J Am Soc Nephrol 14: S81–S87, 2003

Screening for Chronic Kidney Disease: Unresolved Issues

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Abstract. End-stage renal disease is epidemic in the United States. As a measure to control this epidemic, it has been recommended that individuals who are at risk for CKD be tested for undetected kidney disease during routine health care encounters. There are generally accepted criteria against which screening recommendations for CKD control and prevention programs should be judged. If detection strategies are to be adopted for the screening of kidney disease, then CKD must represent a significant public health problem, be characterized by a clear natural history with a detectable asymptomatic period, outcomes should be improved by early treatment, and acceptable screening tests should be available. Health systems must provide adequate and appropriate follow-up medical care for individuals with newly detected CKD. Finally, the cost-effectiveness of screening needs to be demonstrated and the effectiveness of screening as a means of achieving reductions in CKD should be proven in randomized trials.

End-stage renal disease (ESRD) is epidemic in the United States, with an estimated increase in the incidence of ESRD of 4.1%/yr during the next decade (1). Recently published clinical practice guidelines recommend that, as a response to this epidemic, individuals who are at-risk for CKD (Table 1) be tested for undetected kidney disease during routine health care encounters (2). The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) screening recommendations are supported, in part, by similar recommendations for diabetes mellitus (3) and hypertension (4,5) that link CKD to specific interventions to delay progressive renal injury. This paper discusses some of the issues that should be considered when establishing population-based programs to promote screening for CKD.

Are Population-Based Programs to Promote Screening for CKD Needed?

Population-based programs to promote screening for CKD are intended to increase the rate that persons with previously undetected renal injury are identified and linked to further evaluation and disease modifying intervention (6). It is the expectation that early intervention for patients with CKD will delay, if not prevent, subsequent progression to ESRD. Population-based programs to improve CKD screening can be targeted either at health systems (quality improvement programs) or at populations (case detection programs).

Both public education and counseling by health care providers to promote CKD screening can lead to increased awareness about the risks of CKD and benefits of treatment when coupled with educational activities. This effect was observed in early community-based hypertension control programs where screening activities were often used to increase provider awareness about hypertension detection and control, and to encourage screening participants to discuss hypertension care with their physicians (7).

Despite the appeal and potential benefits of population-based programs to promote screening for CKD, it is not clear that the basis for prevention strategies based on screening high-risk populations has been fully established (8). If health care providers are currently providing needed CKD screening or if screening can be easily implemented within existing health care systems, then the resources necessary to develop and implement screening programs might be better applied to other public health problems.

Inadequate Screening for CKD Among Patients with Diabetes

Although information is sparse, there is evidence that, despite widely disseminated guidelines, patients with diabetes mellitus are often not screened for CKD (9–17). Similar evidence is lacking for other high-risk KDOQI populations. Clarification of CKD detection issues for these groups awaits further study.

Our recent experience with a population-based program to improve screening for proteinuria among patients with diabetes mellitus illustrates this issue. During the last 6 yr, billing claims for diabetic Medicare patients in a single southeastern state of the Unites States have been used to report information to physicians about their patient care (18). This practice-specific feedback is intended to help physicians improve care. Efforts to improve screening for diabetic kidney disease began

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1046-6673/1407-0081
Journal of the American Society of Nephrology

DOI: 10.1097/01.ASN.0000070144.86024.04

Table 1. Individuals at risk for chronic kidney disease[a]

At-Risk Population	Estimated Size of Population in Millions	Evidence-Based Guidelines Recommend Routine Screening
Older individuals	45.8	NA
Race and ethnic groups	34.7	NA
African Americans	34.7	NA
American Indians and Alaskan natives	2.5	NA
Hispanic or Latino	35.3	NA
Diabetes mellitus	15.6	4
Hypertension	43.1	3
SLE	0.2	NA
Kidney transplant recipients	0.09	NA
Daily NSAID use	13	NA

[a] SLE, systemic lupus erythematosus; NSAID, Non-steroidal antiinflammatory use.

in 1996 and this extensively promoted program was implemented in 1999.

Despite several years of feedback on practice-specific diabetes care, there was evidence of substantial nonscreening for CKD by these primary care practices. Feedback reports were provided during 2001 to 1964 physicians with at least five diabetic patients in their practice. The mean number (and SEM) of diabetic patients assigned to each practice during 2000 was 34.9 (32.6) and the mean (and SEM) number of visits-per-patient was 10.6 (25.1). The frequency of claim-based urine protein testing among physician practices is shown in Figure 1. Most practices (70%) screened fewer than 10% of their patients, whereas others had screening rates in excess of 50% of their diabetic patients.

