Screening for Proteinuria in US Adults
A Cost-effectiveness Analysis

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Context Chronic kidney disease is a growing public health problem. Screening for early identification could improve health but could also lead to unnecessary harms and excess costs.

Objective To assess the value of periodic, population-based dipstick screening for early detection of urine protein in adults with neither hypertension nor diabetes and in adults with hypertension.

Design, Setting, and Population Cost-effectiveness analysis using a Markov decision analytic model to compare a strategy of annual screening with no screening (usual care) for proteinuria at age 50 years followed by treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II-receptor blocker (ARB).

Main Outcome Measure Cost per quality-adjusted life-year (QALY).

Results For persons with neither hypertension nor diabetes, the cost-effectiveness ratio for screening vs no screening (usual care) was unfavorable ($282 818 per QALY; incremental cost of $616 and a gain of 0.0022 QALYs per person). However, screening such persons beginning at age 60 years yielded a more favorable ratio ($53 372 per QALY). For persons with hypertension, the ratio was highly favorable ($18 621 per QALY; incremental cost of $476 and a gain of 0.03 QALYs per person). Cost-effectiveness was mediated by both chronic kidney disease progression and death prevention benefits of ACE inhibitor and ARB therapy. Influential parameters that might make screening for the general population more cost-effective include a greater incidence of proteinuria, age at screening ($53 372 per QALY for persons beginning screening at age 60 years), or lower frequency of screening (every 10 years: $80 700 per QALY at age 50 years; $6195 per QALY at age 60 years; and $5486 per QALY at age 70 years).

Conclusions Early detection of urine protein to slow progression of chronic kidney disease and decrease mortality is not cost-effective unless selectively directed toward high-risk groups (older persons and persons with hypertension) or conducted at an infrequent interval of 10 years.

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CHRONIC KIDNEY DISEASE IS A growing public health problem. More than 10 million US adults have some kidney damage (serum creatinine levels ≥1.5 mg/dL [132.6 µmol/L]), and the number of persons with end-stage renal disease (ESRD) exceeds 300 000. Persons with ESRD, who have a poor quality of life and accrue high health care costs, are projected to exceed 600 000 in 2010.[1-4] Early identification and treatment of patients who are more likely to progress to ESRD to decrease mortality, morbidity, and costs associated with chronic kidney disease has been debated. Controversy exists because many patients do not progress to ESRD, however, the majority of those who do progress go undetected until it is too late to intervene.[5]

Growing evidence indicates that the presence of relatively low levels of urine protein can be an early marker of increased risk of progressive kidney disease, poor cardiovascular outcomes, and death.[6,7] Prescription of angiotensin-converting enzyme (ACE) inhibitor or angiotensin II-receptor blocker (ARB) therapy in persons with proteinuria and chronic kidney disease has been demonstrated to decrease both the progression of kidney disease toward ESRD as well the incidence of cardiovascular events and death.[6,8-12]

Dipstick urinalysis has imperfect accuracy in the diagnosis of persistent proteinuria, but it is an inexpensive test that can be performed in most medical settings.[13] For persons with diabetes, routine screening for urine protein has been shown to be cost-effective.[12,14-16] In contrast, although there is accruing evidence that the use of ACE inhibitor therapy decreases the incidence of death and slows clinical progression of disease for persons with chronic, nondiabetic proteinuric nephropathies, there is little evidence addressing the cost-effectiveness of routine screening.[9,10,17] It is not clear whether screening of the entire US adult population by physicians is warranted. If screening followed by the implementation of ACE inhibitor or ARB therapy were beneficial in slowing progression toward ESRD, patients could benefit from lengthened survival and im-

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proved quality of life, and the societal economic burden of treatment of ESRD, which is approaching $45 000 per affected patient annually, could be averted.[4] In contrast, inappropriate screening of persons could lead to unnecessary harms and costs. Therefore, we assessed the cost-effectiveness of periodic, population-based dipstick screening for urine protein and subsequent treatment with an ACE inhibitor or ARB therapy in US adults.

METHODS

Study Design

The study design is a cost-effectiveness analysis from a societal perspective for which a state-transition Markov analytic model was developed to simulate the clinical path of patients from normal kidney function to ESRD. We compared a strategy of annual screening for proteinuria and subsequent treatment with ACE inhibitor or ARB therapy with a strategy of routine clinical practice for persons with neither hypertension nor diabetes and for persons with hypertension. Although screening for persons with type 2 diabetes is already widely performed in clinical practice, we also analyzed these strategies for persons with type 2 diabetes (many of whom would also have hypertension) to assess the validity of the Markov analytic model and to provide a reference point for the comparative magnitude of cost-effectiveness ratios derived from screening nondiabetic populations.[18-21]

The base-case model consisted of US adults aged 50 years (with demographic characteristics similar to persons in the third National Health and Nutrition Examination Survey [NHANES III]; 52% were female, 80% non-Hispanic white, 11% non-Hispanic black, 5% Mexican American) presenting to a primary care physician for an annual physical examination with previously undetected proteinuria.[22] This group was chosen because the most definitive evidence on interventions and the natural history of chronic kidney disease has included patients of this age. These patients could undergo a screening strategy or a no-screening strategy.

The screening strategy consisted of a urine dipstick test to detect proteinuria (ie, 1+ result on a colorimetric urine dipstick test for gross proteinuria) during an annual visit with a primary care physician. Positive dipstick test results were followed up with a second physician visit to reassess urine protein levels using quantitative random (albumin to creatinine ratio) or timed urine specimens in addition to measurement of serum creatinine level and estimation of glomerular filtration rate (GFR) using recommended equations.[23] Positive quantitative urine protein test results would prompt either subsequent treatment by a primary care physician with an ACE inhibitor or ARB therapy for persons with normal renal function or referral to and evaluation by a nephrologist followed up by treatment with an ACE inhibitor or ARB therapy for persons with depressed renal function (defined as as a GFR of $<$90 mL/min per 1.73 m^2). Persons with positive screening dipstick test results and negative quantitative assessments of urine protein were considered to have false-positive initial results or nonpersistent proteinuria. These persons did not proceed with further evaluation or treatment and could undergo routine screening in subsequent years.

The no screening strategy consisted of no dipstick testing and natural progression of chronic kidney disease with an annual opportunity for incidental testing or symptom development and disease detection. Health states in the Markov model included normal kidney function (GFR $\geq$90 mL/min per 1.73 m^2 or National Kidney Foundation Kidney Disease Outcomes Quality Initiative [KDOQI] stage 1), chronic renal insufficiency (GFR of 15-89 mL/min per 1.73 m^2 or KDOQI stages 2-4), and ESRD (GFR $<$15 mL/min per 1.73 m^2 or the need for renal replacement therapy or KDOQI stage 5) (FIGURE 1).[23] Distribution of persons in the chronic renal insufficiency health state (KDOQI stages 2-4) were based on prevalence data from NHANES III. Ninety percent of persons have GFRs ranging from 60 to 89 mL/min per 1.73 m^2 (KDOQI stage 2); 9.5%, 30 to 59 mL/min per 1.73 m^2 (KDOQI stage 3); and 0.5%, 15 to 29 mL/min per 1.73 m^2 (KDOQI stage 4).[2] Screening of all persons occurred annually until age 75 years, the development of ESRD, or death.

