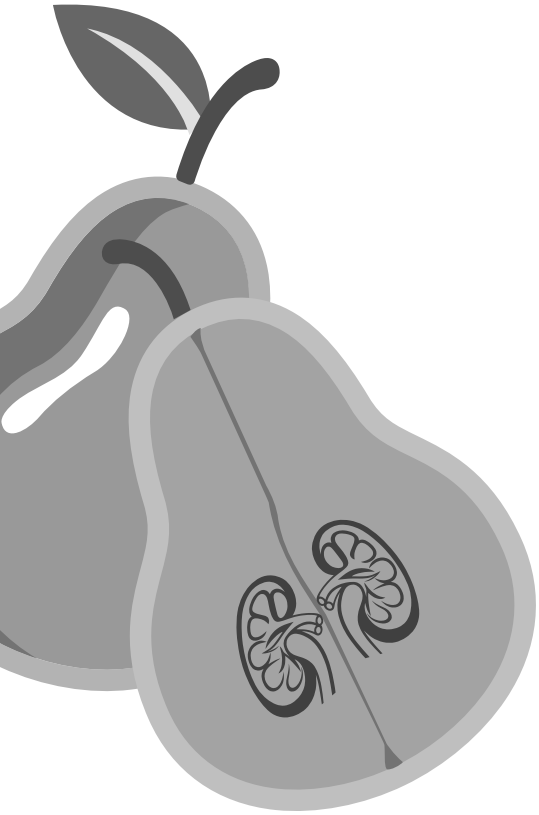
# Prediction and monitoring of chronic kidney disease

Schutte, Elise

# Chapter 8

## Measured GFR: not a gold, but a gold plated standard



Elise Boele – Schutte
Ron. T. Gansevoort

*Nephrol Dial Transplant* 32(suppl_2): ii180-ii184, 2017

## True GFR versus estimated GFR

Because of the circadian rhythm in kidney function the true glomerular filtration rate (GFR) is historically considered to be the average GFR measured by urinary inulin clearance over a 24 hour period.[1] In clinical practice it is impossible to measure GFR during such a prolonged period. Therefore three methods have been developed to estimate GFR. First, GFR can be assessed by measuring during a shorter period of time the clearance of an exogenous filtration marker such as iohexol, iothalamate, $^{51}$Cr-EDTA or DTPA. This is generally regarded to be the gold standard for measuring kidney function, and therefore often referred to as measured GFR (mGFR). However, it should be kept in mind that this is a misunderstanding and that measuring the clearance of these filtration markers is actually also just an estimation of true GFR. Second, the GFR can be estimated by measuring the 24 hour urinary clearance of an endogenous marker, such as creatinine or urea. It is well known that creatinine clearance overestimates true GFR due to tubular creatinine secretion, whereas urea clearance underestimates GFR due to tubular urea reabsorption. For these reasons taking the average of urea and creatinine clearance could provide an acceptable estimation of the true GFR, as the bias induced by creatinine excretion and urea reabsorption are expected to cancel each other out.[2] Although this is an attractive option to estimate true GFR, it is not often used. Third, GFR can be estimated using an equation that incorporates serum creatinine, age, gender and race, such as the CKD-EPI equation.[3] In clinical practice this is the reference method.

Since these three aforementioned methods all yield an estimation of GFR, it is the question which method has the best correlation with true GFR. This issue could be investigated in a cross-sectional study that compares true GFR measured as inulin clearance over a 24 hr period with GFR estimated with each of these three methods. Given that kidney function is causally associated with incidence of end-stage renal disease (ESRD) and mortality, another option is to investigate which of the three GFR estimates has the strongest association with incidence of these hard end points. In this issue of NDT, Methven et al. published the results of an observational study that addressed this question using data from the Swedish CKD registry.[4]

## What are the findings of this study?

The Swedish CKD registry is a unique database, because many chronic kidney disease (CKD) patients in Sweden undergo routine measurement of GFR using iohexol as exogenous filtration marker. In a cohort of 2705 CKD patients, iohexol mGFR, average urinary urea-creatinine clearance and eGFR were compared with regards to their association with all-cause mortality. This manuscript addresses the question whether clinicians should measure mGFR instead of eGFR to assess mortality risk.

