CamGFR v2: A New Model for Estimating the Glomerular Filtration Rate from Standardized or Non-standardized Creatinine in Patients with Cancer

Edward H. Williams[1], Thomas R. Flint[2], Claire M. Connell[1,3], Daniel Giglio[4], Hassal Lee[5], Taehoon Ha[6], Eva Gablenz[6], Nicholas J. Bird[2], James M.J. Weaver[7,8], Harry Potts[5], Cameron T. Whitley[5], Michael A. Bookman[9], Andy G. Lynch[1,10,11], Hannah V. Meyer[6], Simon Tavaré[1,12], and Tobias Janowitz[6,13]

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.

Experimental Design: GFR measurements, biometrics, and IDMS- or non-IDMS–standardized creatinine values were collected for adult patients from three cancer centers. Using statistical modeling, an IDMS and non-IDMS creatinine-compatible eGFR model (CamGFR v2) was developed. Its performance was compared with that of the existing models Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Modification of Diet in Renal Disease (MDRD), Full Age Spectrum (FAS), Lund–Malmö revised, and CamGFR v1, using statistics for bias, precision, accuracy, and clinical robustness.

Results: A total of 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; $P < 0.0001$ and 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, 14.97 mL/minute (95% confidence interval, 13.84–16.13) and non-IDMS, 15.74 mL/minute (14.86–16.63)], most clinically robust [proportion with >20% error of calculated carboplatin dose for IDMS, 0.12 (0.09–0.14) and non-IDMS, 0.17 (0.15–0.2)], and least biased [median residual for IDMS, 0.73 mL/minute (−0.68 to 2.2) and non-IDMS, −0.43 mL/minute (−1.48 to 0.91)] eGFR model, particularly when eGFR was larger than 60 ml/minute.

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; ref. 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, because 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).

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

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Corresponding Author: Tobias Janowitz, Cold Spring Harbor Laboratory, 1 Bungtown Road, Cold Spring Harbor, NY 11724. Phone: 516-367-8422; E-mail: Janowitz@cshl.edu

Clin Cancer Res 2021;27:1381–90

doi: 10.1158/1078-0432.CCR-20-3201

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. When applied to patients with cancer, these variables introduce significant biases and inaccuracies of eGFR that impact 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 application (https://sites.google.com/site/janowitzwilliamsgfr/), but requires independent validation to confirm it as a practice-changing standard of care.

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 features limit the respective models' 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 equation for creatinine clearance (11, 15). The Cockcroft–Gault equation 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 overestimates GFR (3, 11, 13, 17) and is imprecise to the extent that it generates under- or overdosing of carboplatin of more than 20% in more than one 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; ref. 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 Cockcroft–Gault, 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 it 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 article, 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 with 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.

Materials and Methods

Data were collected from three cancer centers: Cambridge University Hospitals NHS Foundation Trust (Cambridge, England, United Kingdom), University Hospital of South Manchester NHS Foundation Trust (Manchester, England, United Kingdom), 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 of ^{51}Cr-EDTA or iohexol (2). Serum creatinine was determined by the enzymatic or Jaffe method within 30 days of the 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; ref. 21) or if the recorded height was below 130 cm. Creatinine data are reported in mg/dL, and these values can be converted to μmol/L via the following formula: creatinine (mg/dL) × 88.4 = creatinine (μmol/L). Body surface area (BSA) was calculated using the DuBois-DuBois equation (22). Repeat GFR measurements in a given patient were included if the time between the measurements exceeded 1 year. Center-specific methods and details of creatinine measurement methodologies over time are provided in the Supplementary Materials and Methods.

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 Supplementary Materials and Methods.

The performances of models were compared using the non-BSA adjusted units (mL/minute), 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/minute/1.73 m^2, results for these models were multiplied by BSA (as calculated by the

