

# Implications of method specific creatinine adjustments on General Medical Services chronic kidney disease classification

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**Aims:** To evaluate the impact of different equations for calculation of estimated glomerular filtration rate (eGFR) on general practitioner (GP) workload.

**Methods:** Retrospective evaluation of routine workload data from a district general hospital chemical pathology laboratory serving a GP patient population of approximately 250 000. The most recent serum creatinine result from 80 583 patients was identified and used for the evaluation. eGFR was calculated using one of three different variants of the four-parameter Modification of Diet in Renal Disease (MDRD) equation.

**Results:** The original MDRD equation (eGFR<sub>186</sub>) and the modified equation with assay-specific data (eGFR<sub>175corrected</sub>) both identified similar numbers of patients with stage 4 and stage 5 chronic kidney disease (ChKD), but the modified equation without assay specific data (eGFR<sub>175</sub>) resulted in a significant increase in stage 4 ChKD. For stage 3 ChKD the eGFR<sub>175</sub> identified 28.69% of the population, the eGFR<sub>186</sub> identified 21.35% of the population and the eGFR<sub>175corrected</sub> identified 13.6% of the population.

**Conclusions:** Depending on the choice of equation there can be very large changes in the proportions of patients identified with the different stages of ChKD. Given that according to the General Medical Services Quality Framework, all patients with ChKD stages 3–5 should be included on a practice renal registry, and receive relevant drug therapy, this could have significant impacts on practice workload and drug budgets. It is essential that practices work with their local laboratories.

A new General Medical Services (GMS) contract was agreed in 2003 between general practitioners (GPs) and the United Kingdom Department of Health. Many of the clinical quality indicators (550 of the 1050 points) are based on clinical biochemistry assays.<sup>1</sup> Nine new areas totalling 138 points were introduced for 2006–07, including chronic kidney disease (ChKD). The four chronic kidney disease codes (ChKD1–ChKD4) make up 27 clinical points (table 1). The aim of ChKD1 is the production of a register of at-risk adults with stages 3–5 ChKD based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification.<sup>2</sup> These guidelines recommended that "the serum creatinine concentration alone should not be used to assess the level of kidney function".<sup>2</sup> The justification for this was that equations estimating glomerular filtration rate (GFR) based on serum creatinine and demographic data are more effective indicators of renal disease than serum creatinine alone.

One potential equation for the derivation of estimated glomerular filtration rate (eGFR) is the four-variable Modification of Diet in Renal Disease (MDRD) equation:

$$\bullet \text{ [eGFR} = 186 \times (\text{creatinine result}/88.4)^{-1.154} \times \text{Age}^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if Afro-Caribbean}]^3$$

(henceforth referred to as eGFR<sub>186</sub>). This was subsequently modified by changing the constant factor from 186 to 175 in December 2005 for use by those clinical laboratories which are using creatinine methods that have been calibrated to be traceable to isotope dilution mass spectroscopy<sup>4</sup> (IDMS) (henceforth referred to as eGFR<sub>175</sub>). It was further suggested by the United Kingdom National External Quality Assessment Service (UKNEQAS) that assay-specific parameters (that is, slope and intercept adjusters for the creatinine result) could be used to

approximate non-IDMS traceable creatinine results to an IDMS standardised method<sup>5</sup> (henceforth referred to as eGFR<sub>175corrected</sub>).

In April 2006, the Department of Health advised that GPs should allow laboratories to calculate eGFR<sup>6</sup> and that laboratories should employ the updated four-variable MDRD equation.<sup>4</sup> Reference was made to the UKNEQAS recommended correction factors for the MDRD equation<sup>5</sup> to adjust for method-related differences compared to the creatinine reference method.

