Screening for early chronic kidney disease

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Author: Nigel Toussaint

GUIDELINES

a. **We recommend screening for chronic kidney disease (CKD) as it is an effective strategy to allow earlier detection and management to reduce the increasing burden of CKD (1C).**
b. **We recommend that screening for CKD be targeted and performed in individuals at increased risk of developing CKD, including those with diabetes mellitus, hypertension, and established cardiovascular disease (1B).**
c. **We recommend screening in those with additional CKD risk factors identified in Guideline 2a. (obesity, cigarette smoking, Aboriginal and Torres Strait Islander peoples, family history of stage 5 CKD or hereditary kidney disease in a first or second degree relative and severe socioeconomic disadvantage) (1D).**
d. **We recommend screening every 1-2 years in adults depending on their risk factor profile as per Table 2 (1D).**
e. **The tests recommended for CKD screening should include both a urine test for albuminuria and a blood test for serum creatinine to determine an estimated glomerular filtration rate (eGFR) (1C).**
f. **We recommend a urinary albumin: creatinine ratio (UACR) measurement in a first void specimen for the detection of proteinuria in both diabetic and non-diabetic patients (1C).**
    i. **Where a first void specimen is not possible or practical, a "spot" (random) urine specimen for UACR is recommended (1C).**
g. **We recommend that a positive UACR screening test should be repeated on 1-2 occasions over a period of three months to confirm persistence of albuminuria. If the first positive UACR is a random spot (as it may be for opportunistic screening), then repeat tests should ideally be first morning void specimens (1D).**
    i. **We recommend following the algorithm depicted in Figure 1 (1D).**

UNGRADED SUGGESTIONS FOR CLINICAL CARE

There are no ungraded statements.

IMPLEMENTATION AND AUDIT

1. Primary practice audits of how many patients with one or more CKD risk factors receive annual evaluation of eGFR, albuminuria and blood pressure.
2. Conduct and evaluate a screening program with respect to the prevention or reduction of renal events (including end-stage kidney disease), cardiovascular events and mortality.

BACKGROUND

Chronic kidney disease (CKD) is a significant global problem creating an increasing worldwide health and economic burden. In Australia CKD affects approximately 15% of the population, with reduced kidney function present in about 10% [1], and this prevalence has likely risen in recent years driven by the increased numbers of people with diabetes and the increasing age of the population. The spectrum of CKD includes those with mild kidney damage who remain relatively healthy and without symptoms, through to end-stage kidney disease (ESKD) where survival is only maintained through forms of renal replacement therapy, including dialysis and transplantation.

As CKD is usually silent until its late stages, many patients with CKD are detected only shortly before the onset of symptomatic kidney failure when there are few opportunities to prevent adverse outcomes. Earlier detection may allow more time for evaluation and treatment but would require explicit testing strategies for asymptomatic individuals at increased risk. In the majority of patients, CKD can be detected with two simple tests: a urine test for the detection of albuminuria or proteinuria and a blood test (serum creatinine) to determine an estimated glomerular filtration rate (eGFR). These two tests facilitate detection allowing for identification of CKD without first requiring determination of its cause and there is now reliable research evidence to support a variety of clinical interventions that will benefit patients with CKD after detection [2, 3]. Application of CKD testing in national and international screening and surveillance programs may potentially improve public health related to CKD but has been subject to much controversy.

Screening for a disease is defined as an activity whereby people in a distinct population who are not aware of disease are tested to identify the disease. The goal of screening is to reduce the risk of progression of disease and reduce its complications. Screening to identify CKD could involve either assessment of the whole population for markers of disease or targeting specific groups of patients at higher risk of CKD. Many international guidelines have been produced for CKD with recognition that early CKD affects a large proportion of the population and appropriate detection and management of this condition at early stages may reduce the number of patients progressing to ESKD or dying prematurely from cardiovascular disease. Studies show that late referrals of patients with CKD to nephrologists result in poorer outcomes, less opportunity for renal protection and inadequate time to prepare for renal replacement therapy [4, 5]. However, about a quarter of all patients in Australia present to their nephrologist with kidney failure less than 90 days before starting dialysis [6]. Early detection of CKD may therefore have value, although criteria for a screening program to detect the disease must be met to balance the aggregate benefits with the risks and costs of the screening tests.

The objective of this guideline is to determine the role and cost-effectiveness of screening for CKD (with review of the evidence for and against), including how the population to which it might be applied could be appropriately targeted (i.e. who to screen and in what setting) and what screening strategies are useful for testing (i.e. most appropriate urine and blood tests).

SEARCH STRATEGY

Databases searched: Text words for chronic kidney disease were combined with MeSH terms and text words for screening. The search was carried out in Medline (1966 – 3 August 2009). No language restrictions were placed on the search. The conference proceedings of the American Society of Nephrology from 1994-2008 were also searched for trials. An update search was conducted in Medline (2009 – March 2012). Text words and MeSH terms for chronic kidney disease were combined with text words and MeSH terms for screening, diagnosis and risk factors.

Date of search/es: 3 August 2009; March 2012

WHAT IS THE EVIDENCE?

As CKD is often not associated with significant symptoms or urinary abnormalities, this condition is unrecognized in 80-90% of cases [1, 7-9]. Early treatment of CKD however has been shown to delay or prevent deterioration in renal function [10-12], so earlier detection of asymptomatic individuals would be important and effective to reduce ESKD and can be achieved at the primary care level. Unfortunately, no randomised controlled trials are available which address outcomes following the application of a CKD screening program to any population in a primary health care or other setting. Although the best evidence for screening would be a randomised controlled screening study performed in large numbers of individuals, throughout various countries in the world, and who are followed up over many years for outcomes, this would be extremely costly and practically very difficult.

A decision to screen is not trivial and should be based on a variety of considerations, including the potential of screening to improve healthcare as well as the best scientific evidence available regarding the utility of screening under differing circumstances. The World Health Organisation (WHO) has published principles of screening for chronic disease and these can largely be fulfilled for CKD [13-15].

Criteria for a successful screening program should include: (i) the disease being an important health problem and relatively prevalent in the population; (ii) the disease having a recognisable latent period and a natural history that is adequately understood; (iii) acceptable screening tests having good performance characteristics including sensitivity, specificity and positive predictive values; (iv) the disease being treatable either for cure or to delay progression, and benefits for obtaining this outcome outweighing the harms of screening; and (v) cost-effectiveness of screening. Other considerations that contribute to the feasibility of implementing screening programs include the tests available for screening (eg. choice of tests), the setting in which screening may be most effective, the group to be screened (eg. high-risk population) and the frequency of screening.

Screening can occur in two ways – (a) population-based screening where a test is widely offered to either all individuals or those in a targeted group and (b) opportunistic screening when a test is offered to an individual without symptoms of the disease when they present to the health-care system for other reasons. Several national and international organisations have made recommendations advocating routine screening for CKD, but details regarding approaches to screening vary [16-21]. There is broad consensus that a necessary feature of any program to reduce the burden of CKD must include mechanisms to screen populations and although population-wide screening is not cost-effective, targeting those at risk may be more appropriate to be able to institute early aspects of management, such as control of blood pressure, management of diabetes, and in patients with advanced CKD, preparation for dialysis or transplantation [22, 23].

1. Who should be screened for CKD? Is there value in targeted- or population-screening?

Screening for CKD targeted to subgroups of the population at increased risk of this disease delivers the screening intervention to those who would derive the most benefit from detection. Although the case for widespread population screening has been argued [24], the advantages of targeting CKD testing to high-risk groups have been demonstrated. Screening programs targeted at known diabetics, hypertensives and those who are older have been described to be the most cost-effective to detect most CKD in the community.

One large-scale general health survey of 65,604 people from a single community in Norway concluded that screening people with hypertension, diabetes or age >55 years was the most effective strategy to detect people with CKD [25]. After an 8-year follow-up, this cross-sectional study examined the occurrence of ESKD and cardiovascular death in this population and retrospectively assessed different screening strategies to compare their ability to detect CKD. By targeting diabetes, hypertension and age >55 years, only 37% of the population would be screened and would have detected 93.2% (95% CI: 92.4 - 94.0%) of all CKD present in the community and only required 8.7 people to be screened per detected case of CKD stages 3-5 (eGFR <60mL/min/1.73m^2). Other strategies of targeting (eg. only people with diabetes and hypertension) detected a lower percentage of CKD (44.2%) and were less effective. Also, in the study cohort with eGFR 30-60mL/min/1.73m^2 the incidence of ESKD was low (0.1%) compared to cardiovascular mortality (4.2%) and in those with eGFR <30mL/min/1.73m^2 the incidence of ESKD and cardiovascular death was 2.6% and 10.1% respectively. In fact only 38 of the 3069 people screened who had an eGFR <60mL/min/1.73m^2 developed ESKD with this risk predominantly being related to those with diabetes, hypertension and age >70 years. Unfortunately there were no cost-analyses performed in this study.

Another study reporting on the performance of similar screening strategies is the United States (US) Kidney Early Evaluation Program (KEEP), which targets individuals with diabetes, hypertension, or family history of diabetes or hypertension or CKD. Reported data from KEEP determined that 7 people with diabetes or hypertension or with first degree relatives with diabetes, hypertension or kidney disease need to be screened for one case of CKD to be found [22, 23, 26]. KEEP also found 19.7% of participants had CKD stages 3 and 1.1% had CKD stages 4-5, although there was an over-representation of African-Americans (who have much greater rates of hypertension as a primary diagnosis for ESKD) and women.

A study in the United Kingdom (UK), the Kidney Evaluation and Awareness Program in Sheffield (KEAPS), reported that the prevalence of microalbuminuria in the general population was 7.1% but only 1.3% in those without known risk factors for CKD [27]. The main determinants for microalbuminuria in this study were age, diabetes, obesity and a family history of hypertension. In another study from the KEAPS data, the prevalence of microalbuminuria in those with a body mass index (BMI) less than 25 was 3.1% compared to 12.1% in those with a BMI between 25-30 and 27.7% in obese subjects with a BMI greater than 30 [28].

An Australian report by Howard et al. using cost-effectiveness modelling outlined the potential effectiveness of screening and intensive management of the "key" CKD risk factors - diabetes, hypertension and proteinuria [29]. Cost-effectiveness was modelled in terms of the effect on overall mortality, on cardiovascular mortality and morbidity and on progression to ESKD and the report determined that a strategy based on screening of 50 to 69 year olds in general practice, plus intensive management of diabetes, hypertension and proteinuria, would be cost-effective.

