Individuals With a Family History of ESRD Are a High-Risk Population for CKD: Implications for Targeted Surveillance and Intervention Activities

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Activities intended to improve the detection, treatment, and control of chronic kidney disease (CKD) should be incorporated into existing health care systems and targeted to high-risk populations to avoid redundancy and waste of resources. One high-risk population consists of first- or second-degree family members of patients with end-stage renal disease (ESRD), who are 2 to 3 times as likely to have incident ESRD, have high rates of impaired kidney function and undetected and uncontrolled high blood pressure, and are more likely to be obese. These individuals usually are unaware of their underlying CKD and may discount their own risk of ESRD. The ESRD Network 6 Family History Project shows that the ESRD Networks, which constitute a national CKD surveillance system for patients with stage 5 CKD, may be an existing resource that can be used to identify relatives of incident patients with ESRD and provide these families with information about CKD. Nationally available resources have been developed by the National Kidney Disease Education Program for use with these at-risk families. Individuals interested in population-based CKD control activities should be aware of and use these resources.
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INDEX WORDS: End-stage renal disease; family history; obesity; African Americans; European Americans.

Chronic kidney disease (CKD) surveillance is the routine collection, analysis, and reporting of information for the purpose of decreasing the incidence and improving the outcomes of care of patients with CKD.[1-3] CKD surveillance activities are conducted by the End-Stage Renal Disease (ESRD) Networks and the US Renal Data System in the United States.[4] This population-based geographically comprehensive system is used to define the epidemiological characteristics of patients with ESRD,[5] identify potential quality-of-care problems in patients with ESRD,[6] and target and evaluate quality improvement efforts directed at improving the care of patients with ESRD.[7,8]

An important question to be answered is the degree to which this unique resource can be used to provide similar surveillance for earlier stages of CKD in high-risk populations most likely to benefit from interventions to reduce the risk of progression to ESRD. The purpose of this report is to describe one high-risk population for progression to ESRD, first- and second-degree relatives of incident patients with ESRD, that is accessible to the existing CKD surveillance system and illustrate how the ESRD Networks have been used to identify and deliver prevention services to this population. Although the benefit of early identification and treatment of individuals with such Mendelian disorders as autosomal dominant polycystic kidney disease is increasingly understood,[9] this review focuses on familial occurrence of the non-Mendelian forms of kidney diseases associated with hypertension, glomerulonephritis, and diabetes that constitute the most common causes of ESRD and in which shared family risk likely is caused by a combination of shared genetic and environmental risk factors. We describe how nationally available resources might be targeted at improving the detection and treatment of CKD in these families. Finally, we show how data routinely collected from incident patients with ESRD might be modified to provide a comprehensive picture of the degree to which family members of patients with ESRD are successfully screened and treated for stage 4 CKD.

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FAMILIAL AGGREGATION OF ESRD

It has been recognized for some time that incident patients with ESRD with non-Mendelian kidney diseases are more likely to identify a first- or second-degree family member who is treated for ESRD.[10,11] Ferguson et al[10] first noted this association in the general population of patients with ESRD, reporting that 26% of prevalent African American patients with ESRD reported a first- or second-degree relative with kidney disease compared with 11% of community controls. Subsequent studies confirmed this association in multiple populations with nondiabetic kidney disease,[11-14] and the association is believed to reflect the interplay between a genetic predisposition to kidney injury and multiple environmental and behavioral risk factors associated with progression of kidney injury that is to some degree independent of the underlying disease.[13]

CKD IN INDIVIDUALS REPORTING A FAMILY MEMBER WITH ESRD

There is increasing evidence for the familial aggregation of kidney injury and related risk factors, and individuals with a family history of ESRD have a distinctive phenotype that has been described most extensively for kidney disease in individuals with diabetic ESRD[15] and extended to nondiabetic populations as well (Table 1). Bergman et al[16] reported that nearly 5% of first-degree relatives of patients with hypertensive ESRD had a serum creatinine level of 1.4 mg/dL or greater and 9.7% had proteinuria, whereas Jurkovitz et al[17] found that stage 3 to 4 CKD, defined as a creatinine clearance less than 60 mL/min, was present in 14% of screened relatives. In addition, in the family members with stage 3 and 4 CKD studied by Jurkovitz et al,[17] only 13.0% were aware of their kidney disease and awareness did not increase in individuals who reported a recent visit to a physician.