Methven et al. found that mGFR had a stronger association with mortality and better performance to predict mortality than eGFR, whereas creatinine clearance did not outperform eGFR in these aspects. In adjusted Cox regression models, each 1 ml/min/1.73m$^2$ lower mGFR, urinary urea-creatinine clearance or eGFR resulted in an increase in mortality risk of 5.3% for mGFR, 2.3% for creatinine clearance and 1.7% for eGFR. In prognostic models, replacing eGFR with mGFR resulted

in an integrated discrimination improvement (IDI) of 0.023. The IDI is a statistical metric that can be used to calculate whether a biomarker improves the prediction of an end point.[5] The further this value is from zero, the better the biomarker performs at identifying patients at risk for the outcome event of interest. The IDI of 0.023 that was found in the study by Methven is considered to be only a modest improvement, leading the authors to conclude that eGFR may be sufficient in clinical practice to predict mortality risk. Of note, urinary urea-creatinine clearance did not improve the IDI for mortality compared to eGFR.

## Accuracy of eGFR and mGFR

eGFR is commonly deemed inferior to mGFR, because the equations to estimate GFR were created to obtain values that correspond to mGFR. During the last decade a flurry of cross-sectional studies has been performed, comparing eGFR to mGFR in various study populations with varying results. In these reports the accuracy of eGFR is compared to mGFR as the reference using Bland-Altman plots. These plots report bias (i.e., systematic error) and dispersion, from which precision is calculated (i.e., variability). By doing so mGFR is adopted as gold standard, suggesting that mGFR measurement is not biased and has excellent precision. However, we should realize that mGFR also has several limitations that make it a gold plated rather than a gold standard.

First of all, there is no standardization of the assays used to measure serum and urine levels of the exogenous GFR markers. A recent study compared iohexol mGFR with iothalamate mGFR.[6] Both markers were assessed contemporaneously in the same patients and in the same blood samples. Interestingly, iohexol was measured by two different assays, liquid chromatography–tandem mass spectrometry (LC-MS/MS) and high performance liquid chromatography (HPLC). Figure 1 shows the Bland-Altman plots that were provided. These plots indicate that the two analytical methods result in substantial differences in mean measured GFR, and also that the two methods have limited agreement. In comparison to iothalamate, mGFR based on iohexol measured by LC-MS/MS resulted in a bias of -10.6% (95% CI -28.2 to 6.9%), whereas the bias for mGFR based on iohexol measured with HPLC was only 1.7% (95% CI -26.5 to 23.0%). Consequently, in a patient with an iothalamate mGFR of 50 ml/min/1.73m$^2$, using iohexol measured by LC-MS/MS could result in a mGFR ranging between 36 to 53 ml/min/1.73m$^2$, and for iohexol measured by HPLC in a mGFR ranging between 37 to 62 ml/min/1.73m$^2$. Another study that compared the urinary clearance of iohexol measured by LC-MS/MS and iothalamate found similar results with regard to bias and dispersion.[7]

Figure 2 depicts the results of the direct comparison of mGFR based on iohexol measured by LC-MS/MS or HPLC. This graph shows that HLPC as analytical method to measure iohexol yielded a mGFR that was 8.9% higher than when LC-MS/MS was used. Not only is there a systematic bias, the dispersion in Figure 2 indicates that there is also substantial imprecision in mGFR when LC-MS/MS or HPLC is used to measure iohexol. Due to a lack of standardization, it is not clear which iohexol assay is responsible for this imprecision. In contrast, the assay for creatinine has been standardized in 2006, to ensure accurate estimation of GFR. Nowadays, clinical chemistry laboratories around the world are advised to use an enzymatic assay to measure creatinine, and to calibrate results to an international standard.[8-10]

