

Appendix (Supplemental Methods)

There has been much confusion in the literature as to how to graphically assess the performance of eGFR against mGFR. Many studies have used mGFR or $(\text{eGFR} + \text{mGFR})/2$ on the x-axis, rather than eGFR. Both the MDRD study equation and the CKD-EPI equations were developed using least squares regression of logarithmic mGFR onto a set of predictors that sum to logarithmic eGFR. This type of regression is asymmetric and validation of eGFR must take into account the inherent asymmetry in the relationship between eGFR and mGFR. The following example shows why eGFR (not mGFR or $(\text{eGFR} + \text{mGFR})/2$) should be on the x-axis during analyses of equation performance. To graphically demonstrate this principle, a new equation was developed in order to show how these principles of regression impact the development and validation of equations.

Step 1. A sample of 618 CKD patients with mGFR (iothalamate renal clearance) and serum creatinine values were randomly divided into a development set (n=309) and a validation set (n=309).

Step 2. A new eGFR equation was optimized for this population in the development set by regressing \ln mGFR onto the following parameters: \ln serum creatinine (in mg/dl), \ln age, sex, and race. For simplicity we used the same statistical model as the MDRD study equation (contains the same variables as the serum creatinine based CKD-EPI equation). The resulting equations were:

$$\begin{aligned}\ln \text{eGFR} &= 5.587 - 1.113 (\ln \text{SCr}) - 0.292 (\ln \text{age}) - 0.261 (\text{if female}) + 0.385 (\text{if black}) \\ \text{eGFR} &= 267 \times \text{SCr}^{-1.113} \times \text{Age}^{-0.292} \times 0.747 (\text{if female}) \times 1.470 (\text{if black})\end{aligned}$$

Step 3: Performance of this new eGFR equation was assessed in the validation cohort by plotting the % bias between eGFR and mGFR (y-axis) against mGFR (Figure A), $(\text{eGFR} + \text{mGFR})/2$ (Figure B), and eGFR (Figure C). A trend line was added to the data on the logarithmic scale, consistent with how the equation was derived.

