Screening for proteinuria in US adults: a cost-effectiveness analysis  
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Record Status  
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology  
Two screening strategies for the early identification of chronic kidney disease were examined. More specifically, the study compared a strategy of annual screening with no screening (usual care) for proteinuria, both of which were followed by treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II-receptor blocker (ARB). The frequency of screening was also investigated through a sensitivity analysis.

Type of intervention  
Screening.

Economic study type  
Cost-utility analysis.

Study population  
The base-case population modelled consisted of adults aged 50 years old, presenting to a primary care physician for an annual physical examination with previously undetected proteinuria. Fifty-two per cent were female, 80% non-Hispanic white, 11% non-Hispanic black and 5% Mexican American. The demographic characteristics were similar to those of the third National Health and Nutrition Examination Survey (NHANES III). This was divided into 3 sub-groups (those with diabetes, those with hypertension and those with neither). Different ages for starting screening were investigated in sensitivity analyses.

Setting  
The setting was primary and secondary care. The economic study was carried out in the USA.

Dates to which data relate  
The epidemiological, effectiveness and utility data were taken from several trials and studies published between 1978 and 2003. The cost and resource use data were taken from several sources dating from 1991 to 2003. The price year was 2002.

Source of effectiveness data  
The effectiveness data were derived from published studies. Some estimates were based on authors’ assumptions.

Modelling  
A state-transition Markov analytic model was developed to simulate the clinical path of patients from normal kidney function to end-stage renal disease (ESRD). This was used to compare a strategy of annual screening for proteinuria, and subsequent treatment with either ACE inhibitor or ARB therapy, with a strategy of routine clinical practice for persons with neither hypertension nor diabetes and for persons with hypertension. The health states in the Markov model were normal kidney function, chronic renal insufficiency and ESRD, or the need for renal replacement therapy.
Screening of all persons occurred annually until the age of 75 years, the development of ESRD, or death.

**Outcomes assessed in the review**
The outcomes considered were the sensitivity and specificity of the screening test, the prevalence and incidence of proteinuria, adherence to screening and treatment, use of ACE inhibitors and symptoms leading to testing. The transition probabilities between the health states in the Markov model were derived from the annual decline in glomerular filtration rates (GFR). Harms of screening such as renal biopsy (including haematuria and clinical haematoma) and adverse effects of ACE inhibitor or ARB therapy (including anaphylaxis or angioedema requiring emergency department visit and 24-hour observation) were also included.

**Study designs and other criteria for inclusion in the review**
The authors reported that they used randomised controlled trials, cohort studies, meta-analyses, observational studies and published literature.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
The authors categorised all evidence used in the model according to a hierarchy of research design put forward by the US Preventive Services Task Force. The highest level of evidence was used.

**Methods used to judge relevance and validity, and for extracting data**
Not stated.

**Number of primary studies included**
At least 50 primary studies were included in the review for different purposes (e.g. the various outcomes assessed).

**Methods of combining primary studies**
Not stated.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
The base-case rates for the outcomes were as follows:

the prevalence rate of proteinuria by clinical history was 0.19% for patients with neither hypertension nor diabetes, 1.2% for hypertension and 5.4% for diabetes;

the incidence rate of proteinuria by clinical history was 0.01% for neither hypertension nor diabetes, 0.5% for hypertension and 2.5% for diabetes;

the sensitivity of the screening test was 76% and the specificity was 79%;

patient adherence to screening and treatment with ACE inhibitor or ARB therapy was 75%;
the base rate for use of ACE inhibitors was 20%; and

the rates for symptoms leading to testing were 4% if the GFR was 90, 30% if the GFR was 15 to 89, and 100% if the GFR was less than 15. The authors assumed the last two values.

The base rate used for potential benefits of screening all sub-groups was a 30% relative risk reduction in progression toward ESRD, and a 23% reduction in all-cause mortality. Reductions afforded by ACE inhibitor or ARB were assumed to be equal.

The base rates used for potential harm of screening were as follows.

renal biopsy rates were 90% for persons with neither hypertension nor diabetes, 5% for persons with hypertension and 5% for persons with diabetes;

complications due to renal biopsy (including haematuria, clinical haematoma, and other complications) were 5%;

medication adverse effect rates included a rate of 0.5% for anaphylaxis secondary to ACE inhibitor or ARB, and a rate of 2% for angioedema secondary to ACE inhibitor.

See the original paper for the rates of annual decline in glomerular filtration.

Methods used to derive estimates of effectiveness
This analysis was based on published data and authors’ assumptions.

Estimates of effectiveness and key assumptions
The model assumptions were as follows.

