

Screening Populations at Increased Risk of CKD: The Kidney Early Evaluation Program (KEEP) and the Public Health Problem

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The epidemiological characteristics of the US end-stage renal disease population growth and increased costs in the late 1980s framed the public health agenda for the development of a community-based chronic kidney disease (CKD) screening program. Development of the National Kidney Foundation Kidney Early Evaluation Program (KEEP) included 2 preliminary screening programs, the Computerized Assessment of Risk and Education and the KEEP pilot, which was organized around the African American Study of Kidney Diseases clinical centers. The current KEEP program, launched in August 2000, targets individuals with diabetes, hypertension, or a family history of diabetes or hypertension or CKD. The screening includes informed consent, health screening questionnaire, diagnostic panel, and physician consultation. Participants are followed up by telephone and mail. Of 100,000 KEEP participants screened, 28.7% have CKD and 6.7% self-reported CKD stages 1 to 5. Conversely, National Health and Nutrition Examination Survey 1999-2002 results show 13.1% CKD prevalence; 2.9% of women and 17.9% of men with an estimated glomerular filtration rate less than 60 mL/min/1.73 m² self-report CKD. CKD prevalences in KEEP by stage are 3.1% for stage 1; 4.8%, stage 2; 19.7%, stage 3; and 1.1%, stages 4 and 5, confirming the ability of this targeted screening program to detect CKD early. In addition to identifying individuals at increased risk of kidney disease, KEEP's structured data collection provides an opportunity to advance knowledge about kidney disease and advance the CKD public health agenda.

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The US end-stage renal disease (ESRD) population requiring replacement therapy with dialysis or kidney transplantation included more than 112,000 patients in 1985 and increased to nearly 187,000 by 1990.¹ During that interval, annual incident ESRD counts increased from 30,000 in 1985 to 50,000 in 1990 (Fig 1). Approximately 70% of the population had a primary diagnosis of diabetes or hypertension. Compared with whites, minority ethnic or racial groups, including African Americans, Hispanics, Asians/Pacific Islanders, and Native Americans, had greater incidences of diabetic kidney failure. Interestingly, African Americans had much greater rates of hypertension as the primary diagnosis for ESRD than other races. The nephrology community recognized that the frequent late presenters experienced poor outcomes, offered few opportunities for preventive interventions, and carried high costs. Delay of what was later to be described as chronic kidney disease (CKD) progression to chronic kidney failure was considered the major means of limiting the growth of the ESRD population. Early detection of kidney disease offered the most potential to improve outcomes by allowing for more time to intervene when most patients were asymptomatic.

TOWARD CKD DETECTION

The Indiana Project: Computerized Assessment of Risk and Education

In 1991, the nephrology community focused on individuals with increased risk of ESRD with the intent to improve medical care and slow the loss of kidney function, a goal that fit 1 of the conclusions of the report by the Institute of Medicine on ESRD of the same year.² The Computerized Assessment of Risk and Education (CARE) was developed by National Kidney Foundation (NKF) of Indiana in collaboration with the Diabetes Research and Training Center of Indiana University as a free community-based screening for first-degree relatives of dialysis

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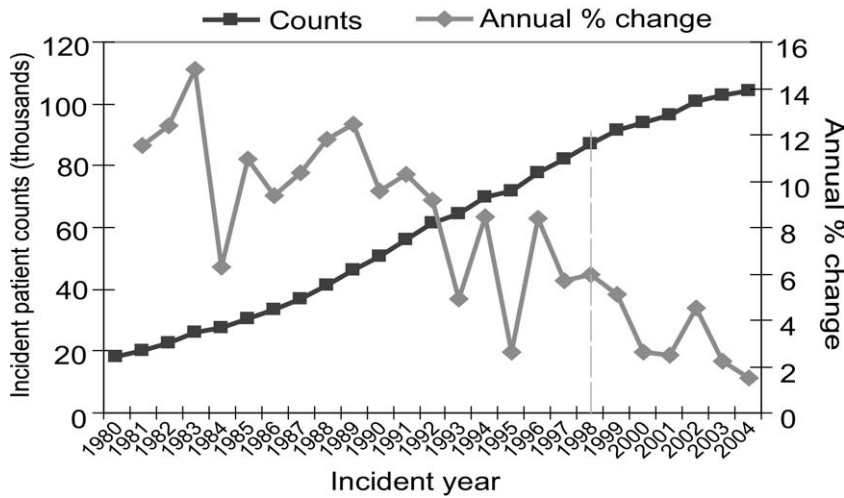


