25.0, 45.0) | 30.0 (23.6, 45.0) | 30.0 (20.6, 42.0) | 30.0 (29.1, 42.3) | 30.0 (23.6, 45.0) | 30.0 (24.0, 45.0) |
| | Drug Type Among Those Prescribed Drug | | | | | | |
| | Hydrocodone SA | 52.6 | 57.5 | 56.7 | 43.3 | 62.3 | 55.1 |
| | Oxycodone SA | 31.4 | 26.7 | 18.4 | 22.1 | 22.7 | 28.5 |
| | Codeine | 9.3 | 7.3 | 13.9 | 15.3 | 8.3 | 8.8 |
| | Tramadol SA | 5.6 | 7.1 | 10.9 | 19.3 | 5.9 | 6.5 |
| | Other | 1.0 | 1.3 | 0.1 | 0.0 | 0.9 | 1.0 |

*All P-values significant at $p<0.001$, with the exception of mean morphine equivalents ($p=0.024$)

Table 4.3. Opioid Outcomes and Dosage by ESRD Network Region

| | | Access Opioid | Number of 5mg Hydrocodone Tablets | | | | Persistent Opioid (Censored) | Persistent Opioid (No Censoring) |
|---|---|---|---|---|---|---|---|---|
| | | | <30 | 30-59 | 60-89 | 90+ | | |
| Overall | N=58,796 | 38.6 | 34.9 | 55.3 | 8.7 | 1.1 | 4.8 | 15.3 |
| 13:LA/AR/OK | N=2,280 | 48.5 | 23.1 | 56.9 | 18.5 | 1.5 | 6.6 | 28.6 |
| 16:WA/OR/ID/MT/AK | N=1,421 | 46.6 | 34.1 | 55.4 | 8.9 | 1.5 | 7.3 | 27.4 |
| 11:MI/WI/MN/ND/SD | N=3,776 | 45.8 | 37.4 | 55.0 | 7.3 | 0.3 | 4.7 | 26.6 |
| 8:TN/AL/MI | N=3,293 | 45.1 | 29.5 | 59.3 | 9.3 | 2.0 | 5.9 | 29.9 |
| 17:NorCal/HI | N=2,613 | 44.6 | 40.6 | 48.3 | 10.8 | 0.3 | 5.3 | 23.5 |
| 12:NE/KS/IA/MO | N=2,576 | 44.4 | 37.4 | 54.9 | 7.0 | 0.7 | 5.6 | 27.5 |
| 6:NC/SC/GA | N=4,857 | 43.5 | 23.3 | 62.3 | 12.4 | 2.0 | 5.3 | 27.9 |
| 5:DC/MD/VA/WV | N=3,538 | 42.5 | 29.0 | 59.0 | 10.2 | 1.8 | 4.1 | 25.2 |
| 10:Indiana | N=3,158 | 41.1 | 51.3 | 44.1 | 4.3 | 0.2 | 4.7 | 22.5 |
| 15:NV/UT/WY/CO/AZ/NM | N=2,019 | 41.0 | 43.0 | 49.4 | 6.6 | 1.0 | 5.8 | 22.8 |
| 9:OH/IL/KY | N=4,597 | 40.6 | 30.8 | 59.2 | 8.9 | 1.1 | 5.5 | 26.9 |
| 1:New England | N=2,496 | 39.8 | 38.1 | 55.7 | 5.7 | 0.4 | 3.4 | 20.9 |
| 4:PA/DE | N=2,599 | 37.7 | 37.6 | 55.9 | 5.6 | 0.9 | 4.1 | 22.3 |
| 14:Texas | N=4,848 | 37.0 | 46.5 | 47.5 | 5.6 | 0.4 | 5.2 | 26.5 |
| 7:Florida | N=3,639 | 34.4 | 26.6 | 60.7 | 11.2 | 1.5 | 3.4 | 23.4 |
| 18:SoCal | N=3,982 | 29.3 | 42.5 | 50.0 | 6.8 | 0.7 | 4.7 | 20.3 |
| 3:New Jersey | N=2,912 | 22.6 | 28.6 | 62.4 | 7.9 | 1.1 | 3.7 | 17.9 |
| 2:New York | N=4,192 | 22.2 | 34.4 | 57.2 | 6.2 | 2.1 | 2.5 | 16.8 |

*Rows sorted by rate of access opioid, descending

Table 4.4. Patient Characteristics by Persistent Opioid Use

| | No Persistent Opioid Use N=55,993 | Persistent Opioid Use (Censored) N=2,803 | |
|---|---|---|---|
| Variables | Row % | Row % | p-value |
| Number of 5mg Hydrocodone Tablets | | | <0.001 |
| None | 95.5 | 4.5 | |
| <30 | 94.9 | 5.1 | |
| 30-59 | 94.9 | 5.1 | |
| 60-89 | 93.8 | 6.2 | |
| 90+ | 91.9 | 8.1 | |
| Post-Access Procedure Opioid | | | <0.001 |
| No Opioid | 95.5 | 4.5 | |
| Received Opioid | 94.8 | 5.2 | |
| Age at access | | | <0.001 |
| 18-29 | 97.4 | 2.6 | |
| 30-49 | 94.7 | 5.3 | |
| 50-64 | 94.5 | 5.5 | |
| 65-79 | 95.3 | 4.7 | |
| 80+ | 95.7 | 4.3 | |
| Sex | | | <0.001 |
| Male | 95.6 | 4.4 | |
| Female | 94.8 | 5.2 | |
| Race | | | <0.001 |
| Non-Hispanic White | 95.2 | 4.8 | |
| Non-Hispanic Black | 95.0 | 5.0 | |
| Hispanic | 95.1 | 4.9 | |
| Asian | 97.0 | 3.0 | |
| Pacific Islander | 96.9 | 3.1 | |
| Native American | 95.0 | 5.0 | |
| Institutionalized | | | 0.013 |
| Non-Institutionalized | 95.3 | 4.7 | |
| Assisted Living, Nursing Home | 94.7 | 5.3 | |
| History of Opioid/Drug Dependence | | | <0.001 |
| No Opioid/Drug Dependence | 95.3 | 4.7 | |
| History of Opioid/Drug Dependence | 92.1 | 7.9 | |
| Alcohol Dependence | | | 0.003 |
| No Alcohol Dependence | 95.3 | 4.7 | |
| Alcohol Dependence | 94.3 | 5.7 | |
| Rural-Urban Continuum Code 2013 | | | <0.001 |
| Metro, 1+ mil | 96.0 | 4.0 | |
| Metro, 0.25-1mil | 94.9 | 5.1 | |
| Metro, <0.25mil | 94.3 | 5.7 | |
| Urban 20k+, Metro Adj. | 94.1 | 5.9 | |
| Urban 20k+, Not Adj. | 92.5 | 7.5 | |
| Urban 2.5-19.9K, Metro Adj. | 94.0 | 6.0 | |
| Urban 2.5-19.9K, Not Adj. | 93.4 | 6.6 | |
| Completely Rural, Metro Adj. | 93.2 | 6.8 | |
| Completely Rural, Not Adj. | 94.8 | 5.2 | |
| Year | | | 0.014 |

| | | | |
|---|---|---|---|
| 2012 | 94.7 | 5.3 | |
| 2013 | 94.8 | 5.2 | |
| 2014 | 95.3 | 4.7 | |
| 2015 | 95.1 | 4.9 | |
| 2016 | 95.4 | 4.6 | |
| 2017 | 95.8 | 4.2 | |

Table 4.5. Persistent Opioid Use at 90 to 180 Days by Age and History of Opioid or Drug Dependence

| | No Persistent Opioid Use N=55,993 | Persistent Opioid Use (Censored) N=2,803 | p-value |
|---|---|---|---|
| Opioid/Drug Dependence History by Age | Row % (n) | Row % (n) | <0.001 |
| No Opioid/Drug Dependence 18-29 | 97.2 (211) | 2.8 (6) | |
| No Opioid /Drug Dependence 30-49 | 94.8 (2,530) | 5.2 (139) | |
| No Opioid /Drug Dependence 50-64 | 94.6 (9,162) | 5.4 (524) | |
| No Opioid /Drug Dependence 65-79 | 95.4 (30,701) | 4.6 (1,496) | |
| No Opioid /Drug Dependence 80+ | 95.7 (12,352) | 4.3 (549) | |
| History of Opioid/Drug Dependence 18-29 | 100.0 (18) | 0.0 (0) | |
| History of Opioid/Drug Dependence 30-49 | 92.8 (181) | 7.2 (14) | |
| History of Opioid/Drug Dependence 50-64 | 92.3 (444) | 7.7 (37) | |
| History of Opioid/Drug Dependence 65-79 | 91.9 (341) | 8.1 (30) | |
| History of Opioid/Drug Dependence 80+ | 86.9 (53) | 13.1 (8) | |

Table 4.6. Variability in Filled Opioid Prescription: Odds Ratios, Marginal Differences, and Marginal Predictions

| | Odd Ratio | 95% CI | p-value | Marginal Diff. | 95% CI | p-value | Estimate | 95% CI |
|---|---|---|---|---|---|---|---|---|
| Access Type | | | | | | | | |
| Fistula | | Reference | | | Reference | | 0.3809 | [0.3511,0.4106] |
| Graft | 1.0292 | [0.9834,1.0771] | 0.2151 | 0.006 | [-0.0035,0.0155] | 0.2158 | 0.3869 | [0.3562,0.4176] |
| Surgeon Type | | | | | | | | |
| Vascular | | Reference | | | Reference | | 0.3795 | [0.3493,0.4097] |
| General | 1.0799 | [1.0130,1.1513] | 0.0185 | 0.0161 | [0.0027,0.0295] | 0.0188 | 0.3956 | [0.3642,0.4270] |
| Thoracic | 0.7161 | [0.6240,0.8217] | <0.0001 | -0.0668 | [-0.0935,-0.0402] | <0.0001 | 0.3127 | [0.2758,0.3495] |
| Cardiac | 0.6548 | [0.5348,0.8016] | <0.0001 | -0.0837 | [-0.1216,-0.0458] | <0.0001 | 0.2958 | [0.2506,0.3410] |
| Unknown | 1.1321 | [1.0363,1.2368] | 0.006 | 0.0261 | [0.0074,0.0448] | 0.0063 | 0.4056 | [0.3713,0.4399] |
| Sex | | | | | | | | |
| Male | | Reference | | | Reference | | 0.3712 | [0.3416,0.4008] |
| Female | 1.1244 | [1.0833,1.1671] | <0.0001 | 0.0244 | [0.0166,0.0322] | <0.0001 | 0.3956 | [0.3653,0.4260] |
| Age at access | | | | | | | | |
| 18-29 | | Reference | | | Reference | | 0.4058 | [0.3392,0.4725] |
| 30-49 | 1.0817 | [0.8083,1.4476] | 0.5973 | 0.0168 | [-0.0451,0.0786] | 0.5956 | 0.4226 | [0.3876,0.4576] |
| 50-64 | 0.9477 | [0.7137,1.2584] | 0.7104 | -0.0114 | [-0.0715,0.0488] | 0.7115 | 0.3945 | [0.3633,0.4257] |
| 65-79 | 0.892 | [0.6730,1.1822] | 0.4264 | -0.024 | [-0.0838,0.0357] | 0.4307 | 0.3818 | [0.3519,0.4117] |
| 80+ | 0.8202 | [0.6175,1.0895] | 0.1713 | -0.0413 | [-0.1016,0.0189] | 0.1784 | 0.3645 | [0.3343,0.3947] |
| Race | | | | | | | | |
| Non-Hispanic White | | Reference | | | Reference | | 0.3789 | [0.3491,0.4088] |
| Non-Hispanic Black | 1.0224 | [0.9724,1.0749] | 0.3872 | 0.0046 | [-0.0058,0.0150] | 0.3876 | 0.3835 | [0.3528,0.4142] |
| Hispanic | 1.0738 | [1.0032,1.1493] | 0.0402 | 0.0149 | [0.0006,0.0291] | 0.041 | 0.3938 | [0.3614,0.4262] |
| Asian | 1.1467 | [1.0366,1.2685] | 0.0079 | 0.0287 | [0.0073,0.0502] | 0.0085 | 0.4077 | [0.3713,0.4440] |
| Pacific Islander | 0.9063 | [0.7239,1.1346] | 0.3906 | -0.0202 | [-0.0659,0.0255] | 0.3858 | 0.3587 | [0.3051,0.4123] |
| Native American | 0.6981 | [0.5614,0.8681] | 0.0012 | -0.0715 | [-0.1130,-0.0301] | 0.0007 | 0.3074 | [0.2585,0.3563] |
| Drug/Opioid Dependence | | | | | | | | |
| No Drug Dependence | | Reference | | | Reference | | 0.3835 | [0.3538,0.4133] |
| Drug Dependence | 0.7318 | [0.6367,0.8409] | <0.0001 | -0.0629 | [-0.0899,-0.0358] | <0.0001 | 0.3206 | [0.2824,0.3588] |
| Alcohol Dependence | | | | | | | | |
| No Alcohol Dependence | | Reference | | | Reference | | 0.3817 | [0.3520,0.4114] |
| Alcohol Dependence | 1.0404 | [0.9686,1.1175] | 0.2775 | 0.0083 | [-0.0067,0.0232] | 0.2789 | 0.39 | [0.3570,0.4229] |
| Median Income in Zip Code | 1.0087 | [0.9976,1.0198] | 0.1243 | 0.0018 | [-0.0005,0.0041] | 0.1242 | N/A (Continuous Scale) | |
| Year of Access Creation | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Year=2012 | | Reference | | | Reference | | 0.3485 | [0.3166,0.3803] |
| Year=2013 | 1.1328 | [1.0422,1.2312] | 0.0034 | 0.0255 | [0.0085,0.0425] | 0.0032 | 0.374 | [0.3431,0.4049] |
| Year=2014 | 0.8528 | [0.7848,0.9266] | 0.0002 | -0.0315 | [-0.0481,-0.0149] | 0.0002 | 0.317 | [0.2883,0.3457] |
| Year=2015 | 1.2811 | [1.1823,1.3881] | <0.0001 | 0.0514 | [0.0349,0.0678] | <0.0001 | 0.3998 | [0.3687,0.4310] |
| Year=2016 | 1.3356 | [1.2327,1.4471] | <0.0001 | 0.0602 | [0.0437,0.0767] | <0.0001 | 0.4087 | [0.3774,0.4400] |
| Year=2017 | 1.3992 | [1.2856,1.5228] | <0.0001 | 0.0702 | [0.0526,0.0877] | <0.0001 | 0.4187 | [0.3866,0.4507] |
| Institutionalization Status | | | | | | | | |
| Non-Institutionalized | | Reference | | | Reference | | 0.4005 | [0.3701,0.4310] |
| Assisted Living, Nursing Home | 0.4948 | [0.4666,0.5246] | <0.0001 | -0.138 | [-0.1499,-0.1261] | <0.0001 | 0.2625 | [0.2359,0.2892] |
| Urban-Rural County Code | | | | | | | | |
| Metro, 1+ mil | | Reference | | | Reference | | 0.3617 | [0.3320,0.3914] |
| Metro, 0.25-1mil | 1.2656 | [1.1866,1.3498] | <0.0001 | 0.0492 | [0.0356,0.0629] | <0.0001 | 0.4109 | [0.3790,0.4428] |
| Metro, <0.25mil | 1.1619 | [1.0738,1.2572] | 0.0002 | 0.0311 | [0.0146,0.0476] | 0.0002 | 0.3928 | [0.3600,0.4256] |
| Urban 20k+, Metro Adj. | 1.281 | [1.1635,1.4103] | <0.0001 | 0.0518 | [0.0313,0.0723] | <0.0001 | 0.4135 | [0.3781,0.4488] |
| Urban 20k+, Not Adj. | 1.2487 | [1.0633,1.4663] | 0.0068 | 0.0464 | [0.0122,0.0805] | 0.0078 | 0.408 | [0.3636,0.4525] |
| Urban 2.5-19.9K, Metro Adj. | 1.2532 | [1.1465,1.3699] | <0.0001 | 0.0471 | [0.0283,0.0660] | <0.0001 | 0.4088 | [0.3745,0.4432] |
| Urban 2.5-19.9K, Not Adj. | 1.1294 | [1.0014,1.2737] | 0.0474 | 0.0252 | [0.0000,0.0503] | 0.0496 | 0.3868 | [0.3492,0.4245] |
| Completely Rural, Metro Adj. | 1.3297 | [1.0843,1.6306] | 0.0062 | 0.0598 | [0.0161,0.1035] | 0.0074 | 0.4215 | [0.3691,0.4739] |
| Completely Rural, Not Adj. | 1.0837 | [0.8836,1.3292] | 0.4401 | 0.0166 | [-0.0258,0.0589] | 0.4436 | 0.3782 | [0.3276,0.4289] |
| ESRD Network Median Odds Ratio | 1.3471 | [1.2355,1.5216] | | | | | | |
| ESRD Network Intraclass Correlation | 0.0240 | [0.0123,0.0466] | | | | | | |
| Surgeon Median Odds Ratio | 1.8768 | [1.8177,1.9411] | | | | | | |
| Surgeon Intraclass Correlation | 0.1372 | [0.1209,0.1554] | | | | | | |
| C-Statistic | 0.744 | [0.7400,0.7480] | | | | | | |

