Routine Screening for CKD Should Be Done in Asymptomatic Adults . . . Selectively

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Abstract

CKD is an important public health problem associated with substantial morbidity, impaired quality of life, shortened life expectancy, and excessive health care costs. Given its long preclinical latency, screening of asymptomatic individuals for CKD has been considered as a potentially useful means of early detection, with a goal of reducing CKD progression and its complications. A recent clinical practice guideline from the American College of Physicians that recommended against screening for CKD in asymptomatic adults without risk factors has reignited debate regarding CKD screening. Despite the lack of randomized controlled trial evidence showing benefits of CKD screening, even among individuals at increased risk for CKD, such as those with diabetes or hypertension or who are of certain high-risk racial or ethnic groups, a thoughtful and selective approach to CKD screening seems to be cost-effective and clinically valuable. CKD screening is recommended by several nephrology professional societies and appropriate in at-risk asymptomatic individuals with the intent of identifying and managing CKD, diagnosing the etiology of CKD, limiting or preventing CKD progression and its associated cardiovascular disease risk, and minimizing risk of AKI, inappropriate drug dosing, and nephrotoxic injury.

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CKD affects a substantial fraction of the adult population in the United States and worldwide, and is associated with reduced quality of life and excess morbidity, mortality, and health care expenditures (1–4). CKD is clinically silent and asymptomatic until its later stages but can be readily and inexpensively detected by urine dipstick testing and measurement of serum creatinine concentration, urine protein or albumin concentration, and urine protein-to-creatinine or albumin-to-creatinine ratios (5). Because therapies are available to slow progression of early CKD to more advanced stages that might require renal transplantation or dialysis initiation and treat the metabolic and hematologic complications of advanced CKD, there has been interest in the role of early detection of CKD (6–8). Whether CKD screening among asymptomatic individuals should be widespread or community-based regardless of risk for CKD or ESRD, limited to only those who are at increased risk for CKD or ESRD, or done at all remains a matter of debate. A recent clinical practice guideline statement from the American College of Physicians recommended against screening for CKD in asymptomatic adults without risk factors and also concluded that, even in adults with CKD risk factors, there was insufficient evidence regarding benefits of screening (9). This "pro" position paper argues that there is a role for CKD screening among certain patient groups and in certain clinical settings.

What Is Screening?

Screening, whether for CKD or any other medical condition, generally refers to use of laboratory tests, physical examination findings, or imaging studies to detect subclinical disease in asymptomatic individuals. An abnormal finding resulting from screening in this context typically is followed by more detailed and specific diagnostic testing, treatment, and long-term follow-up focused on secondary prevention aimed at reversing, preventing, or slowing progression of detected disease and improving patient outcomes (10). Mass screening casts a broad net, often with little or no regard for the specific characteristics of the screened individuals, and does not occur in the context of an individual patient–provider encounter. Routine screening is automatic or repetitive testing based commonly on age or sex alone. Individualized screening, also called convenience testing, is performed in the context of a patient-provider encounter. Individualized screening can be performed regardless of patient risk for the screened condition or be targeted to certain patients who have specific characteristics that favor screening.

Screening for a disease will generally be more successful and cost-effective if the disease is relatively common among those screened. When the prevalence of a disease is low in a screened cohort or the disease is unlikely to be present in an individual patient, the positive predictive value (PPV) of a screening test (true positives/[true positives+false positives]) will be low, while the negative predictive value (true negatives/[true negatives+false negatives]) will be high. The higher the underlying disease prevalence or disease likelihood in an individual patient, the greater the PPV of an abnormal test and the greater its use as a screening tool. Therefore, the benefit of screening, all else being equal, will be greater if the screened population is enhanced for risk of the disease and its sequelae. For CKD, screening patients

with hypertension, diabetes, family history of CKD or ESRD, and who are African American should increase the PPV and, hence, the use of any screening test.

In addition to consideration of population prevalence when considering screening, the benefit of screening is greater when the disease being screened for is clinically important, associated with significant morbidity and mortality if undetected and untreated, has a relatively long preclinical duration, the screening tests are accurate (high sensitivity and specificity or few false-positive and false-negative findings), early identification of the disease enhances its treatment and patient outcomes with acceptable risk, and the costs of the screening test(s), additional tests, physician visits, treatments, *etc.*, are reasonable considering the potential benefit in terms of patient quality of life, morbidity, and mortality. Screening for CKD, typically including assessment of albuminuria or proteinuria and serum creatinine concentration, fits many of these features to one degree or another. Screening for microscopic hematuria has received less attention, at least in adults, but may be of value in some settings (11).

