PRIMARY SCREENING FOR CHRONIC KIDNEY DISEASE

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Abstract

Chronic Kidney Disease (CKD) is a global public health problem associated with a reduced quality of life with significant consequences on patient morbidity and mortality. Because these downstream outcomes are expensive for health care systems, harmful to patients, and therapies are available to slow progression of early CKD, there has been interest in the role of early detection of asymptomatic CKD. Screening asymptomatic individuals for CKD has been considered as a potentially useful means of early detection. Current clinical practice guidelines for CKD screening and monitoring exist from major guideline bodies, however they vary in scope and implementation.

On one end of the screening spectrum, routine, mass screening for CKD among the general population without increased risk for CKD is currently not recommended by the majority of guidelines. On the other end, there is abundant indirect evidence that targeted CKD screening and treatment of high-risk populations, such as those with diabetes, hypertension or other CKD risk factors, represent a valuable, cost-effective opportunity for strengthened intervention with large implications for health care.

Targeted CKD screening programs may be cost-effective in specific high-risk populations, but pitfalls remain in the broad application of screening programs in terms of labeling of disease, excessive costs and risks of treatment in low-risk patients. While opportunistic screening at routine primary care encounters and the utilization of administrative databases may detect some CKD for referral, these strategies are not optimal for all high risk populations with reduced access to care. Efforts must continue to evaluate and refine evidence-based targeted screening programs to reduce the global burden of CKD and improve health outcomes for this emerging public health problem.

Introduction

The concept of screening for health conditions generally enables the detection of subclinical disease in asymptomatic individuals (1). The feasibility of a screening program is based on three fundamental requirements: burden of disease, availability of effective treatment and cost effectiveness and efficiency of the overall screening and treatment program. Screening for diseases, whether for Chronic Kidney Disease (CKD) or any medical condition, may be warranted in populations where the burden of disease is high as measured by severity, prevalence and significantly altering patient outcomes such as morbidity, mortality and overall health related quality of life (2-4). Screening will generally be more successful if chronic diseases, like CKD, typically have a prolonged period of latency during which the disease is present but asymptomatic (4). Early detection resulting from screening programs should typically be followed by specific diagnostic testing to all screen positive individuals; and, if CKD is diagnosed, treatment, long-term follow up and disease modifying management that prevents or delays the progression of CKD must be readily available (1, 4). The screening process itself must be accurate (*e.g.,* high sensitivity and specificity), reliable (*e.g.*, reproducible), safe and acceptable. Cost-effectiveness is one of the most relevant criteria for implementing screening programs (1). Screening can take many forms from the lower-cost, high-risk group screening strategy to the more costly population-based screening intervention (3).

Screening Programs for Chronic Kidney Disease

CKD is a global public health problem with increasing incidence worldwide and an overall prevalence of approximately 10% to 15% of the general population (5). Patients with CKD and its end stage of Kidney Failure (KF) have been associated with a reduced quality of life with significant consequences on patient morbidity and mortality and consume a disproportionate amount of health care expenditures (6, 7). However, early detection, appropriate risk stratification and treatment may delay or prevent the complications of CKD such as cardiovascular disease, kidney failure, and early mortality (8, 9). Because these downstream outcomes are expensive for health care systems, harmful to patients, and therapies are available to slow progression of early CKD, there has been interest in the role of early detection of asymptomatic CKD (10).

CKD screening can be readily and inexpensively performed by urine testing (*e.g.*, to measure urine protein or albumin concentration, and urine protein-to-creatinine or albumin-to-creatinine ratio) and measurement of serum creatinine concentration to calculate an estimated glomerular filtration rate (eGFR) (11). Utilization of a two axis heat map risk stratification tool or estimating equations are considered the standard of care for optimal detection of early CKD (Figure 1).