Table 4.7. Mixed Linear Model for Number of 5 Milligram Hydrocodone Dosage of Filled Opioid Prescription

| | Coef. | 95% CI | p-value |
|---|---|---|---|
| Access Type | | | |
| Fistula | | Reference | |
| Graft | 2.05 | [1.64,2.47] | 0.0000 |
| Sex | | | |
| Male | | Reference | |
| Female | -0.43 | [-0.76,-0.10] | 0.0114 |
| Age at access | -0.10 | [-0.11,-0.08] | 0.0000 |
| Race | | | |
| Non-Hispanic White | | Reference | |
| Non-Hispanic Black | 0.56 | [0.12,1.01] | 0.0119 |
| Hispanic | -0.36 | [-0.98,0.26] | 0.2527 |
| Asian | -0.94 | [-1.86,-0.02] | 0.0444 |
| Pacific Islander | -1.86 | [-3.92,0.20] | 0.0764 |
| Native American | -0.85 | [-2.87,1.18] | 0.4121 |
| History of Opioid/Drug Dependence | | | |
| No Opioid/Drug Dependence | | Reference | |
| History of Opioid/Drug Dependence | 0.99 | [-0.32,2.30] | 0.1390 |
| Institutionalized | | | |
| Non-Institutionalized | | Reference | |
| Assisted Living, Nursing Home | -0.73 | [-1.31,-0.15] | 0.0132 |
| ESRD Network Random-Effect (S.D.) | 2.3673 | [1.6578,3.3805] | |
| ESRD Network Intraclass Correlation | 0.0252 | [0.0125, 0.0501] | |
| Surgeon Random-Effect (S.D.) | 9.0360 | [8.7513, 9.3300] | |
| Surgeon Intraclass Correlation | 0.3925 | [0.3734,0.4120] | |

Table 4.8. Variability in Persistent Opioid Prescription at 90 to 180 Days Post Access Creation

| | HR | 95% CI | P-Value | Predicted Rate | 95% CI |
|---|---|---|---|---|---|
| 5mg Hydrocodone Dose at Access Creation | | | | | |
| None | | Reference | | 0.0468 | [0.0446,0.0490] |
| <30 | 1.0093 | [0.9074,1.1226] | 0.8648 | 0.0473 | [0.0428,0.0517] |
| 30-59 | 1.0238 | [0.9363,1.1194] | 0.6062 | 0.0479 | [0.0443,0.0515] |
| 60-89 | 1.2345 | [1.0345,1.4732] | 0.0195 | 0.0578 | [0.0480,0.0676] |
| 90+ | 1.7838 | [1.1855,2.6841] | 0.0055 | 0.0835 | [0.0496,0.1174] |
| Sex | | | | | |
| Male | | Reference | | 0.0429 | [0.0407,0.0451] |
| Female | 1.2537 | [1.1661,1.3480] | <0.0001 | 0.0538 | [0.0510,0.0565] |
| Age, Opioid/Drug History, & Interaction | | | | | |
| History of Opioid/Drug Dependence (vs No History) | 0.5278 | [0.1894,1.4707] | 0.2217 | | |
| Age among those with no history (10 yr unit continuous) | 0.9627 | [0.9322,0.9943] | 0.0209 | See Figure 4.10 | |
| Age among those with opioid/drug history (10 yr unit continuous) | 1.2162 | [1.0368,1.4266] | 0.0162 | | |
| Race | | | | | |
| Non-Hispanic White | | Reference | | 0.0494 | [0.0470,0.0519] |
| Non-Hispanic Black | 0.9862 | [0.8971,1.0841] | 0.7733 | 0.0488 | [0.0450,0.0525] |
| Hispanic | 0.9347 | [0.8224,1.0624] | 0.3014 | 0.0462 | [0.0410,0.0515] |
| Asian | 0.608 | [0.4814,0.7679] | <0.0001 | 0.0301 | [0.0232,0.0369] |
| Pacific Islander | 0.5522 | [0.3237,0.9419] | 0.0293 | 0.0273 | [0.0128,0.0418] |
| Native American | 0.7122 | [0.4793,1.0581] | 0.0929 | 0.0352 | [0.0214,0.0490] |
| Alcohol Dependence | | | | | |
| No Alcohol Dependence | | Reference | | 0.0468 | [0.0451,0.0486] |
| Alcohol Dependence | 1.2598 | [1.1057,1.4353] | 0.0005 | 0.059 | [0.0516,0.0663] |
| Median Income in Zip Code | 0.9828 | [0.9623,1.0037] | 0.1055 | N/A Continuous Variable | |
| Institutionalization Status | | | | | |
| Non-Institutionalized | | Reference | | 0.046 | [0.0442,0.0478] |
| Assisted Living, Nursing Home | 1.3158 | [1.1901,1.4547] | <0.0001 | 0.0605 | [0.0549,0.0661] |
| Urban-Rural County Code | | | | | |
| Metro, 1+ mil | | Reference | | 0.0428 | [0.0403,0.0453] |
| Metro, 0.25-1mil | 1.1657 | [1.0544,1.2887] | 0.0027 | 0.0499 | [0.0460,0.0538] |
| Metro, <0.25mil | 1.2183 | [1.0737,1.3824] | 0.0022 | 0.0521 | [0.0466,0.0577] |
| Urban 20k+, Metro Adj. | 1.2518 | [1.0657,1.4705] | 0.0063 | 0.0536 | [0.0458,0.0613] |
| Urban 20k+, Not Adj. | 1.4168 | [1.1255,1.7834] | 0.003 | 0.0606 | [0.0474,0.0739] |

| | | | | | |
|---|---|---|---|---|---|
| Urban 2.5-19.9K, Metro Adj. | 1.2574 | [1.0799,1.4641] | 0.0032 | 0.0538 | [0.0466,0.0610] |
| Urban 2.5-19.9K, Not Adj. | 1.3143 | [1.0850,1.5921] | 0.0052 | 0.0562 | [0.0463,0.0662] |
| Completely Rural, Metro Adj. | 1.4354 | [1.0217,2.0166] | 0.0372 | 0.0614 | [0.0410,0.0818] |
| Completely Rural, Not Adj. | 1.0493 | [0.7140,1.5421] | 0.8066 | 0.0449 | [0.0280,0.0619] |
| ESRD Network Region | | | | | |
| 1:New England | | Reference | | 0.037 | [0.0293,0.0447] |
| 2:New York | 0.8276 | [0.6258,1.0945] | 0.1846 | 0.0306 | [0.0248,0.0364] |
| 3:New Jersey | 1.1963 | [0.9078,1.5764] | 0.203 | 0.0443 | [0.0360,0.0526] |
| 4:PA/DE | 1.1258 | [0.8537,1.4847] | 0.4012 | 0.0417 | [0.0340,0.0493] |
| 5:DC/MD/VA/WV | 1.1443 | [0.8820,1.4847] | 0.3101 | 0.0423 | [0.0356,0.0491] |
| 6:NC/SC/GA | 1.3584 | [1.0670,1.7295] | 0.0129 | 0.0503 | [0.0441,0.0564] |
| 7:Florida | 1.0206 | [0.7799,1.3357] | 0.8817 | 0.0378 | [0.0313,0.0442] |
| 8:TN/AL/MI | 1.3594 | [1.0552,1.7512] | 0.0175 | 0.0503 | [0.0432,0.0574] |
| 9:OH/IL/KY | 1.3828 | [1.0879,1.7576] | 0.0081 | 0.0512 | [0.0451,0.0573] |
| 10:Indiana | 1.2999 | [1.0040,1.6830] | 0.0465 | 0.0481 | [0.0406,0.0556] |
| 11:MI/WI/MN/ND/SD | 1.23 | [0.9556,1.5832] | 0.1081 | 0.0455 | [0.0389,0.0521] |
| 12:NE/KS/IA/MO | 1.3336 | [1.0263,1.7328] | 0.0312 | 0.0493 | [0.0415,0.0572] |
| 13:LA/AR/OK | 1.4936 | [1.1496,1.9405] | 0.0027 | 0.0553 | [0.0465,0.0640] |
| 14:Texas | 1.4342 | [1.1255,1.8277] | 0.0035 | 0.0531 | [0.0465,0.0596] |
| 15:NV/UT/WY/CO/AZ/NM | 1.4825 | [1.1281,1.9481] | 0.0047 | 0.0548 | [0.0451,0.0646] |
| 16:WA/OR/ID/MT/AK | 1.7295 | [1.3111,2.2815] | 0.0001 | 0.064 | [0.0522,0.0758] |
| 17:NorCal/HI | 1.4675 | [1.1264,1.9119] | 0.0045 | 0.0543 | [0.0452,0.0634] |
| 18:SoCal | 1.3976 | [1.0854,1.7997] | 0.0095 | 0.0517 | [0.0441,0.0593] |

## Chapter 5: Conclusion

The studies in this dissertation sought to identify potential shortcomings in measurement of variability in vascular access outcomes during the early end-stage kidney disease (ESKD). The findings of Chapters 2 and 3 demonstrate that without adjustment for non-random assignment to health care access and vascular access type, respectively, estimation may be biased. However, the extent to which this bias affects different patient sub-groups varies. The findings of Chapter 4 were unexpected; given known systematic variation in whether or not patients receive an arteriovenous fistula (AVF) versus arteriovenous graft (AVG), it was expected a model accounting for this selection bias would be necessary. However, the absence of this bias was likely because access type was not associated with variation in opioid prescription for vascular access (p=0.2151). This serves as a lesson: though there may be literature and conceptual reasons that support the use of a modeling approach to address endogeneity, it may not always be necessary, particularly if the endogenous variable has a null effect.

Key Findings & Implications

*Chapter 2: Pre-ESKD Nephrology Care & Index Access Type*

The effect of nephrology care was estimated to be 3.76 times greater using a bivariate probit versus a naive probit, suggesting substantial measurement bias in circumstances where selection bias related to a proxy for health care access (i.e., pre-ESKD nephrology care) is not adequately addressed in regression analyses. The reduction of effects sizes related to region after application of a recursive bivariate probit were particularly revealing, suggesting regional variability in initiation of dialysis on a permanent access is more of a reflection of regional variation in health care access, rather than regional variation in health care practices.

Though Chapter 2's study was very narrowly focused, both in terms of outcome and patient population, the policies which may have the greatest potential impacts have a much broader scope of potential positive impact on health outcomes. Seeing a nephrologist at least 6 months before the onset of ESKD is not a unique problem in search of a narrow solution, but rather an example of the broader struggle to improve health outcomes for many patient groups due to health care access limitations. The reason there are low rates of pre-ESKD nephrology care is likely the same reason there is a spike in cancer diagnoses among Americans at age 65;[194] Medicare improves health care access for many Americans when they turn 65. People seek care when they are able to; this isn't a preference, but rather a decision involving stark tradeoffs for Americans living in poverty, including the working poor who may have difficulty finding the time to seek care.[195-197] Under the existing health care framework in the United States, the importance of past and future Medicaid expansion and poverty amelioration policies is paramount in the path to improving health outcomes via improved health care access.

A substantial proportion of United States health policy literature ultimately arrives at the conclusion that being uninsured is detrimental to health outcomes and gaining insurance can be beneficial to some outcomes.[198-201] In the realm of kidney failure in particular, Medicaid expansion was associated with an increase in pre-emptive living-donor and deceased-donor kidney transplants.[202] This is important from a cost perspective because the most recent USRDS Medicare data from 2016 shows that, per person per year hemodialysis costs $90,971, while post-transplant costs $34,780.[1] Other major barriers both indirectly and directly impacting access to care among the ESKD population, who are generally elderly, include: transportation;[203-205] the logistics related to multi-step diagnostic and treatment processes, including care coordination;[89,

[206, 207] and communication issues related to technology (e.g., computer literacy, visual impairment, hearing impairment).[89, 208-211]

The ultimate takeaway of these findings is that policy solutions to improving rates of permanent access lie with health care financing policymakers and stakeholders, rather than among those delivering pre-ESKD nephrology care and creating permanent vascular accesses. Medicare and commercial reimbursement policies pertaining to screening of patient at a high risk for CKD are a likely potential avenue for improving permanent access rates, given this study's findings.

*Chapter 3: Hospitalization for Vascular Access Infection*

The estimated difference in hospitalization for access infection between catheter and permanent access differs substantially based on residence in a nursing home or assisted living facility; while a Cox model correctly estimates differences by access type in infection rates among non-institutionalized patients, it misestimates the direction and magnitude of the difference between access types for ESKD patients living in nursing home or assisted living. After institutionalization status and age, history of drug dependence or opioid abuse had the second largest effect size (0.7 PPY; 95% CI 0.042,0.082), suggesting intravenous drug users with ESKD may be using their access for recreational drug use. Patients with a history of drug or opioid abuse had an adjusted risk of access infection that was 89% greater than those without a history (95% CI 1.39, 2.56).

Given variability in hemodialysis access type is influenced by patient factors, particularly patients' ability to access pre-ESKD nephrology care, retrospective analyses should consider the non-random assignment to access type in estimation of the effects of access type and patients' characteristics on early hemodialysis access outcomes, such as vascular access infection.

*Chapter 4: Opioid Use for Vascular Access Creation*

Rates of filled opioid prescription do not vary between arteriovenous graft and arteriovenous fistula (p=0.2151), and adjustment for nonrandom assignment to access type did not produce a more efficient model. General and vascular surgeons had much higher rates of filled opioid prescription than thoracic and cardiac surgeons. However, opioid dosage does not vary by surgical specialty.

Receiving an opioid dose of less than 30 5 milligram hydrocodone equivalents or between 30 and 59 5mg equivalents was not associated with an increased risk of persistent opioid use. However, relative to those who did not receive an access opioid, receiving an opioid dose equivalent to 60 to 89 5 milligram hydrocodone equivalents was associated with a 23% increase in the risk of persistent opioid use (95% CI 1.03,1.47), and receiving an opioid dose equivalent to 90 or more 5 milligram hydrocodone equivalents was associated with a 78% increase in the risk of persistent opioid use (95% CI 1.18,2.68). Considering this finding in conjunction with individual surgeons accounting for 39% of the variability in opioid dosage, there is a clear and present need for establishing opioid prescription and dosage for post-operative pain from vascular access creation.

Patients with opioid or drug dependence were less likely to have an opioid prescription (OR 0.73; 95% CI 0.64,0.84), and did not have more opioids prescribed to them than those with not history of drug dependence (p=0.14). However, they had a greater risk of persistent opioid at a rate that is moderated by age; a 10-year increase in age was associated with a with a 4% decrease in the risk of persistent opioid use (95% CI 0.93,0.99) among those without a history of opioid abuse, and an increase of 22% (95% CI 1.04,1.43) for every 10 years among those with a history of opioid abuse.

Given the identification of opioid abuse history was accomplished partially through diagnostic codes, it may be feasible to explore standardizing flags for history of opioid abuse in the main page of each patient's electronic health record (EHR). The cost to implement such a modification in an EHR system would be minimal. Given this study focused on opioid naïve patients and excluded patients with recent opioid use, who were more likely to have had a history of opioid or drug abuse, there may be larger than expected benefits to implementing such an EHR system modification.

**Future Research**

*Chapter 2: Pre-ESKD Nephrology Care & Index Access Type*

The literature may benefit from future studies of variability in pre-ESKD nephrology care within a younger cohort, specifically among commercial and Medicare Advantage enrollees who have at least 1 year of enrollment under one of their payer's plans prior to ESKD. Using Optum Clinformatics claims database, which contains all claims from UnitedHealthcare plans and accounts for 25% of Medicare Advantage claims,[212] to perform the same analysis among a generally younger cohort would address the shortcoming in patient population in this dissertation's second chapter, which excluded those without at least 1 year of pre-ESKD Medicare enrollment. An analysis focused primarily on how individual nephrologists facilitate the creation of permanent access creation prior to hemodialysis initiation by using the most frequently billed nephrologist by number of office visits as the identifier for a nephrologist random-intercept. The time between the first visit with the nephrologist and hemodialysis initiation would be required as an exposure variable, which can also be tested for inclusion as a random slope.

*Chapter 3: Hospitalization for Vascular Access Infection*

Future studies should use the methodological framework of Chapter 3 to assess variability in access infection between patients with arteriovenous fistula and arteriovenous graft. An endogenous Poisson with fistula versus graft as the endogenous variable would build upon the present study and clarify the extent to which differences in infection in graft versus fistula are due to non-random assignment to access type. Incorporating an additional selection equation into the model to account for having a permanent access versus a catheter would also improve estimation of the model, and would require application of a structural equation modeling approach.

ESKD patients who use intravenous recreational drugs may typically be aware of their ability to use their catheter or permanent access to inject drugs. Future studies of vascular access infection risk may wish to prioritize surveying ESKD patients who inject recreational drugs to evaluate whether or not most intravenous (IV) drug users with ESKD are aware they can use their access for recreational drug use. Without first understanding this, it may not be ethical to attempt a larger intervention in which IV drug users are made aware of how easily they can become intoxicated with a catheter. However, if most IV drug users are already aware of the possibility of using their catheters and permanent access for recreational purposes, future studies may wish to clarify physicians' ability to reduce infections in this patient population. A pre-post study design implementing an intervention in which nephrologists and vascular surgeons advised patients with a history of opioid or intravenous drug use on the best practices for using their vascular access for recreational drug use would be a low-cost intravenous to being exploring ways to reduce infection among this subpopulation.

Though Native Americans had the greatest unadjusted and adjusted rates of vascular access infection, they had the lowest unadjusted and adjusted likelihoods of vascular access infections being related to MRSA, a common causes of access infection in the study, suggesting the etiologies of their infection are different from patients of other races. More directed exploration using Indian Health Services retrospective institutional data could clarify how the etiology of vascular access infections and infection risk may differ among Native Americans with ESKD.

*Chapter 4: Opioid Use for Vascular Access Creation*

The differences in dosage of opioid between those prescribed for graft versus fistula, combined with the lack of difference in whether or not someone received an opioid due to access type, suggest the decision-making processes for whether or not an opioid is prescribed and how much is prescribed are separate processes; whether or not they are independent or conditional is a topic for future research, either using qualitative, quantitative, or mixed methods approaches for addressing surgeon decision making.

Future analyses may wish to account for variability in access type using a random slope, or by including a selection equation for the opioid dosage model. This study was intended as a preliminary analysis focused on describing the current state of filled opioid prescriptions among vascular access patients, rather than an attempt to model the true state of all relationships underlying opioid prescription for vascular access.