Table 1. Institute of Medicine Standards for Clinical Practice guidelines[a]

Clinical practice guidelines should be on the basis of a systematic review of the existing evidence
Be developed by a knowledgeable multidisciplinary panel of experts and representatives from key affected groups
Consider important patient subgroups and patient preferences as appropriate
Be on the basis of an explicit and transparent process that minimizes distortions, biases, and conflicts of interest
Provide a clear explanation of the logical relationships between alternative care options and health outcomes
Provide ratings of both the quality of evidence and the strength of the recommendations
Be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations

[a]See ref. 12.

Barriers to Screening

There are many potential barriers to screening. Patients may be resistant to the screening test itself (colonoscopy as an example) or lifestyle changes or medical therapies recommended as the result of positive screening findings. Examples of health system barriers include lack of insurance, difficulty in getting to a screening location or physician's office, and lack of computer-based reminders to conduct screening. Physician barriers include such things as reimbursement issues, failure to respond appropriately to abnormal screening tests, uncertainty as to the benefits of available treatments, and time constraints that make disease screening seem less important than other seemingly more pressing clinical issues. Uncertainty as to the costs, cost-effectiveness, and effect on life-years gained and costs per quality-adjusted life-years also complicate decision making regarding population screening.

Although clinical practice guidelines and recommendations from medical specialty societies can enhance the success of screening efforts, they can also hinder screening when there is a lack of consensus between clinical practice guidelines and other recommendations or when clinical practice guidelines are applied to patient groups other than those specifically addressed in the guidelines. Clinical practice guidelines are meant to provide an aid to medical decision making, reduce undue or inappropriate practice variation, enhance translation of research into practice, and improve health care quality and safety by providing practice recommendation on the basis of systematic reviews of published literature and analysis of potential benefits and harms of available options for diagnosis and treatment (12). Recommended features of a clinical practice guideline as identified by the Institute of Medicine are shown in Table 1 (12).

Screening for CKD—Clinical Practice Guidelines and Other Recommendations

A systematic review of screening for and monitoring and treatment of stages 1–3 CKD for the US Preventive Services Task Force (USPSTF) and American College of Physicians (ACP) funded by the Agency for Healthcare Research and Quality (13) was published in 2012 (14). A USPSTF recommendation statement on screening for CKD (15) was followed in late 2013 by a clinical practice guideline from the ACP on screening, monitoring, and treatment of stages 1–3 CKD (9), which prompted this and a companion "con" position paper.

Before addressing the specific recommendations of the USPSTF and ACP, a comment from one of these articles is worth emphasizing: "...clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation" (15). Also pertinent to considering clinical practice guidelines is a recent editorial on evidence-based medicine that highlighted the dangers of the phrase "there is no evidence to suggest," which can mean a variety of different things and lead to misunderstanding of the intent of guideline statements (16).

The 2012 USPSTF recommendation statement that provided the background for the ACP clinical practice guideline actually provided "no recommendation (Grade I: Insufficient Evidence)" regarding CKD screening in asymptomatic adults (15). The USPSTF report noted that evidence that routine CKD screening in asymptomatic adults improved clinical outcomes as well as evidence of its harms were inadequate and that there were no generally accepted tools for assessment of CKD risk or risk of CKD complications. Notably, patients with diabetes or hypertension were excluded from this analysis.

The ACP subsequently recommended "against screening for chronic kidney disease in asymptomatic adults without risk factors for chronic kidney disease (Grade: weak recommendation, low-quality evidence)" (9). The primary basis for this statement was the absence of randomized controlled trials (RCTs) evaluating either the benefits or harms of CKD screening. Although not part of the guideline statement, this report further indicated that evidence regarding benefits and harms of screening in asymptomatic adults with CKD risk factors was also insufficient and stated that

there was no benefit from routine monitoring of patients with stages 1–3 CKD (9). Collectively, these statements leave the impression that screening for CKD is not recommended by the ACP guideline committee, regardless of CKD risk factors.