Another study with cost-effectiveness analysis by Boulware et al. and based on US NHANES (National Health and Nutrition Examination Survey) data used Markov decision modelling to specifically address the question whether it is cost-effective to periodically screen adults aged 30-70 years (with no hypertension or diabetes) for proteinuria with a urine dipstick versus waiting for CKD to clinically emerge and be treated according to usual medical practice [30]. In this study, annual screening, to take place in the general practitioners office, was not shown to be cost-effective unless targeted at such high-risk groups such as those >60 years and those with hypertension. Cost-effectiveness was also shown if the frequency of screening in the general population was conducted at 10-year intervals. Other studies to determine target populations to screen have shown consistent findings from the use of NHANES data. One such examination of CKD prevalence by the predictive effect of demographic factors, co-morbidities and CKD risk factors by Collins et al. concluded that a screening approach targeting individuals over 60 years or those with diabetes or hypertension would also be useful from a public health standpoint, although specific targeting of cardiovascular disease was thought to have a lower yield [31].

One difficulty in targeted-screening to a population with known CKD risk factors such as hypertension and diabetes is that there are several epidemiologic studies showing for every patient with known hypertension or diabetes there is one individual in the population for whom this diagnosis is not yet made but who already could have considerable associated end-organ damage [32-34]. Therefore targeted-screening programs for CKD may potentially miss many at-risk individuals.

Apart from people with diabetes, hypertension and those of older age, screening of a population with increased risk of CKD could also include family members of patients with ESKD as an additional group of at-risk individuals. A cross-sectional survey by way of voluntary screening of relatives of patients with ESKD in the US found there was a high prevalence of CKD and proteinuria among relatives of dialysis patients who participated in screening [35]. 49% of participants had a creatinine clearance (CrCl) <90ml/min and 14% had a CrCl <60ml/min with proteinuria of 1+ or greater on dipstick found in 10% of participants. The main finding of this study according to the authors however was that evidence of CKD in these family members had not been detected previously. Another study, as part of the KEAPS program, also assessed relatives of patients with CKD [36]. Compared to the general population where the prevalence of microalbuminuria was 1.4%, prevalence of microalbuminuria in the 274 relatives of patients with CKD was 9.5%. A more recent study from India involving screening of adult first-degree relatives of patients with ESKD reported that 8.6% had CKD and 88.5% were unaware [37].

In summary, enrichment of the a priori probability of finding an individual with a progressive form of CKD will enhance the positive predictive value and minimise the negative predictive value of screening tests. Therefore, targeted-screening for CKD in people with diabetes, hypertension, cardiovascular disease or family history of renal disease would be more cost-effective than universal population-screening. Also, cost-effectiveness has been reported for this strategy with concentration on at-risk individuals.

2. What should be tested when screening for CKD? Are urine tests, blood tests or blood pressure measurements the most effective?

Blood tests measuring serum creatinine levels for determination of an eGFR and urine tests, with either a dipstick for protein, urinary protein/creatinine ratio (UPCR), urinary albumin concentration (UAC) or urinary albumin/creatinine ratio (UACR), would be the mainstay of CKD screening programs, along with blood pressure measurements. These tests for establishing the presence of CKD are simple, cheap and widely available. The sensitivity and specificity of blood and urine tests have been described previously [38, 39]. Understanding the strengths and limitations of tests for CKD is critical for appropriate implementation into a screening program.

Proteinuria and albuminuria

Proteinuria refers to increased excretion of any urinary protein, including albumin and other serum proteins. Proteinuria and albuminuria are the earliest markers of kidney damage in patients with diabetes, hypertension and glomerular diseases, and persistent increases in levels are the most common markers of kidney damage in adults. Both total protein and albumin excretion can increase transiently because of a number of factors including urinary tract infection, haemodynamic stresses such as exercise, fever and heart failure, and transient metabolic problems such as ketosis and hyperglycaemia. Proteinuria must be persistent over a minimum of 3 months to indicate kidney damage in patients with CKD. The 24-hour urine collection for protein or albumin is regarded as the gold standard but is difficult to implement in routine practice. Measurement of albumin and total protein in spot samples avoids the need for collection of a timed urine specimen but is affected by the state of hydration. Factoring the concentration of albumin or protein by urine creatinine collection and using UACR or UPCR eliminates this variation.

Proteinuria is reported to be the most important determinant of likely progression to ESKD [40] and screening of high-risk individuals with proteinuria may fulfil the criteria to initiate a screening program [41]. The first study to address the issue of the relationship between urinalysis results and the subsequent incidence of ESKD was a Japanese study using registries of both community mass screening and dialysis programs in Okinawa [42]. This study involved 107,192 subjects who participated in urine dipstick and blood pressure measurements in 1983 and, after 10 years follow-up, 193 of the initial cohort were identified to be requiring dialysis. Proteinuria was the most potent predictor of ESKD with an adjusted odds ratio (OR) of 14.9 (95% confidence interval 10.9 - 20.2), with haematuria the next most potent predictor (adjusted OR 2.30, 95% CI 1.62 - 3.28). However, the exact rates of false-positive or false-negative results in this study were unknown. Diastolic blood pressure was also a significant independent predictor of ESKD.

Another study to assess the relationship between proteinuria and ESKD, from Rochester, Minnesota in the US, involved 1832 people with type 2 diabetes followed for 5-40 years, 25 of them developing ESKD. In this study, proteinuria at the time of diagnosis of diabetes was the strongest risk factor for ESKD with a relative risk (RR) 12.1 (95% CI 4.3-34) [43]. Persistent proteinuria developing after the diagnosis of diabetes was associated with a cumulative risk for CKD (10 years later) of 11%. Proteinuria is also a potent risk factor for mortality and an early study (with 16-year follow-up) of 5209 people from the Framingham cohort reported that proteinuria was associated with a substantial increased risk of mortality (three-fold) [44]. In this study proteinuria was predominantly present in hypertensive and diabetic patients, but was otherwise uncommon.

The reported prevalence of proteinuria varies in population studies from 1 to 6%, depending on age and gender [42, 44]. The AusDiab study used UPCR with a threshold of 0.2mg/L reporting 2.3% of subjects who tested positive [1]. As estimates of 24-hour urine protein can be obtained from either dipsticks for proteinuria or from UPCR, Craig et al. [45] extracted data from primary studies of proteinuria testing [46-49] and with pooled meta-analytic methods for diagnostic tests reported that at a specificity of 67%, the sensitivity of dipsticks for proteinuria was 90%. The poor specificity of dipsticks therefore could result in a higher proportion of the population being recalled for more tests before declared as false-positives. Meta-analysis of UPCR tests in this study however reported a sensitivity of 95% at a specificity of 91%. Despite this, Craig et al. conducted a feasibility study of screening for proteinuria using urine dipstick in Australian general practice, followed by commencement of angiotensin-converting enzyme (ACE) inhibitors where indicated, and concluded that mass screening by dipstick in middle-aged and older Australians would prevent cases of ESKD and result in a cost saving for the health care system [45]. This strategy was reported to require 20,000 people aged over 50 years to be screened and 100 people treated with ACE inhibitors for 2-3 years to prevent one case of ESKD, resulting in a saving of approximately AUS$70,000.

In contrast, in the extensive cost-effectiveness analysis of screening for proteinuria in US adults by Boulware et al. described earlier [30], a strategy of annual screening for proteinuria by primary healthcare physicians, with follow-up testing and treatment with ACE inhibitors, was reported not to be cost-effective to slow progression of CKD. Maximising sensitivity of the test was shown to be more important than maximising specificity in this study, however the results have been criticised for being strongly influenced by the low yield of the screening test (again looking for dipstick-positive proteinuria), the high costs for the screening by the general practitioners, and the fact that they only took into account benefits with regard to prevention of ESKD (and not cardiovascular disease).

The use of albuminuria to screen may be less expensive and tests for albuminuria have greater sensitivity and specificity for CKD caused by diabetes, hypertension and glomerular diseases than tests for total protein [50]. Evidence in the general population as well as those with diabetes suggests that microalbuminuria (or urinary albumin excretion ≥30mg/24 hours) is highly predictive for later occurrence of cardiovascular disease [51-54]. The reference method for measurement of urinary albumin excretion is a 24-hour urine collection although for screening purposes this method is impractical. The clinical utility of a dipstick proteinuria test to detect microalbuminuria was studied by Japanese investigators who showed that many patients with dipstick positivity seem to have microalbuminuria [55]. Of individuals who were trace, 1+ or 2+ positive, 61, 71 and 41% respectively, had microalbuminuria, whereas only 1, 7 and 50% had macroalbuminuria. Only the patients with 3+ positivity had most (91%) macroalbuminuria.

Information regarding the usefulness of using albuminuria in screening for CKD has arisen from the PREVEND (Prevention of Renal and Vascular ENd-stage Disease) study, a prospective, population-based cohort study assessing cardiovascular and renal prognosis with risk markers of macroalbuminuria, haematuria and impaired renal function (24-hour CrCl and eGFR). Initially all inhabitants of the city of Groningen (in the Netherlands) aged 28 to 75 years were invited to send in by mail a questionnaire together with a sample of a first-morning urine void for measurement of UAC. Of 85,421 individuals, 40,856 participated. One study from the second phase of PREVEND, where participants with UAC>10mg/L (n = 6000) were invited for more accurate measurements of cardiovascular and renal risk factors and then compared to a computer-generated random sample of the population screened with UAC <10mg/L (n = 2592), examined the use of UAC as a proposed population screening tool to detect microalbuminuria [56]. This study tested the diagnostic performance of UAC and UACR, measured in the spot morning urine sample, in predicting microalbuminuria, as determined by urinary albumin excretion ≥30mg in subsequent 24-hour urines. Both the sensitivity and specificity of UAC was 85%, similar to that of UACR, and it was argued that to reduce the cost and the variability of not needing to measure urinary creatinine, UAC was effective in detecting albuminuria.