**Table 1** Quality outcome framework for chronic kidney disease (ChKD)

Indicator	Points	Payment stages
ChKD1: The practice can produce a register of patients aged $\geq 18$ years with ChKD (US National Kidney Foundation: Stage 3–5 ChKD)	6	
ChKD2: The percentage of patients on the ChKD register whose notes have a record of blood pressure measurement in the previous 15 months	6	40–90%
ChKD3: The percentage of patients on the ChKD register in whom the last blood pressure reading, measured in the previous 15 months, is $\leq 140/85$ mm Hg	11	40–70%
ChKD4: The percentage of patients on the ChKD register who are treated with an ACE inhibitor or angiotensin receptor blocker (unless a contraindication or side effects are recorded)	4	40–80%

**Abbreviations:** ChKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; GP, general practitioner; GMS, General Medical Services; IDMS, isotope dilution mass spectroscopy; MDRD, Modification of Diet in Renal Disease; UKNEQAS, United Kingdom National External Quality Assessment Service

First Name	Last Name	Date of Birth	Reg GP	Usual GP	eGFR	Creatinine	Calc. eGFR	Stage	Afro-Caribbean?
		14 Apr 1931			88.0	57.8		Stage 3	Unknown
		2 May 1918			110.0	58.2		Stage 3	Unknown
		17 Jan 1923			86.0	58.0		Stage 3	Unknown
		22 Sep 1920			91.0	54.0		Stage 3	Unknown
		14 Jun 1945			98.0	53.2		Stage 3	Unknown
		21 Dec 1932			123.0	53.0		Stage 3	Unknown
		5 Apr 1936			140.0	46.2		Stage 3	Unknown
		30 Mar 1938			92.0	55.8		Stage 3	Unknown
		10 May 1933			178.0	34.7		Stage 3	Unknown
		20 Apr 1917			90.0	54.4		Stage 3	Unknown
		11 Sep 1918			87.0	56.6		Stage 3	Unknown
		19 Mar 1918			91.0	53.7		Stage 3	Unknown
		24 May 1940			128.0	51.8		Stage 3	Unknown
		13 May 1924			100.0	48.9		Stage 3	Unknown
		29 Aug 1929			38.0	164.0	37.7	Stage 3	Unknown
		18 Apr 1929			46.0	139.0	45.7	Stage 3	Unknown
		11 Jan 1931			50.0	136.0	47.0	Stage 3	Unknown
		15 Feb 1928			51.0	104.0	47.1	Stage 3	Unknown
		13 Jun 1923			53.0	117.0	54.9	Stage 3	Unknown
		22 Jul 1940			56.0	121.0	55.3	Stage 3	Unknown
		28 Dec 1960			61.0	93.0	58.8	Stage 2	Unknown
		11 Mar 1940			62.0	116.0	57.9	Stage 2	Unknown
		21 Sep 1935			62.0	115.0	57.8	Stage 2	Unknown
		15 Nov 1938			63.0	114.0	58.9	Stage 2	Unknown
		5 Dec 1927			63.0	112.0	58.3	Stage 2	Unknown
		18 Mar 1924			63.0	111.0	58.3	Stage 2	Unknown
		18 Aug 1929			65.0	88.0	57.4	Stage 2	Unknown
		5 Aug 1941			67.0	88.0	58.5	Stage 2	Unknown
		3 Jan 1934			68.0	86.0	59.6	Stage 2	Unknown
		31 Dec 1934			68.0	86.0	58.8	Stage 2	Unknown

**Figure 1** Screenshot from general practitioner (GP) computer system. The estimated glomerular filtration rate (eGFR) column represents the estimated GFR calculated by the laboratory (eGFR<sub>175</sub>) and the Calc. eGFR column represents the estimated GFR calculated by the GP system (eGFR<sub>186</sub>).

Accordingly, some UK laboratories have introduced eGFR using eGFR<sub>175corrected</sub> while others have continued to use eGFR<sub>186</sub>, pending evaluation of the impact of the new guidelines. In addition, some general practice surgeries are using their computer systems to directly calculate eGFR and may use eGFR<sub>175</sub>, on the assumption that this is the correct formula.

