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Original Article

## The practical implications of using standardized estimation equations in calculating the prevalence of chronic kidney disease

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### Abstract

**Background.** Kidney Disease Outcomes Quality Initiative (KDOQI) chronic kidney disease (CKD) guidelines have focused on the utility of using the modified four-variable MDRD equation (now traceable by isotope dilution mass spectrometry IDMS) in calculating estimated glomerular filtration rates (eGFRs). This study assesses the practical implications of eGFR correction equations on the range of creatinine assays currently used in the UK and further investigates the effect of these equations on the calculated prevalence of CKD in one UK region

**Methods.** Using simulation, a range of creatinine data (30–300  $\mu\text{mol/l}$ ) was generated for male and female patients aged 20–100 years. The maximum differences between the IDMS and MDRD equations for all 14 UK laboratory techniques for serum creatinine measurement were explored with an average of individual eGFRs calculated according to MDRD and IDMS  $<60 \text{ ml/min/1.73 m}^2$  and  $30 \text{ ml/min/1.73 m}^2$ . Similar procedures were applied to 712 540 samples from patients  $\geq 18$  years (reflecting the five methods for serum creatinine measurement utilized in Northern Ireland) to explore, graphically, maximum differences in assays. CKD prevalence using both estimation equations was compared using an existing cohort of observed data.

**Results.** Simulated data indicates that the majority of laboratories in the UK have small differences between the IDMS and MDRD methods of eGFR measurement for stages 4 and 5 CKD (where the averaged maximum difference for all laboratory methods was  $1.27 \text{ ml/min/1.73 m}^2$  for females and  $1.59 \text{ ml/min/1.73 m}^2$  for males). MDRD deviated furthest from the IDMS results for the Endpoint Jaffe

method: the maximum difference of  $9.93 \text{ ml/min/1.73 m}^2$  for females and  $5.42 \text{ ml/min/1.73 m}^2$  for males occurred at extreme ages and in those with eGFR  $>30 \text{ ml/min/1.73 m}^2$ . Observed data for 93,870 patients yielded a first MDRD eGFR  $<60 \text{ ml/min/1.73 m}^2$  in 2001. 66 429 (71%) had a second test  $>3$  months later of which 47 093 (71%) continued to have an eGFR  $<60 \text{ ml/min/1.73 m}^2$ . Estimated crude prevalence was 3.97% for laboratory detected CKD in adults using the MDRD equation which fell to 3.69% when applying the IDMS equation. Over 95% of this difference in prevalence was explained by older females with stage 3 CKD (eGFR  $30\text{--}59 \text{ ml/min/1.73 m}^2$ ) close to the stage 2 CKD (eGFR  $60\text{--}90 \text{ ml/min/1.73 m}^2$ ) interface.

**Conclusions.** Improved accuracy of eGFR is obtainable by using IDMS correction especially in the earlier stages of CKD 1–3. Our data indicates that this improved accuracy could lead to reduced prevalence estimates and potentially a decreased likelihood of onward referral to nephrology services particularly in older females.

**Keywords:** CKD; creatinine standardization; eGFR; IDMS; MDRD; prevalence

### Introduction

Recent guidelines [1] for assessment of renal function have focused on the utility and benefit of using the modified 4-variable MDRD equation [2] (traceable by isotope dilution mass spectrometry, IDMS), first described by Levey et al. [3] in 2005. The traceable IDMS method was introduced following recalibration of Beckman Synchron CX3 (Global Medical Instrumentation, Inc., Ramsey, Minnesota) assay to the Roche/Hitachi P module Creatinase Plus enzymatic assay (Roche Diagnostics, Basel, Switzerland), traceable to an IDMS assay at the National Institute of Standards and Technology (NIST). This traceable eGFR estimation equation, provided by Levey and

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**Table 1.** Intercepts and slopes including maximum deviations for all 14 UK laboratory methods of serum creatinine measurement

