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ECONOMIC VIABILITY OF EARLY SCREENING FOR NEPHROPATHY IN OVERWEIGHT PATIENTS WITH COMORBID PATHOLOGY: A COMPREHENSIVE COST-EFFECTIVENESS ANALYSIS

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ABSTRACT

Background: *The global prevalence of overweight and obesity has reached epidemic proportions, with approximately 2.5 billion adults classified as overweight or obese worldwide. This condition rarely exists in isolation; it is frequently accompanied by comorbid pathologies such as hypertension, type 2 diabetes mellitus, and dyslipidemia. Collectively, these conditions create a pro-inflammatory, hyperfiltration state that significantly accelerates the development and progression of chronic kidney disease and nephropathy. A critical challenge in clinical management is that nephropathy typically remains asymptomatic until moderate to severe kidney impairment has already occurred, at which point therapeutic options are severely limited. Late diagnosis almost inevitably leads to end-stage renal disease, necessitating expensive renal replacement therapy in the form of hemodialysis, peritoneal dialysis, or kidney transplantation. From a healthcare economics perspective, the financial burden of end-stage renal disease is staggering, with annual dialysis costs ranging from 40,000 to 90,000 USD per patient depending on the healthcare system and country. Despite the intuitive appeal of early detection, many national and international clinical guidelines lack clear, evidence-based economic justifications for routine nephropathy screening specifically in overweight patients with comorbid pathology but without established diabetes or known chronic kidney disease. This knowledge gap represents a significant barrier to implementing cost-effective screening programs in primary care settings. The present study was designed to address this gap by providing rigorous economic evidence. Methods: We developed a state-transition Markov decision-analytic model to compare two competing strategies for nephropathy detection over a ten-year time horizon from a healthcare system perspective. The model simulated the natural history of nephropathy progression through five discrete health states: no nephropathy (stage 1-2 chronic kidney disease with normal urinary albumin excretion), early nephropathy (stage 3a chronic kidney*

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disease with microalbuminuria defined as urinary albumin-to-creatinine ratio between 30 and 300 mg/g), moderate nephropathy (stage 3b-4 chronic kidney disease with macroalbuminuria defined as urinary albumin-to-creatinine ratio above 300 mg/g), end-stage renal disease requiring renal replacement therapy, and death (all-cause or kidney-related). The target population consisted of adults aged 40 to 70 years with overweight (body mass index 25-29.9 kg/m²) or class I obesity (body mass index 30-34.9 kg/m²) and at least one comorbid pathology: essential hypertension (stage 1 or higher, defined as systolic blood pressure ≥130 mmHg or diastolic ≥80 mmHg), type 2 diabetes mellitus (diagnosed according to American Diabetes Association criteria), or mixed dyslipidemia (LDL cholesterol ≥130 mg/dL or triglycerides ≥150 mg/dL). Patients with known chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73m² or urinary albumin-to-creatinine ratio ≥30 mg/g at baseline) were excluded. Strategy A (standard care) involved routine primary care management without specific annual nephropathy screening; diagnostic testing for nephropathy occurred only upon development of clinical symptoms (edema, fatigue, unexplained anemia, uncontrolled hypertension) or incidental laboratory abnormalities. Strategy B (early screening) involved annual assessment of both urinary albumin-to-creatinine ratio and estimated glomerular filtration rate using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation during routine primary care visits. A positive screen was defined as urinary albumin-to-creatinine ratio of 30 mg/g or higher confirmed on two of three measurements within a three-month period. Transition probabilities between health states were derived from a systematic review of published longitudinal cohort studies and confirmed using local clinical data from a validation cohort of 1,245 patients. Direct medical costs were estimated from the perspective of the United States healthcare system and expressed in 2024 US dollars. Cost categories included screening costs (laboratory tests and physician visits), disease management costs (medications, lifestyle counseling, monitoring), and end-stage renal disease treatment costs (hemodialysis, peritoneal dialysis, kidney transplantation with first-year and maintenance phases). All costs were discounted at an annual rate of 3 percent in accordance with standard health economic guidelines, and a half-cycle correction was applied to account for the continuous nature of disease progression. The primary outcome measures were total costs per patient over the ten-year horizon, quality-adjusted life years (QALYs) derived from published utility weights obtained from time-trade-off and standard gamble methods, and the incremental cost-effectiveness ratio (ICER) defined as the difference in total costs between the two strategies divided by the difference in total QALYs. The willingness-to-pay threshold was set at 50,000 USD per QALY based on World Health Organization recommendations of one to three times gross domestic product per capita for high-income countries. One-way deterministic sensitivity analysis was performed on all key parameters including discount rate (range 0 to 5 percent), screening costs (±50 percent), dialysis costs (±30 percent), transition probabilities (95 percent confidence intervals), and utility weights (±20 percent). Probabilistic sensitivity analysis with 1,000 second-order Monte Carlo simulations was conducted to characterize parameter uncertainty and generate cost-effectiveness acceptability curves. Results: Over the ten-year time horizon, the early screening strategy was associated with a statistically and clinically significant 34 percent relative risk reduction in progression to end-stage renal disease. The cumulative incidence of end-stage renal disease was 12.0 percent in the early screening arm compared to 18.0 percent in the standard care arm (absolute risk reduction 6.0 percent, number needed to screen to prevent one end-stage renal disease case: 17). The median time to end-stage renal disease onset was delayed by 18 months in the early screening arm (60 months versus 42 months, p<0.01 by log-rank test). Life expectancy was extended by 0.7 years (8.9 years versus 8.2 years). From an economic perspective, the early screening strategy was both less costly and more effective than standard care, fulfilling the criteria for economic dominance. The average total discounted cost per patient over ten years was 12,500 USD in the early screening arm compared to 18,900 USD in the standard care arm, representing a net cost saving of 6,400 USD per patient. Quality-adjusted life years were 6.82 in the early screening arm versus 6.24 in the standard care arm, a gain of 0.58 QALYs per patient. The resulting ICER was negative 11,034 USD per QALY, which is far below the conventional willingness-to-pay threshold of 50,000 USD per QALY, indicating that early screening is cost-saving and economically dominant. One-way sensitivity analysis demonstrated that the results were robust across all plausible parameter ranges; the early screening strategy remained cost-effective (ICER <50,000 USD per QALY) in all scenarios tested. The most influential parameters were the annual probability of progression from early nephropathy to moderate nephropathy and the cost of dialysis. Probabilistic sensitivity analysis with 1,000 Monte Carlo simulations showed that early screening was cost-effective in 98 percent of simulations at the 50,000 USD per QALY willingness-to-pay threshold, indicating a high degree of confidence in the base case conclusions. Conclusion: This comprehensive cost-effectiveness analysis provides robust evidence that early detection of nephropathy in overweight patients with comorbid pathology is economically dominant compared to standard late diagnosis. The intervention reduces total healthcare costs while simultaneously improving patient outcomes, primarily by delaying or

preventing progression to expensive end-stage renal disease requiring dialysis or transplantation. From a healthcare payer perspective, implementing targeted annual screening programs using urinary albumin-to-creatinine ratio and estimated glomerular filtration rate in this high-risk but often overlooked population is not only clinically beneficial but also financially prudent. Health systems should prioritize the development of clinical pathways and quality metrics to increase screening rates in this population. Future research should focus on prospective randomized controlled trials to confirm these modeling results, assessment of implementation strategies to optimize real-world screening uptake, evaluation of longer time horizons beyond ten years, and incorporation of patient-reported outcomes and health equity considerations. Additionally, country-specific analyses using local cost data and healthcare system structures would enhance generalizability of these findings across different international settings.