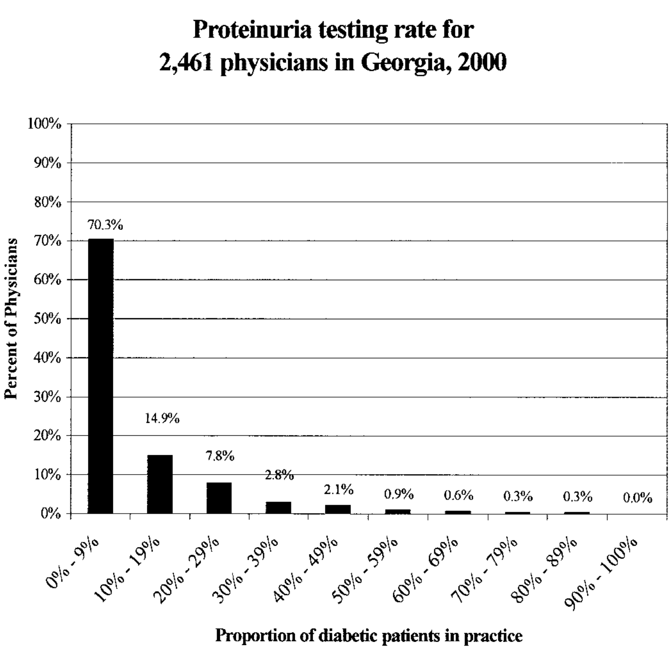

Figure 1. Proteinuria testing rate for 2461 physicians in the state of Georgia, 2000.

Public Health Basis for CKD Screening

Evidence that existing health care systems fail to provide CKD screening services for one or more at-risk populations is insufficient to establish population-based interventions targeted at either the health care system, or individual populations of at-risk individuals or both. Support for a population-based CKD screening strategy must be sought in the characteristics of CKD, the actual screening process, the health system, and health policy analyses (6).

Burden of CKD. Screening for CKD might be warranted in populations where the high prevalence of CKD significantly decreases quality of life or life expectancy. The burden of CKD within the US population is illustrated by the recent report by Kiberd and Clase that estimated that the cumulative life-time risk and reduction in life expectancy associated with ESRD is comparable with that of colorectal cancer, breast cancer, and prostate cancer (19). Furthermore, there is unequivocal evidence that quality of life is impaired in advanced renal failure (20–21). Finally, the total Medicare and non-Medicare costs of the US ESRD program in 1999 exceeded $17 billion (22).

Prevalence of Undetected CKD. Epidemiologic surveys documenting the current state of patient awareness of disease, treatment rates, and the degree of disease control of CKD among individuals in high-risk populations is lacking. However, a number of population-based studies show persistently high levels of undetected, untreated, and uncontrolled diabetes and hypertension in the United States. It is reasonable to suggest that similar deficiencies with respect to CKD will be demonstrated (23–25). However, until the prevalence of undetected renal disease within specific at-risk populations is defined, it may be premature to broadly implement at-risk screening.

Prolonged Period for Undetected CKD. Chronic diseases like CKD typically have a variable latent period during which the disease is present and asymptomatic. Although it is not clear when CKD becomes symptomatic, substantial loss of renal function can occur before clinical events associated with CKD become apparent. For example, increased prevalence of anemia, which may be symptomatic, is generally observed among CKD patients when the GFR falls below 60 ml/min (26). With the onset of advanced renal insufficiency, with GFR less than 30 ml/min, symptoms associated with uremia become frequent. Thus, there is a substantial range of GFR during which patients with CKD, defined by a GFR of 90 ml/min or less, may be asymptomatic and where screening is justified.

Effective Early Treatment for CKD. Early detection of CKD should lead to treatment that delays or prevents the occurrence of significant morbidity and mortality. Management of patients with CKD should incorporate aggressive blood glucose control for diabetic patients (27–29), aggressive BP control (30–32), dietary protein restriction to the recommended daily allowance of 0.8 g/kg per d (33), and use of angiotensin converting enzyme inhibitors (34,35) to delay the progression of CKD. This information has been incorporated into clinical practice guidelines for the management of diabetic renal disease (3). Similar recommendations have been published for renal insufficiency due to hypertension (4,36).

