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Improving ESRD Care among Lupus Nephritis Patients:
A Socioeconomic and Geographic Perspective

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Improving ESRD Care among Lupus Nephritis Patients: A Socioeconomic and Geographic Perspective

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An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
in Epidemiology
2014

Abstract

Improving ESRD Care among Lupus Nephritis Patients:
A Socioeconomic and Geographic Perspective
By Laura Christine Plantinga

Patients with systemic lupus erythematosus (SLE) are at risk for lupus nephritis (LN), which can progress to end-stage renal disease (ESRD). Adequate, timely identification and treatment of LN and ESRD across sociodemographic groups and geographic areas is essential for achieving equitable outcomes in the predominantly young, minority U.S. SLE population.

First, ESRD incidence in SLE patients was estimated via linkage of national ESRD surveillance data to a lupus registry including 345 incident Atlanta SLE patients (**Aim 1**). The overall ESRD incidence rate among newly diagnosed SLE patients was 11.1 per 1000 patient-years, and 5.2% initiated ESRD treatment within 5 years. Young age, black race, and early diagnosis of LN were associated with 2-, 4-, and 7-fold higher ESRD incidence, respectively.

Next, associations of quality-of-ESRD-care indicators with sociodemographics and U.S. region were explored among 6,594 incident LN-ESRD patients (**Aim 2**). Black vs. white patients were less likely to receive pre-ESRD care (OR=0.73, 95% CI 0.63-0.85) and be waitlisted for a kidney transplant in the first year of dialysis (HR=0.78, 95% CI 0.68-0.81). Only 24% had a permanent dialysis access, and those with no vs. private insurance were 40% less likely to have a permanent access. Quality of ESRD care varied 2- to 3-fold across U.S. regions, but patterns were not consistent across indicators.

Finally, the association of duration of time to transplant with risk of graft failure was examined in 4,743 incident kidney transplant recipients with LN-ESRD (**Aim 3**). White LN-ESRD patients transplanted later (vs. <3 months on dialysis) were at increased risk of graft failure [HR (95% CI): 3-12 months, 1.23 (0.93-1.63); 12-24 months, 1.37 (0.92-2.06); 24-36 months, 1.34 (0.92-1.97); and >36 months, 1.98 (1.31-2.99)]. However, no such association was seen among black recipients [3-12 months, 1.07 (0.79-1.45); 12-24 months, 1.01 (0.64-1.60); 24-36 months, 0.78 (0.51-1.18); and >36 months, 0.74 (0.48-1.13)].

These results could be used to inform shared decision-making for SLE patients and their providers. Additionally, these results identify targets for interventions at the patient, provider, and health system levels to improve care overall, as well as reduce sociodemographic and geographic disparities in delivered care, among SLE patients.

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Acknowledgements

I thank my dissertation committee: William McClellan, for his relentless championing of my academic and professional career; Cristina Drenkard, for generously and kindly donating her time and support to me and this project; Mitch Klein, for being a great teacher inside and outside the classroom; Michael Kramer, for always providing thoughtful advice and feedback, no matter the topic; and Rachel Patzer, for providing access to her data, the Emory Transplant Center, and other research and professional opportunities, as well as remaining unfailingly cheerful regardless of the many other demands on her time. I also thank my readers: S. Sam Lim, for supporting this work in multiple ways and allowing me to collaborate with the Georgia Lupus Registry; and Stephen Pastan, for providing valuable feedback and support on this project and beyond.

Emory's Department of Epidemiology, especially Viola Vaccarino, Julie Gazmararian, and Jena Black, provided an exceedingly supportive environment for the completion of this work. Thanks to my family: my parents, Tom and Anne Plantinga; my sister and brother-in-law, Cathy and Anunoy Ghosh; and my nephews, Arun and Anil Ghosh, who tolerate their aunt with good humor. Also thanks for the support I have received over the years from all my friends inside and outside the Department of Epidemiology, especially: Margarethe Goetz, Helen Chin, Janet Hatt, Mike Goodisman, and Lynn Dodson (Atlanta); and Bernard Jaar, Vanessa Grubbs, Delphine Tuot, Wes Eddings, and Beth Hedgeman (elsewhere).

This work is dedicated to the memory of Harland Austin, a great man and teacher, who could always make me laugh.

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1. Introduction and Overview

1.1 Background

Systemic lupus erythematosus (SLE) is an autoimmune disease caused by circulating antibodies against various components of the nuclei of afflicted individuals' cells. The disease is characterized by widespread inflammation across multiple organ systems, resulting in dermatological, musculoskeletal, cardiopulmonary, neurological, and/or renal manifestations. The presence and severity of these manifestations can vary widely, both across individuals and over time. Because of the often vague, non-specific nature of SLE symptoms, diagnosis is frequently missed or delayed. Thus, the true prevalence of SLE in the United States remains unknown but is estimated to be anywhere between 300,000 and 1.5 million. SLE most commonly affects females (nearly 90%) and the young (usual age of onset, 15-44 years of age), and the estimates of incidence and prevalence of SLE are 3- to 4-fold the estimates among whites.[1]

Kidney inflammation in SLE, or lupus nephritis (LN), can lead to end-stage renal disease (ESRD), which requires dialysis or transplant for survival. Significant disparities in the U.S. population incidence of LN-ESRD have been demonstrated, with younger age groups, females, blacks, and Southern residents having the highest incidence, relative to their counterparts.[2-5] Despite many available treatments for SLE and LN, few improvements in LN-ESRD outcomes have been noted over the last 30 years.[6] Through careful epidemiologic study of incidence, quality of care, and outcomes, we hope to

inform and improve the management and outcomes of LN-ESRD through a socioeconomic and geographic perspective.

1.2 Study Motivation

Due to the availability of data from the United States Renal Data System (USRDS) on U.S. citizens who initiate ESRD treatment and from the U.S. Census Bureau on the U.S. population-at-risk, U.S. population incidence of LN-ESRD is relatively well-characterized.[2-5] However, there are few, if any, reliable estimates of the incidence of LN-ESRD among those with SLE. Such information is vital to both providers and patients, particularly those patients newly diagnosed with SLE, to guide collaborative clinical management of SLE and LN. In study one, we will use linkage of an inception-based cohort from a regional registry of validated SLE cases, the Georgia Lupus Registry (GLR), with USRDS data to determine the incidence of LN-ESRD among patients living in the Atlanta metropolitan area and diagnosed with SLE in 2002-2004, both overall and by age, race, sex, and socioeconomic status indicators.

Since 2005, the Centers for Medicaid & Medicare Services (CMS) have disseminated and tracked several ESRD quality-of-care indicators, through its 18 multi-state ESRD Networks. Data to address these indicators, including access to pre-ESRD nephrology care, transplant waitlisting, informing patients of transplant options,[7] and placement of a permanent vascular access for dialysis, have been examined extensively in the overall ESRD population, and these data are currently being used to address 4 of the 14 chronic kidney disease-related Healthy People 2020 goals.[8] However, studies of the translation of

these indicators in the LN-ESRD population, which consists of LN patients who should be receiving regular care from both rheumatologists and nephrologists prior to ESRD and thus should be under close medical supervision, are lacking. Additionally, whether geography and associated areal socioeconomic status are associated with translation, which has been shown for the overall ESRD population,[9-12] is unknown. In study two, we will examine associations between geography and socioeconomic status indicators and successful translation of these quality-of-care indicators.

Transplantation is the preferred treatment modality for ESRD. Previous concerns about the recurrence of SLE and LN affecting transplanted kidneys and causing graft failure have been shown to be mostly unfounded,[13] such that transplantation is now the preferred modality for LN-ESRD patients as well. However, current clinical teachings suggest that waiting prescribed periods of time to perform kidney transplant (3 months in rheumatology[1] and 1 year in nephrology[14]) allows underlying autoimmune processes of SLE and LN to "quiet" and reduces the risk of graft failure. However, this non-evidence-based recommendation is in conflict with data suggesting that longer dialysis duration prior to transplantation results in worse graft outcomes in the overall ESRD population.[15] Thus, our final study will examine the association between time to first kidney transplant in LN-ESRD patients and the risk of graft failure.

1.3 Aims

Aim 1: To estimate the incidence of ESRD among Atlanta-area SLE patients and identify sociodemographic factors that contribute to variation in incidence

Aim 2: To estimate associations of geographic and socioeconomic factors with successful translation of the following ESRD quality-of-care indicators in U.S. LN-ESRD patients:

2a. Whether and when patients saw a nephrologist prior to onset of ESRD

2b. Whether patients were informed of transplant options prior to the start of ESRD

2c. Whether patients were placed on the kidney transplant waitlist

2d. Whether patients were prepared for dialysis with a permanent vascular access

Aim 3: To estimate the association of time from start of ESRD to kidney transplant with subsequent graft failure in U.S. LN-ESRD patients; further, to examine whether geographic and socioeconomic factors modify any associations

1.4 Data Sources

At the regional level, we have access to the GLR, which includes 1666 validated SLE cases living in Fulton and DeKalb counties in 2002-2004, 345 of whom were incident in this time period. Potential cases were identified via hospitals, providers, laboratories, and/or advertising and defined by the presence of ≥4 of 11 American College of Rheumatology (ACR) criteria, or ≥3 of 11 ACR criteria and either a kidney biopsy pathology report indicating LN or an experienced rheumatologist's diagnosis of SLE, documented in abstracted medical records. These regional data can be linked via patient identifiers to the USRDS data to determine whether incident SLE patients progress to treated ESRD.

The Centers for Medicare & Medicaid Services (CMS) provides medical coverage for ESRD, regardless of age or disability status. The USRDS uses data from the CMS, plus data from national transplant networks, to collect prospective data on all U.S. citizens treated for ESRD, from treatment initiation. These data include patient demographics, primary cause of ESRD, transplantation and dialysis treatment information, and mortality. Starting in 2005, information on quality-of-care indicators such as when patients saw nephrologists prior to ESRD and whether patients were informed of transplant options were collected on the CMS ESRD benefits eligibility form (CMS Form 2728).

Finally, socioeconomic data are available from the U.S. Census Bureau's American Community Survey (ACS), which provides data at the level of state, county, census tract, and census block. ACS provides data on age and gender distribution, racial and ethnic composition, socioeconomic indicators (*e.g.*, income, poverty level, Gini index of income inequality), and housing quality. Racial segregation indices and other useful measures of areal SES can also be derived from U.S. Census Bureau data. These data, which at neighborhood and county levels are aggregated over 5-year intervals (2006-2011, 2007-2012), can be linked to both the national and regional LN-ESRD data.

1.5 Public Health Importance

Harnessing the power of various available data sources is a key component of modern translational research, which emphasizes the so-called "beyond the bedside" population

impact of research. Myriad sources of data are now available at both national and regional levels that can be leveraged to investigate the epidemiology of relatively rare, often neglected diseases such as LN and LN-ESRD. The research proposed here will improve our understanding of the epidemiology of LN and LN-ESRD. This improved understanding will significantly contribute to efforts to improve the prognosis and quality of life for those who suffer from, or are at risk for, SLE.

2. Background and Literature Review

2.1 Systemic Lupus Erythematosus (SLE)

SLE is an autoimmune disease involving a multitude of clinical manifestations that often change over time. Females are predominantly affected (10:1 to 15:1 among adults), with a young age of onset, generally between 15 and 44.[1] About 10-20% of SLE is estimated to be pediatric-onset, which is associated with longer disease duration and consequently greater risk of end-organ damage.[16] Blacks (and possibly other non-white populations) have greater prevalence of SLE compared to whites, with U.S. black females having 3- to 4-fold incidence and prevalence of SLE compared to their white counterparts.[1] Notably, prevalence of SLE among blacks in Africa is perceived as relatively low, although the prevalence of SLE-associated auto-antibodies has been shown to be similar in U.S. and African blacks,[17] suggesting that environmental factors may be more strongly associated with development of SLE than genetic or biologic factors.

In SLE, the presence of antibodies directed against components of the cells' nuclei lead to widespread inflammation across several body systems. These auto-antibodies include anti-nuclear antibodies (ANAs); antibodies against double-stranded DNA; antibodies against the Smith nuclear antigen; anti-phospholipid antibodies (APAs); and an array of other auto-antibodies, many of which are also associated with other autoimmune diseases, such as scleroderma and Sjögren's syndrome. The often vague and protean nature of SLE can make case definition difficult. While diagnosis by an experienced rheumatologist is the gold standard, standardized criteria are often, by necessity, used in

epidemiologic research of SLE. The most widely used criteria for the diagnosis of SLE were published by the American College of Rheumatology (ACR) in 1997[18] (Table 2.1). Expanded classification criteria from the Systemic Lupus International Collaborating Clinics have not yet fully validated for use in longitudinal studies.[19,20]

Table 2.1. American College of Rheumatology criteria for classifying systemic lupus erythematosus.

1. Malar rash	Red "butterfly" rash on cheeks and across the bridge of the nose
2. Discoid rash	Red, scaly round skin lesions, usually on face and scalp
3. Photosensitivity	Skin rash triggered by sunlight exposure, by patient history or physician observation
4. Oral ulcers	Usually painless ulcers of the mouth, observed by physician
5. Non-erosive arthritis	Involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or pericarditis	Convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion *or* pericarditis documented by electrocardiogram or rubbing heard by a physician or evidence of pericardial effusion
7. Renal disorder	Persistent protein in the urine (>0.5 g/day in 24-hour urine or >3+ on dipstick tests), *or* presence of cellular casts in the urine
8. Neurologic disorder	Seizures *or* psychosis, both in the absence of drugs or metabolic conditions that can lead to these disorders
9. Hematologic disorder	Hemolytic anemia *or* leukopenia (<4,000 leukocytes/mm^3 on ≥2 occasions) *or* lymphocytopenia (< 1,500 lymphocytes/mm^3 on ≥ 2 occasions) *or* thrombocytopenia (<100,000 platelets/mm^3), all in the absence of drugs that can lead to these disorders
10. Immunologic disorder	Anti-DNA abnormal titer *or* presence of Anti-Sm *or* positive finding of antiphospholipid antibodies on (an abnormal serum level of IgG or IgM anticardiolipin antibodies, a positive test result for lupus anticoagulant using a standard method, or a false-positive syphilis test result for at least 6 months)
11. Positive ANA	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

By the strictest definition, SLE is diagnosed if at least 4 of these 11 criteria are met, either serially or simultaneously. However, access to all the information needed to apply these standardized criteria---especially medical history, which may be spread across various providers and health systems---is often not possible. Recent estimates of U.S. adult SLE incidence vary from 5 to 23/100,000 person-years and estimates of prevalence vary from 79 to 241/100,000 (Table 2.2). This variability is likely due not only to differences in sources available for case definition but also to differences between targeted populations in terms of age, race, sex, and socioeconomic status.[21] To address this variability, the Centers for Disease Control and Prevention (CDC) created the first comprehensive population-based epidemiology study in lupus ever conducted in the United States. With five registry sites located in Georgia, Michigan, California, New York, and the Indian Health Services, the purpose of the National Lupus Registry is to have more accurate and complete estimates of the burden of lupus across racial groups, by using novel methods that take advantage of federal, state and local partnerships. Three of the sites, the Georgia Lupus Registry (GLR),[22] the Michigan Lupus Epidemiology and Surveillance Program (MILES),[23] and the Indian Health Services,[24] recently published their estimates of prevalence and incidence of SLE through more thorough case ascertainment.[25] The overall age-adjusted estimates from the GLR and MILES from the Atlanta and Detroit metropolitan areas are remarkably similar (Table 2.2): incidence of 5.6 and 5.5/100,000 and prevalence of 73.0 and 72.8/100,000 for GLR and MILES.[22,23,26] Both studies suggested substantial racial disparities in SLE incidence.[26] In the GLR, SLE incidence was nearly 3-fold higher among blacks vs. whites: 9.4 vs. 3.2/100,000 overall and 15.2 vs. 5.4/100,000 among women.[22] Interestingly, the observed black vs. white

disparity in SLE incidence reported by MILES was closer to 2-fold: 7.9 vs. 3.8/100,000 overall and 12.8 vs. 6.3/100,000 among women,[23] suggesting possible geographic variation in disparities. The Indian Health Services reported age-adjusted prevalence and incidence of 7.4 and 178/100,00, respectively, as high or higher than the estimates in the U.S. black population.[24]

Table 2.2. Recent estimates of U.S. adult SLE incidence and prevalence.

Author (year)	Location	Years	SLE ascertainment	Incidence (/100,000 py)	Prevalence (/100,000)
Ward (2004)	United States (NHANES III)	1999-2000	Self-report	---	241
Naleway (2005)	Wisconsin (community clinic)	1991-2001	Diagnostic codes	5	79
Klein (2010)	Northern California (Kaiser Permanente)	1999-2004	Diagnostic codes + medical record review	6	---
Furst (2013)	United States (managed care)	2003-2008	Diagnostic codes	7	81-103
Feldman (2013)	United States (Medicaid)	2000-2004	Diagnostic codes	23	144
Lim (2014)	Fulton/DeKalb Counties, Georgia (registry)	2002-2004	Population-based case-finding + medical record review	6	73
Somers (2014)	Wayne/Washtenaw Counties, Michigan (registry)	2002-2004	Population-based case-finding + medical record review	6	73
Ferucci (2014)	Indian Health Services (registry)	2007-2009	Population-based case-finding + medical record review	7	178

2.2 Lupus Nephritis (LN)

LN is an inflammation of the kidneys secondary to SLE, most commonly manifested as glomerulonephritis. Glomerulonephritis refers to inflammation of the working units of

the kidney (glomeruli), which are responsible for the removal of excess fluid, electrolytes, and waste from the bloodstream through urine. The exact pathogenic mechanism in LN remains unknown but may involve cell-mediated injury from infiltrating lymphoid cells.[14] Anecdotally, LN is clinically observed to be more common among those SLE patients with primarily rheumatic symptoms (*e.g.*, joint pain), compared to SLE patients with dermatologic, neurologic, or hematologic symptoms.[27] Additionally, based on selected samples, incidence of LN seems to be higher among blacks and males with SLE, relative to their white and female counterparts, respectively.[27] However, it is important to note that the preponderance of females among those diagnosed with SLE still results in greater population incidence of LN among females compared to males. For example, in a recent study of U.S. Medicaid patients, the adjusted incidence of LN was 6.1-, 2.6-, and 1.7-fold greater among female, black, and Southern Medicaid enrollees, respectively, relative to male, white, and Northeastern enrollees.[28] Further, studies with selected samples suggest that blacks and Hispanic are not only at greater risk of LN, but they also develop LN at younger age[29] and develop more severe histological classes of glomerulonephritis compared to whites.[30]

With the exception of possible urinary changes, hypertension, and/or edema, which are more likely to occur in more severe forms of LN, the disease may be without overt signs or symptoms. The presence and severity of LN are determined by urine tests (proteinuria, hematuria, presence of cast cells), blood tests (elevated serum creatinine), and/or renal biopsy. Renal biopsies are recommended for staging by the ACR for any non-contraindicated patient with clinical or laboratory manifestations of LN, as defined by the

ACR renal SLE criteria (proteinuria or cellular casts; see Table 2.1).[31] The current LN staging system, published by the International Society of Nephrology and Renal Pathology Society in 2004,[32] which is based on pathologic examination of renal biopsy specimens, includes six classes (Table 2.3). Classes III and IV (proliferative nephritis) are the most commonly seen forms of LN, and the diffuse form (class IV) is also the most serious class (5-year renal failure of about 20%).[14]

The treatment for LN involves the use of anti-inflammatory and immunosuppressant medications, such as corticosteroids, cyclophosphamide, azathioprine, mycophenolate mofetil, and cyclosporine. Newer, more experimental therapies for LN include targeted monoclonal antibodies, such as rituximab and belimumab (approved by the U.S. Food & Drug Administration for SLE in 2010). All of the current therapies can have serious side effects, including increased risk of infection. Many of these treatments are also not recommended during pregnancy, which can be problematic for females of childbearing age, who comprise the majority of SLE patients. Despite earlier and more aggressive treatment of LN, recent estimates suggest that at least 5-10% of those with LN progress to end-stage renal disease (ESRD) and that the rates of progression to LN-ESRD vary widely by age, sex, and race.[33-36]

Table 2.3. International Society of Nephrology and Renal Pathology Society classification of lupus nephritis.

Designation	**Pathologic findings**	**Clinical findings**[14]
Class I: minimal mesangial	Near-normal glomeruli by light microscopy; mesangial deposits present by IF/EM	Normal urine or microscopic hematuria
Class II: mesangial proliferative	Mesangial hypercellularity and matrix expansion; mesangial deposits present by IF/EM	Microscopic hematuria and/or low-grade proteinuria

Class III: focal proliferative	<50% of glomeruli display endocapillary proliferation or sclerosis; mesangial and subendothelial deposits present by IF/EM	Nephritic urine sediment and subnephrotic proteinuria
Class IV: diffuse proliferative	>50% of glomeruli display endo- or extracapillary proliferation or sclerosis; mesangial and subendothelial deposits present by IF/EM	Nephritic and nephrotic syndromes, hypertension, azotemia
Class IV-S: segmental diffuse	*>50% of affected glomeruli have segmental lesions*	
Class IV-G: global diffuse	*>50% of affected glomeruli have global lesions*	
Class V: membranous	Capillary loop thickening with subepithelial deposits by IF/EM	Nephrotic syndrome
Class VI: advanced sclerosis	>90% of glomeruli are obsolescent, with substantial activity in remaining glomeruli	Hypertension, reduced kidney function

IF, immunofluorescence; EM, electron microscopy.

2.3 Lupus Nephritis-Associated End-Stage Renal Disease (LN-ESRD)

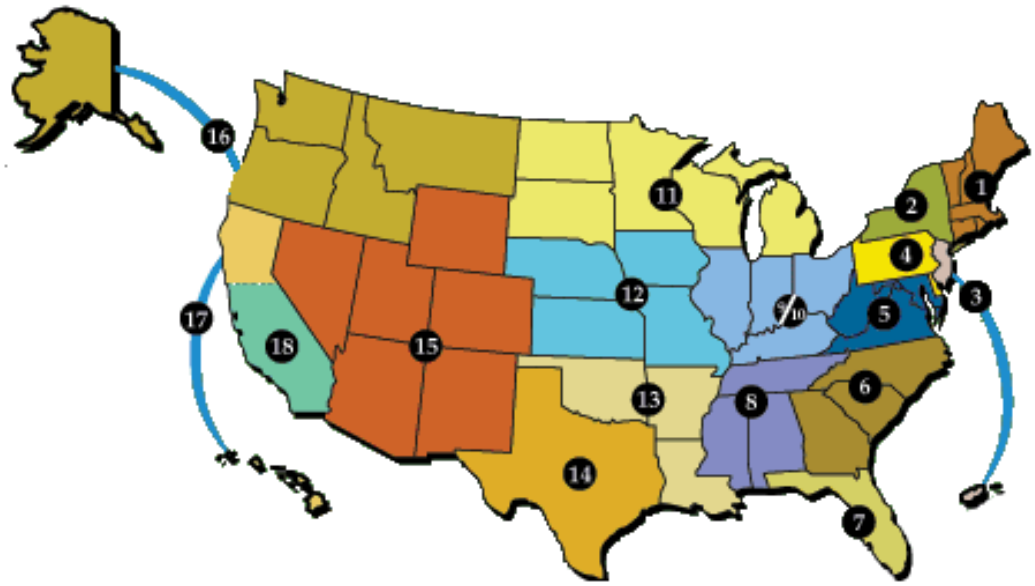
ESRD is the failure of kidneys to function well enough to remove waste and excess water from the body. It is distinguished from the chronic kidney disease (CKD) and kidney failure that precedes it by the requirement for dialysis treatment or kidney transplantation to survive (Table 2.4).[37,38] In October 1972, the U.S. Congress passed legislation (Section 299I of Public Law 92-603) authorizing the End-Stage Renal Disease Program under the Centers for Medicare & Medicaid Services (CMS). Under this program, most U.S. citizens who progress to ESRD are eligible for coverage of their ESRD treatment, regardless of age or disability status, provided they or their spouses have met the required work credits for or are currently receiving Social Security benefits. The United States Renal Data System (USRDS; www.usrds.org), funded by the National Institute for Diabetes and Digestive and Kidney Disorders, tracks ESRD in the United States using data provided by the CMS, the United Network for Organ Sharing (UNOS; www.unos.org) program, and the 18 multistate ESRD Networks, which regionally coordinate quality-of-care efforts (www.esrdnetworks.org; Figure 2.1).

Table 2.4. Classification of chronic kidney disease (National Kidney Foundation guidelines).

Stage	Kidney damage (ACR)	Kidney function (GFR)
1	Yes: ≥30 mg/g	≥90 ml/min/1.73 m^2
2	Yes: ≥30 mg/g	60-89 ml/min/1.73 m^2
3	Yes or no	60-89 ml/min/1.73 m^2
4	Yes or no	60-89 ml/min/1.73 m^2
5*	Yes or no	<15 ml/min/1.73 m^2

ACR, albumin:creatinine ratio; GFR, glomerular filtration rate.
*Includes but does not require end-stage renal disease (dialysis or transplant).

Figure 2.1. The 18 ESRD Networks of the United States.



2.4 U.S. Population Incidence of LN-ESRD

From this nationwide collaborative effort, we know that most ESRD in the United States is attributed to diabetes mellitus (45%) and hypertension (28%). Overall, only 1% of incident ESRD cases in the United States are attributed to LN; however, this represented >5000 incident LN-ESRD patients in 2007-2011.[39] Those with SLE are at ~3-fold risk of mortality relative to their general population counterparts,[40] and LN-ESRD remains the strongest risk factor for early mortality in this population.[41] Both adults and children with ESRD attributed to LN are at approximately twice the risk of mortality relative to patients with ESRD attributed to other causes.[42,43] Despite this increased mortality risk, those treated for LN-ESRD are quite young: in 2007-2011, the median age at the start of ESRD treatment for those with LN-ESRD was only 38, compared to 64 in the overall U.S.

ESRD population.[39] Most (82%) incident LN-ESRD patients in this period were female and 49% were black, illustrating substantial sex and race disparities in LN-ESRD.[39]

Using USRDS data, Ward[3] showed that overall age-, sex-, and race-standardized U.S. population incidence increased from 1.2 per million in 1982 to 3.1 per million in 1995. Stratified analyses showed that incidence was not only higher but also increased disproportionately during this period among blacks vs. whites: for example, among 20- to 44-year-old white women, incidence doubled from about 1 to 2 per million, whereas among similarly aged black women, incidence tripled, from about 6 to 18 per million.[3] Such increases in incidence of LN-ESRD may partially reflect decreases in mortality among LN patients prior to ESRD due to improving treatment over time. Later analyses by the same investigator showed that overall standardized incidence was higher than that in the earlier period but remained relatively stable, from 4.1 per million in 1996 to 4.9 per million in 2004, a difference that was not statistically significant.[2]

Costenbader *et al*.,[4] using the same data, calculated incidence rates standardized for age, sex, race, ethnicity, and geography (Northeast, Midwest, South, and West) over 3-year periods from 1995-2006. They found that incidence increased from 1995-1997 to 2004-2006 in those aged 5-19 (0.8 to 1.4 per million, $P<0.0001$) and those aged 20-39 (5.1 to 6.3 per million, $P=0.005$), but remained relatively stable in older groups (ages 40-59, 4.6 to 4.9 per million; ages 60+, 2.4 to 2.5 per million). Over this same period, incidence also increased statistically significantly among females (5.5 to 6.5 per million, $P=0.007$), males (1.3 to 1.6 per million, $P=0.007$), blacks (12.8 to 15.6 per million, $P=0.008$), and

American Indians (2.2 to 5.1 per million, *P*=0.002), but not among whites (2.0 to 2.1 per million), Asians (4.5 to 5.5 per million), or Hispanics (5.5 per million at both time points).[4] A similar analysis over the same time period in children with LN-ESRD[5] also highlighted racial disparities, with 49% of children aged 5-18 who develop LN-ESRD being black; in comparison, only 16% of the general U.S. population aged 5-18 in the 2000 U.S. Census was black (www.factfinder2.census.gov).

Examinations of disparities in U.S. LN-ESRD incidence by geography have been relatively crude. Costenbader *et al*.[4] examined 3-year standardized incidence in 1996-2005 by four U.S. regions: Northeast, Midwest, South, and West. Relative to other regions, the South had greater LN-ESRD incidence and a greater, statistically significant increase in age-, sex-, race-, and ethnicity-standardized incidence from 1995-1997 to 2004-2006 (4.2 to 5.1 per million; *P*=0.002), compared to the Northeast (3.0 to 3.4 per million), Midwest (2.7 to 3.3 per million), and West (3.4 to 3.8 per million). Similarly, Hiraki *et al*.[5] showed that, overall, 43% of incident LN-ESRD among children aged 5-18 occurred in the South, compared to 14%, 17%, and 25% from the Northeast, Midwest, and West, respectively. Among black children, 56% of incident LN-ESRD was in the South, suggesting that race plays some role in observed geographic disparities.[5]

Disparities by SES have been examined as well. In a retrospective cohort study using USRDS data, Ward[44] showed that age of onset of LN-ESRD in 1996-2004 among U.S. adults was higher among those having private insurance (vs. Medicaid or no insurance) prior to ESRD, particularly for whites (50 vs. 42 years) but also for blacks (42 vs. 36-37

years), Hispanics (38 vs. 35-36 years), and Asians (39 vs. 32-36 years). In the same study, age of onset did not differ by quartile of patient zip code-assigned SES score (including U.S. Census-based indicators of income, poverty, housing, education, and occupation), except for a weak association among whites (46 vs. 48 years, lowest vs. highest quartile; P=0.03). With the same areal SES score and years of data, Ward[45] also showed that U.S. population incidence of LN-ESRD was higher among white females and males in the lowest vs. highest SES quartiles (females, 5.1 vs. 3. 1 per million; males, 1.4 vs. 0.9 per million). For their black counterparts, incidence was much higher, but the difference in incidence for lowest vs. highest SES quartiles was less pronounced on a relative scale (32.0 vs. 28.4 per million; males, 6.9 vs. 6.3 per million). Overall, the differences in LN-ESRD incidence by SES were weaker than those seen in ESRD caused by diabetes mellitus (the most common cause of ESRD in the United States) but stronger than those seen in ESRD caused by autosomal dominant polycystic kidney disease (an uncommon, genetically determined cause of ESRD in the United States).[45]

Finally, Ward[46] specifically examined access to care as a predictor of LN-ESRD incidence in an ecological study conducted in California in 1999-2004. Proportions of hospitalizations by insurance type, proportions of hospitalizations in primary care shortage areas, and rates of hospitalizations that were due to ambulatory care-sensitive conditions (and thus seen as a measure of access to appropriate primary care[47]), all determined at the zip code level, were associated with the outcome of LN-ESRD incidence at the same level using multivariable median regression analysis, adjusting for areal SES score. The change in zip code-defined area median incidence (per million) of

LN-ESRD, per 1-unit increase in the marker of access to care, was 13.1 (95% CI: 9.4, 16.9) for proportion of hospitalizations due to Medicare and 68.3 (95% CI: -2.4,139.1) for rate of hospitalizations due to ambulatory care-sensitive conditions (per million per year). While these studies have substantial limitations, including lack of validation of the assigned cause of ESRD in the national data, lack of individual SES indicators, and ecological design, overall they do suggest that not only race but also geography, SES, and access to care may be associated with variation in U.S. population LN-ESRD incidence.

2.5 Incidence of LN-ESRD among SLE Patients

In contrast to the wealth of information on U.S. population incidence of LN-ESRD, there is little reliable information on the incidence of LN-ESRD among those with SLE. That is, it is unknown what percentage of SLE patients will develop LN-ESRD and over what time period the development of LN and, subsequently, LN-ESRD occurs. Most estimates of incidence of LN and LN-ESRD among SLE patients are given as approximations or ranges, without citations or supportive data, and these estimates are often somewhat contradictory. For example, a rheumatology textbook states that about half of SLE patients will develop clinically significant LN and that most LN will manifest in the first 3 years of SLE.[1] However, patient information provided by the Lupus Foundation of America states that up to 40% of those with SLE may develop clinically significant LN, within the first 5 years of disease (http://www.lupus.org/answers/entry/lupus-and-kidneys).

In some cases, estimates are cited but not entirely supported by the references provided or the data therein. For example, recently updated guidelines for LN[31] suggest that "approximately 35% of U.S. adults with SLE have clinical evidence of LN at the time of diagnosis, with an estimated total of 50–60% developing LN in the first 10 years of SLE," citing several studies.[48-50] However, the study by Kasitanon *et al.*[48] provides only an estimate of cumulative incidence of LN in the first year after diagnosis of SLE in the Hopkins Lupus Cohort, which, not surprisingly, was substantially lower (432/1365 patients, or 32%) than the cited 10-year cumulative risk of 50-60%. Ward *et al.*,[49] examining 408 prevalent SLE patients (within 2 years of diagnosis) at Duke from 1969-1983, found that 246 (60%) had renal manifestations at any time over follow-up---*i.e.*, not limited to within 10 years of diagnosis. Finally, Alarçon *et al.*[50] examined cumulative incidence of renal manifestations (defined by ACR renal criteria but expanded to include declines in renal function) in 554 SLE patients with disease duration <10 years in the multi-center PROFILE cohort. The authors did find cumulative incidence in the 50-60% range, but this was only true for Hispanic (59%) and black (54%) patients, not white (23%) patients. While renal survival curves are shown by race for the entire population and for those free of LN at diagnosis, the percentage presenting with evidence of LN at the time of SLE diagnosis cannot be determined from the data presented.[50]

Although estimates of LN-ESRD incidence among SLE patients are generally lacking, some have published estimates of LN-ESRD among those with LN. However, many of these studies, perhaps due to small sample sizes, used composite outcomes that include death and/or doubling of creatinine to represent renal failure, precluding estimation of

LN-ESRD incidence. Also, the definition of LN differs from study to study. For example, Contreras *et al*.,[51] in their Miami SLE cohort, performed a case-control study of 213 patients with LN (defined by kidney biopsy pathology and ACR criteria for SLE at the time of biopsy) and examined doubling of creatinine, ESRD or death. Over a mean of 37 months of follow-up, they found that 34% of blacks, 20% of Hispanics, and 10% of whites had progressed to this composite outcome. While these data are suggestive, without knowing specific cumulative incidence for ESRD or the rates of LN among those without biopsies, little can be inferred about ESRD progression in LN patients. Appel *et al*.,[52] in a single-center life table analysis of 56 patients with renal biopsies confirming LN, conducted in 1976, showed that 20% reached ESRD. However, the small sample size, requirement of 10 years of follow-up (introducing survival bias), and age of the study render this estimate unreliable at best.

Although the actual estimates of incidence are subject to both random and systematic error, there are consistent patterns across studies suggesting that some patients are relatively more likely than others to develop LN and subsequent LN-ESRD. For example, as mentioned above, in the PROFILE[50] cohort, black and Hispanic SLE patients had higher cumulative incidence of LN than white patients; the cumulative incidence of ESRD was also higher in Hispanics (6.4%) and blacks (3.7%) than whites (2.3%) in this study. In the LUMINA[53] multi-ethnic, multi-center SLE cohort (n=353), which used some of the same centers as PROFILE, similar results were seen, with 61%, 69%, and 29% of Hispanic, black, and white patients, respectively, developing LN within 5 years of diagnosis. Living in poverty vs. not was also suggested to be associated with higher

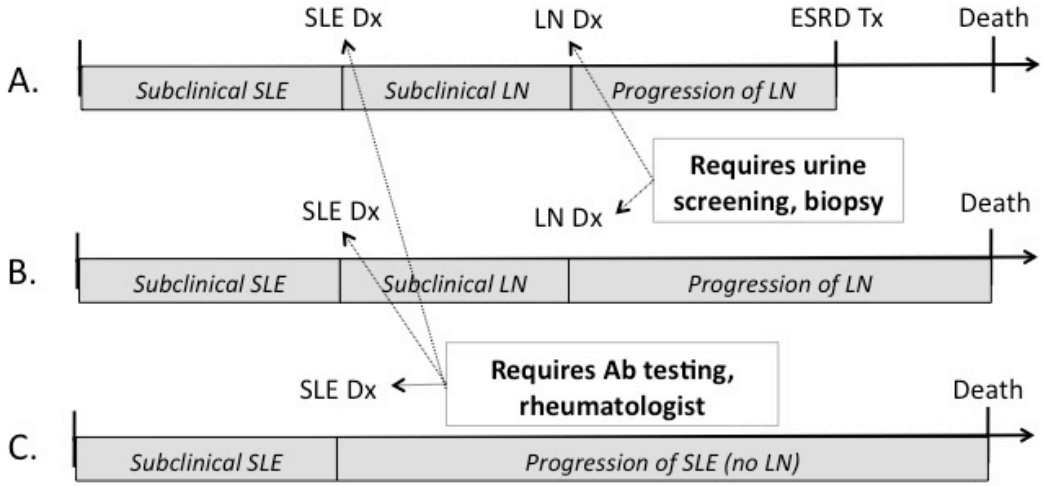
cumulative incidence of LN among SLE patients (45% vs. 28%).[53] Similarly, Contreras *et al.,*[30] in their Miami cohort, showed that the progression to doubling of creatinine or ESRD among LN patients (classes II-V) was 18% (5.9 per 100 patient-years), 31% (10.2 per 100 patient-years), and 10% (2.9 per 100 patient-years) for Hispanic, black, and white patients, respectively. An older follow-up study (1981-1986)[54] of randomized trial participants showed that 51% of black patients with LN (by urine sediment or biopsy and ACR criteria for SLE) experienced doubling of creatinine within 5 years, compared to 24% of white patients. A recent study in Taiwan[55] estimated that 2.5% of newly diagnosed SLE patients developed SLE over 6-8 years of follow-up, but the estimate is likely not generalizable to the United States, due to differences between the Taiwanese and U.S. populations in terms of environment, race, and healthcare system factors.

Great uncertainty remains in estimates of incidence of LN-ESRD among SLE patients, particularly incidence that is not cumulative, and there is a relative lack of information about socioeconomic factors (compared to race/ethnicity) that might be associated with variation in LN-ESRD incidence among SLE patients. Some of the uncertainty in estimates may result from the difficulties inherent in diagnosis of SLE and LN. Possible trajectories of LN and LN-ESRD development are shown in Figure 2.2. Some SLE patients may develop SLE, LN, and ESRD (Figure 2.2A) prior to death. SLE and LN both may remain undiagnosed, at least prior to onset of ESRD. Those with milder disease and with less access to healthcare may be most likely to undiagnosed with either SLE or LN, and LN-ESRD may occur in those without a diagnosis of LN or even of SLE, if LN-ESRD is the first manifestation of SLE. However, ESRD is less likely than SLE or LN to

remain undiagnosed, due to the need for lifesaving dialysis or kidney transplant, but ESRD treatment may remain uncaptured by the USRDS surveillance if a patient refuses ESRD treatment or is not CMS-eligible. Other SLE patients might develop SLE and LN (diagnosed or not) that never progresses to ESRD prior to death (Figure 2.2B). This group may be quite large: it has been suggested that up to 90% of SLE patients have evidence of LN on biopsy but only 50% develop clinically significant LN.[1] Finally, some patients may develop SLE (diagnosed or undiagnosed) but never develop LN (Figure 2.2C).

Figure 2.2. Possible trajectories of systemic lupus erythematosus, lupus nephritis, and end-stage renal disease development.

SLE, systemic lupus erythematosus; LN, lupus nephritis; ESRD, end-stage renal disease; Dx, diagnosis; Tx, treatment; Ab, antibody.



For patients and providers, reliable estimates of incidence of LN-ESRD among SLE patients are critical to guide treatment, screening, and management. The Georgia Lupus Registry (GLR) provides a unique opportunity to estimate incidence of LN-ESRD in a

group of U.S. SLE patients who were initially detected in 2002-2004 (*n*=345) by a variety of means (not just presentation to a rheumatologist) and validated via rheumatologist diagnosis, ACR criteria, and/or kidney biopsy (see Chapter 3: Methods for more detail). USRDS data, which will be linked via identifiers to the GLR data, capture all treated ESRD cases among U.S. citizens who meet Social Security work requirements. This powerful linkage will allow us to examine incidence of LN-ESRD in all validated SLE cases in the Atlanta area, even those with milder SLE who were not necessarily diagnosed---*i.e.*, among SLE patients fitting all three profiles in Figure 2.2. Further, linkage to census tract-level American Community Survey (ACS) data will allow assignment of neighborhood SES indicators, which will supplement limited individual-level SES indicators in the GLR and allow an examination of incidence not just by race/ethnicity but also by other socioeconomic factors that have been examined in studies of population incidence. This leads to:

> ***Aim 1:*** To estimate the incidence of ESRD among Atlanta-area SLE patients and identify sociodemographic factors that contribute to variation in incidence

2.6 U.S. ESRD Quality-of-Care Indicators

The CMS, which covers ESRD care for all eligible patients, is highly invested in promoting quality of care among U.S. ESRD patients. In 2008, as part of the Medicare Improvements for Patients and Providers Act (MIPPA), the CMS developed the ESRD Quality Improvement Program (QIP; www.cms.gov/esrdqualityimproveinit/), a mandated pay-for-performance incentive program that requires dialysis facilities to meet certain criteria for reimbursement. Starting with assessment of anemia management (percentage

of patients whose hemoglobin falls outside the recommended 10-12 g/dl range) and hemodialysis adequacy (percentage of patients whose urea reduction ration was ≥65%) in 2012 to assess payment, the QIP has expanded to include vascular access type, bone mineral metabolism management, patient safety, and patient satisfaction measures.[56] Additionally, through the regional ESRD Networks (see Figure 2.1), the CMS promotes quality improvement, including many measures not currently included in pay-for-performance, and monitors and disseminates information regarding the quality of pre-ESRD, dialysis, and kidney transplant care.

Healthy People (www.healthypeople.gov),[8] another program of the U.S. Department of Health and Human Services, sets 10-year goals for the nation's health in an effort to identify and quantify health and research priorities; unlike the CMS QIP, these goals are not financially incentivized. Healthy People 2020, which comprises the 10-year objectives set in 2010, listed 14 CKD-related objectives (Table 2.5). Of these 14 objectives, half (CKD-8 through CKD-14) relate to ESRD. Further, CKD-10 through CKD-13 relate specifically to ESRD quality-of-care indicators, including pre-ESRD care (CKD-10), access to kidney transplantation (CKD-12 and CKD-13), and vascular access (CKD-11).

Table 2.5. Healthy People 2010 chronic kidney disease objectives.