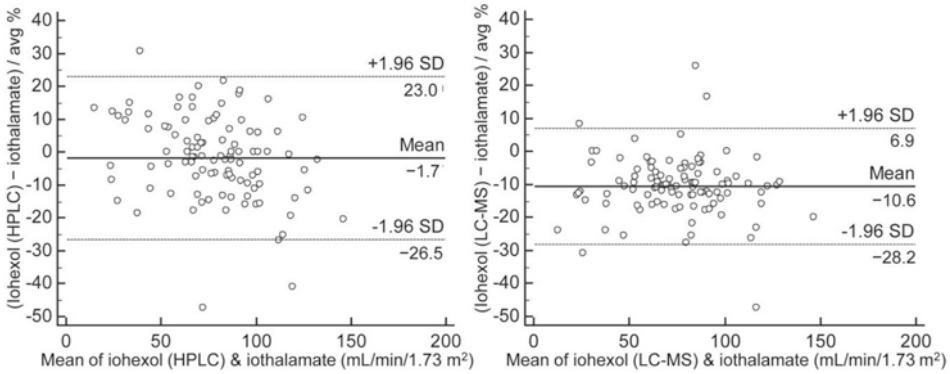



**Figure 1** Bland-Altman analyses: comparison of GFR measured by iothalamate and iohexol measured by HPLC [left] or LC-MS/MS [right]). Adapted from Delanaye et al.[6]

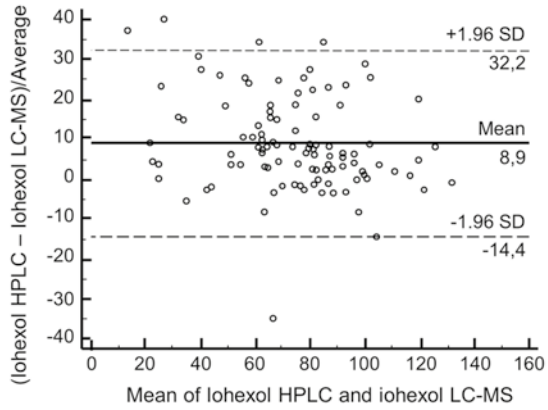



**Figure 2** Bland-Altman analysis: comparison of iohexol measured GFR using a HPLC and an LC-MS/MS assay. Adapted from Delanaye et al. (5)

Second, there is a lack of *protocol standardization* to estimate GFR based on exogenous filtration markers. To obtain a mGFR (almost) equal to true GFR, one should ideally perform a continuous infusion of the exogenous marker and collect multiple blood samples and collect urine over 24 hours. Such a procedure would be impossible to incorporate in clinical care, and would even be difficult in clinical studies. In practice, patients therefore receive a single injection of a labeled exogenous marker and then blood samples are obtained in the hours after the injection to estimate GFR from the plasma disappearance curve. With this method, the GFR is estimated with an equation that incorporates time after injection, the dose of the injected marker, concentration at the time of measurement, and an estimation of the volume of distribution. This form of GFR measurement introduces several sources of bias and variability. For instance, several equations are available to calculate GFR from the plasma disappearance curves, that render different results.[11-13] In addition, results will theoretically be