## Appendices

Appendix 1. Aim 1 Variable Definitions and Operationalizations

| Dependent Variables | | | |
|---|---|---|---|
| **Measure** | **Operationalization** | **Data Elements Used** | **Source** |
| Permanent Vascular Access | 0 = Tunneled Hemodialysis Catheter; 1 = Maturing or Permanent Access (AVF or AVG). Access type from patients supersedes access type in CROWNWeb | **accesstype** (THC = 3; AVF = 1; AVG = 2) from patients. **access**_type_id (THC = 19; AVF = 14,15,16,22; AVG = 17,18,23) in conjunction with report_**month**_year for timing of access, both from CROWNWeb. **avfmaturing** (1 = maturing AVF) and **avgmaturing** (1 = maturing AVG) from 2728. | USRDS: patients, CROWNWeb, and Form 2728 |
| Pre-ESKD Nephrology Care (Form 2728) | 0 = No Care or Care <6mo pre-ESKD; 1 = Care at least 6mo pre-ESKD nephrology care | **nephcarerange** (<6mo, 6-12mo, >12mo) | USRDS: Form 2728 |
| Pre-ESKD Nephrology Care (Medicare Claims) | 0 = No Care or Care <6mo pre-ESKD; 1 = Care at least 6mo pre-ESKD nephrologist office visit | **hcpcs** (99241, 99242, 99243, 99244, 99245, 99211, 99212, 99213, 99214, 99215, 99201, 99202, 99203, 99204, 99205, 9940X, 99410, 99411, 99412, 99381, 99382, 99383, 99384, 99385, 99386, 99387, 99391, 99392, 99393, 99394, 99395, 99396, 99397) from ps_line_xxxx in conjunction with **splty** (39 [nephrologist]) occurring between 6 and 12months | USRDS: ps_line_xxxx (xxxx = 2012-2017) |
| **Independent Variables and Sub-Group Variable** | | | |
| **Measure** | **Operationalization** | **Data Elements Used** | **Source** |
| Medicare 1 Year Pre-ESKD ***(Sub-Group Variable)*** | 1 = Medicare Parts A & B at least 1 Year Prior to Dialysis Start; 0 = Less than 1 year of Medicare prior to Dialysis Start | **first_mcare_pta_start** and **first_mcare_ptb_start** in the patients file; **first_se** from the patients file. | USRDS: patients |
| Year of First Dialysis for ESKD | Continuous Year Values | **incyear** (continuous year at first ESRD service) | USRDS: patients |
| Age | 1 = 18-29; 2 = 30-49; 3 = 50-54; 4 = 65-79; 5 = 80+ | **incage** (continuous age at first ERSD service) | USRDS: patients |
| Sex | 1 = Male; 2 = Female. Patient sex was superseded by form 2728 sex if there was a conflict. Non-missing sex was used if one or the other was missing. | **sex** (1 = male; 2 = female) from patients. **sex** (M = Male; F = female) from 2728. | USRDS: patients & 2728 form |
| Race | 1 = Non-Hispanic White; 2 = Non-Hispanic Black; 3 = Hispanic; 4 = Asian; 5 = Pacific Islander; 6 = Native American; 7 = other/unknown. Patient race from Form 2728 superseded patient race from patients file, unless patient race was White in the 2728 and a minority in the patients file. | **race** (1 = white; 2 = black; 3 = Native American; 4 = Asian; 5 = Pacific Islander) and **ethn** (1 = Hispanic) from the patients file and **race** (same coding) and **hispanic** (same coding) from the 2728. | USRDS: patients & 2728 form |
| Median Zip-Code Level Income | Median Income in Zip Code (in units of $10,000 USD) | **median** (continuous variable in US dollars for median income within each Zip code) | American Community Survey: 2006-2010 & 2017 |

| | | | |
|---|---|---|---|
| Primary Cause of Renal Failure | 1 = Diabetes; 2 = Hypertension; 3 = Glomerulonephritis; 4 = Cystic kidney; 98 = Other urologic; 99 = Other/Unknown/Missing | **disgrpc** (diabetes, hypertension, glomerulonephritis, cystic kidney disease, other urologic, unknown/other/missing) | USRDS: patients |
| Diabetes | 0 = no; 1 = yes | At least one of the following is "Y": **como_diabprim, como_dm_ins, como_dm_nomeds, como_dm_ora, como_dm_ret** | USRDS: Form 2728 |
| Coronary Artery Disease | 0 = no; 1 = yes | At least one of the following is "Y": **como_mi, como_ashd, como_ihd** | USRDS: Form 2728 |
| Peripheral Vascular Disease | 0 = no; 1 = yes | **malignency** (Y, N) | USRDS: Form 2728 |
| Heart Failure | 0 = no; 1 = yes | **como_chr** (Y, N) | USRDS: Form 2728 |
| COPD | 0 = no; 1 = yes | **como_copd** (Y, N) | USRDS: Form 2728 |
| Alcohol Dependence | 0 = no; 1 = yes | **como_alcho** (Y, N) | USRDS: Form 2728 |
| Drug Dependence | 0 = no; 1 = yes | **como_drug** (Y, N) | USRDS: Form 2728 |
| Requires Assistance with ADL | 0 = no; 1 = yes | **como_needasst** (Y, N) | USRDS: Form 2728 |
| Institutionalized | 0 = no; 1 = yes | **como_inst** (Y, N) | USRDS: Form 2728 |
| Rural-Urban Continuum (County-Level) | 1 = Metro, 1+ mil; 2 = Metro, 0.25-1mil; 3 = Metro, <0.25mil; 4 = Urban 20k+, Metro Adj.; 5 = Urban 20k+, Not Adj.; 6 = Urban 2.5-19.9K, Metro Adj.; 7 = Urban 2.5-19.9K, Not Adj.; 8 = Completely Rural, Metro Adj.; 9 = Completely Rural, Not Adj. | **f0002013** (Rural-Urban Continuum Code-2013) | Area Health Resource Files (2015) |
| Internal Medicine Subspecialists (County-Level) | 0 = None; 1 = 1-10; 2 = 11-100; 3 = 101-300; 4 =301+ | **f1172415** (Continuous value for number of internal medicine subspecialists in County) | Area Health Resource Files (2015) |
| ESRD Network | Numeric Categories from 1 to 18 | **network** (Numeric Categories from 1 to 18) | USRDS: patients |

Appendix 2. Cohorts with and without 1+ year pre-ESKD Medicare enrollment

| Variables | Insufficient Medicare N=296,575 | 1+ Year Medicare N=437,933 | p-value |
|---|---|---|---|
| | Row % | Row % | |
| Sex | | | <0.001 |
| Male | 41.5 | 58.5 | |
| Female | 38.9 | 61.1 | |
| Age at first ESKD Service | | | <0.001 |
| 18-29 | 93.5 | 6.5 | |
| 30-49 | 82.6 | 17.4 | |
| 50-64 | 67.9 | 32.1 | |
| 65-79 | 9.6 | 90.4 | |
| 80+ | 3.6 | 96.4 | |
| Race | | | <0.001 |
| Non-Hispanic White | 31.2 | 68.8 | |
| Non-Hispanic Black | 46.5 | 53.5 | |
| Hispanic | 56.8 | 43.2 | |
| Asian | 50.8 | 49.2 | |
| Pacific Islander | 60.6 | 39.4 | |
| Native American | 57.6 | 42.4 | |
| Other/Unknown | 94.8 | 5.2 | |
| Median Income in Zip Code | 5.0 ± 1.9 | 5.2 ± 2.0 | <0.001 |
| Primary Cause of Renal Failure | | | <0.001 |
| Diabetes | 39.5 | 60.5 | |
| Hypertension | 37.2 | 62.8 | |
| Glomerulonephritis | 57.5 | 42.5 | |
| Cystic kidney | 62.4 | 37.6 | |
| Other urologic | 39.0 | 61.0 | |
| Other/Unknown/Missing | 39.2 | 60.8 | |
| Rural-Urban Continuum Code 2013 | | | <0.001 |
| Metro, 1+ mil | 43.0 | 57.0 | |
| Metro, 0.25-1mil | 39.2 | 60.8 | |
| Metro, <0.25mil | 35.9 | 64.1 | |
| Urban 20k+, Metro Adj. | 33.9 | 66.1 | |
| Urban 20k+, Not Adj. | 37.5 | 62.5 | |
| Urban 2.5-19.9K, Metro Adj. | 34.5 | 65.5 | |
| Urban 2.5-19.9K, Not Adj. | 34.7 | 65.3 | |
| Completely Rural, Metro Adj. | 34.7 | 65.3 | |
| Completely Rural, Not Adj. | 34.7 | 65.3 | |

Appendix 3. Naïve and Recursive Bivariate Probit Coefficients, Outcome Equations Only

