Screening: why, when, and how

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Screening refers to the early detection of individuals with unrecognized disease or with early stages of disease among a population. Early detection allows early medical intervention, which may ultimately slow progression of the disease and reduce both morbidity and mortality. As such, screening is an important tool in improving public health. In 1968, Wilson and Jungner proposed 10 criteria to consider prior to starting screening for a disease. This review discusses these criteria when applied to screening for chronic kidney disease with additional focus on (1) the validity of the test to be used for screening; (2) which part of the population to screen; and (3) forms of bias to consider in screening.

In the context of epidemiology and public health, screening refers to the practice of investigating apparently healthy individuals to detect unrecognized disease or early stages of the disease. Such early detection allows measures to be taken, including treatment, which may prevent or delay the onset of disease, slow its progression, and reduce (premature) death. Therefore, the aim of screening is to reduce morbidity and mortality from the disease in cases identified by the screening program. As such, screening has become increasingly recognized as a major tool in improving population health.

In general, the use of screening in disease control involves important assumptions. Criteria for screening were first published by the WHO (World Health Organization) in 1968 to facilitate the selection of conditions that are suitable for screening.[1] These criteria can be classified into five topics, namely the condition or disease, treatment, the screening test, costs, and the screening program (Table 1). Over the past 40 years, several additional and emerging criteria for screening have been proposed,[2] which are mainly in the domain of the screening program.

The aim of this review was to describe and explain relevant considerations in screening, applied to the screening for chronic kidney disease (CKD). To that end, the classic criteria for screening from the list of Wilson and Jungner will be discussed with reference to CKD. Other issues that will be discussed include the following: (1) the validity of the test to be used in screening, (2) which part of the population is to be screened, and (3) forms of bias to consider in screening. The emerging criteria for screening as they have been proposed over the past 40 years (Table 1) will not be further discussed in this paper, but should nevertheless always be considered before embarking on a screening program.

THE CONDITION

CKD is considered to be a public health problem (Table 1, criterium 1a) with prevalence rates of $\sim 13\%$ for stages 1 through 4 worldwide.[3] The prevalence of CKD is expected to increase further because of, for instance, the aging population and the continuing increase in the prevalence of diabetes[4] with potentially enormous financial consequences for many countries. The earlier detection and treatment of CKD is thus considered essential and is recommended by the US National Kidney Foundation.[5]

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Table 1 | Criteria for screening

Original screening criteria proposed by Wilson and Jungner[1]	Emerging criteria for screening proposed over the past 40 years[2]
(1) The condition: (a) Should be an important health problem (b) Should have an (untreated) natural history that is adequately understood (c) Should have a recognizable latent or early symptomatic stage	(d) There should be a defined target population
(2) Treatment: (a) Facilities for diagnosis and treatment should be available (b) There should be an agreed policy on whom to treat as patients (c) There should be an accepted treatment for patients with recognized disease	
(3) The test used in screening: (a) Should be suitable (simple, sensitive, specific, reproducible, validated, safe, and with a known distribution and cutoff points) (b) Should be acceptable to the population	
(4) Cost (a) The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole	
(5) The screening program: (a) Should be a continuing process and not a 'once and for all' project	(b) Should respond to a recognized need (c) The objectives of screening should be defined at the outset (d) The overall benefits of screening should outweigh the harm (e) There should be scientific evidence of screening program effectiveness (f) The program should integrate education, testing, clinical services, and program management (g) There should be quality assurance, with mechanisms to minimize potential risks of screening (h) The program should ensure informed choice, confidentiality, and respect for autonomy (i) The program should promote equity and access to screening for the entire target population (j) Program evaluation should be planned from the outset

CKD is defined as the presence of either kidney damage (pathological abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies) or glomerular filtration rate (GFR) <60 ml/min per 1.73 m^2 for at least 3 months.[6] On the basis of the combination of the presence or absence of kidney damage together with the level of GFR, CKD is subsequently classified into five stages of severity (Table 2). As such, stages 1 and 2 could be considered as early preclinical stages of CKD (Table 1, criterium 1c). Although the classification of CKD as proposed by KDOQI[6] has been criticized to result in overestimations of disease prevalence,[3,7] at present it is the best one to work with. Finally, the natural history of CKD is, at least some extent, understood (Table 1, criterium 1b)[6] and includes progressive loss of renal function, increased risk for the development of cardiovascular disease, and premature mortality.