Objective	Description
CKD-1	Reduce the proportion of the U.S. population with chronic kidney disease
CKD-2	Increase the proportion of persons with chronic kidney disease who know they have impaired renal function
CKD-3	Increase the proportion of hospital patients who incurred acute kidney injury who have follow-up renal evaluation in 6 months post discharge
CKD-4	Increase the proportion of persons with diabetes and chronic kidney disease who receive recommended medical evaluation (serum creatinine, microalbuminuria, A1c, lipids, eye examinations)
CKD-5	Increase the proportion of persons with diabetes and chronic kidney disease who receive recommended medical treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers
CKD-6	Improve cardiovascular care in persons with chronic kidney disease (reduce proportion with elevated blood pressure and lipids)
CKD-7	Reduce the number of deaths among persons with chronic kidney disease
CKD-8	Reduce the number of new cases of end-stage renal disease
CKD-9	Reduce kidney failure due to diabetes
CKD-10	Increase the proportion of chronic kidney disease patients receiving care from a nephrologist at least 12 months before the start of renal replacement therapy
CKD-11	Improve vascular access for hemodialysis patients *-11.1: Increase the proportion of adult hemodialysis patients who use arteriovenous fistulas as the primary mode of vascular access* *-11.2: Reduce the proportion of adult hemodialysis patients who use catheters as the only mode of vascular access* *-11.3: Increase the proportion of adult hemodialysis patients who use arteriovenous fistulas or have a maturing fistula as the primary mode of vascular access at the start of renal replacement therapy*
CKD-12	Increase the proportion of dialysis patients waitlisted and/or receiving a deceased donor kidney transplant within 1 year of end-stage renal disease (ESRD) start (among patients under 70 years of age)
CKD-13	Increase the proportion of patients with treated chronic kidney failure who receive a transplant *-13.1: Increase the proportion of patients receiving a kidney transplant within 3 years of end-stage renal disease (ESRD)* *-13.2: Increase the proportion of patients who receive a preemptive transplant at the start of ESRD*
CKD-14	Reduce deaths in persons with end-stage renal disease (ESRD)

2.6.1 Pre-ESRD care. Pre-ESRD care refers to the receipt of medical care from a nephrologist prior to the start of ESRD. If a patient's first nephrology visit was prior to, rather than at, the start of ESRD treatment (renal replacement therapy), the patient is considered to have had pre-ESRD care; if the first visit was ≥12 months prior to the start of ESRD treatment, the patient is considered to have had adequate pre-ESRD care. The Healthy People 2020 objective for pre-ESRD care (CKD-10) is a 10% improvement in proportion of U.S. patients receiving pre-ESRD care at least 12 months prior to ESRD start (Table 2.5).[8] The source of the Healthy People 2020 data is the CMS Medical Evidence Report (CMS Form 2728; Appendix A), which is completed for all patients at the start of ESRD treatment and includes the following item (#18a): "Prior to ESRD therapy, was the patient under the care of the nephrologist?" with "yes," "no," and "unknown" as possible responses. A follow-up "yes" responses includes options of duration of nephrologist care of "6-12 months" or ">12 months." The data generated from this form are included in the USRDS.

Many previous studies using this Form 2728 item---and similar definitions of pre-ESRD care---have shown that reported receipt of pre-ESRD care is strongly associated with better outcomes subsequent to the initiation of dialysis treatment, including dialysis preparedness (treatment modality choice and vascular access placement),[57-59] access to the transplant waiting list,[60] and survival, with statistically significant risk ratios for death among incident ESRD patients with late vs. early nephrology referrals ranging from 1.4 to 1.8.[61-65] U.S. and international clinical practice guidelines released by the National Kidney Foundation [Kidney Disease Outcomes Quality Initiative (KDOQI)] and

International Society of Nephrology [Kidney Disease: Improving Global Outcomes (KDIGO)], respectively, have synthesized this evidence and recommend referral for ESRD education and preparation when the glomerular filtration rate (GFR) drops below 30 ml/min/1.73 m^2 or significant proteinuria (>300 mg/g) persists[38,66] and, more specifically, when the risk of progressing to ESRD within the following year is more than 10-20%, to allow for adequate pre-ESRD nephrology care duration.[66]

Despite these recommendations, in 2011, 32% of incident ESRD patients initiated treatment having never seen a nephrologist, and only 31% had >12 months of nephrology care prior to ESRD start.[39] Further, geographic variability in pre-ESRD care in the United States has been suggested, with Yan *et al.*[12] reporting greater receipt of pre-ESRD care in small metropolitan areas (31.6%) compared to large metropolitan areas and rural areas (25.7% and 26.9%, respectively). However, in a similar study, Maripuri *et al*.[67] found no differences in receipt of pre-ESRD care by rurality. A potential geographic cluster (in Alabama and Mississippi) of facilities with low proportions of pre-ESRD care among its patients was reported by McClellan *et al*.[10]

2.6.2 Access to kidney transplantation. Kidney transplantation is the preferred treatment modality for most patients with ESRD. Kidney transplantation is associated with lower mortality,[68-70] better reported quality of life,[71,72] and significantly lower costs over the course of treatment,[39] relative to dialysis. Despite this, fewer than one-third of prevalent ESRD patients have a functioning transplant, and only about 3% who initiate ESRD treatment receive a transplant within 90 days.[39] Lack of available donors and

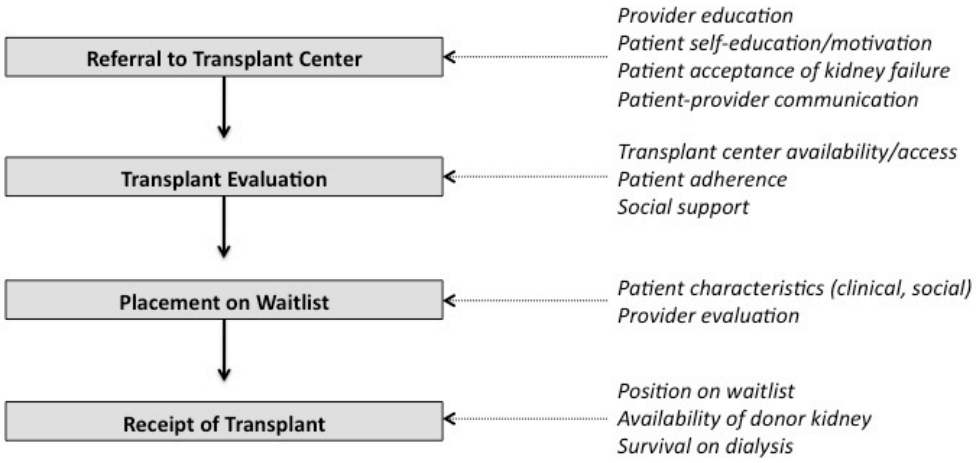
eligibility-compromising recipient characteristics both contribute to this gap, but several other factors are also likely to contribute.

In order to receive a kidney transplant in the United States, patients must complete several steps, ideally prior to kidney failure requiring renal replacement therapy (Figure 2.3). But few of the factors that affect completion of the steps are within the patients' control (Figure 2.3). For example, to receive a referral for transplant evaluation, patients must be informed of the kidney transplant option. While some patients may self-educate about the transplantation process, providers are also obligated to provide education---including a discussion of all options (hemodialysis, peritoneal dialysis, and transplantation) for renal replacement therapy---for all stage 4 CKD patients through the MIPPA kidney disease education benefit. Patients not identified early in stage 4 CKD (see Table 2.4) may are likely to be disadvantaged by this policy, particularly if their CKD is progressing rapidly. Additionally, while CMS covers up to six educational sessions for those patients who are identified, it does not provide clear guidelines for the delivery and content of this education, and research into the effectiveness of various forms of patient education is lacking.[73]

One way that CMS does track U.S. provider education about transplant options is through CMS Form 2728 (Appendix A). Item #26 asks "Has patient been informed of kidney transplant options?" with possible responses of "yes" and "no"; item #27 asks "If patient NOT informed of transplant option, please check all that apply:" with options of "medically unfit," "patient declines information," "unsuitable due to age," "patient has

not been assessed," "psychologically unfit," and "other." Kucirka *et al*.[7] examined these data for 2005-2007 and found that 30.1% of U.S. ESRD patients were not informed of their transplant options at the time of their Form 2728 filing. The authors found that those who were not informed of their transplant options were more likely to be older, obese, uninsured or insured by Medicaid prior to ESRD and to receive dialysis at a for-profit center.[7] Further, those who were not informed were 53% less likely to be waitlisted or receive a transplant than those who had been informed of these options.[7] More recently, the 2013 USRDS annual report[39] showed that 30.4% of patients had not been informed; of these, 44.3% had not yet been assessed at the time of Form 2728 filing. Geography has not been examined as a potential contributing factor to this gap.

Figure 2.3. Steps to receipt of kidney transplant in the United States and factors related to completion of each step.



Kidney transplant waitlisting is another necessary step in the pathway to kidney transplantation that is tracked by the USRDS, through the UNOS data. In 2011, only 17.4% of prevalent dialysis patients were on the kidney transplant waitlist; in ESRD

Network 6 (Georgia, North Carolina, South Carolina; see Figure 2.1) the percentage was 14.9%, much lower than the other regions.[39] Other geographic disparities in waitlisting---particularly, related to neighborhood poverty and areas of high ESRD incidence---have been noted.[11,74] Only 11.9% of 2011 incident patients of any age either were waitlisted or received a deceased donor transplant within the first year of ESRD treatment.[39] While the Healthy People 2020 objective CKD-12 explicitly provides a goal of increasing the proportion of patients aged <70 who are waitlisted or transplanted within the first year of ESRD treatment by 10% (Table 2.5), U.S. clinical practice recommendations refrain from providing any benchmarks for waitlisting. Rather, they state generally that the option of transplantation should be discussed with all patients[75] and that patients should be referred as soon as it is probable that kidney failure will occur in the next year.[76]

2.6.3 Vascular access. For patients who do not receive a pre-emptive transplant (*i.e.*, a kidney transplant placed prior to any dialysis treatment), which included 97.5% of all incident U.S. ESRD patients in 2011,[39] dialysis treatment is the first line of treatment. In 2011, 91.0% of incident dialysis patients were treated with hemodialysis,[39] which requires an external dialyzer and is usually performed in a dialysis facility thrice weekly. Both arterial and venous access are required for hemodialysis, which involves the removal of blood, filtration of toxins, and replacement of "cleaned" blood. The arteriovenous fistula (AVF), which connects an artery directly to a vein, is the preferred permanent vascular access for hemodialysis, due to its decreased risk of infection and clotting and greater patency. However, AVFs require advance planning due to the need for surgery and long maturation time (at least 6 weeks and up to 9 months).[77]

Arteriovenous grafts (AVGs) are synthetic grafts implanted to connect an artery and vein and are often placed by surgeons when veins are too small to create AVFs. AVGs have poorer outcomes than AVFs (more infections, thromboses, and stenoses) but are ready to use in a shorter period (2-3 weeks).[77] AVFs and AVGs together constitute the permanent vascular accesses. Tunneled venous catheters are the "last resort" of vascular access for hemodialysis[77] and are often placed when CKD has progressed quickly and/or little ESRD planning has occurred. Compared to AVFs and AVGs, catheters used for vascular access in hemodialysis patients are associated with increased risk of stenosis[78] and infections, especially sepsis.[79]

AVFs have been shown to last longer than AVGs, with a reported relative risk for time to first failure of 0.53.[80] Given that AVGs and catheters have lower patency and are associated with more infections and problems with clotting, and also given that problems with vascular accesses are a leading cause of hospitalizations in hemodialysis patients,[81] it is not surprising that AVFs are also associated with substantially lower costs than AVGs and, particularly, catheters.[82] Moreover, several investigators reported that mortality in patients with catheters was 40-70% higher than that in patients with permanent accesses[83-87]; however, in longitudinal studies, patients who switched from a catheter to an AVF or AVG seemed to reduce their risk of both mortality and hospitalization.[88,89] Taking this evidence into account, the 2006 update of the KDOQI clinical practice guidelines for vascular access recommended that a functioning permanent access be in place for all patients at the initiation of hemodialysis, preferably an AVF.[90] According to the guidelines, AVFs should be placed at least 6 months in

advance of anticipated hemodialysis start date, and, if AVFs cannot be placed, AVGs should be placed at least 3-6 weeks prior to this date.[90]

The CMS is also invested in increasing AVF use in U.S. hemodialysis patients. Through its ESRD Networks (Figure 2.1), CMS administers the Fistula First Breakthrough Initiative (FFBI; http://www.fistulafirst.org), which began in 2003 to increase the number of fistulae placed and used in hemodialysis patients. Figure 2.4 shows data reported by the FFBI program. The percentage of patients with AVFs used or in place at the start of hemodialysis has increased from around 25% to nearly 40%, whereas the percentage with AVG at initiation has remained fairly steady at 10% (Figure 2.4). In 2011, the percentages of incident hemodialysis patients initiating with an AVF and with a maturing AVF in place, as reported by the USRDS via Form 2728 data, were slightly lower, at 15.8% and 17.0%, respectively.[39]

Studies of geographic variability in U.S. AVF use have mainly been limited to the level of ESRD Network. Prior to the FFBI program, significant network-level variability was noted in data from a 1999 CMS Clinical Performance Measures Project, even after adjustment for sex and race.[91] The reasons for catheter use appear to differ across networks as well, with ESRD Networks reporting a wide range (25-57%) of percentage of patients in whom no AVF was planned in 2004.[92] A summary report from FFBI showed that prevalent AVF use among U.S. hemodialysis patients had increased in all ESRD Networks and that the network-level variation has been attenuated, but not eliminated, over time, with an across-network range of prevalent AVF use of 52.3-65.9%

in 2010 compared to 30.5-54.1% in 2004.[93] State-level variation in incident AVF use is still substantial, with 2011 estimates from the FFBI ranging from 9.1% to 35.8% (Figure 2.5).

Figure 2.4. Improvement in fistulae and grafts used and fistulae placed at initiation of hemodialysis over time in the United States from the inception of the Fistula First Breakthrough Initiative.

HD, hemodialysis.

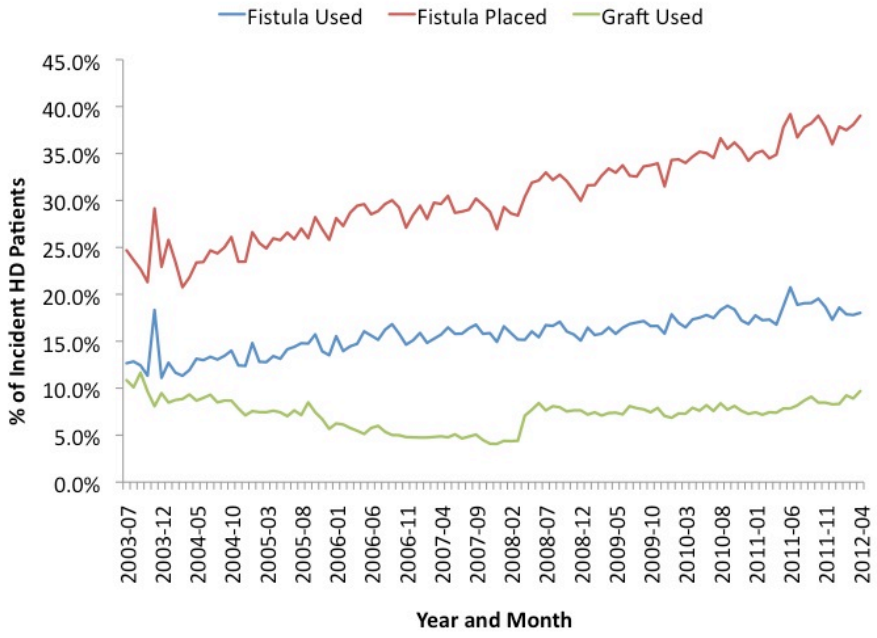
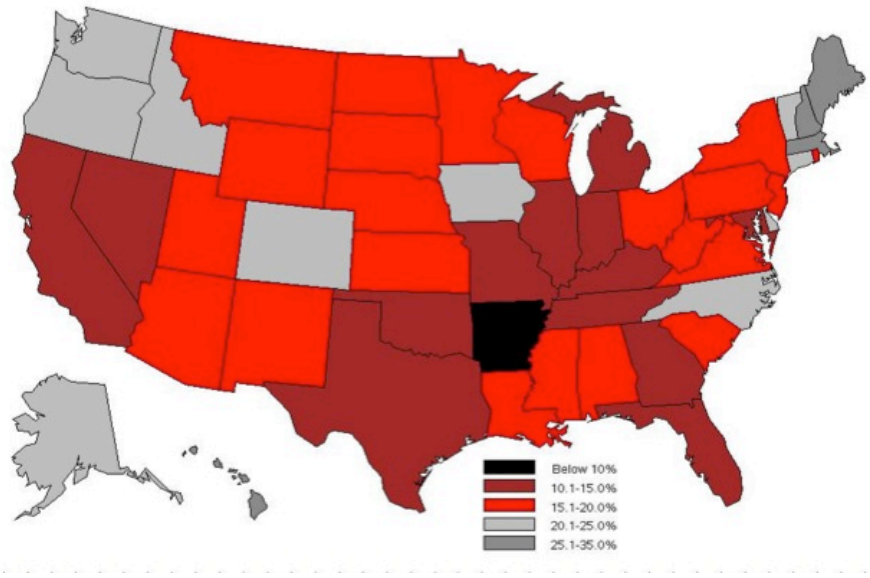


Figure 2.5. State-level variation in arteriovenous fistula use in incident hemodialysis patients, 2011, Fistula First Breakthrough Initiative.



2.7 Translation of ESRD Quality-of-Care Indicators in LN-ESRD Patients

With the exception of kidney transplant waitlisting, which was shown by Costenbader *et al*.[4] to increase slightly from 1995-1997 to 2001-2003 among LN-ESRD patients (35.7% to 37.2% within 3 years; P=0.11 for trend), these markers of quality of care (proportion receiving pre-ESRD care, proportion informed of transplant options, proportion waitlisted for kidney transplantation, and proportion starting hemodialysis with a permanent vascular access) remain unexamined in LN-ESRD patients. Further, translation of these quality-of-care indicators in LN-ESRD patients has not been examined by geographic and socioeconomic factors. The examination of translation of these indicators in LN-ESRD patients specifically is important because these patients are ideally receiving both rheumatology and nephrology care. Translation of quality-of-care

indicators should theoretically be as good---or better---in patient populations under close, multi-provider medical supervision, relative to the overall population.

However, among U.S. patients with the sickle cell disease who developed ESRD in 2005-2009, only 44% were reported to receive pre-ESRD care for at least 6 months prior to starting ESRD treatment, and 47% were reported to have received no nephrology care at all,[94] which is substantially higher than the national percentage of 32% for lack of pre-ESRD care in 2011.[39] Additionally, among those with sickle cell disease who developed ESRD,[94] only 7% had a functioning AVF at the start of ESRD, compared with 16% among all ESRD patients in 2011.[39] Because the LN-ESRD population represents a similar subgroup of ESRD patients, in terms of not only close medical supervision by multiple providers (in this case, hematologists and nephrologists) but also a patient population that is relatively young and predominantly black, it is critical to determine whether translation of quality-of-care indicators differs—and particularly, is worse—in the LN-ESRD population.

Further, a recent study of Medicaid enrollees with incident LN[95] suggests that quality of care in LN prior to ESRD among these patients may be inadequate. At 1 year after LN diagnosis, only 34%, 56%, and 46% of patients had been prescribed the recommended immunosuppressive medications, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and anti-malarial medications, respectively, for treatment of LN.[95] Additionally, younger and black patients were more likely than their counterparts to receive these medications, perhaps reflecting greater severity of disease in these

subpopulations; also, patients in the Northeast were most likely to receive these medications.[95] This suggests that quality of LN-ESRD care may also be insufficient and that sociodemographic and geographic patterns may exist.

Such patterns could be the result of so-called "silos" of care, in which there is lack of communication and coordination among specialty providers and a loss of patient-centeredness.[96] Additionally, there is a general lack of guidelines in rheumatology to address the preparation for ESRD; rather, the focus of LN guidelines for rheumatologists is solely on immunosuppressive regimens to slow LN progression.[31] Such focus may discourage the rheumatologist from actively participating in treatment decisions for their LN-ESRD patients. Identification of any such gaps in quality of care among LN-ESRD patients could improve awareness among both the nephrology and rheumatology communities, improving coordination and translation of these indicators and, ultimately, patient outcomes. This leads to:

Aim 2: To estimate associations of geographic and socioeconomic factors with successful translation of the following ESRD quality-of-care indicators in U.S. LN-ESRD patients:

2a. Whether and when patients saw a nephrologist prior to onset of ESRD

2b. Whether patients were informed of transplant options prior to the start of ESRD

2c. Whether patients were placed on the kidney transplant waitlist

2d. Whether patients were prepared for dialysis with a permanent vascular access

2.8 Barriers to Kidney Transplantation in LN-ESRD Patients

LN-ESRD patients could, in many ways, be considered ideal kidney transplant candidates. As discussed above, SLE patients with progressive LN should be followed closely by both rheumatologists and nephrologists prior to ESRD and, thus, should be better managed and informed than the average incident ESRD patient, both of which lead to better transplant outcomes.[97] These patients are also likely to have demonstrated adherence to a complex immunosuppression regimen, which would theoretically increase their chances of being waitlisted and transplanted, due to the nonadherence contraindication found in most guidelines.[97,98] LN-ESRD patients are also relatively young, with a median age at ESRD onset of 38,[39] and are less likely to have malignancies or cardiovascular contraindications, all of which are mentioned in most clinical practice guidelines for transplantation eligibility.[98]

However, there are also unique barriers to transplant among LN-ESRD patients. The first barrier relates to CMS coverage of immunosuppressant medications for transplant recipients. Immunosuppressant drugs, which are required for the survival of kidney allografts, were covered for only 1 year post-transplant starting with the Omnibus Reconciliation Act of 1986; this coverage was extended to 3 years by mid-1995. The Beneficiary Improvement and Protection Act (BIPA) was passed in December 2000 to provide lifetime coverage of immunosuppressant medications but only to CMS beneficiaries whose eligibility was based on older age ($\geq$65 years) or having non-ESRD-related disability.[99] This exclusion was applied despite studies that have shown that

lifetime coverage would result in better graft and patient survival, as well as lower costs to the system overall.[100] This policy is likely to disadvantage SLE patients who progress to ESRD, as they are likely to be younger than 65, not disabled, and unable to afford these medications after 3 years.[99] Legislation to correct this gap has been introduced multiple times and thus far has been consistently rejected.[101]

Another barrier to transplant among SLE patients involves APAs. APAs are common in SLE, with 15-30% of SLE patients having lupus anticoagulant and up to 80% of SLE patients having anti-cardiolipin antibodies, compared to 1-5% of the healthy population.[102] APAs can be associated with APA syndrome (APAS), which is defined by not only the presence of APAs and but also the occurrence of thrombotic complications, such as deep venous thrombosis, pulmonary embolism, stroke, and late spontaneous abortion in pregnant women. Patients with APAS may not be considered good candidates for kidney transplant due to the risk of post-surgical clotting or bleeding (due to pre-emptive anti-coagulant therapy). Indeed, renal graft survival is lower among those with APAS, despite anti-coagulant therapy, compared to SLE patients with APAs alone and SLE patients without these antibodies.[103,104] Up to 30% of SLE patients may develop APAS,[102] which may serve as a barrier to referral for evaluation, waitlisting, and/or transplant in those patients approaching LN-ESRD.

Finally, another SLE-specific barrier to transplant is related to the possibility of post-transplant recurrence of LN and subsequent development of glomerulonephritis in the graft, possibly leading to graft failure. Estimates of recurrence of LN in transplant

recipients from small studies have varied widely, from 3.8% in a pooled biopsy study to 30%[105] and 44%[106] of recipients in single-center biopsy studies. Contreras *et al*.,[13] in a national study utilizing UNOS data, examined recurrent LN and graft failure among 6850 kidney transplant recipients with SLE. Among these 6850 recipients, only 167 (2.4%) were reported to have recurrent LN; however, 93% of these patients experienced graft failure, as defined by a return to dialysis or need for a new transplant. A total of 1770 patients were reported to have graft rejection without recurrent LN, and 86% of these experienced graft failure. Overall, 43% of graft failures were attributed to rejection among those without recurrent LN; only 7% were attributed to recurrent LN.[13] Under- and/or over-reporting of recurrent LN were possible in this study, since recurrent LN was reported by transplant centers and not defined by clinical or biopsy data. However, these authors concluded that the possibility of recurrent LN should not preclude consideration of SLE patients for kidney transplantation.[13]

2.9 Waiting Time To Kidney Transplantation in LN-ESRD Patients

Since 1975, the option of transplantation has been recommended for LN-ESRD patients.[107] Kidney transplantation outcomes, including graft survival, have continually improved in the LN-ESRD as well as the overall ESRD population. Among U.S. ESRD patients who received a kidney transplant in 1987-1994, deceased donor graft survival at 5 years was slightly lower for LN-ESRD patients (58.1%) compared to other ESRD patients (61.9%); for living donor grafts, 5-year survival did not differ (77.0% and 76.9% for LN-ESRD and other ESRD, respectively).[108] A more recent study of U.S. kidney transplant recipients from 1996 to 2000, a period subsequent to the introduction of

several novel immunosuppressant drugs that improved transplant outcomes overall, showed no differences in graft survival by LN status (1-year graft survival, 88.6% vs. 88.7%; and 5-year graft survival, 67.8% vs. 67.0% for LN-ESRD vs. other ESRD).[109] Over a similar time period (1995-2002), Tang *et al*.[110] showed that black vs. white race (HR=1.55; 95% CI, 1.21-1.97) and female gender (HR=1.32; 95% CI 0.96-1.80) were associated with greater risk of graft failure among 2,882 LN-ESRD patients who received transplants in this period, whereas older recipient age was associated with lower risk (HR=0.96; 95% CI, 0.95-0.98).

Despite the increasing evidence of likely equivalent transplant outcomes among LN-ESRD patients, kidney transplantation is not increasing among LN-ESRD patients. In fact, Costenbader *et al*.[4] reported that, while waitlisting for kidney transplantation among LN-ESRD patients increased slightly from 1995-1997 (35.7%) to 2001-2003 (37.2%), kidney transplantation within 3 years declined over the same period (21.5% to 18.0%). With adjustment for age, sex, race, ethnicity, insurance type, region, diabetes mellitus, hypertension, smoking and initial therapy, those who started ESRD treatment in 2001-2003 were 13% less likely to be transplanted within 3 years than their counterparts who initiated treatment in 1995-1997 (HR=0.87; 95% CI, 0.76-0.99).[4] Note that these declines in transplantation are similar to the declines seen nationally for all ESRD patients: 1-year transplantation in the same two time periods were 10.2-11.2% and 9.3-9.6%, respectively.[39]

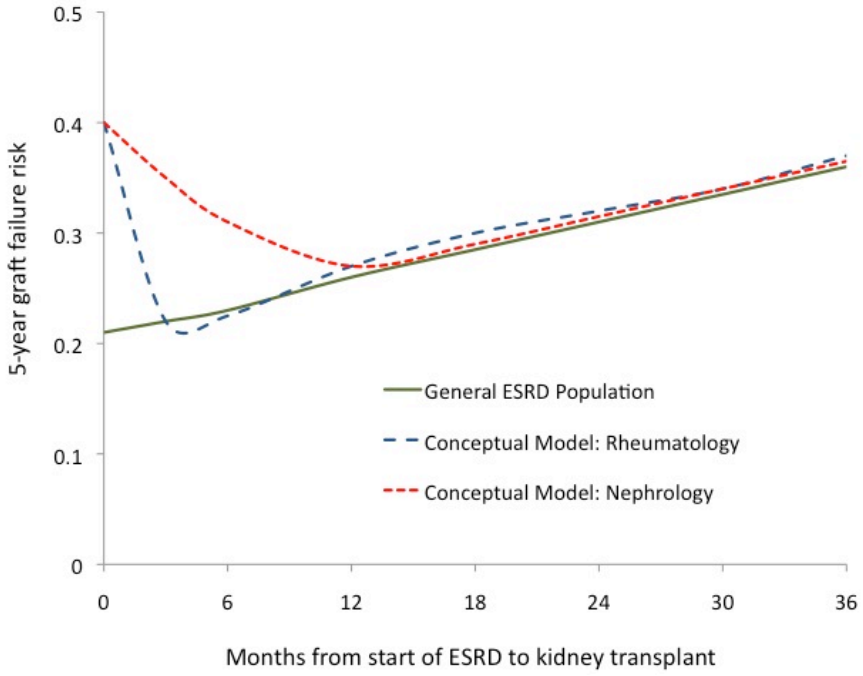
Many phenomena could contribute to this gap, including the increasing demand on the organ supply from the growing overall ESRD population and CMS policies that limit medication coverage after 3 years among younger, non-disabled ESRD patients, as discussed above. However, another contributor could be lingering provider beliefs about kidney transplantation in LN-ESRD patients; particularly, about the necessity of a prescribed waiting period to establish quiescence of SLE prior to transplantation. Indeed, while the current medical consensus among rheumatologists, nephrologists, and transplant surgeons is that LN-ESRD patients should be considered for transplant and that outcomes in LN-ESRD patients are generally comparable to those of other ESRD patients, providers are usually advised by medical textbooks[1,14] and clinical practice guidelines[98] to wait to place LN-ESRD patients on the kidney transplant waitlist and/or perform a kidney transplant. This is due to some evidence from small studies (n<20 for most) that clinical and serological disease activity tends to lessen or "quiet" when patients with SLE reach ESRD, due to unknown physiological mechanisms,[111] although quiescence may not be achieved in all SLE patients with ESRD.[112,113] However, a recent study suggested that longer dialysis time was associated with worse graft outcomes in a small Taiwanese cohort, regardless of SLE activity.[114]

In the United States, rheumatologists suggest that this waiting period for SLE patients should be 3 months,[1] whereas nephrologists advise waiting 1 year.[14] Canadian and European renal transplantation guidelines list 6 months as the appropriate waiting period.[115,116] However, this recommendation does not appear to be evidence-based and is in direct conflict with recommendations for the overall ESRD population: in the general

ESRD population, longer duration of ESRD prior to transplant has shown to be associated with worse transplantation outcomes.[15] Assuming that the prescribed waiting periods are due to fear of graft failure early in ESRD due to active SLE and LN, a conceptual model is presented in Figure 2.6. The straight line represents the linear increase in graft failure risk with duration of ESRD prior to transplant in the general ESRD population and is based on USRDS data, including all ESRD patients (regardless of cause) who received a first transplant in 1990-1999, presented in Goldfarb-Rumyantzev *et al*.[15] The curved lines represent the early elevated graft failure risk assumed by rheumatologists and nephrologists, which drops to the level of risk among all ESRD patients after 3 months (rheumatologists) and 1 year (nephrologists), and then steadily increases with increasing duration of pre-transplant ESRD, along with the general population (Figure 2.6).

Figure 2.6. Graft failure risk (5-year) by time from start of ESRD to kidney transplantation among LN-ESRD patients.

General population risks adapted from data presented by Goldfarb-Rumyantzev et al.[15] Conceptual models for rheumatology[1] and nephrology[14] based upon current clinical recommendations for transplantation among LN-ESRD patients.



If this assumed conceptual model that guides providers is not correct, it is possible that transplantation in LN-ESRD patients is often delayed unnecessarily and may lead to fewer transplantations (when patients die prior to being waitlisted or transplanted) or poorer outcomes among those who do receive transplantations.

Further, such consequences may be worse for certain subgroups of patients, such as children with SLE.[42] Analysis of UNOS data showed that graft failure was 70% among those living in the poorest (>20% poverty) neighborhoods, compared to 58% in those

living in the richest (0-5% poverty) neighborhoods.[117] Similarly in the United Kingdom, greater social deprivation was associated with greater graft failure.[118] Specifically in U.S. LN-ESRD patients, Nee *et al*.[119] showed that lower income predicted greater graft loss, but only among blacks, not whites. However, there appears to be little to no published evidence to address whether waiting time to transplant is associated with worse kidney transplant outcomes among LN-ESRD patients or whether the association is modified by socioeconomic or geographic characteristics. This leads to:

Aim 3: To estimate the association of time from start of ESRD to kidney transplant with subsequent graft failure in U.S. LN-ESRD patients; further, to examine whether geographic and socioeconomic factors modify any associations

3. Methods

3.1 Data Sources

3.1.1 Georgia Lupus Registry (GLR). The primary aim of the GLR was to estimate the prevalence and incidence of SLE in 2002-2004 in Atlanta, Georgia (Fulton and DeKalb Counties).[22] The GLR, which was funded by the Centers for Disease Control and Prevention (CDC), drew from >1 million at-risk individuals across a broad socioeconomic gradient in both blacks and whites. The GLR remains one of the two largest population-based epidemiologic studies of SLE ever performed in the United States.[22] The partnership between Emory investigators and the state health department for the GLR led to the designation of Emory researchers as agents of the state [HIPAA 45 CFR 164.512(b)], who were allowed to review medical records and capture protected health information without patient consent. All pertinent local, university, state, and CDC IRB reviews and approvals were obtained.[22]

Potential SLE cases were identified via hospitals; providers in rheumatology, dermatology, and nephrology; commercial and hospital-based laboratories; regional pathology laboratories; lupus research databases; and population databases, including the USRDS, Veterans Affairs (VA) data, Medicaid claims data, and state mortality and hospital discharge data. Since 2004, more than 20 hospitals, 30 rheumatology practices, 60 nephrology practices, and 40 dermatology practices have participated in the GLR. The presence of diagnostic codes [International Classification of Diseases, 9th revision (ICD-

9)] for SLE (710.0) and related conditions that might evolve into SLE---including discoid lupus (695.4), other specified connective tissue disease (710.8), and other unspecified connective tissue disease (710.9)---in any of these sources flagged a patient as a potential SLE case.[25] Personal identifiers, including residence, were collected for all potential cases to avoid duplicate entries. Medical records for all potential cases with residence in Fulton or DeKalb County in 2002-2004 were fully abstracted (>200 data elements) by trained abstractors. Nearly 45,000 records were screened and >7,000 were abstracted.

From these abstracted medical records, SLE cases were defined by (1) the presence of ≥4 of 11 ACR criteria for the diagnosis of SLE (see Table 2.1) or (2) the presence of 3 of 11 ACR criteria *and* either a kidney biopsy pathology report indicating LN *or* a diagnosis of SLE by an experienced rheumatologist. The latter criteria were introduced to capture milder cases and cases with fewer documented symptoms. Date of diagnosis was defined the earliest date of diagnosis of SLE or related connective disease with systemic features (day=15 if unknown and month=July if unknown).[120] With these criteria, the GLR captured 1666 validated SLE cases living in Fulton and DeKalb counties in 2002-2004, of whom 345 were incident---*i.e.*, their first date of diagnosis was between January 1, 2002, and December 31, 2004. The mean age at diagnosis of incident SLE cases was 40.5 years, and 87% and 74% of these cases were female and black, respectively. The GLR data are summarized in Table 3.1.[120]

Table 3.1. Overview of the Georgia Lupus Registry data.

Population	-All identified prevalent and incident SLE patients (*n*=1666 total; incident *n*=345) living in Fulton and DeKalb Counties in 2002-2004
Data Available	-Date of first diagnosis of SLE -Identifiers (name, date of birth, Social Security Number) -Address in 2002-2004 (geocoded) -Age, sex, race, marital status, primary insurance at diagnosis -Eligibility criteria -Clinical history (pregnancy, thrombosis, ACR criteria, etc.) -Laboratory (cell counts, antibodies, urine protein/cell casts) -Mortality (vital status, cause of death)
Strengths	-Case ascertainment maximized -Medical records on all potential cases captured and reviewed by trained abstractors -Comprehensive clinical data used to validate SLE diagnosis -Cases from a large (~1.5 million), demographically and socioeconomically diverse metropolitan population
Limitations	-Unknown sensitivity of case-finding methodology -No capture of cases without access to healthcare -Socioeconomic data limited to insurance status at diagnosis -Addresses not updated after 2004 -Potentially limited generalizability outside of Fulton and DeKalb Counties

3.1.2 United States Renal Data System (USRDS). The main objective of the USRDS, which is funded by the National Institute of Diabetes and Digestive and Kidney Disorders (NIDDK), is to provide an ongoing, integrated database for outcomes research on the U.S. ESRD population.[39] The USRDS data originate from the Centers for Medicare & Medicaid Services (CMS), United Networks for Organ Sharing (UNOS), the ESRD Networks (see Figure 2.1), and the USRDS special studies. Figure 3.1 provides a schematic for the origins and integration of USRDS data. CMS provides information on patients (including eligibility, hospitalizations, and deaths) and dialysis facilities. ESRD Networks, through ESRD providers, process ESRD Medical Evidence Reports (CMS-

2728; see Appendix A) and ESRD Death Notifications (CMS-2746; see Appendix B), which in turn are processed and provided by CMS. The Standard Information Management System (SIMS), a data tracking collaboration of the ESRD Networks and CMS, provides data on treatment history for non-Medicare ESRD patients. UNOS provides data on donor and recipient characteristics and transplant outcomes on all transplants, including kidney transplants, in the United States. Finally, the USRDS special studies are nested observational studies conducted to address particular objectives.[39]

The Standard Analytical Files (SAFs), provided by the USRDS to researchers, include all treated U.S. ESRD patients starting in 1980, with a lag of about 2 years to allow for resolution of claim adjustments. We currently have access to the Core, Transplant, and Hospital SAFs through September 2011. The Core SAFs include data on patient demographics, residence (to the zip code level), treatment and payment history, CMS-2728 Medical Evidence forms (1995 and 2005), and transplant and waitlisting events. Only the 2005 CMS-2728 Medical Evidence form (Appendix A) includes information on quality-of-care indicators such as timing of nephrology visits and vascular access used at first dialysis.[39] The Transplant SAFs provide more detailed data from CMS and UNOS on kidney transplants (including donor and recipient characteristics) and their follow-up. Finally, the Hospital SAFs provide 100% of inpatient claims (dates of admission and discharge and diagnostic codes) for ESRD patients in the Core SAFs. An overview of the available USRDS data of interest for this dissertation is shown in Table 3.2.

Figure 3.1. Origins and integration of the United States Renal Data System.

CMS, Centers for Medicare & Medicaid Services; ESRD, end-stage renal disease; SIMS, Standard Information Management System; USRDS, United States Renal Data System.

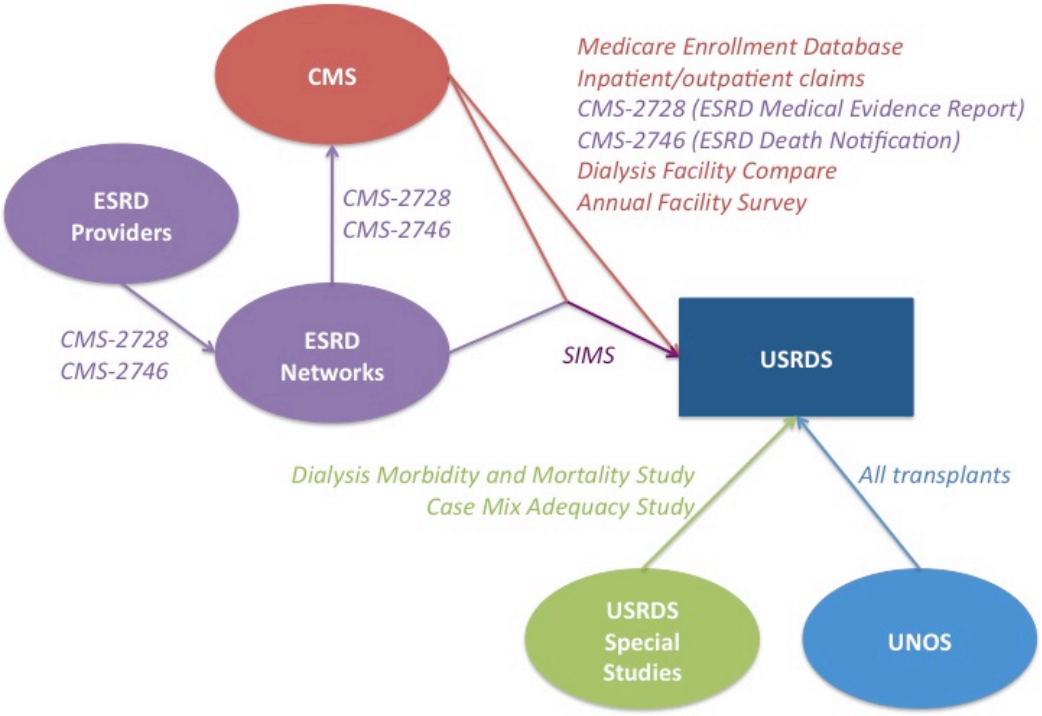


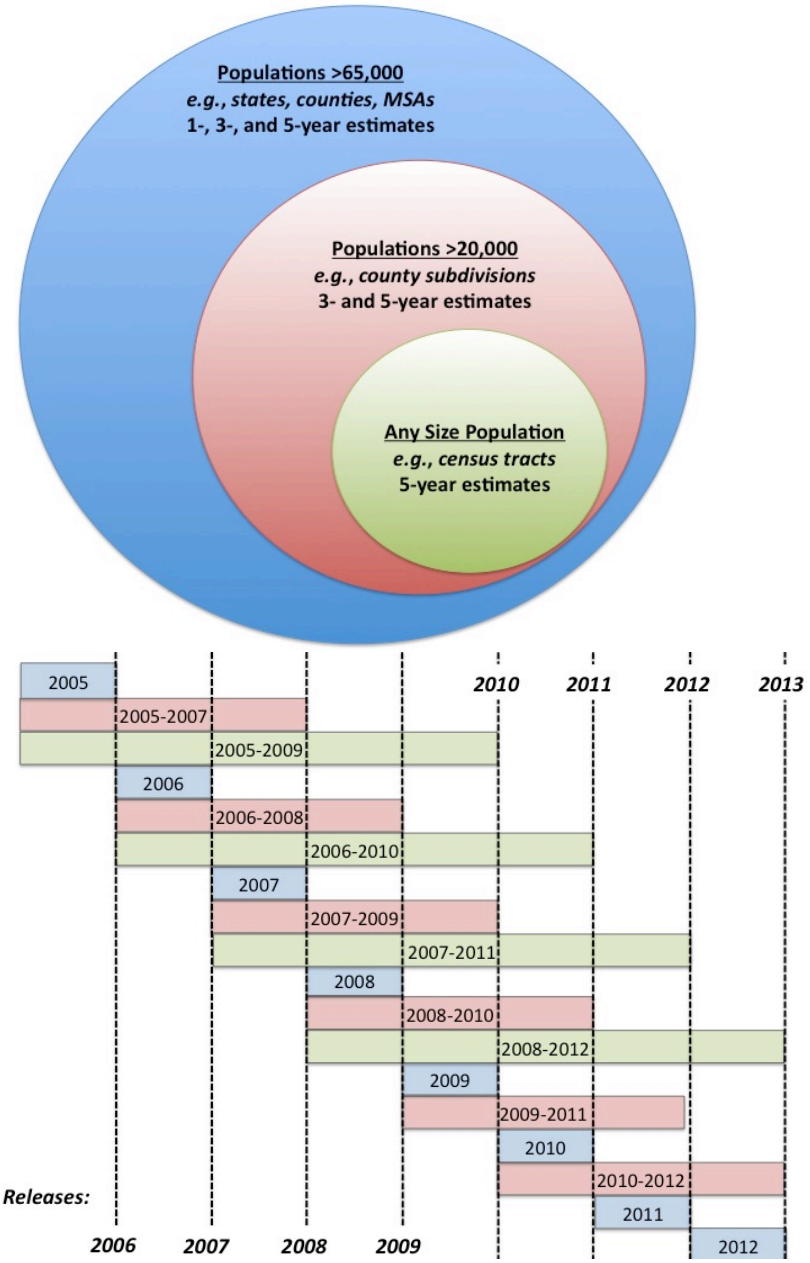
Table 3.2. Overview of the United States Renal Data System data.