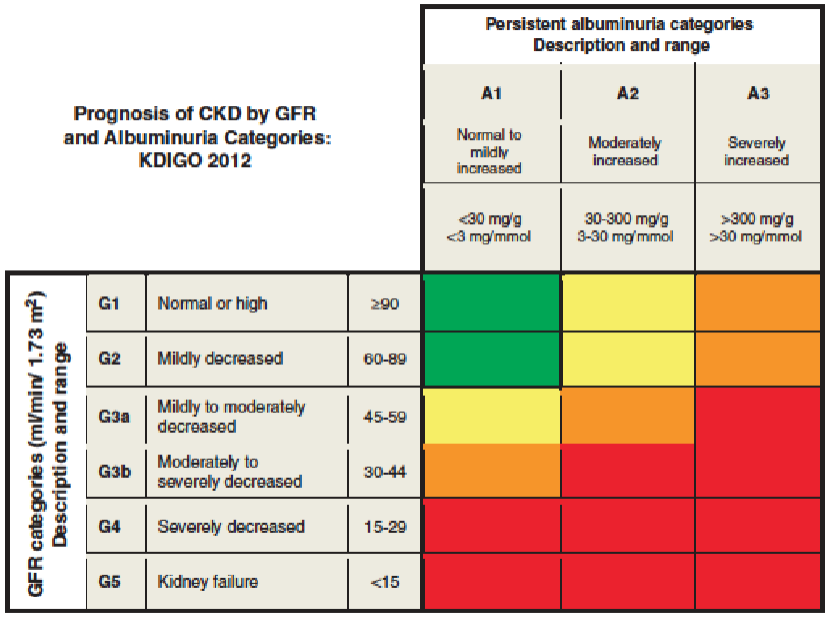

Figure 1: KDIGO 2012 classification of CKD based on GFR and albuminuria(11)

A number of universal and targeted CKD screening initiatives have been undertaken in a variety of populations worldwide (12). The National Kidney Foundation's Kidney Early Evaluation Program (KEEP) provided innovative epidemiologic data on early detection of CKD by screening over 185,000 individuals in the United States, targeting patients with established risk factors for CKD, such as diabetes, hypertension or a family history of kidney disease (13-15). This screening model which tests for eGFR and urinary albumin-creatinine ratio was replicated in many other countries like Japan and Mexico (15). Likewise, Australia utilized a similar targeted approach with its Kidney Evaluation for You Program. Targeted screening for certain high-risk ethnicities, such as Canadian First Nations people, demonstrated increased rates of CKD (16). Contrary to targeted CKD screening, there have also been mass CKD screening studies of the general population in the Netherlands, the United States, Korea, Japan, China and elsewhere (12, 17-19).

Current Clinical Practice Guidelines for CKD Screening

Current clinical practice guidelines for CKD screening and monitoring exist from major guideline bodies, but they vary in scope and implementation. The American Society of Nephrology (ASN) strongly advocated for "regular screening for kidney disease, regardless of an individual's risk factors," near the end of 2013. The ASN suggested that all individuals should be screened for CKD given the potential to prevent and slow progression of disease with simple, low-cost testing. Later that same day in 2013, the American College of Physicians (ACP) released a clinical practice guideline recommending the contrary: not to screen for CKD in asymptomatic adults without risk factors. This report concluded that the evidence was insufficient regarding the balance of benefits and harms of screening for CKD in asymptomatic adults due to the absence of supportive RCT data (20). These ACP guidelines were concordant with the U.S. Preventive Services Task Force (USPSTF) recommendation from the previous year in 2012, which also stated that the evidence was

insufficient regarding routine screening for CKD in asymptomatic adults (21). While the Kidney Disease Improving Global Outcomes (KDIGO) guidelines do not directly address CKD screening, the National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative Commentary Work Group endorsed the recommendation from an earlier guideline: to screen high-risk patients for CKD (22, 23). Other professional organizations, such as the Renal Physicians Association and the American Diabetes Association, also advocate CKD screening in certain high-risk groups, such as individuals with diabetes, hypertension, family history of kidney disease, older age and in African Americans (24, 25).

On one end of the screening spectrum, routine, mass screening for CKD among the general population without increased risk for CKD is currently not recommended by the majority of guidelines (2). Several other studies have assisted in informing decision making about CKD screening by concluding that mass screening using urine dipstick or serum creatinine testing is generally not cost-effective (26, 27). On the other end, there is abundant indirect evidence that targeted CKD screening and treatment of high-risk populations, such as those with diabetes, hypertension or other CKD risk factors, represent a valuable, cost-effective opportunity for strengthened intervention with large implications for health care (11).