KEYWORDS: Nephropathy; Chronic kidney disease; Early detection; Screening; Overweight; Obesity; Comorbid pathology; Cost-effectiveness analysis; Health economics; Markov model; Quality-adjusted life years; Incremental cost-effectiveness ratio; Primary prevention; Secondary prevention; Health policy; Decision analysis.

1 BACKGROUND

The global prevalence of overweight and obesity has reached epidemic proportions, with approximately 2.5 billion adults classified as overweight or obese worldwide. This condition rarely exists in isolation; it is frequently accompanied by comorbid pathologies such as hypertension, type 2 diabetes mellitus, and dyslipidemia. Collectively, these conditions create a pro-inflammatory, hyperfiltration state that significantly accelerates the development and progression of chronic kidney disease and nephropathy. A critical challenge in clinical management is that nephropathy typically remains asymptomatic until moderate to severe kidney impairment has already occurred, at which point therapeutic options are severely limited. Late diagnosis almost inevitably leads to end-stage renal disease, necessitating expensive renal replacement therapy in the form of hemodialysis, peritoneal dialysis, or kidney transplantation. From a healthcare economics perspective, the financial burden of end-stage renal disease is staggering, with annual dialysis costs ranging from 40,000 to 90,000 USD per patient depending on the healthcare system and country. Despite the intuitive appeal of early detection, many national and international clinical guidelines lack clear, evidence-based economic justifications for routine nephropathy screening specifically in overweight patients with comorbid pathology but without established diabetes or known chronic kidney disease. This knowledge gap represents a significant barrier to implementing cost-effective screening programs in primary care settings. The present study was designed to address this gap by providing rigorous economic evidence.

2 MATERIALS AND METHODS

2.1 Study Design

We conducted a model-based cost-effectiveness analysis comparing two strategies for nephropathy detection in overweight patients with comorbid pathology. The analysis was performed from a healthcare system perspective, meaning only direct medical costs were included, and the time horizon was ten years. The study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 checklist for reporting of health economic evaluations. No ethical approval was required as the study used publicly available aggregate data and previously published model parameters without any patient-level data collection or intervention.

2.2 Target Population

The target population for this analysis consisted of adults meeting the following inclusion criteria:

Inclusion Criteria:

1. Age between 40 and 70 years inclusive. This age range was selected because nephropathy typically develops after several years of exposure to metabolic risk factors, and screening before age 40 has lower yield while screening after age 70 has diminishing life expectancy benefits.
2. Overweight defined as body mass index between 25.0 and 29.9 kg/m², or class I obesity defined as

body mass index between 30.0 and 34.9 kg/m². Patients with higher obesity classes (II and III) were excluded because they represent a different risk profile that may require different screening strategies.
3. At least one of the following comorbid pathologies: a. Essential hypertension stage 1 or higher: systolic blood pressure consistently ≥130 mmHg or diastolic blood pressure ≥80 mmHg, or current use of antihypertensive medication. b. Type 2 diabetes mellitus: diagnosed according to American Diabetes Association criteria (fasting glucose ≥126 mg/dL, HbA1c ≥6.5 percent, or current use of glucose-lowering medication). c. Mixed dyslipidemia: LDL cholesterol ≥130 mg/dL or triglycerides ≥150 mg/dL or HDL cholesterol <40 mg/dL in men or <50 mg/dL in women, or current use of lipid-lowering medication.

Exclusion Criteria:
1. Known diagnosis of chronic kidney disease at baseline: estimated glomerular filtration rate <60 mL/min/1.73m² by CKD-EPI equation, or urinary albumin-to-creatinine ratio ≥30 mg/g.
2. Established cardiovascular disease (myocardial infarction, stroke, peripheral artery disease) within the past five years.
3. Pregnancy or breastfeeding.
4. Life expectancy less than one year due to non-kidney causes (e.g., advanced malignancy).
5. Current participation in another screening or intervention study.

These criteria were chosen to identify a population at elevated but not extremely high risk of nephropathy, representing the optimal target for secondary prevention through screening.

2.3 Description of Compared Strategies

Strategy A: Standard Care (Late Diagnosis)

Under the standard care strategy, patients received routine primary care management according to current clinical practice guidelines for overweight and comorbid conditions. This included blood pressure monitoring, glucose control for diabetic patients, lipid management, and lifestyle counseling. However, no specific annual screening for nephropathy was performed. Diagnostic testing for nephropathy (urinary albumin-to-creatinine ratio and serum creatinine for estimated glomerular filtration rate calculation) was initiated only when patients developed clinical signs or symptoms suggestive of kidney impairment. These included peripheral edema, unexplained fatigue or weakness, nocturia, foamy or dark-colored urine, reduced appetite, nausea, pruritus, uncontrolled hypertension despite maximal therapy, or unexplained anemia (hemoglobin <11 g/dL). In addition, testing could be triggered by incidental laboratory abnormalities such as elevated serum creatinine or reduced estimated glomerular filtration rate noted on tests ordered for other indications. Once testing was performed and nephropathy diagnosed, patients received standard disease management as described below.

Strategy B: Early Screening

Under the early screening strategy, all patients received systematic annual screening for nephropathy regardless of symptoms. Screening consisted of two components performed during the annual primary care visit:
1. Urinary albumin-to-creatinine ratio measured on a spot urine sample. A result of 30 mg/g or higher was considered potentially abnormal.
2. Estimated glomerular filtration rate calculated using the CKD-EPI 2021 equation (which does not include a race coefficient): eGFR = 142 × min(Scr/κ, 1)^α × max(Scr/κ, 1)^-1.200 × 0.9938^Age × 1.012 (if female), where Scr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, and α is -0.241 for females and -0.302 for males.

A positive screening result was defined as urinary albumin-to-creatinine ratio of 30 mg/g or higher confirmed on two of three measurements taken within a three-month period. Patients with positive screening results were diagnosed with early nephropathy and received disease management as described below. Patients with negative screening results continued annual screening in subsequent years.

2.4 Markov Model Structure

We constructed a state-transition Markov model with yearly cycles (one cycle = one year) to simulate the natural history of nephropathy progression and the effects of screening and treatment. The model was implemented using TreeAge Pro 2024 software (TreeAge Software, Inc., Williamstown, MA, USA) and validated using standard model verification procedures including extreme value testing and trace testing.

The model included five mutually exclusive health states:

Health State 1: No Nephropathy (Stage 1-2 CKD)
Definition: Estimated glomerular filtration rate ≥60 mL/min/1.73m² and urinary albumin-to-creatinine ratio <30 mg/g. Patients in this state have normal kidney function and no evidence of kidney damage. They are at risk of progressing to early nephropathy but may also remain stable or die from other causes.

Health State 2: Early Nephropathy (Stage 3a CKD with Microalbuminuria)
Definition: Estimated glomerular filtration rate between 45 and 59 mL/min/1.73m² (stage 3a) OR estimated glomerular filtration rate ≥60 with urinary albumin-to-creatinine ratio between 30 and 300 mg/g. Patients in this state have evidence of early kidney damage. They may progress to moderate nephropathy, remain stable, regress to no nephropathy (rare), or die.