We categorized all evidence used in the model according to a hierarchy of research design put forth by the US Preventive Services Task Force and used the highest level of evidence.[24]

Probabilities

Disease Incidence and Prevalence and Test Characteristics. We estimated the age-specific prevalence of proteinuria based on a positive dipstick test result among persons with varying degrees of renal function using data on the prevalence of gross proteinuria (urine protein $>$20-30 mg/dL) from the NHANES III cohort.[2,22] We also used these data to estimate the age-specific prevalence of proteinuria for persons with different clinical histories (persons with neither hypertension nor diabetes, persons with hypertension, and persons with diabetes). We estimated the incidence of proteinuria based on a positive dipstick result among all persons from published literature.[25-33] We obtained estimates regarding the sensitivity and specificity of dipstick testing in identifying asymptomatic proteinuria from published literature on test characteristics in outpatient clinical practice settings (TABLE 1).[34-37]

Adherence With Screening and ACE Inhibitor or ARB Therapy. We estimated adherence to hypothetical screening recommendations for primary care physicians from data for other primary care screening services.[38,39] We estimated patient adherence with ACE inhibitor or ARB therapy from data on discontinuation of the medication due to clinical adverse effects such as cough, hyperkalemia, and hypersensitivity as well as from published data regarding antihypertensive medication adherence rates. For persons with either hypertension or diabetes, in both the screening and no screening (usual care) strategies, we estimated the baseline rate of ACE inhibitor or ARB therapy use (already instituted independent of screen-

ing) from data on rates of hypertensive medication prescription patterns as well as prevalence rates for comorbid conditions (ie, cardiovascular disease risk factors and heart failure), which could prompt therapy with an ACE inhibitor or ARB therapy (Table 1).[10,40-53]

Symptom Development and Incidental Testing. For persons in the no screening strategy, we estimated the rate of symptom development that would prompt incidental testing with a urine dipstick. Symptoms considered were those related to the genitourinary system (eg, dysuria) or to the peripheral vasculature or lymphatics (eg, leg edema) (Table 1).[54]

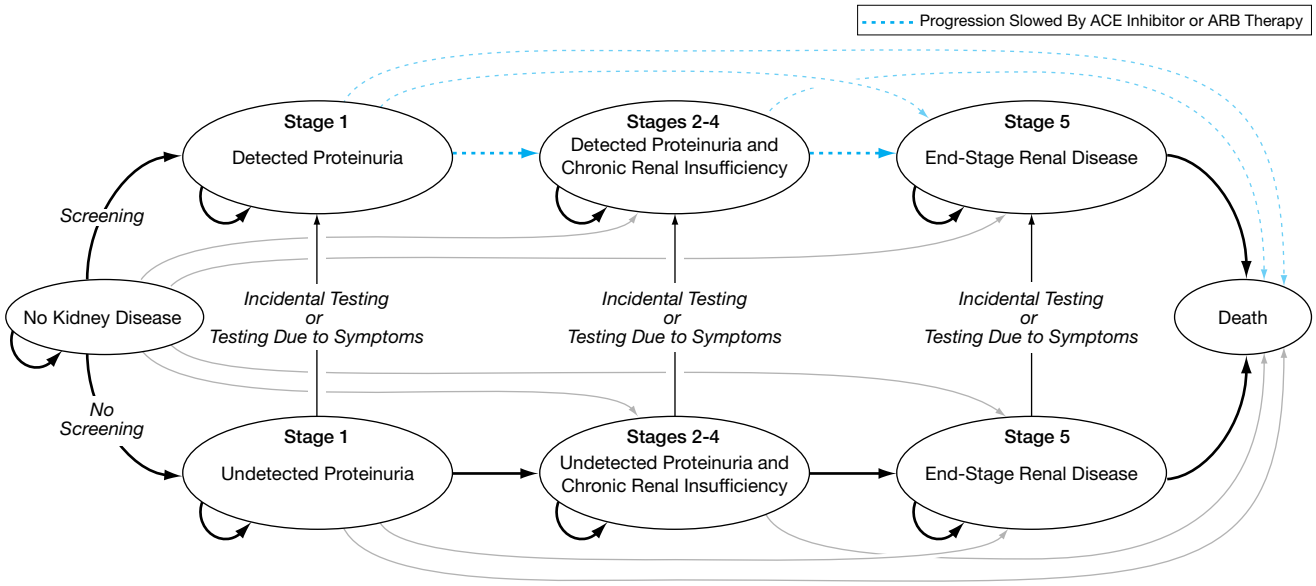
Potential Benefits and Harms of Screening

Potential benefits resulting from screening included reductions in all-cause mortality and progression toward ESRD conferred by ACE inhibitor or ARB therapy estimated from randomized controlled trials of persons with and without type 2 diabetes. In models of persons with neither hypertension nor diabetes or persons with hypertension, ACE inhibitor therapy was prescribed for the screening arm for persons with proteinuria; in models of persons with diabetes, ARB therapy was instituted (TABLE 2).[6,8-12,55]

We used a conservative estimate (30%) from 4 randomized controlled trials and 1 meta-analysis for the benefit provided by ACE inhibitor or ARB therapy in slowing progression toward ESRD for all subgroups studied. For persons with neither hypertension nor diabetes, we used results from a trial reporting a 67% (but nonstatistically significant) relative risk (RR) reduction in progression toward ESRD with ACE inhibitor therapy for persons with IgA nephropathy, interstitial nephritis, and polycystic kidney disease.[55] For persons with hypertension, we used results from a meta-analysis of trials of ACE inhibitor therapy reporting a 30% RR reduction in progression toward ESRD (95% confidence interval [CI], 22%-44%) and we used a single trial studying the effects of ACE inhibitor therapy in blacks reporting a 41% RR reduction in progression toward ESRD (95% CI, 5%-63%).[9,10] For persons with diabetes, we used results from 2 trials studying the effects of ARB therapy reporting statistically significant RR reductions for progression toward ESRD of 33% (no CI provided) and 28% (95% CI, 11%-42%), respectively.[11,12] We used reported CIs to set the extremes of benefit offered by ACE inhibitor or ARB therapy that were used in sensitivity analyses.

