Overview
As to Diseases, Make a Habit of Two Things — To Help, or at Least Do No Harm

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Clase et al. recently questioned a recommendation that clinical laboratories report a GFR value calculated by either the Cockcroft-Gault or the MDRD equation, when a serum creatinine (S_{cr}) is ordered (1,2). The calculated GFR is intended to increase the early recognition and treatment of chronic kidney disease (CKD). Their concern is based on their calculation of Cockcroft-Gault and MDRD estimates of GFR for a representative, cross-sectional sample of the nondiabetic adult population of the United States (2). They found that estimates of CKD prevalence, defined as a GFR of less than 80 ml/min per 1.73 m^2, predicted by the MDRD equation varied between 29.1% for black men to 68% for white women. Cockcroft-Gault prevalence estimates ranged between 25% for white men and 53% for white women. The MDRD equation consistently predicted a greater prevalence of CKD for whites compared with blacks, whereas the Cockcroft-Gault equation predicted a higher prevalence for white women compared with black women and the converse among men. These race-specific patterns were preserved when CKD was stratified into mild (60 to 79 ml/min), moderate (30 to 59 ml/min), and severe (<30 ml/min) levels of function.

These are unexpectedly high and counterintuitive CKD prevalence estimates for the US population, and they led Clase et al. to recommend further study of the equations before their widespread adoption and use (2). Coresh et al. respond to these concerns in this issue of JASN (2a). They call attention to the possibility that Clase et al.’s results may be due to differences between NHANES III and MDRD S_{cr} values and recommended that the calculation adjust the NHANES III S_{cr} values so that they are commensurate with those used to derive the MDRD equation. This adjustment reflects their reanalysis of stored NHANES III sera in which they found that reanalyzed S_{cr} values were lower than those reported originally by the NHANES III laboratory (3). They also reported systematic variations in S_{cr} measurement on the same specimen of NHANES III sera between the MDRD and NANES III laboratories wherein MDRD S_{cr} values were lower than the new NHANES III values. As noted by Coresh et al. between-laboratory and within-laboratory variation poses a major barrier in the application of the MDRD equation to populations other than those that use the MDRD or comparable laboratory.

Adjusting the MDRD equation to account for systematic variations in S_{cr} may not, however, fully account for the unexpected prevalence patterns of CKD reported by Clase et al. They note in reply to Coresh et al. that, after adjustment for differences in S_{cr}, nearly 18% of the US population had a GFR less than 80 ml/min per 1.73 m^2 and that 81% of these individuals had a GFR between 60 and 79 ml/min per 1.73 m^2 (3a). Further, accounting for a constant difference in S_{cr} will not reverse the increased prevalence of CKD among white compared with black Americans.

What else then might account for the unexpectedly high prevalence of CKD predicted by the MDRD equation, and are further adjustments needed for the equation before it is used? Although we need further study to answer these questions, two recent articles in JASN outline avenues of investigation (4,8). First, it is possible that the CKD prevalence estimates are accurate. As pointed out by Coladonato et al. (4), this raises a major question about the prognostic implications of an estimated GFR for different demographic groups in the US population. Specifically, given the disproportionate risk of ESRD among African Americans, what prognostic information do we gain from GFR estimates that tell us the bulk of the CKD problem is in the white population? How should we use this information in ordering patient management priorities? These are important questions to answer before routinely using these estimating equations.

Second, it is possible these equations need a further fix beyond adjustment for S_{cr} before they are ready for use in the general population (5). The MDRD and Cockcroft-Gault equations are certainly reproducible, in that both accurately predict renal function for new members from the population used to derive the equation (6,7). However, a general problem with prediction equations like the MDRD equation occurs when they are applied to other populations with different characteristics. This equation characteristic is called transportability, and it can be assessed by comparing GFR values estimated by the equation to GFR values measured in populations with different demographic characteristics and levels of renal function (5). Problems with transportability are often encountered with other multivariate prognostic equations, and these problems can often be easily corrected by adjusting the equation.

Transportability can be assessed in several ways (5). Two
transportability measures are historical and method transportability. Historical transportability is the expectation that predicted GFR will be comparable for similar populations separated by time. The variation over time reported by Coresh et al. for \(S_{\text{cr}}\), which would result in different estimates of GFR for the same renal function, is an example of lack of historical transportability for the MDRD equation (3). Methodologic transportability is the expectation that predicted GFR for the same (or similar) population will be comparable when different laboratories are used to measure \(S_{\text{cr}}\). The laboratory-to-laboratory variation in \(S_{\text{cr}}\) demonstrated by Coresh et al., which would lead to different GFR estimates for the same individual at one point in time, is an example of lack of methodologic transportability for the MDRD equation (3).