Figure A. % bias across levels of mGFR

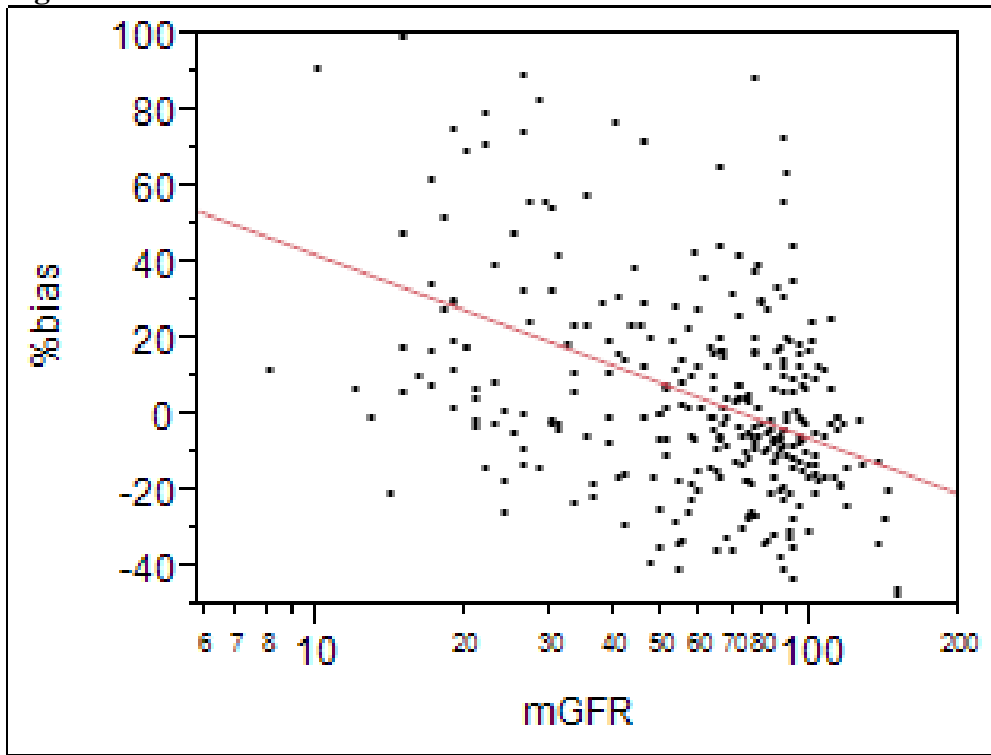


Figure B. % bias across levels of (eGFR + mGFR)/2

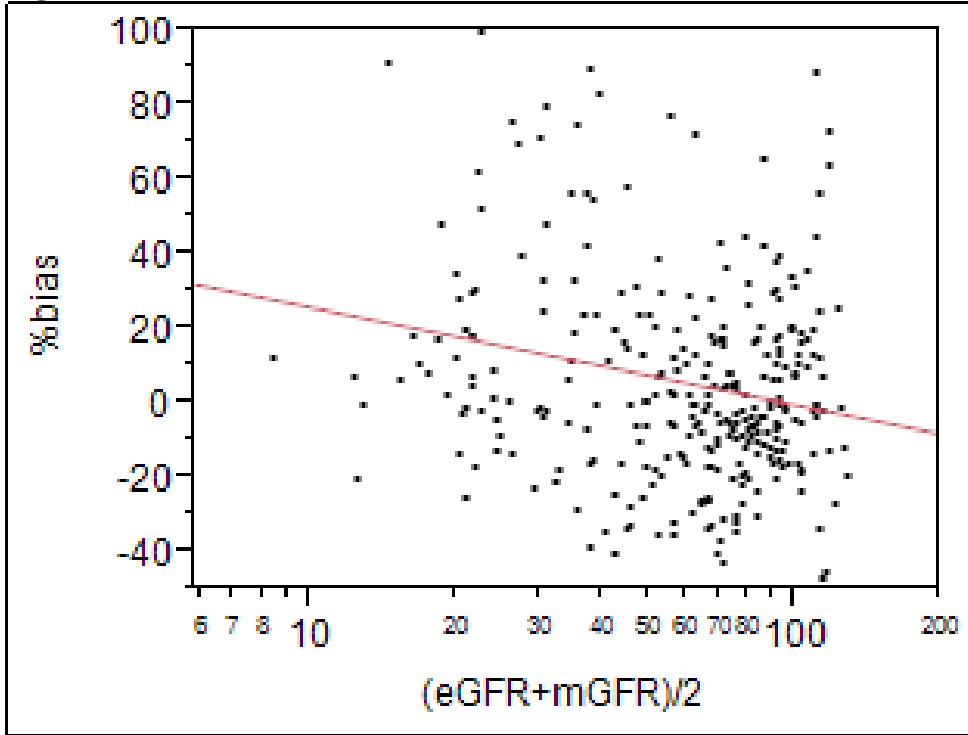
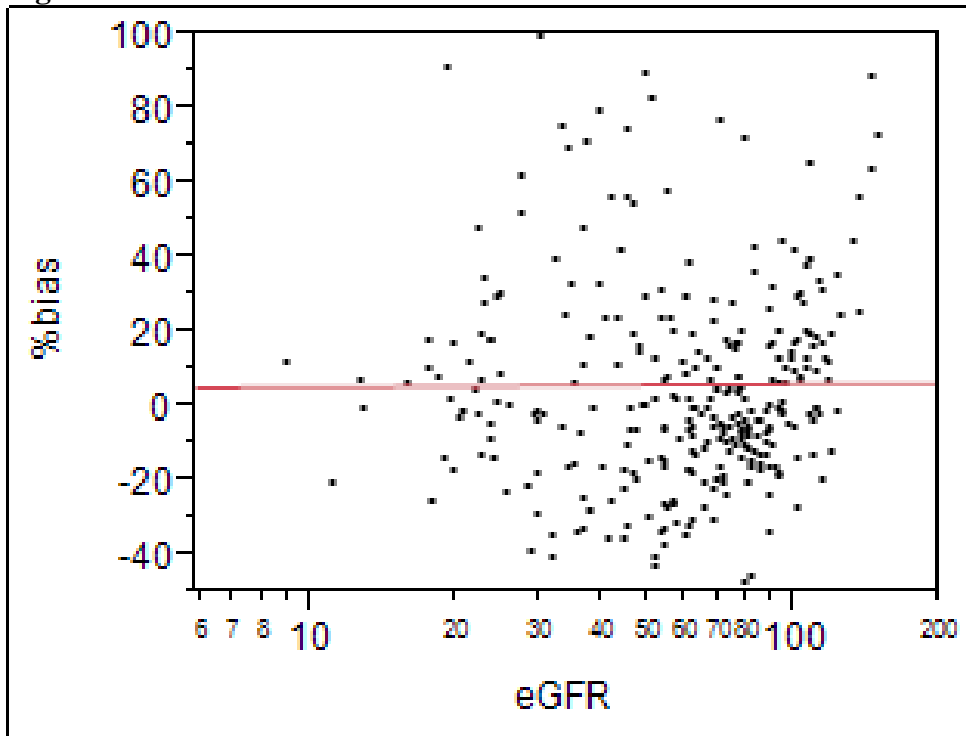