Similarly, we used a conservative estimate (23%) for the benefit provided by ACE inhibitor or ARB therapy in reducing the incidence of death for all subgroups studied. This estimate was based on results from a cohort study of diabetic and nondiabetic individuals (with and without hypertension) reporting statistically significant RR reductions of 21% and 24% (no CIs provided) in all-cause mortality with use of ACE therapy, respectively, and results from a random-

Figure 1. Clinical Pathways in a Markov Decision Model for Screening for Proteinuria



National Kidney Foundation Kidney Disease Outcomes Quality Initiative chronic kidney disease stages: 1, glomerular filtration rate (GFR) of 90 mL/min per 1.73 m^2 or greater; 2-4, GFR of 15 to 89 mL/min per 1.73 m^2; 5, GFR of less than 15 mL/min per 1.73 m^2. Persons with no kidney disease initially can develop proteinuria, progress to chronic renal insufficiency, progress to end-stage renal disease, and die. Most frequent pathways are denoted by heavy arrows. Blue dashed lines represent slower progression based on benefit from angiotensin-converting enzyme (ACE) inhibitor or angiotensin II-receptor blocker (ARB) therapy. Persons who are in the "no screening" (usual care) group do not benefit from ACE inhibitor or ARB therapy unless disease is detected via incidental testing or testing performed as a result of patient symptoms (eg, leg swelling, dysuria, flank pain), which is indicated by the upward arrows from the no screening path to the screening path. The transition from no kidney disease directly to death is not shown but was incorporated into the model.

Table 1. Prevalence, Incidence, and Screening Test Characteristics of Proteinuria

	Base Case, %	Sensitivity Analyses, %		Data Sources	Level of Evidence*
		In Favor of Screening	Against Screening		
Prevalence of proteinuria by clinical history†					
Neither hypertension nor diabetes	0.19	0.29	0.09	Garg et al,[22] 2002	II-2
Hypertension	1.2	1.8	0.6		
Diabetes	5.4	8.1	2.7		
Incidence of proteinuria by clinical history					
Neither hypertension nor diabetes	0.01	0.1	0.001	Wyatt et al,[25] 1998	II-2
				Stratta et al,[26] 1996	II-2
				Igarashi et al,[28] 2002	III
Hypertension	0.5	1.5	0.25	Voyaki et al,[29] 2001	I
				Jee et al,[30] 2003	II-2
Diabetes	2.5	5	1	Klein et al,[27] 1995	II-2
				Torffvit and Agardh,[31] 2001	II-2
				Gall et al,[32] 1997	II-2
				Mattock et al,[33] 1998	II-2
Screening test characteristics					
Sensitivity (1+ proteinuria)	76	95	45	Shaw et al,[34] 1985	II-2
				Woolhandler et al,[35] 1989	II-2
				James et al,[36] 1978	II-2
				Ralston et al,[37] 1988	II-2
Specificity (1+ proteinuria)	79	95	45	Shaw et al,[34] 1985	II-2
				Woolhandler et al,[35] 1989	II-2
				James et al,[36] 1978	II-2
				Ralston et al,[37] 1988	II-2
Adherence					
Screening and treatment with ACE inhibitor or ARB therapy‡	75	95	20	Agodoa et al,[10] 2001	I
				Ramsey et al,[38] 2001	II-2
				Martin et al,[39] 1995	II-3
				Ruggenenti et al,[47] 1999	I
				Lonn et al,[48] 2002	I
				Yusuf et al,[49] 2000	I
				Friedman et al,[50] 1996	I
				Patel and Taylor,[51] 2002	II-2
				Barat et al,[52] 2001	II-2
				Wang et al,[53] 2002	II-3
Baseline rate of use of ACE inhibitors§	20	0	60	Mehta et al,[40] 1999	II-2
				Okosun et al,[41] 2000	II-2
				Erlinger et al,[42] 2000	II-2
				Ni,[43] 2003	II-2
				Hyman et al,[44] 2000	II-2
				Nelson et al,[45] 2000	II-2
				Clause and Hamilton,[46] 2002	II-2
Symptoms leading to testing (by level of GFR, mL/min per 1.73 m^2 per year)‖					
≥90	4	2	6	Cherry and Woodwell,[54] 2002	II-2
15-89	30	15	45	Assumption	NA
<15	100	50	100	Assumption	NA

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II-receptor blocker; GFR, glomerular filtration rate; NA, not applicable.
*Based on hierarchy of research design designated by US Preventive Services Task Force. Level I is the best evidence; level III is the worst evidence.[24]
†Age-specific prevalence estimates also used in model.
‡Adherence rates incorporate discontinuation of therapy due to adverse effects (eg, cough, hyperkalemia, hypersensitivity) and general adherence to prescribed medications.
§Includes screened and nonscreened persons with hypertension. Treatment with an ACE inhibitor in screening strategy would be in addition to baseline ACE inhibitor use.
‖Represents rates of testing due to patient complaints of symptoms or incidental office-based testing for proteinuria.

Table 2. Risks and Benefits of Screening for Proteinuria and Health State Utilities

	Base Case, %	Sensitivity Analyses: In Favor of Screening	Sensitivity Analyses: Against Screening	Data Sources	Level of Evidence*
		Percentage			
Potential benefit of screening all subgroups†					
RR reduction in progression toward ESRD afforded by ACE inhibitor or ARB	30	35	5	Jafar et al,[9] 2001	I
				Agodoa et al,[10] 2001	I
				Lewis et al,[11] 2001	I
				Brenner et al,[12] 2001	I
				Ruggenenti et al,[55] 2000	I
RR reduction in all-cause mortality afforded by ACE inhibitor or ARB	23	30	5	Gerstein et al,[6] 2001	I
				Lindholm et al,[8] 2002	I
Potential harm of screening					
Persons undergoing renal biopsy by clinical history					
Neither hypertension nor diabetes	90	100	50	Fuiano et al,[74] 2000	II-2
Hypertension	5	7.5	2.5	Assumption	NA
Diabetes	5	7.5	2.5		
Complication due to renal biopsy					
Hematuria, clinical hematoma, or other complications secondary to biopsy	5	1	15	Mendelssohn and Cole,[56] 1995	II-3
				Madaio,[57] 1990	II-3
				Marwah and Korbet,[58] 1996	II-3
				Parrish,[59] 1992	II-3
				Nass and O'Neill,[60] 1999	II-3
Time in hospital for persons undergoing renal biopsy, h	23	12	72	Marwah and Korbet,[58] 1996	II-3
				Renal Physicians Association,[96] 2001	III
Adverse medication effects					
Anaphylaxis secondary to ACE inhibitor or ARB	0.5	0.001	1	Thompson Micromedex,[61] 2003	II-3
Angioedema secondary to ACE inhibitor	2	0.002	5	Mann et al,[7] 2001	I
				Speirs et al,[62] 1998	II-2
Disability from ESRD					
Persons working full-time while on dialysis	10	0	20	US Department of Health and Human Services,[81] 2000	II-2
				Kutner et al,[82] 1991	II-3
				Rasgon et al,[83] 1993	II-1
				van Manen et al,[84] 2001	II-2
Persons working full-time after receiving kidney transplant	40	30	70	Raiz,[85] 1997	II-3
				Markell et al,[86] 1997	II-3
				Manninen et al,[87] 1991	II-2
		Number			
Utilities for health states, GFR in mL/min per 1.73 m^2					
≥90 (Without proteinuria)	0.99			Definition	NA
≥90 (Proteinuria)	0.98	0.99	0.97	Assumption	NA
15-89 (With or without proteinuria)	0.95	0.97	0.90	Tengs and Wallace,[89] 2000	II-2
<15 (With or without proteinuria)	0.70	0.50	0.90	Tengs and Wallace,[89] 2000	II-2
				de Wit et al,[90] 2002	II-2
Disutility associated with medication adherence	0.01	0	0.05	Tengs and Wallace,[89] 2000	II-2
Discount rate for utilities, %	3	1	5	Lipscomb et al,[73] 1996	NA

