EDITORIAL

# Predicting Risk of Kidney Disease
## Is Risk-Based Kidney Care on the Horizon?

Sri Lekha Tummalapalli, MD, MBA; Michelle M. Estrella, MD, MHS

**Chronic kidney disease (CKD)** causes an enormous human and financial toll worldwide. In the United States alone, an estimated 37 million persons have CKD, and its incidence globally is rising.[1,2] Patients with CKD are at incrementally increased risk for major cardiovascular events as their disease progresses,[3] and several million will progress to kidney failure.[4] Early, effective management of risk factors, such as hypertension and diabetes, is imperative to prevent the development of CKD and its related adverse consequences, yet less than half of patients with hypertension in the United States attain recommended blood pressure targets.[5] An accurate tool that identifies persons at elevated risk of developing CKD may facilitate efforts to modify relevant risk factors and could be used to determine the frequency of kidney health monitoring among persons at risk of CKD.

Related article page 2104

In this issue of *JAMA*, Nelson and colleagues[6] from the CKD Prognosis Consortium used data from more than 4 million adults without diabetes and nearly 800 000 adults with diabetes from 34 multinational cohorts to develop equations that predict the 5-year risk of developing reduced estimated glomerular filtration rate (eGFR), using the standard definition of less than 60 mL/min/1.73 $m^2$. During a mean follow-up period of 4 years, 15% of individuals without diabetes and 40% of individuals with diabetes developed reduced eGFR. The models included characteristics that could be abstracted from health records: sociodemographic factors, smoking status, cardiovascular disease, hypertension, body mass index, eGFR, and albuminuria. For persons with diabetes, the model also included presence and type of diabetes medications and hemoglobin $A_{1c}$ levels.

The resulting models predicted 5-year risks of reduced eGFR among persons without and with diabetes with respective C statistics of 0.845 and 0.801, demonstrating excellent ability to distinguish an individual's likelihood of developing an eGFR of less than 60 mL/min/1.73 $m^2$ during follow-up. The median slope of observed to predicted risk was 0.94 for both models, indicating that the models were adequately calibrated to the actual risk, although only 69% of the 13 study populations had a slope of observed to predicted risk between 0.80 and 1.25. The predictive performances of these risk equations were similar, with comparable discrimination and calibration, when the more rigorous outcome of reduced eGFR confirmed by a second eGFR value of less than 60 mL/min/1.73 $m^2$ was examined and when the equations were externally validated in 9 clinical cohorts totaling more than 2 million individuals selected from the Optum Database. In additional analyses of calibration for lower eGFR end points, 5 of 13 study populations (38%) showed a slope between 0.80 and 1.25 for eGFR of less than 45 mL/min/1.73 $m^2$, and 4 of 11 study populations (36%) showed a slope between 0.80 and 1.25 for eGFR of less than 30 mL/min/1.73 $m^2$.

An important consideration in interpreting this work is that these risk prediction equations assume that key health factors have been measured, particularly eGFR. In clinical settings, these laboratory measurements may have been performed based on the physician's perception of the patient's CKD risk and thus may affect the generalizability of the risk equation. This requirement to have results of the specific laboratory measurements in the equation available may have enriched the derivation and validation cohorts for at-risk persons, leading to overly optimistic predictive performances of the equations. As with other risk prediction models, the present equations may require recalibration for use across populations with disparate baseline risks and within a specific population if the risk evolves over time.[7] Although the majority of cohorts in the derivation sample had a small proportion of black or Hispanic participants, the risk equations appeared to work well across racial and ethnic groups.

How might these new risk prediction equations be implemented to augment efforts in reversing the increasing incidence of CKD? This study by Nelson and colleagues shifts the focus from secondary to primary prevention of kidney disease—a critical step toward reducing the global burden of kidney disease. While the well-validated Kidney Failure Risk Equation (KFRE) accurately risk-stratifies patients with moderate-to-severe CKD for progression to kidney failure,[8] identifying individuals before the onset of kidney disease would present a much larger opportunity to influence disease trajectory. In placing the new equations into the broader context of CKD prevention and treatment, 2 central implications emerge from the work by Nelson and colleagues: (1) optimal prevention and management of CKD should continue advancing toward risk-based, individualized interventions; and (2) because CKD risk prediction requires kidney-specific testing, this equation can be used to develop an evidence-based approach to personalized rescreening strategies after an initial assessment.

