Estimated Glomerular Filtration Rate From a Panel of Filtration Markers—Hope for Increased Accuracy Beyond Measured Glomerular Filtration Rate?

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The recent Kidney Disease Improving Global Outcomes 2012 CKD guidelines recommend estimating GFR from serum creatinine ($eGFR_{cr}$) as a first-line test to assess kidney function and using cystatin C or measured glomerular filtration rate (GFR) as confirmatory tests. $eGFR_{cr}$ may be inaccurate in people with variation in muscle mass or diet, and $eGFR_{cys}$ is not more accurate than $eGFR_{cr}$. $eGFR_{crcys}$ is more accurate than either, but it is not independent of $eGFR_{cr}$. Measured GFR is not practical and is susceptible to error due to variation in clearance methods and in the behavior of exogenous filtration markers. Over the past few years, we have hypothesized, and begun to test the hypothesis, that a panel of filtration markers (panel eGFR) from a single blood draw would require fewer demographic or clinical variables and could estimate GFR as accurately as measured GFR. In this article, we describe the conceptual background and rationale for this hypothesis and summarize our work thus far including evaluation of novel low-molecular-weight proteins and metabolites and then outline how we envision that such a panel could be used in clinical practice, research, and public health.

Key Words: Glomerular filtration rate, Creatinine, Metabolomics, Cystatin C, Estimated GFR

INTRODUCTION

Assessing kidney function is an integral part of the practice of medicine, research, and public health.[1,2] The recent Kidney Disease Improving Global Outcomes (KDIGOs) 2012 CKD guidelines recommend estimating GFR from serum creatinine ($eGFR_{cr}$) as a first-line test.[3] Indeed, more than hundreds of million measurements of serum creatinine are performed annually by clinical laboratories in the United States, with more than 90% reporting eGFR automatically when serum creatinine is measured.[4-6] $eGFR_{cr}$ may be inaccurate in people with variation in muscle mass or diet, and there is great interest in cystatin C as an alternative filtration marker to creatinine. The KDIGO guidelines recommend using eGFR based on cystatin C ($eGFR_{cys}$) or the combination of the two ($eGFR_{cr\text{-}cys}$) as a confirmatory test for eGFRcr.[3] However, there are limitations of this approach because $eGFR_{cys}$ is not more accurate than $eGFR_{cr}$, and although $eGFR_{cr\text{-}cys}$ is more accurate than either $eGFR_{cr}$ or $eGFR_{cys}$, it is not independent of $eGFR_{cr}$. Measured GFR (mGFR) using clearance of exogenous filtration markers is also recommended by KDIGO as a confirmatory test. While mGFR is not influenced by non-GFR determinants of endogenous filtration markers, it is not practical and is susceptible to error due to variation in clearance methods and in the behavior of exogenous filtration markers. Hence, there is a need for a simple but more accurate estimate of GFR to guide individual decision-making.

Over the past few years, we have hypothesized, and begun to test the hypothesis, that a panel of filtration markers (panel eGFR) from a single blood draw would require fewer demographic or clinical variables and could estimate GFR as accurately as mGFR. The overall goal of this review is to describe the conceptual background and rationale for this hypothesis and summarize our work thus far. To do so, we will first review available data on strengths and limitations of eGFR based on creatinine and cystatin C as well as those of mGFR. We will then review our conceptual framework for why panel of filtration markers might overcome the limitations of current estimating equations and mGFR and discuss our exploration of candidate filtration markers for inclusion in the panel. Finally, we will outline how we envision that such a panel could be used in clinical practice, research, and public health.

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ASSESSMENT OF GFR—HOW ACCURATE ARE WE?

GFR cannot be measured directly in humans; thus, "true"—or physiologic—GFR cannot be known with certainty. Instead, we use serum levels or clearance measurements of filtration markers, exogenous, or endogenous solutes that are eliminated mainly by glomerular filtration to assess GFR. Current methods are associated with systematic or random error (bias and imprecision, respectively) in their determination, which may limit their use depending upon the magnitude of the error and requirement for accuracy for clinical decision-making (Table 1).