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II-receptor blocker; ESRD, end-stage renal disease; GFR, glomerular filtration rate; NA, not applicable; RR, relative risk.
*Based on hierarchy of research design designated by US Preventive Services Task Force. Level I is the best evidence; level III is the worst evidence.[24]
†ACE inhibitor therapy assumed for persons with neither hypertension nor diabetes and persons with hypertension; ARB therapy assumed for persons with type 2 diabetes.

ized controlled trial reporting a 39% RR reduction (95% CI, 26%-55%) in all-cause mortality with use of ARB therapy for persons with diabetes.[6,8]

Potential harms incurred as a result of screening were associated with renal biopsy (including hematuria and clinical hematoma estimated from a case-series of patients) and adverse effects of ACE inhibitor or ARB therapy (including anaphylaxis or angioedema requiring emergency department visit and 24-hour observation) (Table 2).[7,56-62]

Natural Progression of Disease

For persons with each clinical history, we estimated rates of progression from normal kidney function (KDOQI stage 1) toward chronic renal insufficiency (KDOQI stages 2-4) and from chronic renal insufficiency (KDOQI stages 2-4) toward ESRD (KDOQI stage 5) from data obtained from both cohort studies and clinical trials (TABLE 3).[2,10-12,23,55,63-70] Rates for persons with neither hypertension nor diabetes with normal kidney function were obtained from observational studies reporting GFRs for healthy persons.[2,23] Rates for persons with neither hypertension nor diabetes and GFRs of 15 to 89 mL/min per 1.73 m^2 were obtained from trial results reported on persons with IgA nephropathy, interstitial nephritis, and polycystic kidney disease enrolled in a randomized controlled trial of persons with nondiabetic, nonproteinuric nephropathies.[55,63] Rates for persons with hypertension were obtained from 3 trials—2 examined the effect of ACE inhibitor therapy on progression and one examined the effect of diet on progression.[10,55,63,70] For subgroups in which insufficient evidence was available, we made conservative assumptions regarding progression (see "Model Assumptions" below).

We obtained age and cause-specific mortality rates for the US population from the 1999 National Center for Health Statistics Mortality Data File.[71] To estimate the effect of the presence of proteinuria on deaths among persons with varying levels of renal disease, we used data from

Table 3. Annual Decline in Glomerular Filtration Rate by Clinical History and Proteinuria Status

Clinical History and Kidney Function	Annual Decline in Glomerular Filtration Rate, mL/min per 1.73 m^2			Data Sources	Level of Evidence*
	Base Case	In Favor of Screening	Against Screening		
Neither hypertension nor diabetes					
No proteinuria					
≥90 to 15-89	1.0	1.5	0.5	Coresh et al,[2] 2003	II-2
				National Kidney Foundation,[23] 2001	III
15-89 to <15	1.0	1.5	0.5	Assumption	NA
Proteinuria					
≥90 to 15-89	1.1	1.65	0.55	Assumption	NA
15-89 to <15	4.2	6.3	2.1	Ruggenenti et al,[55] 2000	I
				Ruggenenti et al,[63] 1998	I
Hypertension					
No proteinuria					
≥90 to 15-89	1.1	1.65	0.55	Assumption	NA
15-89 to <15	1.4	2.1	0.7	Agodoa et al,[10] 2001	I
Proteinuria					
≥90 to 15-89	1.2	2.4	0.6	Assumption	NA
15-89 to <15	3.9	5.9	1.95	Agodoa et al,[10] 2001	I
				Ruggenenti et al,[55] 2000	I
				Ruggenenti et al,[63] 1998	I
				Klahr et al,[70] 1994	I
Diabetes					
No proteinuria					
≥90 to 15-89	1.1	1.65	0.55	Nelson et al,[64] 1996	II-2
				Nosadini et al,[68] 2000	II-2
				Rachmani et al,[69] 2000	II-2
15-89 to <15	2.8	4.2	1.4	Lebovitz et al,[65] 1994	I
Proteinuria					
≥90 to 15-89	4.1	6.2	2.1	Gaede et al,[66] 1999	I
				Gaede et al,[67] 2003	I
				Nosadini et al,[68] 2000	II-2
15-89 to <15	5.2	10.4	2.6	Lewis et al,[11] 2001	I
				Brenner et al,[12] 2001	I
				Ruggenenti et al,[56] 2000	I

Abbreviation: NA, not applicable.
*Based on hierarchy of research design designated by US Preventive Services Task Force. Level I is the best evidence; level III is the worst evidence.[24]

the NHANES II mortality study.[72] Age and cause-specific mortality rates for persons with ESRD were estimated from the US Renal Data System.[4]

Costs

We included direct costs of medical care as well as the indirect costs of wages lost for persons disabled as a result of ESRD. All costs were in 2002 dollars and were discounted at a rate of 3% per year.[73]

Costs of screening incorporated initial dipstick testing, initial and follow-up visits with generalist and specialist physicians, and associated urine, serum, radiological, and pathological testing.[74] Test costs were estimated using Medicare reimbursement rates based on the Medicare resource-based relative value scale for part B services (TABLE 4).[75,76]

Costs of ACE inhibitor or ARB therapy were estimated by using a weighted average of wholesale prices for 8 proprietary products in the market and one nonproprietary product for ACE inhibitors and for 5 proprietary products in the market for ARB therapies.[77-79] Costs of emergency department visits related to adverse medication events (eg, anaphylaxis or drug hypersensitivity) or hospital time for patient observation after renal biopsy were estimated using data from the Centers for Medicare and Medicaid Services.[80] Costs of treatment for ESRD (KDOQI stage 5) were estimated using data from the US Renal Data System (Table 4).[4]

We estimated annual lost wages for nonworking persons with ESRD (KDOQI stage 5) using a weighted average of published estimates of the mean percentage of persons working full-time while receiving either dialysis or transplantation treatment modalities.[81-87] Persons in all other stages were considered to be working full-time until they turned age 65 years. We used data on average US wages from the US Department of Labor to determine the indirect cost associated with lost wages (Table 4).[88]

Utilities

Health state utilities (ie, numerical values reflecting the relative importance of different health states to patients) ranged from 0 (worst) to 1 (optimal) in the

Table 4. Costs Used for Base-Case Sensitivity Analyses in the Decision Model of Screening for Proteinuria

