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Measurement of Glomerular Filtration Rate as a Diagnostic Test: Old Limitations and New Directions and Challenges Worthy of an Olympic Gold Medal

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EDITORIAL

Measurement of Glomerular Filtration Rate as a Diagnostic Test: Old Limitations and New Directions and Challenges Worthy of an Olympic Gold Medal

Matthew Emmons, one of the most successful elite marksman in recent US sports history and a multiple, Olympic medalist, was on track during the Games of the 28th Olympiad in Athens to win the gold medal in the "50-m 3-position rifle." Emmons was leading the entire field, points ahead of the next competitor, Jia Zhanbo from China. First shot final round of 9 shots, bull's eye! Bull's eye for the wrong target! With that shot—a crossfire—Emmons lost his chance at a medal. Jia Zhanbo wins the gold.

Accurate and precise, and given Emmons' skill, his shot was likely entirely reproducible, but it gave the wrong result, it was off target. Had Emmons hit his intended target, he would have been the gold medalist in his competition.

Hitting the correct target is akin to obtaining results from a valid and useful diagnostic test; patients and clinicians win. Diagnostic tests should be like the expert marksman's shot. We expect our diagnostic tests to be sufficiently reproducible, reliable, and hit the correct target to facilitate diagnostic precision. Typically, we judge a diagnostic test by how well the test tells us the truth, or how uncommonly the test yields false positive or false negative results. We expect these error rates for the diagnostic test to be low when the diagnostic test results are compared to the truth, defined by a criterion or gold standard measure of a particular disease. The true positive rate (proportion of positives that are correctly identified) and false negative rate (1 − Sensitivity = false negative rate) are reported as the test's sensitivity and specificity (true negative rate). However, relatively few clinicians have developed an intrinsic sense of what test sensitivity and specificity mean for the interpretation of a test's results or the management of a patient's disease.

Of equal or even greater importance, we should expect that diagnostic tests will not only classify a patient correctly as having or not having an illness but also provide us with an accurate measure of disease progression and prognosis with treatment. Importantly, for diseases such as CKD, we expect that an accurate and reproducible measure of the stage of CKD will provide us with insights into the potential impact of CKD along a continuum from less to more severe disease on the patient's health status. The latter is particularly important when clinicians are evaluating whether a treatment strategy is benefiting the patient and necessitates that the diagnostic test enable classification of subjects into clinically meaningful subsets according to the severity of their illness and expected response to treatment.

CKD "staging" is most commonly done using a patient's glomerular filtration rate (GFR). It is universally accepted that an accurate measure of GFR should serve well to classify individuals with CKD. For core diagnostic tests such as the measurement of GFR in CKD or acute kidney injury (AKI) patients, 1 property of a diagnostic test is key, namely the test provides reliable insights into prognosis with or without specific treatment(s), so that the result can fundamentally impact management decisions, patient choices, and patient-centered outcomes. The diagnostic test makes a difference for the patient; it has utility.

To fulfill these criteria, measurement of GFR ideally should be reliable, reproducible, and provide an accurate estimate of GFR independent of disease severity and should provide consistent information about prognosis and outcomes. Furthermore, the test should be simple to perform and interpret and allow for comparisons across time and between populations. Current methods to measure or estimate GFR fall short of this ideal. The estimations of GFR from serum creatinine or urea while readily available and generally simple to perform may be particularly inaccurate at extremes of true GFR where

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an accurate measure of GFR may be particularly important to support clinical decision-making. Examples include morbidly obese patients, and in certain individuals such as vegans, professional athletes, weightlifters, and cachectic cancer patients to name a few. Measurement of intrinsic kidney function in patients undergoing dialysis presents a unique challenge, but accurate measurement of residual intrinsic kidney function has important treatment, prescription, and outcome implications.

Strategies to address the limitations of the current methods for measuring GFR are reviewed in the papers in the current issue of Advances in Chronic Kidney Disease edited by Inker and colleagues. These reviews describe newer methods that rely on novel biomarkers and on computer-assisted decision support to develop and validate complex algorithms generating more accurate estimates of GFR. Olympian Emmons, when addressing in retrospect the failure of his 2004 gold medal attempt, noted the breakdown of his carefully practiced system with his failure, in part, attributed to a paucity of redundancy—he did not identify his target before he took "the shot." In a similar vein, a reliance on a single method to measure GFR fails to address the limitations inherent in these GFR measures. In this issue of ACKD, Inker and her colleagues point a way forward through implementation of recently developed biomarkers and introduction of redundant systems, all supported by computer-driven algorithms that are population specific.