In contrast, the American Society of Nephrology "strongly recommends regular screening for kidney disease, regardless of risk factors" given the potential to prevent and slow progression with simple, low-cost testing. The National Kidney Foundation (NKF), the Renal Physicians Association, the American Diabetes Association, and other professional organizations support CKD screening in specific at-risk groups, such as those with hypertension, diabetes, older age, family history of kidney disease, and in African Americans (17–19). Although a recent Kidney Disease Improving Global Outcomes (KDIGO) CKD guideline did not address CKD screening (5), an NKF Kidney Disease Outcome Quality Initiative Commentary Work Group (20) endorsed the recommendation from an earlier guideline (21) to assess for and screen individuals at high risk for CKD. I agree with this approach, namely screening for CKD in individuals with known risk factors for CKD, for reasons detailed below, despite the absence of supportive RCT data.

Although the ACP clinical practice guidelines were driven primarily by the absence of RCT-derived data, other studies do inform decision making about CKD screening. Several studies using various modeling approaches have concluded that mass screening of the general population using urine dipstick or serum creatinine testing is generally not cost-effective (22–24), which is in agreement with the ACP guideline statement. In contrast to the ACP report, however, screening for albuminuria or proteinuria in individuals with diabetes, hypertension, or older age (>55–60 years) has been determined to be efficient in identifying those with CKD and cost-effective (25–30). Hallan *et al.* (25), using data from a general health survey in Norway, examined the percentage of individuals with CKD detected by screening and the number needed to screen (NNTS) to find one patient with CKD using various screening strategies. In this analysis, screening those with diabetes and hypertension detected 44.2% of individuals with CKD, with an NNTS of six. Screening those with diabetes, hypertension, and age>55 years detected 93.2% of cases, with a NNTS of about nine. Given the much higher prevalence of CKD in the United States compared with Norway (31), the NNTS in a United States at-risk population should be even lower. Komenda *et al.* (30), on the basis of their systematic review, found that CKD screening using eGFR calculation or tests for proteinuria/albuminuria in populations with diabetes or hypertension seemed to be cost-effective, with a quality-adjusted life-year cost in the range of $50,000 or less. Screening for microalbuminuria at 5- to 10-year intervals is also cost-effective in African Americans, who are at particularly high risk for ESRD (30,32). Finally, a recent observational study compared outcomes among patients with ESRD who had participated in the community-based CKD screening and education NKF Kidney Early Evaluation Program (KEEP) with others who had not (33,34). Participation in the KEEP screening program was associated with higher rates of nephrologist care before development of ESRD, higher peritoneal dialysis use, higher pre-emptive transplantation waitlisting, higher transplantation rates, and lower mortality risk (hazard ratio, 0.8).

Any assessment of the value of CKD screening must consider specific outcomes that might be improved by screening. The ACP and USPSTF analysis was limited to ESRD, cardiovascular disease events, and death, which, although important, are not all of the clinically relevant outcomes (35). Other important outcomes that could be affected by early identification of CKD include avoidance of AKI, drug nephrotoxicity, and inappropriate drug dosing and opportunity to address and manage frailty, metabolic and laboratory complications of CKD, and CKD progression. In addition, when screening for CKD, regardless of the setting or patient population, the full spectrum of CKD must be considered, and not just stages 1–3. Although much more prevalent than later-stage CKD, individuals with CKD stages 4 and 5 will also occasionally be detected by CKD screening efforts. Because the stage of CKD in an individual without previously identified CKD obviously cannot be known until screening has been performed, the overall use and cost-effectiveness of screening in high-risk populations should consider the potential benefit of identifying those with more advanced CKD.

Patient preferences should be considered as well. An individual with diabetes or hypertension or who has a family history of CKD or ESRD and is concerned that they might have CKD is probably an appropriate candidate for screening, even if asymptomatic. Harms of CKD screening must also be kept in mind, including the potential effect on quality of life from being labeled as having a disease as well as the costs and risks of diagnosis (*i.e.*, kidney biopsy) and treatment (hyperkalemia with an angiotensin-converting enzyme inhibitor).

Summary and Conclusions

Most evidence suggests that mass screening for CKD among asymptomatic adults without increased risk for CKD or ESRD is not cost-effective, but as indicated by the ACP clinical practice recommendation report, this has not been rigorously tested in RCTs. Although also not subjected to RCTs, there is ample indirect evidence that community-based CKD screening can be valuable when those screened have diabetes, hypertension, or other CKD risk factors, or a family history of diabetes, hypertension, or CKD (36,37). Individualized screening that occurs as part of a patient-clinician encounter on the basis of decisions that are patient-specific, including knowledge of patient preferences, also seems to be justifiable and cost-effective in individuals at increased risk of CKD.