| | Probit | | | Biprobit | | | Seemingly Unrelated Estimation |
|---|---|---|---|---|---|---|---|
| | Coef. | 95% CI | P-value | Coef. | 95% CI | P-value | P-value |
| None/Within 6 Months Pre-ESKD | Reference | | | Reference | | | |
| Nephrology Care 6+ Months Pre-ESKD | 0.47 | [0.45,0.48] | <0.0001 | 1.64 | [1.63,1.65] | <0.0001 | <0.0001 |
| Non-Hispanic White | <0.0001 | [0.00,0.00] | | <0.0001 | [0.00,0.00] | . | |
| Non-Hispanic Black | 0.21 | [0.14,0.28] | <0.0001 | 0.12 | [0.06,0.19] | 0.0002 | 0.0001 |
| Hispanic | 0.22 | [0.13,0.31] | <0.0001 | 0.11 | [0.02,0.19] | 0.0143 | 0.0001 |
| Asian | 0.25 | [0.08,0.41] | 0.0036 | 0.1 | [-0.05,0.25] | 0.1904 | 0.0035 |
| Pacific Islander | -0.01 | [-0.47,0.46] | 0.9745 | -0.17 | [-0.59,0.25] | 0.4355 | 0.219 |
| Native American | -0.33 | [-0.85,0.19] | 0.211 | -0.45 | [-0.91,0.02] | 0.0617 | 0.4573 |
| Nephrology Care 6+ Months Pre-ESKD # Non-Hispanic White | Reference | | | Reference | | | |
| Nephrology Care 6+ Months Pre-ESKD # Non-Hispanic Black | -0.15 | [-0.17,-0.13] | <0.0001 | -0.1 | [-0.11,-0.08] | <0.0001 | <0.0001 |
| Nephrology Care 6+ Months Pre-ESKD # Hispanic | -0.19 | [-0.22,-0.16] | <0.0001 | -0.1 | [-0.12,-0.08] | <0.0001 | <0.0001 |
| Nephrology Care 6+ Months Pre-ESKD # Asian | -0.23 | [-0.28,-0.19] | <0.0001 | -0.16 | [-0.19,-0.12] | <0.0001 | <0.0001 |
| Nephrology Care 6+ Months Pre-ESKD # Pacific Islander | -0.29 | [-0.40,-0.18] | <0.0001 | -0.19 | [-0.27,-0.12] | <0.0001 | <0.0001 |
| Nephrology Care 6+ Months Pre-ESKD # Native American | -0.04 | [-0.15,0.06] | 0.3986 | -0.03 | [-0.10,0.05] | 0.4794 | 0.2559 |
| 1:New England | Reference | | | Reference | | | |
| 2:New York | 0.06 | [0.03,0.10] | 0.0001 | 0.2 | [0.17,0.23] | <0.0001 | <0.0001 |
| 3:New Jersey | -0.06 | [-0.10,-0.02] | 0.0019 | -0.04 | [-0.08,-0.01] | 0.0142 | <0.0001 |
| 4:PA/DE | -0.14 | [-0.18,-0.11] | <0.0001 | 0.08 | [0.05,0.11] | <0.0001 | <0.0001 |
| 5:DC/MD/VA/WV | -0.31 | [-0.35,-0.28] | <0.0001 | -0.17 | [-0.20,-0.14] | <0.0001 | <0.0001 |
| 6:NC/SC/GA | -0.1 | [-0.13,-0.07] | <0.0001 | -0.01 | [-0.04,0.02] | 0.3907 | <0.0001 |
| 7:Florida | -0.23 | [-0.26,-0.19] | <0.0001 | -0.1 | [-0.12,-0.07] | <0.0001 | <0.0001 |
| 8:TN/AL/MI | -0.12 | [-0.16,-0.09] | <0.0001 | 0.04 | [0.01,0.07] | 0.01 | <0.0001 |
| 9:OH/IL/KY | -0.17 | [-0.20,-0.14] | <0.0001 | -0.02 | [-0.05,0.01] | 0.1374 | <0.0001 |
| 10:Indiana | -0.34 | [-0.38,-0.31] | <0.0001 | -0.23 | [-0.26,-0.20] | <0.0001 | <0.0001 |
| 11:MI/WI/MN/ND/SD | -0.14 | [-0.17,-0.11] | <0.0001 | 0.05 | [0.03,0.08] | 0.0002 | <0.0001 |
| 12:NE/KS/IA/MO | -0.22 | [-0.25,-0.18] | <0.0001 | -0.1 | [-0.13,-0.07] | <0.0001 | <0.0001 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 13:LA/AR/OK | -0.31 | [-0.35,-0.27] | <0.0001 | -0.14 | [-0.17,-0.10] | <0.0001 | <0.0001 |
| 14:Texas | -0.19 | [-0.23,-0.16] | <0.0001 | -0.07 | [-0.09,-0.04] | <0.0001 | <0.0001 |
| 15:NV/UT/WY/CO/AZ/NM | -0.11 | [-0.15,-0.08] | <0.0001 | 0.05 | [0.02,0.08] | 0.001 | <0.0001 |
| 16:WA/OR/ID/MT/AK | 0.1 | [0.06,0.14] | <0.0001 | 0.21 | [0.18,0.24] | <0.0001 | <0.0001 |
| 17:NorCal/HI | -0.13 | [-0.17,-0.09] | <0.0001 | 0.12 | [0.08,0.15] | <0.0001 | <0.0001 |
| 18:SoCal | -0.22 | [-0.25,-0.18] | <0.0001 | 0.12 | [0.09,0.15] | <0.0001 | <0.0001 |
| 2:New York # Non-Hispanic White | Reference | | | Reference | | | |
| 2:New York # Non-Hispanic Black | 0.01 | [-0.07,0.09] | 0.7922 | 0.11 | [0.04,0.18] | 0.0027 | <0.0001 |
| 2:New York # Hispanic | 0.08 | [-0.03,0.18] | 0.1537 | 0.22 | [0.13,0.32] | <0.0001 | <0.0001 |
| 2:New York # Asian | -0.01 | [-0.19,0.17] | 0.8805 | <0.0001 | [-0.16,0.17] | 0.9628 | 0.7469 |
| 2:New York # Pacific Islander | 0.34 | [-0.19,0.87] | 0.205 | 0.49 | [0.01,0.97] | 0.0464 | 0.3332 |
| 2:New York # Native American | 0.38 | [-0.23,1.00] | 0.2234 | 0.39 | [-0.17,0.95] | 0.1768 | 0.9906 |
| 3:New Jersey # Non-Hispanic White | Reference | | | Reference | | | |
| 3:New Jersey # Non-Hispanic Black | 0.01 | [-0.07,0.10] | 0.7439 | 0.12 | [0.04,0.20] | 0.0034 | 0.0001 |
| 3:New Jersey # Hispanic | <0.0001 | [-0.12,0.12] | 0.9984 | 0.1 | [-0.01,0.21] | 0.0773 | 0.009 |
| 3:New Jersey # Asian | 0.12 | [-0.09,0.33] | 0.2665 | 0.24 | [0.05,0.43] | 0.0136 | 0.0596 |
| 3:New Jersey # Pacific Islander | 0.16 | [-0.40,0.72] | 0.5743 | 0.34 | [-0.16,0.85] | 0.1831 | 0.2428 |
| 3:New Jersey # Native American | 0.3 | [-0.84,1.45] | 0.6066 | 0.94 | [-0.14,2.03] | 0.089 | 0.0015 |
| 4:PA/DE # Non-Hispanic White | Reference | | | Reference | | | |
| 4:PA/DE # Non-Hispanic Black | 0.07 | [-0.01,0.16] | 0.0865 | 0.04 | [-0.03,0.12] | 0.2563 | 0.2467 |
| 4:PA/DE # Hispanic | 0.01 | [-0.13,0.16] | 0.843 | 0.02 | [-0.11,0.15] | 0.7277 | 0.8494 |
| 4:PA/DE # Asian | -0.06 | [-0.32,0.19] | 0.6294 | -0.22 | [-0.46,0.01] | 0.0567 | 0.0377 |
| 4:PA/DE # Pacific Islander | -0.56 | [-1.39,0.26] | 0.1814 | -0.27 | [-0.99,0.44] | 0.4585 | 0.2114 |
| 4:PA/DE # Native American | -0.2 | [-1.62,1.22] | 0.7777 | -0.26 | [-1.50,0.97] | 0.6771 | 0.8914 |
| 5:DC/MD/VA/WV # Non-Hispanic White | Reference | | | Reference | | | |
| 5:DC/MD/VA/WV # Non-Hispanic Black | -0.05 | [-0.12,0.03] | 0.2513 | -0.07 | [-0.14,-0.00] | 0.0499 | 0.2852 |
| 5:DC/MD/VA/WV # Hispanic | 0.06 | [-0.10,0.23] | 0.4396 | 0.08 | [-0.07,0.22] | 0.3052 | 0.8002 |
| 5:DC/MD/VA/WV # Asian | <0.0001 | [-0.20,0.19] | 0.9627 | 0.08 | [-0.11,0.26] | 0.4134 | 0.1942 |
| 5:DC/MD/VA/WV # Pacific Islander | -0.04 | [-0.59,0.52] | 0.896 | 0.22 | [-0.28,0.72] | 0.3857 | 0.1088 |
| 5:DC/MD/VA/WV # Native American | 0.23 | [-0.77,1.24] | 0.6522 | 0.25 | [-0.65,1.16] | 0.579 | 0.9393 |
| 6:NC/SC/GA # Non-Hispanic White | Reference | | | Reference | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 6:NC/SC/GA # Non-Hispanic Black | -0.07 | [-0.14,0.01] | 0.0706 | 0.01 | [-0.06,0.08] | 0.734 | 0.0003 |
| 6:NC/SC/GA # Hispanic | -0.24 | [-0.39,-0.09] | 0.0014 | -0.18 | [-0.32,-0.05] | 0.0084 | 0.1846 |
| 6:NC/SC/GA # Asian | -0.09 | [-0.31,0.14] | 0.4524 | -0.06 | [-0.27,0.14] | 0.5405 | 0.7473 |
| 6:NC/SC/GA # Pacific Islander | 0.18 | [-0.41,0.77] | 0.5488 | 0.33 | [-0.21,0.86] | 0.2314 | 0.4123 |
| 6:NC/SC/GA # Native American | 0.41 | [-0.14,0.97] | 0.142 | 0.22 | [-0.28,0.73] | 0.3794 | 0.2535 |
| 7:Florida # Non-Hispanic White | Reference | | | Reference | | | |
| 7:Florida # Non-Hispanic Black | -0.02 | [-0.10,0.05] | 0.5373 | 0.15 | [0.08,0.22] | <0.0001 | <0.0001 |
| 7:Florida # Hispanic | -0.12 | [-0.23,-0.02] | 0.0182 | 0.16 | [0.07,0.26] | 0.0007 | <0.0001 |
| 7:Florida # Asian | 0.03 | [-0.18,0.25] | 0.7803 | 0.17 | [-0.02,0.37] | 0.0816 | 0.0348 |
| 7:Florida # Pacific Islander | 0.28 | [-0.26,0.83] | 0.3036 | 0.44 | [-0.05,0.93] | 0.0803 | 0.3276 |
| 7:Florida # Native American | 0.68 | [-0.08,1.44] | 0.0779 | 0.61 | [-0.07,1.29] | 0.0783 | 0.7843 |
| 8:TN/AL/MI # Non-Hispanic White | Reference | | | Reference | | | |
| 8:TN/AL/MI # Non-Hispanic Black | -0.07 | [-0.15,0.01] | 0.0734 | -0.03 | [-0.10,0.04] | 0.3877 | 0.0882 |
| 8:TN/AL/MI # Hispanic | -0.19 | [-0.41,0.03] | 0.0832 | -0.12 | [-0.32,0.07] | 0.2188 | 0.2995 |
| 8:TN/AL/MI # Asian | -0.18 | [-0.48,0.12] | 0.2414 | -0.29 | [-0.56,-0.02] | 0.0361 | 0.2351 |
| 8:TN/AL/MI # Pacific Islander | 0.24 | [-0.44,0.92] | 0.4871 | 0.19 | [-0.42,0.80] | 0.5447 | 0.8093 |
| 8:TN/AL/MI # Native American | -0.12 | [-0.77,0.52] | 0.7082 | 0.19 | [-0.38,0.77] | 0.5142 | 0.1031 |
| 9:OH/IL/KY # Non-Hispanic White | Reference | | | Reference | | | |
| 9:OH/IL/KY # Non-Hispanic Black | <0.0001 | [-0.08,0.08] | 0.9857 | -0.01 | [-0.08,0.06] | 0.8197 | 0.7494 |
| 9:OH/IL/KY # Hispanic | -0.19 | [-0.33,-0.04] | 0.0106 | -0.09 | [-0.22,0.03] | 0.1522 | 0.0384 |
| 9:OH/IL/KY # Asian | -0.14 | [-0.41,0.13] | 0.3015 | -0.08 | [-0.32,0.17] | 0.5447 | 0.4126 |
| 9:OH/IL/KY # Pacific Islander | 0.42 | [-0.20,1.04] | 0.186 | 0.41 | [-0.15,0.97] | 0.1517 | 0.9673 |
| 9:OH/IL/KY # Native American | -0.24 | [-1.25,0.77] | 0.6431 | -0.13 | [-0.99,0.74] | 0.7727 | 0.7314 |
| 10:Indiana # Non-Hispanic White | Reference | | | Reference | | | |
| 10:Indiana # Non-Hispanic Black | -0.15 | [-0.24,-0.07] | 0.0003 | -0.03 | [-0.11,0.04] | 0.3794 | <0.0001 |
| 10:Indiana # Hispanic | -0.05 | [-0.17,0.07] | 0.4048 | -0.03 | [-0.14,0.08] | 0.6025 | 0.5554 |
| 10:Indiana # Asian | -0.11 | [-0.31,0.10] | 0.3143 | <0.0001 | [-0.18,0.19] | 0.9665 | 0.0862 |
| 10:Indiana # Pacific Islander | 0.09 | [-0.59,0.77] | 0.7996 | 0.52 | [-0.08,1.13] | 0.0902 | 0.0244 |
| 10:Indiana # Native American | <0.0001 | [-1.10,1.11] | 0.9936 | 0.08 | [-0.89,1.05] | 0.8719 | 0.8263 |
| 11:MI/WI/MN/ND/SD # Non-Hispanic White | Reference | | | Reference | | | |
| 11:MI/WI/MN/ND/SD # Non-Hispanic Black | -0.2 | [-0.28,-0.12] | <0.0001 | -0.2 | [-0.28,-0.13] | <0.0001 | 0.8853 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 11:MI/WI/MN/ND/SD # Hispanic | -0.09 | [-0.23,0.05] | 0.2046 | -0.09 | [-0.21,0.04] | 0.1799 | 0.9303 |
| 11:MI/WI/MN/ND/SD # Asian | -0.14 | [-0.35,0.06] | 0.1701 | -0.17 | [-0.35,0.02] | 0.0773 | 0.6983 |
| 11:MI/WI/MN/ND/SD # Pacific Islander | 0.38 | [-0.21,0.97] | 0.208 | 0.37 | [-0.17,0.90] | 0.1784 | 0.9483 |
| 11:MI/WI/MN/ND/SD # Native American | 0.43 | [-0.09,0.96] | 0.1076 | 0.42 | [-0.06,0.89] | 0.0868 | 0.9238 |
| 12:NE/KS/IA/MO # Non-Hispanic White | Reference | | | Reference | | | |
| 12:NE/KS/IA/MO # Non-Hispanic Black | -0.03 | [-0.11,0.06] | 0.5543 | 0.04 | [-0.04,0.11] | 0.3887 | 0.02 |
| 12:NE/KS/IA/MO # Hispanic | -0.19 | [-0.35,-0.03] | 0.0184 | -0.17 | [-0.31,-0.02] | 0.0227 | 0.6317 |
| 12:NE/KS/IA/MO # Asian | -0.02 | [-0.30,0.26] | 0.8926 | 0.04 | [-0.21,0.30] | 0.7363 | 0.474 |
| 12:NE/KS/IA/MO # Pacific Islander | 0.31 | [-0.38,1.00] | 0.3768 | 0.65 | [0.02,1.27] | 0.0419 | 0.0948 |
| 12:NE/KS/IA/MO # Native American | 0.28 | [-0.32,0.87] | 0.3638 | 0.25 | [-0.29,0.79] | 0.3714 | 0.8678 |
| 13:LA/AR/OK # Non-Hispanic White | Reference | | | Reference | | | |
| 13:LA/AR/OK # Non-Hispanic Black | 0.04 | [-0.04,0.12] | 0.3641 | 0.05 | [-0.02,0.13] | 0.1524 | 0.5093 |
| 13:LA/AR/OK # Hispanic | -0.28 | [-0.46,-0.10] | 0.0022 | -0.15 | [-0.31,0.01] | 0.0644 | 0.0207 |
| 13:LA/AR/OK # Asian | -0.08 | [-0.38,0.22] | 0.5856 | <0.0001 | [-0.27,0.27] | 0.9842 | 0.3755 |
| 13:LA/AR/OK # Pacific Islander | 0.18 | [-0.48,0.84] | 0.5979 | 0.4 | [-0.20,0.99] | 0.1894 | 0.2385 |
| 13:LA/AR/OK # Native American | 0.41 | [-0.11,0.94] | 0.1246 | 0.37 | [-0.11,0.85] | 0.1284 | 0.7902 |
| 14:Texas # Non-Hispanic White | Reference | | | Reference | | | |
| 14:Texas # Non-Hispanic Black | -0.12 | [-0.20,-0.04] | 0.0027 | -0.03 | [-0.10,0.04] | 0.4079 | 0.0001 |
| 14:Texas # Hispanic | -0.23 | [-0.33,-0.13] | <0.0001 | -0.09 | [-0.18,0.00] | 0.0522 | <0.0001 |
| 14:Texas # Asian | -0.21 | [-0.40,-0.01] | 0.0362 | -0.18 | [-0.35,-0.00] | 0.0477 | 0.6235 |
| 14:Texas # Pacific Islander | 0.34 | [-0.19,0.87] | 0.2061 | 0.37 | [-0.11,0.85] | 0.1291 | 0.8408 |
| 14:Texas # Native American | 0.62 | [-0.11,1.34] | 0.095 | 0.62 | [-0.03,1.28] | 0.0621 | 0.979 |
| 15:NV/UT/WY/CO/AZ/NM # Non-Hispanic White | Reference | | | Reference | | | |
| 15:NV/UT/WY/CO/AZ/NM # Non-Hispanic Black | -0.29 | [-0.39,-0.18] | <0.0001 | -0.2 | [-0.30,-0.11] | <0.0001 | 0.0067 |
| 15:NV/UT/WY/CO/AZ/NM # Hispanic | -0.13 | [-0.23,-0.02] | 0.0183 | <0.0001 | [-0.10,0.09] | 0.9299 | 0.0002 |
| 15:NV/UT/WY/CO/AZ/NM # Asian | -0.03 | [-0.24,0.18] | 0.769 | 0.02 | [-0.17,0.21] | 0.8223 | 0.4107 |
| 15:NV/UT/WY/CO/AZ/NM # Pacific Islander | 0.22 | [-0.28,0.72] | 0.3865 | 0.29 | [-0.17,0.74] | 0.2181 | 0.6543 |
| 15:NV/UT/WY/CO/AZ/NM # Native American | 0.54 | [0.02,1.06] | 0.0417 | 0.58 | [0.11,1.05] | 0.0165 | 0.8154 |
| 16:WA/OR/ID/MT/AK # Non-Hispanic White | Reference | | | Reference | | | |
| 16:WA/OR/ID/MT/AK # Non-Hispanic Black | -0.01 | [-0.14,0.12] | 0.9227 | -0.07 | [-0.19,0.05] | 0.2601 | 0.1222 |
| 16:WA/OR/ID/MT/AK # Hispanic | -0.02 | [-0.15,0.12] | 0.8249 | 0.04 | [-0.08,0.17] | 0.4991 | 0.177 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 16:WA/OR/ID/MT/AK # Asian | -0.05 | [-0.25,0.14] | 0.5857 | -0.15 | [-0.33,0.03] | 0.0966 | 0.1103 |
| 16:WA/OR/ID/MT/AK # Pacific Islander | 0.09 | [-0.41,0.59] | 0.722 | 0.13 | [-0.32,0.58] | 0.5698 | 0.7758 |
| 16:WA/OR/ID/MT/AK # Native American | 0.27 | [-0.26,0.81] | 0.3195 | 0.19 | [-0.29,0.68] | 0.4358 | 0.6247 |
| 17:NorCal/HI # Non-Hispanic White | Reference | | | Reference | | | |
| 17:NorCal/HI # Non-Hispanic Black | 0.01 | [-0.08,0.11] | 0.8142 | 0.08 | [-0.00,0.17] | 0.0586 | 0.0113 |
| 17:NorCal/HI # Hispanic | -0.13 | [-0.23,-0.02] | 0.0193 | -0.13 | [-0.23,-0.03] | 0.0077 | 0.8929 |
| 17:NorCal/HI # Asian | 0.11 | [-0.06,0.28] | 0.1985 | 0.21 | [0.05,0.36] | 0.009 | 0.0669 |
| 17:NorCal/HI # Pacific Islander | 0.37 | [-0.10,0.84] | 0.1189 | 0.51 | [0.08,0.94] | 0.0189 | 0.3012 |
| 17:NorCal/HI # Native American | 0.49 | [-0.09,1.07] | 0.0947 | 0.53 | [0.01,1.06] | 0.0472 | 0.8259 |
| 18:SoCal # Non-Hispanic White | Reference | | | Reference | | | |
| 18:SoCal # Non-Hispanic Black | -0.19 | [-0.28,-0.10] | <0.0001 | -0.03 | [-0.11,0.05] | 0.3945 | <0.0001 |
| 18:SoCal # Hispanic | -0.18 | [-0.28,-0.08] | 0.0003 | -0.05 | [-0.14,0.04] | 0.2457 | <0.0001 |
| 18:SoCal # Asian | -0.08 | [-0.25,0.09] | 0.3473 | -0.04 | [-0.19,0.12] | 0.6219 | 0.4085 |
| 18:SoCal # Pacific Islander | 0.19 | [-0.29,0.67] | 0.4339 | 0.36 | [-0.07,0.79] | 0.1032 | 0.206 |
| 18:SoCal # Native American | 0.32 | [-0.29,0.92] | 0.3098 | 0.37 | [-0.18,0.92] | 0.1841 | 0.7522 |
| Male | Reference | | | Reference | | | |
| Female | -0.07 | [-0.08,-0.07] | <0.0001 | -0.08 | [-0.09,-0.08] | <0.0001 | 0.0001 |
| 18-29 | Reference | | | Reference | | | . |
| 30-49 | 0.2 | [0.12,0.29] | <0.0001 | 0.14 | [0.07,0.22] | 0.0001 | 0.0102 |
| 50-64 | 0.25 | [0.17,0.33] | <0.0001 | 0.21 | [0.13,0.28] | <0.0001 | 0.0652 |
| 65-79 | 0.22 | [0.14,0.30] | <0.0001 | 0.18 | [0.11,0.25] | <0.0001 | 0.0754 |
| 80+ | 0.1 | [0.02,0.18] | 0.0148 | 0.07 | [-0.00,0.14] | 0.0632 | 0.1821 |
| No ADL Impairment | Reference | | | Reference | | | |
| 1+ ADL Impairments | -0.18 | [-0.19,-0.17] | <0.0001 | -0.09 | [-0.10,-0.08] | <0.0001 | <0.0001 |
| Non-Institutionalized | Reference | | | Reference | | | |
| Assisted Living, Nursing Home | -0.33 | [-0.34,-0.31] | <0.0001 | -0.15 | [-0.16,-0.14] | <0.0001 | <0.0001 |
| Median Income in Zip Code | 0.01 | [0.01,0.01] | <0.0001 | -0.01 | [-0.02,-0.01] | <0.0001 | <0.0001 |
| Year of first ESRD service=2012 | Reference | | | Reference | | | 0.8092 |
| Year of first ESRD service=2013 | <0.0001 | [-0.02,0.02] | 0.8767 | <0.0001 | [-0.02,0.02] | 0.9894 | 0.0002 |
| Year of first ESRD service=2014 | -0.05 | [-0.06,-0.03] | <0.0001 | -0.03 | [-0.04,-0.01] | 0.0019 | <0.0001 |
| Year of first ESRD service=2015 | -0.06 | [-0.08,-0.04] | <0.0001 | -0.03 | [-0.05,-0.02] | <0.0001 | <0.0001 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Year of first ESRD service=2016 | -0.08 | [-0.10,-0.06] | <0.0001 | -0.04 | [-0.06,-0.03] | <0.0001 | <0.0001 |
| Year of first ESRD service=2017 | -0.08 | [-0.10,-0.06] | <0.0001 | -0.04 | [-0.05,-0.02] | <0.0001 | <0.0001 |
| Year of first ESRD service=2018 | -0.08 | [-0.10,-0.06] | <0.0001 | 0.08 | [0.06,0.10] | <0.0001 | <0.0001 |
| Metro, 1+ mil | Reference | | | Reference | | | |
| Metro, 0.25-1mil | 0.01 | [0.00,0.02] | 0.0252 | -0.05 | [-0.06,-0.04] | <0.0001 | <0.0001 |
| Metro, <0.25mil | -0.03 | [-0.05,-0.01] | 0.0001 | -0.13 | [-0.14,-0.12] | <0.0001 | <0.0001 |
| Urban 20k+, Metro Adj. | -0.02 | [-0.04,-0.00] | 0.0347 | -0.12 | [-0.14,-0.10] | <0.0001 | <0.0001 |
| Urban 20k+, Not Adj. | -0.04 | [-0.07,-0.00] | 0.0321 | -0.19 | [-0.22,-0.16] | <0.0001 | <0.0001 |
| Urban 2.5-19.9K, Metro Adj. | <0.0001 | [-0.02,0.01] | 0.6294 | -0.09 | [-0.11,-0.07] | <0.0001 | <0.0001 |
| Urban 2.5-19.9K, Not Adj. | 0.01 | [-0.01,0.04] | 0.2734 | -0.13 | [-0.15,-0.10] | <0.0001 | <0.0001 |
| Completely Rural, Metro Adj. | -0.03 | [-0.07,0.02] | 0.256 | -0.15 | [-0.19,-0.10] | <0.0001 | <0.0001 |
| Completely Rural, Not Adj. | -0.1 | [-0.14,-0.05] | 0.0001 | -0.21 | [-0.25,-0.17] | <0.0001 | <0.0001 |