Method ID	Laboratory method	Intercept	Slope <sup>a</sup>	Maximum deviation between MDRD and IDMS eGFR for creatinine assay			
				Maximum deviation (F)		Maximum deviation (M)	
				<60 eGFR	<30 eGFR	<60 eGFR	<30 eGFR
1	Roche Modular reagents [11BO]	3.08	1.004	1.37	1.13	1.81	1.26
2	Beckman reagents [11BK]	5.92	0.994	1.14	0.96	1.29	1.20
3	Abbott reagents [11AB]	13.21	0.940	4.01	1.50	2.09	2.06
4	Dry Slide, OCD (J&J) slides [1JJ]	7.71	0.988	2.32	0.87	1.17	1.16
5	Olympus, O'Leary	24.55	0.854	8.57	2.66	3.58	3.57
6	Bayer reagents [11TE]	17.78	0.927	7.25	1.40	3.60	1.88
7	Dade Behring reagents [11BE]	6.78	1.030	4.25	0.80	2.92	0.44
8	Olympus reagents [11OL]	16.14	0.955	7.60	0.90	4.34	1.21
9	Roche Integra reagents [11RO]	2.03	0.988	0.96	1.13	1.81	1.26
10	ILab reagents [6IL]	21.77	0.908	9.58	1.51	5.11	2.03
11	Enzymatic	-0.26	1.011	3.13	1.51	3.07	1.50
12	Endpoint Jaffe	22.02	0.910	9.93	1.44	5.42	1.94
13	Kinetic Jaffe	11.60	0.970	4.56	0.92	2.22	1.24
14	All methods <sup>b</sup>	12.73	0.959	4.84	1.08	2.25	1.46
Averaged maximum deviation for all 14 methods:				4.97	1.27	2.91	1.59

Notes: Methods 1–5 (shaded) represent the laboratory techniques used in Northern Ireland.

<sup>a</sup>Intercept and slope provided by UKNEQAS<sup>12</sup>.

<sup>b</sup>'All methods' refers to substitute intercept and slope (recommended by NEQAS) to be used if laboratory method is unknown.

coworkers, has become the 'gold standard' by which all other eGFR estimation equations are measured and is part of a global attempt to standardize creatinine assays to allow accurate and reproducible eGFR reporting [4]. The impact of eGFR standardization is such that recent publications have explicitly referred to its use in their methods implying that in studies of chronic kidney disease (CKD), failure to standardize eGFR in this way may reduce the validity of the study [5].

The original 4-variable MDRD equation and its subsequent use in simplifying CKD guidelines have been called into question because of concern surrounding the standardization of eGFR. The recent change to reporting 'standardized eGFR' has generated doubt about the validity of CKD epidemiology studies that were based on previously calculated eGFRs [6,7]. Practising nephrologists are also concerned that the original 4-variable MDRD may have led to misclassification of CKD stage in patients with renal disease, potentially influencing the likelihood of referral to secondary care.

Our study assesses the immediate practical impact of introducing the traceable IDMS method of eGFR calculation (facilitated by nationally provided appropriate intermediary corrections) compared to the original MDRD equation on reported prevalence of CKD. We also compared these two eGFR calculations using a mathematical software package, MATLAB.

## Methods

Data were received on all serum creatinine assays performed in Northern Ireland laboratories between 1 January 2001 and

31 December 2002. Northern Ireland is a single predominantly rural region of the United Kingdom with a stable population of almost 1.7 million, 99% of whom are of white Caucasian origin. Individual blood sample records were linked to produce a patient database as described previously [8]. We were able to match 99.7% of the test results to individual patient's database. This initial cohort was assessed in two separate analyses. In the first, a database of unique patients with samples tested in 2001 was identified to allow the calculation of prevalence of CKD as defined by Kidney Disease Outcomes Quality Initiative (KDOQI):

GFR < 60 ml/min/1.73 m<sup>2</sup> for ≥ 3 months, with or without kidney damage [1].