A more important issue for the MDRD equation is spectrum transportability. Spectrum transportability is the expectation that GFR will be accurately estimated when the equation is used in different populations. Spectrum transportability may be lost when an equation is used to extrapolate beyond the range of GFR used to derive the equation. A study by Bostom et al. (8) illustrates the lack of spectrum transportability for both the MDRD and Cockcroft-Gault equations. They compared measured and estimated GFR for both equations in patients with an average iohexol GFR of 109 ml/min per 1.73 m² and a range of 88 to 138 ml/min per 1.73 m². This GFR distribution contrasts with that for subjects used to derive the Cockcroft-Gault equation, where the mean creatinine clearance was 72.7 ml/min, and with that for the population used to derive the MDRD equation, where the mean GFR was 39.8 ml/min per 1.73 m². Bostom et al. (8) found that actual GFR in their subjects was on average underestimated by the Cockcroft-Gault equation by 24% (−26.5 ml/min per 1.73 m²) and by 42.2% (−46.0 ml/min per 1.73 m²) by the MDRD equation used by Clase et al. These observations raise substantial concern about the spectrum transportability of either equation to populations characterized by normal renal function.

If further study in other populations with normal renal function also finds a problem with spectrum transportability, then the MDRD equation may require further adjustment before it can be recommended for general use. This can be easily ascertained by expanding the range of GFR used in MDRD (or other) equation validation studies and identifying the changes in the equation’s parameters that improve fit.

Is the apparent lack of transportability of the MDRD equation of sufficient concern to warrant further study before routinely reporting GFR for healthy populations? Physicians are expected to base important diagnostic and therapeutic decisions on GFR values between 89 and 60 ml/min per 1.73 m². NKF guidelines recommend that a patient with an estimated GFR between 89 and 60 ml/min per 1.73 m² should be evaluated for markers of kidney damage, including hypertension, proteinuria, other abnormalities on urine testing, pathologic abnormalities, or abnormal kidney imaging tests. If abnormalities on one or more of these tests are present, the patient has mild CKD and the clinician is expected to provide a renal diagnosis, implement measures to slow progression of kidney disease, evaluate and intervene to reduce risk of cardiovascular disease, and treat any attendant comorbid conditions (9). Further, patients with mild CKD should be monitored frequently for progression of renal failure.

In contrast, patients who have a GFR between 89 and 60 ml/min per 1.73 m² without an abnormal test result are classified as having low GFR. What are the possible consequences of classifying large numbers of otherwise healthy people into this category of low GFR, as might happen if the current estimating equations do misclassify people in the GFR range of normal renal function? Again, in the absence of further study, we can only speculate about the possible avoidable health costs that this misclassification may impose on otherwise healthy people. Potential adverse consequences include the risk of inappropriate medication dosing based on dose adjustment for kidney function. Other potential adverse consequences include psychological distress and depression from labeling effects (telling healthy people they are ill or different) and impact on future insurability. Substantial misclassification of healthy people as low GFR may also adversely impact the healthcare system by increasing demands for testing and follow-up for nonexistent decreased renal function.

Should we abandon the current generation of estimating equations? The answer to this is unequivocally no. All of the commentators agree that we need a more accurate method to estimate GFR. Should we determine with further study if and how the MDRD and other equations should be fixed for use in the general population? The answer to this question is unequivocally yes and entails several steps: (1) a uniform standard for \(S_{\text{cr}}\) measurement must be adopted; (2) laboratory-to-laboratory variation in \(S_{\text{cr}}\) measurement must be reduced; (3) the MDRD or other candidate estimating equations must be validated using this \(S_{\text{cr}}\) standard; (4) the transportability of the resulting GFR estimating equations should be established in geographically and demographically disperse populations with a broad range of renal function (this might be accomplished by identifying and using study populations with existing GFR measurements in validation studies); (5) if the transportability of the MDRD (or other) equation is not satisfactory, the investigators should determine, using the same statistical models and parameters, which of the original parameter estimates “failed” to capture the relationship between \(S_{\text{cr}}\) and GFR and provide a revised equation; (6) if a valid, broadly transportable estimating equation continues to predict unexpectedly high rates of mild CKD in the US population using NHANES data, then a research program to understand the implications of this observation should be conducted; (7) randomized trials should be conducted to demonstrate that using an estimating equation improves recognition and management of CKD.

In conclusion, Clase et al.’s opinion that “laboratory-generated clearance reports cannot be recommended without further study” seems pragmatic and reasonable. We have been abjured since medicine’s inception to “As to diseases, make a habit of two things — to help, or at least do no harm.” (Hippocrates, Epidemics). It is not clear that the current GFR estimating equations are helpful in their present formulation when used in the general population, and it is distinctly possible that they may do harm if we don’t better understand them. The steps
necessary to resolve this uncertainty can be accomplished largely by insisting on more extensive documentation of the generalizability of the MDRD equation, and there is no compelling reason for us not to do so.

References