Table 1. Characteristics of Individuals With a Family History of End-Stage Renal Disease

Characteristic	Reference
African American race	9-11, 14, 16, 17, 23
Younger age	23
Hypertension	1, 12, 14
Diabetes	12, 16, 23, 26
Obesity	16, 17
Women	16
Increased C-reactive protein	16
Proteinuria	14, 25
Decreased glomerular filtration rate	14, 16

These reports recently have been replicated by a cross-sectional study of individuals in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort, a population-based sample of US residents 45 years and older.[18] A family history of ESRD was ascertained by asking REGARDS participants: "Has anyone in your immediate family ever been told that he or she had kidney failure? This would be someone who is on or had been on dialysis or someone who had a kidney transplant." Individuals who answered yes were asked the relationship of the individual(s) with kidney failure: "What relative or relatives had or has kidney failure?" Verbatim responses of as many relatives as recalled were reported. A positive personal history of ESRD in a first-degree relative was defined as: (1) a yes answer to the first part of the family history question and (2) unprompted identification of at least 1 of the following relatives as having ESRD: sibling, child, or parent.[18] A family history was reported by 9.5% of the more than 12,000 participants in the cohort, and in these individuals, African Americans, but not whites, were more likely to have stage 3 and 4 CKD (glomerular filtration rate < 60 mL/min/1.73 m^2). The prevalence of a family history of ESRD increased in African Americans, but not whites, as glomerular filtration rate decreased.

CHARACTERISTICS OF INDIVIDUALS WITH A FAMILY HISTORY ESRD

Speckman et al[19] examined the prevalence of obesity in 25,883 incident patients with ESRD in Georgia, North Carolina, and South Carolina. In the 23% who reported a family history of ESRD, 28.0% were overweight, 17.3% were obese, and 16.7% were morbidly obese. After controlling for age, race, sex, primary cause of ESRD, history of diabetes, history of hypertension, and estimated glomerular filtration rate at dialysis therapy initiation, individuals with a family history of ESRD were more likely to be overweight

(odds ratio [OR], 1.17; 95% confidence interval [CI], 1.08 to 1.26), obese (OR, 1.25; 95% CI, 1.14 to 1.37), and morbidly obese (OR, 1.40; 95% CI, 1.27 to 1.55).

Similar observations were made in the REGARDS cohort.[18] In multivariate analyses that controlled for age, sex, race, and multiple comorbidity, individual characteristics independently associated with a family history of ESRD included African American race (OR, 2.14; 95% CI, 1.82 to 2.53), female sex (OR, 1.28; 95% CI, 1.08 to 1.51), history of diabetes (OR, 1.22; 95% CI, 1.02 to 1.47), a 1-SD change in log C-reactive protein level (OR, 1.10; 95% CI, 1.01 to 1.19); and World Health Organization body mass index weight categories of normal (OR, 2.11; 95% CI, 0.66 to 6.79), overweight (OR, 2.64; 95% CI, 0.82 to 8.42), and obese (OR, 3.48; 95% CI, 1.09 to 11.1) compared with underweight.

PERCEIVED SEVERITY OF HISTORY OF ESRD BY PATIENTS AND PHYSICIANS

Despite the severity of ESRD, individuals in the general population with a family member with ESRD may not be aware of their increased risk of CKD. Jurkovitz et al[20] found that 3.7% of individuals responding to a population-based telephone survey reported a family history of ESRD, and a positive history was 6 times more frequent in African Americans. Respondents were asked to respond to the question: "How likely are people like you to get kidney disease sometime during their life?" In African Americans with a positive family history, 37% said likely compared with 50% of non–African Americans.

A survey of 465 primary care physicians in 4 communities with populations at high risk of ESRD was recently reported by the National Kidney Disease Education Program (NKDEP).[21] The survey examined awareness of CKD risk factors in respondents who were asked to what degree specified risk factors increased the risk of CKD. Primary care physicians reported that diabetes and hypertension were significant risk factors for CKD, whereas 34.4% reported that a family history of kidney disease and 22% that African American race were not associated with increased risk of CKD.

IDENTIFYING HIGH-RISK PATIENTS WITH ESRD THROUGH THE ESRD SURVEILLANCE SYSTEM

Clearly any incident patient with ESRD identifies a high-risk family that can be expected to include members with undetected kidney disease and who share a number of risk factors for progressive CKD, including diabetes, obesity, increased inflammatory burden, and African American race.[22] In addition, it is likely that some members of these families and their physicians may underestimate the risk of kidney disease associated with a positive family history and thus may neglect current recommendations for screening for high-risk groups for early kidney injury.[23] One possible way to access these individuals is through the existing national ESRD surveillance system.