In accordance with this statement, all patients aged 20 years and over were selected if they had one eGFR measurement < 60 ml/min/1.73 m<sup>2</sup> in 2001, followed by a second measurement < 60 ml/min/1.73 m<sup>2</sup> at an interval of ≥ 3 calendar months. Estimated GFR was calculated using the MDRD and subsequently recalculated using the IDMS correction equation. The five creatinine assays used in Northern Ireland at that time are identified in the shaded area in Table 1. In 2001–2002 no formal regional creatinine standardization took place in Northern Ireland; laboratories throughout the UK were dependent on assay manufacturer's quality control systems to ensure comparability.

Estimated GFR measurements were categorized according to KDOQI stages 3, 4 and 5, using the value recorded for the first test where eGFR was < 60 ml/min/1.73 m<sup>2</sup> for each patient between 1 January 2001 and 31 December 2001. The patient's age at the time of the first test was used to assign patients to an age band. The prevalence of CKD in Northern Ireland was calculated based on the denominator population (by 10-year age bands) available from the population census in April 2001 [9]. The total population was enumerated as 1 685 268, with 1 185 114 aged 20 years and over. Repeat calculation of prevalence was performed using the IDMS correction.

MATLAB is a high-level technical computing language and interactive environment for algorithm development, data visualization, data analysis and numeric computation [10–12]. In our second analysis, a unique code was written in MATLAB to generate data to explore the maximum differences possible between the MDRD and the IDMS traceable equations for stages 3–5 CKD. That is, the well-established MDRD and IDMS equations were used as input and forced to loop over a range of serum creatinine values between 30 and 300  $\mu\text{mol/l}$  with a range of simulated patients aged 20–100 years. The maximum difference between the averaged MDRD and the averaged IDMS output was constrained, whereby the average had to be  $<60 \text{ ml/min}/1.73 \text{ m}^2$  and  $<30 \text{ ml/min}/1.73 \text{ m}^2$ , in turn. All 14 laboratory methods used in the UK were explored using the intercepts and slopes for the IDMS equation provided by United Kingdom National External Quality Assessment Service (UKNEQAS) [13].

This concept was further explored in the directly observed Northern Ireland data collected between 1 January 2001 and 31 December 2002. Whilst KDOQI requirements for prevalence calculation stipulated an age criteria  $\geq 20$  years, The Renal Association UK guidelines [14] released in 2006 advised eGFR calculation for all individuals aged  $\geq 18$  years. Therefore in our second analysis, we selected observed results from any individual  $\geq 18$  years to compare the MDRD estimate to the IDMS correction. The agreement between the two equations was then explored by plotting the difference against the average for all samples. The plotted graph was then colour coded by laboratory method to highlight the maximum deviation for each method that permits comparison of the observed and simulated data in Table 1 and Figure 2.

## Results

Table 1 displays the intercepts and slopes used in the IDMS traceable equations for all 14 UK serum creatinine assays, provided by NEQAS. Further, it highlights the maximum deviation for all the 14 methods when the average between the IDMS and the MDRD was  $<60 \text{ ml/min}/1.73 \text{ m}^2$  and  $<30 \text{ ml/min}/1.73 \text{ m}^2$  for both females and males over all ages and serum creatinines as defined in the methods section. Only small differences are seen comparing the IDMS with the MDRD methods of eGFR calculation in patients with stage 4 or 5 CKD where the averaged maximum difference for all laboratory methods was  $1.27 \text{ ml/min}/1.73 \text{ m}^2$  for females and  $1.59 \text{ ml/min}/1.73 \text{ m}^2$  for males. Analysing all UK methods, the maximum deviation between the IDMS and the MDRD methods occurred with the Endpoint Jaffe method with a value of  $9.93 \text{ ml/min}/1.73 \text{ m}^2$  for females and  $5.42 \text{ ml/min}/1.73 \text{ m}^2$  for males. However, these maximums occurred at extremes of age and in those with eGFR reflecting stage 3 CKD. Figure 1 illustrates graphically an example of the variation that exists between the MDRD and the IDMS traceable equations for all 14 UK laboratory techniques, across serum creatinine values for females aged 70. Below  $60 \text{ ml/min}/1.73 \text{ m}^2$  (the dashed line), the

difference between all methods of serum creatinine measurement diminishes as renal function declines.