Cost Effectiveness of CKD Screening Programs

A recent systematic review published on the cost-effectiveness of primary screening for CKD sheds light on this matter (9). Overall, there were nine studies that were included in the review, all using heterogeneous approaches to screening, but many did use eGFR calculation or tests for proteinuria/albuminuria alone as a screening test. The findings revealed that screening for CKD by eGFR and/or albuminuria in high-risk populations (*e.g.*, individuals with diabetes or hypertension) represented a good value for money in a number of settings and was cost-effective ($5,298-$54,943/quality-adjusted life year (QALY) for diabetes; $23,028-$73,939/QALY for hypertension). In contrast, mass screening of the general population was not found to be cost-effective ($14,063-$160,018/QALY for the general population). However, there were certain situations when the incremental cost-effectiveness ratios improved in the general population. For instance, if screening was performed in older patients or if there were longer intervals between screening events. However, taken together, the evidence suggested that screening for CKD in the general population in the absence of risk stratification and targeted treatment would not be cost-effective.

CKD screening, in general, is deemed cost-effective conditional on a conservative historical $50,000/QALY threshold (28). The use of this established figure as a benchmark for assessing the cost-effectiveness of an intervention surfaced in 1992 and became widely used after 1996. The fascination of the $50,000 figure appears to lie in the practicality of a round number rather than in the costs associated with CKD testing and treatment. To mitigate these concerns, the World Health Organization's cost-effectiveness guidelines endorse a threshold of less than 1-3 times the ratio of the per-capita gross domestic product (GDP) to QALY (29). The threshold range would be at about $40,000-$120,000/QALY for most G8 countries according to the World Bank estimates of GDP per capita for 2011 (9). Cost-effectiveness of CKD screening should be adapted to local regions and health care systems.

Opportunities to Improve Early Detection and Treatment of CKD

Presently, current guidelines recommend CKD screening only in high-risk groups and primary screening is only cost-effective in populations with established hypertension and diabetes. What constitutes a high-risk group may be open to interpretation and the cost-effectiveness of screening these populations may be undefined and sensitive to the type of screening program in place. In higher-risk racial or ethnic groups, in which there is an increased prevalence and

incidence of CKD and/or more rapid trajectory of progression to overt nephropathy or kidney failure, it was unclear whether these recommendations of CKD screening could be applied to these higher-risk groups. Komenda *et al.*, examined this objective on rural and remote Canadian First Nations people, who suffer from a disproportionate risk of CKD, partially explained by a higher rate of diabetes, metabolic syndrome and immune-mediated kidney diseases (30). Findings from the study revealed that offering targeted mass screening for CKD to only Canadian First Nations people with diabetes or hypertension missed nearly a third (28.3%) of individuals who were found to have CKD in the absence of either an elevated HbA_{1c} level (>6.5%) or blood pressure (30). The prevalence of CKD in these communities was comparable to rates observed in high-risk nonindigenous patients (*e.g.,* individuals with hypertension and diabetes). Based on this evidence, the authors reasonably endorsed a policy of general population screening and treatment for CKD in Canadian indigenous communities, as is currently recommended for other high-risk groups. Studies like this are telling examples of potential opportunities in improving early detection and treatment of chronic disease in high-risk populations with reduced access to reliable primary care due to remote location of residence.

Opportunistic screening at primary care encounters might also be considered another avenue to improve early detection and treatment of CKD. Health care systems are generally designed to provide episodic health care for individuals seeking treatment for symptomatic disease. These interactions at routine primary care visits offer possibilities for health care practitioners to screen, identify and treat chronic conditions. In most cases, opportunistically identifying patients presenting for symptomatic care with risk factors for a chronic condition serves most populations well compared to undirected population-wide mass screening (3). Unfortunately, there are still millions of marginalized and disenfranchised individuals who are under- or uninsured for primary care services or live in rural and remote communities with reduced access to primary care and may not benefit from episodic, symptom-driven opportunistic screening (3).