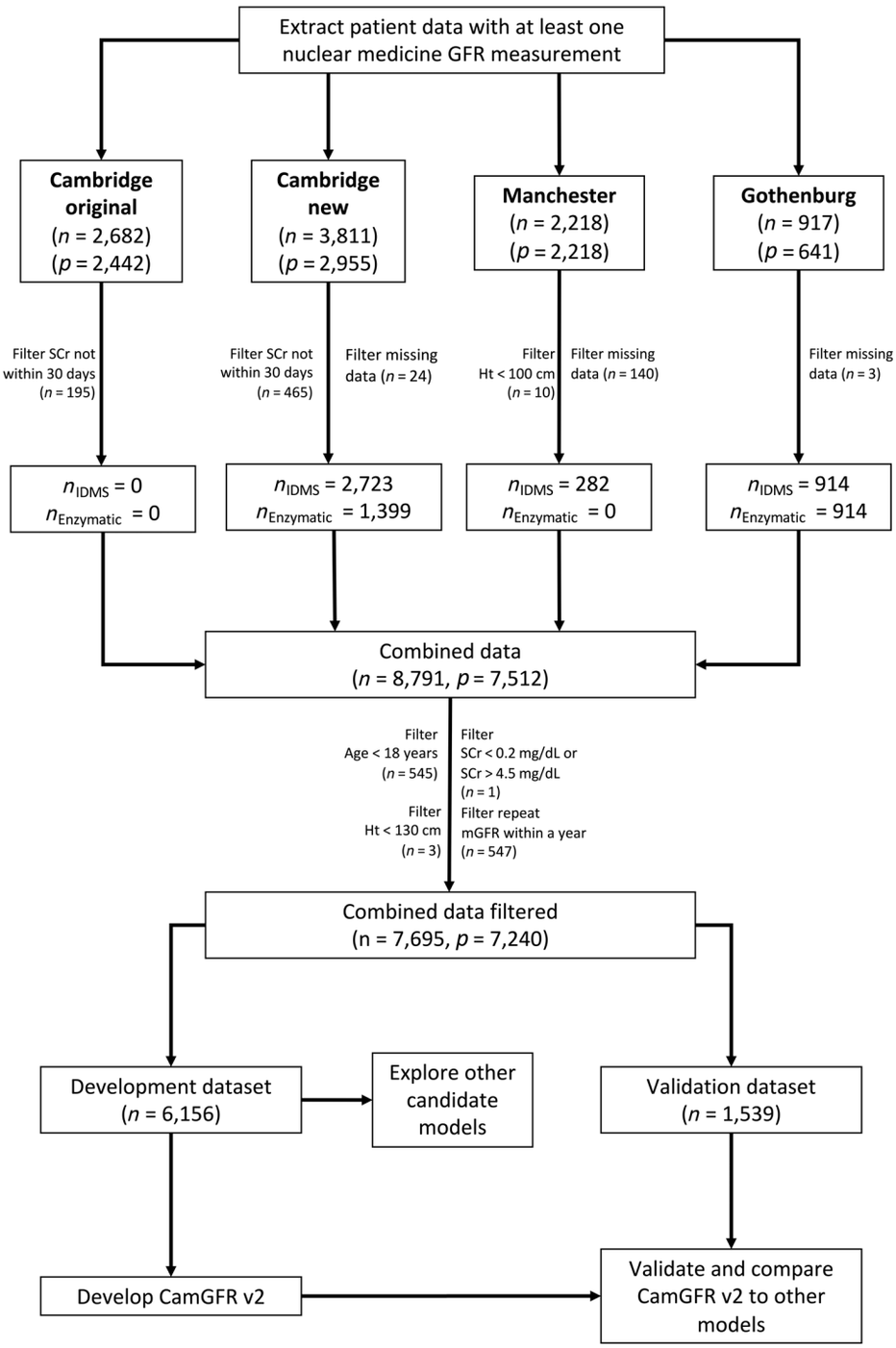

Figure 1.
Schematic representation of data acquisition, filtering, and study workflow. The partitioning into development and validation datasets was performed randomly. *n*, number of GFR measurements (samples); *p*, number of patients; n_{IDMS}, number of samples for which serum creatinine was measured 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.

DuBois-DuBois equation; ref. 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 AUC of 5 mg/mL/minute (AUC5) was calculated for all eGFR values generated using the Calvert equation (1): dose (mg) = AUC (mg/mL/minute) × [GFR (ml/minute) + 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 (CI) was calculated for each performance statistic using a bootstrap resampling procedure. Specifically, 2,000

Table 1. Patient characteristics by center and creatinine assay type.

	IDMS		Non-IDMS		
	Median	IQR	Median	IQR	*P* value
Cambridge (n = 4,983; p = 4,557)					
Age (years)	58.9	21.5	60.6	20.1	0.00199
BSA (m^2)	1.84	0.331	1.84	0.325	0.287
Creatinine (mg/dL)	0.781	0.283	0.905	0.305	<0.0001
GFR (mL/minute)	82	37	82	40	0.332
Height (cm)	168	14.5	168	15	0.63
Weight (kg)	74.5	23.2	73.6	22.9	0.0661
Manchester (n = 2,056; p = 2,056)					
Age (years)	63.1	17.1	65.2	18.5	0.0483
BSA (m^2)	1.78	0.331	1.76	0.33	0.196
Creatinine (mg/dL)	0.758	0.311	0.939	0.249	<0.0001
GFR (mL/minute)	79	39.5	74	38	0.0362
Height (cm)	165	13	164	14	0.489
Weight (kg)	71.6	24.6	69.7	24	0.139
Gothenburg (n = 656; p = 627)					
Age (years)	61	19			
BSA (m^2)	1.83	0.298			
Creatinine (mg/dL)	0.792	0.271			
GFR (mL/minute)	84.8	35			
Height (cm)	170	15			
Weight (kg)	70	20			

