To Screen or Not to Screen: That Is Not (Yet) the Question

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Resolving the question of whether screening for CKD is effective in improving outcomes for affected individuals is one of the most important questions facing the field of nephrology today. The medical community has been bombarded by conflicting statements on screening for CKD published by the American Society of Nephrology, the National Kidney Foundation, and the American College of Physicians, which has led to confusion. An eloquent statement from the US Preventive Services Task Force stated the obvious: No recommendation can be made due to lack of evidence (1). Our immediate decision is not whether we will systematically screen for CKD in the United States, but whether we are serious about gathering the evidence needed to make an informed choice. Such effort will require a committed investment of material and intellectual resources and, most of all, patience and perseverance.

Early detection and prevention are the cornerstones of public health efforts to reduce the burden of common chronic diseases. The nephrology community can derive energy and hope from revisiting the history of the great leaps we have achieved in the reduction of cardiovascular morbidity and mortality in the United States by treating high BP. Although the Framingham cohort identified BP as a "factor of risk" in 1961 (2), many of the seminal randomized controlled trials showing the benefit of lowering diastolic, then systolic BP, were not completed until 2–3 decades later. Screening for elevated BP and instituting appropriate treatment remains a national priority today.

In nephrology, we are just beginning this journey. CKD was first defined by consensus in the Kidney Disease Outcomes Quality Initiative guidelines published in 2002. At that time, CKD was defined solely on the basis of eGFR. Since then, both eGFR and urine albumin/creatinine ratio (UACR) are required for staging of disease (3). The last decade has been rich in increasing understanding of the epidemiology of CKD (4,5), including the high cardiovascular risk in persons with CKD (6) and the identification of high-risk groups such as racial/ethnic minorities and persons with low socioeconomic status (SES) (7). Despite these advances, observational studies have not convincingly shown that screening for CKD using either eGFR or UACR improves health outcomes or is cost-effective (8–10). To date, no randomized controlled trial has evaluated the effectiveness of screening for CKD.

We believe that "preventive nephrology" should be prioritized by the nephrology community. To move forward, we must gather the evidence to make an informed decision about potential benefits and risks of a systematic CKD screening strategy. In particular, we must (*1*) identify the populations at highest risk who are most likely to benefit, (*2*) identify a testing strategy that maximizes sensitivity and specificity and is cost-effective, (*3*) agree on appropriate clinical and patient-centered outcomes relevant to CKD, (*4*) investigate step-wise algorithms for early, individualized management, and (*5*) understand risks, costs, and benefits of community-based versus office-based screening, among other steps. In this issue of *CJASN*, Vart and colleagues move the field further by addressing some of these important questions (11). In this article, the authors aim to identify a CKD screening approach that may enhance the detection of individuals at high risk for cardiovascular complications. Using data from a subset of individuals enrolled in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, the authors examine whether screening for CKD among individuals with low SES or elderly patients in addition to persons with diabetes, hypertension, and cardiovascular disease (traditionally considered high risk) may increase the yield of CKD detection compared with screening for CKD among traditional high-risk individuals alone. In so doing, the authors address the following important questions regarding CKD screening.

Which populations would benefit the most from CKD screening? Screening for chronic diseases has the greatest benefit when utilized among communities at highest risk. In the article by Vart *et al.* (11), the number needed to screen to identify one CKD case was 6.5 in each expanded strategy compared with 5.6 using the traditional strategy. However, the expanded screening strategy including individuals of low SES was able to detect persons with CKD associated with a higher risk for cardiovascular disease compared with persons with no CKD and those with undetected CKD. These data are consistent with prior studies that demonstrated a high burden of CKD, ESRD, cardiovascular disease, and mortality among low-income populations (12,13). Screening for CKD in disadvantaged communities at high risk was used among Aboriginal communities in Australia. In these Aboriginal communities with high prevalence of uncontrolled

BP and macroalbuminuria, CKD screening coupled with an aggressive CKD management program was associated with decreased all-cause death and renal-related deaths compared with historical controls (14). The current data from the PREVEND trial suggest that investigation of the effectiveness of CKD screening in low-income United States populations is warranted, and that persons with CKD detected by this strategy may be at higher cardiovascular risk. However, these findings still do not resolve the uncertainties over the most effective screening strategy for CKD, and a data vacuum remains.