Potential Pitfalls of Mass Screening

Despite the numerous benefits of screening, there are limitations and potential unintended consequences of CKD screening which must be considered. There is a chance that screening may cause unexpected psychological harm and affect quality of life from being labeled with having a serious disease. This may be of concern particularly with false positive screening findings, when a patient is inappropriately labeled as having a disease and reverting to non-CKD status in the future. However, using more conservative thresholds coupled with advances in filtration markings and risk prediction tools in screening may partially mitigate this concern (9). Excessive investigations (*e.g.,* kidney biopsy) and complications of treatments (*e.g.,* hyperkalemia with an angiotensin-converting enzyme inhibitor) of inconsequential disease may pose physical harm to the patient. There is also a potential effect on finances in terms of costs of tests, medications, hospitalization and lost work as an unintended consequence of screening. Another barrier a patient may face is the inability to obtain certain types of insurance (*e.g.,* life or disability insurance) after being labeled with having CKD.

Future Directions

In the case of screening for CKD, strong recommendations on the basis of high-quality data from RCTs that demonstrate the effectiveness of CKD screening strategies in different populations are needed (4). There is an absence of robust RCT-derived data to strongly support CKD screening; however a trial led by Canadians Seeking Solutions and Innovations to Overcome Chronic Kidney Disease (Can-SOLVE CKD) is now underway. This 5-year Pan-Canadian initiative will address three major areas for improvement: early identification of CKD who are at highest risk of poor outcomes; testing and defining best course of treatment to improve outcome and quality of life; and

ensuring best ways to delivery patient centered-care (31).

While these efforts are underway, there are other pragmatic approaches to facilitate efficient CKD screening: point-of-care testing and reliable multivariable risk prediction algorithms. Portable, point-of-care equipment for eGFR calculation and urine albumin: creatinine ratio testing permit rapid reporting of results; while extensively validated kidney failure risk prediction algorithms allow instant stratification of risks in real-time at the point-of-care (9). The feasibility and efficacy of remote real-time CKD screening using point-of-care testing with risk prediction algorithms has been demonstrated in a study with the strategy also being embraced and accepted by high-risk patient population: Canadian indigenous communities. However, future research is needed to establish the cost-effectiveness of this initiative compared to the current standard of opportunistic screening at routine health visits (30). The Pan-Canadian See Kidney Disease (seeKD) Targeted Screening Program is another similar initiative with a refined evidence-based targeted screening program developed to reduce the burden of CKD (3). Patients are first asked about risk factors. Individuals that report at least one risk factor move on to have a point-of-care eGFR calculation and dipstick urinalysis (9).

Conclusion

Targeted CKD screening and treatment of high-risk populations represent a valuable, cost-effective opportunity to improve early detection, risk prediction and treatment of CKD. While opportunistic screening at routine primary care encounters and the utilization of administrative databases may detect some CKD for referral, these strategies are not optimal for all high risk populations with reduced access to care. Efforts must continue to evaluate and refine evidence-based targeted screening programs to reduce the global burden of CKD and improve health outcomes for this emerging public health problem.

REFERENCES

1. Nielsen C, Lang RS. Principles of screening. The Medical clinics of North America. 1999;83(6):1323-37, v.
2. Berns JS. Routine screening for CKD should be done in asymptomatic adults... selectively. Clinical journal of the American Society of Nephrology : CJASN. 2014;9(11):1988-92.
3. Komenda P, Rigatto C, Tangri N. Screening Strategies for Unrecognized CKD. Clinical journal of the American Society of Nephrology : CJASN. 2016;11(6):925-7.
4. McClellan WM, Ramirez SP, Jurkovitz C. Screening for chronic kidney disease: unresolved issues. Journal of the American Society of Nephrology : JASN. 2003;14(7 Suppl 2):S81-7.
5. Levey AS, Coresh J. Chronic kidney disease. Lancet. 2012;379(9811):165-80.
6. Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA. 2014;311(24):2518-31.
7. Nugent RA, Fathima SF, Feigl AB, Chyung D. The burden of chronic kidney disease on developing nations: a 21st century challenge in global health. Nephron Clinical practice. 2011;118(3):c269-77.
8. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. The New England journal of medicine. 2004;351(13):1296-305.
9. Komenda P, Ferguson TW, Macdonald K, Rigatto C, Koolage C, Sood MM, et al. Cost-effectiveness of primary screening for CKD: a systematic review. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2014;63(5):789-97.
10. Ferguson TW, Tangri N, Rigatto C, Komenda P. Cost-effective treatment modalities for reducing morbidity associated with chronic kidney disease. Expert review of pharmacoeconomics & outcomes research. 2015;15(2):243-52.
11. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of
Chronic Kidney Disease. Kidney Int Suppl 3: 1–150, 2013. 2012.
12. Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. BMC public health. 2008;8:117.
13. Howard K, Salkeld G, White S, McDonald S, Chadban S, Craig JC, et al. The cost-effectiveness of increasing kidney transplantation and home-based dialysis. Nephrology (Carlton, Vic). 2009;14(1):123-32.
14. Amin AP, Whaley-Connell AT, Li S, Chen SC, McCullough PA, Kosiborod MN. The synergistic relationship between estimated GFR and microalbuminuria in predicting long-term progression to ESRD or death in patients with diabetes: results from the Kidney Early Evaluation Program (KEEP). American journal of kidney diseases : the official journal of the National Kidney Foundation. 2013;61(4 Suppl 2):S12-23.
15. Whaley-Connell AT, Sowers JR, Stevens LA, McFarlane SI, Shlipak MG, Norris KC, et al. CKD in the United States: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. Am J Kidney Dis. 2008;51(4 Suppl 2):S13-20.