For persons with neither hypertension nor diabetes and with no proteinuria, rates of GFR decline from 15 to 89 mL/minute per 1.73 m2 (KDOQI stage 2-4) to less than 15 mL/minute per 1.73 m2 (KDOQI stage 5) were the same as rates of GFR decline for persons with normal kidney function (KDOQI stage 1). Among persons with neither hypertension nor diabetes and with proteinuria, the rates of GFR decline for persons with a GFR of 90 mL/minute per 1.73 m2 (KDOQI stage 1) were 10% greater than the rates for their counterparts with no proteinuria. Among persons with hypertension and with no proteinuria, the rates of GFR decline for persons with normal kidney function (KDOQI stage 1) were 10% greater than the rates for persons with neither hypertension nor diabetes and with no proteinuria.

Proteinuria is generally asymptomatic and is associated with a minimal decrement in health status.

Measure of benefits used in the economic analysis
The measure of benefits used was the quality-adjusted life-years (QALYs). The health state utilities were drawn from other research (Tengs et al., see Other Publications of Related Interest). The only methodology reported was that the standard gamble or time-tradeoff technique was used. The disutility associated with ACE inhibitor or ARB therapy was estimated from data reporting the adverse effects of medication. The QALYs were discounted at a rate of 3% per year.

Direct costs
The direct costs to the health service were included and were appropriately discounted at a rate of 3% per year. These included initial testing and follow-up visits, therapeutic costs, medication adverse events and ESRD treatment costs. The test costs were estimated using Medicare reimbursement rates based on the Medicare resource-based relative value scale for part B services. The costs of ACE inhibitor or ARB therapy were estimated by using a weighted average of the wholesale prices for proprietary and non-proprietary products on the market. The costs of emergency department visits were estimated using data from the Centres for Medicare and Medicaid services. The costs of treating ESRD (KDOQI stage 5) were estimated using data from the US Renal Data System. All the direct costs were in year 2002 dollars.
**Statistical analysis of costs**
The costs were treated deterministically and no statistical tests were carried out.

**Indirect Costs**
The indirect costs of wages lost for persons unable to work as a result of ESRD were included and were discounted at a rate of 3% per year. The annual lost wages for nonworking persons with ESRD (KDOQI stage 5) were estimated using a weighted average of published estimates of the mean percentage of persons working full-time while receiving either dialysis or transplantation treatment modalities. Persons in all other stages were considered to be working full-time until they turned 65 years. The data on average US wages were taken from the US Department of Labour. All the indirect costs were in year 2002 dollars.

**Currency**
US dollars ($).

**Sensitivity analysis**
The Markov model was analysed using cohort simulations for base-case and several sensitivity analyses. Analyses were carried out on the optimal age for screening (beginning screening at ages 30 to 70 years) and the optimal frequency of screening (from annually to every 10 years). One-way sensitivity analyses were also performed on all model parameters. Each parameter was given values to bias them in favour of or against screening. A change ratio of 50% or more was considered highly influential.

For the multi-way sensitivity analysis, a Monte Carlo analysis consisting of 1,000 simulations in which all parameters were varied simultaneously over their distributions was performed. The types of distribution used were not reported.

**Estimated benefits used in the economic analysis**
The base-case gain in discounted QALYs for screening was 0.0022. One new case of ESRD and 7 deaths per 1 million persons per year in the screening strategy were prevented.

For persons with hypertension, there was a gain of 0.03 QALYs from screening. Fourteen new cases of ESRD and 104 deaths per 1 million persons per year were prevented.

For persons with diabetes, the screening strategy provided a gain of 0.10 QALYs per person. Eighty-four new cases of ESRD and 541 deaths per 1 million persons per year were prevented.

The QALYs were discounted at a rate of 3% per year.

**Cost results**
For persons with neither hypertension nor diabetes, when considering benefits in both death and chronic kidney disease progression, the total cost of the screening strategy was $13,745 versus $13,129 for the usual care strategy. The incremental cost was $616.

For persons with hypertension, when considering benefits in both death and chronic kidney disease progression, the total cost of the screening strategy was $23,927 versus $23,451 for the usual care strategy. The incremental cost was $476.

For persons with neither hypertension nor diabetes, when considering the benefit in life extension only, the total cost of the screening strategy was $13,766 versus $13,131 for the usual care strategy. The incremental cost was $635.

For persons with hypertension, when considering the benefit in life extension only, the total cost of the screening strategy was $24,194 versus $23,496 for the usual care strategy. The incremental cost was $697.
For persons with neither hypertension nor diabetes, when considering the benefit in chronic kidney disease progression only, the total cost of the screening strategy was $13,128 versus $13,740 for the usual care strategy. The incremental cost was $612.

For persons with hypertension, when considering the benefit in chronic kidney disease progression only, the total cost of the screening strategy was $23,865 versus $23,443 for the usual care strategy. The incremental cost was $422.

**Synthesis of costs and benefits**

The base-case cost-effectiveness ratio for screening versus the usual care strategy (no screening) was unfavourable ($282,218 per QALY saved).

