Title
CamGFR v2: a new model for estimating the glomerular filtration rate from standardized or non-standardized creatinine in patients with cancer

Authors
Edward H. Williams¹; Thomas R. Flint²; Claire M. Connell¹,³; Daniel Giglio⁴; Hassal Lee⁵; Taehoon Ha⁶; Eva Gablenz⁶; Nicholas Bird²; James M. J. Weaver⁷,⁸; Harry Potts⁵; Cameron T. Whitley⁵; Michael A. Bookman⁹; Andy G. Lynch¹,¹⁰,¹¹; Hannah V. Meyer⁶; Simon Tavare¹,¹²; Tobias Janowitz⁶,¹³∗.

Affiliations
1. Cancer Research UK Cambridge Institute, University of Cambridge, Cambridge, UK
2. Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
3. University of Cambridge, Cambridge, UK
4. Department of Oncology, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden
5. University of Cambridge School of Clinical Medicine, Cambridge, UK
6. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA
7. The Christie NHS Foundation Trust, Manchester, UK
8. University of Manchester, Manchester, UK
9. Gynecologic Oncology Therapeutics, Kaiser Permanente, San Francisco, USA
10. School of Medicine, University of St Andrews, St Andrews, UK
11. School of Mathematics and Statistics, University of St Andrews, St Andrews, UK
12. Columbia University, New York, USA
13. Northwell Health, New York, USA

Keywords

GFR; eGFR; creatinine; carboplatin; chemotherapy

Running Title

CamGFR v2 estimates GFR in patients with cancer

Financial Support

This work was supported in part by Developmental Funds from the Cold Spring Harbor Laboratory (CSHL) Cancer Center Support Grant 5P30CA045508. Funding is acknowledged from Cancer Research UK (E.H.W., S.T., T.J., and A.G.L.), from CSHL (T.H., H.V.M., and T.J.), from the Simons Center for Quantitative Biology (H.V.M.), from the Pershing Square Foundation (T.J.), from The Experimental Medicine Training Initiative (C.M.C.), from the National Institute for Health Research UK (J.M.J.W.), and from a Carl-Duisberg Scholarship and a German National Merit Scholarship (EG). S.T. is a Consultant for Kallyope, Inc.

Corresponding Author

Dr Tobias Janowitz
Assistant Professor
Cold Spring Harbor Laboratory
New York 11724
Conflicts of Interest

No conflicts of interest are declared by any author.

Manuscript Details

The word count is 4,175 not including title page, abstract, relevance statement, tables, equations, figures, legends, acknowledgments, references, and supplemental material. The manuscript also includes four figures, one table and one equation. The supplemental materials include a further 11 figures and 18 tables.
Translational Relevance

An accurate and broadly applicable approach to determine the estimated glomerular filtration rate (eGFR) is an area of clinical need, because eGFR informs the safe and effective prescription of chemotherapies. This is especially true for carboplatin therapy. To date, models for eGFR were either developed using data from patients with chronic kidney disease, or were restricted to either isotope dilution mass spectrometry (IDMS)- or non-IDMS-standardized creatinine measurements. Applied to patients with cancer, these variables introduce significant biases and inaccuracies of eGFR that impact upon the quality of their care.

Here we use gold-standard GFR measurements from 7,240 patients from three centers to develop and validate a broadly applicable linear model, CamGFR v2, for eGFR in patients with cancer. This new model outperforms all other tested models irrespective of patient demographics or creatinine measurement methodology. It also results in more clinically robust carboplatin dose calculations.

CamGFR v2 can now be utilized through our free online app (https://sites.google.com/site/janowitzwilliamsgfr/), but requires independent validation to confirm it as a practice-changing standard of care.
Abstract

Purpose
Management of patients with cancer, specifically carboplatin dosing, requires accurate knowledge of glomerular filtration rate (GFR). Direct measurement of GFR is resource-limited. Available models for estimated GFR (eGFR) are optimized for patients without cancer and either isotope dilution mass spectrometry (IDMS)- or non-IDMS-standardized creatinine measurements. We present an eGFR model for patients with cancer compatible with both creatinine measurement methods.

Methods
GFR measurements, biometrics, and IDMS- or non-IDMS-standardized creatinine values were collected for adult patients from three cancer centers. Using statistical modelling, an IDMS- and non-IDMS creatinine compatible eGFR model (CamGFR v2) was developed. Its performance was compared to that of the existing models CKD-EPI, MDRD, FAS, Lund-Malmo Revised and CamGFR v1 using statistics for bias, precision, accuracy, and clinical robustness.

