On first reading, the report by Spanaus et al. (1) in this issue of Clinical Chemistry might be dismissed as just another comparison of serum biomarkers of glomerular filtration rate (GFR); however, the data and conclusions should stimulate a reevaluation of the widespread professional misconception that serum creatinine is an insensitive biomarker of GFR and an affirmation of its role in the diagnosis and monitoring of renal disease.

Healthy renal function is essential for the maintenance of physiological homeostasis. It is therefore surprising that without GFR measurements the clinical manifestations of kidney failure remain largely silent until renal function is so low that the patient may be in end-stage renal disease. Early palliative treatments for kidney disease, including the suggestion that patients should be “rigidly dieted to the exclusion of strong meats and drinks” (2), were changed profoundly with the introduction of hemodialysis and renal transplantation. These clinical interventions afforded the initial impetus for clinical laboratories to provide accurate routine measurements of GFR, a momentum consolidated by the increasing prevalence of kidney disease (3) and the appreciation of kidney function in determining cardiovascular disease risk (4).

Formal measurements of GFR, particularly standard renal-clearance techniques with urine collection, are, by their very nature, invasive, time consuming, and costly. As renal function declines, however, the serum/plasma concentration of any analyte produced in the body at a relatively constant rate and removed exclusively by glomerular filtration will increase as a reciprocal function: GFR = (U_x × V)/P_x, where (U_x × V) is the urine excretion rate of analyte x and P_x is the plasma concentration of x (i.e., GFR ≈ 1/P_x). Consequently, simple serum/plasma biomarkers for routine GFR measurement are especially attractive.

Historically, the serum urea concentration was considered a useful biomarker of GFR, but high tubular back diffusion and the dependence on protein intake and hydration made interpretation difficult. The renal clearance of creatinine has a long history as a measure of GFR (5), but it was not until the introduction of analytical techniques, based on the original Jaffe chemistry, incorporating continuous-flow dialysis or detergents enabling direct serum measurement that serum creatinine became the almost universal biomarker of choice for GFR (6). Over the last 40 years, the clinical importance of serum creatinine measurements in diagnosing renal disease and then enabling accurate monitoring of disease progression cannot be over emphasized. The development of formulae for estimating GFR (7) and disease staging (8) based on serum creatinine reiterate the continuing importance of this biomarker.

Why, then, is the professional perception of serum creatinine so negative? It was recognized from the earliest studies that approximately 28% of the renal clearance of creatinine in humans is due to tubular secretion (5). Consequently, drugs that inhibit the tubular secretion of creatinine [e.g., trimethoprim and cimetidine (9)] cause a GFR-independent increase in serum creatinine. Similar problems of interpretation arise from changes in the creatinine-production rate, with observed increases in response to therapeutics [e.g., growth hormone and fenofibrate (10)] and physiologically reduced production in liver disease. Analytically, the situation is even more problematical, with interferences from “noncreatinine chromogens,” despite the introduction of kinetic rather than end-point assays, that not only have been a source of contention but also, until recently, have fueled a lack of consistency among kit manufacturers (11). The vital evidence underlying our negative perception of serum creatinine, however, is the data reported by Shemesh et al. (12), who pointed out that the creatinine concentration remained within the reference interval in a substantial proportion of patients with a highly compromised GFR. This finding severely questioned the value of serum creatinine, particularly in the early diagnosis of renal disease, in which the data were misinterpreted as indicating that creatinine concentrations do not increase until the GFR has fallen by 50% (13), creating a “creatinine-blind range.” Consequently, research has been directed toward finding “an ideal marker of GFR” (13). Several proposed markers, including cystatin C, β-trace protein, and symmetric dimethylarginine, have

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been presented as superior to serum creatinine. The pressure to change to new serum biomarkers of GFR becomes ever more vocal.