First, risk prediction and screening strategies are unlikely to improve outcomes if not paired with effective interventions to prevent kidney disease. The risk equations developed by Nelson et al could enable primary prevention of kidney disease that is tailored to the individual patient's risk. This transformation has long been established for the primary prevention of cardiovascular disease via risk equations like the Framingham[9] and American College of Cardiology/American Heart Association Atherosclerotic Cardiovascular Disease

(ASCVD) risk scores,[10] which inform individualized risk reduction interventions, such as statin therapy.[11] For kidney disease prevention, patients could be counseled about their individualized kidney disease risk and potential interventions, such as lifestyle modification or blood pressure management, to preserve kidney health. Risk communication tools similar to those created for cardiovascular disease[12] could be used to educate patients. An important distinction between kidney and cardiovascular disease risk prediction is that different levels of cardiovascular risk determine the need for statin therapy and other specific interventions, whereas dedicated therapies for primary prevention of kidney disease are currently lacking.

However, among those identified as high-risk, treatment of CKD risk factors could be intensified by increasing the frequency of follow-up visits and implementing behavioral interventions. To be optimally effective and sustainable, risk-based care approaches to CKD prevention will need to be culturally adapted to the clinical population and accommodated to the resources available in the specific health care system. Implementation trials for CKD prevention will be needed to assess the effectiveness of such approaches to improve both processes and outcomes of care. Furthermore, these future studies should also determine the implications for older adults and for those with multimorbidity, in whom more intensive screening and preventive measures might offer reduced benefit due to lower life expectancy or different priorities of care.[13]

For health care systems, these risk equations could facilitate population health management of CKD by guiding optimal allocation of resources to persons who would most benefit. For instance, a KFRE threshold of 3% has been used to triage nephrology referrals in central Canada.[14] This strategy has significantly shortened wait times, from a median of 230 to 58 days,[14] and studies are underway to evaluate whether it improves outcomes among patients with CKD. However, the success of risk-based care allocation inherently relies on health care systems that provide incentives for preventive care and have long-term, public health perspectives. The recent US Executive Order on Advancing Kidney Health, which is based on the premise that "a system that pays for kidney health, rather than kidney sickness, would produce much better outcomes,"[15] has the potential to accelerate efforts focused on kidney disease prevention through developing new payment models and implementing regulatory mandates in addition to bolstering research and patient education.

Second, the risk prediction equations developed by Nelson et al could directly guide a risk-based approach to rescreening for CKD. For example, the American Diabetes Association currently recommends yearly monitoring of eGFR and albuminuria for patients with diabetes, regardless of prior test results, diabetes severity, or other CKD risk factors.[16] Specific 5-year risk thresholds of incident CKD could lead to recommendations for different intervals of repeat testing after an initially negative CKD screen, according to future risk of CKD. Toward this goal, shorter time horizons, such as 2-year risk, may help guide testing frequencies in future work. In addition, further refinement of prediction equations may be needed to better identify individuals at risk of eGFR of less than 45 mL/min/1.73 $m^2$ and less than 30 mL/min/1.73 $m^2$.

Although CKD screening for the general population may not be cost-effective in many health care systems, varying screening frequencies based on individual risk may improve affordability, such that a larger proportion of CKD cases could be detected for the same cost.[17] However, compared with the simplicity of yearly testing, personalized risk-based frequencies for CKD screening would be more challenging to implement within health care systems. Moreover, to develop risk-based approaches for CKD rescreening, specific thresholds for action will need to be tested and refined for different clinical practice settings. These thresholds for rescreening could be incorporated into cost-effectiveness models to estimate the costs and benefits of early CKD detection on preventing kidney and cardiovascular disease events. Ultimately, appropriate therapies must be implemented upon detection of CKD to realize the benefits of risk-based screening. To that end, decision support that is incorporated into electronic health records and integrated into the clinical workflow of primary care clinics will be essential to render personalized screening strategies for kidney disease feasible and effectual.

In the future, risk equations that integrate the prediction of both elevated albuminuria and reduced eGFR would provide a more holistic prediction of CKD, because more than 40% of persons with CKD have increased albuminuria without reduced eGFR.[18] Currently, the development of albuminuria risk equations may be limited by lack of regular urine albumin measurements, as encountered among clinical cohorts in the present study, within whom as many as 65% of individuals with diabetes were missing albuminuria measures. This observation underscores the importance of ongoing efforts to improve testing of kidney disease markers, which is essential for risk stratification and captures high-risk individuals.[19] The breadth of potential data that could further improve the accuracy of CKD risk prediction equations is rapidly expanding, including genetic risk factors and novel biomarkers, if the value of improved prediction can justify their expense and feasibility of implementation.

In summary, due to advancements from the CKD Prognosis Consortium, validated equations developed in diverse populations are available for risk prediction across the kidney disease spectrum, spanning from primary to tertiary prevention. Prevention begins with prediction, and accurate prediction facilitates testing of early prevention strategies. The challenge now begins in evaluating approaches to individualize care based on risk with the overall goal of reducing the health and financial burden of kidney disease.