Which CKD testing strategy maximizes sensitivity and specificity? Vart and colleagues examined a CKD screening strategy that included serum cystatin C, serum creatinine, and 24-hour urine collection for albuminuria quantification (11). Timed urine collections are more labor intensive and less practical than using spot UACR, which offers >90% sensitivity (15) and has clinical predictive value for death and progression to ESRD similar to 24-hour urine collections (16). However, results of this study strengthen the idea of using a triple marker approach—two filtration markers and albuminuria—to identify individuals at highest risk of CKD complications compared with a single marker of CKD (17).

What are meaningful outcomes relevant to CKD? Interestingly, the expanded screening approach including individuals of low SES did not significantly expand the identification of individuals at risk for renal function decline (adjusted odds ratio, 1.28; 95% confidence interval, 0.77 to 2.13); rather, the approach only detected individuals with CKD at higher risk for cardiovascular outcomes. Although these results may be attributable to a lack of statistical power, they remind us that outcomes for which risk could be modified with a CKD screening strategy may not all be nephrocentric. In 2010, the Food and Drug Administration sponsored a conference to evaluate renal outcomes and patient-centered outcomes relevant to CKD (18,19). This was an important first step, but much effort is still needed to identify and understand appropriate CKD-related outcomes for future research studies.

In addition to identification of the above steps, many unresolved questions regarding CKD screening remain, which are also required to move the field forward.

Which interventions can reduce adverse health outcomes? Aggressive BP control, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and glycemic control are associated with decreased albuminuria and fewer adverse health outcomes for specific populations with CKD (20,21). The heterogeneous presentation of CKD and its disparate natural history make it very likely that these interventions, among others, have differing risks/benefits among different CKD populations. More research into individualized CKD management is needed.

Will screening cause any harm? Most patients with early CKD are clinically unrecognized. It is not clear whether labeling asymptomatic individuals with CKD may lead to psychologic harm. This may be particularly important for individuals who receive a false positive diagnosis of CKD, because they could experience unnecessary treatment and diagnostic interventions, with potential harms associated with polypharmacy. This possibility would justify the use of strategies with higher specificity.

What is the cost-effectiveness of screening? Prior studies have suggested that CKD screening among the general population with albuminuria is not cost-effective for the clinical end points of ESRD or death (8). Cost-effectiveness becomes more favorable when a composite outcome including cardiovascular events is considered (22). CKD screening among high-risk groups is likely to enhance its cost-effectiveness, although until the efficacy of CKD screening is established, assessment of cost-effectiveness is limited. While the cost per case detected can be ascertained, the specific value of early detection to prevent adverse outcomes associated with CKD remains unknown.

To move this nascent field forward, we face the immediate challenge of equipping the next generation of scientists with the knowledge and skills needed to tackle these important questions. Who will become the next generation of preventive nephrologists? In addition to our continued investment in developing the careers of investigators in basic science and epidemiology, we would also benefit from training scientists in population health approaches to chronic disease management, community-based participatory research, measuring patient-centered outcomes, economics, informatics, and implementation and dissemination science. Early detection of disease through screening has yielded success in the reduction of cardiovascular morbidity and mortality in the United States. The time has come for CKD prevention, early detection, and individualized management. The Institute of Medicine and the Centers for Disease Control and Prevention have both recognized CKD as a priority. How will the nephrology community rise to this challenge?

Disclosures

None.

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See related article, "Added Value of Screening for CKD among the Elderly or Persons with Low Socioeconomic Status," on pages 562–570.