Figure 1. End-stage renal disease incident rates using patient counts and annual change by year.

patients and individuals with diabetes and hypertension.³ Based on limited preliminary data at the time, the developers viewed mass screening of the population as inefficient, detecting too few individuals with evidence of disease. Initial CARE results identified 56% of 348 individuals as at risk of diabetes, hypertension, and/or kidney disease.³ This project supported the feasibility of a regional targeted kidney disease screening program using simple and clear criteria to identify individuals at risk of kidney disease.

The Kidney Early Evaluation Program Pilot Study

CARE data were reviewed and a national pilot study was planned to determine the feasibility of identifying individuals at increased risk of CKD and to promote public and patient education. The Kidney Early Evaluation Program (KEEP) pilot study was a free community-based screening in 21 cities in which the African American Study of Kidney Diseases (AASK) clinical centers were located from April to October 1997. Individuals at increased CKD risk were identified by using the inclusion and exclusion criteria listed in Table 1. Of 889 screened individuals aged 18 to older than 85 years, 67% were women.³ The target population showed a predominance of family history (diabetes, 57.5%; hypertension, 72.9%; and kidney disease, 25%); preexisting conditions were less prevalent (diabetes, 18.9%, and hypertension, 28.9%). Screening results showed that 71% (635 individuals) had at least 1 test value outside the normal range, 44% (394) had 2 or more test values outside the normal

range, and 58% (514) learned of at least 1 previously unknown condition. Thus, the NKF developed a detection program designed to empower individuals and communities to address kidney disease through early diagnosis and education.

The KEEP Launch

In 1998, seminal reports describing the epidemic of cardiovascular disease (CVD) and premature death in the CKD population were published.^{4,5} To expand on CARE and the KEEP pilot study, KEEP as launched in August 2000 was intended to address coalition building and professional education, in addition to the core mission of patient and community education. The urgency of the public health problem also was highlighted that year in the US Renal Data System (USRDS) Annual Data Report, showing ESRD incident and prevalent rates (1998 data) of 85,992 and 350,040 and 2010 projections of 172,667 and 631,330, respectively.^{6,7} Similarly,

Table 1. Kidney Early Evaluation Program Inclusion and Exclusion Criteria

Included	Excluded
Aged ≥ 18 y	Renal replacement therapy
Personal history	Dialysis
Diabetes	Kidney transplantation
Hypertension	
Family history	
Diabetes	
Hypertension	
Chronic kidney disease	

annual ESRD program costs were projected to increase from \$10.8 billion in 1998 to \$28.3 billion in 2010.⁶

The KEEP launch objectives were to determine the feasibility of identifying and enrolling the target groups, determine the prevalence of risk factors, and show levels of blood pressure, glycemic control, and the prevalence of participants with evidence of CKD. Inclusion and exclusion criteria continued as listed in Table 1. Initial data showed that 6,071 eligible participants were screened from August 2000 through December 2001. A total of 68% were women, 43% were African American, 36% were white, 10% were Hispanic, and 5% were Native American. Screening definitions were met; 27% had diabetes, 64% had hypertension, 29% had albuminuria, 16% had an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m², and 44% were obese.⁸ The targeted KEEP screening was concluded to be effective in identifying persons with poorly controlled kidney disease risk factors.⁸