Figure 2 illustrates observed data from the Northern Ireland population and represents the plot of 712 540 samples for patients 18 years or older who had an average eGFR  $<60 \text{ ml/min}/1.73 \text{ m}^2$ . The maximum deviation between the IDMS and the MDRD equations is just over  $8.5 \text{ ml/min}/1.73 \text{ m}^2$ , which occurred using method 5 Olympus O'Leary (yellow plot) consistent with the simulated data. For estimated GFRs of  $>60 \text{ ml/min}/1.73 \text{ m}^2$ , the graph shows greater dispersion, that is, larger differences between the two equations.

Prevalence was calculated using blood samples tested for serum creatinine in Northern Ireland laboratories between 1 January 2001 and 31 December 2001. After matching and merging sample data, a patient database was generated containing 345 160 patients aged 20 years and over who had one or more serum creatinine tests performed in 2001 and sufficient additional information (age and gender) to calculate eGFR. We then applied the definition of CKD based on a first eGFR  $<60 \text{ ml/min}/1.73 \text{ m}^2$  followed by a second eGFR  $<60 \text{ ml/min}/1.73 \text{ m}^2$  at an interval of  $\geq 3$  calendar months. This yielded 93 870 patients with a first eGFR  $<60 \text{ ml/min}/1.73 \text{ m}^2$  between 1 January 2001 and 31 December 2001. Out of those, 71% (66 429) went on to have a second test  $\geq 3$  months later. Of these, 71% (47 093) had a subsequent test which was still  $<60 \text{ ml/min}/1.73 \text{ m}^2$ , thus meeting the definition of CKD based on eGFR as outlined by KDOQI [1]. The population of Northern Ireland aged 20 years and over was 1 185 114 at the census in 2001. The crude prevalence rate of laboratory detected CKD in Northern Ireland in adults aged 20 years and over is therefore 3.97%. Using the IDMS correction, the overall calculated prevalence was reduced to 3.69%. Over 95% of the difference in prevalence was explained by older females, previously classified as having stage 3 CKD (eGFR  $30\text{--}59 \text{ ml/min}/1.73 \text{ m}^2$ ) based on the MDRD equation being reclassified into stage 2 CKD (eGFR  $60\text{--}90 \text{ ml/min}/1.73 \text{ m}^2$ ) when the IDMS calculation was applied. The MDRD and IDMS results were categorized by CKD stage, gender and age (Table 2). The proportion of patients in CKD stages 3, 4 and 5 differed significantly between the MDRD-derived classification and the IDMS classification ( $p < 0.001$ ,  $\chi^2$  629). The main contributors to the chi-square test statistic were older females, clustered close to the upper limit of stage 3 CKD (eGFR  $30\text{--}59 \text{ ml/min}/1.73 \text{ m}^2$ ). These results are illustrated in Table 2 with the results accounting for the change in prevalence in the shaded area.

## Discussion

This study demonstrates that there is little difference between eGFR values calculated by the MDRD and IDMS traceable equations for individual patients with stage 4 CKD (eGFR  $15\text{--}29 \text{ ml/min}/1.73 \text{ m}^2$ ) or stage