Cost Component	Base Case, $*	Sensitivity Analyses, $*		Data Sources
		In Favor of Screening	Against Screening	
Screening				
Initial generalist physician visit	44.15	22.08	66.23	Centers for Medicare and Medicaid Services,[75] 2003
Follow-up generalist physician visit	33.23	16.62	49.85	
Test (urine dipstick)	3.59	1.80	5.40	
Initial specialist physician evaluation by clinical history				
Neither hypertension nor diabetes	2372.98	1186.57	3539.58	Centers for Medicare and Medicaid Services,[75] 2003
Hypertension	2372.98	1186.57	3539.58	
Diabetes	2742.00	1371.09	4082.57	
Follow-up specialist fees				
Physician	54.48	27.24	81.72	Centers for Medicare and Medicaid Services,[75] 2003
Testing	11.83	5.92	17.75	
Annual cost of therapy				
ACE inhibitor†	388.62	194.31	582.93	Chang,[77] 2002
				IMS Health,[78] 2002
				Medical Economics Co,[79] 2001
ARB†	511.23	255.62	766.85	Chang,[77] 2002
				IMS Health,[78] 2002
				Medical Economics Co,[79] 2001
ESRD‡	44 407.00	66 610.50	22 203.50	US Renal Data System,[4] 2002
Lost wages for nonworking persons	27 569.08	41 353.62	13 784.54	US Department of Health and Human Services,[81] 2000
				Kutner et al,[82] 1991
				Rasgon et al,[83] 1993
				van Manen,[84] 2001
				Raiz,[85] 1997
				Markell et al,[86] 1997
				Manninen et al,[87] 1991
				US Department of Labor,[88] 2002
Discount rate, %	3	1	5	Lipscomb et al,[73] 1996

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II-receptor blocker; ESRD, end-stage renal disease.
*Based on 2002 US dollar amounts.
†Based on weighted average wholesale price of ACE inhibitor or ARB therapy.[77-79]
‡Weighted average cost for persons on hemodialysis, peritoneal dialysis, and transplantation.

Markov model. The values were based on standard gamble or time-tradeoff techniques.[89,90] The disutility associated with ACE inhibitor or ARB therapy was estimated from data reporting medication adverse effects.[89] Utilities were discounted at a rate of 3% per year (Table 2).

Analyses

In our base-case analysis, we estimated the cost-effectiveness of screening beginning at age 50 years for persons with each clinical history, assuming the combined benefits of ACE inhibitor or ARB therapy to slow the progression to ESRD and to prevent death. To more clearly identify the pathway through which ACE inhibitor therapy might mediate cost-effectiveness, we analyzed separate Markov models assuming only the progression-slowing benefits of ACE inhibitor therapy on chronic kidney disease or on death.

We analyzed the Markov model using cohort simulations for base-case and 1-way sensitivity analyses. To ascertain whether there is an optimal age for beginning screening, we performed analyses for persons beginning screening at ages 30, 40, 50, 60, and 70 years. To ascertain whether there is an optimal frequency of screening, we performed analyses for persons in each age group with screening occurring at intervals varying from annually to every 10 years. To determine other variables influential on cost-effectiveness, we performed sensitivity analyses in which model parameters were changed individually to bias them in favor of or against screening (Table 1, Table 2, Table 3, and Table 4). We classified a change in the cost-effectiveness ratio of 50% or more as being highly influential. We considered cost-effectiveness ratios of less than $50 000 per quality-adjusted life-year (QALY) highly favorable toward screening; $50 001 to $100 000 per QALY was considered moderately favorable; and greater than $100 000 per QALY was considered unfavorable.[91-92] For multiway sensitivity analysis, we performed Monte Carlo analysis consisting of 1000 simulations in whichall parameters were varied simultaneously over their distributions (Table 1, Table 2, Table 3, and Table 4). We further tested the validity of the model by using first-order Monte Carlo analysis to assess average time spent in health states. We compared model output with nationally available data on disease incidence and mortality. All analyses were performed using DATA software (Version 4.0, TreeAge Software Inc, Williamstown, Mass).

Model Assumptions

Frequency of Screening. All persons without proteinuria as well as screened persons with undetected proteinuria (false-negative results) have the opportunity to be rescreened annually. The model incorporates the rate of expected nonadherence to rescreening and the frequency with which persons developing symptoms potentially associated with proteinuria would present to a physician and have proteinuria detected using routine dipstick testing methods.

The number of persons not screened but presenting with incidental symptoms, which would prompt testing with a urine dipstick, increases based on the severity of chronic kidney disease with all persons with GFR of less than 15 mL/min per 1.73 m^2 (KDOQI stage 5) presenting with symptoms. Persons diagnosed as having proteinuria after presenting with symptoms undergo the same work-up, evaluation, and subsequent treatment with ACE inhibitor or ARB therapy as those who are detected through annual screening. Persons unable to tolerate ACE inhibitor or ARB therapy secondary to adverse effects are identified early in the course of treatment; the long-term benefit of treatment from such short courses (<1 year) of ACE inhibitor or ARB therapy are minimal. The baseline rate at which persons with neither diabetes nor hypertension are already receiving ACE inhibitor therapy (outside of screening strategy) is equal to zero. Finally, among persons with hypertension, those with newly diagnosed hypertension (approximately 4%) undergo screening as a part of usual care.[93-95]

Rates of Decline in GFR and Utilities. For persons with neither hypertension nor diabetes and with no proteinuria, rates of GFR decline from 15 to 89 mL/min per 1.73 m^2 (KDOQI stages 2 to 4) to less than 15 mL/min per 1.73 m^2 (KDOQI stage 5) are no different than rates of GFR decline for persons with normal kidney function (KDOQI stage 1) (Table 3). Among persons with neither hypertension nor diabetes and with proteinuria, rates of GFR decline for persons with a GFR of 90 mL/min per 1.73 m^2 or greater (KDOQI stage 1) are 10% greater than rates of GFR decline for their counterparts with no proteinuria (Table 3). Among persons with hypertension and with no proteinuria, rates of GFR decline for persons with normal kidney function (KDOQI stage 1) are 10% greater than rates of GFR decline for persons with neither diabetes nor hypertension and with no proteinuria (Table 3). Finally, proteinuria is generally asymptomatic and is associated with a minimal decrement in health status.

Effectiveness of ACE Therapy, Frequency of Physician Visits, and Costs. We assume the effects of ACE inhibitor therapy in reducing risk of death and in reducing progression of renal disease are equal among persons with neither hypertension nor diabetes and persons with hypertension.[6,56] Persons with neither hypertension nor diabetes incur 3 generalist follow-up visits per year as a result of a positive dipstick test result. Additional generalist visits are not incorporated for persons with hypertension or diabetes, as they would already be under routine care. After initial specialist evaluation, persons with a GFR of 15 to 89 mL/min per 1.73 m^2 (KDOQI stages 2 to 4) incur one annual visit that includes the measurement of serum creatinine and other tests. In analyses identifying the cost-effectiveness of beginning screening at different ages, we assume the effectiveness of ACE inhibitor or ARB therapy is the same among persons of all age groups. Finally, persons undergoing renal biopsy have a 23-hour hospital stay, which increases to 48 hours in the event of complications (eg, hematoma) (Table 2).[59,96]

Diagnostic Components. The diagnostic components of urine tests, he-

matologic, serologic, immunological, virological, and radiological tests and pathological evaluation were included in costs for specialist evaluations of persons with a GFR of less than 90 mL/min per 1.73 m^2. Evaluation strategies were tailored according to age and clinical history.