Appendix 4. Bivariate Probit Coefficients, First Stage Equation for Probability of Pre-ESKD Nephrology Care

| | Coef. | 95% CI | P-value |
|---|---|---|---|
| 1:New England | Reference | | |
| 2:New York | -0.3 | [-0.33,-0.26] | <0.0001 |
| 3:New Jersey | -0.04 | [-0.08,-0.00] | 0.0346 |
| 4:PA/DE | -0.36 | [-0.39,-0.33] | <0.0001 |
| 5:DC/MD/VA/WV | -0.14 | [-0.18,-0.11] | <0.0001 |
| 6:NC/SC/GA | -0.15 | [-0.18,-0.12] | <0.0001 |
| 7:Florida | -0.17 | [-0.20,-0.13] | <0.0001 |
| 8:TN/AL/MI | -0.29 | [-0.32,-0.26] | <0.0001 |
| 9:OH/IL/KY | -0.22 | [-0.24,-0.19] | <0.0001 |
| 10:Indiana | -0.07 | [-0.10,-0.04] | 0.0001 |
| 11:MI/WI/MN/ND/SD | -0.3 | [-0.33,-0.27] | <0.0001 |
| 12:NE/KS/IA/MO | -0.13 | [-0.17,-0.10] | <0.0001 |
| 13:LA/AR/OK | -0.21 | [-0.25,-0.18] | <0.0001 |
| 14:Texas | -0.19 | [-0.22,-0.16] | <0.0001 |
| 15:NV/UT/WY/CO/AZ/NM | -0.28 | [-0.31,-0.24] | <0.0001 |
| 16:WA/OR/ID/MT/AK | -0.27 | [-0.30,-0.23] | <0.0001 |
| 17:NorCal/HI | -0.42 | [-0.46,-0.38] | <0.0001 |
| 18:SoCal | -0.56 | [-0.59,-0.53] | <0.0001 |
| Non-Hispanic White | Reference | | |
| Non-Hispanic Black | 0.01 | [-0.06,0.08] | 0.82 |
| Hispanic | 0.01 | [-0.08,0.10] | 0.8354 |
| Asian | 0.07 | [-0.10,0.23] | 0.4324 |
| Pacific Islander | 0.17 | [-0.30,0.65] | 0.4769 |
| Native American | 0.38 | [-0.13,0.88] | 0.1426 |
| 2:New York # Non-Hispanic White | Reference | | |
| 2:New York # Non-Hispanic Black | -0.18 | [-0.26,-0.10] | <0.0001 |
| 2:New York # Hispanic | -0.29 | [-0.40,-0.18] | <0.0001 |
| 2:New York # Asian | 0.01 | [-0.17,0.19] | 0.9073 |
| 2:New York # Pacific Islander | -0.34 | [-0.89,0.20] | 0.2199 |
| Asian | -0.26 | [-0.87,0.35] | 0.3993 |
| 3:New Jersey # Non-Hispanic White | Reference | | |
| 3:New Jersey # Non-Hispanic Black | -0.19 | [-0.27,-0.10] | <0.0001 |
| 3:New Jersey # Hispanic | -0.17 | [-0.29,-0.04] | 0.0079 |
| 3:New Jersey # Asian | -0.25 | [-0.46,-0.04] | 0.0178 |
| 3:New Jersey # Pacific Islander | -0.32 | [-0.89,0.26] | 0.2831 |
| 3:New Jersey # Native American | -1.66 | [-2.95,-0.37] | 0.0119 |
| 4:PA/DE # Non-Hispanic White | Reference | | |
| 4:PA/DE # Non-Hispanic Black | 0.05 | [-0.04,0.13] | 0.2755 |
| 4:PA/DE # Hispanic | 0.02 | [-0.12,0.16] | 0.77 |
| 4:PA/DE # Asian | 0.37 | [0.12,0.63] | 0.0045 |
| 4:PA/DE # Pacific Islander | -0.14 | [-0.88,0.59] | 0.7058 |
| 4:PA/DE # Native American | 0.34 | [-0.84,1.51] | 0.5768 |
| 5:DC/MD/VA/WV # Non-Hispanic White | Reference | | |
| 5:DC/MD/VA/WV # Non-Hispanic Black | 0.08 | [0.01,0.16] | 0.0349 |
| 5:DC/MD/VA/WV # Hispanic | -0.06 | [-0.22,0.10] | 0.4891 |
| 5:DC/MD/VA/WV # Asian | -0.13 | [-0.33,0.07] | 0.2077 |
| 5:DC/MD/VA/WV # Pacific Islander | -0.38 | [-0.93,0.18] | 0.1817 |

| | | | |
|---|---|---|---|
| 5:DC/MD/VA/WV # Native American | -0.2 | [-1.15,0.75] | 0.685 |
| 6:NC/SC/GA # Non-Hispanic White | Reference | | |
| 6:NC/SC/GA # Non-Hispanic Black | -0.1 | [-0.18,-0.03] | 0.0085 |
| 6:NC/SC/GA # Hispanic | 0.03 | [-0.11,0.18] | 0.6527 |
| 6:NC/SC/GA # Asian | 0.02 | [-0.20,0.25] | 0.8487 |
| 6:NC/SC/GA # Pacific Islander | -0.27 | [-0.86,0.33] | 0.3802 |
| 6:NC/SC/GA # Native American | 0.12 | [-0.42,0.67] | 0.6574 |
| 7:Florida # Non-Hispanic White | Reference | | |
| 7:Florida # Non-Hispanic Black | -0.3 | [-0.38,-0.22] | <0.0001 |
| 7:Florida # Hispanic | -0.43 | [-0.54,-0.33] | <0.0001 |
| 7:Florida # Asian | -0.22 | [-0.44,-0.01] | 0.0395 |
| 7:Florida # Pacific Islander | -0.38 | [-0.93,0.17] | 0.1778 |
| 7:Florida # Native American | -0.29 | [-1.01,0.44] | 0.4387 |
| 8:TN/AL/MI # Non-Hispanic White | Reference | | |
| 8:TN/AL/MI # Non-Hispanic Black | -0.02 | [-0.10,0.06] | 0.6405 |
| 8:TN/AL/MI # Hispanic | -0.01 | [-0.22,0.21] | 0.9468 |
| 8:TN/AL/MI # Asian | 0.32 | [0.02,0.62] | 0.0363 |
| 8:TN/AL/MI # Pacific Islander | 0.01 | [-0.67,0.69] | 0.9777 |
| 8:TN/AL/MI # Native American | -0.52 | [-1.13,0.09] | 0.0951 |
| 9:OH/IL/KY # Non-Hispanic White | Reference | | |
| 9:OH/IL/KY # Non-Hispanic Black | 0.04 | [-0.04,0.12] | 0.3377 |
| 9:OH/IL/KY # Hispanic | -0.05 | [-0.19,0.09] | 0.4698 |
| 9:OH/IL/KY # Asian | -0.02 | [-0.29,0.26] | 0.9039 |
| 9:OH/IL/KY # Pacific Islander | -0.14 | [-0.76,0.48] | 0.663 |
| 9:OH/IL/KY # Native American | -0.08 | [-0.94,0.78] | 0.8555 |
| 10:Indiana # Non-Hispanic White | Reference | | |
| 10:Indiana # Non-Hispanic Black | -0.11 | [-0.19,-0.02] | 0.0108 |
| 10:Indiana # Hispanic | 0.01 | [-0.11,0.13] | 0.8997 |
| 10:Indiana # Asian | -0.1 | [-0.31,0.10] | 0.3176 |
| 10:Indiana # Pacific Islander | -0.8 | [-1.46,-0.14] | 0.0169 |
| 10:Indiana # Native American | -0.16 | [-1.16,0.85] | 0.7563 |
| 11:MI/WI/MN/ND/SD # Non-Hispanic White | Reference | | |
| 11:MI/WI/MN/ND/SD # Non-Hispanic Black | 0.13 | [0.05,0.21] | 0.0011 |
| 11:MI/WI/MN/ND/SD # Hispanic | 0.04 | [-0.09,0.18] | 0.5161 |
| 11:MI/WI/MN/ND/SD # Asian | 0.13 | [-0.07,0.34] | 0.207 |
| 11:MI/WI/MN/ND/SD # Pacific Islander | -0.09 | [-0.69,0.50] | 0.7562 |
| 11:MI/WI/MN/ND/SD # Native American | -0.23 | [-0.74,0.29] | 0.3933 |
| 12:NE/KS/IA/MO # Non-Hispanic White | Reference | | |
| 12:NE/KS/IA/MO # Non-Hispanic Black | -0.08 | [-0.17,0.00] | 0.0579 |
| 12:NE/KS/IA/MO # Hispanic | 0.06 | [-0.10,0.22] | 0.4612 |
| 12:NE/KS/IA/MO # Asian | -0.1 | [-0.38,0.18] | 0.4979 |
| 12:NE/KS/IA/MO # Pacific Islander | -0.69 | [-1.38,0.01] | 0.052 |
| 12:NE/KS/IA/MO # Native American | -0.1 | [-0.70,0.49] | 0.7348 |
| 13:LA/AR/OK # Non-Hispanic White | Reference | | |
| 13:LA/AR/OK # Non-Hispanic Black | -0.03 | [-0.12,0.05] | 0.3995 |
| 13:LA/AR/OK # Hispanic | -0.05 | [-0.22,0.12] | 0.5429 |
| 13:LA/AR/OK # Asian | -0.09 | [-0.39,0.20] | 0.5431 |
| 13:LA/AR/OK # Pacific Islander | -0.4 | [-1.06,0.26] | 0.2314 |
| 13:LA/AR/OK # Native American | -0.17 | [-0.69,0.35] | 0.5252 |
| 14:Texas # Non-Hispanic White | Reference | | |

| | | | |
|---|---|---|---|
| 14:Texas # Non-Hispanic Black | -0.07 | [-0.15,0.01] | 0.0682 |
| 14:Texas # Hispanic | -0.12 | [-0.22,-0.03] | 0.0124 |
| 14:Texas # Asian | 0.1 | [-0.10,0.29] | 0.3317 |
| 14:Texas # Pacific Islander | -0.16 | [-0.70,0.39] | 0.5664 |
| 14:Texas # Native American | -0.39 | [-1.09,0.31] | 0.2752 |
| 15:NV/UT/WY/CO/AZ/NM # Non-Hispanic White | Reference | | |
| 15:NV/UT/WY/CO/AZ/NM # Non-Hispanic Black | 0 | [-0.10,0.10] | 0.9754 |
| 15:NV/UT/WY/CO/AZ/NM # Hispanic | -0.15 | [-0.25,-0.04] | 0.0061 |
| 15:NV/UT/WY/CO/AZ/NM # Asian | -0.07 | [-0.28,0.14] | 0.5129 |
| 15:NV/UT/WY/CO/AZ/NM # Pacific Islander | -0.18 | [-0.69,0.34] | 0.5003 |
| 15:NV/UT/WY/CO/AZ/NM # Native American | -0.41 | [-0.92,0.10] | 0.112 |
| 16:WA/OR/ID/MT/AK # Non-Hispanic White | Reference | | |
| 16:WA/OR/ID/MT/AK # Non-Hispanic Black | 0.13 | [0.00,0.26] | 0.0458 |
| 16:WA/OR/ID/MT/AK # Hispanic | -0.1 | [-0.24,0.03] | 0.134 |
| 16:WA/OR/ID/MT/AK # Asian | 0.21 | [0.02,0.41] | 0.0344 |
| 16:WA/OR/ID/MT/AK # Pacific Islander | -0.09 | [-0.61,0.42] | 0.7164 |
| 16:WA/OR/ID/MT/AK # Native American | -0.01 | [-0.54,0.52] | 0.9625 |
| 17:NorCal/HI # Non-Hispanic White | Reference | | |
| 17:NorCal/HI # Non-Hispanic Black | -0.11 | [-0.20,-0.01] | 0.0306 |
| 17:NorCal/HI # Hispanic | 0.09 | [-0.02,0.20] | 0.1053 |
| 17:NorCal/HI # Asian | -0.2 | [-0.37,-0.02] | 0.0249 |
| 17:NorCal/HI # Pacific Islander | -0.37 | [-0.85,0.12] | 0.1396 |
| 17:NorCal/HI # Native American | -0.37 | [-0.95,0.20] | 0.2017 |
| 18:SoCal # Non-Hispanic White | Reference | | |
| 18:SoCal # Non-Hispanic Black | -0.2 | [-0.29,-0.11] | <0.0001 |
| 18:SoCal # Hispanic | -0.12 | [-0.22,-0.02] | 0.0144 |
| 18:SoCal # Asian | 0.02 | [-0.15,0.19] | 0.8208 |
| 18:SoCal # Pacific Islander | -0.33 | [-0.82,0.16] | 0.1917 |
| 18:SoCal # Native American | -0.31 | [-0.90,0.29] | 0.3081 |
| 18-29 | Reference | | |
| 30-49 | -0.02 | [-0.10,0.06] | 0.6142 |
| 50-64 | -0.08 | [-0.16,-0.00] | 0.0458 |
| 65-79 | -0.07 | [-0.15,0.01] | 0.0791 |
| 80+ | -0.02 | [-0.10,0.06] | 0.6091 |
| Male | Reference | | |
| Female | 0.05 | [0.04,0.06] | <0.0001 |
| Median Income in Zip Code | 0.04 | [0.04,0.05] | <0.0001 |
| Diabetes | Reference | | |
| Hypertension | -0.04 | [-0.05,-0.03] | <0.0001 |
| Glomerulonephritis | -0.1 | [-0.11,-0.08] | <0.0001 |
| Cystic kidney | 0.37 | [0.34,0.40] | <0.0001 |
| Other urologic | -0.23 | [-0.26,-0.20] | <0.0001 |
| Other/Unknown/Missing | -0.45 | [-0.46,-0.43] | <0.0001 |
| No ADL Impairment | Reference | | |
| 1+ ADL Impairments | -0.06 | [-0.07,-0.05] | <0.0001 |
| Non-Institutionalized | Reference | | |
| Assisted Living, Nursing Home | -0.14 | [-0.15,-0.12] | <0.0001 |
| Year of first ESRD service=2012 | Reference | | |
| Year of first ESRD service=2013 | 0 | [-0.02,0.01] | 0.6277 |

| | | | |
|---|---|---|---|
| Year of first ESRD service=2014 | -0.02 | [-0.04,-0.00] | 0.0384 |
| Year of first ESRD service=2015 | -0.03 | [-0.04,-0.01] | 0.0031 |
| Year of first ESRD service=2016 | -0.04 | [-0.06,-0.02] | <0.0001 |
| Year of first ESRD service=2017 | -0.05 | [-0.07,-0.04] | <0.0001 |
| Year of first ESRD service=2018 | -0.27 | [-0.29,-0.25] | <0.0001 |
| Metro, 1+ mil | Reference | | |
| Metro, 0.25-1mil | 0.1 | [0.09,0.11] | <0.0001 |
| Metro, <0.25mil | 0.19 | [0.17,0.21] | <0.0001 |
| Urban 20k+, Metro Adj. | 0.18 | [0.16,0.20] | <0.0001 |
| Urban 20k+, Not Adj. | 0.29 | [0.26,0.32] | <0.0001 |
| Urban 2.5-19.9K, Metro Adj. | 0.15 | [0.12,0.17] | <0.0001 |
| Urban 2.5-19.9K, Not Adj. | 0.24 | [0.21,0.27] | <0.0001 |
| Completely Rural, Metro Adj. | 0.22 | [0.17,0.27] | <0.0001 |
| Completely Rural, Not Adj. | 0.24 | [0.20,0.29] | <0.0001 |
| None | Reference | | |
| 1-10 | -0.01 | [-0.02,0.01] | 0.3434 |
| 11-100 | 0 | [-0.02,0.01] | 0.7498 |
| 101-300 | -0.02 | [-0.04,-0.00] | 0.0237 |
| 301+ | -0.05 | [-0.07,-0.03] | <0.0001 |
| Diabetes Mellitus | 0.01 | [-0.00,0.02] | 0.0827 |
| Hypertension | 0.12 | [0.11,0.13] | <0.0001 |
| Coronary Artery Disease | 0.06 | [0.05,0.07] | <0.0001 |
| Peripheral Vascular Disease | 0.02 | [0.01,0.03] | 0.002 |
| Heart Failure | -0.08 | [-0.09,-0.07] | <0.0001 |
| Malignancy | 0.01 | [0.00,0.02] | 0.0321 |
| Stroke | 0 | [-0.01,0.02] | 0.4436 |
| Drug Dependence | -0.2 | [-0.24,-0.15] | <0.0001 |
| Alcohol Dependence | -0.26 | [-0.29,-0.22] | <0.0001 |
| COPD | -0.07 | [-0.08,-0.06] | <0.0001 |

Appendix 5. Aim 2 Variable Definitions and Operationalizations

| **Dependent Variables** | | | |
|---|---|---|---|
| **Measure** | **Operationalization** | **Data Elements Used** | **Source** |
| Hospitalization for Vascular Access Infection | 0 = No Infection; 1 = Access Infection | **primdiag**(996.62, 999.31, 999.32, 999.33, T827XXA, T80218A, T80219A, T80211A, T80212A) | USRDS: hosp_2010on (Hospitalization Data from year 2010 on) |
| MRSA Infection | 0 = Non-MRSA Infection; 1 = MRSA Infection | **hsdiag1-hsdiag26**(03812, 04112, A4902, B9562, A4902, A4102, A4101) | USRDS: hosp_2010on (Hospitalization Data from year 2010 on) |
| Permanent Vascular Access | 1 = Tunneled Hemodialysis Catheter; 0 = Arteriovenous Fistula or Arteriovenous Graft. | **access_type_id**(THC = 19; AVF = 14,15,16,22; AVG = 17,18,23) from CROWNWeb in conjunction with **first_se** for timing of access from first_se. | USRDS: patients, CROWNWeb, and Form 2728 |
| **Independent Variables and Sub-Group Variable** | | | |
| **Measure** | **Operationalization** | **Data Elements Used** | **Source** |
| Medicare 1 Year Pre-ESKD ***(Sub-Group Variable)*** | 1 = Medicare Parts A & B at least 1 Year Prior to Dialysis Start; 0 = Less than 1 year of Medicare prior to Dialysis Start | **first_mcare_pta_start** and **first_mcare_ptb_start** in the patients file; **first_se** from the patients file. | USRDS: patients |
| Pre-ESKD Nephrology Care (Medicare Claims) | 0 = No Care or Care <6mo pre-ESKD; 1 = Care at least 6mo pre-ESKD nephrologist office visit | **hcpcs** (99241, 99242, 99243, 99244, 99245, 99211, 99212, 99213, 99214, 99215, 99201, 99202, 99203, 99204, 99205, 9940X, 99410, 99411, 99412, 99381, 99382, 99383, 99384, 99385, 99386, 99387, 99391, 99392, 99393, 99394, 99395, 99396, 99397) from ps_line_xxxx in conjunction with **splty** (39 [nephrologist]) occurring between 6 and 12months | USRDS: ps_line_xxxx (xxxx = 2012-2017) |
| Year of First Dialysis for ESKD | Continuous Year Values | **incyear** (continuous year at first ESRD service) | USRDS: patients |
| Age | 1 = 18-29; 2 = 30-49; 3 = 50-54; 4 = 65-79; 5 = 80+ | **incage** (continuous age at first ERSD service) | USRDS: patients |
| Sex | 1 = Male; 2 = Female. Patient sex was superseded by form 2728 sex if there was a conflict. Non-missing sex was used if one or the other was missing. | **sex** (1 = male; 2 = female) from patients. **sex** (M = Male; F = female) from 2728. | USRDS: patients & 2728 form |
| Race | 1 = Non-Hispanic White; 2 = Non-Hispanic Black; 3 = Hispanic; 4 = Asian; 5 = Pacific Islander; 6 = Native American; 7 = other/unknown. Patient race from Form 2728 superseded patient race from patients file, unless patient race was White in the 2728 and a minority in the patients file. | **race** (1 = white; 2 = black; 3 = Native American; 4 = Asian; 5 = Pacific Islander) and **ethn** (1 = Hispanic) from the patients file and **race** (same coding) and **hispanic** (same coding) from the 2728. | USRDS: patients & 2728 form |