Using more data from the PREVEND study, after a 4-year follow-up, Halbesma et al. reported that macroalbuminuria was a better risk marker than low eGFR or haematuria to identify individuals at risk for deterioration in renal function in population screening [57]. Macroalbuminuria (defined as ≥300mg albumin/24-hour urine) was present in 0.6% of the population and those with this risk factor showed a -7.2mL/min/1.73m^2 eGFR loss, compared to -2.3mL/min/1.73m^2 in the control group ($p<0.001$). Macroalbuminuria also predicted a worse outcome with regard to cardiovascular morbidity and mortality and was the best risk marker for ESKD.

Another study assessing the association between albuminuria and accelerated loss of renal function and ESKD involved a general population-based cohort of 40,854 individuals in the US aged 28-75 years who collected a first morning void for measurement of albuminuria [58]. In a subset of 6879 participants, 24-hour urinary albumin and eGFR were collected, and after 9-year follow-up 45 individuals were identified to have ESKD using the national renal replacement therapy registry. The study found that the quantity of albuminuria was associated with increased renal risk, so that the higher the level of albuminuria the greater the decline in renal function, and UAC ≥20mg/L identified individuals with ESKD with 58% sensitivity and 92% specificity. The authors in this study concluded that restricting screening to high-risk groups (eg. known hypertension, diabetes, cardiovascular disease, older age) reduced the sensitivity of the test only marginally.

A major limitation of testing for urine protein and albumin however is that both may be increased transiently due to a number of factors as mentioned earlier, although repeated testing of urine can help overcome this limitation and screening for proteinuria and albuminuria has proved to be effective in high-risk populations [22, 59-61].

Albuminuria screening for CKD detection is recommended in individuals with diabetes mellitus because the bulk of published evidence linking screening or treatments with clinical outcomes has centred on albuminuria testing [62, 63]. In individuals who do not have diabetes, it is not yet established whether albuminuria or proteinuria testing is superior for detecting people with CKD at increased risk of progression, although a recent, retrospective longitudinal cohort study of 5586 CKD patients at a single renal centre demonstrated that UACR performed as well as UPCR and 24-hour urinary albumin and protein measurements for the prediction of doubling of serum creatinine, commencement of renal replacement therapy or all-cause mortality [64]. Consequently, the CARI Early CKD Working Group

recommended screening for albuminuria rather than proteinuria as the preferred strategy in the majority of patients at risk of CKD on the basis that laboratory measurement of albuminuria a) accurately predicts renal and cardiovascular risks in population studies and renoprotective benefit in intervention trials [54, 65-70]; b) exhibits greater sensitivity for detecting lower, clinically important proteinuria [71]; c) provides reduced analytical precision at low diagnostically important concentrations [71]; d) allows assay standardisation [72]; e) has been established to be cost-effective compared with protein or albumin reagent strips [73]; and, f) is favoured by a number of other international best practice guidelines [62, 63, 74-78]. Albumin is the most commonly increased urinary protein in most nephropathies. Furthermore, the simplified screening strategy of urinary albumin assessment in all patients at risk of CKD was considered desirable by the Working Group. The principal disadvantages of selecting albuminuria in preference to proteinuria for CKD screening in non-diabetic individuals are that the evidence base for CKD intervention strategies based on proteinuria is greater than it is for albuminuria and that tubular proteinuria may be missed in a small number of individuals

Serum creatinine and estimated glomerular filtration rate

GFR is considered the best overall measure of kidney function. Although it can be difficult to measure, it can be estimated easily from serum creatinine level, age, sex, race and body size. Limitations of serum creatinine as a marker of CKD however include variation in generation (largely dependent on muscle mass and meat intake), proximal tubular secretion and extrarenal elimination in the gastrointestinal tract, as well as variation among laboratories in assays. In patients with CKD, the description of renal function as an estimate of GFR is undoubtedly more informative than the serum creatinine concentration alone. However, the value of GFR as a screening tool for identification of individuals with CKD has not yet been prospectively validated.

From the earlier described Japanese study using registries of both community mass screening and dialysis programs in Okinawa, a subgroup from the initially screened cohort where serum creatinine data was available (n = 14,609) showed that creatinine was strong predictor of ESKD (adjusted OR 5.31, 95% CI: 3.39-8.32) [79]. However, it is well known that there is a substantial prevalence of significantly abnormal renal function among patients with a normal range creatinine. One study of 2781 outpatients in Canada, estimated that 15.5% of patients with serum creatinine in the normal range had significantly reduced GFR (<50mL/min, as calculated by the Cockcroft-Gault formula) [80]. Including calculated estimates of GFR in routine laboratory reporting was suggested by the authors of this study to facilitate the early identification of patients with CKD. Subsequently, with the introduction of automatic reporting of eGFR, as measured by the Modification of Diet in Renal Disease (MDRD) equation, there has been improved recognition of early reductions in GFR and this has advanced the ability to find early cases of people at risk of developing ESKD [81].

Ideally, screening tests would best be measurements at point-of-care and a finger-prick based serum creatinine test is currently under development (although still being validated and standardized). However, the definition of CKD with abnormalities to persist for more than 3 months results in a severe restriction on screening for CKD with a one-off blood test. Unreliability of current formulas for determining eGFR and potential flaws in the current CKD staging classification (such as the lack of recognition of normal age- and gender-related decline in renal function and the lack of proteinuria criteria for CKD stages 3-5) are other limitations of the use of eGFR as a universal screening tool and may lead to erroneous categorisation of an appreciable proportion of the general population [82, 83]. An eGFR <60mL/min/1.73m^2 is more likely to be a true-positive result in a patient at increased risk of CKD (ie. a patient with hypertension, diabetes, cardiovascular disease or a family history of CKD) than in a patient not at increased risk.

One recent study has compared screening of CKD awareness using the newer CKD Epidemiology Collaboration (CKD-EPI) equation with the MDRD equation to determine eGFR in a cross-sectional study using data from KEEP [84]. This study showed that the CKD-EPI equation led to a modest increase in awareness rates predominantly due to reclassification of low-risk unaware participants (10.6% of those unaware of having CKD being reclassified as not having CKD using eGFR by CKD-EPI).

Although eGFR may be integral to a CKD screening program (and required for a diagnosis according to the definition of CKD), additional tests to separate those at special risk of progression are needed. A Norwegian study which tracked 2389 people with GFR 45-59mL/min per 1.73m^2 for 8 years showed only 0.4% progressed to ESKD [25]. Of those with an eGFR 30-45 mL/min/1.73m^2 only 1.3%

progressed to ESKD. In the population-based examinations in the US NHANES 1999-2004 study, 76% of the participants with an eGFR of 30-59 mL/min/1.73m^2 (CKD stage 3) did not have abnormal proteinuria and only 6% had overt macroalbuminuria [85]. 55% of the participants with CKD stage 3 in this study were over 60 years and 37% were over 70 years of age. Screening for CKD with eGFR alone would therefore identify a largely older population many of whom will not have corroborative evidence of "kidney disease" and may potentially lead to increased unnecessary investigations, referrals, cost and anxiety.

Combination of reduced eGFR and proteinuria or albuminuria is especially important as a risk factor for ESKD, as reported in the Multiple Risk Factor Intervention Trial (MRFIT) where an eGFR <60mL/min/1.73m^2 together with proteinuria 2+ or more on dipstick had a relative risk of 33 for progression to ESKD compared with normal GFR and no proteinuria [86]. This study assessed the development of ESKD by 1990 in 332,544 men (35-57 years of age) who were screened between 1973 and 1975 for entry into the trial. The positive predictive value of an eGFR <60mL/min/1.73m^2 in the absence of dipstick proteinuria was only 5.6% for the future development of ESKD compared to 26% for ≥1+ proteinuria. UACR has also been reported with higher rate of GFR decline in men [87].

It has been suggested that using eGFR as a screening tool may also potentially predict and reduce the incidence of cardiovascular events as it is widely reported that well established CKD, with a reduced eGFR well below the normal range, is associated with increased risk of cardiovascular events and death. However, many of the epidemiologic studies suggesting eGFR-related risk of cardiovascular events are unable to determine cause and effect and many are also unable to fully adjust for the concomitant effect of proteinuria and other comorbidities that can contribute to cardiovascular risk. In the largest study (n = 1,120,295) addressing this issue by Go et al., the adjusted hazard ratio for cardiovascular events in subjects with a repeated serum creatinine measurement and an eGFR 45-59mL/min/1.73m^2 was 1.2 (95% CI 1.1-1.3), compared to those with eGFR >60mL/min/1.73m^2 [88]. For all-cause death however there was no difference between these groups. In contrast, only in those with an eGFR <45mL/min/1.73m^2 was the hazard ratio significantly increased for both cardiovascular events and mortality. Despite this significant association (at lower eGFR ranges), the use of eGFR for universal or even targeted-screening has not been tested with respect to reducing cardiovascular disease or mortality. Also, no study to date has shown effective management in CKD patients to improve cardiovascular outcomes. One potential intervention in this population to reduce cardiovascular events would be the use of cholesterol-lowering statin therapy. In a large meta-analysis by Strippoli et al, the use of statins was reported to have no significant impact on all-cause mortality in individuals with CKD (GFR <60mL/min/1.73m^2), despite reductions in lipid levels and cardiovascular endpoints [89]. However a recent randomised controlled trial, the Study of Heart and Renal Protection (SHARP) study, revealed that reduction of cholesterol with simvastatin and ezetimibe safely reduced the incidence of major atherosclerotic events in patients with advanced CKD [90].

Cystatin C is a more recently discovered filtration marker currently undergoing extensive evaluation for GFR estimation. One prospective population-based cohort study in the US involving 26,643 participants reported that the addition of cystatin C to a combination of serum creatinine and UACR may improve the predictive accuracy for all-cause mortality and ESKD [91].

Blood pressure

Although no study has looked at using blood pressure alone to screen for CKD, as discussed earlier, targeting people with hypertension to screen for CKD (with urine and eGFR) is cost-effective given the increased risk. High blood pressure is a known independent risk factor for the development of ESKD [41, 92]. After a 16-year follow-up, participants in the MRFIT study showed a strong graded independent association between both systolic and diastolic blood pressure and ESKD [92], with the risk of ESKD associated with elevations of systolic blood pressure being greater than that linked with elevations of diastolic pressure.