Clinical practice guidelines cannot replace clinical judgment and patient preferences. Providing a caveat similar to that expressed in the USPSTF statement, the 2012 KDIGO guideline on CKD noted that the guideline was "designed to provide information and assist decision making. It is not intended to define a standard of care, and should not be construed as one, nor should it be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice" (5). In the case of CKD screening, strong recommendations on the basis of robust, high-quality data from

multiple RCTs showing evidence of benefit that outweighs harm are desperately needed.

A clinical practice guideline or recommendation statement when "there is no evidence to suggest that" CKD screening is cost-effective or leads to important improvement in clinical outcomes may itself lead to more harm than benefit if individuals who would benefit from identification through screening remain undetected and suffer potentially avoidable consequences. Until evidence dictates otherwise, individualized decision making about CKD screening using periodic measurement of serum creatinine and/or tests for urine albumin or protein periodically seems to be appropriate in at-risk asymptomatic individuals with the intent of identifying and managing CKD, diagnosing the etiology of CKD, limiting or preventing CKD progression and its associated cardiovascular disease risk, and minimizing risk of AKI, inappropriate drug dosing, and nephrotoxic injury.

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References

1. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS: Prevalence of chronic kidney disease in the United States. *JAMA* 298: 2038–2047, 2007
2. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS: Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 41: 1–12, 2003
3. McCullough K, Sharma P, Ali T, Khan I, Smith WC, MacLeod A, Black C: Measuring the population burden of chronic kidney disease: A systematic literature review of the estimated prevalence of impaired kidney function. *Nephrol Dial Transplant* 27: 1812–1821, 2012
4. Grams ME, Chow EK, Segev DL, Coresh J: Lifetime incidence of CKD stages 3-5 in the United States. *Am J Kidney Dis* 62: 245–252, 2013
5. KDIGO CKD Work Group: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 3: 1–150, 2013
6. Vassalotti JA, Li S, Chen SC, Collins AJ: Screening populations at increased risk of CKD: The Kidney Early Evaluation Program (KEEP) and the public health problem. *Am J Kidney Dis* 53[Suppl 3]: S107–S114, 2009
7. McGill JB, Brown WW, Chen SC, Collins AJ, Gannon MR: Kidney Early Evaluation Program (KEEP). Findings from a community screening program. *Diabetes Educ* 30: 196–198, 200–202, 206, 2004
8. McClellan WM, Ramirez SP, Jurkovitz C: Screening for chronic kidney disease: Unresolved issues. *J Am Soc Nephrol* 14[Suppl 2]: S81–S87, 2003
9. Qaseem A, Hopkins RH Jr., Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians: Screening, monitoring, and treatment of stage 1 to 3 chronic kidney disease: A clinical practice guideline from the American College of Physicians. *Ann Intern Med* 159: 835–847, 2013
10. Nielsen C, Lang RS: Principles of screening. *Med Clin North Am* 83: 1323–1337, v, 1999
11. Moreno JA, Martín-Cleary C, Gutiérrez E, Rubio-Navarro A, Ortiz A, Praga M, Egido J: Haematuria: The forgotten CKD factor? *Nephrol Dial Transplant* 27: 28–34, 2012
12. Clinical Practice Guidelines we Can Trust. Available at: http://www.nap.edu/catalog.php?record_id=13058. Accessed June 7, 2014
13. Fink HA, Ishani A, Taylor BC, Greer NL, MacDonald R, Rossini D, Sadiq S, Lankireddy S, Kane RL, Wilt TJ: *Chronic Kidney Disease Stages 1-3: Screening, Monitoring, and Treatment*, Rockville, MD, Agency for Healthcare Research and Quality, 2012
14. Fink HA, Ishani A, Taylor BC, Greer NL, MacDonald R, Rossini D, Sadiq S, Lankireddy S, Kane RL, Wilt TJ: Screening for, monitoring, and treatment of chronic kidney disease stages 1 to 3: A systematic review for the U.S. Preventive Services Task Force and for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 156: 570–581, 2012
15. Moyer VA; US Preventive Services Task Force: Screening for chronic kidney disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 157: 567–570, 2012
16. Braithwaite RS: A piece of my mind. EBM's six dangerous words. *JAMA* 310: 2149–2150, 2013
17. American Diabetes Association: Executive summary: Standards of medical care in diabetes—2011. *Diabetes Care* 34[Suppl 1]: S4–S10, 2011
18. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr., Jones DW, Materson BJ, Oparil S, Wright JT Jr., Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA* 289: 2560–2572, 2003
19. Brosius FC 3rd, Hostetter TH, Kelepouris E, Mitsnefes MM, Moe SM, Moore MA, Pennathur S, Smith GL, Wilson PW; American Heart Association Kidney and Cardiovascular Disease Council; Council on High Blood Pressure Research; Council on Cardiovascular Disease in the Young; Council on Epidemiology and Prevention; Quality of Care and Outcomes Research Interdisciplinary Working Group: Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: A science advisory from the American Heart Association Kidney And Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: Developed in collaboration with the National Kidney Foundation. *Circulation* 114: 1083–1087, 2006
20. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Kurella Tamura M, Feldman HI: KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis* 63: 713–735, 2014
21. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 39[Suppl 1]: S1–S266, 2002
22. Boulware LE, Jaar BG, Tarver-Carr ME, Brancati FL, Powe NR: Screening for proteinuria in US adults: A cost-effectiveness analysis. *JAMA* 290: 3101–3114, 2003
23. Hoerger TJ, Wittenborn JS, Segel JE, Burrows NR, Imai K, Eggers P, Pavkov ME, Jordan R, Hailpern SM, Schoolwerth AC, Williams DE; Centers for Disease Control and Prevention CKD Initiative: A health policy model of CKD: 2. The cost-effectiveness of microalbuminuria screening. *Am J Kidney Dis* 55: 463–473, 2010
24. Craig JC, Barratt A, Cumming R, Irwig L, Salkeld G: Feasibility study of the early detection and treatment of renal disease by mass screening. *Intern Med J* 32: 6–14, 2002
25. Hallan SI, Dahl K, Oien CM, Grootendorst DC, Aasberg A, Holmen J, Dekker FW: Screening strategies for chronic kidney disease in the general population: Follow-up of cross sectional health survey. *BMJ* 333: 1047, 2006
26. Wu HY, Huang JW, Peng YS, Hung KY, Wu KD, Lai MS, Chien KL: Microalbuminuria screening for detecting chronic kidney disease in the general population: A systematic review. *Ren Fail* 35: 607–614, 2013
27. Clark WF, Macnab JJ, Sontrop JM, Jain AK, Moist L, Salvadori M, Suri R, Garg AX: Dipstick proteinuria as a screening strategy to identify rapid renal decline. *J Am Soc Nephrol* 22: 1729–1736, 2011
28. Collins AJ, Vassalotti JA, Wang C, Li S, Gilbertson DT, Liu J, Foley RN, Chen SC, Arneson TJ: Who should be targeted for CKD