Urine Analyses. The urine analyses included urine microscopic examination, quantitative assessment of urine protein with random (albumin to creatinine ratio) or timed urine specimen, urine protein electrophoresis (for persons >50 years), and urine microalbumin (for persons with diabetes).

Hematologic and Serologic Tests. These tests included a comprehensive metabolic panel, lipid profile, serum phosphate, magnesium, and calcium levels, complete blood count with manual differential blood count, prothrombin and partial thromboplastin times, glycated hemoglobin (for persons with diabetes), intact parathyroid hormone (for persons with a GFR <30 mL/min per 1.73 m^2), transferrin, and iron (for persons with a GFR <30 mL/min per 1.73 m^2).

Immunological and Virological Tests. These tests included antinuclear antibodies, a rapid plasma reagent test, hepatitis B and C serologic analysis, enzyme-linked immunosorbent assay for human immunodeficiency virus, serum protein electrophoreseis (for persons >50 years; follow-up for positive serum protein electrophoresis with C3, C4, and serum cryoglobulins).

Radiological Tests. These tests included renal ultrasound and magnetic resonance angiogram of renal arteries (for persons with diabetes aged ≥50 years).

Pathological Evaluation. This evaluation included renal biopsy with ultrasound guidance, pathological interpretation, and 23-hour hospital stay following uncomplicated biopsy.

RESULTS

Cost-effectiveness of Screening for Proteinuria

Taking into account both the reduction in deaths and the slowing of chronic kidney disease progression with ACE inhibitor or ARB therapy for persons with neither hypertension nor diabetes, the base-case cost-effectiveness ratio for screening vs the usual care (no screening) strategy was unfavorable ($282 818 per QALY saved). A gain of 0.0022 QALYs was mediated through the prevention of 1 new case of ESRD and 7 deaths per 1 million persons per year in the screening strategy. For persons with hypertension, the cost-effectiveness ratio for the screening strategy vs no screening (usual care) was highly favorable ($18 621 per QALY saved). A gain of 0.03 QALYs was mediated through the prevention of approximately 14 new cases of ESRD and 104 deaths per 1 million persons per year in the screening strategy. In contrast, for persons with diabetes, the screening strategy was dominant over the no screening strategy (savings of $217 and gain of 0.10 QALYs per person in the screening strategy). A gain of QALYs was mediated through the prevention of approximately 84 new cases of ESRD and 541 deaths per 1 million persons per year in the screening strategy. The death benefit due to ACE inhibitor therapy had a more profound (cost-effective or cost-saving) impact on overall cost-effectiveness than the slowing of the progression of renal disease (TABLE 5).

Harms of Screening

Screening 1 million persons with neither hypertension nor diabetes resulted in 135 biopsies, 7 biopsy complications, and complication costs of $9116 per year. Screening 1 million persons with hypertension resulted in 196 biopsies performed, 16 biopsy complications, and complication costs of $20 000 per year.

Sensitivity Analyses

Age When Screening Begins. For persons with neither hypertension nor diabetes, the cost-effectiveness ratio of annual screening vs no screening (usual care) was unfavorable until screening beginning at age 60 years (TABLE 6). For persons with hypertension, annual screening beginning at age 30 years resulted in highly favorable cost-effectiveness ratios when compared with the no screening strategy and remained highly favorable for screening beginning at older ages (Table 6).

Frequency of Screening. For 50-year-old persons with neither hypertension nor diabetes, screening less frequently resulted in more favorable cost-effectiveness ratios ($120 727 for screening every 5 years and $80 700 for screening every 10 years). Similar results were found for screening persons of older age at different intervals ($6195 per QALY for screening every 10 years beginning at age 60 years and $5486 per QALY for screening every 10 years beginning at age 70 years) (FIGURE 2). For persons with hypertension, screening at less frequent intervals resulted in improved cost-effectiveness for all age groups. Improved cost-effectiveness was mediated by decreased costs of screening but was accompanied by a 50% to 70% decrease in QALYs saved for persons in each screening group.

Influential Parameters. FIGURE 3 shows the highly influential variables for screening of persons with neither hypertension nor diabetes and persons with hypertension. For persons with neither hypertension nor diabetes, screening approached moderately favorable cost-effectiveness if the incidence of proteinuria and the frequency of screening were set to their greatest and smallest extremes, respectively. The cost-effectiveness of screening persons with hypertension remained highly favorable for all variables biased against screening at their extremes.

Results of multiway Monte Carlo analyses, in which all parameters were varied simultaneously over their distributions, supported the base-case results. The proportion of simulations in which screening yielded cost-effectiveness ratios of less than $50 000 per QALY, $50 000 to $100 000 per QALY, greater than $100 000 per QALY, and when the screening strategy was dominant over the no screening strategy (ie, screening resulted in less cost and improved quality of life) were 1.5%, 8.5%, 82.1%, and

Table 5. Cost-effectiveness of Annual Dipstick Testing for Proteinuria*

Clinical History and Screening Strategy	Cost of Strategy, in 2002 US $	Incremental Cost, $	Effectiveness of Strategy (QALY)	Incremental Effectiveness (QALY)	Cost-effectiveness Ratio, $ per QALY Saved
Both Death and CKD Progression Benefits					
Neither hypertension nor diabetes					
Screening	13 745	616	19.4607	0.0022	282 818
No screening	13 129		19.4585		
Hypertension					
Screening	23 927	476	17.2407	0.03	18 621
No screening	23 451		17.2151		
Death Benefit Only					
Neither hypertension nor diabetes					
Screening	13 766	635	19.4600	0.0016	396 600
No screening	13 131		19.4584		
Hypertension					
Screening	24 194	697	17.2324	0.02	37 609
No screening	23 496		17.2138		
CKD Progression Benefit Only					
Neither hypertension nor diabetes					
Screening	13 128	612	19.4585	0.0002	2.8 million
No screening	13 740		19.4583		
Hypertension					
Screening	23 865	422	17.2157	0.003	136 645
No screening	23 443		17.2127		

Abbreviations: CKD, chronic kidney disease; QALY, quality-adjusted life-year.
*Analysis assumes combined death and chronic kidney disease progression benefits of angiotensin-converting enzyme inhibitor or angiotensin II-receptor blocker therapy, only death benefits of therapy, or only renal benefits of therapy.