Note: "n" corresponds to sample number from each center, and "p" corresponds to patient number from each center. *P* values of IDMS versus non-IDMS comparisons were calculated using the Mann–Whitney Wilcoxon test.

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 CI 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 article 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 (**Fig. 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 ml/minute (+/− 39), and the medians of age, weight, height, and BSA were 61.2 years, 72.6 kg, 167 cm, and 1.82 m^2, respectively (**Table 1**). The numbers (and %) of samples from patients with solid cancers, patients with hematologic 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, is presented in Supplementary Tables S1–S3. Supplementary 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 Supplementary 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 (**Fig. 2**). In 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 their 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 (**Fig. 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 Supplementary Materials and Methods for details). No differences were found between IDMS creatinine values obtained using Jaffe or enzymatic methods (Supplementary Fig. 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; Supplementary Fig. 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; $P < 0.0001$ and 0.791 for IDMS enzymatic vs. 0.916 for non-IDMS Jaffe; $P < 0.0001$; Supplementary Fig. 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 (**Fig. 2B–D**; ref. 4) and the systematic difference to the current IDMS standard (**Fig. 2C** and **D**; ref. 17) 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

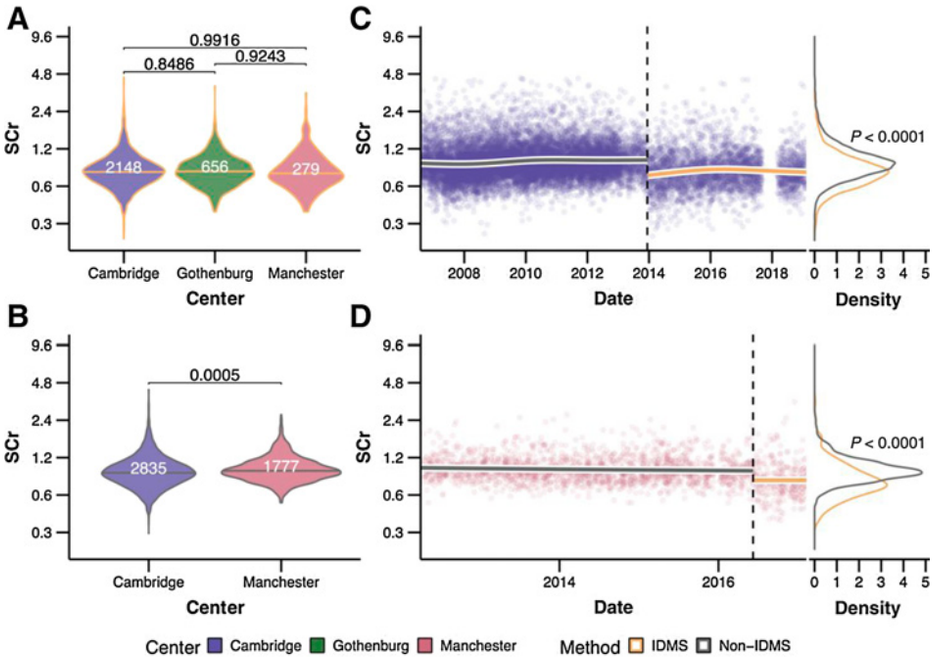

Figure 2.

Comparison of creatinine measurement methods in patients with cancer. Serum creatinine (SCr) is shown on a logarithmic scale. 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 serum creatinine in that group. Timeline of serum creatinine measurements from Cambridge (**C**) and Manchester (**D**). The serum creatinine 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 show the log (serum creatinine) distributions color coded by methodology (right). 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 serum creatinine data around the start of 2018 in **C** was due to changes in the hospital database at that time.

significant differences in demographic parameters (Supplementary 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 A, and its non-IDMS–related coefficients did not differ significantly from their original counterparts in CamGFR v1 (ref. 21; Supplementary Table S6).