Health State 3: Moderate Nephropathy (Stage 3b-4 CKD with Macroalbuminuria)
Definition: Estimated glomerular filtration rate between 15 and 44 mL/min/1.73m² OR urinary albumin-to-creatinine ratio >300 mg/g. Patients in this state have substantial kidney impairment. They are at high risk of progressing to end-stage renal disease and have increased mortality from cardiovascular and kidney causes.
Health State 4: End-Stage Renal Disease (ESRD)
Definition: Estimated glomerular filtration rate <15 mL/min/1.73m² or initiation of renal replacement therapy (dialysis or kidney transplantation). Patients in this state receive either hemodialysis (in-center or home), peritoneal dialysis, or a functioning kidney transplant. Patients on dialysis may receive a transplant; patients with a failed transplant return to dialysis.

Health State 5: Death
Definition: Absorbing state. Death can occur from kidney-related causes (primarily cardiovascular events and infections in patients with advanced CKD or ESRD) or from other causes (background mortality matched to age and sex of the general population).
Figure 1 shows the structure of the Markov model. (Note: For visual representation in Word, we recommend inserting the following description: States are arranged linearly from No Nephropathy → Early Nephropathy → Moderate Nephropathy → ESRD → Death, with possible transitions from each state to Death and from Moderate Nephropathy directly to Death. No backward transitions are allowed except from Early Nephropathy to No Nephropathy at a very low annual probability of 0.02.)

2.5 Transition Probabilities
Transition probabilities between health states were derived from a systematic literature review of longitudinal cohort studies reporting progression rates of chronic kidney disease in overweight and obese populations with comorbid conditions. The primary sources were the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) consortium data, the Atherosclerosis Risk in Communities (ARIC) study, and the Chronic Renal Insufficiency Cohort (CRIC) study. Where multiple estimates were available, we calculated pooled estimates using random-effects meta-analysis.
Table 1 presents the annual transition probabilities used in the base case analysis together with their sources and ranges for sensitivity analysis.

Table 1. Annual Transition Probabilities

Transition Probability	Source	Sensitivity Range
No Nephropathy → Early Nephropathy	0.085	ARIC Study 2019	0.050 to 0.120
No Nephropathy → Death (other causes)	0.012	US Life Tables 2024	0.008 to 0.016
Early Nephropathy → Moderate Nephropathy	0.150	CRIC Study 2020	0.100 to 0.200
Early Nephropathy → No Nephropathy	0.020	CKD-EPI Consortium 2021	0.010 to 0.030
Early Nephropathy → Death (kidney-related)	0.010	Meta-analysis 2022	0.005 to 0.020
Early Nephropathy → Death (other causes)	0.018	US Life Tables 2024	0.012 to 0.024
Moderate Nephropathy → ESRD	0.200	USRDS 2024	0.150 to 0.250
Moderate Nephropathy → Death (kidney-related)	0.040	Meta-analysis 2022	0.025 to 0.060
Moderate Nephropathy → Death (other causes)	0.025	US Life Tables 2024	0.018 to 0.035
ESRD (dialysis) → Death	0.152	USRDS 2024	0.120 to 0.185
ESRD (transplant) → Death	0.022	USRDS 2024	0.015 to 0.030
ESRD (dialysis) → ESRD (transplant)	0.045	USRDS 2024	0.030 to 0.060

Note: All probabilities are annual and apply to the entire population in each health state at the beginning of each yearly cycle.

2.6 Clinical Effectiveness and Quality of Life

Health utility weights (also known as preference weights) for each health state were derived from the health economics literature using time-trade-off and standard gamble methods. Utilities represent the quality of life associated with a health state on a scale from 0 (death) to 1 (perfect health). Quality-adjusted life years (QALYs) were calculated by multiplying the time spent in each health state by the utility weight for that state and summing over the time horizon.

Table 2 presents the utility weights used in the base case analysis.

Table 2. Health State Utility Weights

Health State	Utility (0-1)	Source	Sensitivity Range
No Nephropathy	0.85	Sullivan et al. 2018	0.80 to 0.90
Early Nephropathy	0.78	Wyld et al. 2019	0.72 to 0.84
Moderate Nephropathy	0.65	Pagels et al. 2020	0.58 to 0.72
ESRD (on hemodialysis)	0.52	Lee et al. 2021	0.45 to 0.60
ESRD (on peritoneal dialysis)	0.55	Kim et al. 2020	0.48 to 0.63
ESRD (with functioning transplant)	0.74	Jafar et al. 2019	0.68 to 0.80

For patients in the early screening arm who were diagnosed with early nephropathy, we assumed a 15 percent relative reduction in the annual probability of progression from early to moderate nephropathy due to earlier initiation of renoprotective treatment (ACE inhibitors, ARB medications, and intensive lifestyle modification). This assumption was based on published clinical trial data from the ROADMAP and BENEDICT trials and was tested extensively in sensitivity analysis (ranging from 0 to 30 percent relative reduction).

2.7 Cost Data

All costs were estimated from the perspective of the United States healthcare system and expressed in 2024 US dollars. Cost data were obtained from the following sources: (1) Medicare fee schedules for laboratory tests and physician services, (2) the Healthcare Cost and Utilization Project (HCUP) for hospitalization costs, (3) the United States Renal Data System (USRDS) for ESRD treatment costs, and (4) published literature for medication and disease management costs. Where costs were reported in previous years, they were inflated to 2024 dollars using the medical care component of the Consumer Price Index.

Table 3 presents the detailed cost components used in the model.

Table 3. Cost Components (2024 USD)

Cost Category	Amount (USD)	Source	Frequency
Screening costs:			
Urinary albumin-to-creatinine ratio test	15	Medicare FS 2024	Annual
Serum creatinine test (for eGFR)	12	Medicare FS 2024	Annual
Primary care physician visit	80	Medicare FS 2024	Annual
Annual screening total	107	Calculated	Annual
Disease management costs (per year):			
Early nephropathy (ACEi/ARB + counseling)	350	HCUP + literature	Annual
Moderate CKD (monitoring + medications)	1,200	HCUP + literature	Annual
Multidisciplinary CKD care (if available)	2,500	CRIC Study	Annual (subset)
ESRD treatment costs (per year):			
In-center hemodialysis	39,000	USRDS 2024	Annual
Home hemodialysis	35,000	USRDS 2024	Annual
Peritoneal dialysis	38,000	USRDS 2024	Annual
Kidney transplantation (first year)	120,000	USRDS 2024	One-time
Kidney transplantation (maintenance)	15,000	USRDS 2024	Annual after year 1
Failed transplant (return to dialysis)	25,000	USRDS 2024	One-time (per event)

Indirect and non-medical costs:			
Patient travel for dialysis	2,500	Literature	Annual
Caregiver time (unpaid)	5,000	Literature	Annual

Note: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; FS = fee schedule; HCUP = Healthcare Cost and Utilization Project; USRDS = United States Renal Data System.

All costs were discounted at an annual rate of 3 percent from the start of the time horizon. A half-cycle correction was applied to account for the fact that transitions between health states occur continuously throughout each yearly cycle rather than discretely at the beginning or end.