TREATMENT

The criteria of Wilson and Jungner[1] suggest that facilities not only for screening or diagnosis but also for subsequent treatment of identified patients should be made available (Table 1, criterium 2a). Furthermore, it should be clear

Table 2 | Classification of chronic kidney disease[6]

Stage	Kidney damage	GFR (ml/min per 1.73 m^2)
1	Yes	$\geqslant 90$
2	Yes	60–89
3	Yes or no	30–59
4	Yes or no	15–29
5	Yes or no	<15 or dialysis

GFR, glomerular filtration rate.

whom to treat as patients and finally, there should be treatments available to patients who are identified with disease (Table 1, criteria 2b and c). In the case of CKD, subjects with either kidney damage or an impaired kidney function who are detected on screening should be monitored and treated where possible. Indeed, several studies have shown that there are various treatments that can slow the progression of CKD into end-stage renal disease. For instance, lipid lowering treatment slows the rate of decline of renal function in patients with renal disease.[8] Furthermore, angiotensin-converting enzyme inhibitors decrease proteinuria and improve the GFR in patients with kidney disease.[9]

Moreover, dietary protein restriction,[10] long-term intensive glycemic control in diabetics,[11] and early initiation of erythropoietin treatment[12] have each been shown to be beneficial in patients with early stages of CKD.

It should be noted that screening will also detect people who are already using these medications, but for indications other than CKD.[13] It is likely that these subjects will benefit less from the detection by screening than untreated subjects who are detected by screening and can subsequently be treated by adequate medication.

THE TEST USED IN SCREENING

The test to be used in screening should be suitable to the disease (Table 1, criterium 3a) and valid. To detect patients with an early phase of CKD, it is clear from the definition of the disease that either a marker of kidney damage or assessment of GFR could be used in screening patients at risk. Both tests are thus suitable for the detection of CKD and are acceptable to those who are tested (Table 1, criterium 3b).

Persistently increased protein excretion is usually a marker of kidney damage. The KDOQI guidelines state that the use of dipsticks for proteinuria in untimed urine spot samples for screening in the general population and that of albumin-specific dipsticks in patients at increased risk for CKD is acceptable.[6] Although an advantage of dipstick testing is that it is easy to apply, cheap, and provides results rapidly, a drawback may be false-positive testing. For instance, in a Japanese general population tested with protein dipsticks, it has been shown that dipsticks can quite frequently be false positive ($\sim$29%) when confirmation by microalbuminuria and macroalbuminuria testing is performed.[14] This suggests a limited applicability of protein dipstick testing in population screening, at least in some populations. An alternative for screening of the general population is the measurement of albumin-to-creatinine ratio in urine spot samples.[6] It has been shown that the albumin-to-creatinine ratio in spot urine samples has a high sensitivity (87.5%) and specificity (87.6%) to detect microalbuminuria in 24-h urine collections at a cutoff value of 9.9 mg/g.[15] However, albumin concentration in spot urine samples had only slightly lower sensitivity (85%) and specificity (85%) to detect microalbuminuria (cutoff value: 11.2 mg/l), suggesting that this measure might just as well be used in screening.[15] Furthermore, neither measure is perfect for detecting patients with proteinuria.