dependent on how often and when plasma samples are obtained. It has indeed been shown that the intra-patient coefficient of variation of repeated mGFR measurements decreases when more blood samples are taken.[14] Others showed that the GFR can be systematically overestimated when samples are drawn too early. Agarwal et al. investigated the effect of study duration on subsequently obtained mGFR values. These authors found that the mGFR value after 2 hours is 54% higher and after 5 hours 17% higher when compared to the mGFR value that is obtained after 10 hours of blood sampling.[15] This overestimation was higher when GFR was lower. Furthermore, bolus injection of an exogenous marker leads to serum concentrations of the marker under study that follow a two-compartment pharmacokinetic model (rapid initial decline of plasma levels of the marker reflecting tissue distribution, followed by slower decline during several hours indicating (renal) clearance).[15] Importantly, many studies use a mono-compartment, log-linear decline model to estimate GFR, which does not take into account the initial distribution phase, and may thus be expected to yield biased GFR results. This bias is expected to be present especially in patients with non-standard body composition, such as patients with edema or after limb amputation.[15] To improve GFR estimation from exogenous filtration markers, both the protocol (when and how often to collect blood and urine samples) as well as the equation that is used to estimate mGFR from a plasma disappearance curve need to be optimized and subsequently internationally standardized.

Third, creatinine has been criticized as glomerular filtration marker to be used in estimation equations, because serum concentration of creatinine is dependent not only of GFR, but also of *non-GFR determinants*. As generally appreciated, serum creatinine concentration is influenced by tubular creatinine secretion and by muscle mass. Thus, creatinine based eGFR is less reliable in patients with a high or low muscle mass for a given age and gender.[16] However, creatinine is not the only GFR marker with non-GFR determinants. The ideal marker for measuring GFR is water soluble, inert, freely filtered, not reabsorbed or secreted by the tubule, and has no extra-renal clearance.[17] Most endogenous markers also do not meet these criteria. For example, iothalamate is subject to tubular secretion,[18,19] iohexol and EDTA are subject to tubular reabsorption,[20,21] iohexol and DTPA suffer from protein binding,[7,22] and iothalamate and DTPA are subject to extrarenal clearance, that can vary between individuals.[22,23]

Given the above mentioned factors, it is not surprising that the various exogenous markers for the measurement of GFR do not perform equally. A systematic review that compared renal and plasma clearance of exogenous filtration markers to renal inulin clearance found that plasma clearance of iohexol and $^{51}$Cr-EDTA and renal clearance of iothalamate and $^{51}$Cr-EDTA had the least bias.[24] The P30, the percentage of GFR estimates that lies within 30% of mGFR, is a metric that is often used to express the accuracy of a certain GFR estimation method. For plasma clearance of iohexol and iothalamate, P30 compared to inulin-based GFR was 84% (95% CI 78 to 90) and 61% (95% CI 47 to 80), respectively. In comparison, two other studies showed that the creatinine based CKD-EPI GFR estimation equation yielded a P30 that was similar (78%, 95% CI 72 to 84, compared to inulin mGFR) or even slightly better (87%, 95% CI 85 to 89, compared to iothalamate mGFR).[25,26] Combined, these results indicate that GFR measured with exogenous markers does not consistently outperform creatinine based equations to estimate GFR.

**Table 1** Studies investigating the association of eGFR and mGFR with ESRD and mortality

| Author | Study | N | Study population | MGFR METHOD | Follow-up (Y) | Superior GFR metric | |
|---|---|---|---|---|---|---|---|
| | | | | | | ESRD | Mortality |
| Menon et al. [27] | MDRD | 825 | Non-diabetic ckd, MGFR 13-55 ml/min/1.73m$^2$ | Urinary iothalamate clearance | 10 | EGFR | MGFR |
| Bhavsar et al.[28] | AASK | 865 | hypertensive CKD, MGFR 20-65 ml/min/1.73m$^2$ | Urinary iothalamate clearance | 8.6 | MGFR | MGFR* |
| Foster et al.[29] | | 250 | Pima indians with type 2 DM, any GFR | Urinary iothalamate clearance | 14 | MGFR | NS |
| Foster et al.[30] | CRIC | 3613 | CKD patients (unspecified) EGFR 20-70 ml/min/1.73m$^2$ | Urinary iothalamate clearance | 6 | EQUAL | EQUAL |
| Ku et al.[31] | CRIC | 924 | CKD patients (unspecified) EGFR 20-70 ml/min/1.73m$^2$ | Urinary iothalamate clearance | 6.6 | EGFR | EGFR |
| Methven et al.[4] | | 2705 | CKD patients (unspecified) EGFR <45 ml/min/1.73m$^2$ | Plasma iohexol clearance | 3.8 | NA | MGFR |