Screening Test Characteristics. The NKF-KDOQI guidelines recommend that individuals be screened for CKD using a spot urine for protein and an estimate of GFR based on serum creatinine (2). These two tests are combined to assign the patient to a CKD risk strata. The NKF-KDOQI risk strata, in turn, are linked to management steps for the degree of CKD risk. However, it is not clear that the recommended screening tests (spot urine and serum creatinine) have characteristics acceptable for large-scale screening. For example, a recent study of the test-retest variability for serum creatinine found substantial variability in the same subject across laboratories and time (37). Test-to-test variability was inversely correlated with estimated GFR, particularly when renal function was above 60 ml/min per 1.73 m^2.

Mattix and colleagues have recently reported that when a common test-threshold was used for a single albumin-to-creatinine ratio (ACR) among participants in the NHANES III, the gender-specific prevalence of microalbuminuria was 6.0% among men and 9.2% among women (38). Similar race-specific differences in NHANES III were seen among non-Hispanic whites (7.2%) compared with non-Hispanic blacks (10.2%). In contrast, gender-specific thresholds for ACR eliminated the gender- but not the race-specific differences in prevalence. In a recent report (39), Houlihan *et al.* evaluated the characteristics of ACR as a screening tool. Using gender-specific cutoff values (22.1 mg/g in men and 30.9 mg/g in women), they found that spot ACR provided high sensitivities (men, 95.7%; women, 93.35%) and had excellent receiver operator characteristics curves.

Health Systems and Screening for CKD

Access to Adequate Care. Screening programs for high-risk populations for CKD should ensure that follow-up evaluation and care are available to all screen positive individuals and, if CKD is confirmed, that long-term disease-modifying care is available. This may prove to be a major impediment if access to health care is limited among individuals with CKD. Perneger and associates examined the association between access to health care and ESRD in a case-control study of incident dialysis patients (40). They found an association between risk of ESRD and indicators of access to health care, including receipt of Medicaid benefits and number of missing teeth. These observations and those that show increased ESRD risk among low income populations, a marker for access to health care, suggest that availability of adequate health care that incorporates routine CKD screening may be an important barrier to successful at-risk screening strategies (41,42).

A health care system serving individuals who screen positive for CKD must also provide appropriate care. There is evidence that the detection and care of CKD among individuals with sufficient access to health care may not conform to guideline-based recommendations. For example, surveys of physician knowledge find high levels of misunderstanding of current guideline recommendations for diabetic nephropathy (43). Screening for diabetic nephropathy among patients with diabetes mellitus has been shown to be deficient in diverse clinical populations (9–15). Furthermore, use of angiotensin-converting enzyme (ACE) inhibitors has been shown to be less than optimal among patient populations with CKD (44–46). Finally, control of BP is reported to be less than adequate among patients treated for CKD (46–47). If similar patterns of care persist in other populations, then screening and referral of individuals with undetected CKD to poorly performing health care systems may be ill-advised.

Health Policy and Screening for CKD

Population-based CKD screening programs will not be incorporated as a component of a standard prevention strategy in the absence of a public policy consensus that allocates resources to program implementation. The first public policy decision that seems to be crucial is the choice between strategies targeted at high-risk *versus* general populations. Factors that can contribute to a consensus among policy makers supporting either or both of these approaches include cost-benefit analyses and randomized clinical trials.

High-Risk Screening or Population-Based Intervention Strategies? Although there is no well defined method of identifying "high-risk" populations, the KDOQI guidelines identify demographic groups characterized by high incidence or prevalence of CKD as populations that should be targeted for screening and intervention (2). Note that similar high-risk disease control strategies for cardiovascular disease have been criticized. Rose and others have argued that most cases of cardiovascular disease arise not from the "high-risk" tail of the population, but from the general population (48,49).

A similar situation may pertain to ESRD. African Americans and Native Americans are classified as high-risk populations by KDOQI, with ESRD incidence rates of 953 and 652 per million, respectively, compared with an incidence rate of 237 per million for Caucasian Americans (50). Despite high rates, Native Americans contribute only 1.2% and African Americans 29.1% of all ESRD incident cases whereas Caucasians account for 63.3% of the total cases of ESRD in the US population.

Rose proposed a population-based approach for cardiovascular diseases that lowers mean levels of risk factors in the entire population to shift the whole distribution of exposures toward a favorable direction (48). For example, Strachan (51) shows that a population-based strategy that decreases cholesterol in all men by 0.1 mmol/L is comparable with a high-risk screen-and-treat policy that achieves a cholesterol reduction of 1.0 mmol/L in the top decile of plasma cholesterol. It is reasonable to ask if similar population-based interventions to prevent diabetes mellitus or hypertension might accomplish a greater reduction in ESRD compared with high-risk detection and treatment strategies.