In summary, screening for CKD with proteinuria alone may be easier, cheaper and more reliable in a targeted population. Screening with a measure of proteinuria will also allow for detection of patients with CKD stages 1 and 2, although it is unknown whether screening with microalbuminuria would be better than macroalbuminuria in terms of prevention of progressive CKD. The poor performance of eGFR as a predictor of progression of CKD stages 1 to 3 to ESKD does not support its use alone in screening of CKD. There are also several limitations of screening using current testing of CKD in asymptomatic individuals. There is a variable rate of false-positive test results for both urine protein and eGFR,

although repeated measurements with confirmation of persistence of abnormal results over 3 months will diminish this false-positive rate. In addition, the thresholds for abnormal and normal levels of eGFR and urine protein have been derived primarily from studies of adults in the US and Europe and may not be applicable to all ages or different geographic, racial and ethnic groups (including the indigenous population in Australia).

3. When should people be screened for CKD? In what setting would screening be effective?

Further studies are needed to assess the cost-effectiveness of community- or work-based screening programs, but at present there is a lack of evidence for CKD screening in these settings. Opportunistic screening in general practice for hypertension, diabetes and albuminuria appears the most cost-effective, with subsequent interventions to prevent progression of CKD [29, 30].

4. How often should screening for CKD occur?

The optimal frequency for screening for CKD is not known, although as described earlier annual screening was more cost-effective in a targeted population. The cost-effectiveness of screening also improved with lengthening of the interval between screenings to less frequently than annually. The cost-effective analysis by Boulware et al. showed that in contrast to annual screening, screening people 50 years or older with either hypertension or diabetes at a frequency of every 10 years also approached favourable cost-effectiveness ratios [30].

5. Why should people be screened for CKD? Are there benefits or harms for the participant?

Early detection of CKD allows preventive measures to favourably affect clinical outcomes. The benefits of screening and implementation of interventions to reduce the burden of CKD and cardiovascular disease have been demonstrated in a study by Hoy et al. targeting the Australian Aboriginal and Torres Strait Island population [93]. In 1995, a renal and cardiovascular treatment program was introduced into a Tiwi community (with established high death and ESRD rates) to those with confirmed hypertension, diabetics with microalbuminuria or overt albuminuria, and people with overt albuminuria, regardless of blood pressure and diabetes (n = 267). The UACR was used for screening of CKD and treatment was centred on the use of perindopril, with additional agents as needed to reach defined blood pressure goals, attempts at control of glucose and lipid levels, and health education. Terminal events occurred in 38 controls and 23 people in the treatment group and the estimated rate of natural deaths in the treatment group was 50% that of the controls, (P = 0.012). The reduction in mortality (50%) and ESKD (57%) in the whole community showed the marked benefit of the program and it was concluded by the authors that millions of dollars had been saved, based on avoidance of dialysis alone, although the reduction in premature death was an even greater benefit.

There are always potential harms in a screening program. A positive result of a screening test for CKD can create harm through increasing anxiety in the participant, especially with the incidence of false-positives. There is a lack of precision of serum creatinine measurements and potentially people may be labelled with CKD without essentially having disease. With the definition of CKD requiring the presence of an abnormal eGFR longer than 3 months, a system for referral to a general practitioner for further testing is required after an initial positive screening test. An Australian study evaluated the impact of automated eGFR reporting on the quantity of referrals to nephrology services and found there was an increase in referrals, predominantly in older and diabetic patients with CKD stage 3, with a small but significant decrease in the quality [94].There are no data to establish what psychological harm may result if people are told that they have a higher-than-average risk of developing ESKD and there may also be potentially harmful financial implications, such as increased difficulty in obtaining insurance for life, disability and income protection.

6. Cost-effectiveness of screening for CKD and screening algorithms

The demonstration of cost-effectiveness of screening for CKD requires the demonstration of a clinical benefit in the long term to a screen-detected person. The US KEEP has attempted to follow-up its participants, although with limited follow-up the results are unclear and there has not been any costing analysis [95]. In the Australian study by Howard et al. with cost-effectiveness analysis, the benefit of screening lay in both reducing cardiovascular mortality and ESKD [29]. This study reported that for every 1000 people screened, hypertension screening, diabetes screening and proteinuria screening would prevent 11, 2 and 2 cases of ESKD respectively and 65, 23 and 14 cardiovascular deaths

respectively. The cost of a CKD targeted-screening program was reported to be as cost-effective (or more) than the estimated efficiency of screening programs (eg. breast, cervical, bowel cancer) already available in Australia. A US health economic analysis similarly concluded that screening in those with diabetes and hypertension led to a 44% reduction in the cumulative incidence of ESKD [96]. The cost-effectiveness of a CKD screening program in the US has also recently been compared to established screening programs for other conditions estimating that screening for CKD with urinary protein testing in people 50 years or older with diabetes or hypertension on an annual basis is very favourable and similar to screening programs for other conditions such as cervical cancer [97].

The screening of unselected populations however has the potential for harm and has not been definitively shown to be cost-effective. A recent analysis of the PREVEND data reported a potentially favourable cost-effectiveness of population-based screening for albuminuria in the Dutch population [98]. This study, which used a Markov model to stimulate the natural course of albuminuria-based disease, assessed both cardiovascular and renal outcomes and reported that limiting the screening to those over 50 increased the cost-effectiveness of screening. Another cost-effectiveness study by Atthobari et al. showed that screening of an adult population for elevated UAC (in this case albuminuria >15mg/d) and subsequent treatment of individuals with positive screening results with an ACE inhibitor was cost-effective when calculated to prevent cardiovascular end-points [99]. Differences between this analysis and that done by Boulware et al. in the US population [30] were that cardiovascular benefits were incorporated and screening was undertaken by spot morning urine samples that were delivered by mail in the former study, as opposed to only assessing the reduction of ESKD and performing screening in the general practitioner's office in the latter analysis. A more recent Japanese study also reported potential cost-effectiveness of population screening with urine dipstick with or without the addition of serum creatinine, but argued that the high prevalence of CKD in Asian countries provided justification [100].

There are many international effective screening strategies currently in place. The KEEP screening program in the US shows that only 6.7% of participants are aware of CKD, although 28.7% met diagnostic criteria [22]. KEEP is also a CKD detection program designed to inform the public about the disease burden and complications. The Veterans Health Administration in the US have reported their experience showing effective measures used to accomplish screening and then implementing management to reduce the CKD burden [101]. In Europe, there are many active screening programs at present, including PREVEND in the Netherlands, North Trøndelag Health Study (HUNT) in Norway and Estudio Epidemiológico de la Insuficiencia Renal en España (EPIRCE) in Spain [102]. In the US, the Computerized Assessment of Risk and Education (CARE) was developed by the National Kidney Foundation of Indiana in collaboration with the Diabetes Research and Training Center of Indiana University as a free community-based screening for first-degree relatives of dialysis patients and individuals with diabetes and hypertension [103]. There have also been population-based screening programs in Brazil [104].

In Australia, Kidney Health Australia (KHA) has long been involved in CKD prevention and detection through educational campaigns and other public healthcare initiatives. The Kidney Evaluation for You (KEY) is one such early CKD detection and prevention program for the community aiming to detect early asymptomatic CKD in high risk individuals (those with diabetes, hypertension and those over 50 years or age) and then refer them to primary health care providers for appropriate longer-term care. The KEY health check, conducted by registered nurses and health professionals, is a free and comprehensive evaluation of kidney function, cardiovascular health and diabetes risk and involves blood tests, urinalysis and body measurements.

Because CKD relates strongly to the major comorbid conditions of diabetes, hypertension and cardiovascular disease, developing predictive modelling is difficult, and scoring systems have been created but require addressing multiple comorbid conditions to identify the potential population for screening for CKD. One systematic method to screen for CKD in a targeted-population (including taking multiple risk factors into account) has been reported and validated by Bang et al. [105]. This published scoring system, weighted towards common variables associated with CKD, was designed to prompt healthcare professionals to detect CKD earlier and will be tested in the future in several settings including a community-based screening program.

7. International Consensus and Position statements

Although it is clear that worldwide consensus is building with regards to the need for targeted-screening programs, variation in recommendations reflect the lack of evidence to guide specific aspects of program implementation and uncertainty regarding cost-quality trade-offs. It is also unclear whether CKD screening should be performed in a stand-alone fashion or in combination with other well-established screening programs. In 2004, an International Society of Nephrology (ISN) Consensus Workshop on Prevention of Progression of Renal Disease recommended that patients with diabetes and hypertension and relatives with kidney disease have regular screening for the development of CKD [17]. More recently in 2006, the Kidney Disease: Improving Global Outcomes (KDIGO) initiative has made recommendations (see international guidelines below) that all countries should have a targeted-screening program for CKD, focusing on people known to have diabetes, hypertension and cardiovascular disease [18].

In 2007, a UK Consensus Conference on Early CKD proclaimed there was lack of evidence to support the cost-effectiveness of general population screening, and that the majority of cases will be detected from blood tests and chronic disease management clinics in primary care by using eGFR [19]. A National Kidney Foundation position statement supports early detection of CKD, but recommends only asymptomatic individuals at increased risk be tested, with explicit testing strategies [20]. In Japan, urine testing in annual health examinations has been credited with reducing the number of patients with ESKD caused by glomerulonephritis, and screening programs have been recommended to target people with diabetes, hypertension and metabolic syndrome [21].

SUMMARY OF EVIDENCE

There are no randomized controlled trials on this topic but retrospective and prospective studies suggest that screening for CKD may be valuable if applied appropriately. The early identification of CKD may provide opportunities for effective and safe interventions that reduce the risk of death, ESKD and complications of CKD. Screening for CKD offers the most potential to improve outcomes by allowing more time to intervene when most individuals are asymptomatic.

General population screening is impractical and does not appear to be cost-effective, and much of the evidence suggests that targeted-screening with urine testing followed by eGFR measurements is most beneficial. Screening for CKD should be performed in individuals at increased risk of developing CKD, including those with diabetes mellitus, hypertension and cardiovascular disease.

The most cost-efficient model appears to be opportunistic general practice screening, although the value of screening for CKD may be enhanced by performing it in combination with other screening programs used in the general population. Screening of those at increased risk of CKD could potentially occur either through special events run in the community, workplace or in selected locations, such as pharmacies.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative:[78]
Guideline 3. Individuals at increased risk of chronic kidney disease.
Some individuals without kidney damage and with normal or elevated GFR are at increased risk for development of chronic kidney disease.