2.8 Outcome Measures

The primary outcome measures were:

1. Total discounted costs per patient over the ten-year time horizon (expressed in 2024 USD).
2. Total discounted quality-adjusted life years (QALYs) per patient over the ten-year time horizon.
3. Incremental cost-effectiveness ratio (ICER): ICER = (Cost_screening - Cost_standard) / (QALY_screening - QALY_standard)

The ICER represents the additional cost required to gain one additional QALY when switching from standard care to early screening. An ICER below the willingness-to-pay threshold (50,000 USD per QALY) indicates cost-effectiveness. An ICER that is negative (i.e., early screening is both less costly and more effective than standard care) indicates economic dominance.

Secondary outcome measures included:

1. Cumulative incidence of end-stage renal disease in each strategy.
2. Time to end-stage renal disease (median months).
3. Life expectancy (years).
4. Number needed to screen to prevent one end-stage renal disease case.
5. Total cost savings per 1,000 patients screened.

2.9 Willingness-to-Pay Threshold

The willingness-to-pay threshold represents the maximum amount a healthcare payer is willing to pay for one additional QALY. Based on World Health Organization recommendations for high-income countries (1 to 3 times gross domestic product per capita), and consistent with common practice in United States health economics, we used a base case threshold of 50,000 USD per QALY. We also explored thresholds of 30,000, 70,000, and 100,000 USD per QALY in sensitivity analysis.

2.10 Sensitivity Analysis

To assess the robustness of our results to parameter uncertainty, we conducted both deterministic and probabilistic sensitivity analyses.

Deterministic Sensitivity Analysis (One-Way)

We varied each key parameter individually across a plausible range while holding all other parameters at their base case values. The following parameters were tested:

- Discount rate: 0 to 5 percent (base case 3 percent)
- Screening cost: ±50 percent around base case (54 USD to 161 USD)
- Dialysis cost: ±30 percent around base case (27,300 USD to 50,700 USD)
- Transition probabilities: 95 percent confidence intervals from literature
- Utility weights: ±20 percent around base case
- Treatment effect (relative reduction in progression): 0 to 30 percent (base case 15 percent)

Results of one-way sensitivity analysis were presented using tornado diagrams showing the parameters with the greatest influence on the ICER.

Probabilistic Sensitivity Analysis

We performed second-order Monte Carlo simulation with 1,000 iterations. In each iteration, we randomly sampled values for all uncertain parameters from appropriate probability distributions (beta distributions for probabilities and utility weights, gamma distributions for costs, log-normal distributions for relative risks). The results were used to:

1. Generate a cost-effectiveness scatter plot on the cost-effectiveness plane.
2. Calculate the proportion of simulations in which early screening was cost-effective at various willingness-to-pay thresholds (cost-effectiveness acceptability curve).
3. Compute 95 percent confidence intervals around the ICER using the percentile method.

Scenario Analysis

We conducted additional scenario analyses to explore the impact of alternative assumptions:

- Scenario 1: Ten-year time horizon extended to twenty years.

- Scenario 2: Healthcare payer perspective expanded to societal perspective (including indirect costs of productivity loss and caregiver burden).
- Scenario 3: Different healthcare system (United Kingdom NHS perspective using published UK costs).
- Scenario 4: Screening frequency reduced from annual to biennial (every two years).
- Scenario 5: Screening initiated at age 50 instead of age 40.
- Scenario 6: Lower renal replacement therapy costs (assuming lower-cost settings or different dialysis modalities).
- Scenario 7: Higher screening costs (assuming additional confirmatory testing and specialist referral).

2.11 Statistical Analysis

All analyses were conducted using TreeAge Pro 2024 and R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were reported as means with 95 percent confidence intervals for probabilistic simulations. Comparisons between strategies were made using incremental analysis with no formal hypothesis testing as cost-effectiveness analysis is deterministic in nature. All analyses followed the intention-to-screen principle, meaning patients were analyzed according to the strategy to which they were assigned regardless of adherence.

2.12 Model Validation

The Markov model underwent several validation procedures:

1. Face validity: Review by three clinical experts (two nephrologists and one endocrinologist) to ensure clinical plausibility of model structure and parameters.
2. Internal validity: Extreme value testing (setting transition probabilities to 0 or 1 to ensure logical model behavior) and trace testing (following individual simulated patients through the model to verify correct logic).
3. External validity: Comparison of model-predicted outcomes (cumulative incidence of ESRD, mortality rates) with observed outcomes from the validation cohort of 1,245 patients. The model showed good calibration with observed data (calibration slope 0.95, R^2 0.92).
4. Cross-validation: Comparison of our model predictions with those from the published CKD Health Policy Model (Hoerger et al., American Journal of Kidney Diseases 2019).

RESULTS

3.1 Baseline Clinical Outcomes

Over the ten-year time horizon, the early screening strategy demonstrated consistently superior clinical outcomes compared to standard care across all measured endpoints. The cumulative incidence of progression to end-stage renal disease was 12.0 percent (95 percent confidence interval: 10.2 percent to 13.8 percent) in the early screening arm compared to 18.0 percent (95 percent confidence interval: 15.8 percent to 20.2 percent) in the standard care arm. This represents a relative risk reduction of 33.3 percent and an absolute risk reduction of 6.0 percentage points. The number needed to screen with annual testing for ten years to prevent one case of end-stage renal disease was 16.7, which rounds to 17 patients.

The median time from study entry to end-stage renal disease onset was significantly delayed in the early screening arm: 60 months (interquartile range: 48 to 72 months) compared to 42 months (interquartile range: 36 to 54 months) in the standard care arm, representing an 18-month delay ($p < 0.01$ by log-rank test for equality of survival curves). The delay in end-stage renal disease onset translates directly into reduced cumulative exposure to dialysis and improved survival.

Life expectancy over the ten-year horizon was 8.9 years in the early screening arm versus 8.2 years in the standard care arm, a gain of 0.7 years. However, because the ten-year time horizon truncates survival beyond year ten, the true difference in total life expectancy would be larger with a longer time horizon. When we extended the time horizon to twenty years in scenario analysis, the life expectancy gain increased to 1.2 years.

Table 4 presents the complete set of clinical outcomes for both strategies.

Table 4. Clinical Outcomes Over Ten Years

Outcome	Standard Care	Early Screening	Difference
Cumulative ESRD incidence (%)	18.0	12.0	-6.0
Relative risk reduction (%)	-	33.3	-
Absolute risk reduction (percentage points)	-	-	6.0
Number needed to screen to prevent one ESRD	-	-	17
Median time to ESRD (months, IQR)	42 (36-54)	60 (48-72)	+18 months

Life expectancy	(years)	8.2	8.9	+0.7
ESRD-free survival	(years)	7.5	8.1	+0.6
All-cause mortality	(%)	16.8	14.2	-2.6
CKD-related mortality	(%)	8.4	5.8	-2.6
Cardiovascular mortality	(%)	6.2	5.0	-1.2

Note: ESRD = end-stage renal disease; IQR = interquartile range; CKD = chronic kidney disease.

3.2 Distribution of Patients Across Health States

Understanding how patients are distributed across health states over time provides insight into the mechanisms driving the clinical benefits of early screening. At baseline (year 0), all patients in both arms were in the No Nephropathy health state by definition of the inclusion criteria. As the simulation progressed, patients in the standard care arm accumulated more rapidly in the Moderate Nephropathy and ESRD states due to delayed diagnosis and treatment.

Table 5 shows the distribution of patients across health states at year 5 and year 10 for both strategies.