In the setting of population screening, the measure of kidney function easiest to apply is the one based on estimation equations using serum creatinine. Several formulas have been proposed of which the Cockcroft–Gault and Modification of Diet in Renal Disease (MDRD) equations are the most frequently used. Apart from problems with the measurement of creatinine and with the interpretation of creatinine clearance,[16] neither estimation equation is optimal. For instance, the MDRD equation overestimates true renal function in healthy subjects and is imprecise when the estimated GFR (eGFR) is $\geqslant$60 ml/min per 1.73 m^2.[17] On the other hand, the Cockcroft–Gault formula seems to be less accurate than the MDRD formula in older and obese persons.[18] Nevertheless, both formulas provide a measure of renal function on screening.

Which marker to use in screening for CKD also depends on the outcome of interest: mortality or decline in renal function? In the general population, subjects who screen positive for albuminuria or for impaired renal function are at increased risk of mortality from all causes[19] and from cardiovascular causes.[20] Individuals who screen positive both for albuminuria and for impaired renal function are at the highest mortality risk with a 2.6-fold increased risk of dying during follow-up after screening compared with those without a positive test for either marker.[19] Having a positive test for albuminuria in combination with impaired renal function even seems to interact biologically with each other, as there are relatively more deaths in this group than can be expected from the mortality in those with only albuminuria or with only impaired renal function.[19] In contrast to mortality, the decline in renal function over 6 years of follow-up is relatively the most progressive in patients with macroalbuminuria,[20] whereas it remains relatively stable in those with impaired renal function.[20,21] This implicates that, at least in the general population, the presence of macro-albuminuria, but not impaired renal function, is a risk factor for progressive loss of renal function.

VALIDITY OF THE TEST TO BE USED IN SCREENING

A successful or valid test in screening is considered a test that can separate those with disease from those without disease. As such, a valid test is crucial for the success of the screening program. Assessing the validity of a screening test can be done by appraising its sensitivity and specificity. The sensitivity of a test is reflected by the percentage of subjects who actually have the disease and are identified as such by the test.[22] The specificity of a test is reflected by the percentage of subjects who actually do not have the disease and are identified as such by the test. Ideally, a test is used in screening that has both high sensitivity and high specificity.

The positive and negative predictive values of that test may be clinically more relevant than the sensitivity and specificity of a test. The former is the ability of a positive test to predict the presence of disease, whereas the latter is the ability of a negative test to rule out the presence of disease.[22] It may be clear from this that in populations with a relatively high prevalence of disease, the positive predictive value of the test will also be relatively high.

Finally, the test to be used in screening should be reliable and produce consistent results across repeated testing under the same conditions.

COST

Screening programs should be cost effective (Table 1, criterium 4). Unfortunately, only few studies have addressed the cost effectiveness of screening for CKD. In The Netherlands, it has been shown that screening for albuminuria in the general population and subsequently treating those found

positive with an angiotensin-converting enzyme inhibitor (fosinopril) may be cost effective compared with no screening and adopting regular health care.[23] Furthermore, in the United States, early detection of urinary protein to slow progression of CKD and decrease mortality was only cost effective when applied in high-risk groups who were either older persons or persons with hypertension, or when conducted at an infrequent interval of 10 years.[24] Clearly, research is needed to further examine the cost effectiveness of screening programs for CKD.

TARGET POPULATION FOR SCREENING

On screening for a disease, one could screen the whole population to detect as many cases as possible. On the other hand, screening could be applied to selected high-risk groups. The latter strategy will decrease the number of people needed to be screened to detect one case.

When screening for CKD, several recent studies have focused on the screening of selected and high-risk groups. For instance in the United Kingdom, the KEAPS (Kidney Evaluation and Awareness Program in Sheffield) study was carried out to evaluate the prevalence of microalbuminuria in relatives of patients with CKD compared with that in the general population.[25] In this cross-sectional study, the prevalence of microalbuminuria was 9.5% in those with a family history of CKD as compared with 1.4% in the (age- and sex-matched) general population without a family history of CKD. Furthermore, in the Kidney Early Evaluation Program in the United States, early detection of kidney disease was attempted in the community setting by measurement of microalbuminuria and eGFR.[26] Individuals with either hypertension, diabetes, or with a first-order relative with hypertension, diabetes, or kidney disease were screened. Among participants without a reported history of specified conditions, screening identified 14% with reduced eGFR and 29% with microalbuminuria. Together, these data showed that targeted screening is effective in identifying persons with a moderately decreased eGFR or microalbuminuria.