Figure 1 shows an anonymised screenshot from a GP computer system that was submitted to the Ipswich Hospital Department of Clinical Biochemistry as possible evidence that laboratory eGFR<sub>175</sub> results (see below) were “incorrect” because they differed from those calculated within the GP system (eGFR<sub>186</sub>). We have previously shown that a change of creatinine assay method due to a change of analyser had little impact on prevalence of the different ChKD stages.<sup>7</sup> However, as the use of different methods to derive eGFR could result in different prevalence rates of ChKD, we decided to investigate the degree of any such difference.

## METHODS AND RESULTS

Using the laboratory computer in Queen’s Hospital, Burton-on-Trent, we obtained the most recent serum creatinine result on every primary care patient that had had a creatinine requested between 18 August 2002 and 31 August 2005. Creatinine results

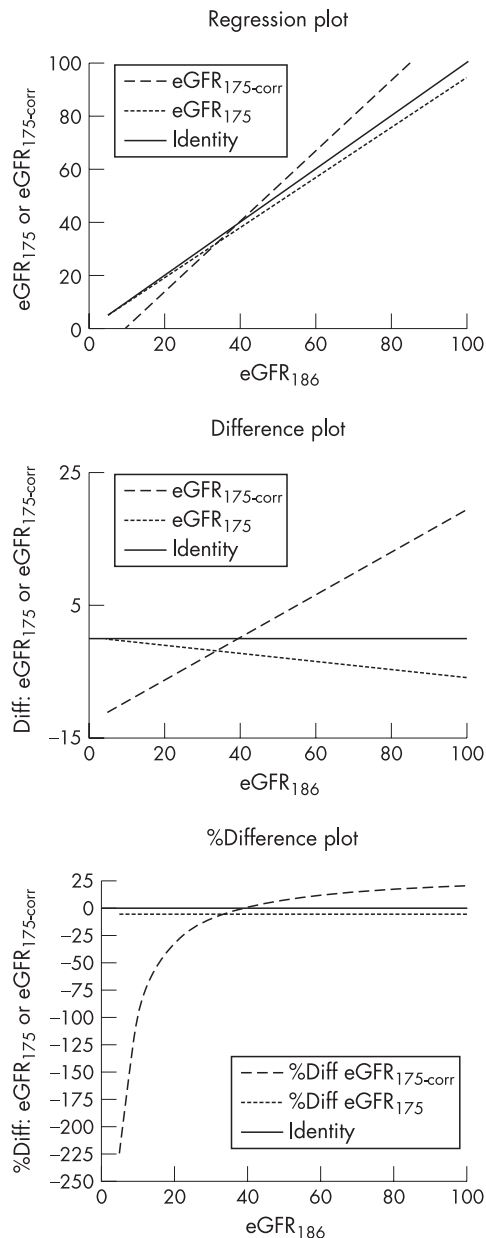
were obtained for 80 583 individual patients. The creatinine method employed was a kinetic alkaline picrate assay (Olympus Diagnostica GmbH, Ireland) on an Olympus AU640 analyser (Olympus Diagnostica). Inter-assay coefficients of variation for creatinine are 1.97% at 70 µmol/l, 1.74% at 180 µmol/l and 1.31% at 564 µmol/l. Using each creatinine concentration and the corresponding patient’s age, ethnicity and gender, we calculated the eGFR<sub>186</sub>, eGFR<sub>175</sub> and eGFR<sub>175corrected</sub>.

The assay specific parameters as defined by UKNEQAS<sup>8</sup> employed for the Olympus creatinine were 0.955 and -16.14 for the slope and the intercept respectively. Pearson’s least squares correlations between eGFR<sub>186</sub>-eGFR<sub>175</sub>, eGFR<sub>186</sub>-eGFR<sub>175corrected</sub> and eGFR<sub>175</sub>-eGFR<sub>175corrected</sub> were unsurprisingly good with  $r = 1.000$ ,  $0.986$  and  $0.986$  respectively. Figure 2 shows regression, difference and %difference plots of eGFR<sub>186</sub> versus eGFR<sub>175</sub> and eGFR<sub>186</sub> versus eGFR<sub>175corrected</sub>.<sup>9</sup> The faint solid line is the line of identity. It is unsurprising but clear that eGFR<sub>175</sub> gives lower results throughout the creatinine range while eGFR<sub>175corrected</sub> gives lower eGFR estimates in the lower regions of the scale, and that above approximately 40 ml/min, the eGFR<sub>175corrected</sub> is higher than the eGFR<sub>186</sub> estimate. One might expect that the net effect of eGFR<sub>175corrected</sub> must be to