*Abbreviations:* mGFR, measured GFR; eGFR, estimated GFR; ESRD, end stage renal disease; y, years; DM, diabetes mellitus; NA, not applicable; NS, no significant associations with end point

*= endpoint was a composite of ESRD and mortality

### eGFR and mGFR versus hard endpoints

Besides the present study by Methven et al, five other studies have compared eGFR to mGFR with regard to their association with incidence of end-stage renal disease and mortality.[27-31] Their results are summarized in Table 1. This table shows divergent results. Some studies found eGFR and others mGFR to have stronger associations with ESRD and mortality, whereas others did not find differences. These varying results cannot be explained by the exogenous filtration marker that was used to estimate GFR, because in 4 out of 5 studies this was urinary iothalamate clearance. It seems that other factors are important, for example the protocol that was used for sample collection and/or the assay for iothalamate. Overall, these data indicate that mGFR does not consistently outperform eGFR with regard to the association with incidence of ESRD and mortality, and that the improvement of risk prediction when using mGFR instead of eGFR is modest at best.

### Repeated measures of eGFR and mGFR

The studies in Table 1 investigated the associations of a single measurement of eGFR and mGFR with incidence of hard end-points. However, in clinical practice repeated measures of eGFR are used to determine kidney disease progression and prognosis. A meta-analysis has shown that change in eGFR during a two year period is associated with subsequent development of ESRD and mortality.[32] Only one study compared change in eGFR versus change in mGFR with respect to their association with incident ESRD and mortality.[31] Interestingly, these investigators found that eGFR slopes had a stronger association with incident ESRD as well as with mortality than mGFR slopes. These data suggest that it may be better to use eGFR rather than mGFR for monitoring change in kidney function over time.

## Conclusion



Creatinine based equations to estimate GFR are often criticized because of their alleged imprecision. The study by Methven et al. in this issue of NDT showed that GFR estimated by iohexol clearance yields only a modest improvement in the prediction of mortality compared to GFR estimated by the CKD-EPI equation in a large population of CKD patients. This result adds to other research which has shown that GFR measured with exogenous filtration markers does not consistently outperform eGFR with respect to precision of GFR measurement, nor with respect to the strength of the associations with incident ESRD and mortality. In our opinion, much of the criticism expressed towards eGFR is actually a result of the fact that in these studies not a gold standard, but merely a gold plated standard is used as reference method. A lack of standardization of the assays that are used to measure the exogenous filtration markers, a lack of standardization of protocols how and when blood and urine samples should be collected, which equation to use to estimate GFR from the plasma disappearance curve, as well as non-GFR determinants of the exogenous filtration markers that are applied, makes that GFR measured by these exogenous markers results in rather variable results. When studies compare the performance of creatinine based GFR estimating equations with GFR measured by exogenous filtration markers, the bias and imprecision that is found is in general

attributed solely to the limitations of the creatinine based GFR estimating equations. Studies that compared the performance of two exogenous filtration markers indicate, however, that much of the bias and imprecision is actually due to the limitations of the exogenous filtration marker that is used as reference method. These considerations indicate that creatinine based equations to estimate GFR will perform considerably better than many clinicians and epidemiologists assume. Moreover, it is important to realize that creatinine is measured by a standardized assay, that is calibrated versus an international standard. This, in combination with the universal application of the same creatinine based equation to estimate GFR, makes that consistent, fairly reliable results across the world can be obtained, for a fraction of the costs of measurement of GFR by exogenous filtration markers. That doesn't seem too bad after all. f

# References


1 Koopman MG, Koomen GC, Krediet RT, de Moor EA, Hoek FJ, Arisz L. Circadian rhythm of glomerular filtration rate in normal individuals. *Clin Sci* (Lond) 77(1): 105-111, 1989.