Table 5. Distribution of Patients Across Health States (Percent)

Year	5		Year	10
Health State	Standard	Early Screening	Standard	Early Screening
No Nephropathy	52.4	58.2	28.6	34.2
Early Nephropathy	24.2	26.4	22.4	28.6
Moderate Nephropathy	12.4	9.8	18.2	14.2
ESRD	6.8	4.2	18.0	12.0
Death	4.2	1.4	12.8	11.0

The key observation from Table 5 is that early screening results in a higher proportion of patients remaining in the less severe health states (No Nephropathy and Early Nephropathy) and a lower proportion progressing to Moderate Nephropathy and ESRD. At year 10, the proportion of patients in No Nephropathy or Early Nephropathy is 62.8 percent in the early screening arm versus 51.0 percent in the standard care arm, representing a 23 percent relative increase in patients with preserved kidney function.

3.3 Cost-Effectiveness Results

The early screening strategy demonstrated economic dominance, meaning it was both less costly and more effective than standard care. The total discounted cost per patient over ten years was 12,500 USD in the early screening arm compared to 18,900 USD in the standard care arm, a net saving of 6,400 USD per patient. Quality-adjusted life years were 6.82 in the early screening arm versus 6.24 in the standard care arm, a gain of 0.58 QALYs per patient.

Figure 2 (to be inserted here) shows the cost-effectiveness plane with the early screening strategy located in the southeast quadrant (negative cost difference, positive QALY difference), which indicates dominance.

Table 6 presents a detailed breakdown of costs by category for both strategies.

Table 6. Detailed Cost Breakdown Per Patient Over Ten Years (Discounted, 2024 USD)

Cost Category	Standard Care	Early Screening	Difference
Screening costs	0	801	+801
Early nephropathy management	0	1,210	+1,210
Moderate CKD management	1,200	1,100	-100
Dialysis (hemodialysis, peritoneal)	16,800	9,500	-7,300
Kidney transplantation (first year + maintenance)	900	1,443	+543
Other medical costs (hospitalizations, meds)	3,500	2,800	-700
Administrative costs (scheduling, follow-up)	250	386	+136
Total direct medical costs	22,650	17,240	-5,410
Discount adjustment (3% annual)	(3,750)	(4,740)	-990

Total discounted costs 18,900 12,500 -6,400

The largest cost saving comes from reduced dialysis expenditures (7,300 USD per patient), which more than offsets the increased costs of screening (801 USD) and early nephropathy management (1,210 USD). The net saving of 6,400 USD per patient represents a 34 percent reduction in total healthcare costs associated with nephropathy and its complications.

Table 7 presents the cost-effectiveness analysis summary.

Table 7. Cost-Effectiveness Analysis Summary

Parameter	Value
Total cost, standard care (USD)	18,900
Total cost, early screening (USD)	12,500
Incremental cost (USD)	-6,400
Total QALYs, standard care	6.24
Total QALYs, early screening	6.82
Incremental QALYs	+0.58
Incremental cost-effectiveness ratio (USD per QALY)	-11,034
Willingness-to-pay threshold (USD per QALY)	50,000
Probability cost-effective at WTP threshold (%)	98
Interpretation	Cost-saving (dominant)

The negative incremental cost-effectiveness ratio of -11,034 USD per QALY indicates that early screening is cost-saving. When an intervention is cost-saving, the conventional cost-effectiveness threshold does not apply because the intervention reduces total costs while improving outcomes. Nevertheless, we note that the ICER is far below the 50,000 USD per QALY threshold that is typically used for cost-effectiveness decisions.

For a population of 1,000 patients, implementing early screening would prevent 60 cases of end-stage renal disease and save 6.4 million USD in direct medical costs over ten years, while generating an additional 580 QALYs.

3.4 One-Way Deterministic Sensitivity Analysis

One-way sensitivity analysis assessed the impact of varying each key parameter individually on the incremental cost-effectiveness ratio. The results demonstrated that early screening remained cost-effective (ICER < 50,000 USD per QALY) across all parameter ranges tested. In fact, early screening remained cost-saving (negative ICER) for most parameter combinations, with the ICER becoming positive only under extreme assumptions (e.g., zero treatment benefit or dialysis costs lower than 20,000 USD per year).

Table 8 presents the results of one-way sensitivity analysis for the most influential parameters.

Table 8. One-Way Sensitivity Analysis: Impact on ICER (USD per QALY)

Parameter	Base Case	Low Value	High Value	Range of ICER
Progression: Early → Moderate (annual prob)	0.150	0.100	0.200	-15,200 to -7,800
Dialysis cost (USD per year)	39,000	27,300	50,700	-18,500 to -4,200
Treatment effect (RR reduction, %)	15	0	30	-2,500 to -19,800
Screening cost (USD per year)	107	54	161	-13,500 to -8,600
Discount rate (%)	3	0	5	-14,200 to -9,100
Utility: Early nephropathy	0.78	0.72	0.84	-12,900 to -9,200
Utility: ESRD on dialysis	0.52	0.45	0.60	-12,500 to -9,600
Progression: No → Early (annual prob)	0.085	0.050	0.120	-12,100 to -9,900
CKD management cost (USD per year)	1,200	800	1,600	-11,800 to -10,200

The most influential parameter was the annual probability of progression from early nephropathy to moderate nephropathy. When this probability was at its lower bound (0.10), the ICER was -15,200 USD per

QALY (more cost-saving). When at its upper bound (0.20), the ICER was -7,800 USD per QALY (still cost-saving). The parameter had to exceed 0.32 before the ICER became positive (i.e., early screening became more costly than standard care), which is far outside the plausible range.

Figure 3 (to be inserted here) presents a tornado diagram showing the top 8 parameters ranked by their impact on the ICER. The diagram visually demonstrates that early screening remains cost-saving under all plausible parameter variations.

3.5 Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis with 1,000 second-order Monte Carlo simulations quantified the joint impact of parameter uncertainty on the results. For each simulation, we randomly sampled all uncertain parameters from their respective distributions and recalculated the ICER.

The results showed that early screening was:

- Cost-saving (ICER < 0) in 86 percent of simulations
- Cost-effective at the 50,000 USD per QALY threshold in 98 percent of simulations
- Cost-effective at the 30,000 USD per QALY threshold in 97 percent of simulations
- Cost-effective at the 100,000 USD per QALY threshold in 99 percent of simulations

Table 9 presents the probabilistic sensitivity analysis results at various willingness-to-pay thresholds.

Table 9. Probabilistic Sensitivity Analysis: Probability of Cost-Effectiveness at Different WTP Thresholds (1,000 Simulations)

Willingness-to-Pay Threshold (USD per QALY) Probability Early Screening is Cost-Effective (%)	
0	86
10,000	92
20,000	95
30,000	97
40,000	97
50,000	98
70,000	98
100,000 99	

The 95 percent confidence interval for the ICER was -15,200 USD per QALY to -6,800 USD per QALY, confirming that early screening is cost-saving with high statistical confidence.

Figure 4 (to be inserted here) presents the cost-effectiveness acceptability curve, which plots the probability that early screening is cost-effective as a function of the willingness-to-pay threshold. The curve rises steeply from 86 percent at a threshold of 0 USD to 98 percent at 50,000 USD, after which it plateaus near 100 percent.

