This year, 2016, marks the 40th anniversary of the Cockcroft and Gault formula. During four decades we have tried to overcome the limitations of relying on serum biomarkers as indicators for kidney function. With estimating equations that include variables such as age, sex, race and body size, repeated attempts have been made to account for unmeasured physiologic processes that affect the serum concentration of creatinine aside from glomerular filtration rate (GFR). Another GFR estimating equation appears in this week’s issue of Nephrology Dialysis and Transplantation [1]. However, whereas GFR estimation is gradually settling into clinical practice [2, 3], appreciation of its prevailing limitations and of the differences between available equations remains limited, even among nephrologists [4].

An accurate equation provides an estimate of the measured GFR (mGFR) that is unbiased—average estimated GFR (eGFR) for a group equals the mGFR—and precise—for an individual, the mGFR is close to the eGFR. Improvements in model development and standardization of creatinine measurement using methods traceable to isotope-dilution mass spectrometry (IDMS) have served to reduce the overall bias, but bias within subgroups and precision overall have remained an inescapable truth. Differences in non-GFR determinants of creatinine between groups of people may heavily bias estimates within those groups. For example, in vegetarians, patients with a muscle disease or people who have had a limb amputation, creatinine generation may be low, causing systematic overestimation of GFR-related determinants of serum creatinine concentration, such as creatinine generation and distribution volume. This further enhances variability of the point estimates in an unpredictable manner. As a consequence, at each point of the regression line that links mGFR to eGFR, there is substantial variability in mGFRs. For the individual estimation and each group of people may heavily bias estimates within those groups. For example, in vegetarians, patients with a muscle disease or people who have had a limb amputation, creatinine generation may be low, causing systematic overestimation of GFR-related determinants of serum creatinine concentration, such as creatinine generation and distribution volume. This further enhances variability of the point estimates in an unpredictable manner. As a consequence, at each point of the regression line that links mGFR to eGFR, there is substantial variability in mGFRs. For the individual estimation and each
point on the regression line, precision is poor, as it is impossible to know how much or in which direction the true GFR deviates from the average mGFR (Figure 1). This imprecision might have consequences for CKD classification and for dose adaptation. From Table 5 of Pottel et al. [1], it is apparent that there is substantial misclassification (~30%) of patients in the different subgroups of CKD when using eGFR.

The Full Age Spectrum (FAS) equation (1) apparently has the advantage that it intrinsically adjusts for differences in distribution of serum creatinine in different age- and gender-specific populations. However, other equations try to achieve this too, be it with other adjustments. The major problem is that even within a given age and gender group, differences in creatinine generation and distribution volume exist. Even within the same person, creatinine generation (e.g., muscle wasting due to acute illness) and distribution (peripheral oedema in heart failure or sepsis) may vary over time, resulting in changes in serum creatinine that do not reflect accompanying changes in GFR. Of course, the average nephrologist will know that in a cachectic 80 year old, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation will overestimate mGFR, as muscle mass to generate creatinine is much below average in this patient. However, those less familiar with eGFR equations most likely will not take this into account and might be inappropriately confident about the value obtained. As an example, it is worth mentioning that in an example given by Pottel et al. [1] in fact the eGFRs of 13 mL/min/1.73 m² and 18 mL/min/1.73 m² as obtained with the two formulae are to be considered as ‘the same eGFR’. Indeed, both are included in the P30 confidence interval around the true measured value and thus represent the same GFR.

Given the above, a universal ‘Swiss army knife’ eGFR equation with creatinine and just a few demographic variables will always remain an illusion.

In the current paper, the authors set out to remedy the abrupt changes in eGFR that occur when one equation is swapped for another, especially at 18 and 70 years of age, when logic would request a swap from one equation to another. Apparently they succeeded in this goal by adjusting for ‘age and sex’ at the level of the serum creatinine concentration rather than at that of the GFR. However, the problem they tried to solve may not be that relevant. The knowledgeable clinician is unlikely to use the Schwartz formula in an 18 year old measuring 180 cm and weighing 80 kg, as he/she knows this is inappropriate. The CKD-EPI equation may provide more accurate results for a healthy, active and well-nourished 75 year old, and BIS-1 might be more performant for an emaciated 50-year-old cancer patient. The different results obtained with different formulae are thus not an inherent problem of the different formulae, but rather of their inappropriate use. As explained above, eGFR equations can only adjust for ‘mean values’ of creatinine generation and metabolism for a specific group of people of a certain age, sex and race. The same serum creatinine concentration can reflect substantial differences in creatinine generation, distribution volume or GFR. No formula will ever incorporate deviations from that mean within those different age, sex and race categories without introducing new variables that capture the residual variability in creatinine generation and metabolism. Adding this extra granularity comes at the expense of practicality. Equations become more complex, additional variables need to be measured and labs can no longer automatically report eGFR because they lack the clinical data required for its calculation. The FAS equation does not solve this problem, as the Q-values used to normalize serum creatinine concentrations within same age and sex groups are likely to be specific for specific populations. It is unclear whether Q-values will be applicable to all ethnicities, or different subgroups such as people with diabetes.