THE KEEP

Current KEEP Screening Process

Over time, the program was modified to incorporate significant developments, most importantly the Kidney Disease Outcomes Quality Initiative (KDOQI) CKD guideline,⁹ which inspired a change in reporting from Cockcroft-Gault creatinine clearance to eGFR using the 4-variable isotope dilution mass spectrometry–traceable Modification of Diet in Renal Disease (MDRD) Study equation. CKD stages⁹ were defined as stage 1, eGFR greater than 90 mL/min/1.73 m², albumin-creatinine ratio of 30 mg/g or greater; stage 2, eGFR of 60 to 89 mL/min/1.73 m², albumin-creatinine ratio of 30 mg/g or greater; stage 3, eGFR of 30 to 59 mL/min/1.73 m²; stage 4, eGFR of 15 to 29 mL/min/1.73 m²; and stage 5, eGFR less than 15 mL/min/1.73 m².

Potential participants are encouraged to attend a screening in a nonclinical location with easy public access. The media, posters, and brochures are used to attract participants who meet entry criteria. Screening time is approximately 1 hour. The event is organized by a series of 6 stations (Table 2). The KEEP screening questionnaire collects information about self-reported personal and family history of diabetes, hypertension,

Table 2. Kidney Early Evaluation Program Screening Event Stations

Station	Comment
1 Registration	Review inclusion and exclusion criteria
2 Screening questionnaire	Informed consent obtained Questionnaire administered by volunteers as needed
3 Physical measurements	Blood pressure, height, weight recorded
4 Blood and urine collection	Blood drawn by phlebotomist
5 Physician consultation	Review risk factors and on-site test results
6 Screening review	Ensure complete data collection

CVD, and kidney disease and includes questions about tobacco use, access to medical care, and drug interventions. The diagnostic panel is described in Table 3. Participants receive same-day results of all on-site tests. A physician reviews risk factors and on-site screening results with each participant and encourages participants to see their primary physicians.

KEEP call-center staff members at the NKF conduct follow-up by telephone to review results, respond to questions, and encourage participants to access health care and review by their primary physicians. Participants with central laboratory critical values are notified by means of a telephone alert system as soon as results are received, within a few days after the event. Approximately 1 month after the screening, participants receive a report by mail that includes on-site and central laboratory results with non-technical explanations. If participants identify their health care professionals, these clinicians receive 3-page KEEP reports by mail that include all test results and a clinical action plan based on KDOQI⁹; the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure¹⁰; and American Diabetes Association¹¹ guidelines. Awareness of CKD could improve outcomes by stimulating clinicians to implement the clinical action plan for comprehensive care, addressing blood pressure targets, glycemic control, lipid management, and avoidance of nephrotoxic medications. For patients with CKD stages 4 and 5, or earlier stages in selected

Table 3. Kidney Early Evaluation Program Screening Panel

On-Site Tests*	Central Laboratory Tests†
Body mass index: height and weight	Serum creatinine, estimated glomerular filtration rate
Blood pressure	Hemoglobin
Blood glucose	Cholesterol and triglycerides‡
Urinary albumin-creatinine ratio	Parathyroid hormone§
Pyuria	Calcium§
Hematuria	Phosphorus§

*Reviewed with a physician on the day of the screening event.

†Mailed to participants and their physicians 4 to 6 weeks after the screening event.

‡Lipid parameters became available beginning May 1, 2005, for fasting or nonfasting participants.

§Beginning November 1, 2005, performed exclusively in participants with estimated glomerular filtration rate less than 60 mL/min/1.73 m².

cases, nephrology referral is recommended to prepare for dialysis or transplantation and provide ongoing management of CKD complications.

Roles of the NKF and Local KEEP Programs

In addition to the call center, NKF headquarters provides training, program or protocol information, staff certification, organization of sponsor-donated supplies and testing materials, and patient and professional educational materials. The NKF arranges for coordination with local media outlets, particularly for such special events as World Kidney Day,¹² and manages communication from the data coordinating center and reports to affiliates. The KEEP national steering committee oversees the program. The clinical oversight subcommittee supervises the quality assurance process to ensure participant safety during the events and the integrity of the data collection.

