The Primary Care Perspective on Routine Urine Dipstick Screening to Identify Patients with Albuminuria

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Summary

Proponents of routine urine dipstick screening to identify patients at risk for ESRD in the primary care setting have argued that urine dipsticks are inexpensive, low risk, acceptable to patients, and now, more accurate. Proponents believe that urine dipstick screening has the potential to improve outcomes for people with early disease and increase awareness of CKD. Most primary care physicians agree that populations who are at high risk for CKD should be tested and appropriately treated to decrease complications of ESRD. However, proponents of mass screening may not appreciate the challenges, limitations, and potential harms of screening. Urine dipstick testing does not meet all of the criteria for a good screening test. Screening the general population with urine dipsticks will generate many false positives—between 50% and 90% of positive tests—that will require follow-up, increase costs, and cause patient anxiety. Routine screening with urine dipsticks is not cost-effective on the order of $200,000 per quality-adjusted life year. Most importantly, there is little evidence that early identification of microalbuminuria in unselected patients influences outcomes of CKD. Without proof of effectiveness, overdiagnosis, a problem for even well established screening tests, is risked. Finally, no specialty society or preventive services group currently recommends general screening. Instead of screening, primary care physicians and nephrologists should work together to identify patients at high risk for ESRD and optimize management to improve outcomes for patients with CKD.

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Commentary

In the face of rising prevalence of CKD and with new data about the accuracy of urine dipstick screening, there has been renewed interest in mass screening of patients without risk factors for kidney disease (1–3). With the emergence of new data, one editorialist compares the value of the risk information that a primary care physician would get from detecting trace proteinuria in the office to the value of the risk information that a primary care physician would get from obtaining a personal history of smoking (2–4). As primary care physicians, we agree that albuminuria is underappreciated as a risk factor for progression of CKD and that it is often missed in primary care. However, urine dipstick as a screening test in the general population meets only four of seven criteria for a good screening test (Figure 1): CKD is prevalent, CKD is morbid, urine dipstick testing is low risk, and the procedure is acceptable to patients. However, the accuracy of urine dipsticks for the detection of albuminuria is low, it is unproven that early identification changes outcomes, and general population screening is not cost-effective (5). Proponents of screening for albuminuria have not taken into account important screening criteria and underestimate the challenges, limitations, and potential harms of mass screening. As primary care physicians, our perspective is that urine dipstick or other forms of urine albumin and urine protein testing should be reserved for patients with known risk factors for progressive CKD, like diabetes.

CKD Is Prevalent and Morbid

CKD is prevalent and morbid. Of adults over the age of 70 years in the United States, 38% have CKD (6). The prevalence of CKD is rising along with the increasing prevalence of obesity and type 2 diabetes. ESRD has a prognosis worse than some cancers; only 50% of dialysis patients survive 3 years of therapy (7).

Albuminuria is increasingly recognized as an important marker of disease and carries higher risk for ESRD than a modestly reduced GFR (8). In a study of 462,293 adults in Taiwan, 7% of adults had trace proteinuria, which carries a mortality risk comparable with smoking (9). These reasons are two reasons why proponents of screening advocate for a mass screening strategy with tests for albuminuria.

Urine Dipstick Testing Is Low Risk and Acceptable to Patients

Two additional arguments in favor of urine dipstick screening are that the test is low risk and acceptable to patients compared with other screening tests. Patients currently undergo invasive, risky, and uncomfortable tests for cancer screening. Mammography and digital rectal examinations are both uncomfortable but commonly agreed to by patients. Colonoscopy involves an unpleasant bowel preparation, requires conscious sedation, and has a perforation rate of about 1 in 1000 (10). Reflecting the acceptability of urine testing,

1. The target condition is prevalent

2. The target condition is morbid

3. The screening test is low-risk

4. The screening test is acceptable to patients

5. There is an accurate screening test

6. We have the ability to influence the outcome

7. The screening test is cost-effective

Figure 1. | Seven criteria of a good screening test. Modified from ref. 5, with permission.

almost one-half of patients already think that urinalysis should be a part of an annual health examination (11). However, even with the positive performance on these four criteria of a good screening test, urine dipstick testing fails at three important criteria and should not be considered for general population screening in primary care offices.

Accuracy of Urine Dipsticks Is Low

First, the accuracy of urine dipsticks is unacceptable. The impetus for a recent commentary about routine screening for albuminuria was an article by White *et al.* (1) assessing the accuracy of urine dipstick testing for proteinuria in an Australian cohort. The work by White *et al.* (1) makes a case for using the urine dipstick by comparing its characteristics to a spot albumin to creatinine ratio (ACR) as the gold standard.

For a screening test to be considered accurate, it must have acceptable sensitivity, specificity, and positive predictive value. Sensitivity is the probability of a positive test given that a patient has disease, or in this case, it is the probability that a urine dipstick will be positive if a patient truly has albuminuria. Specificity is the probability of a negative test in the absence of disease, or in this case, it is the probability that a urine dipstick will be negative if a patient does not have albuminuria. The positive predictive value is the

likelihood that a patient has a condition given a positive test result, or in this case, it is the probability that a patient truly has albuminuria given that the urine dipstick is positive. The positive predictive value is related to both the test characteristics and the prevalence of a condition: the lower the prevalence of a condition, the lower the positive predictive value, regardless of test sensitivity and specificity.