Data from a cross-sectional health survey in the general population of the Nord-Trøndelag county in Norway have been used to assess the type of screening strategy most effective in detecting CKD.[27] Serum creatinine measurements were obtained from 65,604 participants and used to estimate the GFR using the MDRD formula. Subjects were considered to have CKD when the eGFR was < 60 ml/min per $1.73\,m^2$. When using the mass screening approach, including all subjects, 4.7% of the population had CKD stage 3–5 with the eGFR < 60 ml/min per $1.73\,m^2$. Screening for CKD in subjects with hypertension or diabetes detected less than half of the cases (44.2%), but only six people needed to be screened to identify one case. Age restriction up to 50–60 years of age hardly affected the rate of detection of CKD, whereas the population that needed to be screened was dramatically reduced. This effect was particularly observed in subjects without hypertension or diabetes. The analyses

showed that maximum sensitivity and specificity would be achieved by screening those aged more than 55 years of age. The optimal strategy for screening was that which was restricted to subjects with hypertension or diabetes or aged more than 55 years; 93% of the cases would be identified and 9 people would be screened to identify one case.

Recently, a scoring system has been developed in the cross-sectional NHANES (National Health And Nutrition Examination Surveys) (1999–2000 and 2001–2002) in the United States to screen for CKD.[28,29] In this study, CKD was defined as eGFR < 60 ml/min per $1.73\,m^2$. The model-based system makes use of a parsimonious set of medical and demographic characteristics (age, hypertension, diabetes mellitus, cardiovascular disease, proteinuria, and anemia) to identify individuals with a high likelihood of CKD before any evaluation with serum laboratory analysis. Using a cutoff score $\geqslant 4$ for screening, this model shows a high sensitivity and a negative predictive value of 92 and 99%, respectively. Although only 18% of patients with scores $\geqslant 4$ will have CKD (positive predictive value), the potential financial and psychological consequences are arguably minimal. Confirmatory testing with serum creatinine measurement is inexpensive and reliable and does not require invasive or time-consuming measurements. Comparable scoring algorithms were developed in two cohort studies, the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study.[29] Using this algorithm, medical and demographic variables (including age, anemia, female sex, diabetes, peripheral vascular disease, hypertension, history of congestive heart failure, or cardiovascular disease) could be used to predict the development of CKD during 4–9 years of follow-up accurately. Overall 70% of the incident cases were identified when using a cutoff score of 3. Clearly, these scoring methods used for identifying subjects who should be screened need to be validated further.

BIAS IN SCREENING

Bias is an issue in epidemiological studies, including screening.[30] Screening is prone to potential forms of bias, including selection bias, length bias, and lead-time bias.

Selection bias

Selection bias in general occurs when a systematic error in the enrollment of individuals in a study determines a biased association between exposure and outcome.[30] In most screening programs, only those who volunteer to be tested are screened. Subjects who volunteer may be more health conscious and even healthier than those who do not volunteer for testing, resulting in a relatively low detection rate of CKD. On the other hand, those who volunteer for screening may have a strong family history resulting in a relatively high detection rate.