- All individuals should be assessed, as part of routine health encounters, to determine whether they are at increased risk of developing chronic kidney disease, based on clinical and socio-demographic factors.
- Individuals at increased risk of developing chronic kidney disease should undergo testing for markers of kidney damage, and to estimate the level of GFR.
- Individuals at increased risk, but found not to have chronic kidney disease, should be advised to follow a program of risk factor reduction, if appropriate, and undergo repeat periodic evaluation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology:[2]

- Screening for proteinuria should be performed for all patients who are at high risk of kidney disease (patients with diabetes, hypertension, vascular disease, autoimmune disease, estimated glomerular filtration rate < 60 mL/min/1.73m2 or oedema) (grade D, opinion).
- Screening should be performed by random urine samples to measure the ratio of protein to creatinine or of albumin to creatinine. For patients with diabetes, testing of the ratio of albumin to creatinine should be performed to screen for kidney disease (grade B).
- A ratio of protein to creatinine > 100 mg/mmol or a ratio of albumin to creatinine > 60 mg/mmol should be considered as thresholds to indicate high risk of progression to end-stage renal disease (grade D).

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

National Institute for Clinical Excellence (NICE):[74]
- R14. In people without diabetes consider clinically significant proteinuria to be present when the ACR is 30 mg/mmol or more (this is approximately equivalent to PCR 50 mg/mmol or more, or a urinary protein excretion 0.5 g/24 h or more).
- R15. In people with diabetes consider microalbuminuria (ACR more than 2.5 mg/mmol in men and ACR more than 3.5 mg/mmol in women) to be clinically significant.
- R16. All people with diabetes, and people without diabetes with a GFR less than 60 mL/min/1.73 m2, should have their urinary albumin/protein excretion quantified. The first abnormal result should be confirmed on an early morning sample (if not previously obtained).
- R17. Quantify by laboratory testing the urinary albumin/protein excretion of people with an eGFR 60 mL/min/1.73 m2 or more if there is a strong suspicion of CKD (see also 4.2.7).
- R24. Monitor GFR in people prescribed drugs known to be nephrotoxic, such as calcineurin inhibitors and lithium. Check GFR at least annually in people receiving long-term systemic non-steroidal anti-inflammatory drug (NSAID) treatment.
- R25 Offer people testing for CKD if they have any of the following risk factors:
  - diabetes
  - hypertension
  - cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease and cerebral vascular disease)
  - structural renal tract disease, renal calculi or prostatic hypertrophy
  - multisystem diseases with potential kidney involvement, e.g. systemic lupus erythematosus (SLE)
  - family history of stage 5 CKD or hereditary kidney disease
  - opportunistic detection of haematuria or proteinuria.
- R26. In the absence of the above risk factors, do not use age, gender, or ethnicity as risk markers to test people for CKD. In the absence of metabolic syndrome, diabetes or hypertension, do not use obesity alone as a risk marker to test people for CKD.

Scottish Intercollegiate Guidelines Network (SIGN):[75]
- All patients with diabetes should have regular surveillance of renal function.
- Patients who are on antihypertensive or lipid lowering therapy should have renal function at least annually.
- Albumin/creatinine ratio is recommended for detecting and monitoring diabetic nephropathy.
- In patient groups with a high prevalence of proteinuria without diabetes protein/creatinine ratio may be used to exclude chronic kidney disease.

Kidney Disease: Improving Global Outcomes:[106]
All countries should have a targeted screening program for CKD. Target groups should include patients with hypertension, diabetes, and cardiovascular disease. Other groups might include families of patients with CKD; individuals with hyperlipidaemia, obesity, and metabolic syndrome; smokers; patients treated with potentially nephrotoxic drugs; patients with some chronic infectious diseases and cancers; and those >60 years. Tests for CKD screening should include both a urine test for proteinuria and a blood test for creatinine to estimate GFR. Tests for proteinuria should be selected and performed according to local guidelines; verification of proteinuria would require 2 of 3 positive test results. Equations for estimating GFR should be appropriate for standardization of the method and application to majority racial and ethnic groups. Frequency of testing should be according to available guidelines

and the target group to be tested; in absence of specific recommendations, testing need not be more frequent than once per year.

SUGGESTIONS FOR FUTURE RESEARCH

A population-based observational cohort study examining the impact of alternative proteinuria screening strategies (urine dipstick testing and subsequent laboratory confirmation of positive screen tests versus laboratory measurement of urine albumin: creatinine ratio upfront versus laboratory measurement of urine protein: creatinine ratio upfront) in individuals at-risk of CKD on the primary outcomes of accurate and cost-effective identification of individuals with CKD. .

CONFLICT OF INTEREST

Nigel Toussaint has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDICES

Table 1. Characteristics of included studies

Study ID	N	Study design	Participants	Follow up	Comments and results
1. Who should be screened for CKD? Is there value in targeted or population screening?					
Hallan et al (2006) [25]	65,604	Cross sectional	Adults ≥ 20 years, taking part in a health survey (the HUNT II study) Norway	8 years	• 3,069 out of 65,604 (4.7%) people had CKD (eGFR < 60 ml/min/1.73m^2), so 20.6 people have to be screened to identify one case. • Only 38 people out of 3,069 (eGFR < 60 ml/min/1.73m^2) developed end-stage-renal-disease • Restricting screening to those with hypertension, diabetes, or age > 55 years, identifies 93.2% of people with CKD, with a number needed to screen of 8.7 • Restricting screening to those with only hypertension and diabetes identified 44.2% of people with CKD. • For those with eGFR 30-60 ml/min/1.73m^2, the incidence of end-stage renal disease was low (0.1%) compared to cardiovascular mortality (4.2%) • For those with eGFR < 30-60 ml/min/1.73m^2, the incidence of end-stage renal disease was (2.6%) compared to cardiovascular mortality (10.1%) • Of those with an eGFR 45-59 ml/min/1.73m^2 only 0.4% progressed to ESRD • Of those with an eGFR 30-44 ml/min/1.73m^2 only 1.3% progressed to ESRD
Brown et al (2003) [23]	6,071	Cross sectional	Participants >18 years screened from August 2000 – December 2001	N/A	• Screening identified 82 participants (2%) with diabetes, 1,014 (35%) with hypertension, 277 participants (5%) with elevated serum creatinine, 839 participants (14%) with reduced eGFR, and 1,712 participants (29%) with micro-albuminuria. • 35% of the diabetic participants had elevated serum glucose levels at screening (≥ 10 mmol/L) • 64% of participants with a history of hypertension did not have blood pressure controlled to < 140/90 mmHg
Bello et al (2010)[27]	1,128	Cross sectional	Data from participants of The Kidney Evaluation and Awareness Program (KEAPS) in Sheffield, UK.	NA	• Prevalence of microalbuminuria (MA) was found to be 7.1% • Prevalence of MA was 6.2% in non-diabetic, non-hypertensive participants; and was 1.3% in subjects without any known risk factors (old age, diabetes, hypertension, obesity or CVD) • Main determinants of MA were: age OR1.01 (95%CI: 1.00-1.02: P=0.04); diabetes OR 3.25 (95%CI: 1.30-8.13; P=0.01); obesity OR 4.09 (95%CI: 1.71-9.80; P=0.02); and family history of hypertension OR 1.87 (95%CI:1.00-3.47; P=0.05)

Study ID	N	Study design	Participants	Follow up	Comments and results
Kawar et al (2009)[28]	1,179	Cross sectional	Data from participants of the KEAPS and KEOPS (Kidney Evaluation in Overweight Population) includes individuals with BMI >25. Sheffield, UK	NA	• 11.5% of participants were found to be obese (BMI>30) and 20% were overweight (BMI 25 – 29.9) • Prevalence of MA in subjects with BMI <25 was 3.1% compared to 12% in those with BMI 25-30 and 27% in those with BMI >30 (P<0.001) • The adjusted RR for having urine albumin concentration >20 mg/L is 8.0 (95%CI: 3.8-16.8; P<0.0001) if BMI>27.2
Howard et al (2010) [29]	N/A	Modelled Analysis	Markov modelling	N/A	• Intensive treatment of inadequately controlled diabetes was both less costly (average lifetime saving of $A133) and more effective (with an additional 0.075 quality-adjusted life-years (QALYs) per patient) than conventional treatment • Treating all known diabetics with ACE inhibitors was both less costly (an average lifetime saving of $A825 per patient) and more effective than current treatment (resulting in 0.124 additional QALYs per patient) • Screening 50 to 69 year-olds plus intensive diabetic treatment had an incremental cost-effectiveness ratio (ICER) of $A13,781 per QALY gained • Screening 50 to 69 year-olds for hypertension plus intensive blood pressure treatment had an ICER of $A491 per QALY gained • Screening 50 to 69 year-olds for proteinuria plus prescription of ACEi for proteinurics and diabetics had an ICER of $A4,793 1 per QALY gained • Screening and optimal treatment of proteinuria, diabetes and hypertension has the potential to reduce mortality and end-stage-renal disease and represents good value for money.
Boulware et al (2003) [30]	N/A	Cost-effectiveness analysis	Markov modelling	N/A	• For persons without hypertension or diabetes, the cost-effectiveness ratio for screening vs no screening (usual care) was unfavourable ($282,818 per QALY; incremental cost $616 and a gain of 0.0022 QALYs per person). • Screening at age 60 years was more favourable (53,372 per QALY) • Screening every 10 years was more cost-effective ($80,700 per QALY at age 50 years; $6,195 per QALY at age 60 years; and $5,486 per QALY at age 70 years) • Screening high-risk groups is more cost-effective • Screening the general population will be more cost-effective if conducted at 10-year intervals
Collins et al (2009) [31]	15,332	Cross-sectional survey	Participants ≥ 20 years taking part in the National Health and Nutrition Examination Survey (NHANES) 1999-2004	N/A	• CKD increases with age (39.2% for age ≥ 60 years). • For ages 20 to 59 years, the prevalence of CKD was: 33.8% in diabetics; 8.2% in non-diabetics; 43% in those with diabetes and hypertension; 25.5% in diabetics without hypertension; 15.2% in non-diabetics with hypertension.