Population	-All treated U.S. ESRD patients from 1980 to 2011
Data Available	-Patient demographics (age, race, sex) -Patient residence (zip code or county) -Treatment history (dates of dialysis, transplant, return to dialysis, new transplants) -CMS-2728 Medical Evidence Form data (employment prior to ESRD, insurance prior to ESRD, primary cause of ESRD, quality-of-care indicators, comborbid conditions) -Transplant history (dates of waitlisting and transplants, donor, recipient, and matching characteristics) -Deaths (date, cause per CMS-2746 Death Notification)
Strengths	-All treated U.S. ESRD patients are captured -CMS-2728 completed for all patients regardless of Medicare coverage -Data on hospitalizations, transplants, deaths available -Possibility of matching to registry data via personal identifiers -Timely availability of data (2-year lag), annual updates
Limitations	-Non-Medicare-eligible individuals (including undocumented residents) not captured -Variables on quality of care on CMS-2728 captured 2005+ only -No standard CMS-2728 data entry (filled out by provider within 45 days) -Unknown sensitivity and specificity of attribution of cause -Residence by zip code or county only -Limited SES information (employment, insurance at start of dialysis)

3.1.3 American Community Survey (ACS). The ACS, administered by the U.S. Census Bureau, replaced and enhanced the decennial long-form census form, which was discontinued after 2000. The ACS is a continuous, rolling-sample survey with the primary aim of helping Congress to determine funding and policies for federal programs.[121] The annual sample size is 2.5% of the U.S. population, with 3 million U.S. addresses randomly sampled each year. The data have been released annually since 2006, but because data must be accumulated over time to produce reliable estimates, ACS data represent period characteristics, from 1- to 5-year averages (Figure 3.2).[121] Additionally,

the smaller the geographic area of interest, the longer the period of data collection must be (Figure 3.2).

Figure 3.2. Population sizes and possible estimates and corresponding periods of collection and availability for American Community Survey data.



The ACS collects a variety of data on demographic, economic, social, housing, and financial characteristics of individuals and households (Table 3.3), which are then aggregated over geographic areas and averaged over time periods. Both average values and margins of error (which can be converted to standard errors by dividing the values by 1.645)[121] are provided. Some contextual variables, such as the Gini index, which is a measure of income inequality within a defined geographic area,[122] are also calculated by the U.S. Census Bureau from the data collected and provided in the ACS data. ACS data---as well as data from the decennial censuses---can also be used to calculate other contextual measures, such as residential segregation by race.[123,124]

Table 3.3. Overview of the American Community Survey data.

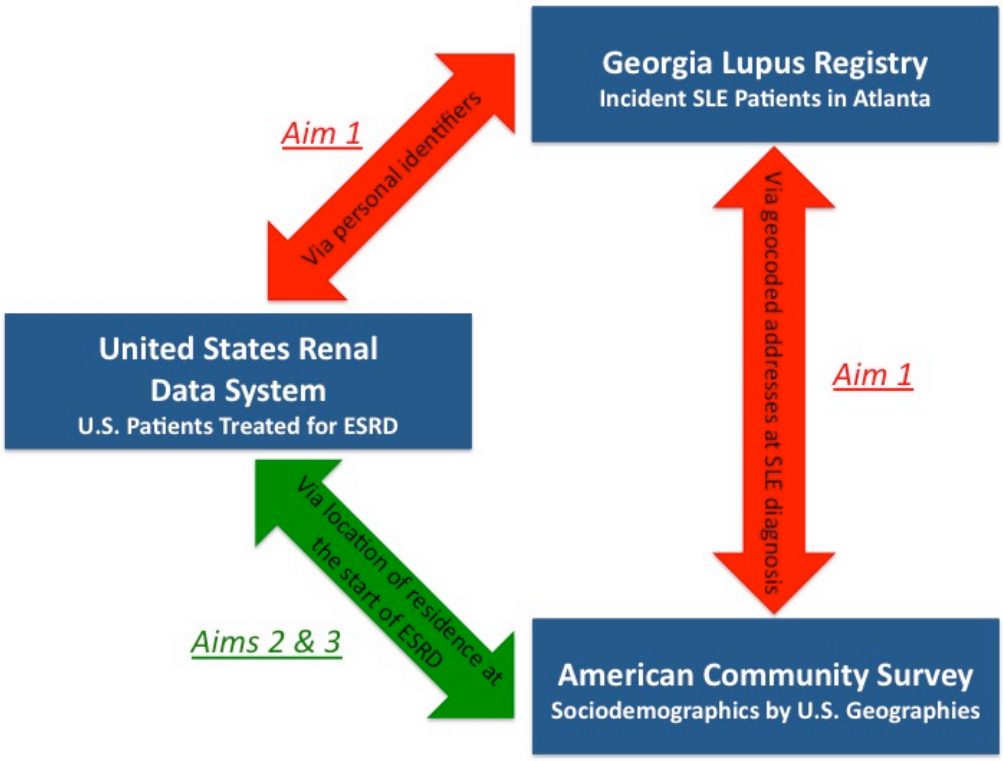
Population	-Rolling samples of the U.S. population for 1-, 3-, and 5-year periods (most recent: 2008-2012)
Data Available	-Demographics (age, race, sex, Hispanic origin) -Economic characteristics (income, receipt of public assistance, employment, occupation, commute, vehicles, health insurance) -Social characteristics (marital status/history, fertility, place of birth, language spoken at home, education, veteran status, disability) -Housing characteristics (year built, number of rooms, kitchen facilities, plumbing, heating, telephone service) -Financial characteristics (owned housing, value, rent)
Strengths	-Uniform methods allow comparison across geographic areas -Timely availability of data (1-year lag), annual updates -Reliability of estimates increases with time period covered
Limitations	-Smaller geographic areas (tracts, blocks) only available over 5-year periods and misclassification is possible in areas undergoing major changes -1-year estimates not as reliable as 3- and 5-year estimates (based on smaller sample size)

3.1.4 Linkage of data sources. Personal identifiers (including name, date of birth, and sex) in the GLR can be used to link matching records in the USRDS data. This linkage

will allow the identification of all 2002-2004 incident SLE patients who initiated treatment for ESRD through the end of 2011 (Figure 3.3). Further, since data on the first treatment date and attributed primary cause of ESRD can be obtained from the USRDS, we will be able to estimate the incidence of LN-ESRD among a cohort of SLE patients diagnosed in 2002-2004 (Aim 1). The linkage process will require a NIDDK-approved study protocol, a signed data use agreement with appropriate waivers, data on personal identifiers for individuals to allow for matching with USRDS data, and payment for labor and matching SAF data.

The ACS data can be linked to any other source of data, given common geographic areas across datasets (*e.g.*, census tract). The use of Federal Information Processing (FIPS) codes ensures standardized, unique identification of all geographic areas. The GLR data can be linked to the ACS data via geocoded patient addresses collected in the GLR (Figure 3.3). For Aim 1, the ACS data can provide information on contextual socioeconomic status around the residence at the time of SLE diagnosis and/or compensate for the lack of data on indicators of individual socioeconomic status in the GLR. The USRDS data can also be linked to ACS data through location of the patients' residence at the start of ESRD treatment to address Aims 2 and 3 (Figure 3.3). As for Aim 1, linkage of the ACS data to the USRDS data for Aims 2 and 3 can provide information on contextual socioeconomic status around the residence at the start of ESRD treatment and/or compensate for the lack of data on indicators of individual socioeconomic status in the USRDS.

Figure 3.3. Data sources and possible linkages between data sources to address dissertation aims.



3.2 Analytic Methods

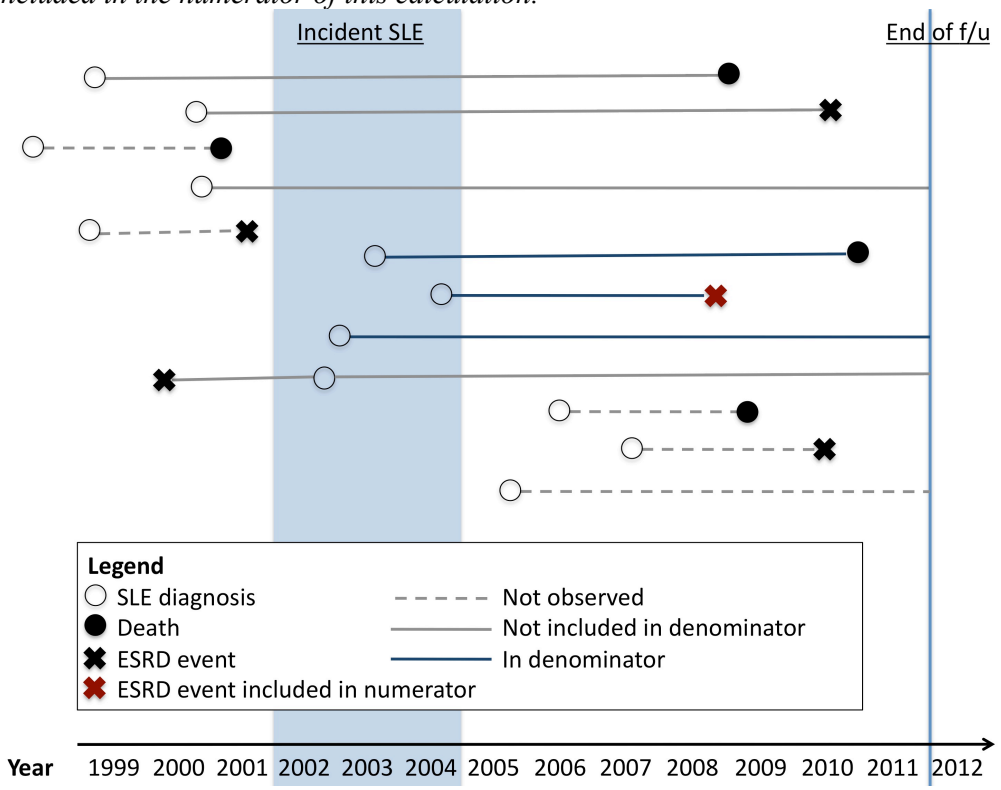
3.2.1 Incidence of ESRD among SLE patients (Aim 1). Incidence of ESRD among SLE patients diagnosed in Fulton and DeKalb counties in 2002-2004 will be determined by linkage of the GLR data to the USRDS data, which will capture all cases of ESRD among those in the GLR who were alive, eligible for ESRD treatment, and living in the United States at the end of 2011.

3.2.1.1 Population and estimation of incidence: Incidence of ESRD will be calculated as a rate per person-year and also cumulative incidence. Overall and race-specific (white vs. black) incidence rates and cumulative incidence will be reported. This incidence will only be calculated among those who were diagnosed in 2002-2004 (*i.e.*, incident SLE patients in the GLR), since including prevalent patients might introduce survival bias (Figure 3.4). Because the follow-up period will begin in 2002-2004, calculation of cumulative incidence will only be available for such intervals as 3, 5, and 7 years; calculation of 10-year cumulative incidence will not be possible until the USRDS data are updated through 2014. Follow-up time will start at time of diagnosis of SLE for incident patients only (diagnosed 2002-2004) and will end at first date of ESRD treatment, death after SLE diagnosis (but prior to ESRD treatment), or last date of follow-up available from the USRDS (likely 12/31/2011; see Figure 3.4). Additionally, if any GLR participants received any ESRD treatment prior to their diagnosis of SLE, they will be excluded from the denominator (Figure 3.4).

All cases of incident ESRD, regardless of attributed cause on the CMS-2728 form, will be included in our primary calculation of incidence. However, depending on the number of cases and on the frequency of attribution of ESRD to causes other than LN among those in the GLR who match records in the USRDS, additional analyses using (1) only those cases with attributed cause of LN-ESRD on the CMS-2728 and (2) those cases with ESRD and either an attributed cause [as in (1)] *or* at least two inpatient codes for LN (ICD-9 code of 710.0) could also be conducted to determine whether estimated incidence rates are affected by varying definitions of LN-ESRD.

Figure 3.4. Possible events and follow-up trajectories for participants in the Georgia Lupus Registry, with linkage to the United States Renal Data System.

Blue paths indicate participant follow-up times that would be included in the denominator of the calculation of incidence; red Xs indicate ESRD events that would be included in the numerator of this calculation.



3.2.1.2 Identification of contributory factors: Because we know that incidence of SLE, LN, and ESRD all differ substantially by race, all examinations of incidence by contributory indicators will also be stratified by individual race. However, multiple stratifications beyond individual race and single additional contributory factors will likely be limited by small sample sizes. It is possible that we will discover few cases of ESRD in our linked data and that our number of events will be quite small.

Since information on individual socioeconomic status is quite limited in the GLR, the contributory factors beyond individual race will be characteristics of the neighborhood (as measured by census tracts) in which the patient resided at the time of SLE diagnosis. The factors of interest are those that relate to sociodemographic and socioeconomic characteristics that are likely to affect behavior, social support, and healthcare access. Specifically, we are interested in the composition of the neighborhood with respect to *race*, *poverty*, and *education*, which are related, but not entirely overlapping, indicators of the social status of a neighborhood. While race composition can be described in terms of multiple races and ethnicities, the established black/white disparity in SLE, LN, and ESRD---and the preponderance of black and white reported race among the incident patients in the GLR (96.7%)---make the percentage of residents in a census tract who are black the most appropriate and interesting indicator of racial composition in this population. Neighborhood poverty composition will be measured as the percentage of households in a census tract living below federal poverty threshold (FPT; as defined in the year residents were surveyed). The FPT is often criticized for being too low and not reflecting geographic variations in cost of living. However, the collective percentage living below the FPT is still likely to provide an indicator of the overall poverty status of a neighborhood, since alternate measures of poverty have provided similar estimated poverty rates in the overall population (16.1% vs. 15.1% in 2011).[125] Finally, the indicator for neighborhood education composition will be the percentage of residents in a census tract aged >25 who are high school graduates or equivalent. The high school degree is an appropriate cutoff for this population because not only did 34% of 2007-2011 Atlanta residents drop out of high school in 2007-2011

(http://factfinder2.census.gov/) but also high school dropouts are far more likely than their counterparts with diplomas to experience underemployment, low earnings, and prison time.[126] In order to examine by incidence by these indicators, these continuous (range, 0-100%) measures will be categorized, with cutoffs determined by distribution of the data (medians, tertiles) and/or defined cutoffs, such as the U.S. Census definition of a "poverty area" (>20% of residents living below FPT).[127] The number of possible categories for stratification will depend on the total number of events in our final linked dataset.

Because we expect that the majority of census tracts in our study area will have few or zero cases, we will limit potential analysis of *geography* as a contributory factor to LN-ESRD incidence in Fulton and DeKalb counties to descriptive mapping. To prevent identifiability of individual cases and also to identify potential clusters or "hotspots," smoothing techniques such as kernel density estimation can be used. Kernel density estimation was originally developed for identifying crime hotpots. In this technique, a grid (whose cell size can be specified) is laid over the area of interest and incidence within each cell is estimated via kernel density functions. These three-dimensional probability functions are centered at over each grid point in turn and the local density of events in the area (determined by the bandwidth) around the grid point is estimated.[128] The sum of the heights of the densities within each cell is then displayed, with the greatest heights indicating the most overlap of densities, or the greatest overall probability of an event, such that the greatest probability of events occurs nearest to the location of actual events.[128]

3.2.1.3 Exploratory analyses: Beyond individual race (black vs. white) and composition of neighborhoods (*i.e*., proportions of residents with various social characteristics of interest within an area), we might also be interested in the spatial distribution of residents with these characteristics, particularly the comparison of spatial scales to investigate heterogeneity or *granularity*. For example, we might expect that black individuals who live in a primarily black neighborhood that is surrounded by other primarily black neighborhoods might have a different experience than those who live in a primarily black neighborhood that is surrounded by primarily white or racially heterogeneous neighborhoods. Measures of this granularity---which relax the assumption that individuals within a boundary have no proximity to or contact with those outside the boundary[124]---could be applied to areal race, poverty, and education. Effects of spatial heterogeneity on LN-ESRD incidence could be positive (*e.g*., heterogeneity in poverty could mean that those in a predominantly poor neighborhood might have close and easy access to wealthier neighborhoods and their associated resources) or negative (*e.g*., racial heterogeneity might be associated with less social cohesion and community support).

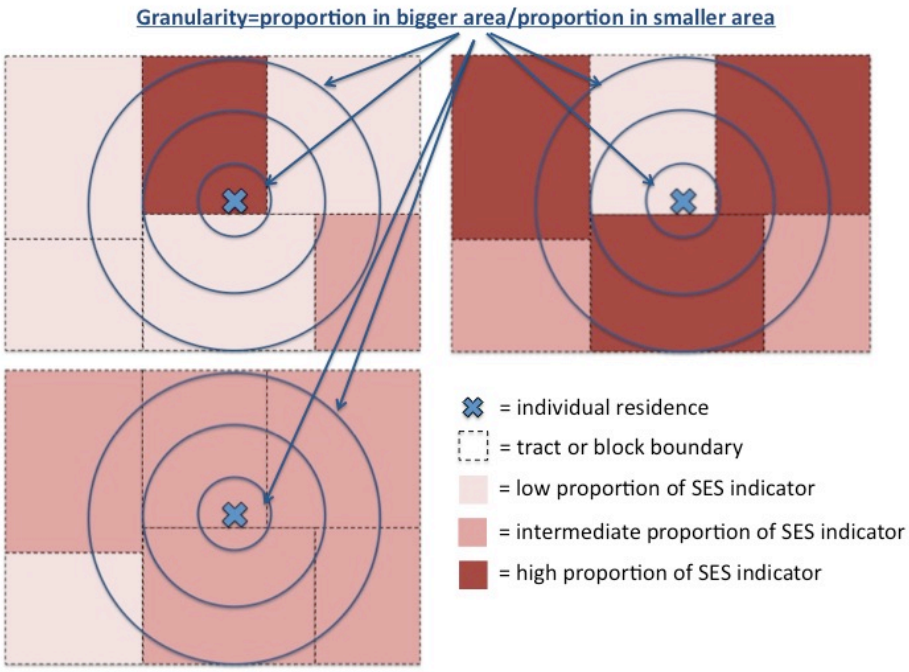
To estimate this granularity, we can imagine several scenarios, some of which are depicted in Figure 3.5. With our primary method, the individual indicated would be assigned the SES proportion (say, percentage living below poverty) in his/her neighborhood, which could be defined for this aim as the census tract. However, in the top panels, the poverty composition in the individual's tract does not reflect the actual level of poverty surrounding the individuals' residence. Further, the proportion is likely

not homogeneous within the tract's boundaries, particularly around the borders, where the depicted abrupt change in unlikely (the so-called "checkerboard" problem[129]).

A ratio of granularity---specifically, proportion in larger area surrounding a residence divided by proportion in a smaller area surrounding the same residence---would tell us the individual lives in a heterogeneous area, either immediately surrounded by high levels of poverty but with mostly wealthy areas outside of that small area (ratio << 1, top left) or immediately surrounded by low levels of poverty but with mostly poorer areas outside of that small area (ratio >> 1, top right; Figure 3.5). A mostly homogeneous large area (Figure 3.5, bottom left) would give a ratio close to 1.

With the GLR data, exact geocoded addresses are available and census block data could be used to to create the kernel surface to calculate this ratio. Similar to the estimation of macro-micro segregation index described by Lee *et al*.,[124] grids (*e.g*., 50 X 50 m) could be laid over the entire area and smoothed percentages of SES indicators per grid cell could be calculated using census block data, with kernel function proximity weighting, such that percentages in nearby cells would provide more weight than percentages in more distant cells.[129] Average percentages in this smoothed grid over various radii of larger and smaller areas could then be explored, with starting points of 4000 m (distance in which most daily functions are performed) and 500 m (pedestrian distance).[124] As with the neighborhood composition indicators in the primary analysis, these estimated ratios would have to be categorized in order to examine incidence stratified by granularity.

Figure 3.5. Estimation of granularity in three possible scenarios of location of individual residence and areal socioeconomic composition.
Top left, ratio << 1; top right, ratio >> 1; bottom left, ratio ≈ 1. Based on a figure in Lee et al.[124] *SES, socioeconomic status (e.g., percentage living below poverty).*



3.2.1.6 Summary: An overview of the analytic plan for Aim 1 is shown in Table 3.4.

Table 3.4. Overview of the analytic plan for Aim 1.

Stated aim	-To estimate the incidence of ESRD among Atlanta-area SLE patients and identify sociodemographic factors that contribute to variation in incidence
Population	-Participants in the Georgia Lupus Registry who were diagnosed with SLE in 2002-2004 and did not receive ESRD treatment prior to the SLE diagnosis
Numerator	-Number of participants meeting inclusion criteria and initiating ESRD treatment prior to the end of USRDS follow-up (currently 12/31/2011)
Denominator	-Total person-time contributed by all patients meeting inclusion criteria (incidence) -Total number of patients meeting inclusion criteria and surviving to the end of the designated risk period (cumulative incidence)
Socioeconomic indicators	*In census tracts corresponding to residential address of participants at the time of diagnosis:* -Race (percentage of residents who are black) -Poverty (percentage of households living below federal poverty threshold) -Education (percentage of residents aged >25 who are high school graduates or equivalent)
Geographic indicators	-Census tracts within Fulton and DeKalb counties, Georgia
Other variables of interest	-Individual race (white, black) -Attributed primary cause of ESRD -Granularity of socioeconomic indicators
Limitations	-Unknown sensitivity of case-finding methodology (denominator limited to diagnosed, observed cases) -Lack of individual socioeconomic status data (limited to insurance status at diagnosis, missing on 43% of incident cases) -Likely insufficient power to detect geographic clustering -Multivariable stratification limited due to small sample size -Residential addresses only available at diagnosis -Potentially limited generalizability outside of Fulton and DeKalb Counties

SLE, systemic lupus erythematosus.

3.2.2 Associations of geographic and socioeconomic factors with successful translation of ESRD quality-of-care indicators in U.S. LN-ESRD patients (Aim 2).

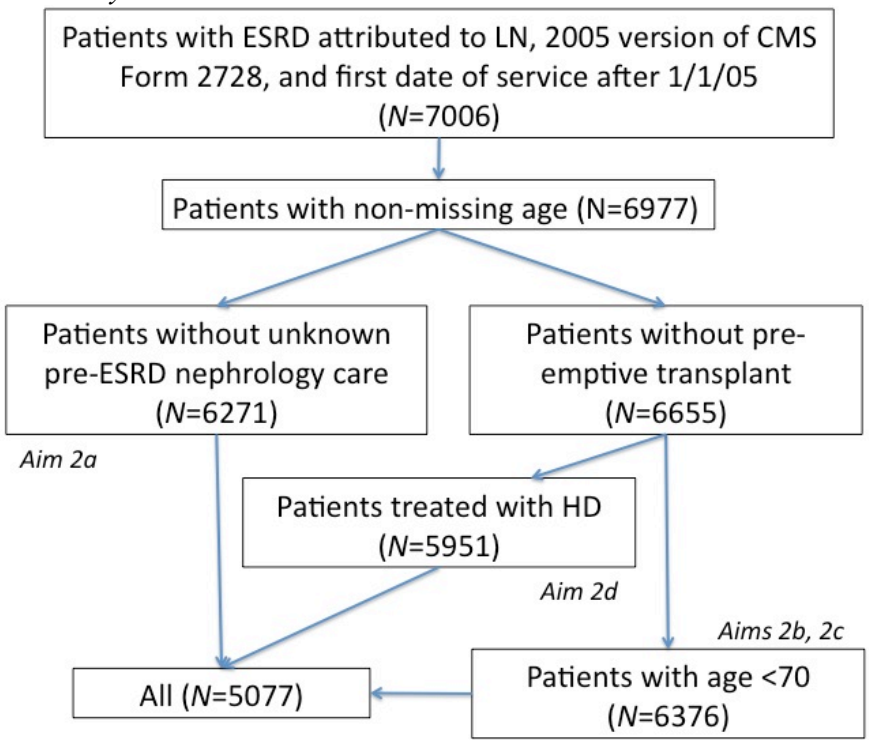
The main source of the data to address Aim 2 is the CMS Medical Evidence Report (CMS Form 2728; Appendix A), which is completed for all patients at the start of ESRD treatment. Generally, the form is used to demonstrate entitlement for Medicare benefits based upon ESRD status; however, even for those ESRD patients who do not apply for Medicare coverage, the form is required. Thus, ascertainment of quality-of-care indicators included on the CMS Form 2728 is complete for all U.S. citizens who are eligible for Medicare.

3.2.2.1 Population: Because we are examining several quality measures that have been collected since 2005 only, we will limit our analyses of all the sub-aims to those patients with a recorded 2005 version of the CMS Form 2728 form who (1) initiated ESRD for the first time in 2005 or later and (2) have a primary cause of ESRD indicated by ICD-9 code 710.0 (lupus nephritis; *N*=7,006; Figure 3.6). The sensitivity and specificity of attribution of ESRD to LN remain unknown, but at least one small study of renal biopsies of patients with glomerular diseases who went on to develop ESRD[130] showed that, of 30 cases confirmed to be LN by renal biopsy in 1979-2000 in Network 6, only 27% were coded as LN-ESRD (whereas specificity was 100%). Although these data were relatively old and the study sample size was small, we cannot rule out that we may only be capturing a fraction of U.S. patients with ESRD that is due to LN. However, this misclassification will only bias our estimates of association if the misclassification is

differential with respect to exposures or outcomes. For example, while it is unlikely that dialysis providers filling out the CMS Form 2728 were involved in patients' pre-ESRD care, it remains possible that patients with greater pre-ESRD care (and thus more likely to have a permanent vascular access and be informed of transplant options at the start of ESRD treatment) could also be more likely to have their cause be properly attributed, due to more complete medical records. This is a potential limitation that cannot be remedied, only acknowledged.

Figure 3.6. Population selection for Aim 2.

HD, hemodialysis.



For the sub-aims, we will apply further exclusions to the population (Figure 3.6). For the first sub-aim (2a), which will examine pre-ESRD nephrology care, we will exclude those

patients whose pre-ESRD care is indicated as "unknown" on the CMS Form 2728. For Aim 2d, in which we will examine permanent vascular access placement for dialysis, we will exclude those with a pre-emptive transplant, defined as a transplant that occurs within 90 days of start of ESRD treatment, and those who are treated with peritoneal dialysis, eliminating the need for a vascular access. For Aims 2b (informed of transplant options) and 2c (transplant waitlisting), we will exclude those aged 70 years of older (who are generally not considered for transplant), as well as those with pre-emptive transplants. Finally, the same population with all the above exclusions applied (N=5,077; Figure 3.6) could also be used for all sub-aims to increase comparability of estimates.

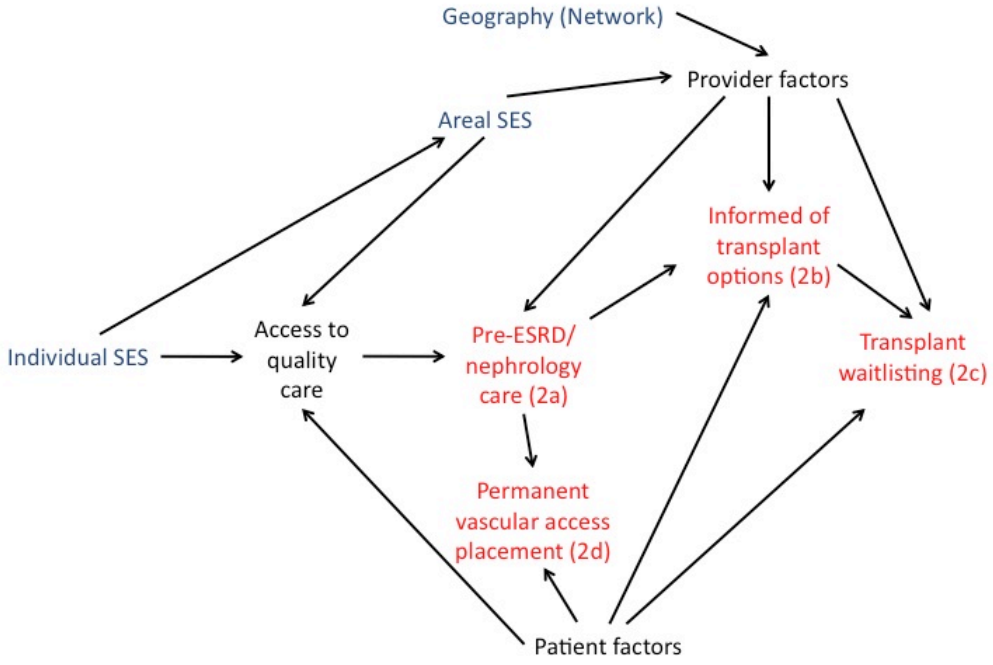
3.2.2.2 Exposures: The exposures of interest for all sub-aims include individual and areal SES and geography (Figure 3.7). Individual race and type of insurance prior to the start of ESRD (private, Medicare, Medicaid, none) will serve as the only patient-level indicators of socioeconomic status, due to limited data collected by the USRDS. From linked ACS data, we are also interested in neighborhood race, poverty, and education, as defined for Aim 1, as exposures (Table 3.5). To prevent identifiability, the USRDS reports patient residence (at the time of ESRD diagnosis) only to the ZIP code level. ZIP Code Tabulation Areas (ZCTAs) are generally considered inferior to census tracts for health studies because they are generally larger areas defined only for the purposes of delivering mail [unlike census tracts, which are "designed to be homogeneous with respect to population characteristics, economic status, and living conditions" (http://www.census.gov/geo/www/geo_defn.html)], and ZCTAs have been shown not to predict outcomes as well as census tracts in health studies.[131] While county-level

aggregated SES data would also be available, averages over a large area such as a county are unlikely to represent individual, daily experiences of SES for all those living in the county. Thus, for our purposes, ZCTAs represent the best balance between what is available and the scale at which we hypothesize effects may occur---*i.e*., the individual's immediate neighborhood. Thus, ZCTA-aggregated data will be used to represent areal SES, which can be examined continuously or in categories (as in Aim 1). In exploratory analyses, we may also examine granularity of these SES indicators as exposures (see *3.1.2.3*), although the methods and parameters would have to be modified to reflect that individual cases cannot be mapped to small areas such as census blocks or even tracts. For example, centroids of ZCTAs could be used instead of census blocks to establish the kernel grid.

We are also interested in the association of geography with our quality-of-care outcomes. The 18 multi-state ESRD Networks (see Figure 2.1) are responsible for locally implementing national quality-of-care indicators, such as the outcomes we are examining in Aim 2 (see below). Thus, we are interested in which, if any, Networks have better or worse performance on these measures among U.S. LN-ESRD, both overall and controlled for individual and areal SES factors, which may differ by Network. Other geographies that may be of interest include the zip-code defined neighborhood or county, but these areas will be too numerous in our national dataset to allow estimation of fixed effects.

Figure 3.7. Directed acyclic graph for Aim 2.

Shown are associations between exposures (in blue; individual and areal SES and geography) and outcomes (in red; pre-ESRD care, informed of transplant options, transplant waitlisting, and permanent vascular access placement) of interest, along with potential confounders and intermediates.



3.2.2.3 Outcomes: In all, four outcomes related to quality of ESRD care will be examined in Aim 2.

3.2.2.3a Pre-ESRD care. Here, we define pre-ESRD care as *whether* and *when* patients saw a nephrologist prior to onset of ESRD. Item 18b on the CMS Form 2728 (Appendix A) asks "Prior to ESRD therapy: was the patient under the care of a nephrologist?" with possible responses of "Yes," "No," and "Unknown." The follow-up item "If Yes, answer:" has possible responses of "6-12 months" and ">12 months." Thus, presence of

pre-ESRD care can be defined as *whether* patients saw a nephrologist ("Yes" vs. "No"), a dichotomous outcome. The duration of pre-ESRD care can be defined as *when* patients saw a nephrologist, with a range of none ("No"), <6 months, 6-12 months, and >12 months, an ordinal outcome. Since the follow-up item does not provide an option for pre-ESRD nephrology care of <6 months, we will assume mutual exclusivity, such that any answer of "Yes" without "6-12 months" or ">12 months" checked as follow-up indicates a duration of <6 months.

Because dialysis providers (who may not have provided any pre-ESRD care) are responsible for the CMS Form 2728, the accuracy of this item has been questioned. A recent report among older adults (≥67) with prior CMS records to indicate nephrology encounters in the 2 years prior to ESRD start showed that agreement of the CMS Form 2728 item with medical records was ~50-75%, depending on the categorization of duration of pre-ESRD care.[132] Despite this evidence of possibly low agreement of this item with actual care, many prior studies have found that this item is strong predictor of better outcomes subsequent to the initiation of dialysis treatment, including dialysis readiness,[57-59] access to the transplant waiting list,[60] and survival.[61-65] Thus, the USRDS[39] and Healthy People (www.healthypeople.gov; see Table 2.5)[8] continue to use this item to track pre-ESRD care in the United States.

3.2.2.3b Informed of kidney transplant options. A recent study suggested that nearly one-third of incident ESRD patients were not informed of their transplant options at the start of ESRD, and that only 3% of these uninformed patients received a transplant or were

waitlisted during the 2-year study period, vs. 14% of informed patients.[7] Whether patients were informed of transplant options prior to the start of ESRD can be measured using item 26 on the CMS Form 2728 (Appendix A), which asks "Has patient been informed of kidney transplant options?" with possible responses of "Yes" and "No." This dichotomous item will serve as the outcome for Aim 2b. Item 27 additionally asks "If patient NOT informed of kidney transplant options, please check all that apply:" with possible responses of "Medically unit," "Patient declines information," "Unsuitable due to age," "Patient has not been assessed," "Psychologically unit," and "Other." While not part of the primary proposed outcome, exploratory stratification of the outcome by reason may be of interest, as previous work showed possible disparities in the rationale for not informing patients of their transplant options. For example, black and Medicaid patients were 27% and 113% more likely to be labeled as psychologically unfit, respectively, than their white and Medicare counterparts,[7] and such patients are common in the LN-ESRD population.

3.2.2.3c Kidney transplant waitlisting. Whether and when patients were placed on the kidney transplant waitlist can be determined from the UNOS component of the USRDS data (Figure 3.1). Because time-to-event outcomes are associated with greater power over simple dichotomous outcome and also take into account varying follow-up times, we will examine the time from first ESRD treatment to date of first waitlisting. Follow-up is complete on these individuals, so censoring will occur at the end of the USRDS follow-up period or at death. Censoring for death could introduce a competing risk problem, in that individuals who would have been placed on the waitlist cannot be observed due to

death. While those patients who die are probably sicker (and less likely to have ever been waitlisted), compared to those who remain under observation, we cannot rule out this potential problem.

3.2.2.2d Placement of permanent vascular access. Finally, whether patients were prepared for dialysis with a permanent vascular access can be determined from Item 18 on CMS Form 2728: "Prior to ESRD therapy: What access was used on first outpatient dialysis?" (with responses of "AVF," "Graft," "Catheter," and "Other"; AVF=arteriovenous fistula). If the response to the item is not AVF, two prompts are given: "Is maturing AVF present?" and "Is maturing graft present?" A combined dichotomous outcome of AVF or graft used on first dialysis, or maturing AVF or graft present, will be used. This combined outcome allows for patient variability in whether fistulae can be successfully created and in amount of time prior to ESRD start that providers may have to prepare the patient for dialysis; but this outcome still adheres to the guidelines, which state that AVFs should be placed, but if AVFs cannot be placed, then grafts should be placed.[90]

3.2.2.4 Confounders: From the directed acyclic graph (Figure 3.7), patient factors serve as potential confounders of all the associations of interest. Specifically, the measured patient factors of age, individual race and ethnicity, and number of comorbid conditions will be considered potential confounders. Additionally, individual SES (here, insurance type prior to start of ESRD) will serve as a potential confounder of the associations between areal SES and outcomes. While provider factors might affect many of these outcomes (*e.g.*, dialysis facility for-profit status might result in less information about

transplants or lower waitlisting), they cannot affect geography or areal SES (Figure 3.7) and thus are not potential confounders, but rather intermediates. Similarly, pre-ESRD care serves as an intermediate for the other three outcomes (while being informed of transplant options serves as an intermediate for transplant waitlisting). Collinearity among the variables in the model will be assessed using condition indices and variance decomposition proportions. Any variables demonstrating condition indices >30 and variance decomposition proportions >0.5 will be examined and contributing variables will be removed as needed.

3.2.2.5 Models: Several types of models will be used to estimate the associations between individual and areal SES and geography and these quality-of-care indicators. For dichotomous outcomes (Aims 2a, 2b, and 2d), logistic regression will be used to assess odds ratios and associated confidence intervals for the associations of interest. Variables will be appropriately coded 0/1 as follows: for pre-ESRD care (Aim 2a), 1 = any pre-ESRD nephrology care, 0 = no pre-ESRD nephrology care; for informed of transplant options, 1 = informed of transplant options, 0 = not informed of transplant options (Aim 2b); and for permanent vascular access placement (Aim 2d), 1 = fistula placed or maturing or graft placed or maturing, 0 = no fistula or graft in place. Generally the logistic models will be of the form:

$$\ln[P(Y=1|\mathbf{X})/P(Y=0|\mathbf{X})] = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \cdots + \beta_k X_k$$

where Y represents our outcome of interest; **X** represents the vector $\{X_1,X_2,\ldots X_k\}$; X_1 is the exposure of interest (SES and geography, which could also be represented by a series of dummy X_is); X_2-X_k are potential confounders; α is the intercept; and the β_is are the coefficients of the X_is. The odds ratios will be the exponentiated estimated values of β_i and the confidence intervals will be the exponentiated estimated values of $\beta_i \pm 1.96*\sqrt{}$(estimated variance of β_i). Odds ratios will represent prevalence ratios of having pre-ESRD care (Aim 2a), having been informed of transplant options (Aim 2b), and having a permanent access in place (Aim 2d) at the start of ESRD, per unit of SES or geography.

For the ordinal outcome in Aim 2a, which categorizes the duration of pre-ESRD nephrology care, ordinal logistic regression will be used to assess odds ratios and associated confidence intervals for the association of interest. The variables will be coded as follows: 0 = no pre-ESRD care, 1 = <6 months of pre-ESRD nephrology care, 2 = 6-12 months of pre-ESRD nephrology care, and 3 = >12 months of pre-ESRD nephrology care. If the proportional odds assumption is not met [as evaluated by examination of the similarity of crude odds ratios for the possible dichotomizations of the outcome (3 vs. 0-2, 2-3 vs. 0-1, and 1-3 vs. 0) and by the score test], the duration will be instead be dichotomized as >12 months vs. <12 months or none, and the association will be estimated using logistic models (as above). Assuming the proportional odds assumption is met, the ordinal logistic model will be of the form:

$$\ln[P(Y\geq g|\mathbf{X})/P(Y<g|\mathbf{X})] = \alpha + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_4 + \cdots + \beta_kX_k$$

where Y represents our outcome of interest; *g* represents the levels of the outcome (*g*=0,1,2,3); **X** represents the vector $\{X_1,X_2,\ldots X_k\}$; X_1 is the exposure of interest (SES and geography, which could also be represented by a series of dummy X_is); X_2-X_k are potential confounders; α is the intercept; and the β_is are the coefficients of the X_is. The odds ratio will be the exponentiated estimated value of β_i and the confidence interval will be the exponentiated estimated value of $\beta_1 \pm 1.96*\sqrt{}$(estimated variance of β_1). Odds ratios will represent prevalence ratios of having had longer vs. shorter duration of ESRD, per unit of SES or geography.

Finally, the outcome of Aim 2c is a time-to-event outcome (time to waitlisting). Kaplan-Meier curves per level of SES and geography will be constructed, although the number of ESRD Networks will preclude all Networks being compared on the same graph, and log-rank tests for equality of curves will be conducted. The proportional hazards assumption---that the hazard ratios comparing levels of exposure do not change over time---will be checked by examining survival curves, testing the significance time-exposure interactions, and performing goodness-of-fit tests of Schoenfeld residuals. If the proportional hazards assumption is met, Cox proportional hazards models will be run:

$$h(t,\mathbf{X}) = h_0(t)*\exp[\beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_4 + \cdots + \beta_kX_k]$$

where t represents our time to event; $h_0(t)$ is the (unspecified) baseline hazard; **X** represents the vector $\{X_1,X_2,\ldots X_k\}$; X_1 is the exposure of interest (SES and geography,

which could also be represented by a series of dummy X_is); X_2-X_k are potential confounders; α is the intercept; and the β_is are the coefficients of the X_is. Hazard ratios of transplant waitlisting, per unit of SES or geography, will be the exponentiated estimated value of β_i and the confidence interval will be the exponentiated estimated value of $\beta_1 \pm 1.96*\sqrt{(\text{estimated variance of } \beta_1)}$. If the proportional hazards assumption is not met for certain predictors, stratified Cox models will be considered; if the assumption is not met for the exposure of interest, we may default to the logistic model described earlier and only examine whether patients were waitlisted within a certain period (*e.g.*, 2 years).

If we wish to account for differences across neighborhoods (defined by zip code), we may consider hierarchical logistic models for the models above, to account for the correlation of individuals within these areas. For such models, we might have a slightly modified original model:

$$\ln[P(Y=1|\mathbf{X})/P(Y=0|\mathbf{X})] = \alpha_{0j} + \beta_{1j}X_{1j} + \beta_2X_2 + \beta_3X_3 + \beta_4X_4 + \cdots + \beta_kX_k$$

where the intercept and coefficient of interest now vary by *j*, the neighborhood and X_{1j} represents an individual-level variable. And we would introduce two additional models at the neighborhood level:

$$\alpha_{0j} = \gamma_{00} + \gamma_{01}Z_j + u_{0j}$$
$$\beta_{1j} = \gamma_{10} + \gamma_{11}Z_j + u_{1j}$$

such that the original intercept α now consists of an intercept (γ_{00}), a random neighborhood-level component of the intercept (u_{0j}), and a fixed slope (γ_{01}) of the

neighborhood-level predictor (here, Z_j = areal SES). Similarly, the coefficient of interest (β_1) now consists of fixed and random elements. These two equalities would be substituted back into the original model and reduced as follows:

$$\ln[P(Y=1|\mathbf{X})/P(Y=0|\mathbf{X})] = (\gamma_{00} + \gamma_{01}Z_j + u_{0j}) + (\gamma_{10} + \gamma_{11}Z_j + u_{1j})X_{1j} + \beta_2X_2 + \beta_3X_3 + \beta_4X_4 + \cdots + \beta_kX_k$$
$$= (\gamma_{00} + u_{0j}) + (\gamma_{10} + u_{1j})X_{1j} + \gamma_{01}Z_j + \gamma_{11}Z_j*X_{1j} + \beta_2X_2 + \beta_3X_3 + \beta_4X_4 + \cdots + \beta_kX_k$$

This model contains a random component of the intercept, a random component of the slope for the individual-level variable, a slope for the neighborhood-level variable, and a slope for an interaction term between the individual- and neighborhood-level variables. These models could also be simplified to contain only random intercepts for the neighborhood. However, given that there are >42,000 zip codes in the United States (http://faq.usps.com/adaptivedesktop/faq.jsp?ef=USPSFAQ) and only ~6,000 patients in our population of interest, it is likely that most U.S. zip codes will have zero cases of LN-ESRD (and thus be excluded) or have only a single case of LN-ESRD. If this is the case, we will simply assign neighborhood factors to individuals and ignore what is likely to be negligible within-neighborhood correlation. Additionally, hierarchical models are not possible with time-to-event analyses (see section *3.2.3.5*).