The ESRD Network 6 Family History Study illustrates this point. Beginning in 1994, social workers and nurses at dialysis centers in North Carolina, South Carolina, and Georgia were asked to record a family history of ESRD in first- and second-degree relatives of all incident dialysis patients.[24] Table 2 lists voluntary participation by treatment centers in the Family History Study between 1995 and 2003, when the project was stopped.[25] Facility participation rates ranged from 74% at the inception to nearly 50% at the close of the project, illustrating the capacity of the ESRD Network system to collect family history information during a sustained period.[25]

Table 2. Proportion of ESRD Treatment Centers Participating in Voluntary Ascertainment of a Family History of ESRD in Incident Hemodialysis Patients

Year	No. of Providers	Providers Collecting Family History Data (% [no.])	Mean Patient Participation Across Providers Collecting Family History Data (%)
1995	257	91.44 (235)	77.89
1996	285	88.07 (251)	72.99
1997	302	81.13 (245)	68.20
1998	319	77.74 (248)	63.03
1999	346	70.81 (245)	56.13
2000	365	73.15 (267)	55.73
2001	392	68.62 (269)	51.86
2002	415	64.58 (268)	43.90
2003	420	45.71 (192)	49.44

Abbreviation: ESRD, end-stage renal disease.
From Freedman et al.[25]

A positive family history was obtained from 20% of the 4,365 dialysis patients and from 83% of all incident patients, without a diagnosis of ESRD attributed to Mendelian diseases or urological causes.[24] Characteristics independently associated with a positive family history included African American race, younger age, higher levels of education, and ESRD caused by diabetes mellitus. During the subsequent course of the ESRD Network 6 Family History Study between January 1, 1995, and December 31, 2003, more than 46% of eligible patients (25,883 of 55,929) provided family history information and 22.8% of these reported having a positive family history of ESRD, again independent of Mendelian or urological causes (Table 3).[25] The associations noted between family history and female sex, younger age, race, and primary cause of ESRD persisted in the larger sample with common complex causes of kidney failure.

LINKING INDIVIDUAL MEMBERS OF HIGH-RISK ESRD FAMILIES TO CKD PREVENTION MEASURES USING THE NATIONAL CKD SURVEILLANCE SYSTEM

This study shows that the surveillance system is capable of obtaining family history from incident patients with ESRD and that these individuals, in turn, can identify high-risk families. An important step in the successful use of this information is linking it to public health action. Two pilot projects have been conducted by ESRD Network 6 investigators to identify screening options within this context. It was imperative to implement a low-cost and relatively nonintrusive screening method in families because these screenings will need to be repeated at regular intervals.

Table 3. Availability of Family History Data by Year

Year	No. of Patients	Total	Reported Having Family History
1995	4,328	3,205 (74.05)	671 (20.94)
1996	5,468	3,618 (66.17)	790 (21.84)
1997	5,842	3,475 (59.48)	772 (22.22)
1998	6,307	3,249 (51.51)	729 (22.44)
1999	6,650	2,887 (43.41)	645 (22.34)
2000	7,201	3,070 (42.63)	699 (22.77)
2001	7,506	2,846 (38.92)	682 (23.96%)
2002	7,418	2,225 (29.99)	593 (26.65%)
Georgia	22,028	8,911 (40.45)	2,022 (22.69)
North Carolina	21,693	12,197 (56.23)	2,813 (23.06)
South Carolina	12,208	4,775 (39.11)	1,066 (22.32)

Note: Values expressed as number (percent) unless noted otherwise.

From Freedman et al.[25]

The Network 6 Family History of ESRD Prevention Project attempted to contact all living first-degree relatives of prevalent dialysis patients to inform them of their heightened risk of subsequent (or silent) kidney disease. These individuals were asked to voluntarily report to their physicians or health departments for performance of specified laboratory tests and blood pressure screening to detect silent kidney disease, hypertension, and diabetes.