In the Australian cohort study, the sensitivity and specificity of urine dipstick testing of greater than or equal to 1+ protein to detect urine albumin ≥300 mg/g were both good (1). However, because the population prevalence of albuminuria ≥300 mg/g was 1% of the population, the positive predictive value was only 10% (Table 1).

Decreasing the gold standard threshold to an ACR ≥30 mg/g improves the positive predictive value of urine dipstick screening to 47%. However, in testing, threshold changes always come with a tradeoff. In decreasing the gold standard threshold, the sensitivity of urine dipstick testing decreases from 99% to 58%. Therefore, a urine dipstick will miss 42% of patients who truly have ≥30 mg/g albuminuria (Table 2). Additionally, the rate of false positives (53% or 469 of 888) would still be unacceptable, because false positives generate a lot of work, cost, and anxiety for physicians and patients with no benefit to patients' health.

What Is the Evidence That Early Identification of Microalbuminuria Changes Outcomes in Patients at Average Risk of ESRD?

It is unproven that identification of microalbuminuria in a primary care population changes outcomes. It is established that overt proteinuria or macroalbuminuria (albuminuria >300 mg/d) is associated with ESRD and adverse cardiovascular outcomes, but as stated above, the prevalence of macroalbuminuria is so low that a positive test for macroalbuminuria will have a low positive predictive value (8). When considering monitoring for a trend to macroalbuminuria, there are observational data that a longitudinal rise in albuminuria correlates with cardiovascular events, leading some experts to recommend testing patients one time every 4–6 years (3,12). However, microalbuminuria identification is not as well supported in patients at average risk of ESRD (*e.g.*, in the absence of diabetes). The Prevention of Renal and Vascular Endstage

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Table 1.   Accuracy of a dipstick result ≥1+ to identify patients with ≥300 mg/g albuminuria

	≥300 mg/g Albuminuria Present by ACR[a]	<300 mg/g Albuminuria Present by ACR[b]	Total
Urine dipstick test-positive[c]	90 (true positives)	798 (false positives)	888
Urine dipstick test-negative[d]	1 (false negative)	9947 (true negatives)	9948
Total	91	10,745	

ACR, albumin to creatinine ratio. Modified from ref. 1, with permission.
[a]Sensitivity = (number of true positives)/(number of true positives + number of false negatives)=99%.
[b]Specificity = (number of true negatives)/(number of true negatives + number of false positives)=93%.
[c]Positive predictive value = (number of true positives)/(number of true positives + number of false positives)=10%.
[d]Negative predictive value = (number of true negatives)/(number of true negatives + number of false negatives)=100%.

Table 2. Accuracy of a dipstick result ≥1+ to identify patients with ≥30 mg/g albuminuria			
	≥30 mg/g Albuminuria Present by ACR[a]	<30 mg/g Albuminuria Present by ACR[b]	Total
Urine dipstick test-positive[c]	419 (true positives)	469 (false positives)	888
Urine dipstick test-negative[d]	306 (false negatives)	9642 (true negatives)	9948
Total	725	10,111	

ACR, albumin to creatinine ratio. Modified from ref. 1, with permission.
[a]Sensitivity = (number of true positives)/(number of true positives + number of false negatives)=58%.
[b]Specificity = (number of true negatives)/(number of true negatives + number of false positives)=95%.
[c]Positive predictive value = (number of true positives)/(number of true positives + number of false positives)=47%.
[d]Negative predictive value = (number of true negatives)/(number of true negatives + number of false negatives)=97%.

Disease (PREVEND) intervention (IT) trial, the only randomized controlled trial of angiotensin converting enzyme inhibitor therapy in CKD patients (including a population with a low number of diabetes patients), did not examine whether fosinopril affected CKD outcomes. In addition, there was no statistically significant improvement in cardiovascular outcomes (3.9% in those patients treated with fosinopril versus 6.5% in the placebo group, P=0.10) (13). In the future, randomized controlled trials should examine primary CKD outcomes to prove a benefit for prevention of ESRD in unselected, otherwise healthy patients. Currently, there is no evidence that early identification of microalbuminuria changes CKD outcomes in unselected patients.

Is Annual Screening of Patients without Risk Factors for CKD Cost-Effective?

The cost-effectiveness of annual screening for proteinuria or albuminuria is questionable. Annual screening starting at age 50 years for US adults without hypertension or diabetes has a cost-effectiveness ratio of $155,000 to $283,000 per quality adjusted life year (14,15). Screening may be more cost-effective with increasing age of screening initiation and increasing screening intervals (3,14,15). Analyses of data from the Dutch PREVEND cohort study indicated that general population screening might be cost-effective, but these analyses are not generalizable for numerous reasons: they were based on patient-mailed specimens, there was a centralized laboratory for follow-up measurement of 24-hour urine albumin concentration, and they based calculations for the effectiveness of screening on the statistically nonsignificant result of the PREVEND IT trial (2,16). It is unknown whether the results would favor urine dipstick screening if the test were performed as part of an annual physical. In the future, cheaper tests for urine ACR may improve the cost-effectiveness ratio.