Results
3,083 IDMS- and 4,612 non-IDMS-standardized creatinine measurements were obtained from 7,240 patients. IDMS-standardized creatinine values were lower than non-IDMS-standardized values in within-center comparisons (13.8% lower in Cambridge, p<0.0001; 19.3% lower in Manchester, p <0.0001), and more consistent between centers. CamGFR v2 was the most accurate (root-mean-squared error for IDMS = 14.97ml/min[95% CI 13.84,16.13]; non-IDMS = 15.74ml/min[14.86,16.63]), most clinically robust (proportion
with >20% error of calculated carboplatin dose for IDMS = 0.12[0.09, 0.14]; non-IDMS = 0.17[0.15, 0.2]) and least biased (median residual for IDMS = 0.73ml/min[-0.68,2.2]; non-IDMS = -0.43ml/min[-1.48,0.91]) eGFR model, particularly when eGFR was larger than 60ml/min.

Conclusions

CamGFR v2 can utilize IDMS- and non-IDMS-standardized creatinine measurements and outperforms previous models. CamGFR v2 should be examined prospectively as a practice-changing standard of care for eGFR-based carboplatin dosing.
Introduction

The filtration function of the kidney is quantified as the glomerular filtration rate (GFR). Knowledge of GFR informs clinical management of many patients with cancer. For example, the dose of carboplatin, a well-established treatment for ovarian, breast, lung, and germ cell cancers, is calculated from GFR using the Calvert equation[1]. GFR can be measured directly (mGFR) using the clearance of chemical tracers, for example, chromium-51 EDTA ($^{51}$Cr-EDTA)[2]. This approach is accurate and precise, but costly and not widely available. In practice, GFR is therefore estimated (eGFR) by modeling of readily available clinical and biochemical data.

Most eGFR models are based on the serum concentrations of creatinine, a metabolite of creatine, because it has robust steady-state concentrations and is freely filtered in the glomerulus, with minimal active secretion[3]. However, since there are several methods to measure creatinine, results can vary significantly between centers for technical reasons[4]. To reduce these differences and thereby to harmonize clinical management decisions based on eGFR, isotope dilution mass spectrometry (IDMS) standardized creatinine assays have been developed and are now widely, but not universally, used[5, 6]. Another source of creatinine variability is due to human physiology: underlying disease processes, relative muscle mass, and/or ethnicity influence the relationship between the serum creatinine concentration and GFR in different patient populations[7, 8].

In the context of cancer medicine, these considerations are highly relevant. Most eGFR models have been developed using data from patients without cancer, but with known kidney disease, and are valid exclusively for IDMS or non-IDMS creatinine data. These
model features limit their general utility in the management of patients with cancer[9], most of whom do not have kidney disease. They also introduce clinically significant inaccuracies, particularly when they are used to dose carboplatin[10–13]. While the Calvert equation has been prospectively validated as a predictor of carboplatin exposure from measured GFR[1, 14], a pervasive clinical practice is to input an eGFR value that has been determined using the Cockcroft-Gault (CG) equation for creatinine clearance[11, 15]. The CG was derived from data from 249 male patients at a single center using non-IDMS standardized creatinine values[16] and was never revalidated with IDMS-standardized creatinine values, or for patients with cancer. Accordingly, this method systematically over-estimates GFR[3, 11, 13, 17] and is imprecise to the extent that it generates under- or overdosing of carboplatin of more than 20% in over a third of patients in study cohorts[10–12], risking reduced response rates[18–20] or myelotoxicity[19] respectively. In summary, clinicians must be mindful that models for eGFR can be biased toward the characteristics of the patient population, as well as the creatinine measurement methods upon which they are built[9].

Previously, we addressed the need for an accurate and unbiased GFR model for patients with cancer by developing a linear model of GFR on a square root scale (CamGFR v1)[21]. Internal, external, and multicenter validation studies have each shown that CamGFR v1 estimates GFR in patients with cancer more accurately than other published models, including CG as well as the more recently developed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) model and Modification of Diet in Renal Disease (MDRD) study equation[10, 21]. CamGFR v1 was distinct from previous models in that it provided accurate prediction intervals for eGFR to help clinicians gauge the uncertainty of each GFR estimate.
By extension, clinicians could use the model to obtain the likelihood of the true GFR being above or below a critical value as is important in many clinical scenarios, for example prior to cisplatin administration[21]. However, the model was developed and validated using only non-IDMS creatinine data, limiting the generalizability of findings across centers.