Although many National Kidney Foundation (NKF) Kidney Early Evaluation Program (KEEP) participants have been relatives of dialysis patients, this Network study attempted to screen only high-risk relatives because they were believed to be at greater risk of subsequent nephropathy compared with hypertensive or diabetic individuals lacking relatives with ESRD. Index cases on dialysis therapy residing in Network 6 (North Carolina, South Carolina, and Georgia) voluntarily provided contact information for their close relatives. Potential participants initially were contacted by mail, with follow-up telephone calls from a study coordinator. Relatives were asked to allow the study investigators access to their recent laboratory results by permitting them to contact their primary physicians after completing the screening. Alternatively, if screening had previously occurred within the 12 months before the study, permission was requested to obtain laboratory results.

Outcomes of this pilot study were disappointing because only 88 of 462 contacted relatives agreed to participate.[26] However, of those screened, 26.2% had newly detected proteinuria, 21.9% had uncontrolled hypertension, and 18.1% had fasting hyperglycemia. Major flaws in design were that relatives were asked to sign a complicated multipage consent form (and return it in a self-addressed stamped envelope), routine screening laboratory tests and the associated medical visit were performed at the participants' expense, and participants were first made aware of the study when they received a letter in the mail. The institutional review board–mandated consent form may have intimidated potential

participants, and the lack of remuneration and cost of laboratory work were disincentives, especially for those without health insurance. Although only a minority of contacted relatives ultimately participated, it is possible that additional relatives were screened outside the study after being informed of their heightened risk of nephropathy. A follow-up study was designed in an attempt to garner more widespread participation and simplify the study design.

The second pilot study used a dedicated nurse coordinator to visit dialysis patients in several large treatment facilities. Dialysis patients were asked to inform their first-degree relatives of the availability of a free medical screening because they are at increased risk of kidney disease. Free screenings were offered either in a local medical clinic or at the dialysis facility, and results were made available to the participants' treating physicians. Although informed consent was still required, the study coordinator personally discussed the study with potential participants and answered questions. As opposed to the first pilot, laboratory work was performed free of charge and participants were contacted first by their relative on dialysis therapy, rather than by a mailing. After calls from the study coordinator, nearly 75% of 200 relatives contacted agreed to participate (although not all dialysis patients agreed to allow their relatives to be contacted).

We conclude that the optimal method for routinely and repeatedly screening high-risk relatives of dialysis patients to detect renal disease and risk factors remains a work in progress. Minor improvements in Network study protocols encouraged a far greater percentage of relatives to participate in the second pilot. However, using dedicated screening nurses and performing large numbers of laboratory tests would be cost prohibitive if applied on a nationwide basis.[27]

Conversely, the Networks have shown a sustained capacity to assess the presence of a family history of ESRD and thus could be used to track the degree to which family members receive appropriate care before the onset of renal replacement therapy. Information currently gathered on the Centers for Medicare & Medicaid Services 2728 form at the start of ESRD therapy includes the duration of pre-ESRD nephrology care, presence of an arteriovenous fistula, detection and treatment of anemia, and predialysis nutritional counseling and nutritional status. A simple application of these data might be to assess the degree to which the pre-ESRD care of family members reflected awareness of their high-risk status (ie, longer duration of nephrology care, greater rates of arteriovenous fistula placement and anemia control, and better nutritional status) at the start of dialysis therapy.

Family-based screening programs could also be monitored by the Networks. The NKF KEEP and similar screening programs are critically important methods for kidney disease detection and prevention. Linking ESRD Network–based screening processes for contacting substantial numbers of family members from incident dialysis patients would provide an effective screening net. We believe that real-world screening programs likely would outperform the Network pilot projects because signed consent forms would not be required. Efforts to screen for and control diabetes, hypertension, proteinuria, and decreased kidney function will need to be performed regularly in family members of patients with ESRD. Attention to "renal" risk factors also may ultimately decrease rates of cardiovascular disease because kidney disease and renal risk factors clearly contribute to the development and progression of heart disease.

Recently, tools have been developed by the NKDEP, an initiative of the National Institutes of Health, that can be used by these families to increase the detection and awareness of CKD and ESRD. The NKDEP *Help Your Family Prevent Kidney Failure* materials encourage patients with ESRD to talk to their family members about their risk of kidney disease and the importance of getting tested. The resources include a brochure, video, poster, and button. The brochure emphasizes that kidney disease runs in families and early detection of kidney disease is important. This piece has a unique feature, a detachable postcard that patients mail to their family members, acting as a personal appeal to find out more about the kidney disease in the family. The educational video, showing one family's experience with kidney disease, reviews the risk factors, highlights the importance of getting tested, and explains what the tests involve. The video is designed to trigger patients to talk to their family members about their risk of kidney disease and talk to their doctors about getting tested. As

visual cues for waiting rooms and treatment areas, NKDEP developed a poster reinforcing the "Help your family prevent kidney failure" message and buttons designed to be worn by technicians, nurses, social workers, and other staff. The button comes attached to a quick reference card with a few key messages about kidney disease to assist staff in their efforts to answer questions about the family history.