| | | | |
|---|---|---|---|
| Employment Status | 0 = Retired, Disabled, Medical Leave; 1 = Unemployed; 2 = Full-Time Employment; 3 = Part-Time Employment; 4 = Student | **empcur** (Full-Time, Part-Time, Unemployed, Disabled, Medical Leave, Retired, Student) | USRDS: 2728 form |
| Median Zip-Code Level Income | Median Income in Zip Code (in units of $10,000 USD) | **median** (continuous variable in US dollars for median income within each Zip code) | American Community Survey: 2006-2010 & 2017 |
| Diabetes | 0 = no; 1 = yes | At least one of the following is "Y": **como_diabprim, como_dm_ins, como_dm_nomeds, como_dm_ora, como_dm_ret** | USRDS: Form 2728 |
| Obese | 0 = no; 1 = yes | **bmi** (continuous variable; recoded into <30 to ≥30) | USRDS: Form 2728 |
| History of Illicit Drug Abuse or ICD for Opioid Abuse | 0 = no; 1 = yes | **como_drug** (Y, N) OR **diag**(304.0X, 304.7X, 305.5X, F11.X) | USRDS: Form 2728; Inpatient, Outpatient, Physician Claims from 2012-2017 |
| Requires Assistance with ADL | 0 = no; 1 = yes | **como_needasst** (Y, N) | USRDS: Form 2728 |
| Institutionalized | 0 = no; 1 = yes | **como_inst** (Y, N) | USRDS: Form 2728 |
| Number of hospitalizations during observation period | Continuous variable from 0 to 38 | Count the number of unique visits where **clm_from** and **clm_thru** are both within the range of observation time between **first_se** and the first event recorded. | USRDS: hosp_2010on (Hospitalization Data from year 2010 on) |
| Rural-Urban Continuum (County-Level) | 1 = Metro, 1+ mil; 2 = Metro, 0.25-1mil; 3 = Metro, <0.25mil; 4 = Urban 20k+, Metro Adj.; 5 = Urban 20k+, Not Adj.; 6 = Urban 2.5-19.9K, Metro Adj.; 7 = Urban 2.5-19.9K, Not Adj.; 8 = Completely Rural, Metro Adj.; 9 = Completely Rural, Not Adj. | **f0002013** (Rural-Urban Continuum Code-2013) | Area Health Resource Files (2015) |
| ESRD Network | Numeric Categories from 1 to 18 | **network** (Numeric Categories from 1 to 18) | USRDS: patients |

Appendix 6. Time to Event Outcomes by Patient Characteristics (Row Percentages)

| | No Hospitalizations | Hospitalized for VA Infection | Other Hospitalization | Transplant | Access Change | Medicare Enrollment Ended |
|---|---|---|---|---|---|---|
| | N=72,438 | N=9,156 | N=151,861 | N=824 | N=80,175 | N=72 |
| Index Access | | | | | | |
| AV[F/G] | 41.6 | 1.1 | 43.6 | 0.6 | 13.1 | 0.0 |
| THC | 16.6 | 3.5 | 49.9 | 0.2 | 29.8 | 0.0 |
| Sex | | | | | | |
| Male | 24.6 | 2.8 | 46.3 | 0.3 | 25.9 | 0.0 |
| Female | 20.9 | 3.0 | 50.8 | 0.2 | 25.0 | 0.0 |
| Age at first ESKD Service | | | | | | |
| 18-29 | 16.2 | 6.8 | 52.8 | 1.3 | 22.2 | 0.7 |
| 30-49 | 19.3 | 5.0 | 48.3 | 0.8 | 26.5 | 0.2 |
| 50-64 | 21.9 | 3.5 | 46.8 | 0.4 | 27.5 | 0.0 |
| 65-79 | 23.6 | 2.7 | 47.4 | 0.3 | 26.0 | 0.0 |
| 80+ | 23.1 | 2.7 | 51.6 | 0.0 | 22.5 | 0.0 |
| Race | | | | | | |
| Non-Hispanic White | 23.0 | 2.7 | 50.4 | 0.3 | 23.6 | 0.0 |
| Non-Hispanic Black | 22.6 | 3.2 | 46.0 | 0.1 | 28.0 | 0.0 |
| Hispanic | 23.1 | 3.4 | 44.0 | 0.3 | 29.1 | 0.1 |
| Asian | 25.8 | 2.7 | 41.4 | 0.3 | 29.7 | 0.1 |
| Pacific Islander | 25.3 | 2.4 | 39.5 | 0.1 | 32.6 | 0.1 |
| Native American | 21.0 | 3.5 | 45.1 | 0.2 | 30.2 | 0.0 |
| Employment Status | | | | | | |
| Retired, Disabled, Medical Leave | 23.0 | 2.8 | 48.7 | 0.2 | 25.2 | 0.0 |
| Unemployed | 21.8 | 3.5 | 48.3 | 0.2 | 26.2 | 0.1 |
| Full-Time Employment | 31.5 | 1.9 | 33.7 | 1.7 | 30.8 | 0.4 |
| Part-Time Employment | 28.6 | 2.2 | 38.7 | 1.3 | 29.1 | 0.1 |
| Student | 22.0 | 3.2 | 49.1 | 0.5 | 25.2 | 0.0 |
| Requires Assistance with ADL | | | | | | |
| No ADL Impairment | 23.7 | 2.8 | 46.5 | 0.3 | 26.7 | 0.0 |
| 1+ ADL Impairments | 19.9 | 3.7 | 57.1 | 0.0 | 19.3 | 0.0 |
| Institutionalized | | | | | | |
| Non-Institutionalized | 23.5 | 2.7 | 46.7 | 0.3 | 26.7 | 0.0 |
| Assisted Living, Nursing Home | 19.3 | 4.2 | 60.5 | 0.0 | 15.9 | 0.0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Obese | | | | | | |
| Not Obese | 23.3 | 2.6 | 49.2 | 0.3 | 24.6 | 0.0 |
| Obese | 22.7 | 3.3 | 46.9 | 0.2 | 26.8 | 0.0 |
| Diabetes Mellitus | | | | | | |
| No Diabetes | 24.3 | 2.7 | 48.8 | 0.4 | 23.8 | 0.0 |
| Diabetic | 22.2 | 3.0 | 48.0 | 0.2 | 26.6 | 0.0 |
| Drug Dependence | | | | | | |
| No Drug History | 23.0 | 2.9 | 48.3 | 0.3 | 25.5 | 0.0 |
| History of Drug or Opioid Abuse | 19.9 | 5.4 | 53.1 | 0.1 | 21.4 | 0.1 |
| Pre-ESKD Nephrology Care | | | | | | |
| None/Within 6 Months Pre-ESKD | 25.0 | 2.9 | 45.6 | 0.2 | 26.2 | 0.0 |
| Nephrology Care 6+ Months Pre-ESKD | 20.7 | 2.9 | 51.4 | 0.3 | 24.6 | 0.0 |
| ESRD Network | | | | | | |
| 1:New England | 22.4 | 2.7 | 50.9 | 0.5 | 23.5 | 0.0 |
| 2:New York | 22.0 | 3.1 | 51.3 | 0.4 | 23.1 | 0.0 |
| 3:New Jersey | 20.9 | 3.3 | 50.9 | 0.4 | 24.5 | 0.0 |
| 4:PA/DE | 23.3 | 3.1 | 49.2 | 0.4 | 24.0 | 0.0 |
| 5:DC/MD/VA/WV | 21.2 | 3.2 | 51.1 | 0.4 | 24.2 | 0.0 |
| 6:NC/SC/GA | 23.9 | 2.8 | 46.4 | 0.2 | 26.7 | 0.0 |
| 7:Florida | 21.6 | 3.9 | 52.2 | 0.2 | 22.0 | 0.0 |
| 8:TN/AL/MI | 23.3 | 2.6 | 47.1 | 0.1 | 26.8 | 0.0 |
| 9:OH/IL/KY | 22.2 | 3.0 | 50.1 | 0.2 | 24.6 | 0.0 |
| 10:Indiana | 20.8 | 3.2 | 51.9 | 0.2 | 23.8 | 0.0 |
| 11:MI/WI/MN/ND/SD | 20.9 | 3.0 | 49.9 | 0.4 | 25.9 | 0.0 |
| 12:NE/KS/IA/MO | 22.1 | 2.3 | 48.4 | 0.4 | 26.8 | 0.1 |
| 13:LA/AR/OK | 22.4 | 2.9 | 49.1 | 0.1 | 25.5 | 0.0 |
| 14:Texas | 23.1 | 2.9 | 47.4 | 0.2 | 26.4 | 0.0 |
| 15:NV/UT/WY/CO/AZ/NM | 26.3 | 2.7 | 43.2 | 0.4 | 27.4 | 0.0 |
| 16:WA/OR/ID/MT/AK | 26.7 | 2.0 | 42.0 | 0.4 | 28.8 | 0.0 |
| 17:NorCal/HI | 27.7 | 2.3 | 41.5 | 0.2 | 28.3 | 0.0 |
| 18:SoCal | 25.4 | 2.6 | 44.0 | 0.2 | 27.8 | 0.1 |
| Rural-Urban Continuum Code 2013 | | | | | | |
| Metro, 1+ mil | 23.0 | 3.1 | 48.4 | 0.3 | 25.2 | 0.0 |
| Metro, 0.25-1mil | 23.8 | 2.8 | 47.5 | 0.2 | 25.7 | 0.0 |
| Metro, <0.25mil | 21.8 | 2.7 | 50.0 | 0.2 | 25.2 | 0.0 |
| Urban 20k+, Metro Adj. | 23.0 | 2.6 | 48.6 | 0.2 | 25.5 | 0.0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Urban 20k+, Not Adj. | 23.1 | 2.5 | 46.2 | 0.3 | 27.9 | 0.0 |
| Urban 2.5-19.9K, Metro Adj. | 22.9 | 2.9 | 48.0 | 0.2 | 25.9 | 0.0 |
| Urban 2.5-19.9K, Not Adj. | 22.8 | 2.3 | 47.3 | 0.2 | 27.3 | 0.0 |
| Completely Rural, Metro Adj. | 23.0 | 2.5 | 47.6 | 0.0 | 26.9 | 0.0 |
| Completely Rural, Not Adj. | 20.7 | 2.1 | 50.0 | 0.3 | 26.9 | 0.0 |
| Year of first ESRD service | | | | | | |
| 2012 | 19.0 | 3.8 | 54.1 | 0.3 | 22.9 | 0.0 |
| 2013 | 20.0 | 3.7 | 53.1 | 0.3 | 23.0 | 0.0 |
| 2014 | 19.8 | 3.1 | 53.3 | 0.2 | 23.5 | 0.0 |
| 2015 | 20.6 | 3.0 | 52.0 | 0.2 | 24.1 | 0.0 |
| 2016 | 23.4 | 2.7 | 47.5 | 0.2 | 26.1 | 0.0 |
| 2017 | 32.1 | 1.8 | 34.6 | 0.3 | 31.1 | 0.0 |

Appendix 7. Coefficients from Poisson and Endogenous Poisson Approaches to Modeling Vascular Access Infection

| | Cox Model | | | Endogenous Poisson | | | Difference Between Coefficients | |
|---|---|---|---|---|---|---|---|---|
| | Log-Hazard | 95% CI | p-val. | Log-Hazard | 95% CI | p-val. | Relative Diff. | p-value |
| AV[F/G] | Reference | | | Reference | | | | |
| THC | 1.685 | [1.6105,1.7595] | 0 | 0.5568 | [0.2708,0.8429] | 0.0001 | 0.33 | <0.0001 |
| Non-Institutionalized | Reference | | | Reference | | | | |
| Assisted Living, Nursing Home | 1.0153 | [0.8143,1.2163] | 0 | 1.5482 | [1.2784,1.8180] | 0 | 1.52 | <0.0001 |
| THC # Assisted Living, Nursing Home | -0.7032 | [-0.9098,-0.4967] | 0 | -1.0159 | [-1.2924,-0.7393] | 0 | 1.44 | <0.0001 |
| 18-29 | Reference | | | Reference | | | | |
| 30-49 | -0.3631 | [-0.6457,-0.0805] | 0.0118 | -0.6239 | [-1.0364,-0.2114] | 0.003 | 1.72 | 0.0008 |
| 50-64 | -0.7691 | [-1.0453,-0.4930] | 0 | -1.1926 | [-1.5954,-0.7899] | 0 | 1.55 | <0.0001 |
| 65-79 | -0.9873 | [-1.2618,-0.7129] | 0 | -1.4941 | [-1.8945,-1.0936] | 0 | 1.51 | <0.0001 |
| 80+ | -0.9858 | [-1.2631,-0.7085] | 0 | -1.4667 | [-1.8709,-1.0624] | 0 | 1.49 | <0.0001 |
| Retired, Disabled, Medical Leave | Reference | | | Reference | | | | |
| Unemployed | 0.0704 | [0.0113,0.1294] | 0.0195 | 0.1047 | [0.0231,0.1863] | 0.0119 | 1.49 | 0.0074 |
| Full-Time Employment | -0.5202 | [-0.7364,-0.3040] | 0 | -0.6261 | [-0.9133,-0.3389] | 0 | 1.20 | 0.0084 |
| Part-Time Employment | -0.2946 | [-0.5141,-0.0752] | 0.0085 | -0.3811 | [-0.6726,-0.0896] | 0.0104 | 1.29 | 0.0369 |
| Student | -0.1122 | [-0.8585,0.6340] | 0.7682 | -0.1983 | [-1.2597,0.8632] | 0.7143 | 1.77 | 0.6448 |
| Male | Reference | | | Reference | | | | |
| Female | 0.0596 | [0.0173,0.1019] | 0.0058 | 0.0973 | [0.0392,0.1555] | 0.001 | 1.63 | <0.0001 |
| Non-Hispanic White | Reference | | | Reference | | | | |
| Non-Hispanic Black | 0.047 | [-0.0072,0.1011] | 0.0893 | 0.0202 | [-0.0540,0.0943] | 0.5939 | 0.43 | 0.0207 |
| Hispanic | 0.1961 | [0.1220,0.2701] | 0 | 0.2708 | [0.1696,0.3719] | 0 | 1.38 | <0.0001 |
| Asian | 0.1818 | [0.0544,0.3092] | 0.0052 | 0.2137 | [0.0419,0.3854] | 0.0148 | 1.18 | 0.2122 |
| Pacific Islander | -0.0015 | [-0.2914,0.2884] | 0.9918 | -0.0694 | [-0.4574,0.3185] | 0.7258 | 46.27 | 0.2259 |
| Native American | 0.2809 | [0.0474,0.5145] | 0.0184 | 0.4171 | [0.0846,0.7496] | 0.0139 | 1.48 | 0.0154 |
| 1:New England | 0.4168 | [0.2334,0.6001] | 0 | 0.5542 | [0.3098,0.7985] | 0 | 1.33 | <0.0001 |
| 2:New York | 0.3881 | [0.2240,0.5522] | 0 | 0.6073 | [0.3883,0.8262] | 0 | 1.56 | <0.0001 |
| 3:New Jersey | 0.4577 | [0.2784,0.6371] | 0 | 0.7033 | [0.4626,0.9439] | 0 | 1.54 | <0.0001 |
| 4:PA/DE | 0.3939 | [0.2248,0.5630] | 0 | 0.5977 | [0.3718,0.8235] | 0 | 1.52 | <0.0001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 5:DC/MD/VA/WV | 0.4251 | [0.2585,0.5916] | 0 | 0.6939 | [0.4706,0.9172] | 0 | 1.63 | <0.0001 |
| 6:NC/SC/GA | 0.2518 | [0.0902,0.4135] | 0.0023 | 0.4107 | [0.1960,0.6254] | 0.0002 | 1.63 | <0.0001 |
| 7:Florida | 0.5848 | [0.4259,0.7438] | 0 | 0.9371 | [0.7240,1.1503] | 0 | 1.60 | <0.0001 |
| 8:TN/AL/MI | 0.2301 | [0.0597,0.4005] | 0.0081 | 0.4049 | [0.1777,0.6321] | 0.0005 | 1.76 | <0.0001 |
| 9:OH/IL/KY | 0.343 | [0.1830,0.5029] | 0 | 0.5559 | [0.3429,0.7690] | 0 | 1.62 | <0.0001 |
| 10:Indiana | 0.3786 | [0.2066,0.5506] | 0 | 0.6394 | [0.4084,0.8704] | 0 | 1.69 | <0.0001 |
| 11:MI/WI/MN/ND/SD | 0.3858 | [0.2226,0.5490] | 0 | 0.5975 | [0.3799,0.8150] | 0 | 1.55 | <0.0001 |
| 12:NE/KS/IA/MO | 0.0923 | [-0.0926,0.2772] | 0.3278 | 0.2486 | [0.0020,0.4952] | 0.0482 | 2.69 | <0.0001 |
| 13:LA/AR/OK | 0.3117 | [0.1350,0.4884] | 0.0005 | 0.5312 | [0.2941,0.7684] | 0 | 1.70 | <0.0001 |
| 14:Texas | 0.1861 | [0.0238,0.3483] | 0.0246 | 0.3642 | [0.1484,0.5800] | 0.0009 | 1.96 | <0.0001 |
| 15:NV/UT/WY/CO/AZ/NM | 0.2107 | [0.0354,0.3860] | 0.0185 | 0.3552 | [0.1211,0.5893] | 0.0029 | 1.69 | <0.0001 |
| 16:WA/OR/ID/MT/AK | | Reference | | | Reference | | | |
| 17:NorCal/HI | 0.0036 | [-0.1828,0.1900] | 0.9697 | 0.0718 | [-0.1751,0.3188] | 0.5687 | 19.94 | 0.0519 |
| 18:SoCal | 0.0272 | [-0.1416,0.1959] | 0.7525 | 0.1631 | [-0.0613,0.3875] | 0.1542 | 6.00 | <0.0001 |
| Year of first ESRD service=2012 | | Reference | | | Reference | | | |
| Year of first ESRD service=2013 | -0.0595 | [-0.1351,0.0162] | 0.1233 | -0.0834 | [-0.1889,0.0220] | 0.1208 | 1.40 | 0.1658 |
| Year of first ESRD service=2014 | -0.3048 | [-0.3822,-0.2273] | 0 | -0.377 | [-0.4845,-0.2695] | 0 | 1.24 | <0.0001 |
| Year of first ESRD service=2015 | -0.3805 | [-0.4571,-0.3039] | 0 | -0.4544 | [-0.5606,-0.3483] | 0 | 1.19 | <0.0001 |
| Year of first ESRD service=2016 | -0.5496 | [-0.6269,-0.4724] | 0 | -0.6428 | [-0.7499,-0.5357] | 0 | 1.17 | <0.0001 |
| Year of first ESRD service=2017 | -1.1669 | [-1.2517,-1.0821] | 0 | -1.4101 | [-1.5252,-1.2949] | 0 | 1.21 | <0.0001 |
| Median Income in Zip Code | -0.0178 | [-0.0304,-0.0052] | 0.0056 | -0.026 | [-0.0430,-0.0090] | 0.0027 | 1.46 | 0.0013 |
| No Diabetes | | Reference | | | Reference | | | |
| Diabetic | 0.0488 | [0.0038,0.0939] | 0.0334 | 0.046 | [-0.0152,0.1072] | 0.141 | 0.94 | 0.7557 |
| Not Obese | | Reference | | | Reference | | | |
| Obese | 0.1847 | [0.1406,0.2288] | 0 | 0.2661 | [0.2057,0.3264] | 0 | 1.44 | <0.0001 |
| No ADL Impairment | | Reference | | | Reference | | | |
| 1+ ADL Impairments | 0.177 | [0.1182,0.2358] | 0 | 0.3271 | [0.2449,0.4094] | 0 | 1.85 | <0.0001 |
| No Drug History | | Reference | | | Reference | | | |
| History of Drug or Opioid Abuse | 0.4242 | [0.2168,0.6316] | 0.0001 | 0.6354 | [0.3324,0.9384] | 0 | 1.50 | 0.0001 |
| Metro, 1+ mil | | Reference | | | Reference | | | |
| Metro, 0.25-1mil | -0.1269 | [-0.1839,-0.0698] | 0 | -0.1893 | [-0.2672,-0.1114] | 0 | 1.49 | <0.0001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Metro, <0.25mil | -0.1474 | [-0.2259,-0.0688] | 0.0002 | -0.1822 | [-0.2893,-0.0751] | 0.0009 | 1.24 | 0.0334 |
| Urban 20k+, Metro Adj. | -0.2169 | [-0.3231,-0.1107] | 0.0001 | -0.2905 | [-0.4347,-0.1463] | 0.0001 | 1.34 | 0.0007 |
| Urban 20k+, Not Adj. | -0.156 | [-0.3369,0.0249] | 0.091 | -0.205 | [-0.4513,0.0412] | 0.1027 | 1.31 | 0.184 |
| Urban 2.5-19.9K, Metro Adj. | -0.1425 | [-0.2406,-0.0444] | 0.0044 | -0.1646 | [-0.2990,-0.0302] | 0.0164 | 1.16 | 0.2862 |
| Urban 2.5-19.9K, Not Adj. | -0.3539 | [-0.5007,-0.2071] | 0 | -0.4559 | [-0.6548,-0.2569] | 0 | 1.29 | 0.0006 |
| Completely Rural, Metro Adj. | -0.3125 | [-0.5699,-0.0550] | 0.0174 | -0.3958 | [-0.7436,-0.0481] | 0.0257 | 1.27 | 0.0989 |
| Completely Rural, Not Adj. | -0.4868 | [-0.7629,-0.2106] | 0.0006 | -0.6607 | [-1.0252,-0.2961] | 0.0004 | 1.36 | 0.0007 |
| **Index Access** | | | | | | | | |
| 18-29 | | | | | Reference | | | |
| 30-49 | | | | -0.118 | [-0.2159,-0.0202] | 0.018 | | |
| 50-64 | | | | -0.1709 | [-0.2664,-0.0753] | 0.0005 | | |
| 65-79 | | | | -0.1865 | [-0.2816,-0.0914] | 0.0001 | | |
| 80+ | | | | -0.1188 | [-0.2143,-0.0233] | 0.0148 | | |
| Male | | | | | Reference | | | |
| Female | | | | 0.0881 | [0.0783,0.0980] | 0 | | |
| Non-Hispanic White | | | | | Reference | | | |
| Non-Hispanic Black | | | | -0.2012 | [-0.3278,-0.0746] | 0.0018 | | |
| Hispanic | | | | -0.1029 | [-0.2217,0.0160] | 0.0898 | | |
| Asian | | | | -0.2038 | [-0.3256,-0.0820] | 0.001 | | |
| Pacific Islander | | | | 0.0304 | [-0.2002,0.2609] | 0.7964 | | |
| Native American | | | | 0.118 | [-0.0742,0.3101] | 0.2289 | | |
| None/Within 6 Months Pre-ESKD | | | | | Reference | | | |
| Nephrology Care 6+ Months Pre-ESKD | | | | -0.452 | [-0.4644,-0.4396] | 0 | | |
| Non-Hispanic Black # Nephrology Care | | | | 0.1197 | [0.0962,0.1431] | 0 | | |
| Hispanic # Nephrology Care | | | | 0.1827 | [0.1494,0.2160] | 0 | | |
| Asian # Nephrology Care | | | | 0.243 | [0.1893,0.2966] | 0 | | |
| Pacific Islander # Nephrology Care | | | | 0.3472 | [0.2259,0.4685] | 0 | | |
| Native American # Nephrology Care | | | | -0.0807 | [-0.2028,0.0413] | 0.1948 | | |
| 1:New England | | | | 0.059 | [0.0182,0.0997] | 0.0046 | | |
| 2:New York | | | | 0.2026 | [0.1637,0.2414] | 0 | | |
| 3:New Jersey | | | | 0.2845 | [0.2398,0.3293] | 0 | | |