In this manuscript, we address this limitation. We quantify the differences between non-IDMS and IDMS creatinine measurements using data from three cancer centers. Next, we expand our initial model (CamGFR v1) to allow for GFR estimation based on either IDMS or non-IDMS standardized creatinine data (CamGFR v2). The accuracy, bias, and clinical robustness of CamGFR v2 are then compared to those of other published IDMS creatinine-based models, both in patients with cancer and a small subset of patients who do not have cancer. We show that CamGFR v2 estimates GFR with the highest accuracy and least bias for both IDMS and non-IDMS standardized creatinine values, across all measured patient demographics.
Methods

Data were collected from three cancer centers: Cambridge University Hospitals NHS Foundation Trust (Cambridge, UK), University Hospital of South Manchester NHS Foundation Trust (Manchester, UK), and Sahlgrenska University Hospital (Gothenburg, Sweden). The study was conducted at each institution according to regulatory and ethical requirements.

We included patients aged 18 years or older whose GFR was measured using tracer clearance in up to three plasma samples taken over time (typically at timepoints 1, 2, and 3 hours) after intravenous injection of 2 megabecquerels (MBq) of $^{51}$Cr-EDTA or iohexol[2]. Serum creatinine was determined by the enzymatic or Jaffe method within 30 days of the $^{51}$Cr-EDTA GFR measurement. If multiple measurements within 30 days were available, the closest in relation to mGFR determination was used. Patients were excluded if their serum creatinine was below the limit of detection (0.20 mg/dL) or above 4.5 mg/dL (three times the upper limit of normal)[21] or if the recorded height was below 130 cm. Creatinine data are reported in mg/dL, and these values can be converted to µM via the following formula: Creatinine [mg/dL] * 88.4 = Creatinine [µM]. Body surface area (BSA) was calculated using the DuBois-DuBois equation[22]. Repeat $^{51}$Cr-EDTA GFR measurements in a given patient were included if the time between the measurements exceeded one year. Center-specific methods and details of creatinine measurement methodologies over time are provided in the Supplemental Material.
Data analysis and modeling

Creatinine values obtained using methods with calibration traceable to an IDMS reference measurement procedure[6], hereafter termed “IDMS-standardized” creatinine values, were compared with non-IDMS standardized creatinine values within and between centers. To develop CamGFR v2, we randomly split the data into a model development dataset and a validation dataset at a ratio of 4:1. Using the development dataset, the new version of CamGFR was fitted with an additional interaction between the creatinine variables and an indicator variable specifying the creatinine measurement type (IDMS or non-IDMS). Other candidate models were explored as detailed in the Supplemental Material.

The performances of models were compared using the non-BSA adjusted units (ml/min), as these are the units of the GFR term in the Calvert equation for calculating carboplatin dosage[1]. As the other models generate GFR estimates in ml/min/1.73m², results for these models were multiplied by BSA (as calculated by the DuBois-DuBois equation[22]) and divided by 1.73. In the case of the MDRD study equation, the IDMS-[23] and non-IDMS-adjusted[24] versions were used for the respective data subsets. The median residual (mGFR - eGFR) was used to assess bias, and the residual interquartile range (IQR) was used to assess precision. Accuracy is a combination of these two metrics and was estimated using the root-mean-squared error (RMSE). Finally, we examined the clinical robustness of the estimation. A carboplatin dose for an area under the curve (AUC) of 5 mg/ml/min (AUC5) was calculated for all eGFR values generated using the Calvert equation[1]: Dose [mg] = AUC[mg/ml/min] * (GFR[ml/min] + 25). For all models, we determined the proportion of patients who would have received a dose with a percentage error greater than 20% (P20)
relative to what the dose would be if the measured GFR, rather than eGFR, was used for the calculation.

A 95% confidence interval was calculated for each performance statistic using a bootstrap resampling procedure. Specifically, 2,000 resamples with replacement (where the sample size was the same as the number of data points) were taken from the data. The metric was then calculated for each of these 2,000 samples and using the normal approximation a confidence interval was constructed[25]. To test whether the predictive accuracy of CamGFR v2 differed significantly from each of the previous models, a permutation test with 10,000 repetitions was used[26]. These tests acknowledged the paired nature of the comparisons, and evaluated the null hypothesis that the distributions of squared residuals were equal[26].

The code for all analyses of this manuscript is available from the following link:

https://github.com/EdwardHWilliams/CamGFRv2
Results

Patient characteristics

Data from 7,240 patients were collated and contained 7,695 GFR measurements following data extraction and filtering (Figure 1). These GFR measurements included 4,983 (64.8%) from Cambridge, 2,056 (26.7%) from Manchester, and 656 (8.5%) from Gothenburg. The median mGFR value for the dataset (+- IQR) was 80.0 ml/min (+- 39), and the medians of age, weight, height, and BSA were 61.2 years, 72.6 kg, 167 cm, and 1.82 m², respectively (Table 1). The numbers (and %) of samples from patients with solid cancers, patients with hematological cancers, and patients without cancer were 6,647 (86.4%), 786 (10.2%), and 262 (3.4%). IDMS-standardized assays were coupled with mGFR in 3,083 (40.1%) measurements, and non-IDMS assays were coupled with mGFR in 4,612 (59.9%) measurements. In the cases of Cambridge and Manchester, where more detailed timing information was available, 90.6% of all creatinine measurements were obtained within 10 days of the corresponding GFR measurement. All other creatinine measurements included were obtained within 30 days of the corresponding GFR measurement.