Cost-Effectiveness Analysis. The cost-effectiveness of screening is one of the most relevant criteria for advocating systematic screening for renal disease. Unfortunately, extremely limited data on the cost, as well as the effect of the early detection of renal disease are available. Indeed, the few publications that have attempted to address this issue have utilized computer simulation models, rather than performing randomized clinical trials evaluating the efficacy of systematic screening. In addition, the majority of these analyses are limited to studying the efficacy of microalbuminuria screening in the context of the prevention of diabetic nephropathy.

For example, a recent review by Scheid *et al.* identified 7 such cost-effectiveness analyses (8), only 2 of which focused on type 2 diabetes mellitus (52,53). In both these analyses, screening for microalbuminuria appeared to be a cost-effective approach. However, it was the systematic treatment of all newly diagnosed patients with type 2 diabetes mellitus that appeared to be most associated with the highest life expectancy, as illustrated by a marginal cost-effectiveness ratio of $7,500 per quality-adjusted-life-year (QALY) gained when all patients were treated with angiotensin-converting enzyme inhibitors compared with systematic screening for microalbuminuria (53). Indeed, these authors further argue that the routine treatment of all patients with type 2 diabetes mellitus using ACE inhibitors would potentially bypass current concern for low rates of microalbuminuria screening by primary care physicians. However, these analyses were limited by strict assumptions as to the efficacy of ACE inhibitors in preventing the progression of normoalbuminuria to microalbuminuria. Furthermore, the marginal cost-effectiveness ratio was extremely sensitive to factors such as age at diagnosis of diabetes mellitus, cost of ACE inhibitors, and side effects of the chronic use of these drugs.

In the only analysis evaluating the cost-effectiveness of screening for nondiabetic renal disease, Craig *et al.* estimated that a single opportunistic dipstick screening in a hypothetical cohort of individuals aged 50 yr and older would be associated with the prevention of 205 patients with ESRD, thereby resulting in significant cost savings (54). However, this analysis, as in other simulation models, is subject to the limitations of the model assumptions such as those the authors made regarding the reliability and reproducibility of screening tools and the natural history of renal disease progression. Indeed, the authors note uncertainty about the risk of progression to ESRD among patients with proteinuria, the risks and benefits of ACE inhibitor therapy among patients at low risk for ESRD, and the adverse psychologic and physical consequences of the screening process. Thus, although these indirect evaluations of the effectiveness of screening using simulation models suggest its usefulness, these findings only emphasize the dearth of definitive studies that examine the effectiveness of screening for renal disease. Table 2 presents a list of clinical data that may be required to perform a thorough cost-effectiveness analysis of the value of screening for renal disease.

Randomized Controlled Trials of Screening. The rationale for population-based screening for CKD should include randomized, controlled trials (RCT) that demonstrate the effectiveness of CKD screening strategies in different populations. Although RCT evidence to support CKD screening has not yet been published, examples of RCT of screening for colorectal carcinoma (55), breast cancer (56), prostate cancer (57) and depression (58) may serve as templates for how such trials might be designed. Note that the relatively low prevalence of CKD in many at-risk populations might render the design of appropriately powered randomized trials extremely difficult.

Populations for Studying CKD Screening

Are there populations of patients wherein the practicality of a population-based screening strategy for CKD might be easily studied? Two studies we have recently reported on suggest this possibility. These studies involve family members of patients with ESRD and patients who are hospitalized for cardiovascular problems.

Family Members of ESRD Patients. The family members study is a cross-sectional survey of screening to identify CKD among family members of ESRD patients conducted at 10 community dialysis centers in Georgia (59). Family members of ESRD patients were recruited for CKD screening. A medical history, measurements of BP, serum glucose, hemoglobin (Hb), serum creatinine, and urinalysis were obtained at community screening sites. Of 221 family members screened between 1999 and 2001 in Georgia, 13.9% had an estimated creatinine clearance (Ccr) $<$60 ml/min. Proteinuria of 1+ or more was found on urinalysis in 9.9%. Among the participants with any evidence of CKD, as measured by Ccr $<$60 ml/min or proteinuria $\geq$1+ or both, only 13.0% were aware of their KD whereas 82.6% had seen a physician in the last 6 mo.