INHERITED VERSUS ENVIRONMENTAL DETERMINANTS OF A FAMILIAL CLUSTERING OF ESRD

Genetic and environmental factors likely contribute to the familial aggregation of common forms of kidney disease. Individuals of lower socioeconomic status are more likely to develop CKD related to inadequate or inaccessible medical care. However, molecular genetic techniques show that genes contributing to structural abnormalities in the kidney (podocin [encoded by the *NPHS2* gene], non-muscle myosin heavy chain 9 [encoded by *MYH9*]) and activation of the sympathetic nervous system (chromogranin A [encoded by *CHGA*]) contribute to what had been labeled hypertension-associated ESRD and also to nonspecified chronic glomerulonephritis–associated ESRD in African Americans.[28-30] Nonetheless, attention to modifiable environmental risk factors can alter disease expression in those who are genetically susceptible to such complex diseases as type 2 diabetes because of mutations in the *TCF7L2* gene.[31] Thus, harboring a risk allele for ESRD should not alter strict attempts at slowing nephropathy progression by using diet, exercise, and medical therapies. Powerful molecular tools, including genome-wide association studies, promise new breakthroughs in this field in the coming years. Although gene polymorphisms may underlie a portion of the familial aggregation of nephropathy, appropriate referral to nephrologists for access placement, anemia treatment, and management of renal-related bone diseases remains critical.

CONCLUSION

Activities intended to improve the detection, treatment, and control of CKD should be incorporated into existing health care systems to avoid redundancy and waste of resources. In addition, these interventions should be targeted at high-risk populations to efficiently use the available public health resources. The ESRD Network 6 Family History project shows that 1 high-risk group for CKD, family members of patients with stage 5 CKD (ESRD), can be identified by the ESRD Networks, which constitute a national CKD surveillance system for stage 5 CKD and may be an existing resource that can be used to target CKD prevention programs to these individuals. One can envision a day when the success of existing health systems in identifying and educating at-risk family members will be routinely monitored and reported by the ESRD Network surveillance system. One would anticipate that individuals like those in the ESRD Network 6 Family History project who answer that they are members of at-risk families also will be found to have high rates of pre-ESRD nephrology care, arteriovenous fistulas, informed modality selection and preemptive transplantation, and control of risk factors for early mortality after the start of renal replacement therapy.

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REFERENCES

1. Teutsch SM, Churchill RE (eds): Principles and Practice of Public Health Surveillance (ed 2). Oxford, NY, Oxford University, 2000

2. McClellan W: Hypertensive end-stage renal disease in blacks: The role of end-stage renal disease surveillance. Am J Kidney Dis 21:S25-S30, 1993 (suppl 1)

3. Geiss LS, Herman WH, Goldschmid MG, et al: Surveillance for diabetes mellitus—United States, 1980-1989. MMWR CDC Surveill Summ 42:1-20, 1993

4. McClellan WM, Krisher JO: Collecting and using patient and treatment center data to improve care: Adequacy of hemodialysis and end-stage renal disease surveillance. Kidney Int Suppl 74:S7-S13, 2000

5. US Renal Data System: USRDS 2007 Annual Data Report. The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2007

6. Rocco MV, Frankenfield DL, Hopson SD, McClellan WM: Relationship between clinical performance measures and outcomes among patients receiving long-term hemodialysis. Ann Intern Med 145:512-519, 2006

7. Helgerson SD, McClellan WM, Frederick PR, Beaver SK, Frankenfield DL, McMullan M: Improvement in adequacy of delivered dialysis for adult in-center hemodialysis patients in the United States, 1993 to 1995. Am J Kidney Dis 29:851-861, 1997

8. McClellan WM, Frankenfield DL, Frederick PR, Helgerson SD, Wish JB, Sugarman JR: Improving the care of ESRD patients: A success story. Health Care Financ Rev 24:89-100, 2003