The core patient demographics, by center and creatinine assay methodology, are presented in Table 1. Further demographic information including patients’ ethnicities and cancer diagnoses are presented in Tables S1–S3. Table S1 stratifies IDMS creatinine measurements further according to whether they were performed using Jaffe or enzymatic methods. Unless otherwise stated, results from these two methods are grouped together for all analyses of IDMS creatinine values. The numbers of patients with repeat GFR measurements are presented in Table S4.
Comparisons of IDMS- and non-IDMS-standardized creatinine values

We first compared IDMS- and non-IDMS-standardized creatinine values within centers. This comparison was possible because Cambridge and Manchester changed from non-IDMS-standardized to IDMS-standardized creatinine measurements during the sampling period of our study. These changes were associated with abrupt drops in median creatinine levels from 0.905 to 0.781 (13.8% decrease, p<0.0001) and from 0.939 to 0.758 (19.3% decrease, p<0.0001), in Cambridge and Manchester respectively (Figure 2). By contrast to the differences in creatinine, there were modest differences in age in both centers, and mGFR in Manchester, but not in weight, height or BSA (Table 1).

Next, we compared IDMS- and non-IDMS-standardized creatinine values between the centers. There was a significant difference in the non-IDMS-standardized creatinine values between Cambridge and Manchester (0.905 vs. 0.939, 3.8% increase, p=0.0005), but not in the respective IDMS-standardized values (p=0.99). Moreover, no significant differences in the IDMS-standardized creatinine values between Cambridge and Gothenburg (p=0.85) or between Manchester and Gothenburg (p=0.92) were found (Figure 2).

Whereas the non-IDMS creatinine data were all acquired using Jaffe methods, the IDMS creatinine data were acquired using either Jaffe or enzymatic methods (see “center-specific methods” in the supplemental material for details). No differences were found between IDMS creatinine values obtained using Jaffe or enzymatic methods (Figure S1, p = 0.15). Equally, no differences were observed for IDMS creatinine when the Jaffe or enzymatic methods were compared between centers (p = 0.58 and 0.32, respectively) (Figure S1). As expected, significant differences were found when IDMS creatinine values obtained using
either Jaffe or enzymatic methods were compared with non-IDMS creatinine values obtained using Jaffe methods (0.769 for IDMS Jaffe vs 0.916 for non-IDMS Jaffe, p<0.0001; 0.791 for IDMS enzymatic vs 0.916 for non-IDMS Jaffe, p<0.0001) (Figure S1).

Developing CamGFR v2 to model GFR based on non-IDMS and IDMS standardized creatinine

For non-IDMS standardized creatinine-based modeling, CamGFR v1 is the most accurate and least biased GFR predictor in patients with cancer, as determined in a validation study with 3,786 patients from seven centers[10]. The inconsistency of creatinine measurement between centers[4] (Figure 2B-D) and the systematic difference to the current IDMS standard[17] (Figure 2C, D) may explain why CamGFR v1’s performance has varied when other groups have applied it to smaller cohorts[12, 27, 28].

We hence sought to improve the overall accuracy of our model by rederiving it to incorporate creatinine assay factors. To this end, the dataset of 7,695 samples from 7,240 patients was divided randomly in a 4:1 ratio for model development (n=6,156) and validation (n=1,539). The development and validation datasets exhibited no significant differences in demographic parameters (Table S5). We first refitted CamGFR v1 to the development dataset including the additional variable of “creatinine type” (1 or 0 depending on the assay used), along with its interaction with the cubic log(creatinine) terms. These features provided consistency with the original model, while permitting independent adjustment of the coefficients for the cubic log(creatinine) terms in the IDMS-standardized data subset. The functional form of this model, hereby termed ‘CamGFR v2’, is
Equation 1, and its non-IDMS related coefficients did not differ significantly from their original counterparts in CamGFR v1[21] (Table S6).

\[
\sqrt{\text{GFR}} = \beta_0 + \beta_1 \text{Age} + \beta_2 \text{BSA} + \beta_3 \text{Sex}_M + \beta_4 \text{Scr}_{\text{IDMS}} + \beta_5 \log(\text{Scr})\text{Scr}_{\text{IDMS}} + \beta_6 \log(\text{Scr})^2\text{Scr}_{\text{IDMS}} + \beta_7 \log(\text{Scr})^3\text{Scr}_{\text{IDMS}} + \beta_8 \log(\text{Scr})\text{Scr}_{\text{non-IDMS}} + \beta_9 \log(\text{Scr})^2\text{Scr}_{\text{non-IDMS}} + \beta_{10} \log(\text{Scr})^3\text{Scr}_{\text{non-IDMS}} + \beta_{11} \text{AgeBSA} + \beta_{12} \text{AgeSex}_M + \epsilon
\]