Study ID	N	Study design	Participants	Follow up	Comments and results
Jurkovitz et al (2002) [35]	769	Cross-sectional survey	Participants were relatives of patients with end-stage renal disease within 10 communities	N/A	• CKD was present in: - 49.3% of participants with CrCl < 90 mL/min - 13.9% of participants with CrCl < 60 mL/min • 9.9% had proteinuria of ≥1+ • 13% of participants with CrCl < 60 mL/min or with proteinuria ≥1+ or with both, were aware of their kidney disease • only 7.9% of those who had seen a physician recently were aware of their kidney disease • Awareness of CKD was less than expected among relatives of patients with ESRD
Bello et al (2008) [36]	274	Cross-sectional	Participants were relatives of patients with CKD. Kidney Evaluation and Awareness program in Sheffield.	N/A	• 9.5% of participants with family history of CKD had micro albuminuria compared to 1.4% in the control group (P=0.001) • Independent determinants of micro albuminuria include family history of diabetes (odds ratio [OR], 2.88; 95% CI: 1.17 to 7.04), obesity (OR, 3.29; 95% CI: 1.61 to 6.69), and family history of CKD (OR, 6.96; 95% CI: 3.48 to 13.92) •
Bagchi et al (2010)[37]	606	Cross-sectional	Adult first-degree relatives (FDRs) of end-stage renal disease patients. New Delhi, India	NA	• 29.7% of participants had hypertension and 3.6% had diabetes mellitus • Screening identified new cases of: hypertension (21.5%); diabetes mellitus (2.0%); impaired fasting glucose (22.4%); hypercholesterolaemia (18.8%) • 61.2% had eGFR in stage 1 (P<0.001); 34.7% in stage 2 (P<0.001); 3.6% in stage 3 (P=0.001); 0.5% in stage 4-5 (P=0.6) • 8.6% had CKD and 88.5% were unaware
2. What should be tested when screening for CKD? **Proteinuria and albuminuria**					
Iseki et al (1996) [42]	107,192	Cohort	Adults > 18 years took part in a screening program in Okinawa, Japan	10 years	• 193 patients commenced dialysis • proteinuria was the biggest predictor of ESRD (adjusted odds ratio 14.9, 95% CI: 10.9 to 20.2), this was followed by haematuria (adj OR, 2.3, 95%CI: 1.62 to 3.28) • male gender and diastolic blood pressure were also significant predictors of ESRD (adj OR, 1.41; 95%CI:1.04 to 1.92) and (adj OR, 1.39; 95%CI: 1.17 to 1.64)
Humphrey et al (1989) [43]	1,832	Cohort	Participants diagnosed with type 2 diabetes mellitus between 1945 and 1979 in Rochester, Minnesota.	5 – 39 years	• 25 people developed CKD (incidence, 133 per 100,000 person-years; 95%CI: 86 to 196) • incidence of CKD in insulin-dependent diabetics was 170 per 100,000 person-years; 95%CI: 35 to 497) • risk of CKD increased 12-fold (hazard ratio, 12.1: 95%CI: 4.3 to 34.0) in participants with proteinuria at the time of diabetes diagnosis • In participants who developed persistent proteinuria after diagnosis of type 2 DM the cumulative risk for CKD (10 years after protein detection) was 11%

Study ID	N	Study design	Participants	Follow up	Comments and results
Kannel et al (1984) [44]	5,209	Cohort	Participants were aged between 50 to 62 years old at start of study	30 years	• Age-adjusted relative risk for mortality was 3.8 (95%CI: 2.5-4.9) for men and 2.2 (95%CI: 1.5-3.8) for women with persistent proteinuria • There was a 3-fold increase in the average annual incidence of cardiovascular death in men and women who had proteinuria.
Craig et al (2002) [45]	12 studies	Feasibility study	12 randomized trials of angiotensin-converting enzyme inhibitors (ACEi), in 1,943 patients with varying degrees of renal impairment	N/A	• Proteinuria is present in about 5% of the general population and confers an approximately 15-fold increased risk for ESRD. • There was a reduced risk of ESRD for patients treated with ACEi (RR=0.66; 95%CI: 0.51-0.85) • For every 20 000 people screened for proteinuria, 1 000 would test positive and 100 would need to be treated with ACEi for 2 to 3 years to prevent one case of ESRD. This would save approximately $A70, 000 health dollars.
Konta et al (2007) [55]	2,321	Cross-sectional	Adult participants 40 to 87 years old, taking part in a community-based health check-up in Takahata, Japan.	N/A	• Prevalence of micro albuminuria was: ♦ 59% for trace ♦ 64% for (1+) ♦ 41% for (2+) ♦ 9% for (3+) • Prevalence of macro albuminuria was: ♦ 1% for trace ♦ 7% for (1+) ♦ 50% for (2+) ♦ 91% for (3+) • In the group with a trace of protein, the prevalence of micro albuminuria was found to be: ♦ 59.3% in all subjects ♦ 73.8% in men ♦ 71.2% in subjects ≥ 60 years ♦ 88.9% in diabetic subjects ♦ 68.0% in hypertensive subjects • By regarding trace proteinuria as positive, the sensitivity of the urine protein dipstick test for micro- and macro-albuminuria improved from 23.3% to 37.1% specificity did not change significantly (from 98.9% to 97.3%)
Gansevoort et al (2005) [56]	2,527	Cross-sectional	Participants 28 to 75 years old taking part in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, in Groningen, The Netherlands.	N/A	• The sensitivity and specificity for UAC in predicting micro-albuminuria is 85 % and 85 % respectively • The sensitivity and specificity for ACR in predicting micro-albuminuria is 87.6 % and 87.5 % respectively • The diagnostic performance of measuring UAC in spot morning urine sample in predicting micro-albuminuria and reduces cost.

Study ID	N	Study design	Participants	Follow up	Comments and results
Halbesma et al (2006) [57]	8,592	Cohort	Participants 28 to 75 years old taking part in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, in Groningen, The Netherlands.	4 years	• 134 patients had macro-albuminuria, 128 with erythrocyturia and 103 with impaired renal function. • Prevalence of macro-albuminuria, erythrocyturia and impaired renal function in the general population was: 0.6, 1.3 and 0.9% respectively. • The incidence of cardiovascular disease was high in the macro-albuminuria group, adjusted hazard ratio for mortality 2.6 (95%CI: 1.1-6.0) and for the impaired renal function group 3.4 (95%CI:1.5-8.0) • The macro-albuminuria group showed a -7.2 mL/min/1.73m2 eGFR loss, compared with -2.3 mL/min/1.73m2 in the control group (P < 0.001). • The eGFR loss in the impaired renal function group was -0.2 mL/min/1.73m2 (P=0.18) and the erythrocyturia group (-2.6 mL/min/1.73m2) was not different from the control group. • Macro-albuminuria is a better risk marker for accelerated GFR loss.
van der Velde et al (2009) [58]	40,854	Cohort	Participants 28 to 75 years old taking part in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, Groningen, The Netherlands.	9 years	• 45 individuals started renal replacement therapy(RRT) • A urinary albumin concentration of ≥ 20 mg/L, identified individuals who started RRT during follow-up with 58% sensitivity and 92% specificity. 39% were previously unknown to have impaired renal function, and 50% where not being treated. • Restricting screening to high risk groups, failed to identify 45% of participants with micro-albuminuria and macro-albuminuria. • The higher the level of albuminuria, the higher the risk of need for RRT and the more rapid decline in renal function
Methven et al (2010) [64]	5,586	Retrospective Cohort	Patients with chronic kidney disease (Scotland)	3.5 years	• Adjusted Hazard Ratios (HRs) were similar for albumin-creatinine ratio (ACR) and protein-creatinine ratio (PCR) (derived from random urine samples and timed collections). HRs (95%CI) for PCR vs ACR were: • All-cause mortality 1.41 (1.31-1.53) vs 1.38 (1.28-1.50) • Start of RRT 1.96 (1.76-2.18) vs 2.33 (2.06-3.01) • Doubling of serum creatinine level 2.03 (1.87-2.19) vs 1.92 (1.78-2.08) • Total proteinuria and albuminuria perform equally as predictors of renal outcomes and mortality in patients with CKD. They were also as effective as 24-hour urine samples at predicting the outcomes

Study ID	N	Study design	Participants	Follow up	Comments and results
Hallan et al (2007) [66]	9,709	Cohort	Adults ≥ 20 years who took part in the Nord-Trondelag Health (HUNT 2) Study	8.3 years	• For participants <70 years, the absolute excess cardiovascular deaths/1000 person-years for: 1. optimal UACR (urinary albumin creatinine ratio) [<5 mg/g in men and <7 mg/g in women] i) 0 (reference) for eGFR ≥ 75 mL/min/1.73m^2 ii) 0.1 (-1.6 to 2.4) for eGFR 60 to 74 mL/min/1.73m^2 iii) -0.3 (-2.4 to 0.9) for eGFR 45 – 59 mL/min/1.73m^2 iv) 0.1 (-3.6 to 4.3) for eGFR < 45 mL/min/1.73m^2 2. high normal UACR [5 to 19 mg/g in men and 7 to 29 mg/g in women] i) 0.6 (-0.3 to 2.4) for eGFR ≥ 75 mL/min/1.73m^2 ii) 0.5 (-0.7 to 2.7) for eGFR 60 to 74 mL/min/1.73m^2 iii) 1.9 (0.02 to 8.1) for eGFR 45 – 59 mL/min/1.73m^2 iv) 1.3 (-0.1 to 5.5) for eGFR < 45 mL/min/1.73m^2 3. microalbuminuria [20 to 199 mg/g in men and 30 to 299 mg/g in women]. i) 0.6 (-0.6 to 3.2) for eGFR ≥ 75 mL/min/1.73m^2 ii) 0.8 (-0.3 to 3.5) for eGFR 60 to 74 mL/min/1.73m^2 iii) 1.0 (-0.1 to 4.0) for eGFR 45 – 59 mL/min/1.73m^2 iv) 4.1 (0.9 to 13.6) for eGFR < 45 mL/min/1.73m^2 • For participants ≥70 years, the absolute excess cardiovascular deaths/1000 person-years for: 1. optimal UACR i) 0 (reference) for eGFR ≥ 75 mL/min/1.73m^2 ii) -2.3 (-20.1 to 9.6) for eGFR 60 to 74 mL/min/1.73m^2 iii) 12.8 (-2.7 to 61.5) for eGFR 45 – 59 mL/min/1.73m^2 iv) 4.2 (-10.1 to 33.3) for eGFR < 45 mL/min/1.73m^2 2. high normal UACR i) 13.6 (-0.2 to 50.1) for eGFR ≥ 75 mL/min/1.73m^2 ii) 5.9 (-5.5 to 31.8) for eGFR 60 to 74 mL/min/1.73m^2 iii) 8.0 (-5.1 to 42.4) for eGFR 45 – 59 mL/min/1.73m^2 iv) 31.9 (4.9 to 112.9) for eGFR < 45 mL/min/1.73m^2 3. microalbuminuria i) 8.4 (-4.2 to 41.9) for eGFR ≥ 75 mL/min/1.73m^2 ii) 24.1 (2.8 to 84.5) for eGFR 60 to 74 mL/min/1.73m^2 iii) 26.6 (4.5 to 85.3) for eGFR 45 – 59 mL/min/1.73m^2 iv) 63.6 (15.8 to 206.0) for eGFR < 45 mL/min/1.73m^2 • Reduced kidney function and microalbuminuria are risk factors for cardiovascular death. Independent of each other and traditional risk factors

