Serum creatinine is measured more than 280 million times annually in the United States, and more than 80% of clinical laboratories now report an estimated glomerular filtration rate (GFR) when serum creatinine is measured.\textsuperscript{1,2} The most commonly used equation is the Modification of Diet and Renal Disease (MDRD) Study equation. Recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) developed and validated a new equation, the CKD-EPI creatinine equation, which uses the same variables as the MDRD Study but is more accurate compared with measured GFR\textsuperscript{3}; however, as for other diagnostic tests, other criteria are also important in clinical practice and public health, including detecting disease and predicting prognosis.

**Why Use GFR Estimating Equations Rather Than Serum Creatinine?**
Clinical assessment of kidney function is part of routine medical care for adults; however, measuring GFR is cumbersome to perform, and, therefore, GFR is often estimated from the serum concentration of endogenous filtration markers. GFR estimating equations incorporate demographic and clinical variables as surrogates for the non-GFR determinants of these filtration markers.\textsuperscript{10} Age, sex, race, and body weight are surrogates for creatinine generation from muscle, which affects serum creatinine concentration independently from GFR. GFR estimating equations provide a more accurate estimate of measured GFR than the serum level of the filtration marker alone. In addition, GFR estimates are provided in the same units as measured GFR, thereby simplifying clinical decisions based on the level of kidney function.

An important consideration when evaluating the performance of estimating equations is the assay used in their development. The most common cause of inaccuracy in creatinine assays is interference by noncreatinine moieties in the serum that react with the creatinine assay, leading to overestimation of the serum creatinine concentration, especially at low values. More accurate creatinine assays, traceable to gold-standard creatinine measurements, are now available, and a creatinine standardization program has been implemented in all clinical laboratories throughout the United States.\textsuperscript{11} The effect of standardizing creatinine assays will vary among clinical laboratories but on average will lead to lower values for serum creatinine and higher values for eGFR compared with before standardization. The MDRD Study equation has now been reexpressed for use with standardized creatinine.\textsuperscript{3,12} Variation among creatinine assays is relevant when categorizing people by level of GFR, since a systematic difference in assays, even if it causes only a small difference in eGFR, can lead to reclassification to a different category.\textsuperscript{13} Thus, when determining prevalence of CKD or categories of eGFR, attention to the creatinine assay used is particularly important. When comparing GFR estimating equations, it is essential to use the form of the equation that is expressed for the serum creatinine assay used in the study population.

**How Does the CKD-EPI Equation Compare With the MDRD Study Equation?**

**Accuracy Compared With Measured GFR**
The MDRD Study equation was developed in 1999 with data from a study of 1628 people using nonstandardized serum
creatinine assays and reexpressed for use with standardized creatinine in 2006.12,14 Because it was developed in a population with CKD, it underestimates measured GFR at higher levels. The CKD-EPI equation was developed in 2009 using data from 8254 people with and without CKD in 10 studies and validated in 3896 people in 16 separate populations.3 Creatinine assays for all studies were standardized to higher-order reference materials15 When used with standardized creatinine assays, the CKD-EPI equation generally yields higher levels for eGFR than the MDRD Study equation, especially for younger people, white individuals, and women. In the original report, the CKD-EPI equation was more accurate than the MDRD Study equation, especially at higher ranges of GFR.2,3 Based on this finding, the CKD-EPI investigators concluded that the CKD-EPI equation should replace the MDRD Study equation in clinical practice and that GFR estimates should be reported throughout the range. Since then, there have been several publications that compare the CKD-EPI and MDRD Study equations, which have generally confirmed the greater accuracy of the CKD-EPI equation in estimating measured GFR.16

### Detecting and Staging Disease

In principle, decreased GFR in acute and chronic kidney diseases is preceded by alterations in structure that can be detected by pathological disturbances or makers of kidney damage. Biopsies are usually not obtained in clinical practice, and markers of kidney damage are not sensitive for all kidney diseases, thus, in many patients, decreased GFR is the earliest sign of kidney disease. Widespread reporting of eGFR simplifies the detection GFR <60 mL/min/1.73 m², one of the criteria for CKD.

Higher eGFR using the CKD-EPI equation would reduce the false-positive diagnoses of CKD based on eGFR compared with the MDRD Study equation. The CKD-EPI investigators compared the eGFR distribution and CKD prevalence using the CKD-EPI and MDRD Study equations among 16,032 adult participants in the US National Health and Nutrition Examination Surveys (NHANES 1999–2006), a nationally representative survey of noninstitutionalized persons in the United States.3 Median eGFR was higher with the CKD-EPI equation compared with the MDRD Study equation (94.5 versus 85.0 mL/min/1.73 m², respectively), and CKD prevalence was lower (11.6% versus 13.1%, respectively).