Figure C. % bias across levels of eGFR



Conclusion: eGFR overestimates mGFR at low levels of mGFR and underestimates mGFR at high levels of mGFR (Figure A). Similar findings are evident with $(eGFR+mGFR)/2$ on the x-axis (Figure B). This reflects the asymmetry of regression and is statistical phenomena rather than biology. The reasons for this have been previously described.^{1,2} Briefly, with least squares regression, eGFR is derived in such a manner that $mGFR > eGFR$ should occur equally as often as $mGFR < eGFR$ across levels of eGFR. When mGFR is high, then $mGFR > eGFR$ is more frequent than $mGFR < eGFR$ leading to a perceived negative bias. When mGFR is low then $mGFR < eGFR$ is more frequent than $mGFR > eGFR$ leading to a perceived positive bias. However, across levels of eGFR, there is no bias (Figure C). Thus, for the analysis in this paper % bias was assessed across levels of \ln eGFR consistent with how the CKD-EPI equations were originally derived (regressing \ln mGFR onto \ln eGFR).

References:

1. Rule AD. Understanding estimated glomerular filtration rate: implications for identifying chronic kidney disease. *Current opinion in nephrology and hypertension*. 2007;16:242-249.
2. Hopkins WG. Bias in Bland-Altman but not Regression Validity Analyses. *Sportscience*. 2004;8:42-46.

Supplemental Table 1. eGFR % bias, Mean (95CI), for patient groups and gender.

	Female	Male
Potential Donors		
eGFR _{Cr}	-10 (-14, -6.3)	-14 (-17, -10)
eGFR _{Cys}	5.6 (0.7, 10)	3.7 (-0.8, 8.2)
eGFR _{Cr-Cys}	-1.3 (-5.3, 2.6)	-4.6 (-7.9, -1.3)
CKD Patients		
eGFR _{Cr}	-1.3 (-4.5, 1.8)	-0.5 (-3.5, 2.4)
eGFR _{Cys}	-0.1 (-3.2, 3.0)	0.3 (-2.5, 3.0)
eGFR _{Cr-Cys}	-2.3 (-4.8, 0.2)	-1.6 (-4.0, 0.7)
Kidney Transplant Recipients		
eGFR _{Cr}	-0.8 (-5.3, 3.7)	1.5 (-1.9, 4.9)
eGFR _{Cys}	-5.2 (-9.7, -0.7)	-5.6 (-8.0, -3.2)
eGFR _{Cr-Cys}	-5.4 (-9.4, -1.3)	-4.3 (-6.7, -2.0)
Other Organ Transplant Recipients		
eGFR _{Cr}	3.5 (-1.6, 8.5)	-0.3 (-5.2, 4.6)
eGFR _{Cys}	-8.3 (-12, -4.9)	-7.3 (-10, -4.1)
eGFR _{Cr-Cys}	-5.4 (-8.5, -2.2)	-5.8 (-8.8, -2.8)

Supplemental Table 2. Reclassification of eGFR by mGFR for clinically relevant categories.