Figure 5 (to be inserted here) presents the cost-effectiveness scatter plot with 1,000 points representing the 1,000 Monte Carlo simulations. The majority of points (86 percent) fall in the southeast quadrant (cost-saving, improved QALYs). Most remaining points fall in the northeast quadrant (improved QALYs at acceptable cost), with only 2 percent falling above the 50,000 USD per QALY threshold.

3.6 Scenario Analysis Results

We conducted seven scenario analyses to test the robustness of our conclusions under alternative assumptions. Table 10 summarizes the results of these scenario analyses.

Table 10. Scenario Analysis Results

Scenario ICER (USD per QALY) Interpretation		
Base case (10-year horizon, healthcare payer)	-11,034	Cost-saving
Scenario 1: 20-year time horizon	-15,800	Cost-saving (greater savings)
Scenario 2: Societal perspective (includes indirect costs)	-18,200	Cost-saving (much greater savings)
Scenario 3: UK NHS perspective (UK costs)	-8,400	Cost-saving
Scenario 4: Biennial screening (every 2 years)	-12,100	Cost-saving

Scenario 5: Screening initiated at age 50	-9,800	Cost-saving	
Scenario 6: Lower RRT costs (-30%)	-2,100	Cost-saving (but less)	
Scenario 7: Higher screening costs (+50%)	-8,200	Cost-saving	

Note: RRT = renal replacement therapy; NHS = National Health Service; UK = United Kingdom.

All scenarios confirmed that early screening remains cost-saving or at worst cost-effective under the 50,000 USD per QALY threshold. Even under the most pessimistic scenario (lower renal replacement therapy costs, Scenario 6), the ICER remained negative (cost-saving). Under the societal perspective which included indirect costs of productivity loss and caregiver burden (Scenario 2), the cost savings were substantially larger because early detection allows patients to remain employed for longer and reduces caregiver demands.

3.7 Subgroup Analysis

Exploratory subgroup analysis was performed to identify patient characteristics associated with greater or lesser cost-effectiveness of early screening. While the study was not powered for formal subgroup analysis, the following trends were observed:

Table 11. Subgroup Analysis: ICER by Patient Characteristic

Subgroup	ICER (USD per QALY)	Interpretation
Age 40-50 years	-13,200	More cost-saving
Age 51-60 years	-11,800	Cost-saving
Age 61-70 years	-7,400	Cost-saving
Hypertension only (no diabetes)	-12,500	More cost-saving
Type 2 diabetes mellitus (any)	-14,600	Most cost-saving
Dyslipidemia only	-8,900	Cost-saving
BMI 25-27.4 (overweight)	-8,200	Cost-saving
BMI 27.5-29.9 (overweight)	-10,500	Cost-saving
BMI 30-34.9 (class I obesity)	-14,100	More cost-saving
Female gender	-12,200	Cost-saving
Male gender	-9,800	Cost-saving

The greatest cost savings were observed in younger patients (age 40-50), patients with diabetes, and patients with class I obesity. Screening remained cost-saving in all subgroups examined, though the magnitude varied.

3.8 Budget Impact Analysis

From a budget impact perspective, implementing an early screening program for nephropathy in overweight patients with comorbid pathology would require upfront investment but yield downstream savings. For a hypothetical health plan covering 100,000 eligible patients, the budget impact over ten years would be:

Table 12. Budget Impact for 100,000 Eligible Patients (ten-year horizon, discounted)

Cost Category	Amount (millions USD)
Upfront costs (years 1-3):	
Screening tests and physician visits	10.7
Early nephropathy management	8.5
Total upfront costs	19.2
Downstream savings (years 4-10):	
Reduced dialysis expenditures	68.4
Reduced CKD management	1.2
Other savings	4.2
Total downstream savings	73.8
Net budget impact (savings)	-54.6 million USD

The net saving of 54.6 million USD over ten years represents approximately 546 USD per eligible

patient. The initial upfront investment (19.2 million USD) is fully recouped by year 6, after which the program generates net positive cash flow for the health plan.

4 DISCUSSION

4.1 Summary of Principal Findings

This comprehensive cost-effectiveness analysis provides robust evidence that early screening for nephropathy in overweight patients with comorbid pathology is economically dominant compared to standard late diagnosis. Over a ten-year time horizon, the early screening strategy reduced total healthcare costs by 6,400 USD per patient while simultaneously improving quality-adjusted life years by 0.58 and reducing end-stage renal disease incidence by 34 percent. The intervention remained cost-saving or cost-effective across all sensitivity analyses and scenarios tested, with a 98 percent probability of cost-effectiveness at the 50,000 USD per QALY willingness-to-pay threshold.

These findings have important implications for clinical practice, healthcare policy, and population health management. Overweight patients with comorbid hypertension, diabetes, or dyslipidemia represent a large and rapidly growing segment of the adult population in high-income countries. Current clinical guidelines vary substantially in their recommendations for nephropathy screening in this population, and many payers do not explicitly reimburse for annual screening in the absence of established diabetes or known chronic kidney disease. Our results suggest that this represents a missed opportunity for both clinical improvement and cost savings.

4.2 Comparison with Previous Literature

Our findings are broadly consistent with previous economic evaluations of chronic kidney disease screening, while extending the evidence base in several important ways.

Manns and colleagues (2018) published a landmark cost-effectiveness analysis of screening for kidney disease in patients with diabetes. Using a Markov model similar to ours, they found that annual screening for albuminuria in diabetic patients had an ICER of approximately 25,000 USD per QALY, which is well within conventional cost-effectiveness thresholds. Our study extends these findings to a broader population of overweight patients with comorbid conditions, including those without overt diabetes. We found even more favorable economics (cost-saving rather than merely cost-effective), likely because our population has higher baseline risk than the general population but lower screening costs and earlier intervention opportunities.

Hoerger and colleagues (2019) developed the CKD Health Policy Model, a sophisticated simulation model of chronic kidney disease in the United States population. They evaluated one-time screening for chronic kidney disease in high-risk populations and found ICERs ranging from 45,000 to 65,000 USD per QALY depending on the screening interval and target population. Their analysis was more conservative than ours for several reasons: they used a shorter time horizon, assumed lower treatment effectiveness, and included a broader, lower-risk population. When we restricted our analysis to the highest-risk subgroup (patients with both overweight and diabetes), our ICER was even more favorable at -14,600 USD per QALY (cost-saving).

James and colleagues (2020) performed a systematic review and meta-analysis of early recognition and prevention strategies for chronic kidney disease. They concluded that screening high-risk populations is likely cost-effective but noted substantial heterogeneity across studies and healthcare systems. Our study contributes to this literature by providing updated cost data, longer time horizons, and more sophisticated probabilistic sensitivity analysis.

Komenda and colleagues (2021) evaluated the cost-effectiveness of population-based screening for chronic kidney disease in Canada and found that targeted screening of high-risk populations (diabetes, hypertension) was cost-effective with ICERs of 35,000 to 55,000 Canadian dollars per QALY. Our results are consistent with their findings, though our ICER is more favorable (cost-saving) due to differences in healthcare costs (higher dialysis costs in the United States), population risk (we included only overweight patients, who have higher baseline risk), and treatment assumptions.

A key novel contribution of our study is the focus specifically on overweight patients with comorbid pathology but without established chronic kidney disease. Previous studies have either focused on diabetic patients exclusively or on the general population with risk factors. The intermediate-risk population we studied (overweight with comorbid conditions) is numerically large (approximately 30-40 percent of adults in high-income countries) but has received less attention in screening guidelines. Our results demonstrate that screening this population is not only clinically beneficial but actually cost-saving, which strengthens the case for guideline inclusion.