| | | | |
|---|---|---|---|
| 4:PA/DE | 0.1725 | [0.1336,0.2114] | 0 |
| 5:DC/MD/VA/WV | 0.3003 | [0.2594,0.3412] | 0 |
| 6:NC/SC/GA | 0.1924 | [0.1547,0.2301] | 0 |
| 7:Florida | 0.2841 | [0.2459,0.3224] | 0 |
| 8:TN/AL/MI | 0.1569 | [0.1174,0.1965] | 0 |
| 9:OH/IL/KY | 0.2203 | [0.1850,0.2556] | 0 |
| 10:Indiana | 0.316 | [0.2743,0.3578] | 0 |
| 11:MI/WI/MN/ND/SD | 0.1821 | [0.1454,0.2189] | 0 |
| 12:NE/KS/IA/MO | 0.2913 | [0.2503,0.3323] | 0 |
| 13:LA/AR/OK | 0.2914 | [0.2480,0.3349] | 0 |
| 14:Texas | 0.2452 | [0.2056,0.2848] | 0 |
| 15:NV/UT/WY/CO/AZ/NM | 0.1024 | [0.0618,0.1430] | 0 |
| 16:WA/OR/ID/MT/AK | Reference | | |
| 17:NorCal/HI | 0.1248 | [0.0787,0.1709] | 0 |
| 18:SoCal | 0.1618 | [0.1202,0.2033] | 0 |
| Non-Hispanic Black # 1:New England | 0.0927 | [-0.0561,0.2416] | 0.2222 |
| Non-Hispanic Black # 2:New York | 0.0502 | [-0.0839,0.1844] | 0.463 |
| Non-Hispanic Black # 3:New Jersey | 0.0629 | [-0.0776,0.2035] | 0.3803 |
| Non-Hispanic Black # 4:PA/DE | -0.0767 | [-0.2137,0.0602] | 0.2722 |
| Non-Hispanic Black # 5:DC/MD/VA/WV | 0.0687 | [-0.0644,0.2018] | 0.3118 |
| Non-Hispanic Black # 6:NC/SC/GA | 0.0552 | [-0.0749,0.1853] | 0.4058 |
| Non-Hispanic Black # 7:Florida | 0.1149 | [-0.0187,0.2486] | 0.0919 |
| Non-Hispanic Black # 8:TN/AL/MI | 0.1078 | [-0.0243,0.2399] | 0.1098 |
| Non-Hispanic Black # 9:OH/IL/KY | 0.0539 | [-0.0791,0.1868] | 0.4273 |
| Non-Hispanic Black # 10:Indiana | 0.1353 | [-0.0021,0.2727] | 0.0536 |
| Non-Hispanic Black # 11:MI/WI/MN/ND/SD | 0.1931 | [0.0582,0.3280] | 0.005 |
| Non-Hispanic Black # 12:NE/KS/IA/MO | 0.1035 | [-0.0384,0.2453] | 0.1529 |
| Non-Hispanic Black # 13:LA/AR/OK | 0.0018 | [-0.1341,0.1376] | 0.9797 |
| Non-Hispanic Black # 14:Texas | 0.1187 | [-0.0149,0.2524] | 0.0817 |
| Non-Hispanic Black # 15:NV/UT/WY/ETC | 0.2562 | [0.1013,0.4111] | 0.0012 |
| Non-Hispanic Black # 16:WA/OR/ID/MT/AK | Reference | | |

| | | | | |
|---|---|---|---|---|
| Non-Hispanic Black # 17:NorCal/HI | | -0.0289 | [-0.1766,0.1188] | 0.7013 |
| Non-Hispanic Black # 18:SoCal | | 0.1387 | [-0.0020,0.2793] | 0.0533 |
| Hispanic # 1:New England | | 0.005 | [-0.1523,0.1622] | 0.9504 |
| Hispanic # 2:New York | | -0.1179 | [-0.2514,0.0156] | 0.0835 |
| Hispanic # 3:New Jersey | | -0.0118 | [-0.1650,0.1413] | 0.8794 |
| Hispanic # 4:PA/DE | | -0.0887 | [-0.2599,0.0826] | 0.3101 |
| Hispanic # 5:DC/MD/VA/WV | | -0.0724 | [-0.2722,0.1274] | 0.4775 |
| Hispanic # 6:NC/SC/GA | | 0.0772 | [-0.1051,0.2595] | 0.4068 |
| Hispanic # 7:Florida | | 0.1361 | [0.0059,0.2662] | 0.0404 |
| Hispanic # 8:TN/AL/MI | | 0.187 | [-0.0748,0.4487] | 0.1615 |
| Hispanic # 9:OH/IL/KY | | 0.1054 | [-0.0716,0.2825] | 0.2432 |
| Hispanic # 10:Indiana | | 0.0359 | [-0.1118,0.1835] | 0.634 |
| Hispanic # 11:MI/WI/MN/ND/SD | | 0.0279 | [-0.1381,0.1939] | 0.7422 |
| Hispanic # 12:NE/KS/IA/MO | | 0.0544 | [-0.1402,0.2489] | 0.584 |
| Hispanic # 13:LA/AR/OK | | 0.0926 | [-0.1182,0.3033] | 0.3892 |
| Hispanic # 14:Texas | | 0.1443 | [0.0203,0.2684] | 0.0226 |
| Hispanic # 15:NV/UT/WY/CO/AZ/NM | | -0.0289 | [-0.1597,0.1019] | 0.6647 |
| Hispanic # 16:WA/OR/ID/MT/AK | | Reference | | |
| Hispanic # 17:NorCal/HI | | 0.0986 | [-0.0368,0.2339] | 0.1536 |
| Hispanic # 18:SoCal | | 0.0946 | [-0.0309,0.2201] | 0.1398 |
| Asian # 1:New England | | 0.0592 | [-0.1585,0.2768] | 0.5941 |
| Asian # 2:New York | | 0.0238 | [-0.1243,0.1720] | 0.7526 |
| Asian # 3:New Jersey | | 0.0045 | [-0.1875,0.1965] | 0.9634 |
| Asian # 4:PA/DE | | 0.1316 | [-0.1125,0.3757] | 0.2908 |
| Asian # 5:DC/MD/VA/WV | | 0.1704 | [-0.0134,0.3542] | 0.0693 |
| Asian # 6:NC/SC/GA | | 0.0578 | [-0.1632,0.2789] | 0.6082 |
| Asian # 7:Florida | | -0.0637 | [-0.2605,0.1331] | 0.5257 |
| Asian # 8:TN/AL/MI | | -0.0179 | [-0.3154,0.2796] | 0.9063 |
| Asian # 9:OH/IL/KY | | 0.0726 | [-0.1984,0.3437] | 0.5995 |
| Asian # 10:Indiana | | -0.0318 | [-0.2187,0.1550] | 0.7383 |
| Asian # 11:MI/WI/MN/ND/SD | | 0.0121 | [-0.1744,0.1986] | 0.8986 |

| | | | | |
|---|---|---|---|---|
| Asian # 12:NE/KS/IA/MO | | 0.2174 | [-0.0857,0.5205] | 0.1598 |
| Asian # 13:LA/AR/OK | | 0.1011 | [-0.2140,0.4162] | 0.5294 |
| Asian # 14:Texas | | 0.1087 | [-0.0592,0.2766] | 0.2046 |
| Asian # 15:NV/UT/WY/CO/AZ/NM | | 0.0703 | [-0.1125,0.2531] | 0.4511 |
| Asian # 16:WA/OR/ID/MT/AK | | | Reference | |
| Asian # 17:NorCal/HI | | -0.0549 | [-0.1873,0.0776] | 0.4168 |
| Asian # 18:SoCal | | 0.0614 | [-0.0710,0.1939] | 0.3633 |
| Pacific Islander # 1:New England | | -0.406 | [-1.0220,0.2101] | 0.1965 |
| Pacific Islander # 2:New York | | -0.0165 | [-0.3831,0.3501] | 0.9296 |
| Pacific Islander # 3:New Jersey | | 0.0132 | [-0.4183,0.4448] | 0.9521 |
| Pacific Islander # 4:PA/DE | | 0.3238 | [-0.4877,1.1354] | 0.4342 |
| Pacific Islander # 5:DC/MD/VA/WV | | 0.0012 | [-0.4411,0.4435] | 0.9957 |
| Pacific Islander # 6:NC/SC/GA | | -0.3479 | [-0.7915,0.0957] | 0.1243 |
| Pacific Islander # 7:Florida | | -0.1831 | [-0.5846,0.2184] | 0.3714 |
| Pacific Islander # 8:TN/AL/MI | | -0.1251 | [-0.7245,0.4742] | 0.6824 |
| Pacific Islander # 9:OH/IL/KY | | -0.6075 | [-1.1628,-0.0523] | 0.032 |
| Pacific Islander # 10:Indiana | | -0.0601 | [-0.6409,0.5207] | 0.8392 |
| Pacific Islander # 11:MI/WI/MN/ND/SD | | -0.1181 | [-0.6936,0.4574] | 0.6876 |
| Pacific Islander # 12:NE/KS/IA/MO | | -0.592 | [-1.2977,0.1137] | 0.1001 |
| Pacific Islander # 13:LA/AR/OK | | 0.004 | [-0.6355,0.6435] | 0.9902 |
| Pacific Islander # 14:Texas | | -0.2943 | [-0.6712,0.0826] | 0.1259 |
| Pacific Islander # 15:NV/UT/WY/CO/AZ/NM | | -0.2512 | [-0.5613,0.0589] | 0.1124 |
| Pacific Islander # 16:WA/OR/ID/MT/AK | | | Reference | |
| Pacific Islander # 17:NorCal/HI | | -0.3615 | [-0.6057,-0.1173] | 0.0037 |
| Pacific Islander # 18:SoCal | | -0.1927 | [-0.4545,0.0690] | 0.149 |
| Native American # 1:New England | | 0.1212 | [-0.4697,0.7121] | 0.6877 |
| Native American # 2:New York | | -0.2035 | [-0.6332,0.2262] | 0.3533 |
| Native American # 3:New Jersey | | 4.0553 | [3.7299,4.3808] | 0 |
| Native American # 4:PA/DE | | -0.1989 | [-1.5312,1.1334] | 0.7699 |
| Native American # 5:DC/MD/VA/WV | | 0.0741 | [-0.8744,1.0226] | 0.8783 |
| Native American # 6:NC/SC/GA | | -0.303 | [-0.5912,-0.0148] | 0.0393 |