Spanaus et al. (1) compare the performance of 2 low molecular weight protein markers, cystatin C and β-trace protein, with serum creatinine for the diagnosis, disease staging, and prediction of progression in a 227-patient cohort with primary nondiabetic chronic kidney disease. Formal GFR was measured by iohexol clearance. The authors provide a detailed discussion of the limitations of their study, but their conclusions that the 3 biomarkers are equivalent, both in terms of diagnostic performance—even for minor degrees of deterioration of renal function—and in terms of risk prediction for progression, should help to improve our perception of serum creatinine. The authors provide unequivocal evidence that the concept of a “creatinine-blind range” is false. Any serum biomarker of GFR must obey the laws of physics: As the GFR declines, the serum concentration should increase. The fact that the relationship between serum concentration and GFR is a reciprocal function explains how the relatively small changes in concentration that occur in the early stages of renal function decline are followed by an accelerating increase. Consequently, for decades nephrologists in clinical practice have monitored the rate of progression of renal disease in patients by simply plotting the reciprocal of the serum creatinine concentration against time. This reciprocal function is not unique to creatinine but is true for any biomarker of GFR. The physics is confirmed by Spanaus et al. (1) in the disease staging according to Kidney Disease Outcomes Quality Initiative guidelines. As the GFR falls further at each stage, the concentrations of the 3 biomarkers increase proportionally from 91 μmol/L (1.03 mg/dL) to 333 μmol/L (3.77 mg/dL), 0.91 mg/L to 3.51 mg/L, and 0.73 mg/L to 2.88 mg/L, for creatinine, cystatin C, and β-trace protein, respectively.

Further exploration of the discrepancy between our perception of serum creatinine and the conclusions of Spanaus et al. (1) provides an insight into how we interpret laboratory tests and evaluate new biomarkers. Publications promoting new serum biomarkers of GFR have tended to use ROC curve analysis to demonstrate better, usually only marginally, diagnostic performance; however, diagnosis represents only one of the clinical applications of measuring serum creatinine. A clinically crucial situation in which creatinine is considered both diagnostically sensitive and reliable is the monitoring of graft function after renal transplantation, for which alterations in the dosing of immunosuppressive drugs are based on small changes in the serum creatinine concentration, usually within the reference interval. The explanation for the contradiction to our perception lies in an understanding of biological variation, a fundamental concept in clinical chemistry. In their seminal report on biological variation in serum creatinine (14), Gowans and Fraser demonstrated that the biological variation of serum creatinine is very low, approximately 4%, within any individual; consequently, application of a routine assay with an analytical variation of <2% enables very small changes in GFR to be identified. The implicit conclusions are that applying a reference interval for serum creatinine is inappropriate, thereby resolving the apparent incongruity of the Shemesh data (12), and that longitudinal monitoring of serum creatinine in any individual will ensure early detection of GFR decline and incipient renal disease. This example of truly personalized medicine in which reference intervals do not apply is applicable only when the biological variation of the analyte is low and analytical methods with the appropriate imprecision are available.

Unfortunately, this simple truth is not universally appreciated. In the example provided to justify the insensitivity of serum creatinine, the 50% decrease in GFR is associated with a creatinine increase from 53 μmol/L to 106 μmol/L (0.60 mg/dL to 1.20 mg/dL). The benign interpretation is based on not knowing the original value of 53 μmol/L (0.60 mg/dL) and the final value remaining within the reference interval (13). The creatinine concentration increases, and there is no “creatinine-blind range.” The problem is the misuse of a reference interval (14). With a precise assay, an increase from 53 μmol/L to 60 μmol/L (0.60 mg/dL to 0.68 mg/dL) in an individual becomes clinically important. The true clinical value of serum creatinine is its diagnostic sensitivity in detecting small changes in GFR. Spanaus et al. (1) reach their conclusions because reference intervals are not evaluated, and the data analysis, quite correctly, considers all 3 biomarkers as continuous variables.

Comparing the biological variation of creatinine and cystatin C (no equivalent data are available for β-trace protein) quickly demonstrates how different these 2 serum biomarkers are (15). The contribution of the intraindividual variance to the biological variation is 75% for cystatin C but only 7% for creatinine. Consequently, the use of cystatin C to monitor renal function in an individual, particularly in the early stages of kidney disease or after transplantation, is not valid. It can be used to evaluate the posttransplantation GFR (16) but not the small changes that will determine adjustments to immunosuppressive therapy.

Serum creatinine is not a perfect biomarker of GFR. Tubular secretion, an altered production rate, and analytical specificity mean that it is not applicable in all clinical situations, and interpretation often remains an art. The professional perception that serum creatinine is an insensitive biomarker of early changes
in GFR is totally incorrect. The data presented by Spanaus et al. (1) help to correct that perception by demonstrating that serum creatinine is at least as good as cystatin C or β-trace protein. The reality is that serum creatinine is still a very good measure of GFR and is by far the most sensitive serum biomarker for detecting small GFR changes in an individual.

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