A second potential form of bias in screening is length bias, which is considered by some as a special form of selection bias. Screening is usually carried out in time intervals (Table 1, criterium 5). Patients with slowly progressive
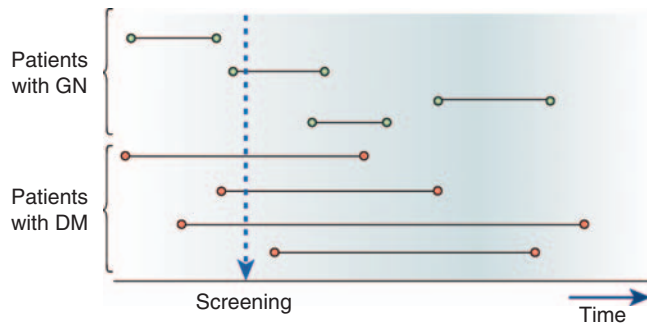
Figure 1 | Length-time bias. Length-time bias is associated with the type of the disease that is screened for. Some patients have short preclinical and clinical phases. For instance, patients who are diagnosed with rapidly progressive glomerulonephritis have a short natural history until renal replacement therapy. Other patients may have the opposite, that is, relatively long preclinical and clinical phases. Among patients with CKD, those with diabetes mellitus (DM) have such a long natural history. Eight hypothetical patients are depicted; four with glomerulonephritis (GN) and four with diabetic nephropathy (DM). The length of the line represents the duration of the preclinical phase. Even though the prevalence of the two diseases is the same in this hypothetical cohort, screening would detect more patients with a long preclinical phase (3 DM) than with a short clinical phase (1 GN). Patients who are detected through screening will therefore more often have DM than GN. Furthermore, the time to renal replacement therapy is longer in diabetic patients than in glomerulonephritis patients. Therefore, the time to renal replacement therapy would be artificially longer in this screened population. This is known as length-time bias.
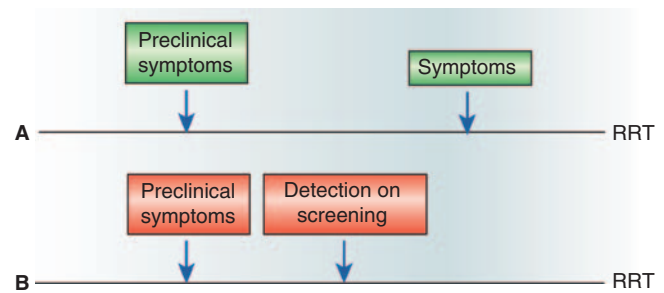

Figure 2 | Lead-time bias. Depicted are two hypothetical patients (A and B) who are born on the same day, develop the same primary renal disease, and who have to start renal replacement therapy on the same day. In both patients, preclinical signs of renal disease are present as of from the same day. Patient A presents himself to a doctor on symptoms of disease, whereas patient B does so after positive screening. Follow-up of both patients after diagnosis of renal disease until the time of start of renal replacement therapy, suggests that patient B had a longer time to renal replacement therapy although in fact this was only a result of the earlier detection by screening. This is known as lead-time bias. It should be noted that the example is quite extreme and would only hold when medical intervention on positive screening is not effective in changing the natural course of the disease. RRT, renal replacement therapy.

disease and therefore a better prognosis are more likely to be identified during such interval screening compared with those with aggressive disease and a poor prognosis. Thus, patients with slowly progressive disease are likely to be overrepresented in the cohort suitable for screening. Consequently, cases who are identified in a screening program will appear to have a better prognosis than subjects who are diagnosed on symptomatic recognition, even if screening has no effect on prognosis. This phenomenon is known as the length bias (Figure 1).

Lead-time bias
As a consequence of screening, subjects may be diagnosed earlier than would have happened when awaiting symptomatic recognition in the natural course of the disease. The interval between pre-symptomatic diagnosis and symptomatic recognition is known as the lead-time due to screening. Earlier diagnosis will then lead to an apparent lengthening of survival. However, this is mostly because of the earlier diagnosis rather than efficacious intervention. This phenomenon is known as lead-time bias (Figure 2). In CKD, lead-time bias may have a role when studying the effect of early versus late initiation of dialysis. It has been shown that the earlier initiation of dialysis, as judged from a better renal function at the start of dialysis, is beneficial as shown by a decrease in mortality and hospitalization.[31] However, this effect could be explained by the fact that those with a better renal function at the start of dialysis simply are at an earlier