Equation 1. \(\beta\) = coefficients fitted by least-squares regression [see Table S5]; Age = Age [years]; BSA = body surface area [m\(^2\)]; Sex\(_M\) = 1 for male, 0 for female; Scr = serum creatinine [mg/dl]; Scr\(_{\text{IDMS}}\) = 1 if IDMS, 0 if non-IDMS; Scr\(_{\text{non-IDMS}}\) = 0 if IDMS, 1 if non-IDMS. The error term “\(\epsilon\)” is an independent, mean zero normally distributed random variable with a constant variance.

In addition to deriving new coefficients for CamGFR v2, alternate models with different predictors to CamGFR v2 were also explored. This survey of the possible models for GFR included other methodological approaches, namely stepwise regression or segmental regression. However, performance metrics of these models were comparable to those of CamGFR v2, and none of the other models had significantly superior accuracy to the CamGFR v2 model across both IDMS and non-IDMS creatinine as assessed using permutation tests[26](Supplemental Material: Figures S2-4; Tables S7, 8). To maintain consistency with previous external validation work[10, 21], the CamGFR v2 model was selected for further analysis.

As with the original CamGFR v1[21], CamGFR v2 trained on the development set satisfied key assumptions of a linear model (Figure S5) and thus permitted the generation of accurate prediction intervals for eGFR.

**Performance of CamGFR v2 in the non-IDMS and IDMS creatinine validation datasets**
We next used the non-IDMS and IDMS validation datasets to compare the performance of the CamGFR v2 model with CamGFR v1 and previously published creatinine-based models, namely the CKD-EPI[29], Lund-Malmö Revised (LM)[30] and Full Age Spectrum (FAS)[31] models, as well as the MDRD study equation[23, 24]. All of these models, with the exception of CamGFR v1, were developed using creatinine data calibrated to IDMS-standardized measurement methodologies. In the case of MDRD study equation, the non-IDMS adjusted version[24] was used for non-IDMS input data.

The accuracy and bias of the models were compared for IDMS-standardized (n=618) and non-IDMS-standardized (n=921) data separately. For non-IDMS-standardized data, the CamGFR v2 model was the most accurate (RMSE 15.74 ml/min; 95% CI 14.86, 16.63), followed by CamGFR v1 (RMSE 15.83 ml/min; 95% CI 14.95, 16.72) (Figure 3; Table S9). CKD-EPI was the most accurate of the other published models (RMSE 16.94 ml/min; 95% CI 16.01, 17.86). These three models were also unbiased for non-IDMS-standardized creatinine data, while the LM model, FAS model and MDRD study equation each showed significant bias (Figure 3; Table S9).

For IDMS-standardized data, CamGFR v2 was the most accurate (RMSE 14.97; 95% CI 13.84, 16.13) and the only unbiased (median residual 0.73; 95% CI -0.68, 2.20) model. The LM model performed second best, in that it had a similar accuracy (RMSE 15.91; 95% CI 14.68, 17.17) and only a slight bias toward overestimating GFR (median residual -2.33; 95% CI -3.61, -1.02) (Figure 3). As expected, the CamGFR v1, which was developed based on non-IDMS creatinine data, was comparatively less accurate and biased toward overestimating GFR. However, despite being developed on IDMS creatinine data, the CKD-EPI model and
the MDRD study equation were also biased toward overestimating GFR (median residual -11.30; 95% CI -12.68, -9.90, and -9.18; 95% CI -10.61, -7.60, respectively) (Figure 3; Table S9).

Subgroup analyses in the validation cohort stratified by age, sex, BSA, cancer diagnosis (i.e. solid, hematological, or no cancer), and eGFR were performed. CamGFR v2 outperformed the other models across all subgroups, including in the small subset of patients without cancer, in both the IDMS- and non-IDMS datasets (Figure 4; Figures S6-10; Tables S10-14). We also evaluated the performance of CamGFR v2 in the validation set after excluding all samples from patients that had repeat measurements in the development set. The numbers of samples excluded for this analysis amounted to 74 (8.03%) of the non-IDMS samples and 72 (11.7%) of the IDMS samples. With these samples excluded, CamGFR v2 still outperformed all other tested models (Table S15).