Table 6. Cost-effectiveness Ratios for Annual Dipstick Testing Starting at Different Ages*

	Age Screening Begins, y				
Clinical History	30	40	50	60	70
	Cost-effectiveness Ratio, $ per QALY Saved				
No hypertension or diabetes	631 474	437 201	282 818	53 372	26 929
Hypertension	26 320	18 589	18 621	18 561	15 484

Abbreviation: QALY, quality-adjusted life-year.
*Analysis assumes combined death and chronic kidney disease progression benefits of angiotensin-converting enzyme inhibitor or angiotensin II-receptor blocker therapy according to age and clinical history.

7.9%, respectively, for persons with neither diabetes nor hypertension and 50.3%, 21.3%. 22.8%, and 5.6%, respectively, for persons with hypertension.

COMMENT

Given the inexpensive and safe nature of urine dipstick testing, physicians might assume that frequent universal testing of all adults for early detection of proteinuria would have value. This study examined the cost-effectiveness of testing populations (other than persons with diabetes)[14] commonly seen in routine clinical settings, elucidated the relative mechanisms through which ACE inhibitor or ARB therapy mediate the presence or lack of cost-effectiveness of screening, and identified factors most likely to affect the cost-effectiveness of screening. Our results show that for the majority of the US population (persons with neither hypertension nor diabetes), annual screening to detect proteinuria is not cost-effective. However, based on the best available evidence to date, selective annual testing focusing on high-risk groups is highly cost-effective. For persons with neither hypertension nor diabetes, annual screening starting at age 60 years or older is moderately cost-effective. For persons with hypertension, annual screening from ages 30 to 70 years is highly cost-effective.

Direct and indirect cost savings associated with screening are primarily achieved through the prevention of new (and expensive) ESRD cases. Years of life saved through the death prevention effects of ACE inhibitor and ARB therapy are augmented by the prevention of ESRD cases and their associated high mortality. Lack of cost-effectiveness arises when the prevalence and incidence of proteinuria are very low (leading to few preventable cases of ESRD) and when the risk of death is very low. When taking into account separately the chronic kidney disease progression slowing benefits or the death prevention benefits of ACE inhibitor therapy for persons with neither hypertension nor diabetes, who have low incidence and prevalence of proteinuria, screening averts very few ESRD cases and prevents few deaths. The resulting minimal gain in QALYs is too small to balance the costs of screening and cost-effectiveness ratios are very high. The combined chronic kidney disease progression slowing and death prevention effects of ACE inhibitor or ARB therapy for persons with neither hypertension or diabetes results in an additive gain in QALYs, yielding an improved but still unfavorable cost-effectiveness ratio. In

the subgroup of persons with neither hypertension nor diabetes who are aged 60 years or older, the incidence of ESRD and death are high enough to balance the cost of screening and subsequent treatment with ACE inhibitor therapy. Cost-effectiveness ratios are far more favorable in persons with hypertension, in which the incidence and prevalence of proteinuria, renal disease progression, and the risk of death are greater.

Physicians must incorporate a variety of considerations into decisions regarding early disease detection. Our analysis helps to elucidate the most important determinants of the value of screening for proteinuria. Influential variables that might make cost-effectiveness more favorable include: adherence to ACE inhibitor or ARB therapy, the incidence of proteinuria, sensitivity and specificity of testing, the effectiveness of ACE inhibitor or ARB therapy in slowing progression toward ESRD or preventing death, and decreasing the frequency of screening.

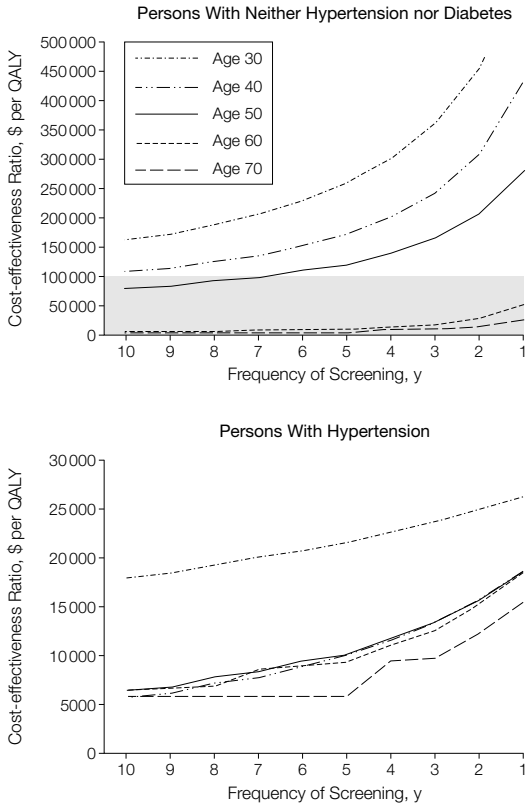
It is well-known that adherence to recommended screening and treatment strategies is associated with better outcomes, but it is less than optimal for many chronic illnesses.[97-101] Reasons for poor adherence include: both patient and physician factors such as difficulty with taking medications due to adverse effects or costs, patients' perceived control over their illness, trust in physician recommendations, ability to understand how to correctly use prescribed medications, perceptions regarding the patient-physician relationship, and physician adherence to recommendations.[51,102-107] The success of screening for urine protein will depend heavily on whether patients and physicians are able to overcome such barriers to adherence.

Fortunately, nationally representative data were available to estimate the prevalence of proteinuria among US adults with varying degrees of renal function, which greatly strengthens our findings.[2,22] While national evidence regarding incidence is not available, we obtained estimates from the highest quality data sources available. For persons with neither hypertension nor diabetes, slightly greater proteinuria incidence could substantially improve cost-effectiveness estimates.

The imperfect sensitivity and specificity of dipstick testing as an initial screening for urine protein pose a challenge for clinicians. Inaccurate identification of persons with false-positive urine dipstick results could adversely affect the cost-effectiveness of screening by subjecting unaffected persons to unnecessary additional testing and evaluation by physicians. Misidentification of persons with false-negative results could increase rates of ESRD with accompanying lesser quality of life and substantial costs of renal replacement therapy. Further study is needed to determine whether the use of more sensitive and specific quantitative methods for ascertainment of urine protein (which could be associated with increased cost and more difficult implementation) would enhance the cost-effectiveness of population-based screening.