16. Oster RT, Virani S, Strong D, Shade S, Toth EL. Diabetes care and health status of First Nations individuals with type 2 diabetes in Alberta. Canadian family physician Medecin de famille canadien. 2009;55(4):386-93.
17. Kondo M, Yamagata K, Hoshi SL, Saito C, Asahi K, Moriyama T, et al. Cost-effectiveness of chronic kidney disease mass screening test in Japan. Clinical and experimental nephrology. 2012;16(2):279-91.
18. van der Velde M, Halbesma N, de Charro FT, Bakker SJ, de Zeeuw D, de Jong PE, et al. Screening for albuminuria identifies individuals at increased renal risk. J Am Soc Nephrol. 2009;20(4):852-62.
19. Chang TI, Li S, Chen SC, Peralta CA, Shlipak MG, Fried LF, et al. Risk factors for ESRD in individuals with preserved estimated GFR with and without albuminuria: results from the Kidney Early Evaluation Program (KEEP). American journal of kidney diseases : the official journal of the National Kidney Foundation. 2013;61(4 Suppl 2):S4-11.
20. Qaseem A, Hopkins RH, Jr., Sweet DE, Starkey M, Shekelle P, Clinical Guidelines Committee of the American College of P. 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. 2013;159(12):835-47.
21. Moyer VA, Force USPST. Screening for chronic kidney disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012;157(8):567-70.
22. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2002;39(2 Suppl 1):S1-266.
23. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014;63(5):713-35.
24. Executive summary: standards of medical care in diabetes--2011. Diabetes care. 2011;34 Suppl 1:S4-10.
25. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. Jama. 2003;289(19):2560-72.
26. Boulware LE, Jaar BG, Tarver-Carr ME, Brancati FL, Powe NR. Screening for proteinuria in US adults: a cost-effectiveness analysis. Jama. 2003;290(23):3101-14.
27. Craig JC, Barratt A, Cumming R, Irwig L, Salkeld G. Feasibility study of the early detection and treatment of renal disease by mass screening. Internal medicine journal. 2002;32(1-2):6-14.
28. Grosse SD. Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold. Expert review of pharmacoeconomics & outcomes research. 2008;8(2):165-78.
29. Schold J, Srinivas TR, Sehgal AR, Meier-Kriesche HU. Half of kidney transplant candidates who are older than 60 years now placed on the waiting list will die before receiving a deceased-donor transplant. Clinical journal of the American Society of Nephrology : CJASN. 2009;4(7):1239-45.
30. Komenda P, Lavallee B, Ferguson TW, Tangri N, Chartrand C, McLeod L, et al.

The Prevalence of CKD in Rural Canadian Indigenous Peoples: Results From the First Nations Community Based Screening to Improve Kidney Health and Prevent Dialysis (FINISHED) Screen, Triage, and Treat Program. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2016;68(4):582-90.

31. Siegel JE, Krolewski AS, Warram JH, Weinstein MC. Cost-effectiveness of screening and early treatment of nephropathy in patients with insulin-dependent diabetes mellitus. Journal of the American Society of Nephrology : JASN. 1992;3(4 Suppl):S111-9.