**Table 2** Prevalence of chronic kidney disease (ChKD) based on the three different versions of the four-variable Modification of Diet in Renal Disease equation

ChKD stage	5	4	3	2	1
eGFR (ml/min)	<15	15–29	30–59	60–89	>90
eGFR <sub>186</sub>	176 (0.22%)	848 (1.05%)	17202 (21.35%)	53222 (66.06%)	9135 (11.34%)
eGFR <sub>175</sub>	196 (0.24%)	1098 (1.36%)	23121 (28.69%)	51094 (63.41%)	5074 (6.30%)
eGFR <sub>175corrected</sub>	190 (0.24%)	831 (1.03%)	10956 (13.60%)	43025 (53.41%)	25581 (31.75%)

eGFR, estimated glomerular filtration rate.  
n=80 583.



**Figure 2** Plots showing the relationship between eGFR<sub>186</sub>, and eGFR<sub>175</sub> and eGFR<sub>175corrected</sub>. eGFR, estimated glomerular filtration rate.

increase the proportion of cases in which the eGFR<sub>175</sub> indicates ChKD stages 4 (eGFR 15–30) and 5 (eGFR <15). However, table 2 shows that there is, in fact, little difference between eGFR<sub>186</sub> versus eGFR<sub>175corrected</sub> with respect to ChKD stages 4 and 5. With respect to the prevalence of stage 3 however, the eGFR<sub>175corrected</sub> shows a significant reduction, with more patients being identified in stages 1 and 2. Use of eGFR<sub>175</sub> significantly increases the prevalence of stage 3 such that over 30% of patients would require inclusion on the renal register.

## CONCLUSIONS

We conclude that significant population differences exist between the three equations studied. The initial MDRD equation is based on 1628 samples from people with ChKD analysed using a kinetic alkaline picrate creatinine method.<sup>8</sup> Subsequent modifications of the four-variable equation,<sup>3</sup> such as changing the constant factor or the addition of multiple assay-specific adjustment factors, have the potential to be a recipe for confusion. The advice currently on the Department of Health website recommends that the eGFR<sub>175</sub>

## Take-home messages

- Estimated glomerular filtration rate (eGFR) is not a simple value that can easily be calculated.
- Different formulae for calculation of eGFR lead to different chronic kidney disease (ChKD) identification outcomes.
- Use of the “wrong” eGFR formula can significantly increase the screen positive rate (ie, numbers of patients with ChKD stage 3).
- Identifying more patients with ChKD3 increases general practitioner (GP) workload and costs, and also increases problems for patients.
- Laboratories and not GPs should calculate eGFR.

equation with the inclusion of adjustments provided by UKNEQAS should be used.<sup>6</sup> We have shown that use of the wrong formula results in a greater number of patients in the at-risk groups. We concur with the Department of Health that clinical biochemistry laboratories are best placed to produce eGFR results once they strictly adhere to the instructions of the manufacturer of the creatinine assay.

General practices that use their practice computer system may potentially diagnose more patients with ChKD than actually have it, and thus significantly and needlessly increase the work they have to perform to achieve quality targets. Furthermore, since quality targets also define prescription of ACE inhibitors or angiotensin receptor blockers, this also has the potential to seriously impact on primary care trust budgets. Perhaps more importantly, in addition to the possibility of receiving incorrect/unnecessary treatment, there are many potential disadvantages to the individual (psychological, financial, and so forth) of being given the diagnosis “chronic kidney disease”. We cannot therefore stress more highly the importance of using the correct equation for calculation.

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