eGFR (mL/min/1.73m ²)	eGFR _{Cr}				eGFR _{Cys}				eGFR _{Cr-Cys}			
	n	Lower	Same	Higher	n	Lower	Same	Higher	n	Lower	Same	Higher
>90												
Potential Donors	57	10.5%	89.5%	n/a	117	21.4%	78.6%	n/a	102	13.7%	86.3%	n/a
Clinical CKD	140	35.0%	65.0%	n/a	145	32.4%	67.6%	n/a	133	25.6%	74.4%*	n/a
Kidney Recipients	19	57.9%	42.1%	n/a	17	47.1%	52.9%	n/a	10	30.0%	70.0%*	n/a
Other Organ Recipients	29	48.3%	51.7%	n/a	27	22.2%	77.8%	n/a	22	27.3%	72.7%*	n/a
60-89												
Potential Donors	79	2.5%	35.4%	62.0%	23	4.3%	56.5%*	39.1%*	40	7.5%	60.0%**	32.5%*
Clinical CKD	176	11.9%	58.0%	30.1%	175	9.7%	65.1%	25.1%	203	10.3%	65.5%	24.1%
Kidney Recipients	149	24.8%	65.8%	9.4%	145	23.4%	70.3%	6.2%	150	19.3%	70.7%	10.0%
Other Organ Recipients	88	22.7%	56.8%	20.5%	84	10.7%	77.4%	11.9%	88	10.2%	71.6%	18.2%
45-59												
Potential Donors	11	0.0%	18.2%	81.8%	7	0.0%	14.3%	85.7%	5	0.0%	20.0%	80.0%
Clinical CKD	114	20.2%	30.7%	49.1%	100	17.0%	38.0%	45.0%	89	15.7%	41.6%	42.7%
Kidney Recipients	190	10.5%	49.5%	40.0%	171	5.3%	51.5%	43.3%	186	5.4%	53.8%	40.9%
Other Organ Recipients	85	23.5%	37.6%	38.8%	76	14.5%	43.4%	42.1%	73	9.6%	45.2%	45.2%
30-44												
Potential Donors	0	-	-	-	0	-	-	-	0	-	-	-
Clinical CKD	83	18.1%	39.8%	42.2%	80	13.8%	40.0%	46.3%	77	13.0%	46.8%	40.3%
Kidney Recipients	159	11.3%	42.1%	46.5%	157	4.5%	43.9%	51.6%	157	5.7%	48.4%	45.9%
Other Organ Recipients	90	7.8%	42.2%	50.0%	81	3.7%	40.7%	55.6%	101	5.9%	47.5%	46.5%
<30												
Potential Donors	0	n/a	-	-	0	n/a	-	-	0	n/a	-	-
Clinical CKD	105	n/a	81.0%	19.0%	118	n/a	78.8%	21.2%	116	n/a	81.0%	19.0%
Kidney Recipients	51	n/a	74.5%	25.5%	78	n/a	65.4%	34.6%	65	n/a	73.8%	26.2%
Other Organ Recipients	27	n/a	66.7%	33.3%	51	n/a	51.0%	49.0%	35	n/a	65.7%	34.3%
Total												
Potential Donors	147	5.4%	55.1%	39.5%	147	17.7%**	71.5%**	10.8%**	147	11.6%	76.9%**	11.6%**
Clinical CKD	618	18.4%	54.2%	27.4%	618	15.9%	58.7%	25.4%	618	13.6%	62.9%*	23.5%
Kidney Recipients	568	16.2%	52.4%	31.4%	568	10.1%*	55.1%	34.8%	568	9.0%*	58.0%	33.0%
Other Organ Recipients	319	19.9%	46.9%	33.2%	319	9.1%**	55.3%	35.6%	319	8.8%**	56.8%	34.4%

Significantly different compared to eGFR_{Cr} * p<0.01 **p<0.001

Supplemental Figure 1. Equation bias as a function of age. %Bias plotted as a function of age for (A) $eGFR_{Cr}$, (B) $eGFR_{Cys}$, and (C) $eGFR_{Cr-Cys}$. Equation bias decreased with age among other organ transplant recipients for $eGFR_{Cr}$ ($P=0.02$) and $eGFR_{Cr-Cys}$ ($P=0.02$) but not $eGFR_{Cys}$ ($P=0.07$).