3.2.2.6 Summary: Overviews of the analytic plans for Aims 2a-2d are shown in Tables 3.5-3.8.

Table 3.5. Overview of analytic plan for Aim 2a.

Stated aim	-To estimate associations of geographic and socioeconomic factors with *whether and when patients saw a nephrologist prior to onset of ESRD*
Population	-All U.S. patients initiating ESRD treatment for the first time in 2005-2011 with known pre-ESRD nephrology care status
Exposures (socioeconomic and geographic indicators)	-Individual race -Individual insurance prior to start of ESRD *In zip codes corresponding to residential address of participants at the start of ESRD treatment:* -Race (percentage of residents who are black) -Poverty (percentage of households living below federal poverty threshold) -Education (percentage of residents aged >25 who are high school graduates or equivalent) -ESRD Network
Outcomes	-Patient saw a nephrologists prior to start of ESRD care, yes vs. no -Duration of nephrology care prior to start of ESRD: none, 0-6 months, 6-12 months, >12 months
Models	-Logistic and ordinal logistic regression
Other variables of interest	-Patient factors (age, individual race and ethnicity, and number of comorbidities) -Granularity of socioeconomic indicators (exploratory)
Limitations	-Non-Medicare-eligible individuals (including undocumented residents) not captured -Variable captured 2005+ only -No standard CMS-2728 data entry (filled out by provider within 45 days) -Unknown sensitivity and specificity of attribution of cause -Residence by zip code only -Limited individual SES information

Table 3.6. Overview of analytic plan for Aim 2b.

Stated aim	-To estimate associations of geographic and socioeconomic factors with w*hether patients were informed of transplant options prior to the start of ESRD*
Population	-All U.S. patients initiating ESRD treatment for the first time without a pre-emptive transplant in 2005-2011 who were <70 and medically and psychologically fit for transplant
Exposures (socioeconomic and geographic indicators)	-Individual race -Individual insurance prior to start of ESRD *In zip codes corresponding to residential address of participants at the start of ESRD treatment:* -Race (percentage of residents who are black) -Poverty (percentage of households living below federal poverty threshold) -Education (percentage of residents aged >25 who are high school graduates or equivalent) -ESRD Network
Outcome	-Patient was informed of transplant options, yes vs. no
Models	-Logistic regression
Other variables of interest	-Patient factors (age, individual race and ethnicity, and number of comorbidities) -Granularity of socioeconomic indicators
Limitations	-Medically/psychologically unfit status not further documented -Non-Medicare-eligible individuals (including undocumented residents) not captured -Variable captured 2005+ only -No standard CMS-2728 data entry (filled out by provider within 45 days) -Unknown sensitivity and specificity of attribution of cause -Residence by zip code only -Limited individual SES information

Table 3.7. Overview of analytic plan for Aim 2c.

Stated aim	-To estimate associations of geographic and socioeconomic factors with *whether patients were placed on the kidney transplant waitlist*
Population	-All U.S. patients initiating ESRD treatment for the first time without a pre-emptive transplant in 2005-2011 who were <70 and medically and psychologically fit for transplant
Exposures (socioeconomic and geographic indicators)	-Individual race -Individual insurance prior to start of ESRD *In zip codes corresponding to residential address of participants at the start of ESRD treatment:* -Race (percentage of residents who are black) -Poverty (percentage of households living below federal poverty threshold) -Education (percentage of residents aged >25 who are high school graduates or equivalent) -ESRD Network
Outcome	-Time from start of ESRD treatment to transplant waitlisting, with censoring for death and end of follow-up
Models	-Cox proportional hazards regression
Other variables of interest	-Patient factors (age, individual race and ethnicity, and number of comorbidities) -Granularity of socioeconomic indicators
Limitations	-Medically/psychologically unfit status not further documented -Non-Medicare-eligible individuals (including undocumented residents) not captured -Unknown sensitivity and specificity of attribution of cause -Residence by zip code only -Limited individual SES information

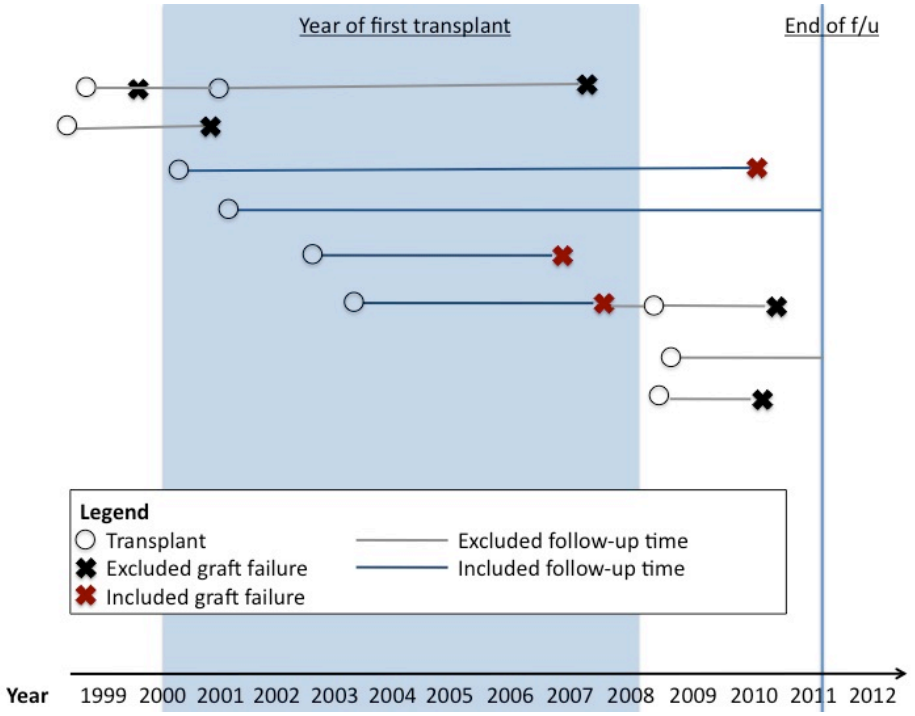
Table 3.8. Overview of analytic plan for Aim 2d.

Stated aim	-To estimate associations of geographic and socioeconomic factors with *whether patients were prepared for dialysis with a permanent vascular access*
Population	-All U.S. patients initiating ESRD treatment for the first time without a pre-emptive transplant in 2005-2011
Exposures (socioeconomic and geographic indicators)	-Individual race -Individual insurance prior to start of ESRD *In zip codes corresponding to residential address of participants at the start of ESRD treatment:* -Race (percentage of residents who are black) -Poverty (percentage of households living below federal poverty threshold) -Education (percentage of residents aged >25 who are high school graduates or equivalent) -ESRD Network
Outcome	-Patient started dialysis with a working or in-place arteriovenous fistula or graft, yes vs. no
Models	-Logistic regression
Other variables of interest	-Patient factors (age, individual race and ethnicity, and number of comorbidities) -Granularity of socioeconomic indicators
Limitations	-Inability to place fistula not documented -Non-Medicare-eligible individuals (including undocumented residents) not captured -Variable captured 2005+ only -No standard CMS-2728 data entry (filled out by provider within 45 days) -Unknown sensitivity and specificity of attribution of cause -Residence by zip code only -Limited individual SES information

3.2.3 Association of time from start of ESRD to kidney transplant with subsequent graft failure in U.S. LN-ESRD patients (Aim 3). For this aim, the UNOS component of the USRDS data will be the primary data source. Transplant and dialysis information on all U.S. citizens who are eligible for Medicare are available, including the date of first ESRD treatment, date of first kidney transplant, and dates of subsequent treatments (additional transplants or dialysis) and death. Potential effect modification by geographic and socioeconomic factors will be explored as well, with linked ACS data.

3.2.3.1 Population: Only ESRD patients who have a primary cause of ESRD indicated by ICD-9 code 710.0 (lupus nephritis; *N*=19,244) on the CMS Form 2728 (any version) will be included. Therefore, this aim will also be subject to the potential limitation that not all cases of LN-ESRD are captured. Because we are examining graft failure as an outcome, we must also limit the population to those who had at least one transplant (*N*=6,864). Further, since we are interested in the wait time to transplant from start of ESRD as the exposure, only the time to and outcome of the first transplant will be examined (Figure 3.8). Finally, we will examine first transplants that occurred between 1/1/00 and 9/30/08 (*N*=3,469; Figure 3.8). This time frame ensures that: (1) failures of older grafts---which may partially depend on failure of less advanced immunosuppressive regimens and/or differing graft allocation algorithms---are not included in our sample; and (2) at least three years of follow-up are potentially available on every patient in our sample. This second restriction allows analysis of graft failure within 3 years, which may be important in this population, in light of the 3-year limit on coverage of immunosuppressant medications among younger, non-disabled ESRD patients treated with a transplant.[99]

Figure 3.8. Events (graft failures, defined as second transplant, return to dialysis, or patient death) and follow-up time included in Aim 3.



3.2.3.2 Exposure: Our exposure of interest is transplant time (= time from date of first ESRD treatment to date of first kidney transplantation). Medical consensus[1,14] is that a waiting period between onset of ESRD and transplantation is necessary, based on underlying assumptions about early increased risk of graft failure due to still-elevated autoimmune activity at the start ESRD, which subsides over time (see Figure 2.5). Treating the transplant time exposure as a continuous outcome would force a linear association between transplant time and risk of graft failure, as has been assumed for the general ESRD population,[15] but would not allow for the non-linear associations proposed in Figure 2.5. Transplant time could also be categorized based upon these non-linear

associations, by the waiting times suggested by nephrologists (12 months)[14] and/or rheumatologists (3-6 months).[1] However, categorization would also force the assumptions that the relationship between time to transplant and graft failure---particularly, that these likely arbitrarily chosen cutoffs are meaningful and that the hazard is the same for all individuals in the category.

Rather than simply treating time to transplant as a continuous variable or categorizing time to transplant by pre-defined cutoffs, we will utilize splines, which allows relaxation of some of these assumptions.[133] In general, splines are smoothed piecewise polynomial transformations of the explanatory variable that connect over the range of the variable at specified points called knots. Linear splines are first-order polynomials that simply divide the variable into intervals defined by the knots. With linear splines, the slopes within these intervals can vary freely. However, linear splines do not have continuous first or second derivatives and thus produce a spiked association that can appear unnatural. Restricted cubic splines are third-order polynomials constrained to be linear at the tails of the range of the predictor (*i.e.*, before the first knot and after the last knot) but that allow cubic, smoothed polynomials over each middle interval.[133] The appropriate number and placement of knots can be based not only on *a priori* assumptions (such as 3, 6, and 12 months) but also by equally spaced intervals and/or visual examination of the crude association of transplant time and graft failure (*e.g.*, 3-year graft failure).

3.2.3.3 Outcome: The outcome of interest for Aim 3 is time to graft failure. The date of graft failure can be defined as (1) the date of transplantation of another kidney graft; (2) the date of the return of the patient to dialysis; or (3) the date of death of the patient, with

or without a functioning graft. Both (1) and (2) can be determined by the patients' treatment histories, which are compiled in a file provided by the USRDS. The date of patient death is also provided by the USRDS, via the CMS Form 2746 (Death Notification; Appendix B) required of ESRD providers. By this definition, censoring can only occur at the end of follow-up and there are no competing risks.

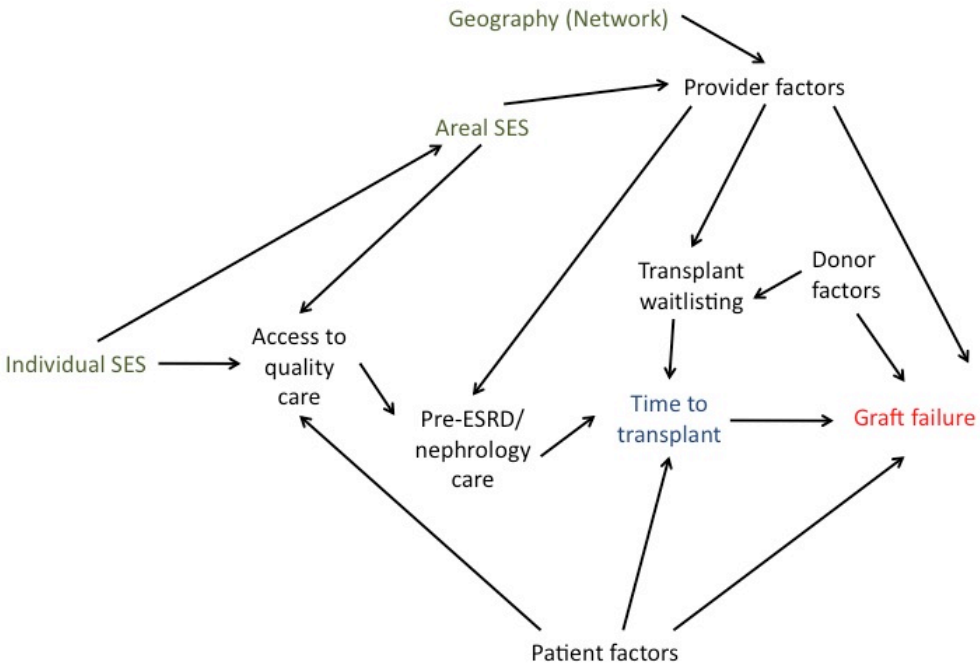
However, many transplanted patients may die with a functioning graft.[134] Thus, in exploratory analysis, we may examine an outcome that includes only deaths without a functioning graft (item 15c in CMS 2746; Appendix B). Such an outcome would include only true graft failure but would have the limitation of introducing competing risks from those who die with a functioning graft and so can no longer be observed for failure of the graft.

3.2.3.4 Confounders and effect modifiers: From the directed acyclic graph (Figure 3.9), patient and donor factors serve as potential confounders. Specifically, the measured patient factors of age, individual race and ethnicity, and number of comorbid conditions and donor factors of age, living vs. deceased status, and number of matching criteria satisfied will be considered potential confounders of our association of interest. Provider factors can also be confounders, but information on provider factors is limited. Pre-ESRD care, as a proxy or intermediate for pre-ESRD provider factors, could serve as a potential confounder (Figure 3.9); however, this information will only be available starting in 2005, so adjustment for this variable could only be performed in sensitivity analyses. Time to transplant waitlisting might also serve as an intermediate for ESRD provider

factors (Figure 3.9); in fact, it has been suggested that time to waitlisting provide more information than time after waitlisting for graft outcomes.[135] Thus, adjustment for this factor could also be performed in sensitivity analyses. As in Aim 2, collinearity among the variables in the model will be assessed using condition indices and variance decomposition proportions, and collinear variables will be removed as needed.

Figure 3.9. Directed acyclic graph for Aim 3.

Shown are associations between exposure (in blue; time to transplant) and outcome (in red; graft failure) of interest, along with potential confounders and intermediates. Factors in green (individual and areal SES and ESRD Network) are also potential effect modifiers.



The examination of this aim is subject to residual confounding by several unmeasured factors, including patient adherence to immunosuppression regimen. Restriction of

analyses to 3 years post-transplant may partially mitigate this problem, by eliminating the effect of nonadherence due to lack of coverage; however, there are many reasons (*e.g.*, substantial side effects, co-pay expenses, and/or memory problems) that might lower adherence in the first 3 years as well. Other unmeasured potential confounders related to the underlying disease include SLE activity at the start of ESRD and presence of the anti-phospholipid antibody syndrome (APAS), which can cause post-surgical complications and not only delay transplant but also affect graft outcomes.

The potential effect modifiers of interest include individual and areal SES and geography (Figure 3.9). As in Aim 2, individual race and type of insurance prior to the start of ESRD; neighborhood (zip code-level) race, poverty, and education; and ESRD Network will be examined as potential effect modifiers (Table 3.9). Granularity of these SES indicators as effect modifiers (see *3.1.2.3*) could also be examined in exploratory analyses, with modifications for the geographic units available in the USRDS.

3.2.3.5 Models: With time to graft failure as the outcome, we will run Cox proportional hazards models, as in Aim 2:

$$h(t,\mathbf{X}) = h_0(t)*\exp[\boldsymbol{\beta}\mathbf{X}]$$

where $h_0(t)$ is the baseline hazard function, t is the survival time, $\mathbf{X}$ is the vector of predictors (including exposure of interest, transplant time, and confounders), and $\boldsymbol{\beta}$ is the vector of associated coefficients.

With a linear spline transformation of the exposure variable, our model would be modified as follows:

$$h(t,\mathbf{X}) = h_0(t)*\exp[\beta_1 \text{transtime} + \Sigma_k \beta_k(\text{trans}_k) + \Sigma_i \beta_i X_i]$$

where transtime is the transplant time (in days), *k* ranges from 2 to the number of specified knots + 1, X_i represents the coefficients and values of potential confounders, *i* ranges from *k* + 1 to the total number of variables in the model, and trans_k is the linear spline of the exposure. If the chosen knots were at 90, 180, and 365 days (3, 6, and 12 months), the spline would be specified as follows:

trans_2 = (transtime – 90) if 90 $\leq$ transtime < 180; 0 otherwise
trans_3 = (transtime – 180) if 180 $\leq$ transtime <365; 0 otherwise
trans_4 = (transtime – 365) if transtime $\geq$ 365; 0 otherwise

Thus, the estimate in the interval from 0 to 90 days would be β_1 (the slope for transtime); the estimate from 90 to 180 days would be $\beta_1 + \beta_2$; the estimate from 180 to 365 days would be $\beta_1 + \beta_2 + \beta_3$; and the estimate after 365 days would be $\beta_1 + \beta_2 + \beta_3 + \beta_4$. As specified, the function would be continuous [i.e., no jumps in log(baseline hazard) at the knots].

For the corresponding restricted cubic spline, the spline would instead be a cubic function between all the knots but constrained to be linear before the first knot and after the last knot, as follows:

$$trans_2 = (transtime - 90)^3 \text{ if } 90 \leq transtime < 180; 0 \text{ otherwise}$$
$$trans_3 = (transtime - 180)^3 \text{ if } 180 \leq transtime < 365; 0 \text{ otherwise}$$
$$trans_4 = (transtime - 365) \text{ if } transtime \geq 365; 0 \text{ otherwise}$$

Thus, in this case, the model is replaced with the more complex:

$$h(t,\mathbf{X}) = h_0(t)*\exp[\beta_1 transtime + \beta_2(trans_2)^3 + 3*90*\beta_3(trans_2)^2 + 3*90^2**\beta_4(trans_2 + 30) + \beta_5(trans_3)^3 + 3*180*\beta_6(trans_3)^2 + 3*180^2**\beta_7(trans_3 + 60) + \beta_8(trans_4 - 365) + \Sigma_i\beta_i X_i]$$

where transtime is the transplant time (in days), *i* ranges from *3k* to the total number of variables in the model, and $trans_k$ is the cubic spline of the exposure. While the restricted cubic spline provides more natural smoothing, the results in terms of estimates are less interpretable. Rather, the predicted hazard could be estimated over the windows of exposure and examined graphically. A combination of linear splines (for interpretable estimates of hazard ratios over intervals of interest) and cubic splines (for graphical examination) could be used in the analysis of these data. Additionally, if the spline analyses indicate that there is no evidence of differing associations over windows of survival times---*i.e.*, the hypothesis that all the βs associated with spline terms are zero is not rejected---we will primarily report results without splines, for ease of interpretation.

As in Aim 2, it is unlikely but possible that there will be correlation within neighborhoods defined by zip code. If such a pattern is detected, hierarchical models cannot be used to account for this correlation in the setting of the Cox model. Shared frailty methods[136] will instead be used, where over *j* individuals and *i* groups (here, zip code-defined neighborhoods), the model will be:

$$h(t_{ij},\mathbf{X},\alpha_i) = h_0(t)*\alpha_i*\exp[\boldsymbol{\beta}\mathbf{X}]$$

where α_I is the frailty, which is distributed (generally, gamma-distributed) with a mean of 1 and some variance θ that is determined by the data. In the event that $\theta = 0$ (*i.e.*, there is no difference in baseline hazard between the groups), the model would reduce to the standard Cox model.

Finally, to check for effect modification, interaction terms between the exposure and SES and geographic indicators will be introduced and tested via likelihood ratio tests. If interactions of any variables with the exposure are statistically significant, results will be presented stratified by the variable(s). If no potential effect modification is detected, overall main results will be presented, along with the null results of statistical testing for interactions.

3.2.3.6 Summary: An overview of the analytic plan for Aim 3 is shown in Table 3.9.

Table 3.9. Overview of analytic plan for Aim 3.

Stated aim	-To estimate the association of time from start of ESRD to kidney transplant with subsequent graft failure in U.S. LN-ESRD patients; further, to examine whether geographic and socioeconomic factors modify any associations
Population	-All U.S. patients initiating ESRD treatment for the first time without a pre-emptive transplant in 2000-2008 with an attributed cause of LN
Exposure	-Time from start of ESRD to transplantation, examined via splines
Outcome	-Time to graft failure (death, second transplant, or return to dialysis)
Model	-Cox proportional hazards with splines of exposure to allow for non-linearity
Effect modifiers (socioeconomic and geographic indicators)	-Individual race -Individual insurance prior to start of ESRD *In zip codes corresponding to residential address of participants at the start of ESRD treatment:* -Race (percentage of residents who are black) -Poverty (percentage of households living below federal poverty threshold) -Education (percentage of residents aged >25 who are high school graduates or equivalent) -ESRD Network
Other variables of interest	-Patient factors (*e.g.*, age, comorbid conditions) -Donor factors (*e.g.*, living vs. deceased) -Granularity of socioeconomic indicators
Limitations	-Non-Medicare-eligible individuals (including undocumented residents) not captured -Number of transplants within 6 months may be small -Unknown or unmeasured confounders (*e.g.*, SLE activity) -Unknown sensitivity and specificity of attribution of cause -Residence by zip code only -Limited individual SES information

4. Aim 1: Incidence of End-Stage Renal Disease among Newly Diagnosed Systemic Lupus Erythematosus Patients

4.1 Manuscript Information

Target Journal: Arthritis & Rheumatology

Title: Incidence of End-Stage Renal Disease among Newly Diagnosed Systemic Lupus Erythematosus Patients: The Georgia Lupus Registry

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4.2 Abstract

Objective. To estimate incidence of end-stage renal disease (ESRD) among newly diagnosed systemic lupus erythematosus (SLE) patients and identify potential social predictors of higher ESRD incidence. **Methods.** Data from a national registry of treated ESRD (United States Renal Data System) were linked to 345 patients who were newly diagnosed with SLE and were living in Fulton and DeKalb Counties, Georgia, in 2002-2004. Cumulative incidence and incidence rates (ESRD treatment initiations per 1000 patient-years) were calculated overall and by sociodemographic characteristics. Poisson models were used to calculate age- and race-adjusted incidence rate ratios (IRRs) and confidence intervals (CIs). **Results.** Among newly diagnosed SLE patients, 5.2% initiated ESRD treatment within 5 years, and the overall incidence rate was 11.1 per 1000 patient-years (95% CI, 7.7-16.0). Patients who were <18 years (vs. ≥30 years) at diagnosis were more than twice as likely to progress to ESRD (IRR=2.14, 95% CI, 0.86-5.33). Sex was not associated with ESRD incidence, but a striking difference in ESRD incidence was seen among black vs. white patients (IRR=3.85, 95% CI, 0.91-16.35). The early diagnosis of LN at SLE diagnosis, which occurred in 80% of those who progressed to ESRD, was the strongest risk factor for incident ESRD (IRR=6.72, 95% CI, 2.69-16.82;

incidence rate=27.6/1000 patient-years). **Conclusion.** Incidence of ESRD is high among newly diagnosed SLE patients in Georgia. While all SLE patients should be considered high-risk for ESRD, improvements in screening and treatment should be targeted to young and black patients to decrease ESRD incidence.

4.3 Introduction

Only 1% of incident end-stage renal disease (ESRD) cases in the United States are attributed to lupus nephritis (LN). However, this relatively small percentage represented >5000 incident LN-ESRD patients in 2007-2011,[39] and population incidence of LN-ESRD has been increasing over the past 30 years, even with adjustment for changes in the age, sex, and race distributions of the U.S. population.[2-4] Further, substantial disparities have been demonstrated, with greater population incidence of LN-ESRD being associated with younger age,[4,5] female sex,[4] black race,[3-5] lower individual and area-based socioeconomic status (SES),[44,45] reduced access to care,[46] and residence in the South.[4,5]

In contrast to the wealth of information on U.S. population incidence of LN-ESRD, there is little reliable information on the incidence of ESRD among those with systemic lupus erythematosus (SLE). That is, it is unknown how many newly diagnosed SLE patients, and over what time period, will develop ESRD. Estimates of LN incidence among SLE patients range widely, from 35% to 60%[1,31,48-50]; similarly, estimates of ESRD among those with existing LN range from 10% to 35%.[51,52] The variability and the biases inherent in these studies and their estimates—survival bias due to calculation of

cumulative incidence rather than incidence rates; differing follow-up times, population demographics, and case definitions, which often depend on administrative data to identify SLE and LN; and error associated with small sample sizes—make the risk of progression to ESRD among SLE patients difficult to estimate with confidence. The lack of reliable estimates of this incidence is important because ESRD remains the strongest risk factor for early mortality in the SLE population,[41,137] with those with ESRD attributed to LN being at approximately twice the risk of mortality relative to patients with ESRD attributed to other causes.[42,43]

While a recent study in Taiwan[55] estimated that 2.5% of newly diagnosed SLE patients developed SLE over 6-8 years of follow-up, the estimate is not only cumulative, which ignores high mortality rates in the SLE population, but also likely not generalizable to the United States, due to differences between the Taiwanese and U.S. populations in terms of environment, race, and healthcare system factors. For U.S. patients and providers, reliable and generalizable estimates of the incidence rate of ESRD among SLE patients are critical to guide treatment, screening, and management of this population. The Georgia Lupus Registry (GLR),[21,25] which recently published estimates of population incidence of SLE in metropolitan Atlanta,[22] provides a unique opportunity to estimate ESRD incidence in a group of newly diagnosed SLE patients in the southeastern United States. The GLR provides a population-based registry of validated incident SLE cases, and its target population is large (1.5 million), metropolitan, and diverse (~50% black). Black race has been shown across studies to be associated with greater susceptibility to SLE and its complications, particularly the risk of development of LN and subsequent

ESRD.[22,23,28,30,50,53,54] Thus, we aimed to provide reliable estimates of the incidence of ESRD in a diverse U.S. population of SLE patients from the GLR. Further, we aimed to identify individual and neighborhood sociodemographic factors that might have contributed to variation in ESRD incidence among SLE patients.

4.4. Patients and Methods

4.4.1. Study population and data sources

4.4.1.1. Georgia Lupus Registry: The primary aim of the Georgia Lupus Registry (GLR) was to estimate the prevalence and incidence of SLE in 2002-2004 in Atlanta, Georgia (Fulton and DeKalb Counties).[22] Emory investigators served as designated agents of the Georgia Department of Public Health, who, as a "public health authority," used its public health surveillance exemption to the HIPAA Privacy Rule (45 CFR parts 160 and 164) to review medical records and capture protected health information without patient consent [HIPAA 45 CFR 164.512(b)]. The project was reviewed and approved by the Emory University and Georgia Department of Public Health Institutional Review Boards. Potential SLE cases were identified from multiple sources, including hospitals; providers in rheumatology, dermatology, and nephrology; commercial and hospital-based laboratories; regional pathology laboratories; lupus research databases; and population databases, including the United States Renal Data System (USRDS), Veterans Affairs data, Medicaid claims data, and state mortality and hospital discharge data. The presence of diagnostic codes [International Classification of Diseases, 9th revision (ICD-9)] for SLE (710.0) and related conditions that might evolve into SLE—including discoid lupus (695.4), other specified connective tissue disease (710.8), and other unspecified

connective tissue disease (710.9)—in any of these sources flagged patients as potential SLE cases.[25] Personal identifiers, including residence, were collected for all potential cases to avoid duplicate entries. Medical records for all potential cases with residence in Fulton or DeKalb County in 2002-2004 were fully abstracted by trained abstractors. Patient date of SLE diagnosis, age, sex, race, ethnicity, abstracted medical information, residential address, and dates of death were available from GLR.

4.4.1.2. United States Renal Data System: The USRDS provides an ongoing, integrated database for outcomes research on the entire treated U.S. ESRD population [39]. The USRDS data originate primarily from the Centers for Medicare & Medicaid Services (CMS), which covers the costs of ESRD treatment for all Medicare-eligible individuals in the United States, and the United Networks for Organ Sharing. Date of initiation of ESRD treatment (through 9/30/12) and primary attributed cause of ESRD were obtained from the USRDS.

4.4.1.3. U.S. Census: Publicly available data on characteristics of U.S. residential neighborhoods, as defined by census tracts and block groups, were obtained from the 2000 U.S. Census (www.census.gov) via the Minnesota Population Center (www.nghis.org).[138] Aggregate data on racial composition, education, and poverty at the census tract and block group levels were obtained from the Census.

4.4.1.4. Data linkage: Identifiers [Social Security number (SSN), date of birth, sex, first name, and surname] on these individuals were sent to the USRDS for a probabilistic match to identify those SLE cases who progressed to ESRD from diagnosis of SLE

(2002-2004) to the last date of follow-up currently available from the USRDS (9/30/12). Census data were spatially linked to the GLR via geocodes of patients' residential addresses (first address recorded in Fulton or DeKalb County in 2002-2004). The data linkage was approved by the Emory Institutional Review Board.

4.4.1.5 Study population: For this study, SLE cases were defined by a combined case definition described previously[22] to estimate population prevalence and incidence of SLE, as follows: (*i*) presence of ≥ 4 American College of Rheumatology (ACR) criteria [18] in the medical record; (*ii*) presence of 3 ACR criteria plus a treating, board-certified rheumatologist's diagnosis of SLE; or (*iii*) <4 ACR criteria plus SLE kidney disease, as defined by a biopsy consistent with class II-VI LN[32,139] or ESRD requiring dialysis or renal transplantation with documentation of SLE in the medical record. The study population included incident SLE cases (*n*=345), defined as those with a SLE diagnosis date from January 1, 2002 through December 31, 2004.

4.4.2. Study variables and definitions

4.4.2.1. Incident ESRD: Incident ESRD was defined by a first ESRD treatment (dialysis or kidney transplantation) start date, on or after the date of diagnosis of SLE (Figure 1).

4.4.2.2. Individual-level characteristics: Individual sociodemographic factors of interest were obtained from the GLR and included age, sex, and race (limited to black and white, due to low numbers of other races). Early LN, defined by documentation within 3 years of SLE diagnosis of (*i*) urine abnormalities (≥3g by 24-hour urine, ≥300 mg/dl by random

urine, spot protein:creatinine ratio of ≥0.5, or positive urine cellular casts), (*ii*) any renal biopsy consistent with LN classes II-VI,[32] or (*iii*) documentation of LN by a treating rheumatologist or nephrologist, was also available in the GLR.

4.4.2.3: Neighborhood-level characteristics: Due to the relative lack of information at the individual level on socioeconomic status (SES) and the potential for neighborhood effects on incidence independent of individual SES, we also examined aggregate residential census tract-level data on the percentage of residents reporting black race, the percentage of high school dropouts (residents aged ≥25 without a high school degree or equivalent), and the percentage poor (households living below 100% of the federal poverty threshold) from the 2000 U.S. Census. Beyond composition of neighborhoods (*i.e.*, proportions of residents with various social characteristics of interest within an area), we were also interested in the spatial distribution of residents with these characteristics—particularly, the comparison of spatial scales to investigate granularity, which relaxes the assumptions that individuals within a boundary have no proximity to or contact with those outside the boundary.[124] Ratios of granularity (composition in a larger area surrounding a residence divided by composition in a smaller area surrounding the same residence) provide information on the relative spatial scale of social disadvantage, with ratios > 1 indicating the region surrounding the immediate neighborhood is more sociodemographically deprived, ratios < 1 indicating the region surrounding the immediate neighborhood is less deprived, and ratios of ~1 indicating relative homogeneity across the two spatial scales. These ratios were calculated for black race, high school dropouts, and poverty.

4.4.3. Statistical analysis. Patient characteristics were summarized for newly diagnosed SLE patients, overall and by ESRD status as of 4/30/11. Incidence rates were calculated as the number of ESRD events divided by total patient-years contributed. The number of events was the total number of patients who initiated ESRD treatment over follow-up. Total patient-years were calculated as the sum of all patients' contributed follow-up time in years. Follow-up time was defined as the time from date of SLE diagnosis to the time of death, ESRD, or last date of follow-up. For primary analyses, the last date of follow-up was 4/30/11, which is the last available date of death follow-up in the GLR (Figure 1). Overall incidence was calculated among incident patients with SLE defined by the combined case definition (≥4 ACR criteria, 3 ACR criteria plus a treating rheumatologist diagnosis, or evidence of SLE-related kidney disease). For comparison, incidence was also calculated among newly diagnosed SLE patients by more stringent SLE case definition criteria (≥4 ACR criteria only) and among a point prevalent cohort of patients in the GLR, including 1488 patients who were alive with an existing diagnosis of SLE (primary combined case definition) and free of ESRD as of 12/31/04 (cumulative incidence only). Confidence intervals for rates were obtained by quadratic approximation based on the Poisson log-likelihood. In sensitivity analyses, incidence rates and cumulative incidence were calculated (*i*) using 7/31/11 as the last date of follow-up, which includes all patients who progressed to ESRD but which is subject to potential survival bias due to lack of death follow-up in the 3 months following 4/30/11; and (*ii*) using an intermediate definition of newly diagnosed SLE, including ≥4 ACR criteria or 3 ACR criteria plus a treating rheumatologist diagnosis, but not SLE renal involvement. Incidence rates were stratified by individual and neighborhood sociodemographics.

Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for the associations between individual and neighborhood sociodemographics were estimated with Poisson models. Stratified crude and adjusted incidence rates were calculated, and IRRs were adjusted for age group (<18 years, 18-30 years, and >30 years) and race (black and white only).

Tract-level racial composition, education, and poverty were mapped, and kernel density estimation of events and person-time using a 150 × 150 m grid and 8000-m radius was used to map patterns of incidence while masking identifiable residential location. Spatial autocorrelation was estimated with Moran's *I*. Similar to the estimation of macro-micro segregation index described by Lee *et al*.,[124] granularity ratios were determined by kernel density estimation (150 × 150 m grid) using census block-level data at 4000 m (distance within which most daily functions are performed) and 500 m (pedestrian distance).[124,129] Ratios of average densities in these smoothed grids were then calculated for each SLE patient's point of residence and categorized to represent relative spatial homogeneity (0.9-1.1) and spatial heterogeneity in either direction (<0.9 or >1.1). Stata v. 13 (StataCorp, College Station, TX) was used for all analyses and the threshold for statistical significance was set at α=0.05. Mapping and spatial analyses were performed using ArcGIS v. 10.1 (ESRI, Redlands, CA) and GeoDa v. 1.6.[140]

4.5 Results

4.5.1. Characteristics of newly diagnosed SLE patients. Among the 345 Atlanta-area SLE patients newly diagnosed in 2002-2004, 31 (9.0%) were identified in the USRDS as

having received treatment for ESRD in the period 1/1/80-9/30/12. For analyses, one patient was excluded for having initiated ESRD treatment prior to SLE diagnosis. Another patient who initiated ESRD treatment after 4/30/11 (last date of death follow-up) was censored in primary analyses. These exclusions left 29 ESRD events over 2603.8 years of follow-up among 344 patients diagnosed with SLE, but free of ESRD, in 2002-2004. Of these 344 patients, 299 (86.9%) were linked successfully via geocoded residential addresses to 2000 Census sociodemographic data.

Atlanta-area SLE patients were young at diagnosis of SLE (mean age, 36.4 years), predominantly female (86.9%), and majority black (73.6%). They lived in neighborhoods where 84.9% black residents were black, 13.2% of residents had not completed high school, and 11.1% of households lived below 100% the federal poverty threshold, although these percentages varied widely across Atlanta's Fulton and DeKalb Counties (Figure 2, A-C). About one-third of these patients had early LN (Table 1), within 3 years of diagnosis, although this differed by race (19.9% and 38.5% of whites and blacks; P=0.001). Among those with LN and biopsy information (n=112), 66 (58.9%) had at least one kidney biopsy (53.3% and 59.8% of whites and blacks, respectively; P=0.8); only 7.1% had multiple kidney biopsies (13.3% and 6.2% of whites and blacks, respectively, P=0.3).

Those who progressed to ESRD were younger at SLE diagnosis, more likely to be black (vs. white), and lived in neighborhoods with greater percentages of high school dropouts (Table 1). Among those progressing to ESRD over study follow-up, 79.3% had early LN

(documented within 3 years of SLE diagnosis), compared to only 29.8% of those who did not progress to ESRD ($P<0.001$; Table 1). There were no statistically significant differences in individual or neighborhood characteristics between those with and without documentation of early LN in the medical record among those who progressed to ESRD ($n=29$). Of the 26 black SLE patients progressing to ESRD, 20 (76.9%) had clinical evidence of early LN, whereas 16 (61.5%) had had at least one renal biopsy. Both white SLE patients who progressed to ESRD had early LN and at least one kidney biopsy in the medical record.

4.5.2. Incidence of ESRD among newly diagnosed SLE patients. The 5-year cumulative incidence of ESRD among newly diagnosed SLE patients in our study was 5.2% (Table 2). Over these 5 years, 15 (4.4%) died without an ESRD diagnosis. The median time to ESRD among those who progressed to ESRD by 4/30/11 was ~4 years (Table 2) among incident SLE patients, and there was no evidence of leveling off of rates in later years of follow-up in either blacks (Figure 3) or whites (not shown due to small numbers of cases). The overall crude incidence rate was 11.1 per 1000 patient-years for those with newly diagnosed SLE by the combined case definition; incidence was slightly higher (12.5 per 1000 patient-years) for those with SLE by ≥4 ACR criteria alone (Table 2). Among point prevalent patients who were alive and diagnosed with SLE, but not ESRD, on 12/31/04, the 5-year cumulative incidence of ESRD was 5.2% (Table 2) and 16/1488 (1.1%) had incident ESRD within 1 year. ESRD incidence estimates in sensitivity analyses were similar to those seen in the primary analysis: for extended ESRD follow-up time (through 7/31/11) among those with SLE by the combined case

definition, the incidence rate was 11.2 per 1000 patient years (cumulative incidence=5.2%); and for those defined as having SLE by an intermediate definition (≥4 ACR criteria and or 3 criteria plus a treating rheumatologist diagnosis), the incidence rate was 11.1 per 1000 patient-years (cumulative incidence=5.4%).

4.5.3. Sociodemographic correlates of ESRD incidence among newly diagnosed SLE patients

4.5.3.1. Individual characteristics: Pediatric (age < 18 years; incidence rate=20.0 per 1000 patient-years) patients at SLE diagnosis were >2-fold more likely than their older adult (≥30 years; incidence rate=9.3 per 1000 patient-years) counterparts to progress to ESRD (not statistically significant; Table 3). Male sex was associated with lower ESRD incidence but with wide confidence intervals (Table 3). Blacks (incidence rate=13.6 per 1000 patient-years) were nearly 4 times more likely than whites (incidence rate=3.5 per 1000 patient-years) to progress to ESRD (Table 3). In comparison, those with early LN (within 3 years of diagnosis) had nearly 7-fold greater rates of developing ESRD compared to those without this evidence, with incidence rates of 27.6 and 3.4 per 1000 patient-years, respectively (Table 3). Age- and race-adjusted incidence rates, omitted due to small sample sizes, did not differ substantially from the crude incidence rates presented in Table 3: <18 years vs. ≥30 years, 20.0 vs. 9.3 per 1000 patient-years; blacks vs. whites, 13.6 vs. 3.5 per 1000 patient-years; and early LN vs. not, 25.2 vs. 3.8 per 1000 patient-years.

4.5.3.2. Neighborhood characteristics: Table 3 shows that lower neighborhood socioeconomic status, in terms of higher percentages of black residents, high school dropouts, and poor households in residential census tracts, was modestly but non-statistically significantly associated with higher risk of incident ESRD among SLE patients. Granularity ratios, which take spatial heterogeneity in neighborhood influences into account, were also generally not statistically significantly associated with ESRD incidence (Table 3). However, granularity ratios below 0.9 and above 1.1 for area poverty were both associated with reduced risk of incident ESRD, and those living in areas with poverty granularity ratios >1.1 (greater poverty in surrounding area than immediate area) were at >60% reduced risk of ESRD, relative to those in more homogeneous areas (Table 3). Again, age- and race-adjusted incidence rates did not differ substantially from the crude incidence rates presented in Table 3.

4.5.3.3. Spatial distribution of incidence: A kernel density-estimated incidence surface map (Figure 2D) shows that incidence appeared to be potentially concentrated not only in the most populated areas but also in the areas with the highest percentages of black residents, high school dropouts, and poor households (see Figure 2, A-C) in Fulton and DeKalb Counties. However, there was no evidence of spatial patterning in incidence, with Moran's *I* for spatial autocorrelation being close to zero (-0.036; *P*=0.19). Further, Moran's *I* was similarly close to zero (-0.024; *P*=0.29) among blacks only, indicating no autocorrelation taking residential racial segregation into account (i.e., the values of spatial autocorrelation for ESRD incidence are not related to the underlying spatial pattern of race—a strong predictor of ESRD incidence—across Fulton and DeKalb Counties).

4.6 Discussion

In a population-based cohort of 344 patients who were newly diagnosed with SLE in 2002-2004 in metropolitan Atlanta (Fulton and DeKalb Counties), we found that the incidence rate of subsequent ESRD was 11.1 per 1000 patient-years. Estimated incidence was higher (12.5 per 1000 patient-years) when SLE was defined only by the patient having four or more ACR criteria [18] for SLE diagnosis, excluding those defined by only three criteria plus a rheumatologist SLE diagnosis or with SLE renal involvement. We estimated 5-year cumulative incidence to be 5.2-6.0%, which is at least twice the estimate from Chung *et al.*,[55] who estimated that 2.5% of newly diagnosed Taiwanese SLE patients developed SLE over 6-8 years of follow-up. Similarly, our estimate is nearly twice that from an older population-based study in Okinawa, Japan,[141] which found that 3.1% of SLE patients diagnosed in 1971-1991 progressed to renal failure within 5 years. Our study is, to our knowledge, the first to report ESRD incidence among a population-based cohort of U.S. patients with newly diagnosed SLE—not identified and validated by administrative data alone—where patient, provider, and health system characteristics likely differ substantially from those in previously reported studies. Additionally, using the nearly complete follow-up afforded by universal coverage of ESRD treatment by CMS, we were able to take varying follow-up times into account and compute incidence rates, which is important in the SLE population, in whom mortality is relatively high. In fact, we found that 4.4% of the incident SLE cohort died within 5 years, without initiating ESRD treatment.