Hypertension defined as either a measured high BP (HBP) and/or a personal history of HBP was present in 58% of the study population. Of these, 17% were unaware of their HBP, 6% were aware but not treated and 34.1% had their HBP treated but not controlled (59). Similarly, 18.6% had a random blood glucose level $\geq$200 mg/dl or had a history of diabetes mellitus (59). Based on these preliminary findings, there appears to be a high prevalence of CKD in family members of patients with ESRD. These individuals demonstrated diminished GFR, proteinuria, poorly controlled hypertension, and/or diabetes. Finally, they were often unaware of their impaired renal function despite a recent visit to the physician.

Hospitalized Heart Failure Patients. The Heart Failure and Chronic Kidney Disease Study is a retrospective cohort study of the Medicare patients in Georgia comprised of a random sample of 645 Medicare beneficiaries discharged

Table 2. Clinical information required for cost-effectiveness analysis

Assumptions to be made	• Stages of renal disease progression
	• Diagnostic work-up according to each type of renal disease
	• Frequency of screening
Disease-related factors	• Distribution of renal disease according to etiology
	• Prevalence of undiagnosed renal disease in the population (prevalence of each stage, microalbuminuric, proteinuric but no renal insufficiency, *etc.*)
Screening tests-related factors	• Screening test or combination of screening tests as options for diagnosis (*e.g.*, urine dipstick, then urine protein/creatinine to confirm and serum creatinine OR urine micral dipstick then urine protein/creatinine to confirm and serum creatinine)
	• Sensitivity/specificity of the individual screening test, as well as the combination of screening tests for determining true kidney disease
	• Average prediagnosis interval by screening
Transition probabilities	• Probability of transition through each stage of renal disease in the absence of treatment (as a function of proteinuria and blood pressure control).
	• Probability of transition through each stage of renal disease with treatment
	• Probability of coexisting complications (*e.g.*, cardiovascular) at each stage of renal disease by race, level of blood pressure control, etc.
	• Mortality rate of each stage of renal disease progression
Cost issues	• Costs associated with screening for
	• population-based (including logistical costs); cost per abnormal case
	• selective (high-risk only)
	• opportunistic (after a regular clinic visit)
	• Cost of treatment at each stage of renal disease, with or without complications, including:
	• outpatient costs: how many visits at each stage of renal disease?
	• drug therapy: what types or combinations of drugs are commonly prescribed at each stage?
	• hospitalization costs (need to know hospitalization rates at each stage) Chronic dialysis costs (hospitalization costs related to access, cardiovascular complications, coexisting diabetes, *etc.*)

from Georgia hospitals during 1998 with a diagnosis of congestive heart failure (60). The mean age of this population was 75.7 yr; approximately 60% were women and 29% were black. As expected, 66% of patients had a history of hypertension, 44% had diabetes, and 20% had a history of cardiovascular event. Other cardiovascular comorbidities included coronary artery disease (51%), myocardial infarction (26%), and angina (15%). A multivariate analysis showed that CKD was independently associated with increased risk of death. Patients with CKD (defined as Scr $\geq$1.5 mg/dl) had a 28% increase in the risk of mortality during the first year of follow-up. The use of ACE inhibitors declined with increasing Scr in this population. Only 58% of patients with Scr $<$1.4 mg/dl were prescribed an ACE inhibitor, declining to 42% for patients with a Scr $>$2.0 mg/dl. These results indicate that CKD is both prevalent among patients with congestive heart failure, and confers substantial increased risk of mortality in this population.

Conclusion

The public health basis for population-based CKD screening has not been convincingly demonstrated for many high-risk populations and it is not clear that existing health care systems can provide appropriate care for screen positive individuals. It is also unclear that programs to improve CKD detection in high-risk populations other than diabetes mellitus would be cost-effective. Furthermore, definitive randomized clinical trials may not be feasible given the need for a large number of study subjects and a prolonged follow-up period. As an alternative to the performance of randomized clinical trials of screening in community-based populations, prospective cohort studies comparing screened and unscreened populations of hospitalized patients or family members of ESRD patients may be more practical. Finally, it has not been established that the best CKD prevention strategies should target risk factor modification in high-risk rather than the general population.

Until these issues are resolved, it seems prudent to reserve strong recommendations for population-based strategies to improve CKD detection to those populations where strong, if not convincing, evidence for the utility of CKD screening exists. It is also important to note that population-based screening strategies might be used to change physician and patient behaviors with respect to the detection and management of CKD rather than only reducing the prevalence of undetected renal injury. This latter possibility deserves further study.

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