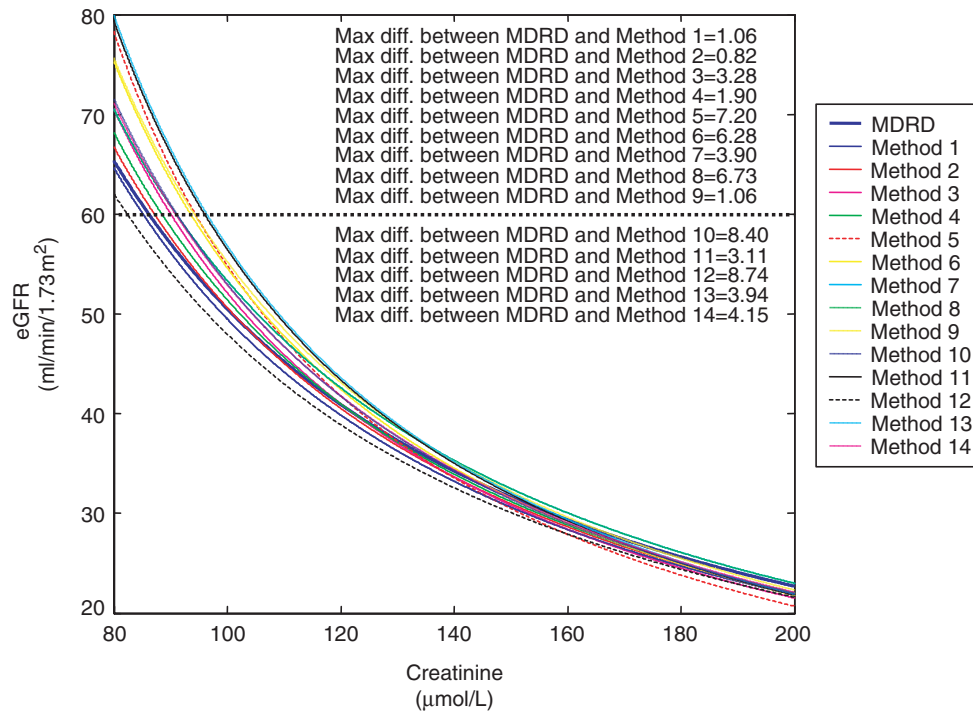
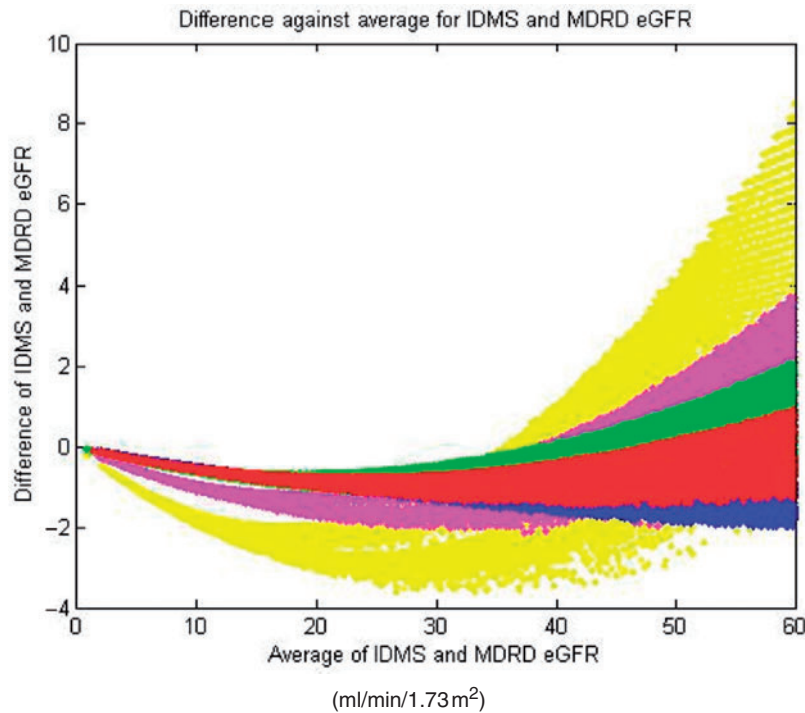


Fig. 1. Variation between MDRD and IDMS traceable equations for all 14 laboratory methods of serum creatinine measurement in a simulated female patient aged 70.