| | | | | |
|---|---|---|---|---|
| Native American # 7:Florida | | -0.1319 | [-0.7499,0.4860] | 0.6756 |
| Native American # 8:TN/AL/MI | | -0.0552 | [-0.5165,0.4060] | 0.8144 |
| Native American # 9:OH/IL/KY | | 0.3662 | [-0.7879,1.5203] | 0.534 |
| Native American # 10:Indiana | | 4.2817 | [3.9430,4.6205] | 0 |
| Native American # 11:MI/WI/MN/ND/SD | | 0.0579 | [-0.1703,0.2860] | 0.6192 |
| Native American # 12:NE/KS/IA/MO | | 0.0313 | [-0.3905,0.4530] | 0.8845 |
| Native American # 13:LA/AR/OK | | -0.1334 | [-0.3612,0.0944] | 0.2511 |
| Native American # 14:Texas | | -0.2305 | [-0.8028,0.3418] | 0.4299 |
| Native American # 15:NV/UT/WY/CO/AZ/NM | | 0.1218 | [-0.0832,0.3268] | 0.2441 |
| Native American # 16:WA/OR/ID/MT/AK | | | Reference | |
| Native American # 17:NorCal/HI | | -0.1409 | [-0.5120,0.2301] | 0.4566 |
| Native American # 18:SoCal | | -0.0536 | [-0.4721,0.3648] | 0.8016 |
| Year of first ESRD service=2012 | | | Reference | |
| Year of first ESRD service=2013 | | -0.002 | [-0.0213,0.0172] | 0.8352 |
| Year of first ESRD service=2014 | | 0.1333 | [0.1139,0.1527] | 0 |
| Year of first ESRD service=2015 | | 0.1846 | [0.1655,0.2038] | 0 |
| Year of first ESRD service=2016 | | 0.2149 | [0.1959,0.2338] | 0 |
| Year of first ESRD service=2017 | | 0.2047 | [0.1857,0.2237] | 0 |
| Median Income in Zip Code | | -0.0021 | [-0.0049,0.0007] | 0.136 |
| No ADL Impairment | | | Reference | |
| 1+ ADL Impairments | | 0.2151 | [0.2001,0.2302] | 0 |
| Non-Institutionalized | | | Reference | |
| Assisted Living, Nursing Home | | 0.3582 | [0.3397,0.3768] | 0 |
| Metro, 1+ mil | | | Reference | |
| Metro, 0.25-1mil | | -0.0034 | [-0.0166,0.0099] | 0.6187 |
| Metro, <0.25mil | | 0.062 | [0.0439,0.0800] | 0 |
| Urban 20k+, Metro Adj. | | 0.0517 | [0.0277,0.0757] | 0 |
| Urban 20k+, Not Adj. | | 0.0046 | [-0.0343,0.0436] | 0.8151 |
| Urban 2.5-19.9K, Metro Adj. | | 0.039 | [0.0160,0.0619] | 0.0009 |
| Urban 2.5-19.9K, Not Adj. | | 0.0512 | [0.0199,0.0825] | 0.0013 |

| | | | | |
|---|---|---|---|---|
| Completely Rural, Metro Adj. | | 0.0919 | [0.0359,0.1478] | 0.0013 |
| Completely Rural, Not Adj. | | 0.1533 | [0.0957,0.2109] | 0 |
| Native American # 9:OH/IL/KY | | 0.3662 | [-0.7879,1.5203] | 0.534 |
| Native American # 10:Indiana | | 4.2817 | [3.9430,4.6205] | 0 |
| Native American # 11:MI/WI/MN/ND/SD | | 0.0579 | [-0.1703,0.2860] | 0.6192 |
| Native American # 12:NE/KS/IA/MO | | 0.0313 | [-0.3905,0.4530] | 0.8845 |
| Native American # 13:LA/AR/OK | | -0.1334 | [-0.3612,0.0944] | 0.2511 |
| Native American # 14:Texas | | -0.2305 | [-0.8028,0.3418] | 0.4299 |
| Native American # 15:NV/UT/WY/CO/AZ/NM | | 0.1218 | [-0.0832,0.3268] | 0.2441 |
| Native American # 16:WA/OR/ID/MT/AK | | | Reference | |
| Native American # 17:NorCal/HI | | -0.1409 | [-0.5120,0.2301] | 0.4566 |
| Native American # 18:SoCal | | -0.0536 | [-0.4721,0.3648] | 0.8016 |
| Year of first ESRD service=2012 | | | Reference | |
| Year of first ESRD service=2013 | | -0.002 | [-0.0213,0.0172] | 0.8352 |
| Year of first ESRD service=2014 | | 0.1333 | [0.1139,0.1527] | 0 |
| Year of first ESRD service=2015 | | 0.1846 | [0.1655,0.2038] | 0 |
| Year of first ESRD service=2016 | | 0.2149 | [0.1959,0.2338] | 0 |
| Year of first ESRD service=2017 | | 0.2047 | [0.1857,0.2237] | 0 |
| Median Income in Zip Code | | -0.0021 | [-0.0049,0.0007] | 0.136 |
| No ADL Impairment | | | Reference | |
| 1+ ADL Impairments | | 0.2151 | [0.2001,0.2302] | 0 |
| Non-Institutionalized | | | Reference | |
| Assisted Living, Nursing Home | | 0.3582 | [0.3397,0.3768] | 0 |
| Metro, 1+ mil | | | Reference | |
| Metro, 0.25-1mil | | -0.0034 | [-0.0166,0.0099] | 0.6187 |
| Metro, <0.25mil | | 0.062 | [0.0439,0.0800] | 0 |
| Urban 20k+, Metro Adj. | | 0.0517 | [0.0277,0.0757] | 0 |
| Urban 20k+, Not Adj. | | 0.0046 | [-0.0343,0.0436] | 0.8151 |
| Urban 2.5-19.9K, Metro Adj. | | 0.039 | [0.0160,0.0619] | 0.0009 |
| Urban 2.5-19.9K, Not Adj. | | 0.0512 | [0.0199,0.0825] | 0.0013 |

| | | | | | |
|---|---|---|---|---|---|
| Completely Rural, Metro Adj. | | 0.0919 | [0.0359,0.1478] | 0.0013 | |
| Completely Rural, Not Adj. | | 0.1533 | [0.0957,0.2109] | 0 | |

Appendix 8. Likelihood of MRSA infection among those admitted for vascular access infection

| | Log Odds | 95% CI | P-value |
|---|---|---|---|
| Non-Institutionalized | | Reference | |
| Assisted Living, Nursing Home | 0.9421 | [0.6005,1.2837] | <0.0001 |
| Year of Access Infection=2012 | | Reference | |
| Year of Access Infection=2013 | -0.0741 | [-0.2689,0.1207] | 0.4558 |
| Year of Access Infection=2014 | -0.194 | [-0.3969,0.0090] | 0.061 |
| Year of Access Infection=2015 | 0.2568 | [0.0652,0.4484] | 0.0086 |
| Year of Access Infection=2016 | 0.75 | [0.5621,0.9378] | <0.0001 |
| Year of Access Infection=2017 | 0.8888 | [0.6862,1.0914] | <0.0001 |
| Assisted Living, Nursing Home # Year of Access Infection=2013 | -0.3708 | [-0.8035,0.0618] | 0.093 |
| Assisted Living, Nursing Home # Year of Access Infection=2014 | -0.3361 | [-0.7835,0.1112] | 0.1408 |
| Assisted Living, Nursing Home # Year of Access Infection=2015 | -0.5535 | [-0.9889,-0.1182] | 0.0127 |
| Assisted Living, Nursing Home # Year of Access Infection=2016 | -0.8271 | [-1.2578,-0.3965] | 0.0002 |
| Assisted Living, Nursing Home # Year of Access Infection=2017 | -0.8251 | [-1.2893,-0.3609] | 0.0005 |
| 18-29 | | Reference | |
| 30-49 | -0.2488 | [-0.8209,0.3233] | 0.394 |
| 50-64 | -0.5076 | [-1.0637,0.0485] | 0.0736 |
| 65-79 | -0.5163 | [-1.0676,0.0349] | 0.0664 |
| 80+ | -0.4102 | [-0.9675,0.1471] | 0.1491 |
| Male | | Reference | |
| Female | -0.1071 | [-0.2002,-0.0140] | 0.0241 |
| Non-Hispanic White | | Reference | |
| Non-Hispanic Black | -0.0165 | [-0.1292,0.0962] | 0.7744 |
| Hispanic | -0.302 | [-0.4626,-0.1414] | 0.0002 |
| Asian | -0.3862 | [-0.6785,-0.0939] | 0.0096 |
| Pacific Islander | -0.6841 | [-1.3983,0.0302] | 0.0605 |
| Native American | -0.7799 | [-1.3664,-0.1934] | 0.0091 |
| 1:New England | | Reference | |
| 2:New York | -0.2937 | [-0.5931,0.0056] | 0.0544 |
| 3:New Jersey | -0.4394 | [-0.7824,-0.0964] | 0.0121 |
| 4:PA/DE | -0.5465 | [-0.8690,-0.2240] | 0.0009 |
| 5:DC/MD/VA/WV | -0.0832 | [-0.3867,0.2203] | 0.591 |
| 6:NC/SC/GA | -0.2449 | [-0.5374,0.0475] | 0.1007 |
| 7:Florida | -0.3222 | [-0.6077,-0.0366] | 0.027 |
| 8:TN/AL/MI | -0.1958 | [-0.5091,0.1176] | 0.2208 |
| 9:OH/IL/KY | -0.2887 | [-0.5778,0.0003] | 0.0503 |
| 10:Indiana | -0.5139 | [-0.8398,-0.1880] | 0.002 |
| 11:MI/WI/MN/ND/SD | -0.2884 | [-0.5877,0.0110] | 0.059 |
| 12:NE/KS/IA/MO | -0.2459 | [-0.6007,0.1089] | 0.1743 |

| | | | |
|---|---|---|---|
| 13:LA/AR/OK | -0.1273 | [-0.4565,0.2020] | 0.4486 |
| 14:Texas | -0.1939 | [-0.4876,0.0998] | 0.1957 |
| 15:NV/UT/WY/CO/AZ/NM | -0.0623 | [-0.3946,0.2700] | 0.7134 |
| 16:WA/OR/ID/MT/AK | -0.0239 | [-0.4151,0.3672] | 0.9045 |
| 17:NorCal/HI | -0.0236 | [-0.3756,0.3283] | 0.8953 |
| 18:SoCal | -0.1457 | [-0.4534,0.1620] | 0.3534 |

Appendix 9. Aim 3 Variable Definitions and Operationalizations

| Dependent Variables | | | |
|---|---|---|---|
| **Measure** | **Operationalization** | **Data Elements Used** | **Source** |
| Opiate Prescribed for Vascular Access Procedure | 0 = No opiate prescribed within 1 days (plus or minus) of a vascular access procedure; 1 = Any opiate prescribed within 1 day (plus or minus) of a vascular access procedure | **ndcnum** (string values for National Drug Code) from pde_xxxx that matches one of the NDC values from the CDC's file for oral morphine dosages | USRDS: pde_xxxx (xxxx = 2012-2017); CDC's Oral Morphine Milligram Equivalents (Sept. 2018) |
| Access Type | 1 = Arteriovenous Fistula; 2 = Arteriovenous Graft | **hcpcs** (AVF = 36818, 36819, 36820, 36821; AVG = 37830) from ps_line_xxxx. | USRDS: ps_line_xxxx (xxxx = 2012-2017) |
| Persistent Opioid Use (90 to 180 days post access) | 0 = No opiate prescribed within 90 to 180 days of a vascular access procedure or censoring event prior to opioid prescription between 90 to 180 days; 1 = Any opiate prescribed within 90 to 180 days of vascular access procedure. | **ndcnum** (string values for National Drug Code) from pde_xxxx that matches one of the NDC values from the CDC's file for oral morphine dosages | USRDS: pde_xxxx (xxxx = 2012-2017); CDC's Oral Morphine Milligram Equivalents (Sept. 2018) |
| **Independent Variables and Sub-Group Variable** | | | |
| **Measure** | **Operationalization** | **Data Elements Used** | **Source** |
| Medicare 180 Days Pre-ESKD ***(Sub-Group Variable)*** | 1 = Medicare Parts A & B at least 180 days Prior to Dialysis Start; 0 = Less than 180 days of Medicare prior to Dialysis Start | **first_mcare_pta_start** and **first_mcare_ptb_start** in the patients file; **first_se** from the patients file. | USRDS: patients |
| Year of Access | Continuous Year Values | **linefrom** (date of service for access claim) | USRDS: ps_line_xxxx (xxxx = 2012-2017) |
| Age | 1 = 18-29; 2 = 30-49; 3 = 50-54; 4 = 65-79; 5 = 80+ | **incage** (continuous age at first ERSD service) | USRDS: patients |
| Sex | 1 = Male; 2 = Female. Patient sex was superseded by form 2728 sex if there was a conflict. Non-missing sex was used if one or the other was missing. | **sex** (1 = male; 2 = female) from patients. **sex** (M = Male; F = female) from 2728. | USRDS: patients & 2728 form |
| Race | 1 = Non-Hispanic White; 2 = Non-Hispanic Black; 3 = Hispanic; 4 = Asian; 5 = Pacific Islander; 6 = Native American; 7 = other/unknown. Patient race from Form 2728 superseded patient race from patients file, unless patient race was White in the 2728 and a minority in the patients file. | **race** (1 = white; 2 = black; 3 = Native American; 4 = Asian; 5 = Pacific Islander) and **ethn** (1 = Hispanic) from the patients file and **race** (same coding) and **hispanic** (same coding) from the 2728. | USRDS: patients & 2728 form |
| Obese | 0 = no; 1 = yes | **bmi** (continuous variable; recoded into <30 to ≥30) | USRDS: Form 2728 |
| Coronary Artery Disease | 0 = no; 1 = yes | At least one of the following is "Y": **como_mi, como_ashd, como_ihd** | USRDS: Form 2728 |

| | | | |
|---|---|---|---|
| Peripheral Vascular Disease | 0 = no; 1 = yes | **malignency** (Y, N) | USRDS: Form 2728 |
| History of Illicit Drug Abuse or ICD for Opioid Abuse | 0 = no; 1 = yes | **como_drug** (Y, N) OR **diag**(304.0X, 304.7X, 305.5X, F11.X) | USRDS: Form 2728; Inpatient, Outpatient, Physician Claims from 2012-2017 |
| History of Alcohol Abuse or ICD for Alcohol Abuse | 0 = no; 1 = yes | **como_alco** (Y, N) OR **diag**(303.XX, 291.XX, 305.50 571.2X, 571.3X, F10.XX) | USRDS: Form 2728; Inpatient, Outpatient, Physician Claims from 2012-2017 |
| Requires Assistance with ADL | 0 = no; 1 = yes | **como_needasst** (Y, N) | USRDS: Form 2728 |
| Institutionalized | 0 = no; 1 = yes | **como_inst** (Y, N) | USRDS: Form 2728 |
| Median Zip-Code Level Income | Median Income in Zip Code (in units of $10,000 USD) | **median** (continuous variable in US dollars for median income within each Zip code) | American Community Survey: 2006-2010 & 2017 |
| Rural-Urban Continuum (County-Level) | 1 = Metro, 1+ mil; 2 = Metro, 0.25-1mil; 3 = Metro, <0.25mil; 4 = Urban 20k+, Metro Adj.; 5 = Urban 20k+, Not Adj.; 6 = Urban 2.5-19.9K, Metro Adj.; 7 = Urban 2.5-19.9K, Not Adj.; 8 = Completely Rural, Metro Adj.; 9 = Completely Rural, Not Adj. | **f0002013** (Rural-Urban Continuum Code-2013) | Area Health Resource Files (2015) |
| State | Numeric Categories from 1 to 51 (includes DC) | **state** (Two letter state postal abbreviations for state) | USRDS: patients |
| ESRD Network | Numeric Categories from 1 to 18 | **network** (Numeric Categories from 1 to 18) | USRDS: patients |
| Surgeon Type | 1 = Vascular; 2 = General; 3 = Thoracic; 4 = Cardiac | **spclty** (Vascular = 77; General = 02; Thoracic = 33; Cardiac = 78) from ps_line_xxxx | USRDS: ps_line_xxxx (xxxx = 2012-2017) |
| Surgeon ID | (Random Numeric Value) | **phys_id** (Continuous Random Numeric Value) from ps_line_xxxx | USRDS: ps_line_xxxx (xxxx = 2012-2017) |

Appendix 10. Patients by Recent Filled Opioid Prescription

| Variables | No Recent Opioid N=58,796 Row % | Opioid w/in 90 days pre-access creation N=32,001 Row % | p-value |
|---|---|---|---|
| Access Type | | | <0.001 |
| Fistula | 65.2 | 34.8 | |
| Graft | 63.4 | 36.6 | |
| Post-Access Procedure Opioid | | | 0.003 |
| No Opioid | 65.1 | 34.9 | |
| Received Opioid | 64.2 | 35.8 | |
| Surgeon Type | | | <0.001 |
| Vascular | 65.6 | 34.4 | |
| General | 63.6 | 36.4 | |
| Thoracic | 63.3 | 36.7 | |
| Cardiac | 62.9 | 37.1 | |
| Unknown | 64.6 | 35.4 | |
| Sex | | | <0.001 |
| Male | 67.7 | 32.3 | |
| Female | 61.5 | 38.5 | |
| Age at first ESKD Service | 70.6 ± 11.4 | 66.5 ± 12.3 | <0.001 |
| Age at first ESKD Service | | | <0.001 |
| 18-29 | 51.2 | 48.8 | |
| 30-49 | 49.7 | 50.3 | |
| 50-64 | 54.3 | 45.7 | |
| 65-79 | 67.0 | 33.0 | |
| 80+ | 75.4 | 24.6 | |
| Race | | | <0.001 |
| Non-Hispanic White | 63.8 | 36.2 | |
| Non-Hispanic Black | 62.6 | 37.4 | |
| Hispanic | 69.3 | 30.7 | |
| Asian | 81.0 | 19.0 | |
| Pacific Islander | 77.9 | 22.1 | |
| Native American | 64.4 | 35.6 | |
| Institutionalized | 13.2 | 11.3 | <0.001 |
| Alcohol Dependence | 7.3 | 10.4 | <0.001 |
| History of Opioid/Drug Dependence | 1.9 | 8.2 | <0.001 |
| Median Income in Zip Code | 5.3 ± 2.2 | 4.9 ± 1.9 | <0.001 |
| Rural-Urban Continuum Code 2013 | | | <0.001 |
| Metro, 1+ mil | 68.4 | 31.6 | |
| Metro, 0.25-1mil | 63.2 | 36.8 | |
| Metro, <0.25mil | 60.5 | 39.5 | |
| Urban 20k+, Metro Adj. | 60.8 | 39.2 | |
| Urban 20k+, Not Adj. | 56.9 | 43.1 | |
| Urban 2.5-19.9K, Metro Adj. | 59.4 | 40.6 | |
| Urban 2.5-19.9K, Not Adj. | 59.4 | 40.6 | |
| Completely Rural, Metro Adj. | 56.3 | 43.7 | |
| Completely Rural, Not Adj. | 56.9 | 43.1 | |
| Year | | | <0.001 |

| | | | |
|---|---|---|---|
| 2012 | 63.7 | 36.3 | |
| 2013 | 62.9 | 37.1 | |
| 2014 | 64.8 | 35.2 | |
| 2015 | 65.3 | 34.7 | |
| 2016 | 65.1 | 34.9 | |
| 2017 | 66.0 | 34.0 | |

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