We know that most ESRD in the United States is attributed to diabetes mellitus (45%) and hypertension (28%) and that only 1% of incident ESRD cases are attributed to SLE.[39] However, we have shown that, among U.S. SLE patients, ESRD is a common outcome. In fact, we found that 16 of 1488 point prevalent SLE patients in 2004 had incident ESRD in 2005, equivalent to 10,753 per million SLE population, which is ~30-fold the annual incidence reported for the U.S. general population in 2005 (355 per million).[39] Comparing only to the similarly aged general U.S. population, this incidence is ~80- to ~700-fold, with the annual ESRD incidence being only 15 and 129 per million in the 2005 U.S. population aged 0-19 and 20-44 years, respectively.[39]

Our results also point to several correlates of higher ESRD incidence among U.S. SLE patients. Not surprisingly, having early LN (within 3 years of diagnosis) was associated higher (nearly 7-fold) ESRD incidence, relative to not having this evidence in the medical record, even after adjustment for age and race. Among black SLE patients who did have early LN and progressed to ESRD, 20% did not have evidence of a renal biopsy, suggesting that LN may not always be properly diagnosed, staged, and treated according to ACR guidelines for LN treatment,[31] which recommend that all patients with signs of nephritis be biopsied and that all patients with Class III or IV LN be treated aggressively. This potential gap in the care of U.S. LN patients aligns with evidence from the Medicaid population, which suggested that, even among patients with a documented diagnosis of incident LN (2000-2006), at 1 year after diagnosis, only 34%, 56%, and 46% of these patients were being treated with immunosuppressants, ACE inhibitors, and antimalarials, respectively, to slow the progression of LN.[142]

Despite early LN being the strongest risk factor for progression to ESRD that we examined, 1 in 5 SLE patients who progressed to ESRD in our cohort did not have any early signs of LN documented in the medical record. Thus, other individual characteristics that associate with ESRD progression may be useful to providers and researchers in assessing ESRD risk among SLE patients who have not been screened for renal complications. We found that patients who were black or pediatric (age < 18 years) were at substantially greater risk of incident ESRD (nearly 4- and 2-fold, respectively), compared to patients who were white or ≥30 years old at SLE diagnosis. While these results were not statistically significant after adjustment, due to the small numbers of events in these subgroups, these factors likely represent reliable predictors of progression to ESRD, as they have previously been associated with development and progression of LN and LN-ESRD in the population.[2,4,5,51,143,144]

Black race is associated with greater U.S. population incidence of ESRD due to SLE,[4] relative to whites (12.8 vs. 2.0 per million). While this at least partially reflects the underlying racial distribution of the U.S. SLE population, we found that, even among SLE patients, blacks were nearly 4 times as likely as whites to progress to ESRD, after accounting for age, a pattern similar to that seen in selected cohort studies of patients with SLE and LN.[51,144] Further, we showed steadily increasing ESRD incidence immediately after diagnosis of SLE among black patients, with no evidence of leveling off of risk over follow-up, suggesting rapid progression. Faster progression among blacks relative to other patients would contribute to disparities by providing a shorter window to identify LN and intervene with aggressive treatments to prevent or delay ESRD.

Environmental factors, including those that influence access to care, early diagnosis, and treatment (*e.g.*, perceived individual and institutional racism, differential availability of subspecialty care) could contribute to this racial disparity. However, black race has not been shown to be associated with decreased likelihood of accessing rheumatology care [145], and delays in care were actually less likely among black patients in the Medicaid population with incident lupus nephritis.[142] Other environmental contributors to this disparity may be the inadequate treatment of comorbid hypertension and diabetes, which are common in SLE[146,147] and associated ESRD[4] and represent the strongest risk factors for ESRD in the general population.[39] Genetic factors may play a role as well: for example, the *APOL1* gene, which is more frequent in the U.S. blacks vs. whites, has recently been shown to be associated with risk of ESRD among SLE patients in a case-control study.[148]

While children have the lowest incidence rates of LN-ESRD in the general population,[4] we found that, among SLE patients, they had ESRD incidence rates that were nearly twice those of adults aged ≥30 years. Among children, genetic and family history factors may play a greater role in ESRD progression risk,[149] as compared to adults. However, even among children there are suggestions that sociodemographic factors play a role: previous studies have shown that nearly 40% of children with SLE have LN,[143] that female and non-white children with SLE in the Medicaid population are more likely to have LN,[143] that half of children with ESRD due to SLE are on Medicaid insurance,[5] and that black children with ESRD due to SLE have increased mortality relative to their white counterparts in the United States.[5] Decreasing the incidence of ESRD in this pediatric

population is of paramount importance, given that progression to ESRD among children is associated with additional, age-specific consequences, such as decreased growth and school performance.[150,151]

Unlike previous studies, we found that male SLE patients were not at higher risk of ESRD. For example, in the Okinawa study of 515 females and 51 males, Iseki *et al.*[141] found that the risk of incident ESRD was nearly 4-fold for males vs. females with SLE. In a U.S. multiethnic, multicenter PROFILE cohort, male sex was associated with 1.7-fold increased risk of ESRD, but the results were not statistically significant.[144] Our results may reflect differences across populations or may simply reflect chance findings due to low numbers of male SLE patients. Confirmation in other U.S. SLE cohorts is needed before male sex can ruled out as a potential predictor of incident ESRD.

Generally, we found that neighborhood-level sociodemographics were not associated with ESRD incidence. This observation could reflect the truth that neighborhood has no effect on ESRD incidence among SLE patients, or it could reflect our lack of power to detect modest neighborhood effects. Alternatively, it is possible that neighborhood effects on progression of SLE and LN occur in a critical period prior to the diagnosis of SLE or that cumulative lifetime effects of neighborhood are more important than characteristics at SLE diagnosis,[152] and such effects could not be captured here. While not statistically significant, higher and lower granularity ratios for poverty were associated with nearly 60% and 45% reduced risk of ESRD, suggesting that living in spatially heterogeneous areas of disadvantage may be associated with reduced risk of ESRD, relative to living in

areas with widespread homogenous concentrated poverty, which may reflect better access in such heterogeneous regions, although it could also reflect chance findings. Overall, we found no statistical evidence of spatial patterning of ESRD incidence across Fulton and DeKalb Counties, but our lack of statistical power precludes concluding that no such patterns exist.

This study has several limitations. First, while the SLE case-finding approach was comprehensive and population-based, the sensitivity of this approach is unknown. Second, the estimates of incidence and associations of incidence with sociodemographic factors may not be generalizable to other U.S. SLE populations, particularly outside of the South, or to non-U.S. SLE populations. Third, we had limited power to detect modest associations, due to small numbers of events and relatively short follow-up. Fourth, we lacked individual socioeconomic data at SLE diagnosis. Finally, with regard to ESRD ascertainment, we were not able to capture any non-Medicare-eligible patients (e.g., undocumented residents) or any patients who may have moved out of the United States. However, this study also has many strengths. The GLR is one of five CDC National Lupus Registries, the first comprehensive population-based epidemiological study of lupus conducted in the United States.[22,23,25] SLE case ascertainment was not dependent on administrative data and was maximized by the use of multiple sources, and diagnoses were validated by comprehensive clinical data collected from individual records. Fulton and DeKalb Counties represent a large (~1.5 million), demographically and socioeconomically diverse (~50% black) U.S. metropolitan population, and all ESRD patients treated in the United States were captured. Thus, this study provides the first

real-world, "as-treated" estimates of incidence of ESRD from time of SLE diagnosis in the United States.

The estimates and associations presented here bridge an important gap in our understanding of the epidemiology of SLE and ESRD in the United States. Knowing the rate of ESRD among SLE patients, particularly in the Southeast, is essential because the incidence of ESRD due to SLE and LN is increasing on a population level and the South has the highest LN-ESRD incidence among U.S. regions.[4,28] Further, progression to ESRD has potentially devastating consequences for these patients. A previous large, multi-cohort study found that those with SLE are at nearly 8-fold risk of mortality due to renal causes, relative to their general population counterparts,[40] and ESRD remains the strongest risk factor for early mortality in this population.[41,137] However, in this young, predominantly female population, ESRD may lead not only to death but also to increased morbidity, decreased functioning (affecting the ability to complete education, work, and/or raise children), decreased overall quality of life, depression, infertility, and sexual dysfunction.[153] The high incidence of ESRD in this population also represents a potentially high societal burden for lifetime costs of care, given these patients' young age, with ESRD currently costing the healthcare system $30,000-$90,000 per person per year.[39]

In conclusion, this study provides reliable incidence estimates to guide U.S. patients and providers in shared decision-making regarding screening and treatment. It also provides an estimate of the burden of ESRD among U.S. SLE patients, which is important for

future research and healthcare policy. Additionally, we have described SLE populations (particularly, children and black patients) who may benefit from earlier identification as higher-risk for LN, more aggressive treatment to prevent or delay ESRD, and targeted preventive and quality improvement research efforts. These results also warrant future research aimed at increasing health care access among those with SLE, improving early LN diagnosis and quality of SLE care related to LN and its progression, and developing more effective treatments for LN.

4.7 Acknowledgements and Financial Support

This research was supported by the Lupus Foundation of America. The Georgia Lupus Registry was supported in part by the CDC, and by cooperative agreement CDC-RFA-DP08-806 and earlier by cooperative agreement PA03022 from the CDC. The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the U.S. government.

4.8 Tables and Figures

Table 4.1. Characteristics of newly diagnosed (2002-2004) systemic lupus erythematosus patients in Fulton and DeKalb Counties, Georgia, overall and by end-stage renal disease status through 4/30/11

Characteristic	*N*	Overall (*n*=344)	ESRD status as of 4/30/11[a,b]		*P*[c]
			Yes (*n*=29)	No (*n*=315)	
Individual characteristics					
Age at diagnosis of SLE, mean (SD)	*344*	36.4 (16.4)	31.4 (17.7)	36.9 (16.2)	*0.08*
Sex, %	*244*				*>0.9*
Male		45 (13.1%)	3 (10.3%)	42 (13.3%)	
Female		299 (86.9%)	26 (89.7%)	273 (86.7%)	
Race,[d] %	*330*				*0.04*
White		79 (23.9%)	2 (7.1%)	77 (25.5%)	
Black		251 (76.1%)	26 (92.9%)	225 (74.5%)	
Early lupus nephritis, %	*344*				*<0.001*
No		225 (65.4%)	6 (20.7%)	219 (69.5%)	
Yes		119 (34.6%)	23 (79.3%)	96 (30.5%)	
Neighborhood characteristics					
Black race, median (IQR)					
% black in census tract	*299*	84.9 (24.7-94.6)	88.5 (75.7-96.7)	83.6 (20.3-94.5)	*0.10*
Granularity ratio[e] for % black	*299*	0.97 (0.87-1.01)	0.96 (0.84-1.01)	0.97 (0.88-1.01)	*0.67*
Education, median (IQR)					
% HS dropouts in census tract	*299*	13.2 (6.6-22.8)	14.9 (9.5-31.2)	11.7 (6.6-21.9)	*0.06*
Granularity ratio[e] for % HS dropouts	*299*	1.01 (0.87-1.31)	0.91 (0.75-1.13)	1.02 (0.88-1.33)	*0.04*
Poverty, median (IQR)					
% poor in census tract	*299*	11.1 (5.8-22.6)	13.8 (6.7-25.8	10.7 (5.5-20.5)	*0.29*
Granularity ratio[e] for % poor	*299*	1.03 (0.80-1.38)	0.99 (0.79-1.20)	1.05 (0.80-1.39)	*0.49*

ESRD, end-stage renal disease; SLE, systemic lupus erythematosus; IQR, inter-quartile range; HS, high school. Poor defined as living below 100% federal poverty threshold. Early lupus nephritis defined by urine or biopsy evidence or treatment rheumatologist or nephrologist documentation of LN in the medical record, within 3 years of SLE diagnosis.

[a]By combined case definition: ≥4 ACR criteria, 3 ACR criteria plus treating rheumatologist's diagnosis, or renal involvement as indicated by biopsy consistent with class II-VI lupus nephritis or ESRD requiring dialysis or renal transplantation.

[b]Last date of death follow-up in the Georgia Lupus Registry. A total of 30 patients initiated ESRD treatment between date of SLE diagnosis and 9/30/12, the last date of ESRD follow-up.

[c]By Fisher's exact test or Wilcoxon rank test.

[d]Restricted to white and black patients only, due to small numbers of patients of other races.

[e]Ratio of kernel density-smoothed percentages (from block groups) in 4000-m to 500-m radii around patient residence. If the ratio is >1, there are greater values in surrounding areas (4000-m) vs. walkable neighborhood (500-m). For example, if poverty granularity ratio is >1 then person lives in an area with less concentrated poverty than the surrounding area; <1 then smaller area has more concentrated poverty than surrounding area.

Table 4.2. Incidence of end-stage renal disease among systemic lupus erythematosus patients in Fulton and DeKalb Counties, Georgia, from 2002-2004 through 4/30/11

Cohort	No. of patients at risk	No. of ESRD events[a]	Total patient-years at risk	Median (IQR) years to ESRD[b]	Incidence rate, per 1000 patient-years (95% CI)	5-year cumulative incidence, %
Incident SLE by combined case definition[c]	344	29	2603.8	4.1 (2.0-5.9)	11.1 (7.7-16.0)	5.2
Incident SLE by ≥4 ACR criteria only	266	25	2007.8	4.1 (1.3-5.8)	12.5 (8.4-18.4)	6.0
Point prevalent SLE[d] by combined case definition[c]	1488	106	---	3.0 (1.6-5.2)	---	5.2

ACR, American College of Rheumatology; ESRD, end-stage renal disease; IQR, interquartile range; SLE, systemic lupus erythematosus.

[a]Through last date of death follow-up in the Georgia Lupus Registry. A total of 30 patients initiated ESRD treatment between date of SLE diagnosis and 9/30/12, the last date of ESRD follow-up.

[b]Among those who progress to ESRD by 4/30/11.

[c]Combined case definition, ≥4 ACR criteria, 3 ACR criteria plus treating rheumatologist's diagnosis, or renal involvement as indicated by biopsy consistent with class II-VI lupus nephritis or ESRD requiring dialysis or renal transplantation.

[d]Point prevalent cohort of patients in the GLR alive with an existing diagnosis of SLE (primary combined case definition) and free of ESRD on 12/31/04. Because patients who died with SLE prior to 12/31/04 were at risk for ESRD, patient-years and incidence rates were not calculated for this cohort.

Table 4.3. End-stage renal disease incidence among newly diagnosed (2002-2004) systemic lupus erythematosus patients, by individual and area sociodemographic characteristics, in Fulton and DeKalb Counties, Georgia, through 4/30/11

Characteristic	Crude ESRD[a,b] incidence, per 1000 patient-years (95% CI)	Age- and race-adjusted[c] incidence rate ratio (95% CI)
Individual characteristics		
Age at SLE diagnosis		
<18	20.3 (9.7-42.7)	2.14 (0.86-5.33)
18-30	12.6 (6.3-25.1)	1.19 (0.48-2.96)
>30	8.6 (5.1-14.6)	1.00 (ref)
Sex		
Female	11.5 (7.8-16.9)	1.00 (ref)
Male	8.7 (2.8-27.0)	0.77 (0.23-2.56)
Race		
White	3.3 (0.8-13.0)	1.00 (ref.)
Black	13.8 (9.4-20.3)	3.85 (0.91-16.35)
Early lupus nephritis		
No	3.4 (1.5-7.5)	1.00 (ref.)
Yes	27.6 (18.2-41.5)	6.72 (2.69-16.82)
Neighborhood characteristics		
Black race		
% black in tract		
Below median[d]	10.3 (5.8-18.1)	1.00 (ref)
Above median[d]	14.6 (9.0-23.9)	1.05 (0.47-2.37)
Granularity ratio[e]		
<0.9	14.2 (7.4-27.4)	1.44 (0.61-3.36)
0.9-1.1	11.5 (6.8-19.4)	1.00 (ref)
>1.1	11.5 (4.3-30.8)	1.51 (0.40-5.78)
Education		
% HS dropouts in tract		
Below median[d]	8.7 (4.7-16.3)	1.00 (ref)
Above median[d]	16.1 (10.1-25.5)	1.24 (0.55-2.80)
Granularity ratio[e]		
<0.9	16.2 (9.0-29.3)	1.51 (0.60-3.78)
0.9-1.1	13.2 (6.9-25.4)	1.00 (ref)
>1.1	8.3 (4.0-17.5)	0.82 (0.29-2.30)
Poverty		
% poor in tract		
Below median[d]	10.6 (6.0-18.6)	1.00 (ref)
Above median[d]	14.2 (8.7-23.2)	1.14 (0.52-2.50)
Granularity ratio[e]		
<0.9	11.2 (5.8-21.5)	0.47 (0.19-1.21)
0.9-1.1	21.9 (11.8-40.8)	1.00 (ref)
>1.1	8.5 (4.3-17.0)	0.38 (0.15-0.98)

CI, confidence interval; ESRD, end-stage renal disease; SLE systemic lupus erythematosus. Early lupus nephritis defined by urine or biopsy evidence or treatment rheumatologist or nephrologist documentation of LN in the medical record, within 3 years of SLE diagnosis.

[a]Among those with SLE by combined case definition: ≥4 ACR criteria, 3 ACR criteria plus treating rheumatologist's diagnosis, or renal involvement as indicated by biopsy consistent with class II-VI lupus nephritis or ESRD requiring dialysis or renal transplantation.
[b]Through last date of death follow-up in the Georgia Lupus Registry. A total of 30 patients initiated ESRD treatment between date of SLE diagnosis and 9/30/12, the last date of ESRD follow-up.
[c]Adjustment for age group (<18, 18-30, >30 years) and race (black and white only).
[d]Median values: % black, 84.9%; % high school dropouts, 13.2%; % poor, 11.1%.
[e]Ratio of kernel density-smoothed percentages (from block groups) in 4000-m to 500-m radii around patient residence. If the ratio is >1, there are greater values in surrounding areas (4000-m) vs. walkable neighborhood (500-m). For example, if poverty granularity ratio is >1 then person lives in an area with less concentrated poverty than the surrounding area; <1 then smaller area has more concentrated poverty than surrounding area.

Figure 4.1. Included and excluded end-stage renal disease events and follow-up time in the estimation of incidence among newly diagnosed (2002-2004) systemic lupus erythematosus patients in Fulton and DeKalb Counties, Georgia

End of death follow-up, 4/30/11; end of end-stage renal disease follow-up, 9/30/12.

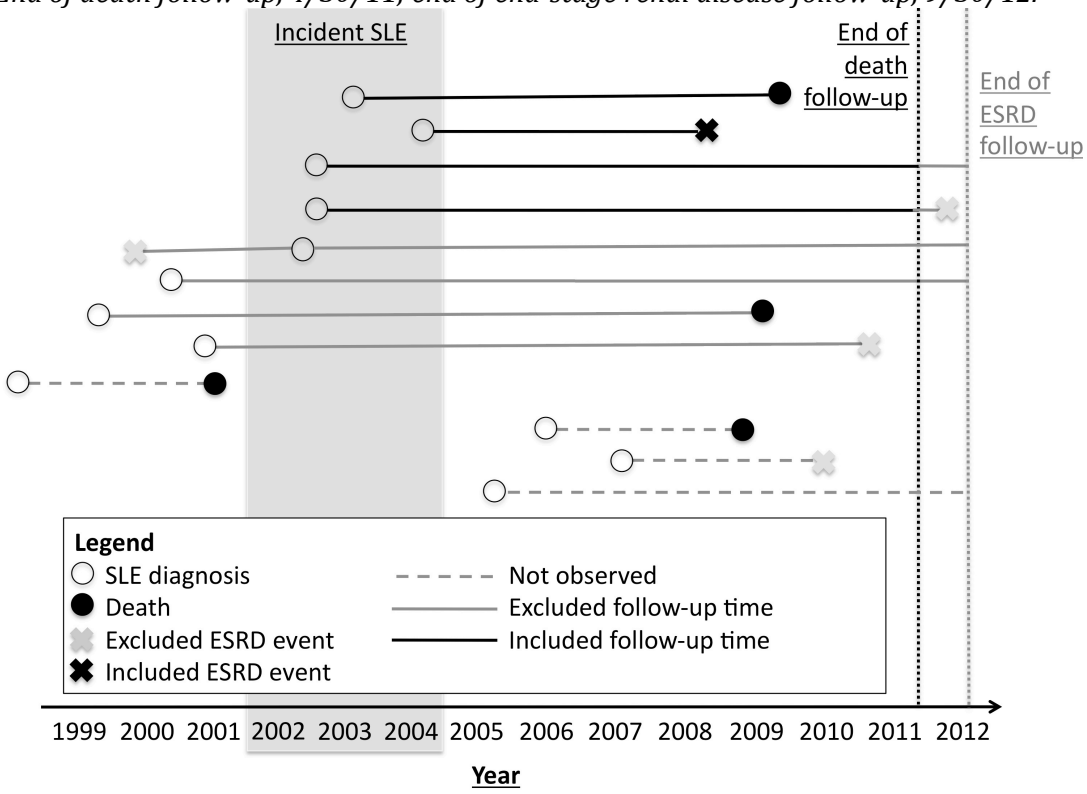
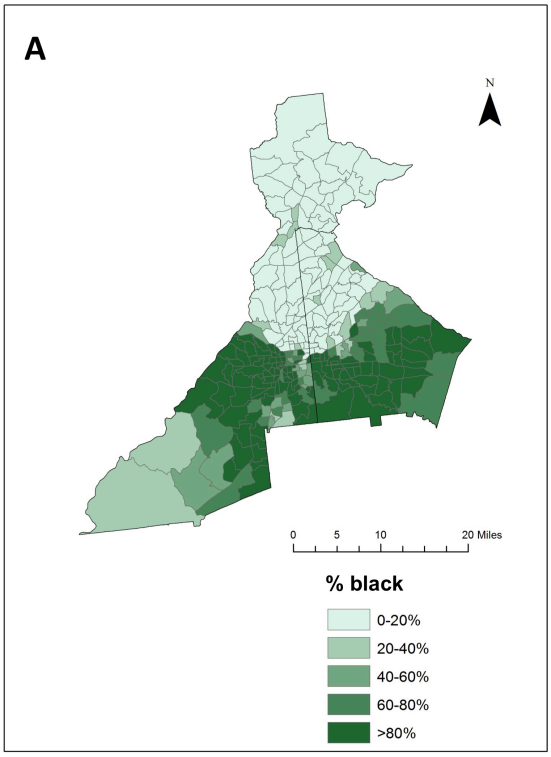
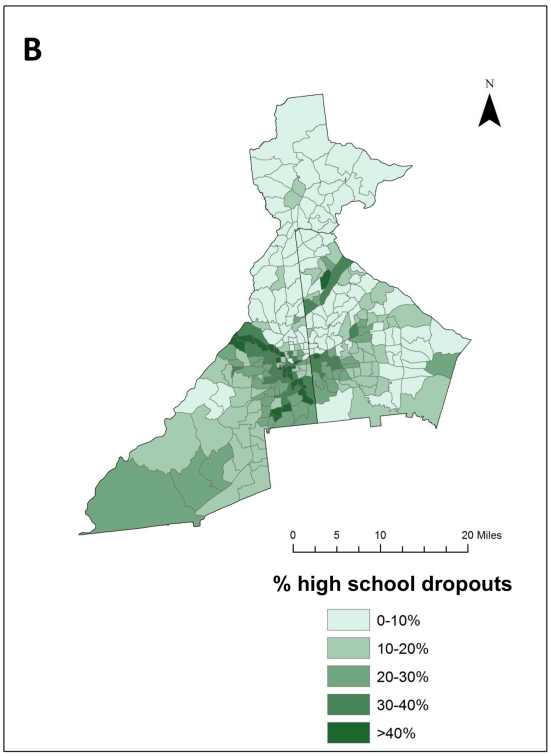


Figure 4.2. Maps of neighborhood (census tract) composition by race, education , and poverty, as well as incidence of ESRD, in Fulton and DeKalb Counties, Georgia

*Composition by race (% black; **A**), education (% high school dropouts; **B**), and poverty (% living below federal poverty threshold; **C**) in Fulton (left) and DeKalb (right) Counties, Georgia, in 2000, as well as kernel density-smoothed incidence of ESRD through 4/30/11 among systemic lupus erythematosus patients diagnosed in Fulton and DeKalb Counties in 2002-2004 (**D**). Values for Moran's I for spatial autocorrelation were: **A**, 0.86 (P<0.001); **B**, 0.61 (P<0.001); **C**, 0.64 (P<0.001); **D**, -0.04 (P=0.19). For **D**, kernel densities were estimated at 8000 m and Moran's I was calculated using census tract-summarized incidence. White spaces indicate no cases within 8000 m to estimate kernel densities.*

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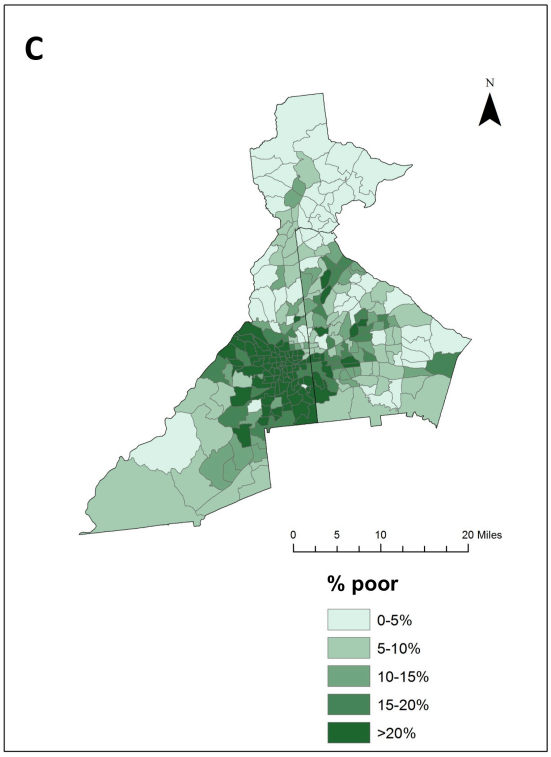
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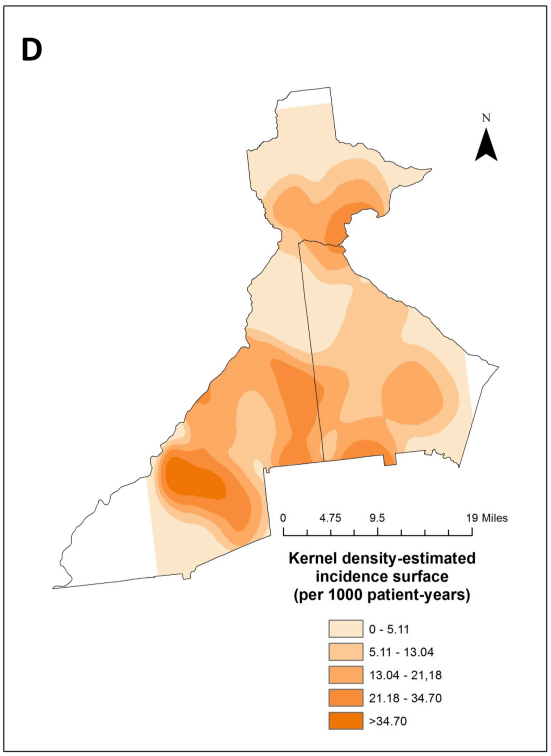
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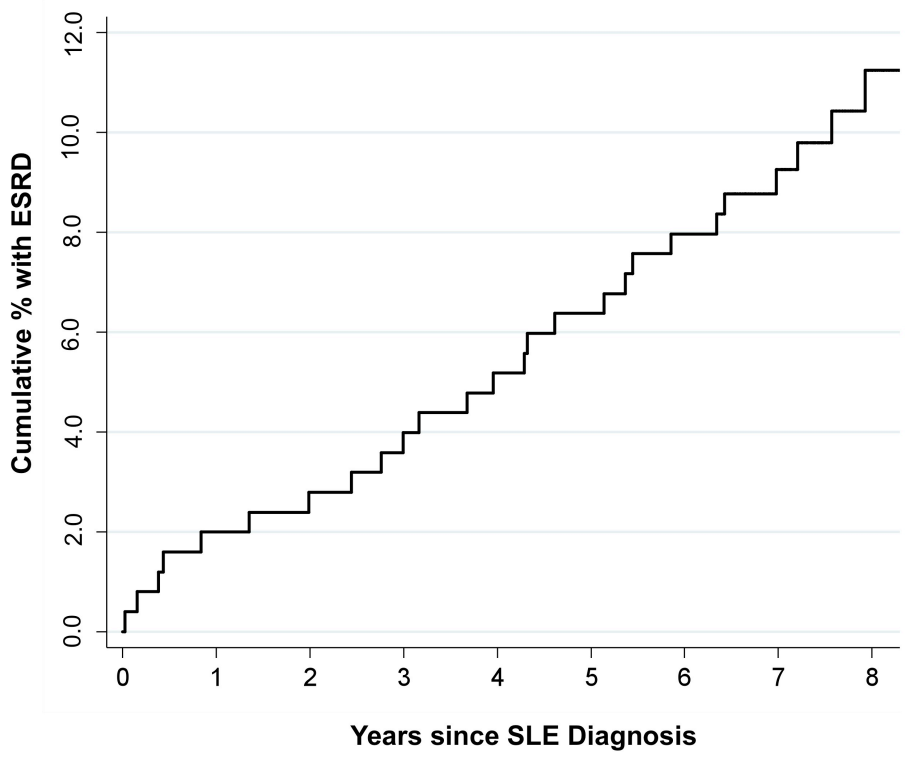
21.18 - 34.70
>34.70

Figure 4.3. Cumulative ESRD incidence among 251 black systemic lupus erythematosus patients diagnosed in Fulton and DeKalb Counties, Georgia, in 2002-2004



4.9 Supplementary Tables

Table 4.4. Description of probabilistic matching between Georgia Lupus Registry patients and the United States Renal Data System

Matched by:					No. of matches
SSN	**DOB**	**Sex**	**First Name**	**Last Name**	
Y	Y	Y	Y	Y	22
Y	Y	Y	P	Y	4
Y	Y	Y	Y	P	2
Y	Y	Y	Y	N	1
Y	N	Y	Y	Y	2
Total					**31**

SSN, Social Security Number; DOB, date of birth.

Table 4.5. Attributed cause of ESRD among 31 Georgia Lupus Registry patients matched to the United States Renal Data System

Attributed cause of ESRD	**No. (%)**
Systemic lupus erythematosus/lupus nephritis	21 (67.7%)
Hypertension, not otherwise specified	6 (19.4%)
Diabetes mellitus type II	1 (3.2%)
Sickle cell disease	1 (3.2%)
Focal segmental glomerulosclerosis	1 (3.2%)
Scleroderma	1 (3.2%)
Total	31

5. Aim 2: Sociodemographic and Geographic Predictors of Quality of Care in U.S. Patients with End-Stage Renal Disease due to Lupus Nephritis

5.1 Manuscript Information

Target Journal: Arthritis & Rheumatology

Title: Sociodemographic and Geographic Predictors of Quality of Care in U.S. Patients with End-Stage Renal Disease due to Lupus Nephritis

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5.2 Abstract

Objective. To describe end-stage renal disease (ESRD) quality of care (receipt of pre-ESRD nephrology care, access to kidney transplantation, and permanent vascular access placement for dialysis) in U.S. patients with ESRD due to lupus nephritis (LN-ESRD) and examine whether quality measures differed by patient sociodemographics or U.S. region. **Methods.** In 6,594 U.S. patients initiating treatment for LN-ESRD (7/05-9/11), we estimated odds ratios (ORs) and hazard ratios (HRs) of each quality measure with sociodemographics and U.S. region using national surveillance data. **Results.** Overall, 71% received nephrology care prior to ESRD. Blacks and Hispanics were less likely than whites to receive pre-ESRD care (OR=0.73, 95% CI 0.63-0.85 and OR=0.72, 95% CI 0.60-0.88) and to be placed on the kidney transplant waitlist (HR=0.78, 95% CI 0.68-0.81 and HR=0.82, 95% CI 0.68-0.98). Those with Medicaid (HR=0.51, 95% CI 0.44-0.58) or no insurance (HR=0.36, 95% CI 0.29-0.44) were less likely than those with private insurance to be placed on the waitlist. Only 24% had a permanent vascular access, and placement was even less likely among the uninsured (OR=0.62, 95% CI 0.49-0.79). ESRD quality-of-care measures varied 2- to 3-fold across regions, with patients in the Northeast and Northwest generally having higher probabilities of adequate care. **Conclusion.** LN-ESRD patients have suboptimal ESRD care, particularly with regard to vascular access placement. Minority race/ethnicity and lack of private insurance were associated with inadequate ESRD care. Further studies are warranted to examine multi-level barriers to—and develop targeted interventions to improve delivery of—care among LN-ESRD patients.

5.3 Introduction

Centers for Medicare & Medicaid Services (CMS), which covers end-stage renal disease (ESRD) care for all eligible U.S. patients, is highly invested in promoting quality of care, including mandated pay-for-performance.[56] Through its 18 ESRD Networks (www.esrdnetworks.org), CMS regionally monitors ESRD care and facilitates quality improvement. Quality of ESRD care is also a Healthy People 2020 (www.healthypeople.gov) priority,[8] supported by evidence that receipt of pre-ESRD care,[57-65] access to kidney transplantation,[39,68-72] and permanent vascular accesses for dialysis, which include arteriovenous fistulae (AVFs) and grafts,[80-87] are all associated with better patient outcomes and lower healthcare costs. Since 2005, CMS has collected information addressing these objectives on all incident ESRD patients via the CMS Medical Evidence Report (CMS Form 2728), which is completed for all patients at the start of ESRD treatment. These data have been used to describe not only the translation of these quality-of-care measures but also disparities in the success of this translation. In the overall ESRD population, black race, lower socioeconomic status, and U.S. region (particularly, the Southeast) have all been associated with lower attainment of goals for pre-ESRD care,[10,12,154] being informed of the transplant option,[7] placement on the national deceased donor kidney waitlist,[11,39,155] and permanent vascular access.[92,93]

With the exception of placement on the kidney transplant,[4,5] these markers of quality of ESRD care remain relatively unexamined in patients with systemic lupus erythematosus (SLE) and ESRD secondary to lupus nephritis (LN-ESRD). The examination of

translation of these measures in LN-ESRD patients is important because guidelines to address the preparation for ESRD are generally lacking for rheumatologists,[31] who could partner with nephrologists and other providers to improve ESRD care among these patients. Identification of sociodemographic and geographic disparities in quality of ESRD care in SLE patients, as seen in LN care,[95] could potentially guide the development of regional interventions targeted to patients most likely to receive inadequate ESRD care. Our aim was to describe the translation of ESRD quality-of-care measures among U.S. LN-ESRD patients and to estimate the associations of sociodemographic and geographic factors with successful translation in these patients.

5.4. Patients and Methods

5.4.1. Study population and data sources. The primary data source was the United States Renal Data System (USRDS). Data from the CMS-2728, completed on all treated U.S. incident ESRD patients, were obtained from the USRDS.[39] A total of 6,594 incident LN-ESRD patients who initiated treatment from 7/1/05 to 9/30/11 and had data from the most recent (2005) version of the CMS-2728 were identified via a primary attributed cause of ESRD secondary to lupus glomerulonephritis on the CMS-2728 (ICD-9 code = 710.0), the method of identification used in most recent studies of population LN-ESRD incidence.[4,5] Of these, 655 (9.9%) had unknown pre-ESRD nephrology care status and were excluded from these analyses (Figure 1). For analysis of measures of access to transplant (informed of transplant options, placement on the kidney transplant waitlist), those who were pre-emptively transplanted (n=292, 4.4%) or waitlisted (*n*=424, 6.4%) or who were aged ≥70 years (*n*=259, 3.9%) were excluded from the 6,594 LN-ESRD

patients, leaving 5,619 (85.2%) for analyses (Figure 1). For analyses of permanent vascular access, those with pre-emptive transplants (*n*=292, 4.4%) and those treated with peritoneal dialysis (*n*=678, 10.3%) were excluded, leaving 5,624 (85.3%) (Figure 1).

Primary attributed cause of ESRD, quality-of-care measures (nephrology care prior to ESRD, informed of transplant options, and vascular access at first dialysis), race/ethnicity, insurance, clinical factors were all obtained from the CMS-2728 through the USRDS. United Network for Organ Sharing (UNOS) maintains the national deceased donor kidney waitlist and provides these data to the USRDS. Data on characteristics of the patients' residential neighborhoods, as defined by patient 5-digit ZIP code tabulation area (ZCTA), were obtained from the 2007-2011 American Community Survey (www.census.gov/acs/www/) via the Minnesota Population Center[138] (www.nghis.org) and linked by patient ZIP code at the start of ESRD to the USRDS data.

5.4.2. Study variables.

5.4.2.1. Sociodemographics and geography: Individual sociodemographic exposures of interest included race/ethnicity (defined as white, black, Hispanic, and other) and insurance prior to ESRD (defined as private, Medicaid, none, or other). Due to the relative lack of information at the individual level on socioeconomic status (SES) and the potential for neighborhood effects independent of individual SES, we also examined aggregate residential ZCTA-level data on the percentage of residents reporting black race, the percentage of residents reporting Hispanic ethnicity, the percentage of high

school dropouts (residents aged ≥25 without a high school degree or equivalent), and the percentage poor (households living below 100% of the federal poverty threshold) from the American Community Survey. Finally, due to the regional implementation of CMS quality-of-care measures via the 18 ESRD Networks, the Network in which the patient received treatment served as a geographic exposure of interest.

5.4.2.2. Quality-of-care measures: The outcomes of interest were ESRD quality-of-care measures, specifically: (i) pre-ESRD nephrology care; (ii) access to transplant, including being informed of transplant options at the start of ESRD and being placed on the national deceased donor kidney transplant waitlist (=kidney transplant waitlisting); and (iii) permanent vascular access placement prior to the start of dialysis. Pre-ESRD nephrology care was defined by an answer of "Yes" to item 18b on the CMS-2728: "Prior to ESRD therapy: was the patient under the care of a nephrologist?" Whether patients were informed of transplant option was defined by CMS-2728 item 26: "Has patient been informed of kidney transplant options?" with possible responses of "Yes" and "No." Date of placement on the deceased donor transplant waitlist was determined from UNOS data and used to calculate time to transplant waitlisting (date of placement on the waitlist – first ESRD service date). Censoring occurred at death [of 3552 patients who were not waitlisted, 1093 (30.8%) died, 562 (15.8%) within the first year] or at the end of follow-up (9/30/11; median follow-up, 1.3 years). Finally, vascular access was determined from CMS-2728 item 18d: "What access was used on first outpatient dialysis?," with possible responses of "AVF," "Graft," "Catheter," and "Other" and two additional prompts for maturing permanent accesses in place ("Is maturing AVF

present?" and "Is maturing graft present?"). Permanent vascular access was defined as AVF or graft used or in place on first dialysis.

5.4.2.3. Other variables: Incident age and sex were obtained from the USRDS patient demographics file. Smoking status, BMI, presence of comorbid conditions, and serum albumin and hemoglobin at the start of ESRD were obtained from the CMS-2728.

5.4.3. Statistical analysis. Patient characteristics including sociodemographics and ESRD Network were summarized over all LN-ESRD patients, and quality-of-care measures were summarized and compared across sociodemographic characteristics and region within appropriate study populations. Odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between dichotomous outcomes (pre-ESRD nephrology care, informed of transplant options, and permanent vascular access placement) were estimated with multivariable logistic regression models. For transplant waitlisting, incidence rates were calculated as the number of patients placed on the kidney transplant waitlist per person-time, which included all time contributed by all patients from start of ESRD to waitlisting, death, or last date of follow-up. Violations of the Cox proportional hazards assumptions were assessed by tests of Schoenfeld residuals and examination of log-log plots. Hazard ratios (HRs) and CIs were obtained from multivariable Cox proportional hazards models run over the entire follow-up as well as using Heaviside functions to split the follow-up time. To avoid the arbitrary choice of referent group among U.S. regions, adjusted probabilities and incidence rates were also estimated using marginal post-estimation of logistic and Poisson models and mapped

using approximate quartiles or medians of the distribution, as appropriate. Factors that were associated with both sociodemographic predictors and quality-of-care measures and were not thought *a priori* to be mediators of the association were considered potential confounders. Clustering (multiple LN-ESRD patients in ZCTAs) at the ZCTA level was minimal, with 85% of patients living in ZCTAs with only one (46%), two (25%) or three (14%) patients. Sensitivity analyses at two extremes—where all missing values of pre-ESRD care were assigned "yes" or "no"—were performed and compared to the primary results, to determine how much the estimates might be biased if missing data were differential with respect to delivery of pre-ESRD care. Stata v. 13 (StataCorp, College Station, TX) was used for all analyses and the threshold for statistical significance was set at α=0.05. Mapping was performed using ArcGIS v. 10.1 (ESRI, Redlands, CA).

5.5 Results

5.5.1. Characteristics of the study population. The mean age of incident U.S. LN-ESRD patients (*n*=6,594) during the study period was 40 years; most were female (although, disproportionate to the SLE population, nearly 19% were male), and half were black (Table 1). One-third of these patients had Medicaid and more than 1 in 10 were uninsured at the start of ESRD. The median percentages of residents who were black, high school dropouts, and living in poverty in patients' residential ZCTAs were 14%, 17%, and 17%, respectively (Table 1). The most common comorbidity among these young patients was hypertension, followed by cardiovascular disease including pericarditis (Table 1). The percentages of all LN-ESRD patients treated within ESRD Networks ranged from ~2% (Network 16, Northwest) to >10% (Networks 6 and 14,

Southeast and Texas). Those missing information on pre-ESRD care (n=655; excluded from pre-ESRD care analyses) were similar to those included in terms of most patient characteristics, except that they were more likely than those included to be black (53.1% vs. 49.3%) or Hispanic (20.3 vs. 17.4%; *P*=0.003) and to have Medicaid (36.3% vs. 32.4%) or no insurance (15.6% vs. 11.1%; *P*<0.001) and less likely to have a BMI ≥35 kg/m^2 (9.7% vs. 12.9%; *P*=0.02).