Measured GFR

The "gold standard" for the measurement of GFR is urinary clearance of an ideal filtration marker, defined as substance that is freely filtered at the glomerulus, neither reabsorbed, secreted, synthesized, or metabolized by the tubules and does not alter the function of the kidney. The "classic" method of Smith[7] used urinary clearance of inulin, a 5200 Da polymer of fructose, during a continuous intravenous infusion. Inulin is difficult to use and not available in the United States, and urinary clearance measurements are cumbersome, so alternative filtration markers and methods have been proposed but all deviate from the "gold standard" leading to potential sources of bias as compared to true GFR. For example, plasma clearance after a bolus intravenous infusion is simpler to perform but may differ from urinary clearance due to nonequilibration across body fluid compartments and extra-renal elimination of the filtration marker. In addition, all alternative filtration markers deviate from ideal behavior.[8] A recent systematic review evaluated alternative methods in comparison to the classic procedure of Smith and noted wide variation in performance even within the same method.[9]

CLINICAL SUMMARY

- Current glomerular filtration rate (GFR) estimates are limited in their accuracy.
- Combining filtration markers in a panel from a single blood draw could require fewer demographic or clinical variables and could estimate GFR as accurately as measured GFR.

Clearance measurements are difficult to perform leading to imprecision in mGFR. The usual method to quantify imprecision in mGFR is through repeated measures. The within person coefficient of variation for repeated measures on different days for GFR measurement methods varies from approximately 5% to 15%, with higher values for urinary clearance than plasma clearances.[10-16] True GFR may vary over short intervals, so observed variation in mGFR likely reflects normal biological variation in true GFR as well as measurement error. By contrast, the imprecision in measurements of serum concentrations of endogenous filtration markers can be less than mGFR, in part because fluctuations in true GFR affect serum concentrations of filtration markers more slowly than clearances, and in part, because it is simpler to measure a serum concentration than to perform a clearance measurement.

Beyond emphasizing the need for a more accurate confirmatory test, error in mGFR has important implications for interpretation of error in eGFR. Error in mGFR does not affect the serum levels of endogenous filtration markers. However, since we use mGFR as the reference test for evaluating the accuracy of eGFR, observed errors in eGFR may in part be due to error in mGFR (Table 1). With advances in GFR estimation, accuracy of eGFR will improve, and the relative contribution of error in mGFR to the observed error in eGFR will increase. To demonstrate the impact of error in mGFR on the observed error in eGFR, we assessed the effect of variability of GFR measurement on the performance of the Modification of Diet in Renal Diseases (MDRDs) Study equation and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) in two clinical trials with GFR measured using urinary clearance of iothalamate.[17] The left hand panel of Figure 1 shows the difference between two mGFRs on average 62 days apart in the African American Study of Kidney Diseases (AASK) and MDRD Study. A total of 12% of subjects had measures that were discrepant, as defined by a difference of more than 25%. The right hand panel of Figure 1 shows the improvement in accuracy when more precise mGFR was used as the reference test [reduction in large errors ($1\text{-}P_{30}$) from 17% to 3.9%].

Estimating GFR

Determinants of Endogenous Filtration Markers. Serum levels of an endogenous filtration marker are determined not only by the level of GFR, but also by physiological processes other than GFR (generation, kidney tubular secretion and reabsorption, and extra-renal elimination). Collectively, these physiological processes are termed non-GFR determinants, and their steady-state relationships to GFR and serum concentrations are shown in Figure 2.[8] These physiological processes are generally not measured, so estimating equations use easily measured demographic and clinical variables as surrogates. GFR estimates are more accurate than the serum level of the marker alone but have two principal limitations which are possible sources of error. First, surrogates only capture the average relationships between the marker and its non-GFR determinants. Second, the relationship between the marker and its non-GFR determinants may vary across populations. The non-GFR determinants may vary across markers even though the serum level for each marker is correlated to GFR.

Estimating GFR Using Creatinine and Cystatin C. Creatinine is the most commonly used endogenous filtration marker. It is freely filtered by the glomerulus but undergoes extra-renal elimination by the gut, is secreted by the tubules, and is generated by muscle mass or diet. Creatinine-based estimating equations include age, sex, race, or weight as surrogates for creatinine generation from muscle mass or diet.[2]

Regardless of the specific equation, the accuracy of $eGFR_{cr}$ is limited by variation in muscle mass or diet