Finally, direct comparisons of predictive accuracy were performed between CamGFR v2 and each of the other tested models using permutation tests[26]. CamGFR v2 was significantly more accurate than all other models tested for both the IDMS and non-IDMS datasets (Table S16): all comparisons with CamGFR v2 for both IDMS and non-IDMS creatinine were significant (p=0.006 for the comparison with LM for IDMS creatinine and p<0.0001 for all other comparisons), with the expected exception of the comparison with CamGFR v1 for non-IDMS creatinine (p=0.144).

Clinical robustness of CamGFR v2
To examine the clinical relevance of our findings, we assessed clinical robustness—defined as the proportion of GFR estimates that would lead to >20% over- or under-dosing of carboplatin using the Calvert equation[1]—of each model in turn. This threshold was selected based on review of the dose-response relationships documented for carboplatin AUC in the literature, where fluctuations in the order of 10-20% were sufficient to impact upon rates of clinical response and hematological toxicities, respectively[14, 18–20, 32].

In each of the IDMS and non-IDMS data subsets, and across all measured patient demographics, CamGFR v2 was the most robust model (Figures 3, 4; Figures S6-10; Tables S9-14). CamGFR v2 was also the most robust model when the proportions of patients with estimates that would lead to >10% and >30% over- or under-dosing were examined (Table S9). The overall fractions (95% CI) of patients with a dosing inaccuracy of more than 20% for IDMS-standardized creatinine were 0.12(0.09,0.14) for CamGFR v2, 0.16(0.13,0.18) for LM, 0.21(0.17,0.24) for CamGFR v1, 0.26(0.23, 0.3) for FAS, 0.29(0.25,0.32) for CKD-EPI, and 0.32(0.29, 0.36) for MDRD.

Performance of CamGFR v2 in an external, non-IDMS creatinine multicenter dataset

The aim of our work was to deliver an accurate and broadly applicable model that accepts input creatinine data from non-IDMS or IDMS measurements. We compared CamGFR v2 with other models using an independent, non-IDMS creatinine dataset from our previous multicenter validation study[10], excluding data from Cambridge and Manchester that are presented elsewhere in this manuscript. Data were included from 1,605 patients across five centers. Using this external dataset, we confirmed that CamGFR v2 was unbiased and, as with CamGFR v1 previously[10, 21], that it outperformed all other tested models in terms of accuracy, precision, and clinical robustness (Table S17).
Generalizability of coefficients for IDMS and non-IDMS creatinine across centers

Unlike with non-IDMS creatinine, we did not have an external dataset with which to validate CamGFR v2 for IDMS creatinine. However, we did assess generalizability of the coefficients of CamGFR v2 across centers by refitting the model using data from two centers and testing performance on the third, for all combinations of centers. In this analysis, CamGFR v2 outperformed all other tested models in terms of accuracy, precision and clinical robustness, irrespective of whether creatinine values were IDMS- or non-IDMS standardized, and irrespective of the combination of centers used for development and testing (Table S18). The one exception to this was refitting CamGFR v2 using the data from Cambridge and Manchester followed by testing on the data from Gothenburg, where CamGFR v2 was slightly outperformed by the LM model (Table S18).
Discussion

Accurate eGFR determination is essential for patient management. For patients with cancer, this includes the safe and effective prescription and dosing of chemotherapies, especially carboplatin therapy. Here, we developed a method for more accurate GFR estimation in patients with cancer by addressing three major causes of inaccurate eGFR modeling: the patient population, the creatinine measurement method, and the modeling itself. Using data from 7,240 patients across three centers, we confirmed that creatinine levels measured using IDMS-standardized assays are more consistent between centers[5], but on average lower than those measured using non-IDMS-standardized assays[17] (Figure 2). These findings justified the development and validation of a broadly applicable model, CamGFR v2, for eGFR. The new model outperformed all other tested models irrespective of patient demographics or creatinine measurement methodology (Figures 3, 4; Figures S6-10; Tables S9-14).

Our analyses were focused on the gain in the performance of GFR estimation, and were not directly linked to clinical outcomes. Nevertheless, we simulated carboplatin dosing using the prospectively validated and FDA-endorsed Calvert equation[1, 14], and observed that the frequencies of dosing errors that were more than 20% were reduced in CamGFR v2 compared to other models (Figure 3; Table S9). Errors of this magnitude have been associated with important outcomes, specifically reduced clinical response rates in ovarian cancer[19], increased treatment failure risk in metastatic non-seminomatous germ cell tumors[20], increased relapse rates in stage I seminoma[18], and both drug-induced thrombocytopenia and leukopenia[14, 19, 32]. A clear advantage of CamGFR v2 for chemotherapy dosing is that its greatest gains in accuracy, relative to other models, are
within the range of eGFRs commonly observed in patients with cancer (>60 ml/min) (Figure 4, Table S14). It is also the only model other than CamGFR v1 that generates accurate prediction intervals for each GFR estimate (Figures S5, S11). Applied to carboplatin, CamGFR v2 may therefore represent a new standard of care.