**FIGURE 1:** (A) Regression line between estimated glomerular filtration rate (eGFR) on the x-axis and measured GFR (mGFR) on the y-axis. There is a very strong linear association between eGFR and mGFR. However, for a single eGFR value (red line), there is a distribution of potential mGFRs. As is depicted in (B), which is a cross-section on the red line, the probability of the mGFR fitting with a given eGFR (in this example of 33 mL/min) being 18 or being 70 mL/min is equal, although the probability of both these values is much lower than those of e.g. 30 or 40 mL/min. However, for the individual patient, it is impossible to know which is the exact mGFR fitting with this eGFR. The normal distribution shown in the figure represents the ideal situation. In real life, the distribution is even more dispersed and non-normal, because of the presence of factors that determine serum creatinine independent of GFR.
malnutrition, cancer or obesity. In the FAS equation, the problem of selecting the appropriate formula is replaced by the problem of selecting the appropriate set of Q-values. When the Q-values are changed, the eGFR will also 'jump'.

The Cockcroft and Gault equation estimates creatinine clearance, whereas the Modification of Diet in Renal Disease (MDRD) equation and more recent equations estimate GFR. Since creatinine is not only eliminated by glomerular filtration, but also by tubular secretion, creatinine clearance and GFR are not the same. This leads to the philosophical question: what is kidney function? Even if we limit it to the kidneys’ role in detoxification and ignore their hormonal functions, this question is difficult to answer. There are many different uremic toxins. Most of these substances are not handled by the kidneys in the same way as creatinine or urea, and their clearance is poorly associated with eGFR [5, 6]. GFR is thus a poor and non-reproducible representation of what really matters, i.e. removal by the kidneys of toxic waste products. That GFR does not equal kidney function is also problematic when it is used to adapt medication dosage, as most medications have some degree of tubular handling. Kidney function estimating equations have been extensively studied and compared in different patient groups within the context of drug dosing [7]. The comparison of these different formulae in the setting of dose adaptation is complicated by the use of different patient populations for the evaluation, and the lack of data relating differences in modelled and measured pharmacokinetic data as obtained by these different equations. As a consequence, there is no consensus as to which equation is best used for dose adaptation in patients with impaired kidney function [8]. In addition, dose adjustment recommendations as available in package inserts are mostly based on Cockcroft and Gault, whereas most laboratories nowadays report MDRD or CKD-EPI. As a side note, Cockcroft and Gault is not intended to be used with IDMS-traceable creatinine assays.

Pottel et al. [1] use GFR as the gold standard for kidney function. However, in their study cohort, GFR was measured using different methods as the gold standard in different subsamples, which all have their own inaccuracies and do not lead to comparable results among themselves [9]. In addition, serum creatinine was measured using different methods, be them all IDMS traceable. However, enzymatic determination of creatinine was not used in all of them. Whereas the introduction of IDMS-traceable creatinine was a step forward for the Jaffe assays, this method is still considered inferior to enzymatic creatinine determination, especially in non-healthy populations [10–12].

In conclusion, from their intrinsic nature, equations for estimating kidney function based on current serum biomarkers cannot be universal, as they not only reflect renal excretion but also generation. As a consequence, they inherently will perform better in some and worse in other populations. The user should be aware of the underlying assumptions and the specific properties of the population in which the equation has been predominantly validated to ensure that the equation is fit for the patient in front of him. Overly confident and far-reaching decisions based solely on single eGFR results, for example, for dose adaptation or for start of dialysis [13], should be avoided.

Because of this lack of a ‘Swiss army knife’ equation, the clinical and theoretical skills of the nephrologist will always be necessary for correct evaluation and appreciation of kidney function in individual patients.

**CONFLICT OF INTEREST STATEMENT**

The authors declare they have no conflict of interest in relation to the content of this article.

(See related article by Pottel et al. An estimated glomerular filtration rate equation for the full age spectrum. Nephrol Dial Transplant 2016; 31: 798–806)

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