2 Traynor J, Mactier R, Geddes CC, Fox JG. How to measure renal function in clinical practice. *Bmj* 333(7571): 733-737, 2006.

3 Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF,3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150(9): 604-612, 2009.

4 Methven S, Gasparini A, Juan J, Caskey F, Evans M. Routinely measured iohexol GFR versus creatinine based eGFR as predictors of mortality in patients with advanced CKD: A swedish CKD registry cohort study. *Nephrol Dial Transplant* 2016.

5 Pencina MJ, D'Agostino RB S, D'Agostino RB,Jr, Vasan RS. Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. *Stat Med* 27(2): 157-72; discussion 207-12, 2008.

6 Delanaye P, Jouret F, Le Goff C, Cavalier E. Concordance between iothalamate and iohexol plasma clearance. *American Journal of Kidney Diseases* 68(2): 329-330, 2016.

7 Seegmiller JC, Burns BE, Schinstock CA, Lieske JC, Larson TS. Discordance between iothalamate and iohexol urinary clearances. *Am J Kidney Dis* 67(1): 49-55, 2016.

8 Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, Hostetter T, Levey AS, Panteghini M, Welch M, Eckfeldt JH, for the National Kidney Disease Education Program Laboratory Working Group. Recommendations for improving serum creatinine measurement: A report from the laboratory working group of the national kidney disease education program. *Clinical Chemistry* 52(1): 5-18, 2006.

9 Panteghini M. Enzymatic assays for creatinine: Time for action. *Clin Chem Lab Med* 462008.

10 Drion I, Cobbaert C, Groenier KH, Weykamp C, Bilo HJG, Wetzels JFM, Kleefstra N. Clinical evaluation of analytical variations in serum creatinine measurements: Why laboratories should abandon jaffe techniques. *BMC Nephrology* 13: 133-133, 2012.

11 Fleming JS. An improved equation for correcting slope-intercept measurements of glomerular filtration rate for the single exponential approximation. *Nucl Med Commun* 28(4): 315-320, 2007.

12 Jodal L, & Brochner-Mortensen J. Reassessment of a classical single injection 51Cr-EDTA clearance method for determination of renal function in children and adults. part I: Analytically correct relationship between total and one-pool clearance. *Scand J Clin Lab Invest* 69(3): 305-313, 2009.

13 Brochner-Mortensen J, & Jodal L. Reassessment of a classical single injection 51Cr-EDTA clearance method for determination of renal function in children and adults. part II: Empirically determined relationships between total and one-pool clearance. *Scand J Clin Lab Invest* 69(3): 314-322, 2009.

14 Agarwal R, Bills JE, Yigazu PM, Abraham T, Gizaw AB, Light RP, Bekele DM, Tegegne GG. Assessment of iothalamate plasma clearance: Duration of study affects quality of GFR. *Clin J Am Soc Nephrol* 4(1): 77-85, 2009

15 Agarwal R, Bills JE, Yigazu PM, Abraham T, Gizaw AB, Light RP, Bekele DM, Tegegne GG. Assessment of iothalamate plasma clearance: Duration of study affects quality of GFR. *Clin J Am Soc Nephrol* 4(1): 77-85, 2009.

16 Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: New insights into old concepts. *Clin Chem* 38(10): 1933-1953, 1992.

17 Levey AS, Inker LA, Coresh J. GFR estimation: From physiology to public health. American *Journal of Kidney Diseases* 63(5): 820-834, 2014.

18 Odlind B, Hällgren R, Sohtell M, Lindström B. Is 125I iothalamate an ideal marker for glomerular filtration? [Electronic version]. *Kidney Int* 27(1): 9-16, 1985.