stage of disease and therefore, live longer on dialysis. Indeed, Korevaar et al.[32] tried to estimate the lead time in patients with a timely versus a late start of dialysis with a prediction software using literature data of the decline in renal function during pre-dialysis (stage 4–5 CKD). The study showed that the gain in survival in patients with a timely start of dialysis is approximately equal to the lead time and therefore, not the result of improvement in the course of the disease. Alternatively and more precisely, to correct for the difference in stage of disease, survival should not be counted from the start of dialysis but rather from a fixed level of renal function before the start of dialysis, for instance a renal function of 20 ml/min. Using such an approach to correct for lead-time bias, Traynor et al.[33] have shown that there is no survival benefit in patients with higher levels of renal function at the start of dialysis compared with patients with lower levels of renal function.

The efficacy of screening is often defended by the argument that patients with disease who are detected at screening tend to have less advanced disease and survive longer after diagnosis than patients whose disease was detected on presentation of symptoms in the natural course of the disease. However, in particular, in diseases with a relatively long but variable duration, as is the case in CKD, the survival benefit of screening can largely be explained by lead-time bias and length bias.

EFFICACY OF SCREENING IN CKD
The benefits of screening programs for CKD should be evaluated in a two-way manner. One the one hand, screening and early detection of CKD and subsequent treatment will have a beneficial effect on renal outcomes, such as the rate of

decline in GFR and the time to renal replacement therapy. On the other hand, evaluation should include the prevention of cardiovascular events.

CONCLUSIONS

Valid tests are available for the screening of patients with CKD. At present, several screening programs exist worldwide. Each of these is carried out in patients at increased risk for CKD rather than in the whole population. Clearly, screening of a high-risk target population increases the detection rate of cases and decreases the number needed to screen to detect one case. In the setting of CKD, several treatments are available, which may contribute to slowing the progression of CKD. Finally, as in any screening program, forms of bias need to be considered, including selection bias, length bias, and lead-time bias.

DISCLOSURE

All authors declared no competing interests.