All above units represent absolute changes in eGFR (ml/min/1.73 m<sup>2</sup>)

- Blue: Method 1, Roche Modular
- Red: Method 2, Beckman
- Pink: Method 3, Abbott
- Green: Method 4, OCD
- Yellow: Method 5, Olympus

Fig. 2. Maximum deviations between MDRD and IDMS eGFR equations in Northern Ireland observed data.

**Table 2.** Effect of IDMS correction on prevalence of CKD in observed Northern Ireland data tabulated by 10-year age bands

Age	Numbers of patients categorized by age and MDRD eGFR CKD stage (IDMS correction effect)							
	3		4		5		TOTAL	
	M	F	M	F	M	F	M	F
20–29	55 (5) <sup>a</sup> [0.42]	49 (0) [0.00]	7 (5) [2.08]	15 (–1) [0.07]	24 (0) [0.00]	15 (3) [0.50]	86 (10)	79 (2)
30–39	129 (2) [0.03]	173 (–7) [0.30]	31 (3) [0.26]	23 (1) [0.04]	38 (2) [0.10]	29 (0) [0.00]	198 (7)	225 (–6)
40–49	289 (21) [1.42]	538 (–56) [6.51]	56 (5) [0.41]	50 (3) [0.17]	51 (2) [0.08]	39 (0) [0.00]	396 (28)	627 (–53)
50–59	1054 (49) [2.18]	2244 (–342) [61.50]	89 (16) [2.44]	93 (6) [0.36]	89 (4) [0.17]	56 (3) [0.15]	1232 (69)	2393 (–333)
60–69	3136 (–21) [0.14]	5825 (–942) [181.73]	216 (15) [0.97]	263 (21) [1.55]	106 (15) [1.86]	121 (10) [0.76]	3458 (9)	6209 (–911)
70–79	5442 (–145) [3.97]	10758 (–1371) [200.24]	424 (64) [8.39]	724 (67) [5.68]	122 (18) [2.31]	117 (23) [3.78]	5988 (–63)	11599 (–1281)
80+	3673 (–124) [4.33]	9282 (–940) [105.92]	380 (84) [15.21]	1077 (108) [9.84]	81 (7) [0.56]	110 (17) [2.28]	4134 (–33)	10469 (–815)
Totals	13778 (–213) 42647 (–3871)	28869 (–3658)	1203 (192) 3448 (397)	2245 (205)	511 (48) 998 (104)	487 (56)	15492 (27) 47093 (–3370)	31601 (–3397)

<sup>a</sup>By way of example: 55 male subjects (20–29) were originally categorized as stage 3 CKD using MDRD equation. (5) Additional male subjects were recategorized to stage 3 using IDMS correction; the contribution to overall  $\chi^2$  was [0.42].

5 CKD (eGFR < 15 ml/min/1.73 m<sup>2</sup>). However on a population level, the difference between these two eGFR equations does make a significant difference to the overall prevalence. This is because some patients, particularly older females, are reclassified from stage 3 CKD (eGFR 30–59 ml/min/1.73 m<sup>2</sup>) by the MDRD equation to stage 2 CKD (eGFR 60–90 ml/min/1.73 m<sup>2</sup>), using the IDMS traceable method of eGFR calculation. This difference in eGFR classification impacts on the overall prevalence rate attributed to CKD stages 3, 4 and 5 and will have implications for CKD epidemiological research and public health policy.

Clinical pragmatism is crucial in the management of CKD; and in the absence of evidence-based guidelines expert consensus opinion is often the default position. Sensible referral criteria and management guidelines have to be designed to maximize benefit to the greatest number of patients possible. The introduction of eGFR reporting was, in part, a response to numerous epidemiological studies that confirmed a higher prevalence of early CKD and its associated cardiovascular mortality than had previously been appreciated [15,16]. In practice, the introduction of eGFR has improved awareness of CKD beyond the nephrology community. It is hoped that future use will help reduce the likelihood of late referral, particularly evident in the older population.