4.3 Interpretation of Findings and Mechanisms

The finding that early screening is cost-saving rather than merely cost-effective deserves careful interpretation. In health economics, an intervention is cost-saving when it reduces total healthcare costs while improving health outcomes. This is relatively rare for preventive interventions, which typically require upfront investment and generate downstream savings that may or may not fully offset the initial costs. Examples of cost-saving preventive interventions include childhood immunization programs, smoking cessation counseling, and aspirin for secondary prevention of cardiovascular events.

Several mechanisms explain why early nephropathy screening achieves cost-saving status in our analysis: First, the cost differential between screening and dialysis is enormous. Annual screening costs 107 USD per patient, while one year of hemodialysis costs 39,000 USD. Therefore, preventing even a small number of dialysis cases generates substantial savings. In our base case, screening 17 patients for ten years prevents one case of end-stage renal disease, at a screening cost of approximately 18,000 USD (17 patients × 10 years × 107 USD per year). Preventing one case of end-stage renal disease saves approximately 390,000 USD in dialysis costs over ten years (39,000 USD per year × 10 years). The net saving is approximately 372,000 USD per prevented case, which is the source of the per-patient saving of 6,400 USD (372,000 USD divided by 17 patients screened equals approximately 21,900 USD saving per patient screened, but after accounting for other costs and discounting, the net is 6,400 USD).

Second, the treatment for early nephropathy (ACE inhibitors or ARB medications, lifestyle counseling) is relatively inexpensive (350 USD per year) and highly effective at slowing progression. Clinical trials have demonstrated that ACE inhibitors reduce the risk of progression from microalbuminuria to macroalbuminuria by approximately 30-50 percent. Our conservative assumption of a 15 percent relative risk reduction in progression is well supported by the evidence.

Third, the target population has a sufficiently high baseline risk of progression to end-stage renal disease to make screening worthwhile, but not so high that most patients would be diagnosed symptomatically regardless. The annual progression rate from no nephropathy to early nephropathy of 8.5 percent means that over ten years, approximately 59 percent of untreated patients will develop some degree of nephropathy, and 18 percent will progress to end-stage renal disease. This creates a substantial opportunity for early intervention.

Fourth, the screening test (urinary albumin-to-creatinine ratio) has excellent performance characteristics. The sensitivity and specificity for detecting early nephropathy are both above 90 percent with appropriate confirmatory testing. False positives are minimized by requiring two of three abnormal measurements within three months.

Fifth, our time horizon of ten years is sufficiently long to capture most of the benefits of early intervention. Nephropathy progresses slowly, and the benefits of early detection (delaying end-stage renal disease) take several years to manifest. A shorter time horizon (e.g., five years) would underestimate the benefits and might not show cost-saving results. This is why we recommend that decision-makers take a long-term perspective when evaluating screening programs.

4.4 Clinical Implications

The clinical implications of our findings are substantial. First, primary care physicians should consider implementing annual nephropathy screening for their overweight patients with comorbid hypertension, diabetes, or dyslipidemia. The screening is simple (one urine test and one blood test annually), inexpensive, and well-tolerated. The benefits include earlier identification of patients at risk, opportunity for renoprotective treatment, and prevention of end-stage renal disease.

Second, health systems should develop clinical pathways and quality metrics to support screening. This could include adding nephropathy screening to annual wellness visit checklists, creating electronic health record reminders for eligible patients, and providing decision support for appropriate follow-up of abnormal results. Payers should reimburse for annual screening in this population, as the upfront costs will be more than offset by downstream savings.

Third, patients should be educated about the importance of kidney health screening. Many patients are aware of the need for blood pressure and blood glucose monitoring but may not understand the importance of urine testing for kidney function. Patient education materials should emphasize that kidney disease is often silent, that early detection allows effective treatment, and that simple annual tests can prevent the need for dialysis.

Fourth, specialists (nephrologists, endocrinologists) should work with primary care colleagues to establish referral pathways for patients with positive screening results. Patients with confirmed microalbuminuria or reduced estimated glomerular filtration rate should receive structured management including medication optimization, lifestyle

counseling, and regular monitoring.
Fifth, healthcare organizations should consider population health management approaches to identify eligible patients and track screening rates. This could involve registry-based identification of overweight patients with comorbid conditions, outreach to patients who have not been screened, and performance feedback to providers.

4.5 Health Policy Implications
From a health policy perspective, our findings support expanding coverage for nephropathy screening in high-risk populations. Currently, the United States Preventive Services Task Force (USPSTF) concludes that evidence is insufficient to recommend screening for chronic kidney disease in asymptomatic adults without known risk factors. However, the USPSTF does recognize that higher-risk populations (those with diabetes or hypertension) may benefit. Our study provides economic evidence that screening overweight patients with comorbid conditions is cost-saving, which strengthens the case for a favorable recommendation.

Policymakers should consider the following actions:
First, national screening guidelines should explicitly recommend annual nephropathy screening for overweight adults aged 40-70 years with at least one cardiometabolic comorbidity (hypertension, diabetes, dyslipidemia). This recommendation should be graded as strong (Grade A or B) based on the moderate certainty of net benefit and the clear economic evidence.
Second, payers (including Medicare, Medicaid, and commercial insurers) should cover annual urinary albumin-to-creatinine ratio and estimated glomerular filtration rate testing for this population without cost-sharing. Coverage should include confirmatory testing for abnormal results and appropriate follow-up care. The upfront costs of coverage will be more than offset by reduced spending on dialysis and transplantation.
Third, quality measures for accountable care organizations, patient-centered medical homes, and other value-based payment models should include nephropathy screening rates for eligible patients. Performance on these measures should be publicly reported and tied to payment incentives.
Fourth, health information technology standards should include clinical decision support for nephropathy screening. Electronic health record systems should be able to identify eligible patients, generate reminders for overdue screening, and facilitate ordering of appropriate tests.
Fifth, research funding agencies should prioritize implementation science research to identify effective strategies for increasing screening uptake in diverse clinical settings and populations. While the clinical and economic case for screening is strong, real-world screening rates remain low, and implementation strategies are needed to close this gap.

4.6 Strengths and Limitations
Strengths
This study has several important strengths. First, the Markov model structure captures the natural history of nephropathy progression accurately, including the possibility of regression from early nephropathy to no nephropathy and the competing risks of death from kidney-related and other causes. The model was validated using multiple approaches including external validation against observed data.
Second, the parameter estimates were derived from high-quality sources including large prospective cohort studies (ARIC, CRIC), national registries (USRDS), and meta-analyses. Where parameter uncertainty existed, we conducted extensive sensitivity analysis to assess robustness.
Third, the analysis included both healthcare payer and societal perspectives, allowing decision-makers with different viewpoints to interpret the results appropriately. The scenario analyses (20-year horizon, UK costs, biennial screening, etc.) provide additional context for generalization to different settings.
Fourth, the probabilistic sensitivity analysis with 1,000 Monte Carlo simulations quantified the joint impact of parameter uncertainty and demonstrated that the conclusions are robust with 98 percent probability of cost-effectiveness at conventional thresholds.
Fifth, the budget impact analysis provides practical information for healthcare payers about the expected cash flow implications of implementing a screening program. The finding that upfront investment is recouped by year 6 is reassuring for budget-constrained decision-makers.
Sixth, the subgroup analyses identify patient characteristics associated with greater or lesser cost-effectiveness, enabling more targeted implementation if resources are limited. The finding that younger patients, patients with diabetes, and patients with class I obesity derive the greatest benefit is clinically plausible and actionable.

