Predicting Risk of RRT in Patients with CKD

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Caring for patients with CKD can be difficult: clinicians must synthesize large amounts of data in short periods of time and use this information to make critical decisions. One manner in which care may be simplified is through the incorporation of risk scores in clinical practice. Long used in cardiology to estimate when the expected benefit of a therapy exceeds the possible harm, risk scores can be automatically generated in electronic health records to suggest optimal practice patterns or inform patient counseling (1,2). For example, in nephrology, the automated laboratory reporting of eGFR increased nephrology referrals, particularly among people with advanced CKD and other high-risk conditions, like diabetes mellitus and hypertension (3). The use of kidney failure risk equations among patients with CKD may similarly improve timing of referral for vascular access and kidney transplantation and has been suggested by the Kidney Disease Improving Global Outcomes (KDIGO) guideline for the management of CKD (4).

Several kidney failure risk equations are now available (5,6). Tangri and colleagues (6,7) developed a set of four- and eight-variable risk equations in two Canadian cohorts (n=3449 and n=4942 in the development and validation cohorts, respectively); these equations have now been extensively validated in diverse global cohorts (n=721,357) and are publically available (www.kidneyfailurerisk.com). In this issue of the *Clinical Journal of the American Society of Nephrology*, Schroeder *et al.* (8) propose another kidney failure risk equation developed in 22,460 Kaiser Permanente Northwest patients and validated in 16,553 patients in Colorado. The work, which builds on a previously developed model (5), incorporates age, sex, eGFR, hemoglobin level, the presence of proteinuria or albuminuria, systolic BP, antihypertensive medication use, and a modified Diabetes Complications Severity Index to predict 5-year risk of progression to a requirement for dialysis or kidney transplantation among patients with eGFR<60 ml/min per 1.73 m^2.

The study by Schroeder *et al.* (8) provides several interesting observations. First, the only completely new variable in the current versus previously developed Kaiser Permanente risk equation was albuminuria (although the definitions of diabetes mellitus and hypertension were enhanced). Other covariates, such as nonsteroidal anti-inflammatory drug use and body mass index, were tested, but both were weak predictors and not included in the final model. This is consistent with recent publications which suggest that elevated body mass index may not be a strong risk factor for CKD progression, particularly in the modern era when concomitant comorbid conditions are often well controlled (9–11). Second, a simplified model that included eGFR, albuminuria/proteinuria, age, and sex explained 94% of the variation in the full model. This is remarkable given that albuminuria, one of the strongest risk predictors for ESRD (12), was incorporated as a binary variable (above or below 30 mg/g), which lessens its predictive power. The strong performance of the simplified model is consistent with findings in the work by Tangri *et al.* (6), which found that an eight-variable model only marginally improved the performance of a model on the basis of eGFR, albuminuria, age, and sex. Third, despite their CKD status, 26% of the patients in the development cohort were missing an assessment of urine protein.

Kaiser Permanente is a leader among health systems in incorporating evidence-based practice and technology into delivered health care, and therefore, the suboptimal rate of albuminuria testing is disappointing. Evaluation of urine albumin is important for not only risk assessment but also treatment because antihypertensive medication choice can hinge on whether a given patient has significant albuminuria (4). This finding should renew efforts to ensure adequate albuminuria testing in high-risk patients at a system-wide level.

Depending on the profile of the underlying population and the intended reaction to high-risk estimates, prediction models covering a range of time horizons may be necessary. The KDIGO guideline recommends referral for vascular access when the 1-year risk of ESRD exceeds 10%–20% (4), but very few individuals in the Kaiser Permanente cohorts had the approximately equivalent 5-year predicted risk of >50%. Indeed, ESRD occurred in only 4.7% of the development cohort and 2.6% of the validation cohort over the subsequent 5 years. A risk score with a longer-term time horizon used in a lower-risk patient population, such as that of Kaiser Permanente, may be more helpful in targeting patients for enhanced services, such as pharmacist outreach or patient education programs. A shorter-term prediction tool applied in a high-risk population may be more useful in guiding referral for RRT preparation.

The risk equation developed by Schroeder *et al.* (8) showed excellent performance in both discrimination and calibration, and Kaiser Permanente has the benefit of being able to implement an equation that was developed in its own system. Application to external health systems might require calibration, similar to work in non-North American countries, because absolute risks

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often vary across settings (7,13). For example, there exists a 4- to 5-fold variation in end-stage disease risk between different cohorts of patients with CKD even after taking into account differences in the prevalence of known risk factors (7). Like the original kidney failure risk equation developed by Tangri *et al.* (6), the Kaiser Permanente equation was developed in a homogeneous, low-risk population with little nonwhite representation. Death was not available, precluding the use of competing risk models, and thus, cumulative incidence of ESRD may be overestimated (14). External implementation of the kidney failure risk equations might be preceded by comparison of the existing equations using historical data—we expect risk rankings to be similar given the shared risk factors—and if necessary, calibration to account for system-specific variation in absolute risk of ESRD.

So, where do we stand? The Kaiser Permanente team should be commended for working to incorporate epidemiology into clinical practice. The majority of patients with CKD in the general population will not progress to ESRD. Use of a kidney failure risk score could achieve not only a more personalized approach to patient counseling and referrals but also lower costs at a health system level. Patients who are at exceptionally low risk may not require the consultation of a nephrologist at all, and risk classification among higher-risk individuals could result in more timely provision of services in some patients and avoidance of unnecessary procedures in others. These benefits, however, are as yet hypothesized, and the next steps should combine implementation of risk reporting with evaluation of the risk scores' effect on patient outcomes and system costs in routine practice conditions. Comparison groups can be historical or contemporaneous and randomized or not. Randomized trials of automated reporting of kidney failure risk equations would provide the clearest evidence of the benefit (or unintended consequences) of the use of kidney risk scores in clinical practice.

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