For persons with hypertension, the cost-effectiveness ratio for the screening strategy versus no screening was highly favourable ($18,621 per QALY saved).

For persons with diabetes, the screening strategy was dominant over the no screening strategy (savings of $217 and a gain of 0.10 QALYs per person in the screening strategy).

The results of the sensitivity analyses were as follows.

For persons with neither hypertension nor diabetes, the cost-effectiveness of screening was unfavourable until screening beginning at age 60 years. For persons with hypertension, annual screening beginning at age 30 years resulted in highly favourable cost-effectiveness ratios.

Decreasing the frequency of screening in the base-case for persons with neither hypertension nor diabetes resulted in more favourable cost-effectiveness ratios ($120,727 every 5 years and $80,700 every 10 years). Similar results were found for screening persons of older ages at different intervals. For persons with hypertension, screening at less frequent intervals resulted in improved cost-effectiveness for all age groups.

For persons with neither hypertension nor diabetes, screening approached moderately favourable cost-effectiveness if the incidence of proteinuria was set to its greatest extreme and the frequency of screening was set to its smallest extreme. The cost-effectiveness of screening persons with hypertension remained highly favourable for all variables biased against screening at their extremes.

The multi-way Monte Carlo analysis supported the base-case results.

For persons with neither diabetes nor hypertension, the proportion of simulations in which screening yielded cost-effectiveness ratios of less than $50,000 per QALY was 1.5%.

For persons with hypertension, the proportion of simulations in which screening yielded cost-effectiveness ratios of less than $50,000 per QALY was 50.3%.

**Authors' conclusions**

Screening 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 towards high-risk groups.

**CRD COMMENTARY - Selection of comparators**

The authors investigated several strategies through sensitivity analysis, varying the age at which screening began and the frequency of screening. It was a thorough analysis, which included no screening.

**Validity of estimate of measure of effectiveness**

The authors conducted a review of the literature but there was no indication that it conducted systematically. The authors also made some assumptions that were justified with reference to the medical literature. The methodology for
selecting and reviewing the literature used was not reported. The authors used data from the primary studies selectively.

**Validity of estimate of measure of benefit**
The authors used the QALYs as a measure of benefits. The estimation of utility weights was taken from the literature, and no further detail was provided. The estimation of benefits was modelled through a state-transition Markov model to simulate the natural progression of the disease. To test the validity of the model, a first-order Monte Carlo analysis was used to assess the average time spent in the health states. The model outputs were compared with nationally available data on disease incidence and mortality.

**Validity of estimate of costs**
The authors reported that the costs were estimated from a societal perspective and, as such, all the relevant cost categories appear to have been included. Although all the costs were taken from different sources and years, they were discounted at a rate of 3% per year. Prices were taken from published sources but the resource use quantities were not reported separately. Sensitivity analyses of the resource quantities and prices were not conducted.

**Other issues**
The authors did not report any other economic evaluation on this topic. The issue of generalisability to other settings was not directly addressed. Nevertheless, the authors stated that physicians are faced with treating diverse patient populations that may not completely reflect the characteristics of persons studied in trials. Therefore, it is difficult to achieve, in routine clinical practice, a complete translation of therapeutic effectiveness observed in the clinical trial setting. The authors’ conclusions reflected the scope of the analysis. The authors reported that there was limited evidence on incidence and disease progression.

**Implications of the study**
The authors stated that the success of screening for proteinuria will depend heavily on whether patients and physicians are able to overcome barriers to adherence in order to recommend screening and treatment strategies. Further research is needed to determine whether the use of more sensitive and specific quantitative methods for urine protein would enhance the cost-effectiveness of population-based screening.

**Source of funding**
Supported by a mini-grant from the National Kidney Foundation of Maryland, grants RO1DK596160251 and K240502643 from the National Institute of Diabetes and Digestive and Kidney Diseases, and the Robert Wood Johnson Minority Medical Faculty Program.

**Bibliographic details**

**Other publications of related interest**


Garg AX, Kiberd BA, Clark WF, Haynes RB, Clase CM. Albuminuria and renal insufficiency prevalence guides

Tengs TO, Wallace A. One thousand health-related quality of life estimates. Medical Care 2000;38:583-637.

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Aged; Angiotensin-Converting Enzyme Inhibitors /economics /therapeutic use; Antihypertensive Agents /economics /therapeutic use; Cost-Benefit Analysis; Disease Progression; Humans; Hypertension /complications /drug therapy; Kidney Failure, Chronic /economics /epidemiology /prevention & control; Markov Chains; Mass Screening /economics; Middle Aged; Proteinuria /complications /diagnosis /economics; Quality-Adjusted Life Years; Receptor, Angiotensin, Type 2 /antagonists & inhibitors; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.; Risk Assessment; United States /epidemiology; Urinalysis /economics

**AccessionNumber**
22004008021

**Date bibliographic record published**
30/11/2004

**Date abstract record published**
30/11/2004