Harms of Screening and Overdiagnosis

Proponents often ignore the potential harms of screening. There are obvious harms, like complications associated with additional diagnostic testing such as kidney biopsy, which can cause pain, bleeding, and infection. However, harms of screening include anxiety on the part of patients and other downstream effects. Prostate cancer screening and breast cancer screening both cause significant patient anxiety, which in turn, has been proven to lead to additional unnecessary testing (17,18).

Diagnostic labeling has effects: hypertension screening has been associated with increased absenteeism (19,20). In the case of CKD, harms associated with angiotensin converting enzyme inhibitors include AKI, hyperkalemia, cough, and drug allergies. Therefore, we need the highest quality evidence before we expose asymptomatic patients to the risks of treatment.

In addition, overdiagnosis has become recognized as a serious problem in many screening programs. Overdiagnosis is the diagnosis of disease for which treatment does not alter outcomes, because the disease is so subtle that it never would have become a clinical problem for the patient. Individual patients are unaware that they have been overdiagnosed. As physicians, we cannot know if we have overdiagnosed a patient. Overdiagnosis can only be discovered when entire populations are examined. Taking breast cancer as an example, it was recently estimated that breast cancer screening only saves the lives of 13% of women who are later diagnosed with breast cancer. The majority of women who receive a diagnosis of breast cancer as a result of screening are diagnosed with no effect on mortality (21). The recent US Preventive Services Task Force Recommendation that men not be routinely offered prostate-specific antigen-based prostate cancer screening took into account the low rate of deaths prevented by screening and the harms associated with diagnosis and treatment of screen-detected cancer (22).

We should also consider epidemiologic bias when applying the findings of epidemiologic studies to practice. There are two types of epidemiologic bias that are pertinent. Lead time bias occurs when disease is detected earlier by screening and thus, increases the perceived survival time. Length time bias occurs when nonprogressive disease is overrepresented because of screening. These types of bias are particularly salient when we include geriatric patients in observational studies, because older patients with nonprogressive disease will seem to live longer and be more likely to have mild CKD than other age groups. However, we would not want to subject these patients to potential harms of CKD treatment if they are more likely to die from other causes than develop ESRD. Because of potential harms of screening, risk of overdiagnosis, and epidemiologic bias (particularly in regard to older patients), we

should have conclusive proof that screening and treatment can alter the natural history of disease before we offer mass screening tests.

Workforce Challenges in Primary Care and Nephrology

Adding routine urine dipsticks to clinical practice is fraught with logistical problems. There are not enough nephrologists in the United States to handle prevalent cases of CKD, much less to investigate screen-detected incident albuminuria; therefore, the challenge of accurately identifying patients at risk of ESRD would fall to primary care providers (23). Primary care, as presently organized, is already overtaxed. For a typical primary care physician with a 2500-patient panel, compliance with all current recommendations of the US Preventive Services Task Force has been estimated to require 7.4 h/d (24). In addition, compliance with current guidelines for the top 10 chronic conditions seen in primary care practice (of which CKD is not one) could require up to 10 h/d (25). To be successful, screening strategies must keep in mind logistical limitations of medical practice in the United States.

Guideline Recommendations

Organizations that vet screening tests have not recommended screening for albuminuria. The National Kidney Foundation Kidney Disease Outcome Quality Initiative only recommends screening high-risk groups, such as patients with diabetes or hypertension (26). The United Kingdom's National Institute for Health and Clinical Excellence also recommends screening high-risk groups and expressly discourages general screening (27). The Cochrane group has not yet conducted a review on this subject. The Agency for Healthcare Research and Quality Evidence-Based Practice Center in Minnesota has recently reviewed the evidence and found that there is insufficient evidence to recommend general screening for albuminuria, and the US Preventive Services Task Force has issued a draft recommendation to this effect (28).

Conclusion

Given the high false positive result rate of urine dipstick testing, the associated costs of inappropriate follow-up testing, the unproven benefit of treatment of microalbuminuria in otherwise healthy patients, the potential harms of screening, and healthcare system limitations, routine urine dipstick screening in the general population is not advisable (29). As primary care physicians, our perspective is that urine dipstick or other forms of urine albumin and urine protein testing should be reserved for patients with known risk factors for CKD, like diabetes. To improve identification, monitoring, and treatment, we should employ electronic clinical decision support systems to risk-stratify patients at the point of care; therefore, those patients at high risk are appropriately offered urine albumin or urine protein testing. Because only 22% of primary care physicians report that the CKD guidelines impact their CKD management, these clinical decision support systems may have major impact (30). Hospitals could implement

e-referral systems to increase access to nephrology expertise (31). Practice networks and health insurance companies could incentivize these high-technology solutions with policies and service agreements (32). As a society, it is important to pick our battles given our limited resources. For now, we should focus our combined primary care and nephrology efforts on identifying the high-risk patients who pass through our practices every day. Screening the general population may be inadvisable, but there is much that we can do to improve the care of our patients who are at high risk for CKD.

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