Affiliates determine sites and frequency of local programs and contact local sponsors. They recruit volunteers, including physicians, to implement the screening. Advantages of using local volunteers include reduced overhead and additional community engagement. After each screening, affiliate volunteers package blood tubes and ship them to the central laboratory. Volunteers also provide educational brochures on site to participants. Local NKF offices are well posi-

tioned to identify local medical resources, primary care centers, and social work support for participants with such challenges to health care access as absence of health insurance and mistrust of health care professionals.

Demographic Characteristics

From August 2000 to December 31, 2005, KEEP screenings took place in 49 of 50 US states, with Alaska being the exception (Fig 2).¹³ Of the participants, 25% had a history of diabetes, 52% had a history of hypertension, and 24% had a family history of diabetes, hypertension, or kidney disease. Compared with the stratified general-population noninstitutionalized adult sample, National Health and Nutrition Examination Survey (NHANES) 1999-2002, the KEEP population is older, more are women, fewer are white, more are African American, and levels of education are higher.¹³ Participation of African Americans in KEEP is about 4 times greater than in NHANES, or almost 20%. In the KEEP population, 5.7% have a grade school education or less compared with 23% in NHANES, and 57.8% of KEEP participants have some college education or higher compared with 51% in NHANES.¹³

KEEP FINDINGS

Chronic Kidney Disease

Based on KEEP screening results, CKD prevalence by stage is 3.1%, stage 1; 4.8%, stage 2; 19.7%, stage 3; and 1.1%, stages 4 and 5, confirm-

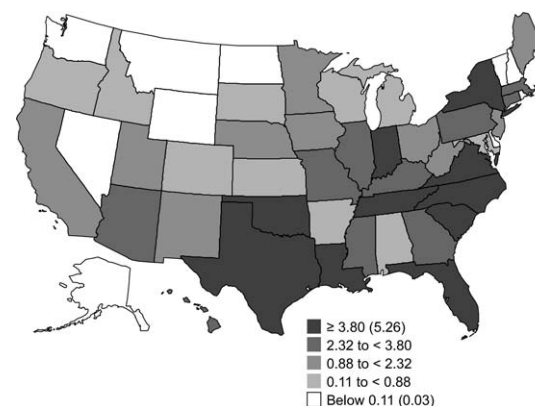


Figure 2. Percentage of distribution of Kidney Early Evaluation Program participants by state¹³ through 2005, n = 55,200. Values in parentheses represent the means of the quintiles.

ing the ability of this targeted screening program to detect CKD early.¹³ The overall CKD prevalence of 28.7% is an extraordinary demonstration of low CKD awareness because only 6.7% of participants in this enriched population self-reported CKD. Conversely, 2.9% of women and 17.9% of men in NHANES 1999-2002 with an eGFR less than 60 mL/min/1.73 m² self-reported CKD. KEEP participants self-reported kidney disease in general reflecting all stages, whereas the NHANES screening question pertains to weak or failing kidneys, implying only stages 3 to 5 CKD. Overall, percentages of the KEEP population with CKD by race are 32.4%, whites; 25%, African Americans; 22.5% Hispanics; and 25.6%, other races. This finding is in contrast to ethnic/racial disparities for ESRD and may be related to death and progression biases. The targeted screening is also shown by the NHANES CKD prevalence of 13%, representative of the general population, compared with 29% in the enriched KEEP population.

Hypertension

Of KEEP participants, 65.8% have increased blood pressure, 52.8% have self-reported hypertension (compared with 25% in NHANES), and 15.7% have isolated measured hypertension.¹³ These data suggest that 16% of participants become aware of hypertension at the screening. Older participants and African Americans are more likely to have hypertension; the prevalence is 91% for participants older than 75 years. Blood pressure targets are attained for fewer than half the entire KEEP population and for 20% to 30% of those with evidence of CKD (Fig 3).