5.5.2. Association of social predictors with quality-of-care measures.

5.5.2.1. Pre-ESRD care: Overall, 71.1% of U.S. LN-ESRD patients received pre-ESRD nephrology care (Table 2), and the percentage did not differ by incident year (*P*=0.47; data not shown). After adjustment for potential confounders, black and Hispanic LN-ESRD patients were 27% less likely to receive pre-ESRD care than their white counterparts, and those with Medicaid and no insurance prior to ESRD start were 26% and 74% less likely to receive this care, relative to those with private insurance (Table 2). Results were not substantially different when models were further adjusted for hemoglobin or albumin (data not shown). Of the 5,939 patients with pre-ESRD care information, 26 (0.4%) were potentially misclassified, in that the patient either had a pre-emptive transplant or were pre-emptively waitlisted; redefining these individuals as having pre-ESRD care did not change the results (data not shown). LN-ESRD patients living in ZCTAs with percentage black, Hispanic, high school dropouts, and poor above median values were 5%, 17%, 11%, and 16% less likely, respectively, to have pre-ESRD care after adjustment, although only the association with poverty was statistically significant (Table 2). Sensitivity analyses showed that associations with imputed missing

values of pre-ESRD care were similar in terms of magnitude and statistical significance, ranging from 0.72 to 0.77 for black vs. white race; 0.70 to 0.78 for Hispanic vs. white; 0.72 to 0.80 for Medicaid vs. private insurance; and 0.28 to 0.31 for no vs. private insurance.

5.5.2.2. Access to transplant: Overall, 84.8% of U.S. LN-ESRD patients were informed of transplant options at the start of ESRD, with 83.6% and 87.8% being informed in incident years 2006 and 2010, respectively (P=0.05 for time trend). Having Medicaid, no insurance, or other types of insurance were associated with 32-39% decreased likelihood of being informed of transplant options, relative to having private insurance at the start of ESRD, after adjustment for potential confounders (Table 2). Race/ethnicity and ZCTA-level black race and poverty were not associated with LN-ESRD patients being informed of transplant options. ZCTA-level education (percentage high school dropouts) was associated with 13% decreased likelihood of being informed of transplant options, although the association was not statistically significant (Table 2).

Rates of transplant waitlisting were 206 per 1000 patient-years overall, ranging from 177 to 263 per 1000 patient-years in 2006 and 2010 (P<0.001 for time trend). Tests of the proportional hazards assumption indicated potential violations (P<0.05 for all sociodemographic predictors). Examination of log-log plots did not reveal substantial departures from parallel, except at around the end of the first year, when data were sparse but suggested potential crossing of the curves; thus, follow-up split at 1 year as well as overall were utilized (data not shown). Adjusted hazards of kidney transplant waitlisting

over follow-up were substantially lower among LN-ESRD patients with Medicaid, no, or other insurance, relative to those with private insurance at ESRD start (48%, 51%, and 30% lower, respectively); results were similar in the first year of ESRD and after the first year of ESRD (Table 3). Black and Hispanic LN-ESRD patients were 22% and 18% less likely to be waitlisted than white LN-ESRD patients, but only within the first year of ESRD (Table 3). LN-ESRD patients living in ZCTAs with less educational attainment and more poverty were less likely (25% and 35%) to be waitlisted but also only within the first year of ESRD (Table 3). Results including both waitlisting and living donor transplants without prior waitlisting (*n*=69), with censoring at the time of transplant, were slightly further from the null but were not substantially different from results reported in Table 3 (data not shown). Results were similar including only those patients who survived 1 year, except that ZCTA-level black race remained statistically significantly associated with lower likelihood of waitlisting in the first year of ESRD after adjustment (HR=0.79; 95% CI, 0.69-0.90).

5.5.2.3. Permanent vascular access: Only one-quarter (24.4%) of LN-ESRD patients who initiated ESRD treatment on hemodialysis had a fistula or graft used or in place on first dialysis (Table 2), with no differences over time (*P*=0.45). The percentage of LN-ESRD patients with a permanent vascular access did not differ by early transplant status (transplanted within 1 year vs. not: 27.2% vs. 24.3%, *P*=0.32). Likelihood of having such a permanent vascular access did not differ by race/ethnicity or ZCTA-level sociodemographics. Private, Medicaid or other insurance were associated with equivalent

likelihood of permanent vascular access, but having no insurance was associated with 38% lower likelihood of permanent vascular access among LN-ESRD patients (Table 2).

5.5.3. Association of ESRD Network with Quality-of-Care Measures.

5.5.3.1: Pre-ESRD care: Receipt of pre-ESRD nephrology among LN-ESRD patients differed substantially by ESRD Network (Table 4). Age-, sex-, race/ethnicity- and insurance-adjusted probabilities of pre-ESRD care ranged from 0.66 (95% CI, 0.60-0.71) in Illinois (Network 10) to 0.81 (95% CI, 0.74-0.87) in New England (Network 1; Figure 2A).

5.5.3.2: Access to transplant: Being informed of transplant options did not differ by Network (Table 4), and the range of adjusted probabilities was small (Figure 2B), from 0.81 (95% CI, 0.74-0.88; Network 16, Northwest) to 0.90 (95% CI, 0.85-0.93; Network 3, New Jersey). However, there is some evidence that waitlisting in LN-ESRD patients, particularly in the first year of ESRD, does differ by ESRD Network (Table 4). Age-, sex-, race/ethnicity-, and insurance-adjusted incidence of kidney transplant waitlisting over the entire period varied >2.5-fold, from 148 (95% CI, 121-175; Network 7, Florida) to 373 (95% CI, 307-440; Network 17, Northern California and Hawaii) per 1000 patient-years (Figure 2C).

5.5.3.3. Permanent vascular access: There was substantial, statistically significant Network-level variation in likelihood of permanent vascular access (Table 4), with age-, sex-, race/ethnicity-, and insurance-adjusted probabilities of permanent vascular access

used or in place at first dialysis ranging from 0.17 (95% CI, 0.12-0.21; Network 10) to 0.33 (95% CI, 0.24-0.41; Network 16; Figure 2D).

5.6 Discussion

Despite multiple national and regional quality-of-care initiatives and incentives aimed at improving care in the overall ESRD population,[8,56,93] we found that, among LN-ESRD patients, care remains suboptimal, particularly with respect to permanent vascular access placement. Nearly one-third of patients with LN-ESRD had received no pre-ESRD nephrology care at the start of ESRD treatment, similar to the overall ESRD population, in whom 34-35% had not received this care in 2007-2010.[39] While some of these patients may have experienced ESRD as their earliest manifestation of SLE, precluding pre-ESRD care, it is likely that most of these patients were not referred to a nephrologist in a timely manner, putting them at risk for poor outcomes.[156] Most (85%) potentially eligible patients were reported to be informed of transplant options at ESRD start, higher than the overall population (70% in 2005-2007),[7] but incidence of subsequent waitlisting was only ~20% per year. However, both being informed of transplant options and transplant waitlisting increased over the study period among LN-ESRD patients and waitlisting was much higher than in the general ESRD population, in whom only 11-12% were waitlisted in the first year in 2007-2010.[39] Notably, fewer than one-quarter of LN-ESRD patients treated by hemodialysis had a permanent vascular access in place at the start of treatment, vs. 35-36% in 2007-2020 in the overall ESRD population.[39] This percentage was higher among those transplanted early, suggesting that provider decisions to forego vascular

access surgery in patients expected to receive a transplant imminently do not explain the low likelihood of permanent vascular access placement among LN-ESRD patients.

Our findings also indicate substantial sociodemographic and regional disparities in the translation of quality-of-care measures related to pre-ESRD care, access to transplant, and placement of permanent vascular access among LN-ESRD patients. After adjustment for other sociodemographic and clinical factors, black and Hispanic patients were less likely to have pre-ESRD nephrology care and permanent vascular accesses than their white counterparts, as in the overall ESRD population,[12,93] although differences by race/ethnicity in permanent vascular access were not statistically significant after adjustment for other factors. Black race and Hispanic ethnicity were also associated with lower likelihood of kidney transplant waitlisting relative to white race in the first year of ESRD treatment, similarly to patterns in the overall ESRD population.[11,155,157] Faster progression of lupus nephritis[144,158] and reduced engagement with the healthcare system among minority LN-ESRD patients may contribute to racial and ethnic disparities in pre-ESRD nephrology care and early transplant waitlisting in this population. While patient race/ethnicity was not associated with being informed of transplant options or with waitlisting after the first year, these apparent equivalencies may not be sufficient to close racial and ethnic gaps in kidney transplantation created by the early lag in waitlisting, relative to white patients. Further, how well patients are actually informed of transplant options—and whether this translates to useable knowledge of the options—may differ by race/ethnicity. Among patients not informed, it is likely that reasons for withholding information from patients differ by race/ethnicity and that reasons among minority and

female patients (the majority of LN-ESRD patients) are more likely to represent subjective assessments.[7] Thus, being appropriately and thoroughly informed of options may not be equivalent by race/ethnicity.

Lack of insurance at the start of ESRD was strongly associated with less successful translation of all examined quality-of-care measures, similar to the overall ESRD population,[159,160] with adjustment for other sociodemographic and clinical characteristics. This disparity is likely at least partially related to the actual or perceived inability of uninsured patients to cover expenses associated with specialty care, including nephrology, transplant evaluation, and vascular access surgery. However, not having private insurance at ESRD start was also associated with lower likelihood of pre-ESRD nephrology care, being informed of transplant options, and waitlisting. After the first year of ESRD, when all treated patients have CMS coverage for ESRD services, the association of having no or public insurance with lower likelihood of waitlisting persisted. For example, LN-ESRD patients with Medicaid remained nearly 50% less likely to be waitlisted than LN-ESRD patients with private insurance at the start of ESRD, suggesting these patients are less likely to be perceived as suitable candidates for transplant, even after they gain equivalent access to CMS ESRD coverage. Although the 3-year limit on immunosuppressant coverage among transplant patients who qualify for Medicare based solely on ESRD may act as a provider deterrent to waitlisting among young, un- or publicly insured LN-ESRD patients, this pattern is likely not fully explained by this policy.[99]

Area-based socioeconomic measures of lower educational attainment and greater poverty were associated with inadequate pre-ESRD nephrology care and access to transplant, although the effects adjusted for individual factors were generally more modest and less statistically significant than those of individual race/ethnicity and insurance. Whether these effects represent proxy effects for individual poverty and education not captured by individual race/ethnicity and insurance status or contextual effects is unknown, without information on individual education and poverty status. Racial composition of patients' residential area was not associated with most of these quality-of-care measures after adjustment, except transplant waitlisting over the entire follow-up period, suggesting that individual race/ethnicity, along with age, sex, insurance status, and comorbid conditions, may explain most differences in quality of care by area-based race.

Translation of most examined quality-of-care measures, with the exception of being informed of transplant options, also differed among LN-ESRD patients by U.S. region, as defined by ESRD Network. Even with adjustment for Network differences in age, sex, race/ethnicity, and insurance, LN-ESRD patients in the Northeast and, especially, New England had relatively high likelihood of pre-ESRD nephrology care, transplant waitlisting, and permanent vascular access placement, mirroring patterns seen in the overall ESRD population.[9,10,92,161,162] Patients in the Northwest similarly had high likelihood of pre-ESRD care and permanent vascular access placement, but these same patients had relatively low likelihood of transplant waitlisting. LN-ESRD patients in Southern California were generally less likely than patients in other Networks to have pre-ESRD nephrology care, transplant waitlisting, and permanent vascular access

placement. The inconsistency of these geographic disparities across quality measures may be the result of Network differences in resources and priorities—despite national programs that, in part, sought to eliminate these regional differences, such as the Fistula First Breakthrough Initiative.[91-93] Alternatively, the varying prevalence of LN-ESRD across Networks could lead to differences in provider experience and comfort with the care of lupus nephritis and associated ESRD, leading to differences in the translation of these quality-of-care measures. Of course, in Networks with small proportions of the overall LN-ESRD population, statistical differences may also be due to chance.

This study has several limitations. The USRDS does not capture non-Medicare-eligible individuals, including undocumented residents who are likely to be socioeconomically deprived and geographically concentrated. Also, attribution of ESRD cause on the CMS-2728 has unknown validity; one small validation study[130] conducted using biopsy samples prior to 2001 suggests potentially low sensitivity, although attributed causes were mostly missing, contributing to low agreement. If these validation results apply in the more modern era, with nearly complete data on attributed cause, our study population may not capture all individuals with LN-ESRD and, if differential by sociodemographics, region, and/or quality of care, this could potentially bias our results. Provider accuracy in recording other patient variables, including race/ethnicity and insurance as well as quality measures, may also be imperfect. Death may serve as a competing risk to analyses of time to waitlisting, although sensitivity analyses using only those who did not die during the first year suggests that the effect of this bias is likely minimal. ZCTAs and measures at this level may serve as insufficient proxies for neighborhoods and characteristics of the

individuals within these areas, respectively. Further, information on more granular ethnicity and language needs, which may be important for the comprehensive assessment of disparities, was not available. There is the potential for selection bias due to excluded data in analyses of pre-ESRD care, since included and excluded patients differed by several characteristics, but <10% of individuals had unknown pre-ESRD care status and sensitivity analyses showed any bias was likely minimal. Misclassification of quality of care on the CMS-2728 is also possible, although pre-ESRD care appears to be accurately captured with respect to patients with preemptive transplants and waitlisting. Many confounding factors may instead or also serve as mediating factors, leading to potential overadjustment, and, as with any observational study, there is possible residual confounding, particularly due to provider factors, such as availability of nephrologists and rheumatologists. However, this study also has several powerful strengths, including the capture of all U.S. patients treated for ESRD, limited loss to follow-up due to universal coverage of ESRD services by CMS, and the provision of the Medicare Eligibility form (CMS-2728)—which includes ESRD quality-of-care information of interest to CMS—for all treated patients.

Despite its limitations, this study provides a comprehensive, national snapshot of ESRD quality of care for U.S. patients with LN-ESRD, overall and by patient characteristics and U.S. region. These results encourage hypothesis generation and further study regarding potential barriers to improving quality of ESRD care in this population at the levels of the health system, ESRD Networks, providers (including rheumatologists, nephrologists, and transplant and vascular access surgeons), and patients. Our results also identify potential

specific targets with respect to inadequate translation of quality-of-care measures in this population (particularly, permanent vascular access placement) and the LN-ESRD patient subpopulations that are least likely to receive high-quality care, as assessed by these measures. For example, a Network-level intervention to enhance rheumatology–nephrology partnerships aimed at improving ESRD care could be targeted to a region with a large population of uninsured, black LN-ESRD patients, such as the Southeast. Such efforts have the potential to ensure better and more equitable quality of ESRD care among patients with SLE.

5.7 Acknowledgements and Financial Support

The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the U.S. government. R.E.P. was supported in part by grants from the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH; ULl TR000454 and KL2TR000455). R.E.P. and S.O.P are both supported in part by 1R24MD008077-01 through the National Institute on Minority Health and Health Disparities. M.R.K. is supported by the Eunice Kennedy Shriver National Institute Of Child Health & Human Development of the NIH (K01HD074726). S.S.L. and C.D. are supported in part by the NIH (R01AR065493). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

5.8 Tables and Figures

Table 5.1. Characteristics of U.S. patients initiating treatment for end-stage renal disease attributed to lupus nephritis, 7/1/05-9/30/11

Characteristic	***n***	**Value at ESRD Start**
Patient Factors		
Mean age (SD), years	6594	39.6 (15.4)
Sex (%)	6594	
Female		81.1%
Male		18.9%
Race/ethnicity (%)	6594	
White		24.7%
Black		49.7%
Hispanic		17.7%
Other		7.9%
Insurance (%)	6594	
Private		37.4%
Medicare/other*		18.4%
Medicaid		32.8%
None		11.5%
Smoking (%)	6594	
Yes		4.3%
No		95.7%
Mean (SD) BMI, kg/m^2	6522	26.9 (7.4)
BMI $\geq$35 kg/m^2	6522	
Yes		12.6%
No		87.4%
No. of comorbidities (%)	6594	
0		10.9%
1		56.0%
2+		33.1%
Hypertension (%)	6594	
Yes		83.6%
No		16.4%
CVD (%)	6594	
Yes		18.6%
No		81.4%
Mean serum albumin (SD)	5201	2.9 (0.8)
Mean serum hemoglobin (SD)	6124	9.5 (1.7)
ESRD Network (%)	6549	
1-CT, ME, MA, NH, RI, VT		2.5%

Characteristic	*n*	Value at ESRD Start
2-NY		7.5%
3-NJ		3.9%
4-DE, PA		3.5%
5-DC, MD, VA, WV		5.6%
6-GA, NC, SC		10.3%
7-FL		7.0%
8-AL, MS, TN		6.3%
9-IN, KY, OH		5.1%
10-IL		4.6%
11-MI, MN, ND, SD, WI		6.2%
12-IA, KS, MO, NE		2.7%
13-AR, LA, OK		4.1%
14-TX		10.6%
15-AZ, CO, NM, NV, UT, WY		5.1%
16-AK, ID, MT, OR, WA		2.3%
17-HI, Northern CA		5.1%
18-Southern CA		7.6%
Patient residential neighborhood (ZCTA) factors		
Median percentage black (IQR)	6449	14.1 (3.7-41.4)
Median percentage Hispanic (IQR)	6449	9.9 (3.4-29.9)
Median percentage HS dropouts (IQR)	6449	16.7 (10.1-24.4)
Median percentage living in poverty (IQR)	6449	16.5 (9.8-24.9)

ESRD, end-stage renal disease; BMI, body mass index; CVD, cardiovascular disease (includes pericarditis); ZCTA, zip code tabulation area; IQR, inter-quartile range; HS, high school.
*Includes Medicare (*n*=681), VA (*n*=47), and other (*n*=483).

Table 5.2. Crude and adjusted odds ratios for dichotomous end-stage renal disease quality-of-care indicators by sociodemographic factors, among U.S. patients initiating treatment for end-stage renal disease attributed to lupus nephritis, 7/1/05-9/30/11

	Patient received pre-ESRD nephrology care			Patient informed of transplant options			Fistula/graft used or in place at first dialysis		
Sociodemographic factor	**Crude %**	**Odds ratio (95% CI) Unadjusted**	**Adjusted**	**Crude %**	**Odds ratio (95% CI) Unadjusted**	**Adjusted**	**Crude %**	**Odds ratio (95% CI) Unadjusted**	**Adjusted**
Overall	71.1	---	---	84.8			24.4		
Individual sociodemographic factors									
N	*5939*	*5875*		*5619*	*5558*		*5624*	*5562*	
Race/ethnicity (%)									
White	76.7	1.00 (ref)	1.00 (ref)	84.0	1.00 (ref)	1.00 (ref)	28.2	1.00 (ref)	1.00 (ref)
Black	69.1	0.68 (0.59-0.79)	0.73 (0.63-0.85)	85.4	1.21 (0.99-1.48)	1.07 (0.88-1.30)	24.1	0.81 (0.70-0.94)	0.96 (0.81-1.12)
Hispanic	67.1	0.61 (0.52-0.73)	0.73 (0.60-0.88)	83.9	1.02 (0.80-1.31)	0.95 (0.75-1.20)	20.5	0.65 (0.54-0.80)	0.85 (0.69-1.05)
Other	74.8	0.90 (0.70-1.14)	0.95 (0.74-1.22)	84.8	1.15 (0.83-1.61)	0.99 (0.72-1.35)	24.4	0.83 (0.64-1.07)	1.06 (0.81-1.38)
Insurance (%)									
Private	78.4	1.00 (ref)	1.00 (ref)	87.6	1.00 (ref)	1.00 (ref)	25.3	1.00 (ref)	1.00 (ref)
Medicare/other*	73.4	0.77 (0.65-0.91)	0.76 (0.63-0.90)	82.8	0.66 (0.51-0.85)	0.61 (0.47-0.80)	28.5	1.18 (0.99-1.10)	1.03 (0.86-1.23)
Medicaid	69.3	0.62 (0.54-0.72)	0.64 (0.56-0.74)	83.4	0.71 (0.59-0.87)	0.66 (0.54-0.80)	24.4	0.95 (0.82-1.10)	1.05 (0.91-1.22)
None	47.5	0.25 (0.21-0.30)	0.26 (0.21-0.31)	83.4	0.65 (0.51-0.83)	0.68 (0.54-0.87)	16.0	0.55 (0.43-0.69)	0.62 (0.49-0.79)
Residential neighborhood (ZCTA) sociodemographic factors									
N	*5810*	*5746*		*5492*	*5431*		*5500*	*5438*	
% black									
Below median	73.4	1.00 (ref)	1.00 (ref)	84.2	1.00 (ref)	1.00 (ref)	24.6	1.00 (ref)	1.00 (ref)
Above median	68.9	0.81 (0.72-0.91)	0.95 (0.82-1.09)	85.4	1.09 (0.94-1.26)	1.04 (0.87-1.25)	24.2	0.97 (0.86-1.10)	1.01 (0.86-1.18)
% Hispanic									
Below median	73.4	1.00 (ref)	1.00 (ref)	84.5	1.00 (ref)	1.00 (ref)	25.2	1.00 (ref)	1.00 (ref)
Above median	68.9	0.81 (0.72-0.91)	0.83 (0.73-0.95)	85.2	1.06 (0.91-1.23)	1.05 (0.91-1.23)	23.6	0.92 (0.81-1.04)	0.99 (0.87-1.12)
% HS dropouts									
Below median	74.0	1.00 (ref)	1.00 (ref)	85.8	1.00 (ref)	1.00 (ref)	25.0	1.00 (ref)	1.00 (ref)
Above median	68.3	0.76 (0.68-0.85)	0.89 (0.79-1.01)	83.9	0.85 (0.73-0.98)	0.87 (0.74-1.02)	23.9	0.93 (0.83-1.06)	1.01 (0.88-1.15)
% poor									
Below median	74.6	1.00 (ref)	1.00 (ref)	85.3	1.00 (ref)	1.00 (ref)	25.9	1.00 (ref)	1.00 (ref)
Above median	67.7	0.72 (0.64-0.81)	0.84 (0.74-0.95)	84.3	0.91 (0.79-1.06)	0.93 (0.79-1.09)	23.0	0.85 (0.75-0.96)	0.88 (0.85-1.18)

Adjusted models (complete case analysis) include age, race/ethnicity, insurance, BMI (≥35 vs. <35), hypertension, and cardiovascular disease. ZCTA, zip code tabulation area; HS, high school.

*Includes Medicare, VA, and other.

Table 5.3. Crude and adjusted hazard ratios for time to kidney transplant waitlisting by sociodemographic factors, among U.S. patients initiating treatment for end-stage renal disease attributed to lupus nephritis, 7/1/05-9/30/11

Sociodemographic factor	Events/ 1000 patient-years	Hazard ratio (95% CI)					
		Entire follow-up		In first year after ESRD start		After first year of ESRD	
		Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Overall	206	---	---	---	---	---	---
Individual sociodemographic factors							
N	*5619*	*5558*		*5558*		*3203*	
Race/ethnicity (%)							
White	215	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Black	195	0.91 (0.81-1.02)	0.91 (0.81-1.03)	0.79 (0.68-0.91)	0.78 (0.68-0.91)	1.13 (0.94-1.36)	1.15 (0.95-1.38)
Hispanic	208	0.99 (0.86-1.13)	0.97 (0.84-1.11)	0.84 (0.70-1.01)	0.82 (0.68-0.98)	1.23 (1.00-1.53)	1.22 (0.98-1.52)
Other	261	1.22 (1.03-1.45)	1.09 (0.87-1.30)	1.29 (1.04-1.60)	1.16 (0.93-1.43)	1.12 (0.83-1.50)	1.00 (0.75-1.34)
Insurance (%)							
Private	293	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Medicare/other*	194	0.67 (0.59-0.77)	0.70 (0.62-0.80)	0.63 (0.53-0.74)	0.65 (0.55-0.77)	0.74 (0.61-0.91)	0.78 (0.64-0.95)
Medicaid	158	0.55 (0.50-0.61)	0.52 (0.47-0.58)	0.54 (0.47-0.62)	0.51 (0.44-0.58)	0.58 (0.50-0.68)	0.55 (0.47-0.65)
None	159	0.55 (0.47-0.63)	0.49 (0.43-0.57)	0.39 (0.32-0.49)	0.36 (0.29-0.44)	0.77 (0.63-0.94)	0.69 (0.57-0.84)
Residential neighborhood (ZCTA) sociodemographic factors							
N	*5493*	*5432*		*5432*		*3119*	
% black							
Below median	225	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Above median	168	0.84 (0.77-0.92)	0.88 (0.79-0.98)	0.76 (0.68-0.86)	0.96 (0.84-1.10)	0.80 (0.70-0.91)	1.00 (0.86-1.16)
% Hispanic							
Below median	201	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Above median	213	1.07 (0.98-1.17)	1.03 (0.93-1.13)	1.02 (0.91-1.15)	0.98 (0.86-1.10)	1.14 (0.99-1.30)	1.10 (0.95-1.26)
% HS dropouts							
Below median	239	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Above median	180	0.77 (0.70-0.84)	0.82 (0.74-0.90)	0.70 (0.63-0.79)	0.75 (0.67-0.85)	0.86 (0.75-0.98)	0.91 (0.79-1.04)
% poor							
Below median	250	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Above median	172	0.70 (0.64-0.76)	0.76 (0.69-0.83)	0.60 (0.53-0.67)	0.65 (0.58-0.73)	0.87 (0.76-0.99)	0.94 (0.82-1.07)

Adjusted models (complete case analysis) include age, race/ethnicity, insurance, BMI (≥35 vs. <35), hypertension, and cardiovascular disease. ZCTA, zip code tabulation area; HS, high school.

*Includes Medicare, VA, and other.

Table 5.4. Age-, sex-, race/ethnicity-, and insurance-adjusted risk ratio estimates for quality-of-care indicators by ESRD Network, among U.S. patients initiating treatment for end-stage renal disease attributed to lupus nephritis, 7/1/05-9/30/11

Network	Odds ratio (95% CI) for receipt of pre-ESRD care	Odds ratio (95% CI) for informed of transplant options	Hazard ratio (95% CI) for transplant waitlisting		Odds ratio (95% CI) for fistula/graft at dialysis start
			In first year after ESRD start	After first year of ESRD	
1-CT, ME, MA, NH, RI, VT	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2-NY	0.63 (0.40-1.02)	1.33 (0.78-2.28)	1.56 (1.05-2.32)	1.27 (0.79-2.06)	1.07 (0.70-1.63)
3-NJ	0.47 (0.29-0.78)	1.73 (0.93-3.21)	1.10 (0.71-1.70)	0.76 (0.43-1.33)	1.12 (0.70-1.78)
4-DE, PA	0.64 (0.37-1.08)	1.09 (0.60-1.98)	1.78 (1.16-2.73)	0.56 (0.29-1.09)	0.79 (0.49-1.28)
5-DC, MD, VA, WV	0.59 (0.36-0.96)	1.20 (0.69-2.09)	0.85 (0.55-1.32)	0.83 (0.50-1.38)	0.72 (0.46-1.14)
6-GA, NC, SC	0.68 (0.43-1.08)	0.93 (0.57-1.53)	0.60 (0.40-0.90)	0.95 (0.60-1.51)	0.74 (0.49-1.12)
7-FL	0.55 (0.34-0.88)	1.15 (0.68-1.95)	0.38 (0.24-0.61)	0.89 (0.55-1.44)	0.58 (0.37-0.91)
8-AL, MS, TN	0.58 (0.36-0.93)	1.48 (0.85-2.58)	0.99 (0.65-1.50)	0.85 (0.52-1.41)	1.09 (0.71-1.68)
9-IN, KY, OH	0.60 (0.36-0.98)	1.17 (0.67-2.02)	0.61 (0.39-0.97)	0.82 (0.49-1.37)	0.57 (0.36-0.91)
10-IL	0.45 (0.27-0.73)	1.29 (0.73-2.29)	1.02 (0.66-1.57)	0.82 (0.49-1.38)	0.47 (0.29-0.77)
11-MI, MN, ND, SD, WI	0.65 (0.40-1.06)	0.90 (0.53-1.53)	0.85 (0.56-1.31)	0.91 (0.55-1.49)	0.57 (0.36-0.90)
12-IA, KS, MO, NE	0.61 (0.36-1.06)	0.88 (0.48-1.62)	0.67 (0.39-1.13)	0.69 (0.38-1.26)	0.53 (0.31-0.91)
13-AR, LA, OK	0.48 (0.29-0.79)	0.88 (0.51-1.53)	0.61 (0.38-0.99)	0.68 (0.39-1.16)	0.65 (0.40-1.05)
14-TX	0.51 (0.32-0.80)	1.48 (0.89-2.46)	0.74 (0.50-1.10)	0.98 (0.62-1.55)	0.89 (0.59-1.35)
15-AZ, CO, NM, NV, UT, WY	0.54 (0.33-0.88)	1.01 (0.59-1.75)	0.76 (0.49-1.18)	0.69 (0.41-1.15)	0.68 (0.43-1.08)
16-AK, ID, MT, OR, WA	0.99 (0.54-1.84)	0.86 (0.46-1.63)	0.60 (0.34-1.07)	0.66 (0.35-1.24)	1.14 (0.66-1.96)
17-HI, Northern CA	0.71 (0.42-1.18)	0.88 (0.51-1.53)	1.96 (1.31-2.94)	0.86 (0.49-1.48)	0.96 (0.61-1.53)
18-Southern CA	0.46 (0.28-0.74)	1.16 (0.69-1.95)	0.70 (0.46-1.07)	0.84 (0.51-1.36)	0.51 (0.33-0.80)

Figure 5.1. Selection of study populations for quality measures related to pre-end-stage renal disease nephrology care, access to transplant (informed of transplant options, time to placement on the kidney transplant waitlist), and presence of a permanent vascular access for dialysis, among U.S. patients initiating treatment for end-stage renal disease attributed to lupus nephritis, 7/1/05-9/30/11. LN, lupus nephritis; ESRD, end-stage renal disease

LN, lupus nephritis; ESRD, end-stage renal disease; HD, hemodialysis.

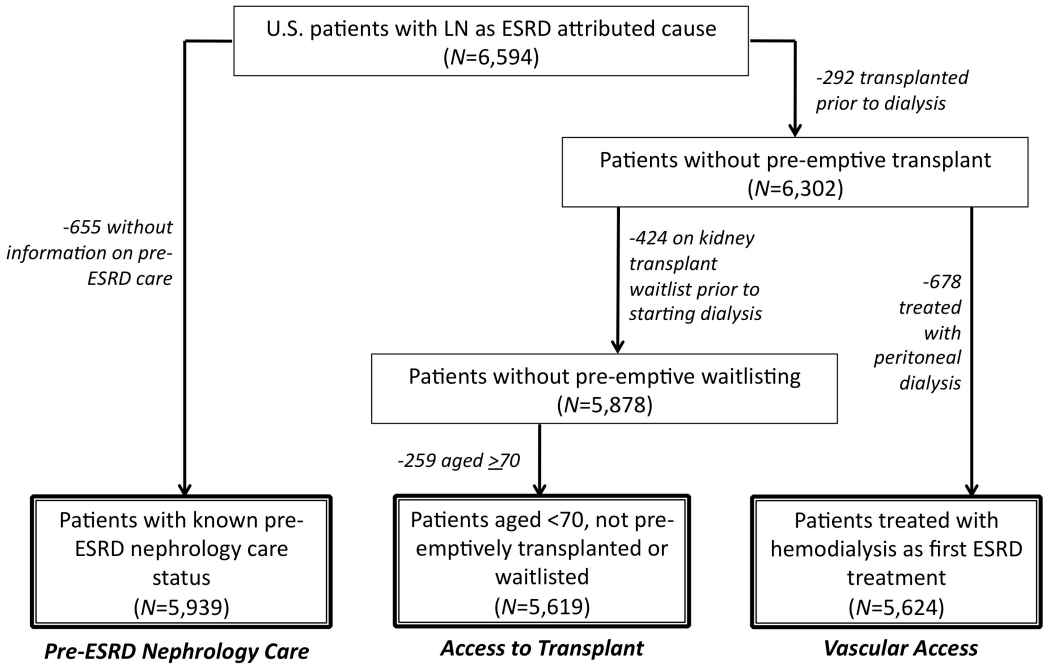
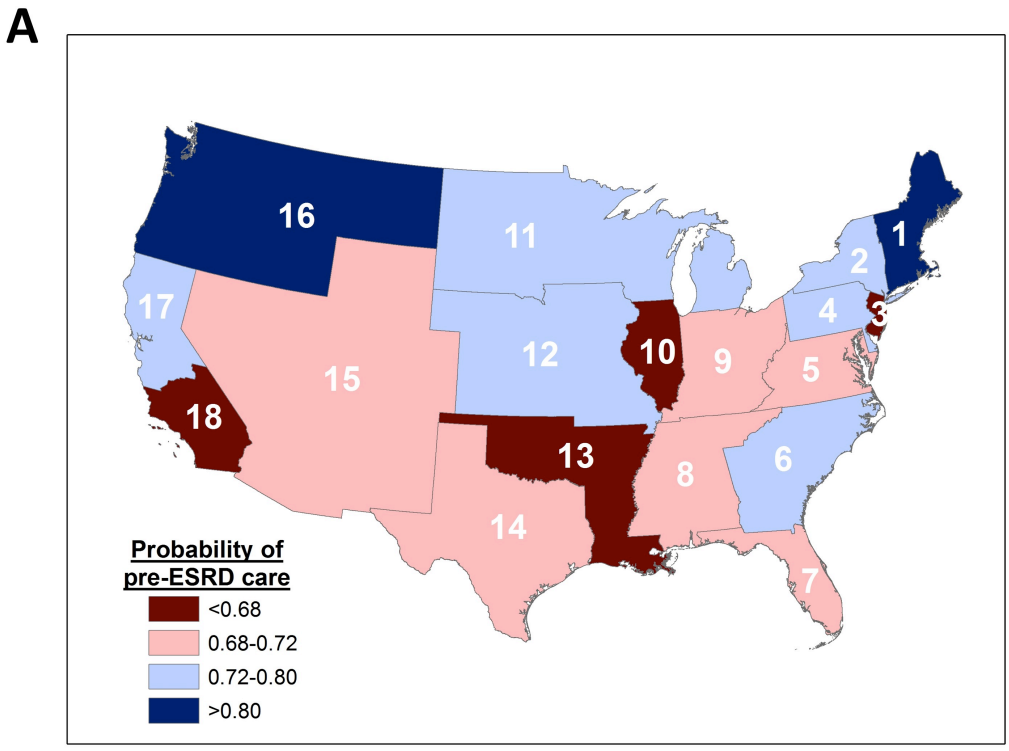
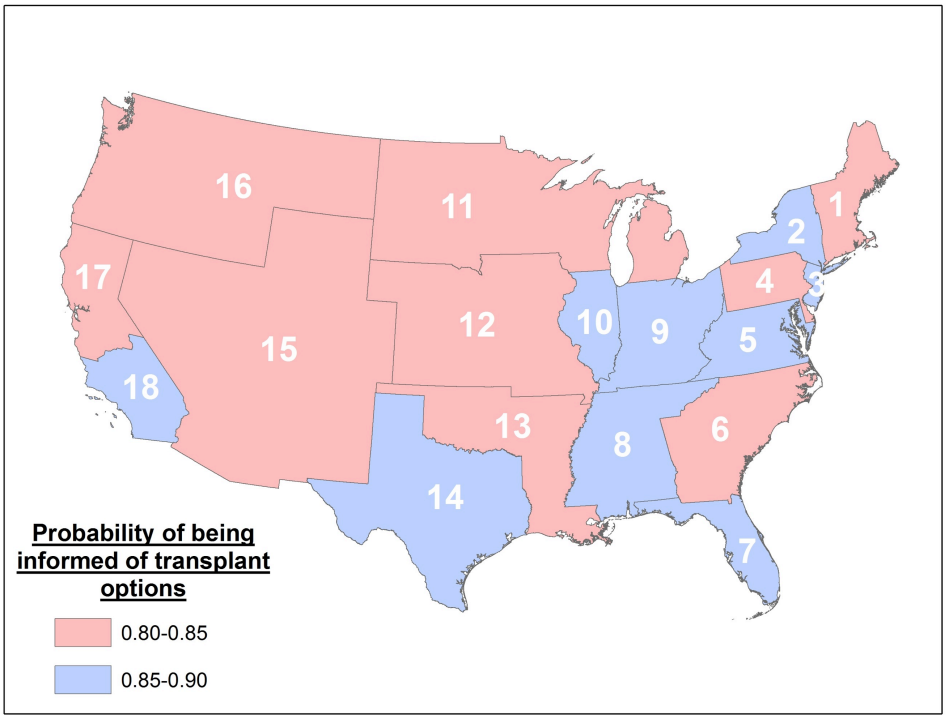


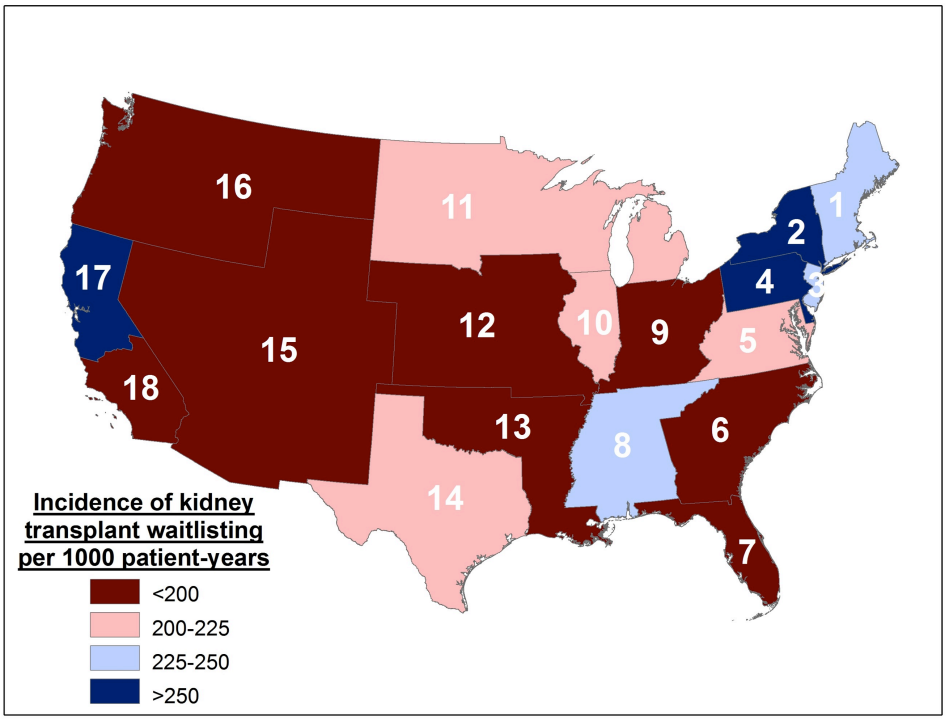
Figure 5.2. Age-, sex-, race/ethnicity-, and insurance-adjusted probabilities of receipt of nephrology care prior to end-stage renal disease (A); probabilities of being informed of transplant options at the start of dialysis (B); rates of placement on the kidney transplant (C); and probabilities of a permanent vascular access used or in place at first dialysis (D), by U.S. regions defined by Centers for Medicare & Medicaid networks, among U.S. patients initiating treatment for end-stage renal disease attributed to lupus nephritis, 7/1/05-9/30/11



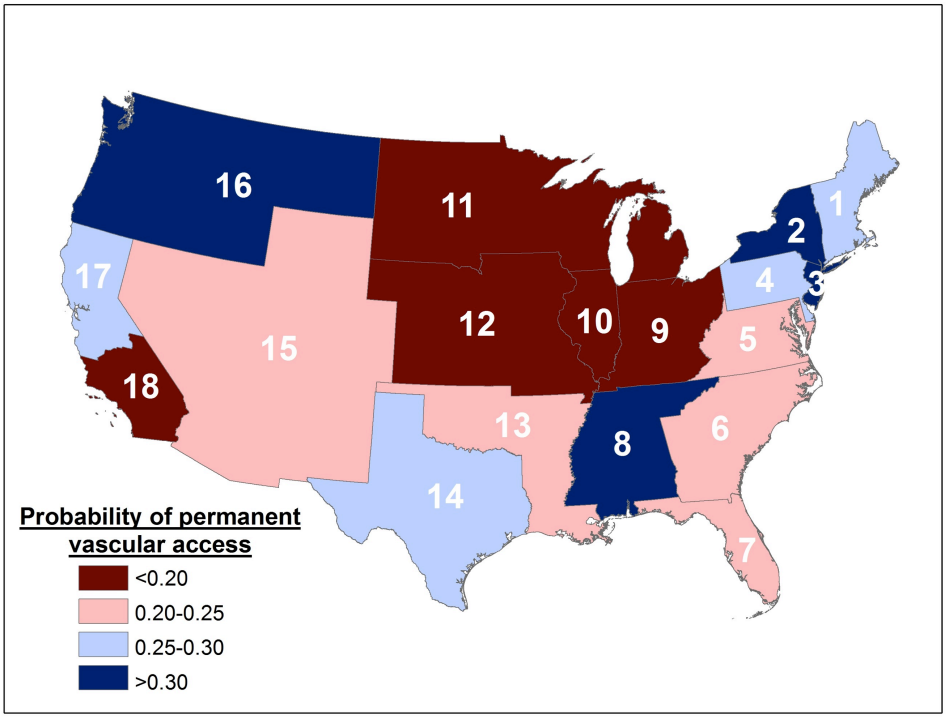
B


16
11
2
1
17
4
3
12
10
9
15
5
18
13
8
6
14
7
Probability of being informed of transplant options
0.80-0.85
0.85-0.90

C


16
11
2
1
17
4
3
12
10
9
15
5
18
13
8
6
14
7
Incidence of kidney transplant waitlisting per 1000 patient-years
<200
200-225
225-250
>250

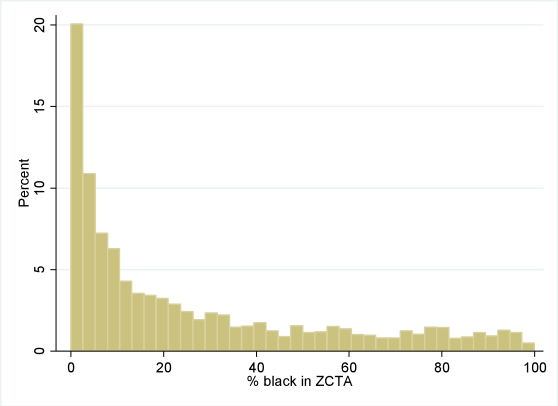
D

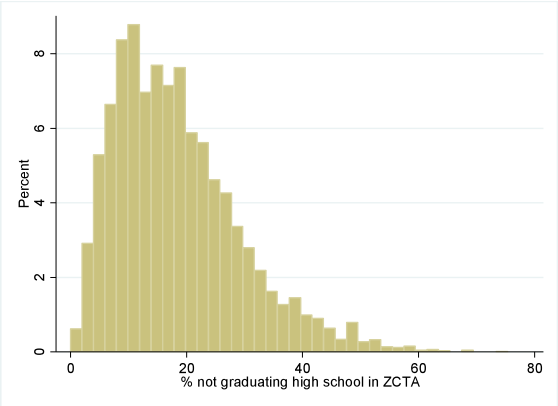

16
11
2
1
17
4
3
12
10
9
5
15
18
13
8
6
14
7
Probability of permanent vascular access
<0.20
0.20-0.25
0.25-0.30
>0.30

5.9 Supplementary Tables and Figures

Figure 5.3. Distributions of zip code tabulation area (ZCTA)-level measures

All of the variables are right-skewed and median cutoffs were used in analysis.