Study ID	N	Study design	Participants	Follow up	Comments and results
Hallan et al (2009) [67]	65,589	Cohort	Adults ≥ 20 years who took part in the Nord-Trondelag Health (HUNT 2) Study	10.3 years	• 124 patients progressed to ESRD • The adjusted hazard ratios for progression to ESRD for Normal ACR, microalbuminuria and macroalbuminuria were: • 1.0, 27.3 and 196.3 respectively for eGFR ≥ 60 ml/min/1.73m^2; • 23.4, 146.5 and 641.1 for eGFR 45 to 59 ml/min/1.73m^2; • 51.9, 448.9 and 2036 for eGFR 30 to 44 ml/min/1.73m^2; • 368.7, 2202 and 4146 for eGFR 15 to 29 ml/min/1.73m^2. • Time-dependent receiver operating characteristic analysis (ROC) showed that urinary albumin-to-creatinine ratio and eGFR substantially improved diagnostic accuracy
Ninomiya et al (2009) [69]	10,640	Cohort	Participants aged ≥ 55 years with type 2 diabetes	4.3 years (mean)	• 938 (8.8%) of patients experienced a cardiovascular event and 107 (1.0%) experienced a renal event. • The multivariable-adjusted hazard ratio for cardiovascular events was 2.48 (95%Ci: 1.74 to 3.52) for every 10-fold increase in baseline urinary albumin-to-creatinine ratio (UACR) and 2.2 (95%CI: 1.09 to 4.43) for every halving of baseline eGFR, after adjustment for regression dilution. • Patients with both UACR >300mg/g and eGFR<60ml/min/1.73m2 at baseline had a 3.2-fold higher risk for cardiovascular events and a 22.2-fold higher risk for renal events compared with patients with neither of these risk factors.
Farbom et al (2008) [70]	10,881	Cohort	Swedish and Norwegian hypertensive patients taking part in the Nordic Diltiazem Study.	4.5 years	• Increased creatinine (P<0.001) and decreased GFR (P=0.001) were independent risk factors for the primary end points: fatal and non-fatal myocardial infarction, stroke and other cardiovascular deaths • There was a significant interaction between microalbuminuria and eGFR (P=0.04) in prediction of the primary end points.
Serum creatinine and estimated glomerular filtration rate					
Iseki et al (1997) [79]	107,192 14,609 subgroup	Cohort	Adults over 18 years of age took part in a mass screening program in Okinawa, Japan.	10 years	• 60 dialysis patients were identified • The adjusted odds ratio for serum creatinine was 5.31 (95%CI: 3.39 to 8.32) in men when compared to a baseline SCr level of 1.2 mg/dL; the adj OR was 3.92 (95%CI: 2.88 to 5.34) in women when compared to a baseline SCr level of < 1.0 mg/dL. • Diastolic BP was not a predictor of ESRD • serum creatinine is a strong predictor of ESRD
Duncan et al (2001) [80]	2,781	Cross-sectional	Outpatients' ≥ 16 years of age from British Columbia.	N/A	• 91.4% had normal SCr levels. Of these 15.2% had eGFR ≤ 50 mL/min (Cockcroft-Gault formula) • Among patients with normal SCr, abnormal C-G values were identified in: 47.3% of ≥ 70 years old; 12.6% of 60 - 69 year olds; and 1.2% 40 - 59 year olds.

Study ID	N	Study design	Participants	Follow up	Comments and results
Coresh et al (2007) [85]	28,721	Cross-sectional	Adults aged > 20 years taking part in the National Health and Nutrition Examination Surveys (NHANES 1988 – 1994 and 1999 – 2004)	N/A	• Both albuminuria and reduction in eGFR increased from 1988-1994 to 1999-2004. • Prevalence of CKD stages 1 to 4 increased from 10.0% (95%CI: 9.2 – 10.9%) in 1988 – 1994 to 13.1% (95%CI: 12.0 – 14.1%) in 1999 – 2004 with a prevalence ratio of 1.3 (95%CI: 1.2 – 1.4) • Prevalence estimates for CKD stages in 1988 – 1994 and 1999 – 2004 respectively, were: • 1.7% (95%CI: 1.3–2.2%) and 1.8% (95%CI: 1.4–2.3%) for stage 1 • 2.7% (95%CI: 2.2–3.2%) and 3.2% (95%CI: 2.6–3.9%) for stage 2 • 5.4% (95%CI: 4.9–6.0%) and 7.7% (95%CI: 7.0–8.4%) for stage 3 • 0.21% (95%CI: 0.15–0.27%) and 0.35% (95%CI: 0.25–0.45%) for stage 4 • In the 1999-2004 cohort, 76% of participants had normal proteinuria even though they had an eGFR of 30-59 ml/min/1.73m^2 and only 6% had overt macro albuminuria. • A higher prevalence of diagnosed diabetes, hypertension and higher body mass index, explains the increase in albuminuria but only part of the increase in the prevalence of decreased GFR.
Ishani et al (2006) [86]	361,662 12,866 subgroup	Cohort	Men at high risk for cardiovascular disease aged 35 to 57years taking part in the Multiple Risk Factor Intervention Trial (MRFIT) U.S.A	25 years	• 213 (1.7%) men developed ESRD • Predictors of ESRD were dipstick proteinuria of 1+ or ≥ 2+ (hazard ratio [HR] 3.1; 95%CI: 1.8 to 5.4) and 15.7 (95%CI: 10.3 to 23.9) respectively, and an eGFR of < 60 mL/min/1.73m^2 (HR 2.4; 95%CI: 1.5 to 3.8) • There was a 41% increase risk of ESRD in those with an eGFR < 60 mL/min/1.73m^2 and ≥ 2+ proteinuria (95%CI: 15.2 to 71.1) and a hazard ratio (HR) 32.9 (95%CI: 15.2 – 71.1)
Go et al (2004) [88]	1,120,295	Longitudinal cohort 1996 – 2000	Participants were registered members of the Kaiser Permanente Renal Registry. Mean participant age 52 years	2.84 years	The Adj HR for death was: • 1.2 (95%CI: 1.1 – 1.2) for an eGFR 45 – 59 ml/min/1.73m^2; • 1.8 (95% CI: 1.7 – 1.9) for eGFR 30 – 44 ml/min/1.73m^2 • 3.2 (95% CI: 3.1 -3.4) for eGFR 15 -29 ml/min/1.73m^2 • 5.9 (95% CI: 5.4 – 6.5) for eGFR ≤ 15 ml/min/1.73m^2 • The adjusted hazard ratio for cardiovascular events also increased inversely with eGFR: 1.4 (95% CI: 1.4 - 1.5); 2.0 (95% CI: 1.9 – 2.0); 2.8 (95% CI: 2.6 -2.9); 3.4 (95% CI: 3.1 -3.8) respectively.

Study ID	N	Study design	Participants	Follow up	Comments and results
Strippoli et al (2008) [89]	50 trials (30,144 patients)	Meta-analysis	Study selection: randomised and quasi-randomised controlled trials of statins compared with placebo or other statins in chronic kidney disease	N/A	• Compared to placebo, statins significantly reduced total cholesterol, weighted mean difference -42.28 mg/dL (95%CI: -47.25 to -37.32); low density lipoprotein cholesterol -43.12 mg/dL (95%CI: -47.85 to -38.40); and proteinuria -0.73 g/24 hrs (95%CI: -0.95 to -0.52) • Statins did not improve GFR (1.48 ml/min; 95%CI: -2.32 to 5.28) • Fatal and non-fatal cardiovascular events were reduced with statins (relative risk [RR} 0.81; 95% CI: 0.73 to 0.90) and 0.78 (95%CI: 0.73 to 0.84) respectively, however statins did not have a significant effect on all-cause mortality 0.92 (95% CI: 0.82 to 1.03)
Baigent et al (2011)[90]	9,270	RCT	Adults with chronic kidney disease with no known history of myocardial infarction or coronary revascularisation. SHARP trial, Multicentre, multinational. Intervention: simvastatin (20mg) plus ezetimibe (10 mg) Control: matching placebo	Median 4.9 years	• Patients in the intervention group had a significant reduction in LDL cholesterol (0.85 mmol/L (SE 0.02) and a 17% reduction in major atherosclerotic events (526 vs 619) intervention compared to control RR 0.83 (95%CI: 0.74-0.94; p=0.002) • Significant reductions were also observed in: non-haemorrhagic stroke RR 0.75 (95%CI: 0.60-0.94; P=0.01); arterial revascularisation procedures RR 0.79 (95%CI: 0.68-0.93;P=0.004); but not significantly in non-fatal myocardial infarction or death from coronary heart disease RR0.92 (95%CI: 0.76-1.11; P=0.37) • Excess risk of myopathy was only 2 per 10,000 patients per year of treatment (0.2% vs 0.1%) in the control group. • There was no evidence of excess risks of hepatitis (0.5% vs 0.4%); gallstones (2.3% vs 2.3%); or cancer (9.4% vs 9.5%); p=0.89 • There was no significant excess of death from any non-vascular cause (14.4% vs 13.2%; p=0.13) • The intervention did not significantly reduce end-stage renal disease (ESRD) (33.9% vs 34.6%; RR 0.97, 95%CI: 0.89-1.05; P=0.41); ESRD or death (47.4% vs 48.3%; RR 0.97, 95%CI: 0.90-1.04; p=0.34); and ESRD or doubling of baseline creatinine (38.2% vs 40.2%; RR 0.93, 95%CI: 0.86-1.01; p=0.09)
Peralta et al (2011)[91]	26,643	Prospective cohort	Adult participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study	4.6 years	• Compared with those with CKD defined by creatinine alone, the hazard ratio for death was 3.3 (95%CI: 2.0-5.6) for participants with CKD defined by creatinine and ACR; 3.2 (95%CI: 2.2-4.7) for those with CKD defined by creatinine and cystatin C; and 5.6 (95%CI: 3.9-8.2) for those with CKD defined by all markers • The risk of incident ESRD was higher among those with CKD defined by all markers (34.1 per 1000 person-years; 95%CI: 28.7-40.5 vs 0.33; 95%CI: 0.05-2.3) for those with CKD defined by creatinine alone
Blood pressure					