REFERENCES

1. Wilson J, Jungner G. Principles and practice of screening for disease. *WHO Public Health Papers* 1968; **34**: 1–163.
2. Andermann A, Blancquaert I, Beauchamp S et al. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bull World Health Organ* 2008; **86**: 317–319.
3. Glassock RJ, Winearls C. The global burden of chronic kidney disease: how valid are the estimates? *Nephron Clin Pract* 2008; **110**: c39–c46.
4. Meguid El NA, Bello AK. Chronic kidney disease: the global challenge. *Lancet* 2005; **365**: 331–340.
5. Vassalotti JA, Stevens LA, Levey AS. Testing for chronic kidney disease: a position statement from the National Kidney Foundation. *Am J Kidney Dis* 2007; **50**: 169–180.
6. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**: S1–S266.
7. Glassock RJ, Winearls C. Screening for CKD with eGFR: doubts and dangers. *Clin J Am Soc Nephrol* 2008; **3**: 1563–1568.
8. Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. *Kidney Int* 2001; **59**: 260–269.
9. Maki DD, Ma JZ, Louis TA et al. Long-term effects of antihypertensive agents on proteinuria and renal function. *Arch Intern Med* 1995; **155**: 1073–1080.
10. Pedrini MT, Levey AS, Lau J et al. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. *Ann Intern Med* 1996; **124**: 627–632.
11. Wang PH, Lau J, Chalmers TC. Meta-analysis of effects of intensive blood-glucose control on late complications of type I diabetes. *Lancet* 1993; **341**: 1306–1309.
12. Gouva C, Nikolopoulos P, Ioannidis JP et al. Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. *Kidney Int* 2004; **66**: 753–760.
13. Clase CM. Glomerular filtration rate: screening cannot be recommended on the basis of current knowledge. *BMJ* 2006; **333**: 1030–1031.
14. Konta T, Hao Z, Takasaki S et al. Clinical utility of trace proteinuria for microalbuminuria screening in the general population. *Clin Exp Nephrol* 2007; **11**: 51–55.
15. Gansevoort RT, Verhave JC, Hillege HL et al. The validity of screening based on spot morning urine samples to detect subjects with microalbuminuria in the general population. *Kidney Int Suppl* 2005; **94**: S28–S35.
16. de Jong PE, Halbesma N, Gansevoort RT. Screening for early chronic kidney disease – what method fits best? *Nephrol Dial Transplant* 2006; **21**: 2358–2361.
17. Delanaye P, Cohen EP. Formula-based estimates of the GFR: equations variable and uncertain. *Nephron Clin Pract* 2008; **110**: c48–c53.
18. Stevens LA, Coresh J, Greene T et al. Assessing kidney function – measured and estimated glomerular filtration rate. *N Engl J Med* 2006; **354**: 2473–2483.
19. Foster MC, Hwang SJ, Larson MG et al. Cross-classification of microalbuminuria and reduced glomerular filtration rate: associations between cardiovascular disease risk factors and clinical outcomes. *Arch Intern Med* 2007; **167**: 1386–1392.
20. Halbesma N, Kuiken DS, Brantsma AH et al. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. *J Am Soc Nephrol* 2006; **17**: 2582–2590.
21. John R, Webb M, Young A et al. Unreferred chronic kidney disease: a longitudinal study. *Am J Kidney Dis* 2004; **43**: 825–835.
22. van Stralen KJ, Stel VS, Reitsma JB et al. Diagnostic methods I: sensitivity, specificity, and other measures of accuracy. *Kidney Int* 2009 (in press).
23. Atthobari J, Asselbergs FW, Boersma C et al. Cost-effectiveness of screening for albuminuria with subsequent fosinopril treatment to prevent cardiovascular events: a pharmacoeconomic analysis linked to the prevention of renal and vascular endstage disease (PREVEND) study and the prevention of renal and vascular endstage disease intervention trial (PREVEND IT). *Clin Ther* 2006; **28**: 432–444.
24. Boulware LE, Jaar BG, Tarver-Carr ME et al. Screening for proteinuria in US adults: a cost-effectiveness analysis. *JAMA* 2003; **290**: 3101–3114.
25. Bello AK, Peters J, Wight J et al. A population-based screening for microalbuminuria among relatives of CKD patients: the Kidney Evaluation and Awareness Program in Sheffield (KEAPS). *Am J Kidney Dis* 2008; **52**: 434–443.
26. Brown WW, Peters RM, Ohmit SE et al. Early detection of kidney disease in community settings: the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2003; **42**: 22–35.
27. Hallan SI, Dahl K, Oien CM et al. Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey. *BMJ* 2006; **333**: 1047.
28. Bang H, Vupputuri S, Shoham DA et al. SCreening for Occult REnal Disease (SCORED): a simple prediction model for chronic kidney disease. *Arch Intern Med* 2007; **167**: 374–381.
29. Kshirsagar AV, Bang H, Bomback AS et al. A simple algorithm to predict incident kidney disease. *Arch Intern Med* 2008; **168**: 2466–2473.
30. Tripepi G, Jager KJ, Dekker FW et al. Bias in clinical research. *Kidney Int* 2008; **73**: 148–153.
31. Churchill DN. An evidence-based approach to earlier initiation of dialysis. *Am J Kidney Dis* 1997; **30**: 899–906.
32. Korevaar JC, Jansen MA, Dekker FW et al. When to initiate dialysis: effect of proposed US guidelines on survival. *Lancet* 2001; **358**: 1046–1050.
33. Traynor JP, Simpson K, Geddes CC et al. Early initiation of dialysis fails to prolong survival in patients with end-stage renal failure. *J Am Soc Nephrol* 2002; **13**: 2125–2132.