A challenge inherent to modelling non-IDMS creatinine values is the significant variation in calibration between centers (Figure 2)[17]. However, as adoption of IDMS-standardization becomes more widespread[6], this limitation will become less relevant to clinical practice. At present, incorporation of either IDMS- or non-IDMS-standardized creatinine measurements best ensures robustness of CamGFR v2 to technical variation between centers and internationally (Figure 2)[5, 6, 17]. Additional technical limitations to modelling the relationship between creatinine and GFR come from the imprecision of methods available for directly measuring GFR[33, 34]: for example, the Cambridge center has reported a coefficient of variation of 7.4% from a study of repeat GFR measurements in healthy volunteers[35].

Future multicenter validation work is required to assess the effects of ethnic diversity[8, 29, 36, 37], center and country-specific biases, and diagnoses other than solid or hematological cancers[9, 10] on the accuracy of CamGFR v2. The small size and restricted demographics of the population of patients in this study who did not have cancer (Tables S1-3) limit our conclusions for the relative accuracy of CamGFR v2 in this setting. While our current analyses of predicted carboplatin exposure are supported by the prospective validation of the Calvert equation[14], the ability of CamGFR v2 to predict actual carboplatin exposures requires formal pharmacokinetic analysis. Toxicity and efficacy of eGFR-informed dosing of
carboplatin using CamGFR v2, as opposed to carboplatin dosing that is informed by direct GFR measurements or alternative eGFR models, requires assessment in the form of randomized controlled trials. Here the comparison to other models is of particular relevance, because carboplatin doses are routinely calculated and adjusted at each treatment cycle based on eGFR. To accelerate future large-scale validation efforts, our free online app for CamGFR v2 now has an analytical function whereby researchers can batch-analyze patient datasets from uploaded .csv files[38] (Figure S11).

The LM model performed second best in the IDMS-creatinine validation dataset in terms of bias, accuracy and clinical robustness, outperforming the FAS as well as the more widely used CKD-EPI model and MDRD study equations (Figure 3; Table S9), each of which were developed using data from patient populations enriched for patients with CKD[23, 24, 29]. It is possible that the source of the bias in the CKD-EPI model and MDRD study equation when applied to our IDMS creatinine source data (Figure 3; Table S9) is a combination of differences in gold-standard GFR measurement (renal iothalamate clearance in CKD-EPI/MDRD vs. plasma $^{51}$Cr-EDTA clearance in CamGFR v2), patient demographics (US-based and CKD-enriched in CKD-EPI/MDRD vs. UK/Sweden-based and cancer-enriched in CamGFR v2), non-specificity bias in IDMS-standardized assays[5], and the effects of inter-center calibration procedures[17].

Creatinine is influenced by diet, muscle mass, therapeutics, and disease states, fundamentally limiting the accuracy of any creatinine-based eGFR model[39]. Cystatin C, by contrast, is a 13kDa protein that is produced by most nucleated cells and is freely filtered by the glomerulus without secretion or reabsorption. In addition, its levels are less influenced
by muscle mass than creatinine. Incorporating cystatin C rather than creatinine into the CKD-EPI model leads to superior prediction of GFR, as well as of cardiovascular risk, end stage renal disease, and all-cause mortality[39, 40]. However, its usage is restricted by cost, the lack of widespread standardized methodologies, and altered physiology in the settings of thyroid dysfunction[41], inflammation[42] and cancer[43–48]. Tumor size- and treatment response-dependent fluctuations of cystatin C have been documented in diverse cancer types[43–48] and represent significant obstacles to the use of cystatin C-informed eGFR in the management of patients with cancer and, in particular, the dosing of chemotherapy.

In summary, CamGFR v2 can incorporate either IDMS-standardized or non-IDMS-standardized creatinine assays and is the most accurate model for estimating GFR in patients with cancer. It is uniquely designed to assess the likelihood of clinically significant under- or over-dosing, is most immediately relevant in the context of carboplatin, and should be examined and prospectively validated by other groups to determine if it presents a new standard of care.
Acknowledgements

We thank all patients who participated in the study. We are grateful to the three anonymous reviewers for constructive feedback.

Author Contributions

References


9. Beumer JH, Inker LA, Levey AS. Improving Carboplatin Dosing Based on Estimated


18. Oliver RTD, Mead GM, Rustin GJS et al. Randomized trial of carboplatin versus


38. CamGFR v2 Live App: https://sites.google.com/site/janowitzwilliamsgrf/. A screenshot of the interface is presented in the supplemental materials (Figure S11).