Study ID	N	Study design	Participants	Follow up	Comments and results
Klag et al (1996) [92]	332,544	Cohort	Men at high risk for cardiovascular disease aged 35 to 57years taking part in the Multiple Risk Factor Intervention Trial (MRFIT) U.S.A	16 years	• 814 participants had either died of ESRD or were being treated for same. • The relative risk (RR) for men with stage 4 hypertension (systolic blood pressure (SBP) ≥ 210 mmHg or diastolic blood pressure (DBP) ≥ 120 mmHg was 22.1 (P< 0.001) when compared to men optimal level BP (SBP < 120 mmHg and DBP < 80 mmHg) • 543 men with ESRD had hypertension: stage 1 (mild) 0.3%; stage 2 (moderate) 0.7%; stage 3 (severe) 1.3%; and stage 4 (very severe) 2.5% • The association with increased risk of ESRD was greater for elevations of systolic blood pressure than elevations of diastolic blood pressure
5. Why should people be screened for CKD?					
Hoy et al (2003) [93]	594 267 trial 327 control	Non-randomised controlled trial	Participants aged ≥ 20 years with: hypertension, diabetes with micro-albuminuria or overt micro-albuminuria, and people with overt micro-albuminuria	3.4years	• 38 deaths occurred in the control group and 23 in the treatment group • Reduction in all-cause mortality (50%; P=0.01) and renal related deaths (57%; P=0.04)
Cost-effectiveness of screening for CKD & screening algorithms					
Palmer et al (2008) [96]	N/A	Modelled analysis	Markov modelling and second order Monte Carlo simulation for the lifetime impact of screening with urine dipsticks for hypertensive patients with type 2 diabetes and subsequent treatment.	N/A	• Screening followed by optimized treatment, led to a 44% reduction in the cumulative incidence of ESRD and improvements in non-discounted life expectancy of 0.25 ± 0.22 years/patient • Quality-adjusted life expectancy was improved by 0.18 ± 0.15 quality-adjusted life years (QALYs) per patient and direct costs increased by $244 ± 3499 per patient • The incremental cost effectiveness ratio (ICER) was $20 011 per QALY gained for screening with optimum treatment versus no screening • There was a 77% probability that screening and optimized therapy would be considered cost effective
Boersma et al (2010)[98]	8,592	Modelled analysis	Markov modelling based on the data from the (PREVEND) study Prevention of Renal and Vascular End Stage Renal Disease conducted in the Netherlands.	NA	• Limiting screening to those subjects aged ≥50 and ≥60 years resulted in more favourable cost-effectiveness compared with population–based screening without age restriction

Study ID	N	Study design	Participants	Follow up	Comments and results
Atthobari et al (2006) [99]	864	Cost-effectiveness analysis	Cost-effectiveness of screening for albuminuria in the Dutch population to prevent cardiovascular events. Data from the Prevention of REnal and Vascular ENdstage Disease Intervention Trial (PREVEND IT) was used.	3.8 years	• Cardiovascular events (CVEs) occurred in 45 (5.2%) subjects • 40% lower incidence of CVEs in the treatment group compared to placebo (3.9% vs 6.5%, respectively; P=NS) • The cost-effectiveness of screening for albuminuria was found to be € 16,700 / life-year gained (LYG) for the study population. • The probability of cost-effectiveness below € 20,000/LYG would increase if only subjects with UAE > 50 mg/d were treated with fosinopril • Limiting the screening to subjects aged > 50 years and > 60 years also improved cost-effectiveness

Table 2. Early detection of CKD using Kidney Health Check

Indication for testing*	Recommended tests	Frequency of testing
Smoker	Urine ACR§, eGFR, blood pressure	Every 12 months
Diabetes		
Hypertension		
Obesity		
Established cardiovascular disease†		
Family history of CKD		
Aboriginal or Torres Strait Islander aged ≥ 30 years‡		Every 24 months

Source: Modified from RACGP Red Book [107] and NACCHO: National Guide [108]

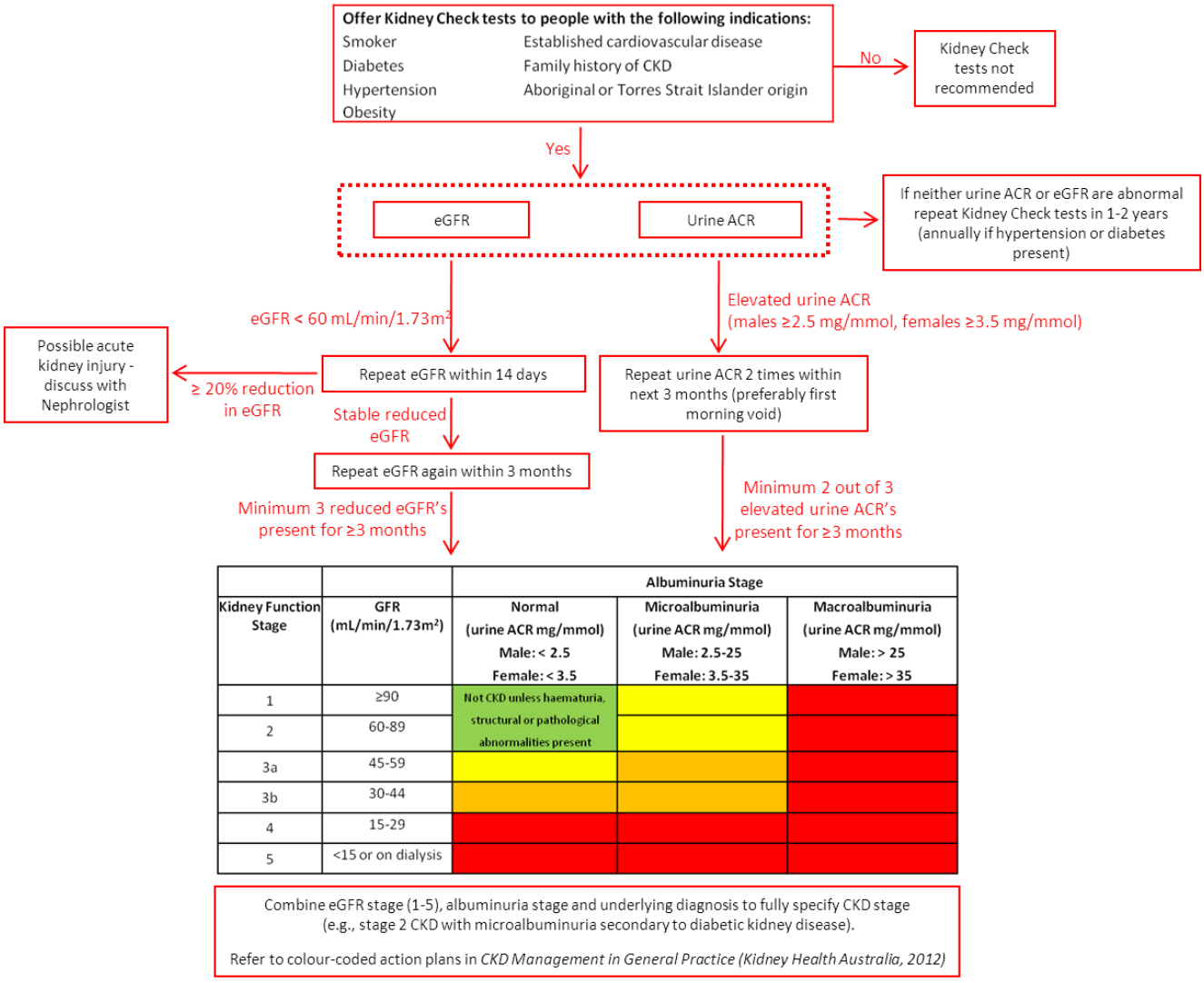
***** Whilst being aged 60 years of age or over is considered to be a risk factor for CKD, in the absence of other risk factors it is not necessary to routinely test these individuals for kidney disease.

† Established cardiovascular disease is defined as a previous diagnosis of coronary heart disease, cerebrovascular disease or peripheral vascular disease

‡ See National Guide to a Preventive Health Assessment in Aboriginal and Torres Strait Islander Peoples (NACCHO) 2012 for more detail regarding indication for testing in Aboriginal and Torres Strait Islander People.

§ If Urine ACR positive, arrange two further tests over three months (preferably first morning void). If eGFR<60mL/min/1.73m^2, repeat test within 14 days.

Figure 1. Recommended screening algorithm for the detection of CKD.



		Albuminuria Stage		
Kidney Function Stage	**GFR (mL/min/1.73m²)**	**Normal (urine ACR mg/mmol) Male: < 2.5 Female: < 3.5**	**Microalbuminuria (urine ACR mg/mmol) Male: 2.5-25 Female: 3.5-35**	**Macroalbuminuria (urine ACR mg/mmol) Male: > 25 Female: > 35**
1	≥90	Not CKD unless haematuria, structural or pathological abnormalities present		
2	60-89			
3a	45-59			
3b	30-44			
4	15-29			
5	<15 or on dialysis			

Combine eGFR stage (1-5), albuminuria stage and underlying diagnosis to fully specify CKD stage (e.g., stage 2 CKD with microalbuminuria secondary to diabetic kidney disease).

Refer to colour-coded action plans in *CKD Management in General Practice (Kidney Health Australia, 2012)*

Sources:
The Royal Australian College of General Practitioners (RACGP) 'Red Book' Taskforce.[107]
National Aboriginal Community Controlled Health Organisation (NACCHO/RACGP) [108]