Diabetes

Overall, 30% of KEEP participants have diabetes, self-reported (25%) or based on glucose testing alone (5%).¹³ Of participants with diabetes, 54% have albuminuria. Diabetes prevalence increases with CKD stage and is present in 52% of KEEP participants at stage 4. By race, diabetes is self-reported in 26.3% of whites, 24.0% of African Americans, 25.9% of Hispanics, and 28.2% of other races.¹³ Fifty percent of KEEP participants who self-report diabetes have a measured glucose level greater than the normal limit during the KEEP screening.

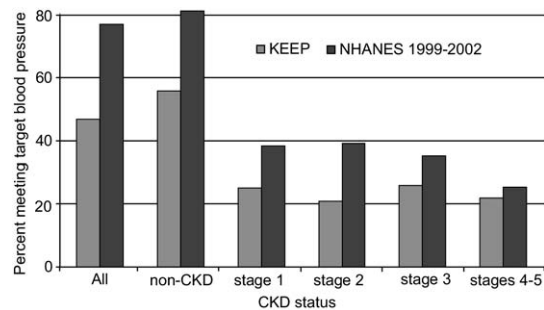


Figure 3. Kidney Early Evaluation Program (KEEP) participants meeting target blood pressure (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure¹⁰) by chronic kidney disease (CKD) stage.¹³ KEEP, n = 44,673; National Health and Nutrition Examination Survey (NHANES), n = 9,423.

Lipids and Body Mass Index

Only serum cholesterol and triglycerides are included in the KEEP screening because participants come to screenings in both fasting and nonfasting states. Preliminary data show that more than half the KEEP population has increased serum cholesterol levels. These tests are intended to stimulate ongoing physician care, including fasting lipid profiles. In the KEEP population, 77.5% are overweight or obese compared with 64.4% in NHANES.¹³ In both KEEP and NHANES, self-reported diabetes and hypertension increase steadily as body mass index increases.

Anemia and Bone and Mineral Metabolism

Using the anemia definition of hemoglobin level less than 13 g/dL in men and less than 12 g/dL in women, 17% of KEEP participants with CKD are anemic compared with 10% of participants without CKD.¹³ In participants with diabetes, anemia prevalence was 8.7% at CKD stage 1, 7.5% at stage 2, 22.2% at stage 3, and 52.4% at stages 4 and 5 compared with 6.9%, 5.0%, 7.9%, and 50.0% for participants without diabetes.¹⁴ Thus, anemia is more likely at advanced stages of CKD and in participants with diabetes. Bone and mineral metabolism parameters by KDOQI ranges,¹⁵ measured for only individuals with eGFR less than 60 mL/min/1.73 m², show calcium and phosphorus mainly at target levels, but increased intact parathyroid hormone levels in 74% of participants with an eGFR less than 30

mL/min/1.73 m² and 21% of those with an eGFR of 55 to less than 60 mL/min/1.73 m².¹³

Cardiovascular Disease

The interaction of CKD with CVD in KEEP, by using national death and ESRD data systems, showed that albuminuria, eGFR less than 60 mL/min/1.73 m², and anemia were each independently associated with self-reported CVD and mortality.¹⁶ In addition, survival for participants with both CKD and CVD was significantly decreased compared with intermediate survival for those with either condition alone, and survival was significantly improved for participants with neither condition.

KEEP: PUBLIC HEALTH ADVOCACY

KEEP is primarily a patient and family advocacy program to address the burden of kidney disease. KEEP is broadly directed toward encouraging action on the CKD public health problem, including educating the general public about CKD risk factors, encouraging at-risk individuals and families to seek clinician care, educating clinicians about CKD detection and treatment, and encouraging health plans and employers to focus on CKD and the government to continue trends addressing CKD beyond exclusive attention to ESRD.