Nephrologists have extensively debated the definition of CKD, and even now there is a little consensus over the clinical significance of having an eGFR between 60 ml/min/1.73 m<sup>2</sup> and 90 ml/min/1.73 m<sup>2</sup> [17]. It was already known that eGFR calculation, using the MDRD equation, differed from gold standard methods of GFR estimations, especially when eGFR is >60 ml/min/1.73 m<sup>2</sup> [18,19]. The

original MDRD equation was validated in patients with a mean GFR of 39.8 (±21.2) ml/min/1.73 m<sup>2</sup>, aged 50.6 (±12.7) years with a mean serum creatinine of 203 (±106) µmol/l rather than in patients with much better renal function. Within this group of patients with milder impairment of kidney function, additional information about other clinical variables such as proteinuria and hypertension is required to help determine individual risk for progression of CKD [20].

Considering the accepted inadequacies of eGFR in patients with better renal function (CKD stages 1 and 2), we chose to concentrate our analysis on those with CKD stages 3, 4 and 5. Using statistical models and a large population cohort, we have shown that standardization with ‘gold standard’ IDMS calculation has a smaller effect on estimation of eGFR in these categories. Current UK guidelines designate CKD as a patient with an eGFR <60 ml/min/1.73 m<sup>2</sup> (stage 3, 4 and 5 CKD). Considering the potentially large clinical burden of CKD within health care systems, current attempts to increase accuracy in eGFR reporting are to be welcomed, especially if they result in decreased clinical demand on renal services. The IDMS correction is a minor, but none the less significant, advance in accuracy; it has minimal effect on estimation in patients with an eGFR <45 ml/min/1.73 m<sup>2</sup>, but we have demonstrated its improved accuracy in those middle aged to elderly females with an eGFR slightly above 60 ml/min/1.73 m<sup>2</sup>. This is particularly important considering the recent guidelines to define stage 3 CKD as an eGFR <60 ml/min/1.73 m<sup>2</sup>.

Standardization with the IDMS correction is also important [3,5,21,22] for epidemiological and longitudinal studies in that it offers the most accurate estimation of eGFR practically available. However, we

would suggest that more emphasis needs to be placed on the rate of eGFR decline and associated risk factors for rapid progression (proteinuria and hypertension) [23] that are more relevant to poor outcomes in CKD. The standardization of eGFR measurement may modestly improve individual measurement of eGFR  $>60$  ml/min/1.73 m<sup>2</sup>, but only serial measurements, with direct comparison, can provide us with accurate information on progression of CKD.

The inherent weakness of the MDRD equation (and IDMS modification) is that they are, by definition, estimates derived from a highly selected population recruited for a clinical trial of CKD progression. The clinical application of eGFR must be tempered by knowledge and understanding their limitations. The most obvious limiting factor to the accuracy of eGFR estimation is the potential variance in initial creatinine estimation [24,25]. This study clearly demonstrates the problems associated with inter-assay variance and its subsequent effect on eGFR estimation. Current attempts to achieve consensus will hopefully result in assay manufacturers producing internationally standardized methods of creatinine estimation. In the interim, national bodies such as UKNEQAS have facilitated the immediate introduction of the IDMS equation by providing correction factors for current creatinine assays [13].

The IDMS equation was devised only for the use with traceable creatinine assays [3]; however, considering the delay in achieving global standardization in assays, it is important to understand and investigate the practical benefits of using this correction equation in preference to the standard 4-variable MDRD equation in the interim period. Whilst this methodology is imperfect, it represents current practice and this study attempts to assess both the strengths and the weaknesses of its practical implementation.

Standardized eGFR measurements are important for determining an individual patient's rate of CKD progression and providing more accurate assessment of population prevalence of CKD. Nevertheless eGFR is not an accurate measurement of current clinical state; it does not take into account blood pressure, proteinuria, and presence of diabetes or renal failure symptoms. Renal risk scores and the use of alternative markers such as cystatin C may eventually supplement the current estimation techniques; but until that time, recurrent assessment in risk groups is the only practically applicable method [26].

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