ARTICLE INFORMATION

**Author Affiliations:** Kidney Health Research Collaborative, University of California, San Francisco and San Francisco VA Health Care System, San Francisco.

**Corresponding Author:** Michelle M. Estrella, MD, MHS, University of California, San Francisco, 4150 Clement St, Bldg 2, Room 145, San Francisco, CA 94121 (michelle.estrella@ucsf.edu).

**Published Online:** November 8, 2019. doi:10.1001/jama.2019.17378

## REFERENCES


1. Centers for Disease Control and Prevention. Chronic kidney disease in the United States, 2019. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention. https://www.cdc.gov/kidneydisease/publications-resources/2019-national-facts.html. Last reviewed March 11, 2019. Accessed October 28, 2019.

2. Xie Y, Bowe B, Mokdad AH, et al. Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. *Kidney Int*. 2018;94(3):567-581. doi:10.1016/j.kint.2018.04.011

3. Matsushita K, Coresh J, Sang Y, et al; CKD Prognosis Consortium. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol*. 2015;3(7):514-525. doi:10.1016/S2213-8587(15)00040-6

4. Grams ME, Chow EKH, Segev DL, Coresh J. Lifetime incidence of CKD stages 3-5 in the United States. *Am J Kidney Dis*. 2013;62(2):245-252. doi:10.1053/j.ajkd.2013.03.009

5. Wang D, Hatahet M, Wang Y, Liang H, Bazikian Y, Bray CL. Multivariate analysis of hypertension in general US adults based on the 2017 ACC/AHA guideline: data from the national health and nutrition examination survey 1999 to 2016. *Blood Press*. 2019;28(3):191-198. doi:10.1080/08037051.2019.1593042

6. Nelson RG, Grams ME, Ballew SH, et al; CKD Prognosis Consortium. Development of risk prediction equations for incident chronic kidney disease [published online November 11, 2019]. *JAMA*. doi:10.1001/jama.2019.17379.

7. DeFilippis AP, Young R, Carrubba CJ, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med*. 2015;162(4):266-275. doi:10.7326/M14-1281

8. Tangri N, Grams ME, Levey AS, et al; CKD Prognosis Consortium. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *JAMA*. 2016;315(2):164-174. doi:10.1001/jama.2015.18202

9. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117(6):743-753. doi:10.1161/CIRCULATIONAHA.107.699579

10. Andrus B, Lacaille D. 2013 ACC/AHA guideline on the assessment of cardiovascular risk. *J Am Coll Cardiol*. 2014;63(25 pt A):2886. doi:10.1016/j.jacc.2014.02.606

11. Grundy SM, Stone NJ. 2018 American Heart Association/American College of Cardiology multisociety guideline on the management of blood cholesterol: primary prevention. *JAMA Cardiol*. 2019;4(5):488-489. doi:10.1001/jamacardio.2019.0777

12. Navar AM, Wang TY, Mi X, et al. Influence of cardiovascular risk communication tools and presentation formats on patient perceptions and preferences. *JAMA Cardiol*. 2018;3(12):1192-1199. doi:10.1001/jamacardio.2018.3680

13. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA*. 2005;294(6):716-724. doi:10.1001/jama.294.6.716

14. Hingwala J, Wojciechowski P, Hiebert B, et al. Risk-based triage for nephrology referrals using the kidney failure risk equation. *Can J Kidney Health Dis*. 2017;4:2054358117722782. doi:10.1177/2054358117722782

15. Whitehouse website. Executive order on advancing american kidney health. https://www.whitehouse.gov/presidential-actions/executive-order-advancing-american-kidney-health/. Issued July 10, 2019. Accessed October 23, 2019.

16. American Diabetes Association. 10. Microvascular complications and foot care: *Standards of Medical Care in Diabetes-2018*. *Diabetes Care*. 2018;41(suppl 1):S105-S118. doi:10.2337/dc18-S010

17. Komenda P, Ferguson TW, Macdonald K, et al. Cost-effectiveness of primary screening for CKD: a systematic review. *Am J Kidney Dis*. 2014;63(5):789-797. doi:10.1053/j.ajkd.2013.12.012

18. Andrassy KM; KDIGO-KCW KDIGO 2012. Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*. 2013;84(3)(suppl):622-623. doi:10.1038/ki.2013.243

19. Sim JJ, Batech M, Danforth KN, Rutkowski MP, Jacobsen SJ, Kanter MH. End-Stage renal disease outcomes among the Kaiser Permanente Southern California creatinine safety program (Creatinine SureNet): opportunities to reflect and improve. *Perm J*. 2017;21:16-143. doi:10.7812/TPP/16-143