ESRD Incidence Rates for Diabetes Decrease

Each year, the cost of the ESRD program continues to consume a greater percentage of the Medicare budget than the previous year. However, the ESRD population growth has slowed recently, with incidence counts lagging behind previous estimates^{4,5} and incidence rates caused by diabetes decreasing.^{1,17} Increased use of kidney-protective treatments is the most plausible explanation (Fig 4).¹ Alternatively, misclassification of diabetes as the cause of ESRD could contribute to the decrease, but this is unlikely because rates are also decreased or stable for those with hypertension and glomerulonephritis. In addition, early detection or better ascertainment of diabetes may contribute to lead-time bias to develop ESRD. An increased diabetes death rate is the competing event supported by the data, but the precise magnitude of bias is unclear. The burden of type 2 diabetes and hyper-

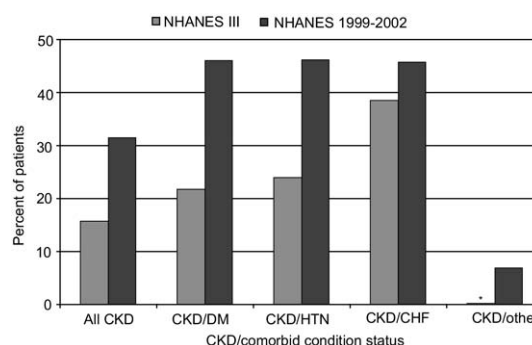


Figure 4. Patients with chronic kidney disease (CKD) treated with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.¹⁸ Abbreviations: CHF, congestive heart failure; DM, diabetes; HTN, hypertension; NHANES, National Health and Nutrition Examination Survey. *Sample size less than 30.

tension will grow as the US population ages, particularly the baby boomer generation born in 1946 to 1964, and as increasing body mass index continues at epidemic levels.

Limitations

The major limitation of the screening process is overdiagnosis bias, because a 1-time “snap shot” of the target population means that screening definitions of eGFR less than 60 mL/min/1.73 m² and albumin-creatinine ratio greater than 30 mg/g do not always imply diagnosis; the CKD definition requires at least 2 sets of results separated by 3 or more months.⁹ In addition to being enriched for CKD, self-selection bias of the volunteer KEEP population compared with the general NHANES population shows the former to be older, with greater proportions of women and African Americans, higher levels of education, and participants presumably more highly motivated. Repeated diagnostic panel assessments are expected to show regression to the mean, a phenomenon that would better reflect changes in the screening population over time.⁴ Last, the program’s impact on outcomes is yet to be precisely determined.

Future Directions

The assessment of the impact of KEEP will improve by transforming it from a cross-sectional to a longitudinal program. Currently, the KEEP database is longitudinal only incidentally because some participants have returned for re-

peated screenings in an unsolicited and sporadic fashion. Approximately 2,717 of the 100,000 individuals screened as of November 15, 2007, have attended 2 or more KEEP events. A formal longitudinal phase currently is being field tested. Expansion of the diagnostic panel to include measurement of hemoglobin A_{1c}, direct low-density and high-density lipoprotein cholesterol, and waist circumference is planned. In the United States, the cooperative agreement among the Centers for Disease Control and Prevention, the NKF, and the Chronic Disease Research Group to modify KEEP for a state-based CKD screening demonstration project will contribute additional data. Localized versions of KEEP screenings in other countries have begun; Japan has the first collaborative detection program between the US KEEP and the International Kidney Evaluation Association of Japan. Other countries may follow.

CONCLUSION

Only 6.7% of KEEP participants are aware of CKD, whereas 28.7% meet diagnostic criteria. Low awareness of CKD exists in an at-risk US population. Mass or untargeted screening is anticipated to yield CKD proportions similar to NHANES, or approximately 13%. KEEP is a CKD detection program designed to inform the public about disease burden and complications. The detection program staff communicates with clear messages to at-risk populations, using simple tests to detect evidence of CKD and major complications and informing participants and their physicians. In addition to identifying individuals at increased risk of kidney disease, the program's structured data collection provides an opportunity to use what we know about kidney disease to influence public health policies and practices in state health departments and among elected officials, managed care and insurance companies, and medical societies.

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