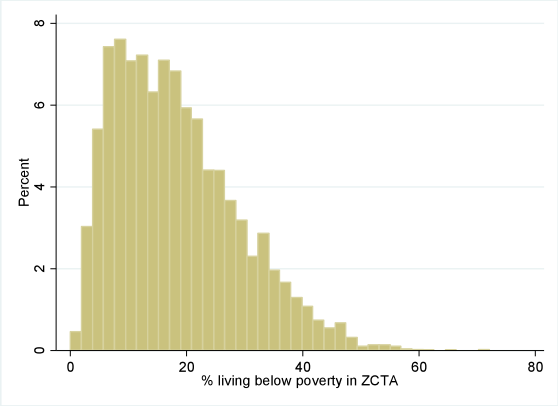


Table 5.5. Distribution of dates of start of end-stage renal disease treatment

Percentile	Date of ESRD start
Minimum	7/1/05
10%	1/23/06
25%	12/29/06
50%	6/23/08
75%	1/8/10
90%	1/10/11
Maximum	9/21/11

Zip code is determined from residence at start of end-stage renal disease treatment. American Community Survey data cover 2007-2011, when approximately three-quarters of patients started treatment.

Table 5.6. Clustering of patients within zip code tabulation areas

No. of LN-ESRD patients with transplant living in zip code	No. of zip codes
1	3061
2	810
3	298
4	119
5	40
6	24
7	14
8	4
9	5*
10	1**
11	1***

*Zip code 10029 (Manhattan, NY), 19124 (Philadelphia, PA), 33313 (Ft. Lauderdale, FL), 60619 (Chicago/Grand Crossing, IL), 60649 (Chicago, IL).
**Zip code 11212 (Brooklyn, NY).
***Zip code 30058 (Lithonia, GA).

Table 5.7. Percentage of study patients dying in the first year of end-stage renal disease treatment, by characteristic

Exposure:	**No. (%) dying in first year**	***P* (chi-square)**
Total	689/6594 (10.5%)	---
Race/ethnicity		*<0.001*
White	221/1631 (13.6%)	
Black	356/3277 (10.9%)	
Hispanic	74/1167 (6.3%)	
Other	38/519 (7.3%)	
Insurance		*<0.001*
Private	218/2463 (8.9%)	
Medicaid	231/2161 (10.7%)	
Other	176/1211 (14.5%)	
None	64/759 (8.4%)	
% black in ZCTA		
Above median (14.1%)	341/3224 (10.6%)	*0.680*
At or below median	331/3225 (10.3%)	
% HS dropouts in ZCTA		
Above median (16.9%)	347/3224 (10.8%)	*0.368*
At or below median	325/3225 (10.1%)	
% living in poverty in ZCTA		*0.100*
Above median (16.7%)	356/3222 (11.1%)	
At or below median	316/3226 (9.8%)	

HS, high school; ZCTA, zip code tabulation area.

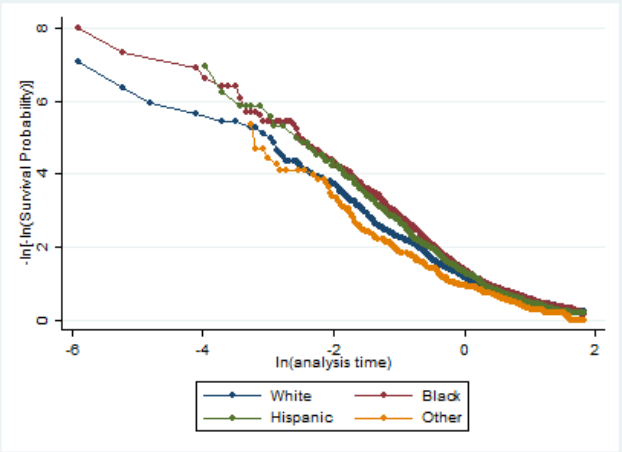
Table 5.8. Crude associations between sociodemographic exposures and ordered categories of pre-ESRD care

Exposure	**Crude OR (95%) for pre-ESRD care** by **ordinal logistic regression**			
	Per each greater category of duration	**<6 months vs. none**	**6-12 vs. <6 months**	**>12 vs. 6-12 months**
Race/ethnicity (*n*=5939)				
White	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Black	0.71 (0.63-0.79)	0.67 (0.54-0.82)	1.33 (1.08-1.65)	0.66 (0.56-0.79)
Hispanic	0.68 (0.59-0.79)	0.56 (0.43-0.73)	1.44 (1.09-1.91)	0.69 (0.55-0.86)
Other	0.91 (0.76-1.10)	0.98 (0.71-1.37)	0.88 (0.62-1.25)	1.03 (0.77-1.37)
*P (proportional odds)**	*0.38/0.36*			
Insurance (*n*=5939)				
Private	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Medicaid	0.68 (0.60-0.75)	0.67 (0.55-0.82)	1.07 (0.87-1.31)	0.77 (0.65-0.90)
Other	0.84 (0.74-0.96)	0.76 (0.60-0.97)	1.03 (0.80-1.32)	0.96 (0.79-1.16)
None	0.31 (0.26-0.36)	0.26 (0.19-0.35)	1.28 (0.91-1.80)	0.63 (0.48-0.82)
*P (proportional odds)**	*<0.001/<0.001*			
% black in zip code (*n*=5810)				
Above median (14.1%)	0.83 (0.75-0.91)	0.78 (0.66-0.93)	1.17 (0.98-1.39)	0.82 (0.71-0.94)
At or below median	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
*P (proportional odds)**	*0.04/0.04*			
% non-HS grads in zip code (*n*=5810)				
Above median (16.9%)	0.78 (0.71-0.86)	0.72 (0.60-0.85)	1.31 (1.10-1.57)	0.72 (0.63-0.83)
At or below median	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
*P (proportional odds)**	*<0.001/<0.001*			
% living in poverty in zip code (*n*=5809)				
Above median (16.7%)	0.77 (0.71-0.85)	0.66 (0.56-0.78)	1.27 (1.07-1.52)	0.80 (0.69-0.92)
At or below median	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
*P (proportional odds)**	*<0.001/<0.001*			

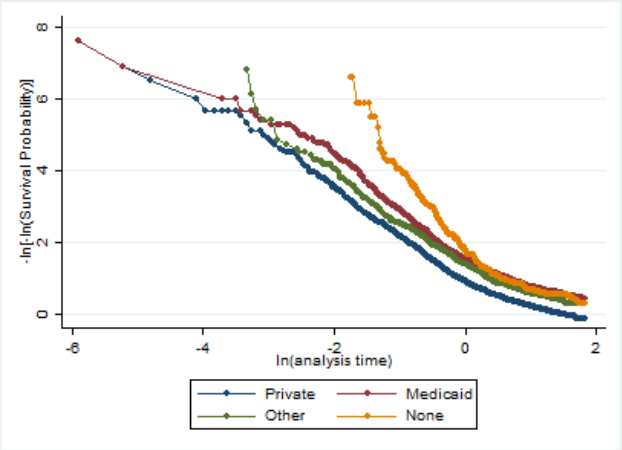
*By likelihood ratio/Brant test. Only dichotomous outcomes were used in the analysis due to the violations of the proportional odds assumption, as well as previous evidence that duration of pre-ESRD care on the CMS-2728 might not be valid.[132]

Figure 5.4. Log-log plots for time to waitlisting by study exposures

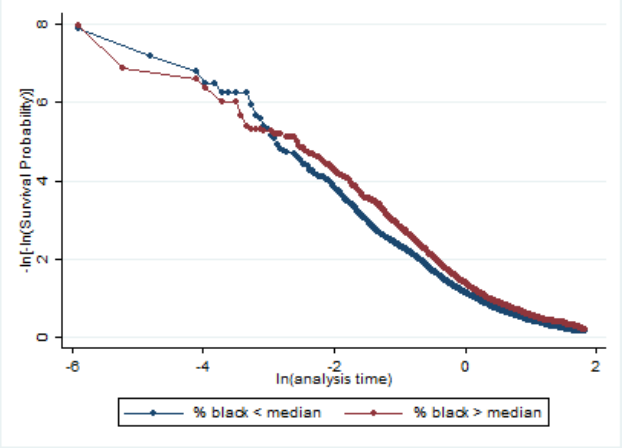
A. Race



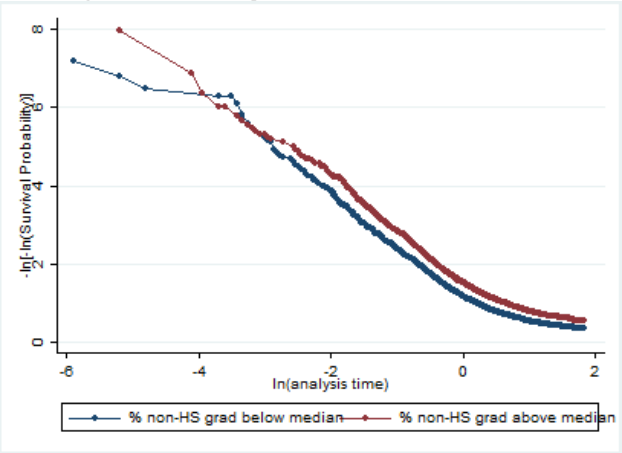
B. Insurance



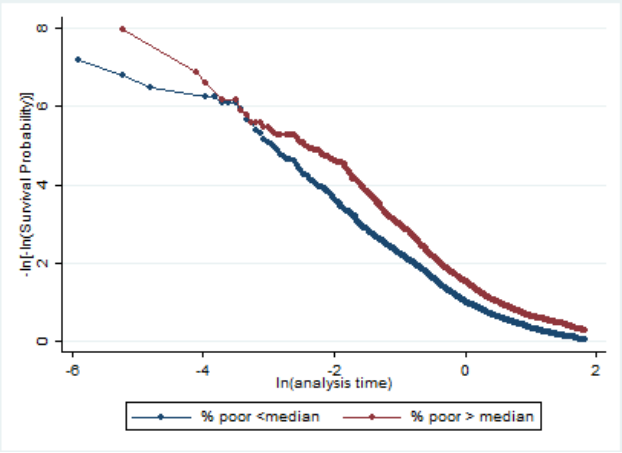
C. % black



D. % high school dropouts



E. % poor



6. Aim 3: Association of Time to Kidney Transplantation with Graft Failure among U.S. Patients with End-Stage Renal Disease Due to Lupus Nephritis

6.1 Manuscript Information

Citation: Plantinga LC**,** Patzer RE, Drenkard C, Kramer MR, Klein M, Lim SS, McClellan WM, Pastan SO. Association of time to kidney transplantation with graft failure among U.S. patients with end-stage renal disease due to lupus nephritis. Arthritis Care Res. 2014: in press.[163]

Title: Association of Time to Kidney Transplantation with Graft Failure among U.S. Patients with End-Stage Renal Disease Due to Lupus Nephritis

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6.2 Abstract

Objective: Providers recommend waiting to transplant patients with end-stage renal disease (ESRD) secondary to lupus nephritis (LN), to allow for quiescence of systemic lupus erythematosus (SLE)-related immune activity. However, these recommendations are not standardized, and we sought to examine whether duration of time to transplant was associated with risk of graft failure in U.S. LN-ESRD patients. **Methods:** Using national ESRD surveillance data (United States Renal Data System), we identified 4743 U.S. patients with LN-ESRD who received a first transplant on or after 1/1/00 (follow-up through 9/30/11). The association of wait time (time from ESRD start to transplant) with graft failure was assessed with Cox proportional hazards models, with splines of the exposure to allow for non-linearity of the association and with adjustment for potential confounding demographic, clinical, and transplant factors. **Results:** White LN-ESRD patients who were transplanted later (vs. <3 months on dialysis) were at increased risk of graft failure [adjusted HR (95% confidence interval): 3-12 months, 1.23 (0.93-1.63); 12-24 months, 1.37 (0.92-2.06); 24-36 months, 1.34 (0.92-1.97); and >36 months, 1.98 (1.31-2.99)]. However, no such association was seen among black recipients [3-12 months, 1.07 (0.79-1.45); 12-24 months, 1.01 (0.64-1.60); 24-36 months, 0.78 (0.51-1.18); and >36 months, 0.74 (0.48-1.13)]. **Conclusion:** While future studies are needed to

examine the potential confounding effect of clinically recognized SLE activity on the observed associations, these results suggest that longer wait times to transplant may be associated with equivalent or worse, not better, graft outcomes among LN-ESRD patients.

6.3 Introduction

Kidney transplantation has long been considered a viable option for most patients with end-stage renal disease (ESRD) due to systemic lupus erythematosus (SLE) and associated lupus nephritis (LN).[107] However, many U.S. providers suggest waiting to transplant patients until SLE is quiescent, as indicated by clinical signs such as low steroid requirement and normal complement levels, and rheumatologists and nephrologists often suggest waiting 3 months[1,111] to 1 year,[14,164] respectively, after the start of ESRD, to allow for this quiescence. These recommendations—which appear to be based upon weak and contradictory evidence of patterns of immune activity in LN-ESRD patients[164]—are not standard and conflict with evidence from the overall ESRD population, in whom longer duration of ESRD prior to transplant is associated with worse transplantation outcomes.[15] If these recommendations to wait are not associated with improved graft outcomes, transplantation in LN-ESRD patients may often be delayed unnecessarily, potentially leading to fewer transplantations or worse outcomes. Further, such consequences may be worse for certain subgroups, such as poor[117-119] and black[119] patients, who generally have worse graft outcomes than their wealthier and white counterparts.

A recent single-center study of Taiwanese LN-ESRD patients challenges recommendations for delaying transplantation, with findings suggesting that patients with longer dialysis time prior to transplant had worse graft outcomes.[114] To our knowledge, there is no similar evidence addressing whether longer time to transplant is associated with worse kidney transplant outcomes among U.S. LN-ESRD patients. Further, the degree to which these associations may be modified by sociodemographic characteristics is not known. We address these questions using national surveillance data on ESRD patients to estimate the association of time from start of ESRD to kidney transplant with subsequent graft failure in U.S. LN-ESRD patients and to examine whether sociodemographic factors modify these associations.

6.4. Patients and Methods

6.4.1. Study population and data sources. We examined U.S. patients with LN-ESRD who received a kidney transplant on or after 1/1/00 (follow-up through 9/30/11) using United States Renal Data System (USRDS) data.[39] Use of these data, which include administrative data supplied by the Centers for Medicare & Medicaid Services (CMS) and the United Network for Organ Sharing (UNOS) on all U.S. patients treated for ESRD, was approved by the Emory Institutional Review Board. Follow-up in the USRDS is nearly complete due to universal coverage of ESRD-related services.[39] We obtained primary attributed cause of ESRD, sociodemographics, and clinical factors from the CMS Medical Evidence Form (CMS-2728), completed on all incident ESRD patients. LN-ESRD was defined by a primary attributed cause of ESRD of secondary glomerulonephritis due to SLE on the CMS-2728 (ICD-9 code = 710.0). We obtained

transplant and donor characteristics from UNOS. Census 2000 data on characteristics of the residential neighborhood, as defined by patient 5-digit ZIP code tabulation area (ZCTA), were obtained from the Minnesota Population Center[138] and linked by patient ZIP code to the USRDS data. Of the 4786 U.S. LN-ESRD patients receiving a first transplant on or after 1/1/00, 43 were excluded due to missing race/ethnicity, leaving 4743 for descriptive analyses (99.1% of available cases), and an additional 463 were excluded from models due to missing covariates of interest, leaving 4280 (89.4% of available cases) in the final models.

6.4.2. Study variables

6.4.2.1.Wait time to transplant: Our exposure was the wait time to transplant, defined as time on dialysis prior to receiving a first transplant (date of first kidney transplant – date of first ESRD service). Because of *a priori* assumptions about the non-linearity of the association of the exposure with graft failure,[1,14,111,164] wait time to transplant was examined based on categories by proposed rheumatology and nephrology cutoffs (<3, 3-12, 12-24, 24-36, and ≥36 months) as well as by splines (see ***Statistical Analysis***).

6.4.2.2. Time to graft failure: Our outcome was time from transplant to graft failure (return to dialysis, receipt of a second kidney transplant, or death), defined as: (date of graft failure or censoring) – (date of transplant). Patients who did not have a graft failure in the observed study period were censored at the last date of follow-up (9/30/11).

6.4.2.3. Other variables: Sociodemographics of interest included age, sex, race/ethnicity, and insurance prior to ESRD (from the CMS-2728). Due to the relative lack of information at the individual level on socioeconomic status (SES) and the potential for neighborhood effects independent of individual SES, we also examined the percentage of residents reporting black race, the percentage of households living below 100% of the federal poverty threshold, and the percentage of residents aged ≥25 without a high school degree or equivalent in the patient's residential ZCTA. Access to pre-ESRD care was determined by whether patients saw a nephrologist prior to starting ESRD treatment, from the CMS-2728. Smoking, BMI, comorbid conditions, and serum albumin and hemoglobin at the start of ESRD were also obtained from the CMS-2728. Recipient blood group, recipient peak panel reactive antibody (PRA) status, donor type (living vs. deceased), donor age, number of human leukocyte antigen (HLA) mismatches between donor and recipient, graft cold ischemia time, and occurrence of delayed graft function (defined as dialysis treatment in the week following transplantation) were obtained from UNOS.

6.4.3. Statistical analysis. Patient characteristics were summarized overall and by categories of time to transplant, and Kaplan-Meier curves of time to graft failure by time to transplant were constructed. Scatter plots of crude graft failure risk showed a potential non-linear association of time to transplant with graft failure, and statistically significant departures from linearity were seen ($P<0.001$, $P=0.32$, and $P=0.005$ for overall, black, and white patients, respectively). Thus, Cox proportional hazards models with time to transplant parameterized as a restricted cubic spline with five knots placed at Harrell's

percentiles[165] were used to graph continuous, potentially non-linear functions of hazard ratios (HRs) for graft failure, as well as estimate HRs[166] at the medians of the intervals of interest (<3, 3-12, 12-24, 24-36, and ≥36 months). Those factors we found to be associated with both time to transplant and time to graft failure and were not thought *a priori* to be mediators of the association (*e.g.*, delayed graft function) were considered potential confounders. Potential effect modification by individual race and insurance and by neighborhood composition of race, poverty, and education was tested using pairwise *z* tests of log(HR) values. Those variables without significant missing data (*e.g.*, peak PRA) and that resulted in a ≥10% change in the estimate of the association of wait time to transplant with time to graft failure—after backward elimination of all potential confounders that did not change the estimate by at least 10% when removed—were included in the full model. Multilevel models with clustering at the neighborhood level were not necessary because 93% of neighborhoods (ZCTAs) included in this analysis had only one (77%) or two (16%) cases. Stata v. 13 (StataCorp, College Station, TX) was used for all analyses.

We examined the robustness of our results in several sensitivity analyses. First, models additionally adjusting for peak PRA and for pre-ESRD care (available 2005+ only)—as well as albumin, additional transplant factors, and propensity for early transplantation—were used to examine the effect of these potentially important confounders on our results. Propensity for early kidney transplantation (within <3 months vs. ≥3 months) was calculated from logistic models with adjustment for the same predictors used in the full Cox models. Because graft failures within 30 days might represent technical failures of

the transplant surgery, analyses excluding these observations were performed. Analyses of graft failures excluding death and of patient death were also performed for comparison. While not an *a priori* effect modification of interest, we ran stratified models to examine whether the observed effects differed by donor type. Because disease course, wait times, and outcomes may differ for children vs. adults, we adjusted for pediatric status in addition to age. Finally, results using simple categorization (without allowing for a non-linear, continuous association) were estimated and compared to the main results.

6.5 Results

6.5.1. Characteristics of the study population. There were 1239 graft failures among 4743 transplant recipients with LN-ESRD, contributing a total of 21,507 person-years (median follow-up, 4 years). In general, the percentage of recipients who experienced graft failure over study follow-up was higher among those who waited longer periods on dialysis (25% for 3-12 months and 27-30% for >12 months) compared to those who were transplanted <3 months after start of dialysis (16%; Table 1). The mean age of incident ESRD was 35 years; 81% were female, 41% were black, and 25% had Medicaid (Table 1). Patients with longer wait times to transplant were generally younger, more likely to be black, to have Medicaid coverage, and to live in areas with higher proportions black, poor, and uneducated residents. They were also less likely to have pre-ESRD care and have a living donor; and had greater peak PRA, lower albumin and hemoglobin levels, and greater numbers of HLA mismatches, relative to those who waited shorter periods for their transplants (Table 1). Overall, nonparametric tests for trend across categories gave similar *P* values to ANOVA and χ^2 tests (data not shown). Patients excluded from the

models below due to missing covariates were not different from the overall population, including by race (38.0% vs. 40.9% black; *P*=0.13), except that those excluded were more likely to experience graft failure (32.2% vs. 25.5%; *P*=0.002) and were less likely to have a living donor (37.1% vs. 45.4%; *P*=0.001) or have hypertension (67.6% vs. 76.2%; *P*<0.001).

6.5.2. Association of wait time to transplant with graft failure

6.5.2.1. Crude analyses: In Kaplan-Meier analyses by categorized time to transplant, LN-ESRD patients whose wait time to transplant was <3 months had longer times to graft failure than those whose wait times were ≥3 months (Figure 1A). Race-stratified analyses (Figure 1, B and C) suggested that this overall pattern held among whites (Figure 1C) but not among blacks (Figure 1B).

6.5.2.2. Effect modification: Interactions of wait time to transplant with black vs. white race in full models were statistically significant in the 24- to 36-month and >36-month intervals of wait time to transplant (*P*=0.029 and <0.001, respectively) but not in earlier intervals (*P*=0.15 and 0.10 in 3-12 and 12-24 vs. <3 months). However, there were no statistically significant interactions of wait time to transplant with Medicaid vs. private insurance or high vs. low neighborhood SES indicators, with adjustment. Thus, further analyses were shown overall and stratified by black vs. white race only.

6.5.2.3. Adjusted analyses: In the overall LN-ESRD population, wait times to transplant of 3-12 months and >12 months were associated with about 1.5- and 2-fold increased risk

of graft failure, respectively, relative to <3 months of wait time, in crude analyses (Table 2). While these associations were attenuated with adjustment, particularly for age and race, even with full adjustment, wait times of 3-12 or 12-24 months were associated with 25% and 37% increased risk of graft failure, respectively, relative to wait times of <3 months. Similar associations and patterns were seen among whites, except that wait times >36 months were associated with nearly 2-fold risk of graft failure with full adjustment (Table 2). Among blacks, crude associations showed elevated risks that were not statistically significant among those with longer time to transplant; with adjustment, longer wait time was not associated with graft failure and even appeared (among those waiting >24 months) possibly protective against graft failure, relative to wait times <3 months (Table 2). Plots indicate a fairly steep increase in the adjusted HR of graft failure for wait time to transplant up to ~20 months in the overall population, with a subsequent slight decline and a slight increase after ~40 months (Figure 2A). Among blacks, the HR is maximized at ~12 months, with wide confidence intervals containing the null value at all time points (Figure 2B), whereas whites show a steadily increasing pattern (Figure 2C). It is worth noting that, with adjustment for age, insurance, hemoglobin, and donor type, blacks in this population remained at >40% greater risk of graft failure overall compared to whites (HR=1.41, 95% confidence interval, 1.21-1.63).

6.5.2.4. Sensitivity analyses: With additional adjustment for PRA, we found that longer wait time to transplant was associated with higher risk of graft failure among whites but lower risk among blacks, although these associations were not statistically significant for either group, except for >36 vs. <3 months in whites (Table 3). Adjustment for albumin

did not change the results (data not shown). Adjustment for pre-ESRD care (among those incident in 2005 or later) showed similar patterns of results to the primary analyses but with much less precision due to the reduced sample size, particularly among the groups with longer wait times. Adjustment for delayed graft function (a potential mediator), donor characteristics (age and race), and HLA mismatches did not change results, nor did adjustment for propensity to receive an early transplant (data not shown). Adjustment for proxies of secular trends in treatment, transplant year and treatment with mycophenolate mofetil (vs. azathioprine or other immunosuppressants), also did not change the results (data not shown). Excluding graft failures within 30 days and excluding deaths with functioning grafts from the graft failure definition (309/1239 graft failures) did not substantially change the results (Table 3). Risk of mortality after transplant did not differ by wait time to transplant, overall or stratified by race (data not shown). Analyses stratified by donor type showed that the effects seen in the primary analyses were stronger among those with living vs. deceased donors; additionally, the protective effects of longer wait time suggested among blacks in the primary analyses were statistically significant among those with deceased donors (Table 3). However, numbers of deceased donors in the referent groups were small (n=21 and 68 for blacks and whites, respectively), and these patients were older (48.6 and 50.4 years) and more likely to have private insurance (81.0% and 63.2%). Finally, indicators for pediatric status did not substantially change overall results, and associations from the primary analyses using restricted cubic splines of wait time to transplant were similar to those seen in analyses with simple categorization of wait time (data not shown).

6.6 Discussion

In this national study of kidney transplant recipients with ESRD secondary to LN, we found that longer wait times to transplant were not associated with lower risk of graft failure among these patients, as might be expected from current clinical recommendations.[1,14,111,164] Rather, we found that longer time on dialysis was generally associated with increased risk of graft failure among LN-ESRD patients, relative to those patients who were transplanted in the first 3 months of ESRD treatment, although results were not always statistically significant. Our effect estimates were similar to those seen in the overall ESRD population, in whom wait times to transplantation of >6 months and >1 year, relative to 0-15 days, have been shown to be associated with approximately 25% and 40% increased graft failure risk.[15] In our study, relative to waiting <3 months, waiting ≥3 years for kidney transplantation was associated with a 2-fold risk of graft failure among white LN-ESRD patients, whereas longer wait time was generally associated with similar risk of graft failure among black LN-ESRD patients. Even in the fully adjusted models, where there was a non-statistically significant suggestion of a protective effect among black LN-ESRD patients whose wait times were ≥2 years, we did not see increased risk of graft failure among those transplanted early. While the confounding effect of SLE activity at the start of ESRD cannot be fully accounted for with adjustment for markers such as albumin, hemoglobin, and peak PRA, nevertheless these results provide, to our knowledge, a first examination of the association between wait time to transplant and graft outcomes in a nationally representative population of U.S. LN-ESRD patients that can be used to generate hypotheses and guide future study of this issue.

Patients with LN-ESRD could, in many ways, be considered ideal kidney transplant candidates, due to their relative youth (median age, 38),[39] lower likelihood of malignancies or cardiovascular contraindications,[98] close medical supervision and potentially better pre-ESRD management by multiple providers (including rheumatologists and nephrologists),[97] and demonstrated adherence to complex immunosuppression regimens.[97,98] These patients may also be more likely to identify living donors; we found that transplants from living donors were overrepresented in these recipients with LN-ESRD (45%, compared to 33% of all U.S. transplant recipients in 2011).[39]

There are also unique barriers to transplant among LN-ESRD patients, such as the potential for post-transplant recurrence of LN and subsequent development of glomerulonephritis in the graft, making SLE a potential contraindication to transplantation.[167] However, in a recent national study of transplant recipients with SLE (n=6850),[13] only 2% were reported to have recurrent LN, and only 7% of all graft failures in this population were attributed to recurrent LN.[13] Further, graft and patient survival are comparable among U.S. patients with ESRD due to LN vs. other causes.[108,109]

Despite the increasing evidence of likely equivalent transplant outcomes among LN-ESRD patients,[13,108,109] the incidence of kidney transplantation is not increasing among LN-ESRD patients.[4] Greater demand on the organ supply from the growing overall ESRD population as well as CMS policies that currently limit medication coverage

among younger patients who qualify for Medicare based solely on ESRD status[99] may contribute to this observed discrepancy. However, lingering provider beliefs about the necessity of waiting periods to establish relative quiescence of SLE in the setting of ESRD prior to kidney transplantation[111,164] may also play a role.

Our results suggest U.S. recommendations for transplantation in LN-ESRD[1,14,111,164] may not align with evidence from the target population. To our knowledge, no studies have reported the association of graft failure with duration of wait time to transplant in LN-ESRD patients in the United States, or in Canada or Europe, where renal transplantation guidelines similarly recommend waiting periods prior to transplantation for LN-ESRD patients.[115,116] Chung *et al*.[114] recently examined this issue in a single-center study (n=31) in Taiwan and found a slightly increased risk for graft dysfunction and equivalent risk for graft failure with longer wait times, although their results were not statistically significant.

Importantly for the U.S. population, we found a potential effect modification by race, in that longer wait times were associated with greater risk of graft failure among white but not black kidney transplant recipients with LN-ESRD and that there was a possible protective effect of wait times of $\geq$2 years among blacks. This observation could be due to unexplained differences in disease pathology and course between white and black LN-ESRD patients. We found that early transplant, possibly indicating SLE quiescence prior to the need for renal replacement therapy, was more common among whites than blacks. Black ESRD patients treated with dialysis have long been known to have a survival

advantage over their white counterparts,[69,70] although this pattern may be reversed in younger ESRD patients.[168] Social differences associated with race that affect access to care could also play a role, although our failure to find evidence of effect modification by insurance status, poverty, or education does not support this explanation. Unavoidable bias inherent in the study design, namely index event bias—which occurs when examined risk factors (here, longer wait time to transplant) are not seen in the unselected (non-transplanted) population[169]—may also explain the results. It is also possible that the overwhelming effect of race on graft failure in the LN-ESRD population masks any effect of prolonged wait time in this subpopulation, although our estimates and estimates in another national U.S. study suggested only a 1.4-fold increased risk of graft failure for blacks vs. whites.[119]

Confounding due to differences in unmeasured SLE activity (confounding by indication) may be the most serious threat to the internal validity of our findings. Although we tried to control for potential proxies (hemoglobin, albumin, and peak PRA) and for the propensity to be transplanted early, the USRDS does not have information on SLE-specific disease activity prior to transplantation and during the first year of dialysis, which could have been associated with decisions to delay transplantation for some patients and may have also influenced graft outcomes. However, in their Taiwanese population, Chung *et al.*[114] found that pre-transplant SLE activity was not associated with graft dysfunction or failure. Future studies in U.S. SLE cohorts or registries that collect information on SLE activity could potentially examine whether a similar lack of effect of SLE activity exists in the U.S. kidney transplant recipients with SLE.

Other residual confounders may have influenced our results. Receipt of a kidney graft has long been known to be differential by race in the overall ESRD population.[170,171] This could lead to important, unobserved differences in the white and black LN-ESRD kidney transplant recipient populations. However, we found that 41% of transplant recipients with LN-ESRD were black, compared to 45% of all LN-ESRD patients,[39] suggesting receipt, if not timing, of transplant may not be differential by race among U.S. LN-ESRD patients. Unmeasured provider characteristics that are associated with wait times could also be associated with graft outcomes.

In addition to the limitations noted above, the potentially low sensitivity of attributed ESRD cause[130] could bias our results. Additionally, our individual socioeconomic status data were limited and some misclassification due to assigning neighborhood-level characteristics to individuals, particularly using ZCTAs rather than census tract or blocks,[131] is likely. However, our study also has several strengths, including the capture of all U.S. patients who receive kidney transplants, limited loss to follow-up with no competing risks, and limited potential for selection bias due to excluded data.

In summary, we found that, among U.S. LN-ESRD patients receiving a kidney transplant, waiting 3 or 12 months on dialysis treatment was generally associated with equal or even greater risk of graft failure compared to being transplanted within 3 months, which is not expected given current clinical recommendations. As in the general ESRD population, waiting to transplant may not advantage LN-ESRD kidney transplant recipients in terms

of graft outcomes. Even in the case of apparently equivalent graft outcomes among black LN-ESRD transplant recipients, regardless of waiting time, delays in transplantation may be not only unnecessary but also detrimental to other outcomes important to this young population, particularly quality of life, perceived health status, and employment.[172] While these results should be considered hypothesis-generating due to the limitations of the data, future studies with SLE cohorts could determine whether longer wait times are associated with increased risk of graft failure, independent of SLE activity, strengthening the evidence for standardizing recommendations. Further, compared to the general ESRD population, LN-ESRD patients receive medical care by multiple providers, resulting in greater opportunities to intervene early to decrease wait time to transplant and, potentially, to improve transplant outcomes.

6.7 Acknowledgements and Financial Support

The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the U.S. government. This work was presented in part at the World Transplant Congress, held July 26-31, 2014, in San Francisco, California. R.E.P. was supported in part by grants from the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH; ULl TR000454 and KL2TR000455). R.E.P. and S.O.P are both supported in part by 1R24MD008077-01 through the National Institute on Minority Health and Health Disparities. M.R.K. is supported by the Eunice Kennedy Shriver National Institute Of Child Health & Human Development of the NIH (K01HD074726). S.S.L. and C.D.

are supported in part by the NIH (R01AR065493). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

6.8 Tables and Figures

Table 6.1. Characteristics of U.S. patients with end-stage renal disease attributed to lupus nephritis, who received a transplant (1/1/00-9/30/11), overall and by categories of time to transplant

			Time to transplant					
Characteristic	***N***	**Overall**	**0-3 months**	**3-12 months**	**12-24 months**	**24-36 months**	**>36 months**	***P****
N (%)	*4743*	---	*569 (12.0%)*	*655 (13.8%)*	*801 (16.9%)*	*643 (13.6%)*	*2075 (43.8%)*	---
Outcome								
No. (%) graft failures in category	4743	1239 (26.1%)	91 (16.0%)	163 (24.9%)	232 (29.0%)	195 (30.3%)	558 (26.9%)	*<0.001*
Individual patient factors								
Mean age (SD)	4743	35.1 (12.5)	41.7 (12.1)	35.8 (12.6)	34.0 (13.0)	34.3 (12.9)	33.6 (11.6)	*<0.001*
Sex (%)	4743							*0.22*
Female		81.2	83.8	79.5	80.0	82.9	80.9	
Male		18.8	16.2	20.5	20.0	17.1	19.1	
Race/ethnicity (%)	4743							*<0.001*
White		32.1	56.9	45.8	32.8	29.9	21.4	
Black		40.6	15.8	28.4	39.1	42.3	51.3	
Hispanic		17.2	12.7	17.9	17.9	18.0	17.8	
Other		10.1	14.6	7.9	10.2	9.8	9.5	
Insurance pre-ESRD (%)	4719							*<0.001*
Private		46.7	69.4	55.9	47.5	43.5	38.1	
Medicaid		25.0	8.3	18.5	25.2	30.8	29.9	
Other**		28.3	22.3	25.6	27.3	25.7	31.9	
Pre-ESRD care (%)***	1356							*<0.001*
Yes		85.7	97.4	87.3	78.9	79.5	82.6	
No		14.3	2.6	12.7	21.1	20.5	17.4	
Median days to waitlisting (IQR) ****	4306	278 (79,620)	-160 (-407,-55)	-86 (-23,172)	242 (114,363)	343 (176,606)	524 (240,1094)	*<0.001*
Smoking (%)	4743							*0.14*
Yes		2.5	1.4	2.1	3.0	1.7	2.9	
No		97.5	98.6	97.9	97.0	98.3	97.1	
Mean (SD) BMI	4572	25.5 (6.2)	25.3 (5.8)	25.2 (5.6)	25.3 (6.2)	25.3 (6.1)	25.7 (6.4)	*0.21*

Characteristic	*N*	Overall	Time to transplant					*P**
			0-3 months	3-12 months	12-24 months	24-36 months	>36 months	
BMI ≥35 (%)	4572							*0.02*
Yes		7.4	6.0	5.9	6.3	7.0	9.0	
No		92.6	94.0	94.1	93.7	93.0	91.0	
No. of comorbidities (%)	4743							*0.08*
0		21.0	21.1	20.6	19.9	20.4	21.8	
1		62.2	65.2	65.2	61.3	60.3	61.3	
2+		16.8	13.7	14.2	18.8	19.3	16.9	
Hypertension (%)	4743							*0.56*
Yes		75.4	76.6	76.6	76.4	75.4	74.2	
No		24.6	23.4	23.4	23.6	24.6	25.8	
CVD (%)	4743							*0.53*
Yes		11.1	11.1	10.4	12.2	12.4	10.6	
No		88.9	88.9	89.6	87.8	87.6	89.5	
Blood group (%)	4444							*<0.001*
AB		4.2	5.1	4.3	5.5	5.6	2.9	
A		32.2	38.2	34.9	36.6	31.6	28.2	
B		14.5	11.1	13.9	15.3	12.9	15.9	
O		49.1	45.7	47.0	42.7	49.9	53.0	
Peak PRA (%)	2781							*<0.001*
<20%		54.6	70.0	68.0	61.0	56.8	44.1	
20-80%		28.2	18.7	22.1	25.3	26.3	33.9	
>80%		17.2	11.3	9.9	13.6	16.9	22.0	
Mean serum albumin at ESRD start (SD)	3732	3.1 (0.8)	3.7 (0.5)	3.2 (0.8)	3.0 (0.8)	2.9 (0.8)	3.0 (0.8)	*<0.001*
Mean serum hemoglobin at ESRD start (SD)	4307	9.5 (1.9)	10.7 (1.7)	9.8 (1.9)	9.5 (1.8)	9.3 (1.9)	9.2 (1.9)	*<0.001*
Patient neighborhood factors								
Percentage black in zip code (%)	4527							*<0.001*
Above median (8.0%)		50.1	33.5	42.2	47.8	52.1	57.6	
At or below median		49.9	66.5	57.8	52.2	47.9	42.4	
Percentage non-HS grads in zip code (%)	4527							*<0.001*
Above median (16.9%)		50.0	32.2	41.8	48.3	51.1	57.9	
At or below median		50.0	67.8	58.2	51.7	48.9	42.1	
Percentage living in poverty in zip code (%)	4527							*<0.001*
Above median (11.2%)		50.1	36.4	40.7	47.7	51.7	57.4	

Characteristic	*N*	Overall	Time to transplant					*P**
			0-3 months	3-12 months	12-24 months	24-36 months	>36 months	
At or below median		49.9	63.6	59.3	52.3	48.3	42.6	
Donor/transplant factors								
Type (%)	4730							*<0.001*
Living		44.6	79.3	74.7	61.6	40.8	20.4	
Deceased		55.4	20.7	25.3	38.4	59.2	79.6	
Mean donor age (SD)	4509	36.6 (14.5)	39.4 (12.9)	38.1 (12.3)	35.9 (14.4)	35.6 (14.7)	36.0 (15.4)	*<0.001*
No. HLA mismatches (%)	4642							*<0.001*
0		11.9	16.5	16.0	13.6	12.5	8.5	
1-2		15.1	23.5	22.6	20.3	15.5	8.5	
3-4		38.5	35.9	37.8	41.1	38.7	38.4	
5-6		34.4	24.1	23.6	25.0	33.3	44.6	
Mycophenolate mofetil use	4304							*0.43*
No		15.3	16.7	10.9	16.3	17.2	15.4	
Yes		84.7	83.3	89.1	83.7	82.9	84.6	
Mean cold ischemia time, hours (SD)******	2344	18.2 (9.8)	18.2 (9.2)	17.7 (9.5)	18.8 (9.7)	17.6 (9.4)	18.3 (10.0)	*0.53*
Delayed graft function (%)	4670							*<0.001*
Yes		12.0	1.4	4.8	8.1	11.8	18.7	
No		88.0	98.6	95.2	91.9	88.2	81.3	

SD, standard deviation; ESRD, end-stage renal disease; BMI, body mass index; CVD, cardiovascular disease (includes pericarditis); PRA, panel reactive antibody; HLA, human leukocyte antigens. **P* by ANOVA (continuous variables) or chi-square (categorical variables). **Includes none, Medicare, VA, and other. ***2005+ only. ****Days from start of ESRD treatment to waitlisting; negative values indicate placement on the waitlist prior to start of ESRD treatment (pre-emptive waitlisting). *****Among transplants with deceased donors only.

Table 6.2. Crude and adjusted hazard ratios for graft failure among U.S. patients with end-stage renal disease attributed to lupus nephritis, who received a transplant (1/1/00-9/30/11), from restricted cubic splines of time to transplant

Time to transplant (months)	Median value in interval	Hazard ratio (95% CI) for graft failure at median value in interval*			
			Adjusted		
		Unadjusted	+Demographic	+Clinical	+Transplant
Overall					
<3	0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
3-12	7.92	1.51 (1.27-1.80)	1.32 (1.10-1.57)	1.28 (1.07-1.53)	1.25 (1.05-1.49)
12-24	17.15	1.95 (1.51-2.51)	1.54 (1.19-2.00)	1.47 (1.13-1.92)	1.37 (1.05-1.79)
24-36	30.11	1.89 (1.50-2.37)	1.46 (1.15-1.85)	1.39 (1.10-1.77)	1.20 (0.94-1.53)
>36	59.20	2.20 (1.76-2.76)	1.59 (1.25-2.02)	1.49 (1.17-1.90)	1.21 (0.94-1.57)
Black					
<3	0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
3-12	8.38	1.28 (0.96-1.72)	1.14 (0.84-1.54)	1.12 (0.83-1.51)	1.07 (0.79-1.45)
12-24	17.71	1.42 (0.91-2.22)	1.16 (0.73-1.82)	1.12 (0.71-1.77)	1.01 (0.64-1.60)
24-36	29.30	1.21 (0.81-1.79)	0.97 (0.65-1.46)	0.94 (0.63-1.42)	0.78 (0.51-1.18)
>36	61.01	1.21 (0.82-1.78)	0.98 (0.66-1.47)	0.94 (0.63-1.41)	0.74 (0.48-1.13)
White					
<3	0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
3-12	7.52	1.32 (1.01-1.74)	1.31 (1.00-1.72)	1.24 (0.94-1.64)	1.23 (0.93-1.63)
12-24	17.41	1.57 (1.07-2.31)	1.53 (1.04-2.27)	1.42 (0.95-2.11)	1.37 (0.92-2.06)
24-36	29.86	1.59 (1.12-2.26)	1.54 (1.08-2.21)	1.45 (1.01-2.08)	1.34 (0.92-1.97)
>36	54.99	2.52 (1.76-3.63)	2.42 (1.66-3.51)	2.16 (1.47-3.18)	1.98 (1.31-2.99)

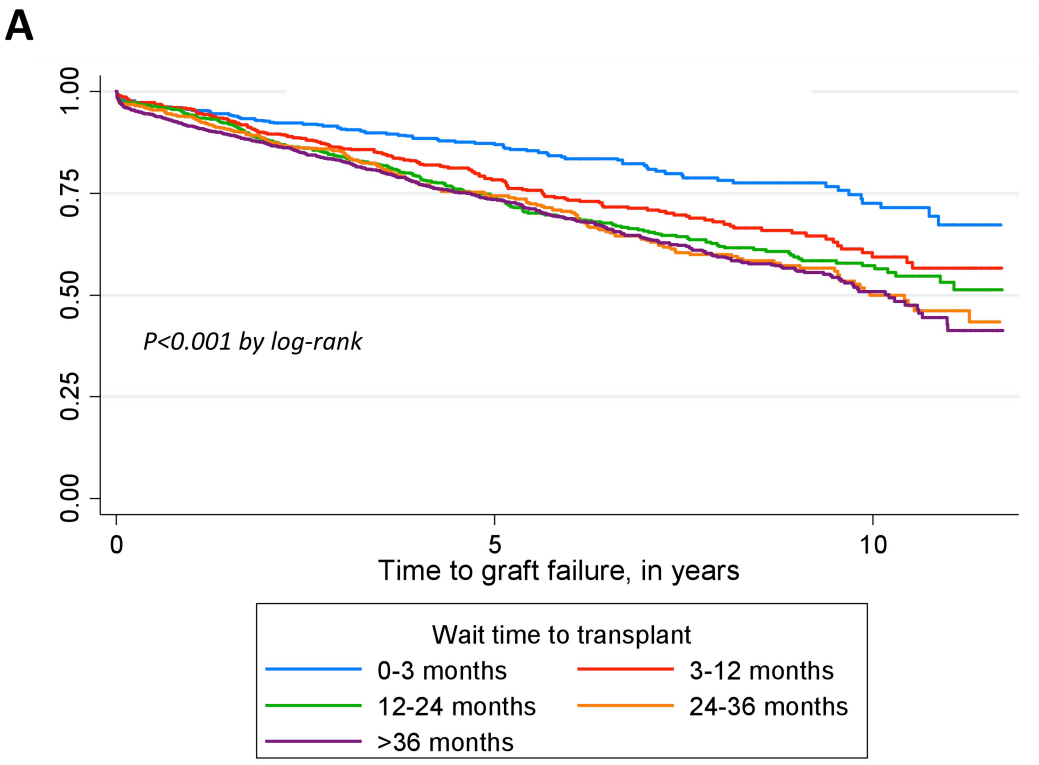
CI, confidence interval. *N*=4280, 1750, and 1354 for overall, black, and white models, respectively. Demographic = age, race (overall model only; referent group=white), and insurance at start of end-stage renal disease (referent group=Medicaid); clinical = hemoglobin at start of end-stage renal disease; transplant = donor type (referent group=living donor). *Overall median values used for race-stratified analyses for comparability of hazard ratios.