screening? Impact of diabetes, hypertension, and cardiovascular disease. *Am J Kidney Dis* 53[Suppl 3]: S71–S77, 2009
29. de Jong PE, Curhan GC: Screening, monitoring, and treatment of albuminuria: Public health perspectives. *J Am Soc Nephrol* 17: 2120–2126, 2006
30. Komenda P, Ferguson TW, Macdonald K, Rigatto C, Koolage C, Sood MM, Tangri N: Cost-effectiveness of primary screening for CKD: A systematic review. *Am J Kidney Dis* 63: 789–797, 2014
31. Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, Romundstad S, Hallan HA, Lydersen S, Holmen J: International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol* 17: 2275–2284, 2006
32. Hoerger TJ, Wittenborn JS, Zhuo X, Pavkov ME, Burrows NR, Eggers P, Jordan R, Saydah S, Williams DE: Cost-effectiveness of screening for microalbuminuria among African Americans. *J Am Soc Nephrol* 23: 2035–2041, 2012
33. Kurella Tamura M, Li S, Chen SC, Cavanaugh KL, Whaley-Connell AT, McCullough PA, Mehrotra RL: Educational programs improve the preparation for dialysis and survival of patients with chronic kidney disease. *Kidney Int* 85: 686–692, 2014
34. Huang X, Carrero JJ: Better prevention than cure: Optimal patient preparation for renal replacement therapy. *Kidney Int* 85: 507–510, 2014
35. Uhlig K, Levey AS: Developing guidelines for chronic kidney disease: We should include all of the outcomes. *Ann Intern Med* 156: 599–601, 2012
36. Brown WW, Peters RM, Ohmit SE, Keane WF, Collins A, Chen SC, King K, Klag MJ, Molony DA, Flack JM: Early detection of kidney disease in community settings: The Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 42: 22–35, 2003
37. Vassalotti JA, Li S, Chen SC, Collins AJ: Screening populations at increased risk of CKD: the Kidney Early Evaluation Program (KEEP) and the public health problem. *Am J Kidney Dis* 53[Suppl 3]: S107–S114, 2009

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