9. Chapman AB: Autosomal dominant polycystic kidney disease: Time for a change? J Am Soc Nephrol 18:1399-1407, 2007

10. Ferguson R, Grim CE, Opgenorth TJ: A familial risk of chronic renal failure among blacks on dialysis? J Clin Epidemiol 41:1189-1196, 1988

11. Freedman BI, Spray BJ, Tuttle AB, Buckalew VM Jr: The familial risk of end-stage renal disease in African Americans. Am J Kidney Dis 21:387-393, 1993

12. Lei HH, Perneger TV, Klag MJ, Whelton PK, Coresh J: Familial aggregation of renal disease in a population-based case-control study. J Am Soc Nephrol 9:1270-1276, 1998

13. O'Dea DF, Murphy SW, Hefferton D, Parfrey PS: Higher risk for renal failure in first-degree relatives of white patients with end-stage renal disease: A population-based study. Am J Kidney Dis 32:794-801, 1998

14. Satko SG, Sedor JR, Iyengar SK, Freedman BI: Familial clustering of chronic kidney disease. Semin Dial 20:229-236, 2007

15. Bleyer AJ, Sedor JR, Freedman BI, et al: Risk factors for development and progression of diabetic kidney disease and treatment patterns among diabetic siblings of patients with diabetic kidney disease. Am J Kidney Dis 51:29-37, 2008

16. Bergman S, Key BO, Kirk KA, Warnock DG, Rostant SG: Kidney disease in the first-degree relatives of African-Americans with hypertensive end-stage renal disease. Am J Kidney Dis 27:341-346, 1996

17. Jurkovitz C, Franch H, Shoham D, Bellenger J, McClellan W: Family members of patients treated for ESRD have high rates of undetected kidney disease. Am J Kidney Dis 40:1173-1178, 2002

18. McClellan W, Speckman R, McClure L, et al: Prevalence and characteristics of a family history of end-stage renal disease among adults in the United States population: Reasons for Geographic and Racial Differences in Stroke (REGARDS) renal cohort study. J Am Soc Nephrol 18:1344-1352, 2007

19. Speckman RA, McClellan WM, Volkova NV, et al: Obesity is associated with family history of ESRD in incident dialysis patients. Am J Kidney Dis 48:50-58, 2006

20. Jurkovitz C, Hylton TN, McClellan WM: Prevalence of family history of kidney disease and perception of risk for kidney disease: A population-based study. Am J Kidney Dis 46:11-17, 2005

21. Lea JP, McClellan WM, Melcher C, Gladstone E, Hostetter T: CKD risk factors reported by primary care physicians: Do guidelines make a difference? Am J Kidney Dis 47:72-77, 2006

22. McClellan WM: Epidemiology and risk factors for chronic kidney disease. Med Clin North Am 89:419-445, 2005

23. Levey AS, Coresh J, Balk E, et al, for the National Kidney Foundation: National Kidney Foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Ann Intern Med 139:137-147, 2003

24. Freedman BI, Soucie JM, McClellan WM: Family history of end-stage renal disease among incident dialysis patients. J Am Soc Nephrol 8:1942-1945, 1997

25. Freedman BI, Volkova NV, Satko SG, et al: Population-based screening for family history of end-stage renal disease among incident dialysis patients. Am J Nephrol 25:529-535, 2005

26. Satko SG, Freedman BI: The importance of family history on the development of renal disease. Curr Opin Nephrol Hypertens 13:337-341, 2004

27. Ramirez SP, McClellan W, Port FK, Hsu SI: Risk factors for proteinuria in a large, multiracial, southeast Asian population. J Am Soc Nephrol 13:1907-1917, 2002

28. Dusel JA, Burdon KP, Hicks PJ, Hawkins GA, Bowden DW, Freedman BI: Identification of podocin (NPHS2) gene mutations in African Americans with nondiabetic end-stage renal disease. Kidney Int 68:256-262, 2005

29. Salem RM, Cadman PE, Chen Y, et al: Chromogranin A polymorphisms are associated with hypertensive renal disease. J Am Soc Nephrol 19:600-614, 2008

30. Freedman BI, Sedor JR: Hypertension-associated end-stage renal disease: Perhaps no more. J Am Soc Nephrol 19:2047-2051, 2008

31. Florez JC, Jablonski KA, Bayley N, et al, for the Diabetes Prevention Program Research Group. TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. N Engl J Med 355:241-250, 2006