Table 6.3. Sensitivity analyses: adjusted hazard ratios among U.S. patients with end-stage renal disease attributed to lupus nephritis, who received a transplant (1/1/00-9/30/11), from restricted cubic splines of time to transplant

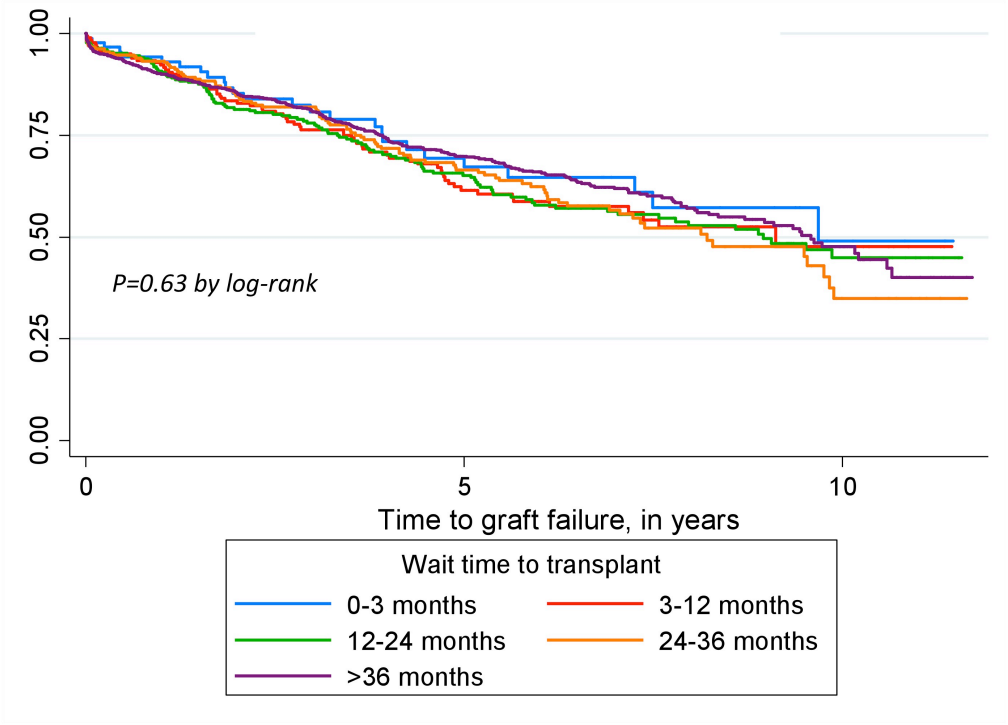
	Hazard ratio (95% CI) for graft failure at median value in interval					
					Stratified by donor type:	
Time to transplant (months)	**Adjusted for peak PRA (*N*=2442)**	**Adjusted for pre-ESRD care (2005+ only; *N*=1275)**	**Graft failures excluding deaths with functioning transplant* (*N*=4280)**	**Graft failures within 30 days excluded (*N*=4149)**	**Living (*N*=1944)**	**Deceased (*N*=2336)**
Overall						
<3	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
3-12	1.10 (0.89-1.35)	1.56 (1.08-2.25)	1.26 (1.02-1.55)	1.25 (1.05-1.49)	1.19 (0.94-1.50)	1.12 (0.85-1.49)
12-24	1.12 (0.82-1.53)	1.79 (1.05-3.05)	1.37 (1.05-1.88)	1.37 (1.05-1.79)	1.46 (1.04-2.04)	1.05 (0.69-1.62)
24-36	1.03 (0.77-1.37)	1.25 (0.72-2.16)	1.16 (0.87-1.55)	1.20 (0.94-1.53)	1.76 (1.28-2.42)	0.76 (0.52-1.11)
>36	1.09 (0.81-1.47)	1.51 (0.77-2.98)	1.07 (0.79-1.45)	1.21 (0.94-1.57)	1.27 (0.87-1.86)	0.86 (0.59-1.26)
Black						
<3	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
3-12	0.93 (0.65-1.33)	1.17 (0.68-2.00)	1.07 (0.76-1.51)	1.07 (0.79-1.45)	1.09 (0.73-1.64)	0.83 (0.52-1.33)
12-24	0.83 (0.48-1.42)	1.12 (0.51-2.43)	1.02 (0.61-1.72)	1.01 (0.64-1.60)	1.14 (0.63-2.08)	0.64 (0.31-1.34)
24-36	0.69 (0.42-1.13)	0.76 (0.35-1.64)	0.79 (0.49-1.27)	0.78 (0.51-1.18)	1.06 (0.61-1.83)	0.47 (0.24-0.91)
>36	0.68 (0.41-1.12)	0.67 (0.27-1.68)	0.67 (0.41-1.08)	0.74 (0.48-1.13)	0.70 (0.37-1.31)	0.49 (0.26-0.95)
White						
<3	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
3-12	1.15 (0.83-1.61)	1.44 (0.72-2.85)	1.20 (0.84-1.71)	1.23 (0.93-1.63)	0.99 (0.69-1.42)	1.47 (0.94-2.30)
12-24	1.23 (0.77-1.98)	1.51 (0.58-3.96)	1.26 (0.76-2.10)	1.37 (0.92-2.06)	1.26 (0.76-2.10)	1.41 (0.74-2.72)
24-36	1.21 (0.78-1.89)	1.22 (0.38-3.97)	1.12 (0.69-1.81)	1.34 (0.92-1.97)	2.29 (1.43-3.66)	0.75 (0.41-1.36)
>36	1.97 (1.21-3.21)	11.0 (2.61-46.1)	1.83 (1.11-3.04)	1.98 (1.31-2.99)	1.88 (1.05-3.35)	1.66 (0.90-3.04)

CI, confidence interval; PRA, panel reactive antibody ; ESRD, end-stage renal disease. Adjusted for age, race (overall model only; referent group=white), insurance at start of end-stage renal disease (referent group=Medicaid), hemoglobin at start of end-stage renal disease, and donor type (non-donor type-stratified models only; referent group=living donor). PRA: <20% (referent group), 20-80%, and ≥80%); pre-ESRD care: yes and no (=referent group). *Censoring 309/1239 graft failure events that were deaths with a functioning transplant.

Figure 6.1. Kaplan-Meier curves for time to graft failure among all (A), black (B), and white (C) U.S. patients with end-stage renal disease attributed to lupus nephritis, who received a transplant (1/1/00-9/30/11), by categories of time to transplant



B


1.00
0.75
0.50
0.25
0.00
P=0.63 by log-rank
0
5
10
Time to graft failure, in years
Wait time to transplant
0-3 months
3-12 months
12-24 months
24-36 months
>36 months

C

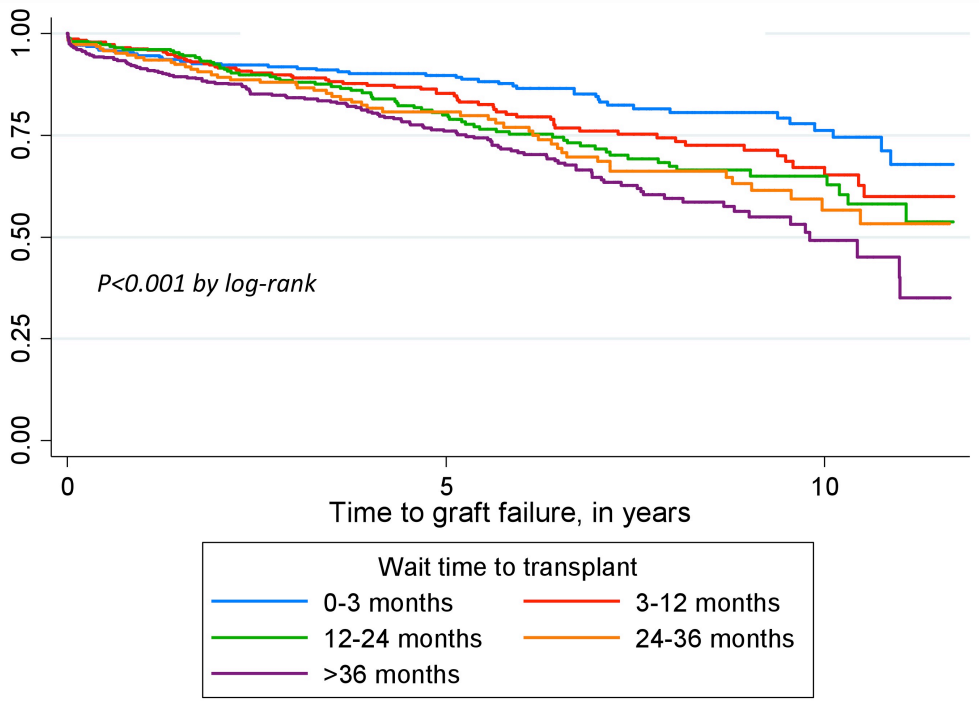
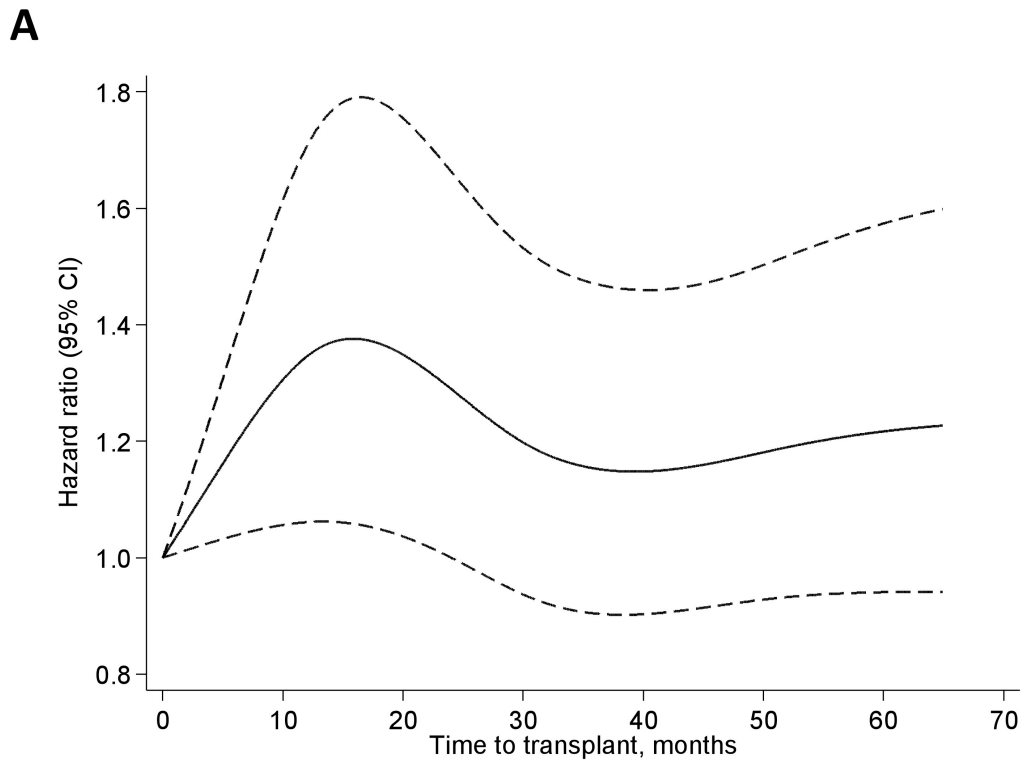
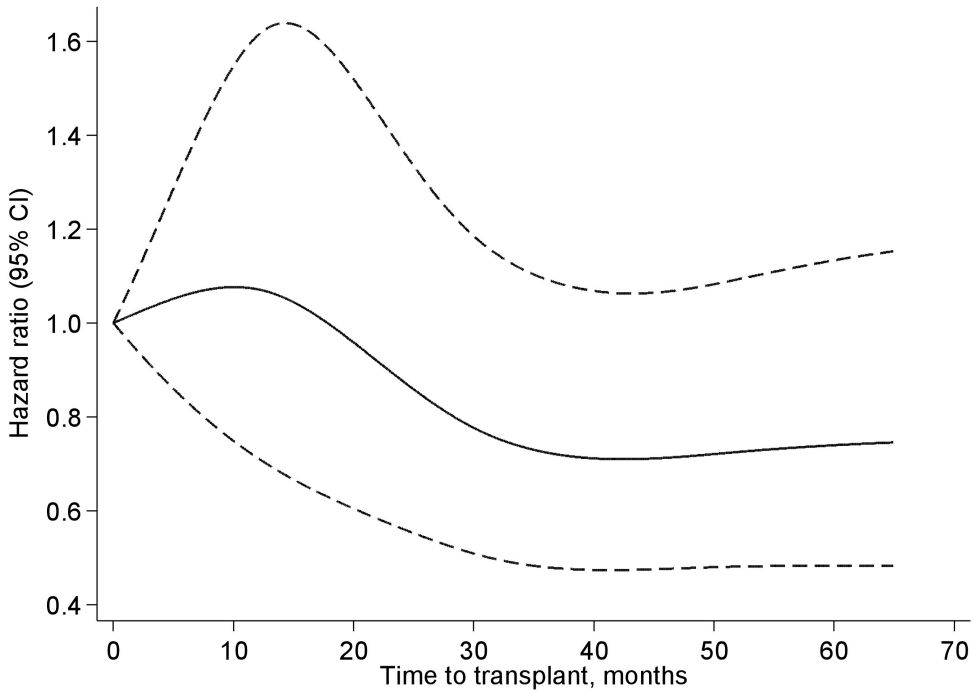

1.00
0.75
0.50
0.25
0.00
P<0.001 by log-rank
0
5
10
Time to graft failure, in years
Wait time to transplant
0-3 months
3-12 months
12-24 months
24-36 months
>36 months

Figure 6.2. Hazard ratios by restricted cubic splines among all (A), black (B), and white (C) U.S. patients with end-stage renal disease attributed to lupus nephritis, who received a transplant (1/1/00-9/30/11)

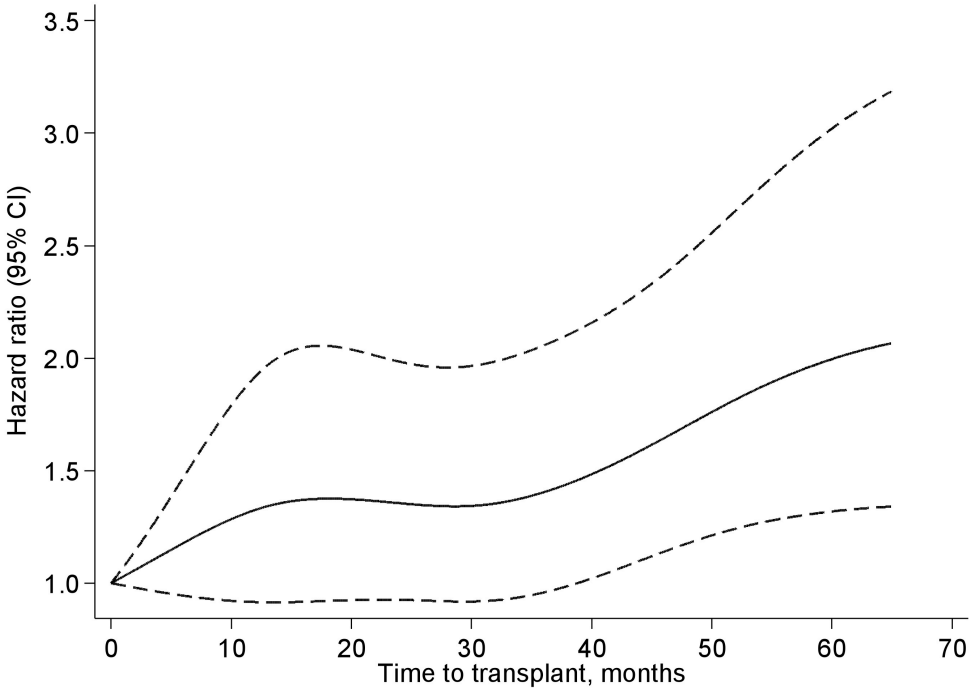
Adjusted for age, race (A only), insurance at start of ESRD, hemoglobin at start of ESRD, and donor type. Knots were placed at Harrell's percentiles (corresponding to values of 0, 13.1, 30.6, 52.2, and 103.4 months).



B


Hazard ratio (95% CI)
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0
10
20
30
40
50
60
70
Time to transplant, months

C


3.5
3.0
2.5
2.0
1.5
1.0
Hazard ratio (95% CI)
0
10
20
30
40
50
60
70
Time to transplant, months

6.9 Supplementary Tables and Figures

Table 6.4. Crude hazard ratios for graft failure by time to transplant, overall and by race: comparison of models

Time to transplant (months)	Median	# at risk	# with graft failure	HR (95% CI)				
				Categorical	Linear spline[a]	Restricted cubic spline[a]	Restricted cubic spline[b]	Restricted cubic spline[c]
Overall								
<3	0	569	91	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
3-12	7.88	655	163	1.58 (1.22-2.04)	1.88 (1.42-2.50)	1.57 (1.30-1.91)	1.15 (1.10-1.20)	1.52 (1.29-1.78)
12-24	17.28	801	232	1.89 (1.48-2.41)	2.12 (1.63-2.76)	2.54 (1.74-3.70)	1.34 (1.23-1.46)	1.97 (1.55-2.51)
24-36	30.05	643	195	2.05 (1.60-2.63)	2.21 (1.70-2.87)	3.74 (2.34-5.97)	1.59 (1.38-1.82)	1.93 (1.55-2.39)
>36	59.43	2075	558	2.12 (1.70-2.65)	2.46 (1.90-3.17)	1.82 (0.82-4.07)	1.84 (1.55-2.18)	2.24 (1.81-2.77)
P for departure from linearity (H_0: all spline terms = 0):					***0.006***	***<0.001***	***<0.001***	***<0.001***
Black								
<3	*0*	90	26	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
3-12	*8.38*	186	68	1.20 (0.76-1.89)	1.49 (0.87-2.53)	1.34 (0.96-1.85)	0.98 (0.92-1.04)	1.17 (0.89-1.54)
12-24	*17.90*	313	113	1.20 (0.78-1.83)	1.43 (0.87-2.36)	1.39 (0.89-2.16)	0.95 (0.83-1.09)	1.23 (0.81-1.87)
24-36	*29.30*	272	99	1.21 (0.79-1.87)	1.19 (0.72-1.96)	1.14 (0.78-1.66)	0.93 (0.75-1.15)	1.09 (0.75-1.57)
>36	*61.03*	1065	301	1.07 (0.71-1.59)	1.31 (0.80-2.14)	1.18 (0.81-1.70)	0.92 (0.70-1.20)	1.08 (0.75-1.55)
P for departure from linearity (H_0: all spline terms = 0):					*0.169*	*0.110*	*0.479*	*0.527*
White								
<3	*0*	324	50	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
3-12	*7.49*	300	64	1.42 (0.98-2.06)	1.61 (1.09-2.37)	1.33 (1.00-1.76)	1.22 (1.13-1.31)	1.43 (1.11-1.84)
12-24	*17.35*	263	68	1.72 (1.19-2.48)	1.76 (1.21-2.56)	1.77 (1.23-1.53)	1.51 (1.30-1.76)	1.77 (1.23-2.55)
24-36	*29.84*	192	51	1.87 (1.27-2.77)	2.19 (1.51-3.17)	2.09 (1.55-2.84)	1.92 (1.52-2.43)	1.76 (1.26-2.44)
>36	*54.99*	444	126	2.38 (1.71-3.30)	2.47 (1.72-3.54)	2.09 (1.55-2.80)	2.31 (1.72-3.10)	2.84 (2.01-4.02)
P for departure from linearity (H_0: all spline terms = 0):					***0.023***	***<0.001***	***<0.001***	***<0.001***

Values for HRs/95% CIs from splines are assessed at medians within knot-defined intervals for the overall population.

[a]Chosen knots at 3, 12, 24, and 36 months.

[b]Harrell's percentiles with 3 knots.

[c]Harrell's percentiles with 5 knots.

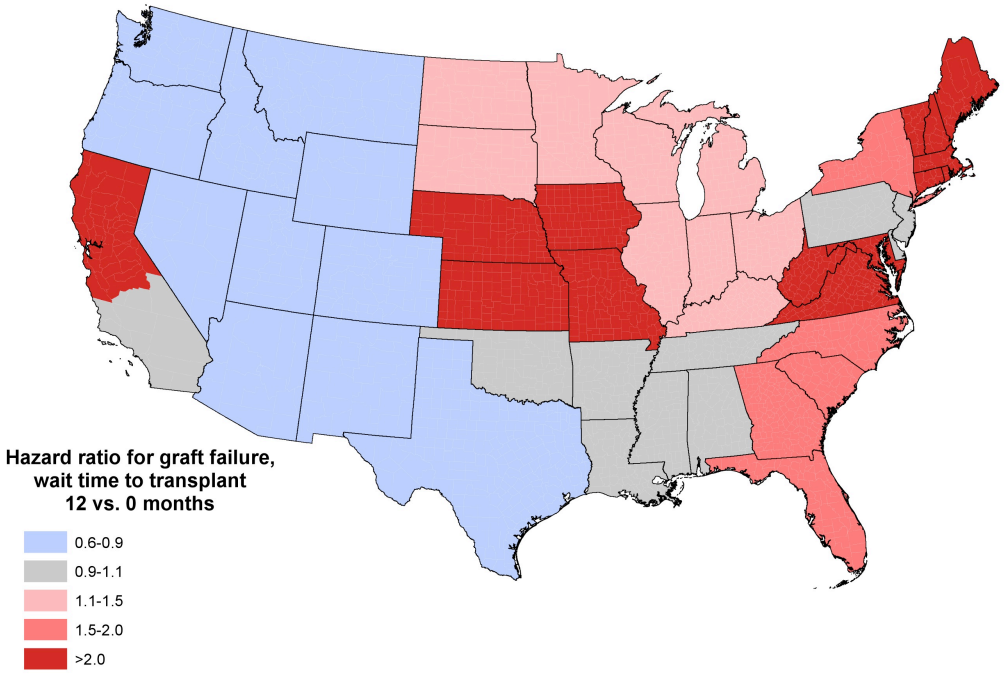
Table 6.5. Additional sensitivity analyses: adjusted hazard ratios among U.S. patients with end-stage renal disease attributed to lupus nephritis, who received a transplant (1/1/00-9/30/11), from restricted cubic splines of time to transplant

	Hazard ratio (95% CI) for graft failure at median value in interval, fully adjusted model plus:							
Time to transplant, months	**Delayed graft function (*n*=4280)**	**Donor age (*n*=4086)**	**Donor race (*n*=4274)**	**HLA mismatches (*n*=4189)**	**Donor age, donor race, HLA mismatches (*n*=4000)**	**Transplant year (*n*=4280)**	**Mycophenolate mofetil use (*n*=3877)**	**Propensity for early transplant (*n*=4280)**
Overall								
<3	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
3-12	1.23 (1.03-.147)	1.26 (1.04-1.51)	1.26 (1.05-1.50)	1.25 (1.05-1.50)	1.26 (1.05-1.52)	1.24 (1.04-1.48)	1.27 (1.05-1.52)	1.28 (1.07-1.53)
12-24	1.32 (1.01-1.72)	1.41 (1.07-1.85)	1.38 (1.06-1.80)	1.37 (1.05-1.79)	1.41 (1.07-1.87)	1.35 (1.04-1.76)	1.38 (1.05-1.82)	1.42 (1.09-1.87)
24-36	1.12 (0.88-1.44)	1.28 (0.99-1.65)	1.20 (0.94-1.54)	1.18 (0.92-1.51)	1.26 (0.98-1.63)	1.18 (0.93-1.52)	1.16 (0.90-1.50)	1.24 (0.96-1.60)
>36	1.10 (0.85-1.43)	1.20 (0.92-1.57)	1.23 (0.95-1.59)	1.17 (0.90-1.52)	1.17 (0.89-1.53)	1.25 (0.96-1.61)	1.16 (0.89-1.52)	1.25 (0.97-1.63)
Black								
<3	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
3-12	1.05 (0.78-1.42)	1.15 (0.83-1.58)	1.07 (0.79-1.45)	1.08 (0.80-1.47)	1.18 (0.86-1.62)	1.05 (0.78-1.42)	0.99 (0.72-1.34)	1.08 (0.79-1.46)
12-24	0.98 (0.62-1.55)	1.14 (0.70-1.85)	1.01 (0.64-1.60)	1.03 (0.65-1.63)	1.18 (0.72-1.92)	0.99 (0.78-1.42)	0.88 (0.55-1.41)	1.02 (0.64-1.63)
24-36	0.74 (0.48-1.13)	0.89 (0.57-1.38)	0.77 (0.51-1.18)	0.78 (0.51-1.19)	0.90 (0.58-1.39)	0.77 (0.50-1.17)	0.68 (0.44-1.04)	0.78 (0.51-1.20)
>36	0.67 (0.44-1.03)	0.79 (0.51-1.24)	0.75 (0.49-1.14)	0.72 (0.47-1.11)	0.79 (0.50-1.23)	0.76 (0.50-1.16)	0.64 (0.42-0.99)	0.75 (0.49-1.15)
White								
<3	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
3-12	1.21 (0.92-1.61)	1.20 (0.90-1.61)	1.23 (0.93-1.63)	1.22 (0.92-1.63)	1.19 (0.88-1.60)	1.22 (0.93-.162)	1.34 (1.00-1.81)	1.25 (0.95-1.66)
12-24	1.32 (0.88-1.99)	1.37 (0.90-2.08)	1.37 (0.92-2.05)	1.36 (0.90-2.05)	1.35 (0.88-2.07)	1.36 (0.91-2.03)	1.52 (0.99-2.33)	1.42 (0.94-2.13)
24-36	1.25 (0.85-1.84)	1.44 (0.97-2.14)	1.35 (0.92-1.97)	1.33 (0.90-1.95)	1.44 (0.97-2.15)	1.33 (0.91-1.95)	1.33 (0.88-2.00)	1.38 (0.94-2.03)
>36	1.78 (1.17-2.70)	1.96 (1.27-3.00)	2.01 (1.33-3.05)	1.92 (1.26-2.93)	1.97 (1.26-3.06)	2.05 (1.35-3.09)	2.04 (1.32-3.16)	2.01 (1.33-3.04)

Delayed graft function: yes and no (=referent); donor race: white (referent), black, and other; HLA mismatches: 0 (referent), 1-2, 3-4, and 5-6; propensity for early transplant: probability of transplant with wait time of <3 months, adjusted for age, race, insurance, hemoglobin, and donor type.

Figure 6.3. Hazard ratios for graft failure for wait time to transplant of >12 vs. 0 months, by ESRD Network

There were no statistically significant differences in associations across ESRD Networks, with the exception of Network 12 (P=0.01-0.04 in most pairwise comparisons, without adjustment for multiple comparisons).



7. Summary and Future Directions

7.1 Summary of Findings

In **Aim 1** (Chapter 4; manuscript in preparation), we found that, in a population-based registry of 344 patients who were newly diagnosed with systemic lupus erythematosus (SLE) in 2002-2004 in metropolitan Atlanta (Fulton and DeKalb Counties), the incidence rate of subsequent end-stage renal disease (ESRD), as ascertained via linkage to a national registry of treated ESRD patients [United States Renal Data System (USRDS)], was 11.1 per 1000 patient-years. Estimated incidence was higher (12.5 per 1000 patient-years) when SLE was defined only by the patient having four or more ACR criteria[18] for SLE diagnosis, excluding those defined by only three criteria plus a rheumatologist SLE diagnosis or with SLE renal involvement. We estimated 5-year cumulative incidence to be 5.2-6.0%, which is at least twice the estimate from a recent study in Taiwan,[55] which estimated that 2.5% of newly diagnosed SLE patients developed SLE over 6-8 years of follow-up. Further, we found that young age, black race, and early diagnosis of LN—but not sex or neighborhood–level racial composition, educational attainment, or poverty—were all associated with higher ESRD incidence (approximately 2-, 4-, and 7-fold, respectively) among these newly diagnosed SLE patients. To our knowledge, these results provide the first real-world, "as-treated" estimates of incidence of ESRD from time of SLE diagnosis in the United States. The estimates and associations presented in this dissertation bridge an important gap in our understanding of the epidemiology of SLE and ESRD in the United States.

Despite multiple national and regional quality-of-care initiatives and incentives aimed at improving care in the overall ESRD population,[8,56,93] in **Aim 2** (Chapter 5; manuscript under review), we found that, among patients with ESRD attributed to lupus nephritis (LN-ESRD) identified in the USRDS, care remains suboptimal. Nearly one-third of patients with LN-ESRD had received no pre-ESRD nephrology care at the start of ESRD treatment. Most potentially eligible patients were reported to be informed of transplant options at ESRD start, but incidence of subsequent waitlisting was only ~20% per year, although both being informed of transplant options and transplant waitlisting increased over the study period among LN-ESRD patients. Notably, fewer than one-quarter of LN-ESRD patients treated by hemodialysis had a permanent vascular access in place at the start of treatment. In a related paper (**Appendix C**; manuscript under review), we also compared the attainment of these quality-of-care indicators between LN-ESRD patients and patients with ESRD due to other causes and found that, even after adjustment for striking differences across the patient populations—including age, sex, race, and insurance, as well as clinical characteristics—LN-ESRD patients remained more likely than other ESRD patients to have had pre-ESRD care (68% more likely), to be informed of transplant options at the start of ESRD (10% more likely), and to be waitlisted for kidney transplantation while on dialysis (45% and 56% more likely in and after the first year of dialysis, respectively). However, after this adjustment, LN-ESRD patients remained nearly 40% less likely to have a permanent vascular access in place, compared to patients with other attributed causes of ESRD.

Our findings from **Aim 2** (Chapter 5; manuscript under review) indicate not only potentially inadequate care overall but also substantial sociodemographic and regional disparities in the translation of quality-of-care indicators related to pre-ESRD care, access to transplant, and placement of permanent vascular access among LN-ESRD patients. After adjustment for other sociodemographic and clinical factors, black and Hispanic patients were less likely to have pre-ESRD nephrology care and permanent vascular accesses than their white counterparts, as in the overall ESRD population.[12,93] Black race and Hispanic ethnicity were also associated with lower likelihood of kidney transplant waitlisting relative to white race in the first year of ESRD treatment, as in the overall ESRD population.[11,155,157] Lack of insurance at the start of ESRD was strongly associated with less successful translation of all examined quality-of-care indicators, similar to the overall ESRD population,[159,160] with adjustment for other sociodemographic and clinical characteristics. Areal socioeconomic indicators of lower educational attainment and greater poverty were associated with inadequate pre-ESRD nephrology care and early access to transplant, although the effects adjusted for individual factors were generally more modest and less statistically significant than those of individual race/ethnicity and insurance. Finally, translation of most examined quality-of-care indicators, with the exception of being informed of transplant options, also differed (2- to 3-fold) among LN-ESRD patients by U.S. region, as defined by ESRD Network. However, patterns of geographic disparities were inconsistent across indicators of quality of care. Thus, **Aim 2** provides a comprehensive, national snapshot of ESRD quality of care for U.S. patients with LN-ESRD, overall and by patient characteristics and U.S. region.

Finally, in a national study of kidney transplant recipients with ESRD secondary to LN identified in the USRDS (**Aim 3**),[163] we found that longer wait times to transplant were not associated with lower risk of graft failure among these patients, as might be expected from current clinical recommendations.[1,14,111,164] Rather, we found that longer time on dialysis was generally associated with increased risk of graft failure among LN-ESRD patients, relative to those patients who were transplanted in the first 3 months of ESRD treatment, although results were not always statistically significant. Our effect estimates were similar to those seen in the overall ESRD population, in whom wait times to transplantation of >6 months and >1 year, relative to 0-15 days, have been shown to be associated with approximately 25% and 40% increased graft failure risk.[15] In our study, relative to waiting <3 months, waiting ≥3 years for kidney transplantation was associated with a 2-fold risk of graft failure among white LN-ESRD patients, whereas longer wait time was generally associated with similar risk of graft failure among black LN-ESRD patients. Even in the fully adjusted models, where there was a non-statistically significant suggestion of a protective effect among black LN-ESRD patients whose wait times were ≥2 years, we did not see increased risk of graft failure among those transplanted early. These results provide, to our knowledge, a first examination of the association between wait time to transplant and graft outcomes in a nationally representative population of U.S. LN-ESRD patients that can be used to generate hypotheses and guide future study of this issue.

7.2 Strengths and Limitations

These studies have several limitations. While the SLE case-finding approach of the Georgia Lupus Registry (GLR), which was used to define newly diagnosed SLE patients in **Aim 1**, was comprehensive and population-based, the sensitivity of this approach is unknown. The estimates of incidence and associations of incidence with sociodemographic factors among Atlanta-area SLE may not be generalizable to other U.S. SLE populations, particularly outside of the South, or to non-U.S. SLE populations. We also had limited power to detect modest associations, due to small numbers of events and relatively short follow-up, and we lacked individual socioeconomic data at diagnosis among the newly diagnosed SLE patients in **Aim 1**. For all aims, ESRD ascertainment may not be complete, as we were unable to capture any non-Medicare-eligible patients (*e.g.*, undocumented residents) or any patients who may have moved out of the United States. In **Aims 2** and **3**, the validity of ESRD cause attribution, which was used to identify ESRD patients with SLE, is unknown. One small validation study[130] suggests potentially low sensitivity and high specificity, and our own linked data from **Aim 1** (Table 1.5) suggest a sensitivity of only 68% for capturing underlying SLE via attributed cause of ESRD. Provider accuracy in recording other patient variables, including race/ethnicity and insurance as well as quality indicators, on the CMS-2728 (**Appendix A**), may also be imperfect. For area-based measures, census tracts (**Aim 1**) and zip code tabulation areas (**Aims 2** and **3**) may serve as insufficient proxies for neighborhoods. Residual confounding may be an issue in all these observational studies, and the lack of information of SLE activity is the most serious threat to the internal validity of **Aim 3**.

Potential survival and/or collider bias in **Aim 3** may also be an issue, since patients had to receive a kidney transplant to be included and it is likely that those SLE patients who receive transplants differ from those who do not.

However, the studies presented here also have many strengths. The GLR is one of five CDC National Lupus Registries, the first comprehensive population-based epidemiological study of lupus conducted in the United States.[22,23,25] SLE case ascertainment was not dependent on administrative data and was maximized by the use of multiple sources, and diagnoses were validated by comprehensive clinical data collected from individual records. Fulton and DeKalb Counties represent a large (~1.5 million), demographically and socioeconomically diverse (~50% black) U.S. metropolitan population, and all ESRD patients treated in the United States were captured. In **Aims 2** and **3**, the potential for selection bias due to excluded data was minimal. The USRDS data used in these studies are national and capture all U.S. patients treated for ESRD, including all kidney transplant recipients. The Medicare Eligibility form (CMS-2728)—which includes ESRD quality-of-care information—is provided for all treated ESRD patients regardless of insurance status. For all aims, loss to follow-up was minimized due to universal coverage of ESRD services by Centers for Medicare & Medicaid Services (CMS); because of this nearly complete follow-up, we were able to take varying follow-up times into account and compute incidence rates rather than just cumulative incidence in **Aim 1**; follow patients to waitlisting, death, or end of follow-up in **Aim 2**; and follow patients to graft failure or end of follow-up in **Aim 3**. Finally, in **Aim 3**, death was

included as part of the definition of graft failure, which eliminated potential bias due to competing risks.

7.3 Future Directions

Results from **Aim 1** analyses suggest that 1 in 5 SLE patients progress to ESRD without early evidence of LN and that certain subgroups of SLE patients, including children and blacks, would benefit from earlier identification as higher-risk for LN and ESRD. Additionally, nearly 40% of black SLE patients who progressed to ESRD did not have a record of a renal biopsy, potentially against clinical recommendations that recommend biopsy in the presence of signs of renal damage,[31] pointing to missed opportunities to identify LN early and provide more aggressive treatment to prevent or delay ESRD. Thus, future research into predictors of biopsy and other screening practices (*e.g.*, urinanalysis) among those with SLE, LN, and ESRD in this population—and potentially multi-site studies including other cohorts and/or registries—may be warranted. Further, such research could lead to targeted preventive and quality improvement efforts to increase access to LN screening in the SLE population and decrease the incidence of ESRD in the SLE population.

Our results from Aim 1 also suggest that percentage of SLE patients with ESRD whose attributed ESRD cause is SLE in the national USRDS data may be low (68%; Table 1.5). While this could simply suggest low sensitivity,[130] it could also suggest that many of these patients have comorbid conditions to which providers may attribute ESRD cause. In fact, we found that that 60% of those patients whose attributed ESRD cause was not SLE

had hypertension listed as their primary cause, which is possible given that the high prevalence of hypertension among LN patients. Further, preliminary examination of biopsy data for some of these patients suggest that the attribution of cause may indeed match the medical evidence. This would suggest that national studies of patients with SLE and ESRD, such as those presented in **Aims 2** and **3**, that use only attributed cause from the CMS-2728 (**Appendix A**) may miss a substantial proportion of these patients and that those not captured may suffer from multiple conditions, lessening the generalizability of these results to the entire population of patients with SLE and ESRD. Thus, future directions could include an examination of the sensitivity of attributed cause of ESRD in our linked data (incident and prevalent patients) and potential alternative methods of identification in these surveillance data (*e.g*., through hospitalization claims) that might capture a greater proportion of ESRD patients who have SLE.

In **Aim 2**, we found that there was room for improvement in all quality-of-care indicators in the LN-ESRD population. Further study is needed regarding potential barriers to improving quality of ESRD care in this population at the levels of the health system, ESRD Networks, providers (including rheumatologists, nephrologists, and transplant and vascular access surgeons), and patients. Such efforts would require studying patients prior to the initiation of ESRD treatment, perhaps by targeting SLE providers. Surveys of providers regarding their clinical practices with respect to ESRD in SLE could be an important initial step for such studies. Our results also identify potential specific targets with respect to inadequate translation of quality-of-care indicators in this population and the LN-ESRD patient subpopulations that are least likely to receive high-quality care, as

measured by these indicators. For example, a Network-level intervention to enhance rheumatology-nephrology partnerships aimed at improving ESRD care could be targeted to a region with a large population of uninsured, black LN-ESRD patients, such as the Southeast. Such efforts have the potential to ensure better and more equitable quality of ESRD care among patients with SLE.

Because we found that fewer than one-quarter of LN-ESRD patients started dialysis with a permanent vascular access, despite national incentive programs to increase such placement in the overall ESRD population,[93] exploration of the specific barriers to placement of permanent vascular access in this population is most needed. While having no insurance (common in this young, minority population) was associated with even lower likelihood of permanent access placement among LN-ESRD patients, it did not explain the strikingly lower placement among LN-ESRD vs. other ESRD patients (nearly 40%; **Appendix C**), suggesting other social or clinical barriers to timely placement of permanent vascular access.

Beyond whether adequate care was received (**Aim 2**), outcomes in LN-ESRD patients by receipt of such care could also be examined. While these indicators are tracked by the CMS because of their known associations with clinical outcomes in the overall ESRD population, little is known about how quality of ESRD care affects outcomes in the SLE population, which differs in many important ways and may differ in their outcomes as well. A recent study indicated that choice of dialysis modality (hemodialysis vs. peritoneal dialysis) was not associated with mortality among LN-ESRD patients,[173]

which does not reflect findings in the overall population. Also, in preliminary analyses of mortality by permanent vascular access placement among LN-ESRD patients, we found that, unlike the general population,[80-87] those with only temporary catheters at first dialysis were only at slightly increased risk of mortality. Additionally, outcomes beyond mortality and morbidity may be important to examine in this young, predominantly female population, outcomes such as quality of life, depression, functioning, costs, and fertility[153] may be equally important to address, to determine the true impact of adequate ESRD care on SLE patients.

Finally, we found that, although SLE patients had comparable or better access to kidney transplantation, as compared to other ESRD patients (**Aim 2**; **Appendix C**), many SLE patients were waiting long periods for transplantation, and that those who did wait, allowing time for SLE quiescence, were not at any advantage regarding subsequent survival of the graft, relative to those transplanted close to ESRD start (**Aim 3**).[163] However, the lack of data on SLE activity at ESRD start among those LN-ESRD patients who received a kidney transplant potentially biased our results (confounding by indication). Our **Aim 1** data, which links SLE patients to their ESRD status, could be used to examine this issue accounting for SLE disease markers, although the combination of multiple linked registries would likely be necessary to accumulate a sufficient number of kidney transplant recipients with SLE. Single-center studies of transplant center data, limiting to SLE patients, might also be useful to track the transplant process in such patients—referral, evaluation, waitlisting, and transplantation—and could provide insights into SLE activity and clinical decision-making at each stage. If the lack of

advantage to waiting to transplant SLE patients were confirmed in other studies accounting for SLE activity, multi-provider interventions to decrease wait time to transplant and, potentially, to improve transplant outcomes could be designed and implemented.

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