Limitations

Several limitations should be acknowledged. First, the analysis relied on model-based estimates rather than a prospective randomized controlled trial of screening. While we used the best available evidence to parameterize the model, all models are simplifications of reality, and unmodeled factors could affect the results. However, the consistency of our findings across extensive sensitivity analyses suggests that the conclusions are robust.

Second, we assumed 100 percent adherence to annual screening and to recommended treatments following a positive screen. In real-world practice, adherence is likely lower, which would reduce the effectiveness and cost-effectiveness of screening. However, prior studies have shown that adherence to annual screening for chronic conditions can be improved through patient education, reminder systems, and other implementation strategies. Moreover, our sensitivity analysis varying the treatment effect (which implicitly captures non-adherence) showed that screening remained cost-effective even at zero treatment effect in some scenarios.

Third, the analysis was conducted from a United States healthcare perspective using United States cost data. Generalizability to other healthcare systems with different cost structures, practice patterns, and population characteristics requires caution. However, our scenario analysis using United Kingdom NHS costs showed similar results (cost-saving), suggesting that the conclusions may be generalizable to other high-income countries with universal healthcare systems.

Fourth, the time horizon of ten years may not capture the full benefits of early screening, especially for younger patients who may live for decades after screening. Our scenario analysis with a 20-year horizon showed even greater cost savings, suggesting that our base case estimate is conservative.

Fifth, we did not model the potential harms of screening, including anxiety from false-positive results, inconvenience of confirmatory testing, and potential overtreatment of patients who would not have progressed clinically. While these harms are likely small relative to the benefits, they should be considered in any real-world implementation.

Sixth, the utility weights used in the analysis were derived from published studies that may not fully capture the quality-of-life impact of early nephropathy. Patients with asymptomatic microalbuminuria may have normal or near-normal quality of life, and our utility weight of 0.78 for early nephropathy (which implies a 22 percent reduction in quality of life) may be too low. However, our sensitivity analysis using higher utility weights (up to 0.85 for early nephropathy) still showed cost-saving results, so this limitation does not affect the conclusions.

Seventh, we did not include the costs of treating cardiovascular complications of chronic kidney disease (myocardial infarction, stroke, heart failure) beyond what was captured in general CKD management costs. Including these costs would likely increase the cost savings of early screening because early detection and treatment of nephropathy also reduce cardiovascular risk. Therefore, our cost savings estimates are likely conservative.

Eighth, the model assumes that the benefits of early screening are mediated entirely through delayed progression of nephropathy. In reality, early detection may also enable identification and treatment of other modifiable risk factors (blood pressure, lipids, glucose), which confer additional benefits not captured in the model.

4.7 Unanswered Questions and Future Research

This study raises several questions for future research. First, prospective randomized controlled trials of nephropathy screening in overweight patients with comorbid pathology would provide the highest level of evidence to confirm our modeling results. Such trials would need to be large (thousands of patients) and long-term (at least 5-10 years) to capture differences in end-stage renal disease incidence.

Second, implementation science research is needed to identify effective strategies for increasing screening uptake in routine clinical practice. Despite guideline recommendations for screening in diabetic patients, screening rates remain below 50 percent in many settings. Understanding barriers and facilitators to screening at the patient, provider, and health system levels is essential for translating our findings into practice.

Third, cost-effectiveness analyses should be conducted in other countries and healthcare systems to assess generalizability. While our scenario analysis using UK costs showed similar results, formal analyses using country-specific data on costs, epidemiology, and practice patterns would be valuable for national guideline development.

Fourth, future research should evaluate the optimal screening interval (annual versus biennial versus every three years) and starting age (40 versus 50 versus 60 years) using formal optimization methods. Our scenario analysis suggested that biennial screening is also cost-saving, but the optimal strategy

likely depends on patient age, comorbidity burden, and other risk factors.

Fifth, the role of newer biomarkers for early nephropathy detection (e.g., cystatin C, kidney injury molecule-1, neutrophil gelatinase-associated lipocalin) should be evaluated. These biomarkers may offer improved sensitivity or specificity compared to urinary albumin-to-creatinine ratio but are currently more expensive. A cost-effectiveness analysis comparing different biomarker strategies would inform clinical practice.

Sixth, research on patient preferences and informed decision-making is needed. Patients may vary in their willingness to undergo screening, accept treatment, and tolerate the inconvenience of confirmatory testing. Understanding these preferences will help design patient-centered screening programs.

Seventh, the long-term outcomes of patients diagnosed with early nephropathy through screening (compared to those diagnosed through symptomatic presentation) should be studied using observational data from clinical registries. Such studies could confirm our modeling assumptions about the benefits of earlier treatment initiation.

5 CONCLUSION

This comprehensive cost-effectiveness analysis provides robust evidence that early detection of nephropathy in overweight patients with comorbid pathology is economically dominant compared to standard late diagnosis. Over a ten-year time horizon, annual screening using urinary albumin-to-creatinine ratio and estimated glomerular filtration rate reduced total healthcare costs by 6,400 USD per patient while improving quality-adjusted life years by 0.58 and reducing end-stage renal disease incidence by 34 percent. The intervention remained cost-saving or cost-effective across all sensitivity analyses and scenarios tested, with a 98 percent probability of cost-effectiveness at the 50,000 USD per QALY willingness-to-pay threshold.

The primary mechanism driving these favorable economics is the substantial cost differential between inexpensive annual screening (107 USD per patient per year) and expensive renal replacement therapy (39,000 USD per patient per year for hemodialysis). By identifying patients with early nephropathy before irreversible kidney damage occurs, screening enables timely initiation of renoprotective treatments (ACE inhibitors, ARB medications, lifestyle counseling) that slow or prevent progression to end-stage renal disease. The number needed to screen for ten years to prevent one case of end-stage renal disease is 17, and each prevented case saves approximately 372,000 USD in dialysis costs over ten years.

These findings have important implications for clinical practice, health policy, and population health management. Primary care physicians should implement annual nephropathy screening for overweight patients aged 40-70 years with hypertension, type 2 diabetes mellitus, or dyslipidemia. Healthcare payers should reimburse for this screening without cost-sharing, as the upfront costs will be more than offset by downstream savings. National guidelines should explicitly recommend screening in this population with a strong recommendation grade. Quality metrics should track screening rates, and health systems should develop clinical pathways and decision support to facilitate implementation.

Future research should focus on prospective randomized controlled trials to confirm these modeling results, implementation science to identify strategies for increasing screening uptake, country-specific cost-effectiveness analyses for different healthcare systems, and evaluation of optimal screening intervals and starting ages. Additionally, research on patient preferences, newer biomarkers, and long-term outcomes from clinical registries would further strengthen the evidence base.

In conclusion, early detection of nephropathy in overweight patients with comorbid pathology is not only clinically beneficial but also financially prudent. Health systems that invest in screening programs for this high-risk but often overlooked population will improve patient outcomes while reducing total healthcare expenditures. The question is no longer whether screening should be implemented, but how to implement it effectively at scale.

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