Inker and each of the contributors to this issue of ACKD clearly acknowledge the challenges ahead and enumerate specific aspects of these. A major theme of a number of the papers is introduced by Inker, Levey, and Coresh who propose a framework for a more complex methodology to estimate GFR from a panel of filtration markers, as a strategy to potentially increase accuracy beyond the conventional estimated GFR or measured GFR determinations. The essential first step in addressing the limitations in the utility of GFR measurements is to validate reliable measures that provide accurate determinations of GFR across all levels of function, in obese and nonobese individuals, in the very young and the very old, in cancer patients, in patients on dialysis, in Asian populations and others, to determine prognosis, identification of AKI on CKD, and/or for drug dosing. The chapters in this issue of ACKD address the measurement of GFR in each of these specific populations and largely acknowledge the limitations inherent in selecting the "gold standard" for validation of these proposed GFR estimation strategies.

Once the properties of the new GFR measurement are described and "validated" with evidence from cross-sectional observational studies comparing the new GFR measures to the criterion or gold standard, the second stage of GFR measurement development commences. This second stage is the validation of the GFR measurement in terms of how well the measurement predicts clinical outcomes. The full utility of the newer GFR measures can only be appreciated with such data. This aspect of the development of strategies to measure GFR while essential is much more difficult. At a minimum, one requires longitudinal cohort studies to evaluate long-term prognosis and outcomes. Ideally, the utility of the newer strategies could be studied using a randomized clinical trial design. With a randomized controlled trial one might ask; "Are patient's "better off" with regard to some important patient-centered outcomes due to implementation of the new test. If so, which patients or populations attain the greatest benefit, and what is the magnitude of this benefit?" Afterward, prospective, clinical trials can explore implementation of the test, defined by principles of "choosing wisely," and define to whom and when and how often such measures of GFR should be employed in routine clinical practice.

Most of the authors in this issue of ACKD conclude their reviews with an acknowledgment of the need for a final validation of the GFR measurements that they have described with prospective clinical trials. Inker and her colleagues have shown us where to start this journey by first describing the evidence of the limitations of our current measures and then proposing new measures to overcome these limitations. Collectively, the authors in this issue of ACKD describe the outlines of better GFR measures for diverse populations and a strategy to develop and test these GFR measures.

Clearly, there is still much work to be done. Some of this work may seem far afield, but they may soon become available strategies that warrant more widespread use that determine kidney prognosis. A test based on ultrasound technology, shock wave elastography, may inform practitioners of kidney fibrosis.[1] The technique, such as hepatic fibroscans, determines kidney stiffness and correlates with histological fibrosis.[2] If tissue artifact interferences can be mitigated, this method may be generalizable to common-day practice. Assessment of individuals' single-nephron glomerular filtration rates (SNGFRs) may prove informative in the future.[3] This sophisticated computed tomography methodology independently correlated greater SNGFRs with disease. Individuals with higher-than-normal SNGFRs demonstrated relative nephromegaly, more glomerulosclerosis, and arteriosclerosis by morphometric and stereologic analyses of 1388 biopsies of human kidney transplant donors. Finally, kidney blood oxygen–level dependent magnetic resonance is a novel imaging tool that detects changes in tissue oxygenation.[4] This methodology, developed to identify those individuals who may benefit from kidney artery stenosis intervention, has shown promise. The technique requires computational expertise more than newer MR equipment, and the preponderance of data has been generated at the Mayo Clinic, Rochester, MN. Further validation studies will be required before this noninvasive technique can be extended for the determination of CKD severity.

After his 1 loss in 2004, Matthew Emmons learned from his mistake. He developed and tested new competition strategies and went on to win Olympic medals in 3 Olympiads. The personal rewards were substantial. It is likely that developing better predictive GFR measures will also have large rewards for better patient care, better patient

counseling, and better patient choices. It would be prudent to invest the nation's resources required for such studies.

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