Our estimates of the benefits of ACE inhibitor or ARB therapy are based entirely on data from randomized controlled clinical trials, which are considered to be the best study design for assessing the efficacy of pharmacological interventions.[6,8-12,24,55] However, complete translation of therapeutic effectiveness observed in the clinical trial setting is often difficult to achieve in routine clinical practice because practicing physicians are faced with treating diverse patient populations that may not completely reflect the characteristics of persons studied in trials. Thus,

Figure 2. Cost-effectiveness of Screening vs Not Screening for Proteinuria at Different Frequencies and Different Ages

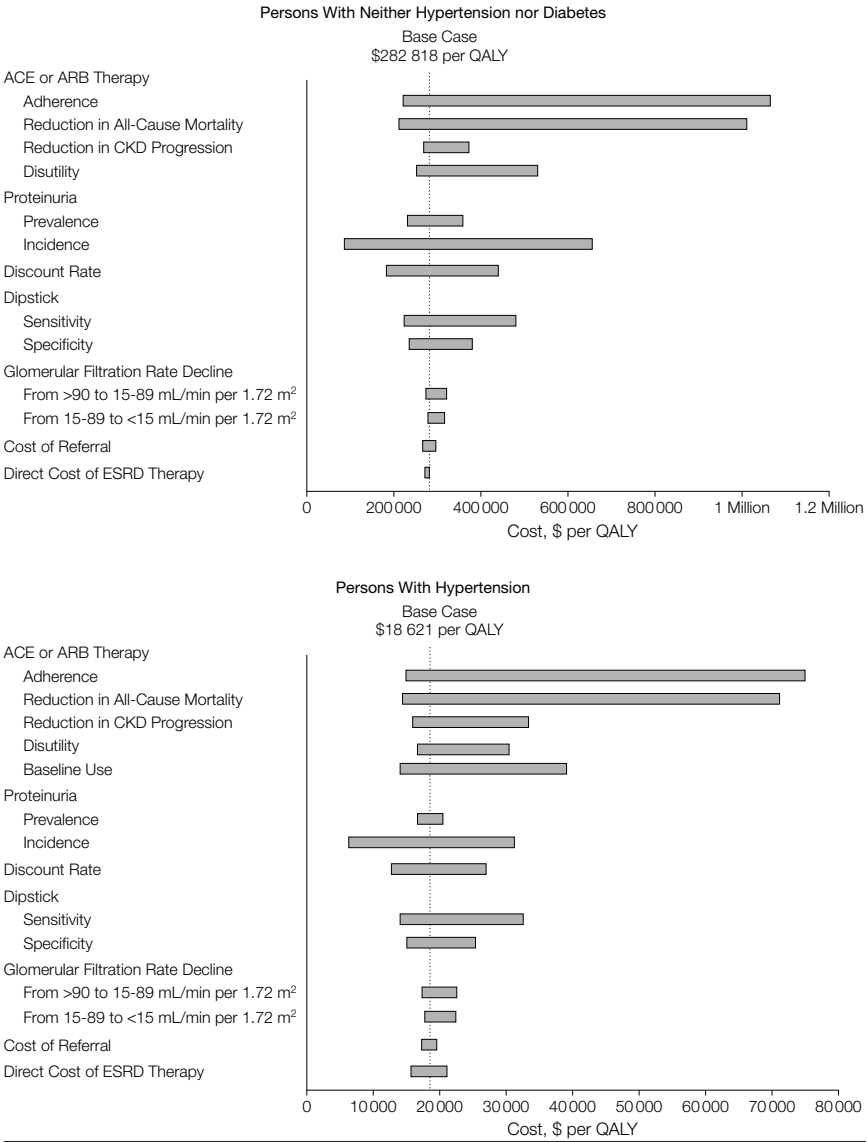


For persons with neither hypertension nor diabetes, the shaded area indicates screening associated with more favorable cost-effectiveness ratios (<$100 000 per quality-adjusted life-year [QALY]). For persons with hypertension, screening beginning at all ages was highly favorable toward screening (<50 000 per QALY).

cost-effectiveness ratios could be different for some practice settings.

Identification of the optimal screening frequency requires consideration of both the clinical benefits patients may gain and the added cost.[108] Infrequent screening yielded moderately favorable cost-effectiveness ratios for persons with neither diabetes nor hypertension and further improved cost-effectiveness of screening for persons with hypertension. However, improved cost-effectiveness resulted from not only less costs accrued from screening and treatment of persons with proteinuria but also from decreased QALYs gained as a result of fewer persons benefiting from chronic kidney disease progression and death prevention benefits of ACE inhibitor or ARB therapy. Groups making recommendations on the frequency of screening will have to decide whether the clinical benefit of preventing a few more cases of ESRD or death outweighs the added cost of more frequent screening.

Figure 3. Cost-effectiveness of Annual Screening for Proteinuria When Different Values Are Used for Parameters



CKD indicates chronic kidney disease; ESRD, end-stage renal disease. Bars represent how the cost-effectiveness ratio changes when extreme values for parameters are used compared with the parameter values used in the base-case analysis of the model.

Limitations of this analysis deserve mention. First, few data exist regarding the manner in which US physicians currently evaluate proteinuria or the frequency with which US nephrologists perform diagnostic studies on patients with different clinical histories.[74] A variety of other tests with different sensitivities and specificities for detection of proteinuria (eg, direct measurement of urine microalbumin or assessment of urinary albumin to creatinine ratio) are available.[109] Our sensitivity analyses provide insight into the cost-effectiveness of more or less sensitive or specific tests. However, evidence is needed to determine the importance of detecting microalbuminuria in the progression of chronic kidney disease among persons without diabetes. Second, few data are available regarding the incidence with which intermittent testing is performed as a result of patient symptoms or in response to other abnormal laboratory test results (such as elevated serum creatinine measurements). If incidental testing were to occur at higher rates, the cost-effectiveness of screening would be less favorable. Third, little published evidence is available to estimate the rates of decline in kidney function for persons with neither diabetes nor hypertension, for persons with hypertension who have no proteinuria, and for persons in these groups who have relatively normal kidney function.[55,56] However, we made conservative estimates of progression rates when evidence was not available and screening estimates were not highly influenced at the extremes of our estimates in sensitivity analyses. Finally, while cost-effectiveness ratios for urine dipstick screening in certain groups may be termed *favorable* using conventional thresholds for reporting cost-effectiveness, this model portrays screening largely in isolation from other screening practices being performed in clinical settings. In addition, this model does not account for often debated, unrelated health-care costs that may accrue as a result of the implementation of life-

prolonging interventions.[110] Considerations regarding implementing strategies deemed cost-effective should incorporate recognition of the limited total resources available for the provision of health care services to society and should seek to allocate resources in a manner that allows the maximum net benefit from their use.[111]

In conclusion, screening of US adults for early detection of urine protein to slow the progression of chronic kidney disease and to decrease mortality is not cost-effective unless selectively directed toward high-risk groups (older persons and persons with hypertension). Adherence to ACE inhibitor or ARB therapy, the incidence of proteinuria, the effectiveness of ACE inhibitor or ARB therapy in preventing death or progression toward ESRD, and the frequency of screening play a prominent role in the cost-effectiveness of screening in the general population.

Author Contributions: Dr Boulware had full access to data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Boulware, Jaar, Brancati, Powe.
Acquisition of data: Boulware, Jaar, Tarver-Carr, Powe.
Analysis and interpretation of data: Boulware, Tarver-Carr, Powe.
Drafting of the manuscript: Boulware, Powe.
Critical revision of the manuscript for important intellectual content: Boulware, Jaar, Tarver-Carr, Brancati, Powe.
Statistical expertise: Boulware, Tarver-Carr.
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