<table>
<thead>
<tr>
<th>Center</th>
<th>IDMS</th>
<th>Non-IDMS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>58.9 (21.5)</td>
<td>60.6 (20.1)</td>
<td>0.00199</td>
</tr>
<tr>
<td>BSA [m²]</td>
<td>1.84 (0.33)</td>
<td>1.84 (0.325)</td>
<td>0.287</td>
</tr>
<tr>
<td>Creatinine [mg/dL]</td>
<td>0.781 (0.283)</td>
<td>0.905 (0.305)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GFR [ml/min]</td>
<td>82 (37)</td>
<td>82 (40)</td>
<td>0.332</td>
</tr>
<tr>
<td>Height [cm]</td>
<td>168 (14.5)</td>
<td>168 (15)</td>
<td>0.63</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>74.5 (23.2)</td>
<td>73.6 (22.9)</td>
<td>0.0661</td>
</tr>
</tbody>
</table>

Table 1

Patient characteristics by center and creatinine assay type. “n” corresponds to sample number from each center, and “p” corresponds to patient number from each center. P-values of IDMS vs. non-IDMS comparisons were calculated using the Mann-Whitney Wilcoxon test.
Figure Legends

Figure 1

Schematic representation of data acquisition, filtering, and study workflow. The partitioning into development and validation datasets was performed randomly. \( n = \) number of GFR measurements (samples), \( p = \) number of patients, \( n_{IDMS} = \) number of samples for which serum creatinine was measured with an IDMS-standardized method, \( n_{Enzymatic} = \) number of samples for which serum creatinine was measured with an enzymatic method. The 7,695 samples in the “Combined data filtered” box include 4,983 from Cambridge, 2,056 from Manchester, and 656 from Gothenburg. The filter of repeat measurements was the final filtering step prior to creation of the “Combined data filtered” dataset.

Figure 2

Comparison of creatinine measurement methods in patients with cancer. Serum creatinine (SCr) is shown on a logarithmic scale. (A,B) Violin plots for IDMS (A) and non-IDMS (B) creatinine measurements by center. The values above brackets across the violins correspond to the t-test p-values for the respective comparisons. The numbers in the violin plots correspond to the respective number of samples. The horizontal lines correspond to the median SCr in that group. (C,D) Timeline of SCr measurements from Cambridge (C) and Manchester (D). The SCr is log-transformed and the vertical line corresponds to the date when the creatinine measurement methodology changed from non-IDMS-standardized to IDMS-standardized. The density plots on the right side of the panels show the log(SCr) distributions by color-coded by methodology. The p-values were computed by t-test. Smoothed lines were calculated using a generalized additive model with a cubic spline basis.
The gap in SCr data around the start of 2018 in (C) was due to changes in the hospital database at that time.

**Figure 3**
Summary statistics comparing the CamGFR v1, CamGFR v2, CKD-EPI, LM, and FAS models, as well as the MDRD study equation. Statistics were calculated separately for patients with IDMS-standardized creatinine and patients with non-IDMS-standardized creatinine. The residual (measured GFR - estimated GFR) median (first row), residual interquartile range (second row), root-mean-squared error (third row), and the clinical robustness, approximated as the proportion of patients who have an percentage error of more than 20% of calculated carboplatin dose (Dose P20) (fourth row), are displayed. All error bars are 95% confidence intervals calculated using bootstrap resampling with 2,000 repetitions and a normal distribution approximation. The CG model performed less well than any other model and has not been included because it was developed for non-IDMS-standardized creatinine. Source data for this figure and results of testing for statistical significance by permutation tests[26] are presented in Tables S9, 16.

**Figure 4**
Residual (measured GFR - estimated GFR) median, dose p20 and RMSE for the CamGFR v1, CamGFR v2, CKD-EPI, LM and FAS models, as well as the MDRD study equation, as stratified by eGFR. Source data is presented in Table S14.
Figure 3
Figure 4

The figure compares the performance of different equations for estimating glomerular filtration rate (eGFR) across different eGFR ranges using two different approaches: IDMS and Non-IDMS. The equations compared are CamGFR v2, CamGFR v1, LM, CKD-EPI, FAS, and MDRD. The graphs show the median, P20 dose, and RMSE for each eGFR range (<60, 60-90, >90 ml/min) and equation combination.
Clinical Cancer Research

CamGFR v2: a new model for estimating the glomerular filtration rate from standardized or non-standardized creatinine in patients with cancer

Edward H. Williams, Thomas R. Flint, Claire M Connell, et al.

Clin Cancer Res  Published OnlineFirst December 10, 2020.

Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-20-3201

Supplementary Material
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2020/12/08/1078-0432.CCR-20-3201.DC1

Author Manuscript
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link:
http://clincancerres.aacrjournals.org/content/early/2020/12/08/1078-0432.CCR-20-3201.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.