In the study by McAlister et al, prevalence of CKD (eGFR <60 mL/min per 1.73 m²) was 51% using the MDRD Study equation and 55% using the CKD-EPI equation. Overall, the CKD-EPI equation reclassified 3760 (18%) patients to different GFR categories than the MDRD Study equation. Of those reclassified, 18% were placed in a higher GFR category, and the remaining 82% were placed in a lower GFR category. We suspect that the higher prevalence of CKD using the CKD-EPI equation and more frequent reclassification to lower rather than higher GFR categories in this study likely reflects an error arising from using the CKD-EPI equation with nonstandardized creatinine assays. The CKD-EPI equation is expressed for standardized values, which were 5% lower than nonstandardized values in the research laboratory used for the development of the MDRD Study and CKD-EPI equations. The form of the MDRD Study equation used in the analyses by McAlister et al is appropriate for use...
with nonstandardized creatinine values, which is appropriate, since it is most likely that among the 25 studies included in MAGGIC, the majority of the creatinine measurements were performed before the standardization program; however, using these higher creatinine values in the CKD-EPI equation would lead to a lower eGFR than was intended by the equation. Other studies have accounted for this difference in creatinine assays by reducing the nonstandardized serum creatinine assays by 5% for use with the MDRD Study and CKD-EPI equations that are expressed for standardized creatinine, thus enabling a “fair comparison” of eGFR computed using both equations.

Predicting Prognosis
Decreased GFR is now a well-established risk factor for cardiovascular disease and mortality, as well as kidney failure. There is now an increasing literature on the advantage of the CKD-EPI equation compared with the MDRD Study equation for prediction of risk in general population samples, patients at high risk for CKD, and in patients with cardiovascular disease (Table). In these studies, the individuals reclassified to higher eGFR using the CKD-EPI equation generally had lower risk than those not reclassified, while those reclassified to lower eGFR generally had a higher risk than those not reclassified.

The current paper contributes to the literature by comparing these equations in patients with heart failure, and overall, the results seem to confirm the findings from the previous studies. The CKD-EPI eGFR provided a better risk prediction than the MDRD Study equation [AUC of 0.644 (0.635 to 0.653) versus 0.634 (0.626 to 0.644)]. For example, in those reclassified from the MDRD Study equation eGFR category (45 to 59 mL/min per 1.73 m², CKD stage 3) to a higher eGFR category (60 to 74 mL/min/1.73 m²), no CKD) using the CKD-EPI equation, the mortality rate was 101 (95% confidence intervals, 74 to 135) per 1000 person years, which was lower than those not reclassified (142 [133 to 151]) and those reclassified to a lower eGFR category (204.9 [18–229]). Thus, despite the error in creatinine calibration, the study by McAlister et al is consistent with other studies in that patients with lesser risk appear to be reclassified to higher GFR, and patients with higher risk appear to be reclassified to lower GFR.

Where Do We Go From Here?
The CKD-EPI creatinine equation is currently the most accurate method for estimating GFR for diverse populations. Compared with the MDRD Study equation, the CKD-EPI equation permits more accurate GFR estimation, fewer false-positive diagnosis of CKD, lower prevalence estimates for CKD, and more accurate risk prediction for adverse outcomes. This accumulating evidence supports the recommendations of the CKD-EPI investigators that the CKD-EPI equation should replace the MDRD Study equation for general use. There are few drawbacks to more widespread implementation of the CKD-EPI equation. Implementing a new GFR estimating equation requires an ongoing educational effort to understanding its strengths and limitations, similar to advances in other diagnostic tests. Since the same 4 variables are used, the impact on information systems is minimal, and the differences observed by clinicians will be equivalent to reporting any analyte using a new assay.

We have come a long way since serum creatinine alone was used for GFR estimation. Despite these improvements in GFR estimation, much uncertainty remains. More research is required to determine the usual levels of GFR and non-GFR determinants of creatinine in representative populations, including the elderly and diverse racial and ethnic groups, and to determine the optimal application of GFR estimates in clinical medicine and public health. The availability of additional filtration markers that are less dependent on muscle mass, such as cystatin C, offers the promise of even more accurate GFR estimates.

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