19 Sterner G, Back SE, Nyman U. Iohexol versus iothalamate for GFR measurement. *Am J Kidney Dis* 67(6): 991, 2016.

20 Brochner-Mortensen J. Routine methods and their reliability for assessment of glomerular filtration rate in adults, with special reference to total [51Cr]EDTA plasma clearance. *Dan Med Bull* 25(5): 181-202, 1978.

21 Masereeuw R, Moons MM, Smits P, Russel FGM. Glomerular filtration and saturable absorption of iohexol in the rat isolated perfused kidney. Br J Pharmacol 119(1): 57-64, 1996.

22 Stevens LA, & Levey AS. Measured GFR as a confirmatory test for estimated GFR. *J Am Soc Nephrol* 20(11): 2305-2313, 2009.

23 LaFrance ND, Drew HH, Walser M. Radioisotopic measurement of glomerular filtration rate in severe chronic renal failure. *J Nucl Med* 29(12): 1927-1930, 1988.

24 Soveri I, Berg UB, Björk J, Elinder C, Grubb A, Mejare I, Sterner G, Bäck S. Measuring GFR: A systematic review. *American Journal of Kidney Diseases* 64(3): 411-424, 2014.

25 Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS, CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 367(1): 20-29, 2012.

26 Lemoine S, Guebre-Egziabher F, Sens F, Nguyen-Tu MS, Juillard L, Dubourg L, Hadj-Aissa A. Accuracy of GFR estimation in obese patients. *Clin J Am Soc Nephrol* 9(4): 720-727, 2014.

27 Menon V, Shlipak MG, Wang X, Coresh J, Greene T, Stevens L, Kusek JW, Beck GJ, Collins AJ, Levey AS, Sarnak MJ. Cystatin C as a risk factor for outcomes in chronic kidney disease. *Ann Intern Med* 147(1): 19-27, 2007.

28 Bhavsar NA, Appel LJ, Kusek JW, Contreras G, Bakris G, Coresh J, Astor BC. Comparison of measured GFR, serum creatinine, cystatin C, and beta-trace protein to predict ESRD in african americans with hypertensive CKD. *Am J Kidney Dis* 58(6): 886-893, 2011.

29 Foster MC, Inker LA, Hsu C, Eckfeldt JH, Levey AS, Pavkov ME, Myers BD, Bennett PH, Kimmel PL, Vasan RS, Coresh J, Nelson RG. Filtration markers as predictors of ESRD and mortality in southwestern american indians with type 2 diabetes. *American Journal of Kidney Diseases* 2015.

30 Foster MC, Coresh J, Hsu C, Xie D, Levey AS, Nelson RG, Eckfeldt JH, Vasan RS, Kimmel PL, Schelling J, Simonson M, Sondheimer JH, Anderson AH, Akkina S, Feldman HI, Kusek JW, Ojo AO, Inker LA. Serum ß-trace protein and ß2-microglobulin as predictors of ESRD, mortality, and cardiovascular disease in adults with CKD in the chronic renal insufficiency cohort (CRIC) study. *American Journal of Kidney* Diseases 2016.

31 Ku E, Xie D, Shlipak M, Hyre Anderson A, Chen J, Go AS, He J, Horwitz EJ, Rahman M, Ricardo AC, Sondheimer JH, Townsend RR, Hsu CY, CRIC Study Investigators. Change in measured GFR versus eGFR and CKD outcomes. *J Am Soc Nephrol* 27: 2196-2204, 2016.

32 Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ, Arima H, Chadban SJ, Cirillo M, Djurdjev O, Green JA, Heine GH, Inker LA, Irie F, Ishani A, Ix JH, Kovesdy CP, Marks A, Ohkubo T, Shalev V, Shankar A, Wen CP, de Jong PE, Iseki K, Stengel B, Gansevoort RT, Levey AS, CKD Prognosis Consortium. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *Jama* 311(24): 2518-2531, 2014.