$$\sqrt{GFR} = \beta_0 + \beta_1 \mathrm{Age} + \beta_2 \mathrm{BSA} + \beta_3 \mathrm{Sex_M} + \beta_4 \mathrm{Scr_{IDMS}} + \beta_5 \log(\mathrm{Scr})\mathrm{Scr_{IDMS}} + \beta_6 \log(\mathrm{Scr})^2 \mathrm{Scr_{IDMS}} + \beta_7 \log(\mathrm{Scr})^3 \mathrm{Scr_{IDMS}} + \beta_8 \log(\mathrm{Scr})\mathrm{Scr_{non\text{-}IDMS}} + \beta_9 \log(\mathrm{Scr})^2 \mathrm{Scr_{non\text{-}IDMS}} + \beta_{10} \log(\mathrm{Scr})^3 \mathrm{Scr_{non\text{-}IDMS}} + \beta_{11} \mathrm{AgeBSA} + \beta_{12} \mathrm{AgeSex_M} + \epsilon \quad \text{(A)}$$

β = coefficients fitted by least-squares regression (see Supplementary Table S5); Age = age (years); BSA = BSA (m^2); $\mathrm{Sex_M} = 1$ for male, 0 for female; Scr = serum creatinine (mg/dL); $\mathrm{Scr_{IDMS}} = 1$ if IDMS, 0 if non-IDMS; and $\mathrm{Scr_{non\text{-}IDMS}} = 0$ if IDMS, 1 if non-IDMS. The error term "ϵ" 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 methodologic approaches, namely stepwise regression or segmental regression. However, performance metrics of these models were comparable with 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 (ref. 26; Supplementary Materials and Methods; Supplementary Figs. S2–S4; Supplementary Tables S7 and S8). 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 (Supplementary Fig. 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 (30), and Full Age Spectrum (FAS; ref. 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.

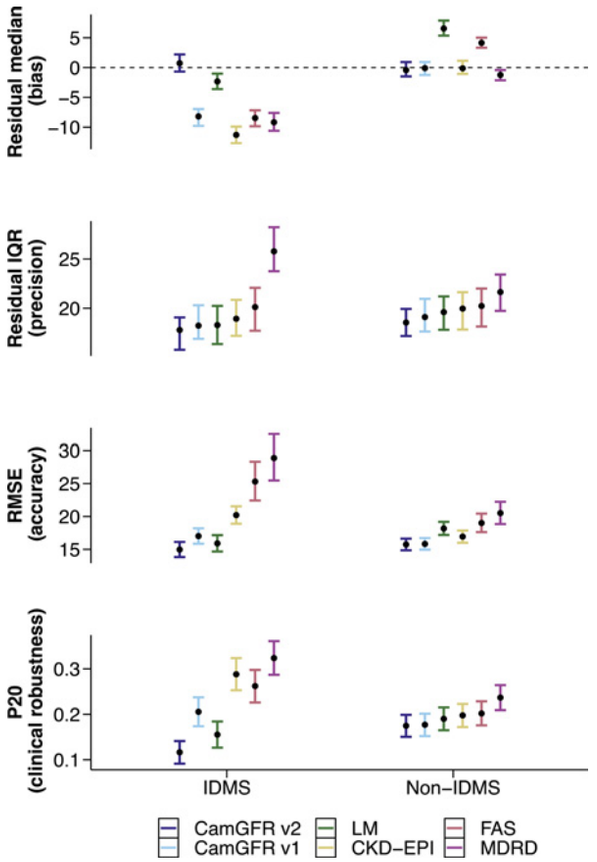

Figure 3.

Summary statistics comparing the CamGFR v1, CamGFR v2, CKD-EPI, Lund–Malmö (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 − eGFR) median (first row), residual IQR (second row), RMSE (third row), and the clinical robustness, approximated as the proportion of patients who have a percentage error of more than 20% of calculated carboplatin dose (dose P20; fourth row), are displayed. All error bars are 95% CIs calculated using bootstrap resampling with 2,000 repetitions and a normal distribution approximation. The Cockcroft–Gault 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 Supplementary Tables S9 and S16.

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/minute; 95% CI, 14.86–16.63), followed by CamGFR v1 (RMSE, 15.83 mL/minute; 95% CI, 14.95–16.72; **Fig. 3**; Supplementary Table S9). CKD-EPI was the most accurate of the other published models (RMSE, 16.94 ml/minute; 95% CI, 16.01–17.86). These three models were also unbiased for non-IDMS–standardized creatinine data, while the Lund–Malmö model, FAS model, and MDRD study equation each showed significant bias (**Fig. 3**; Supplementary 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 to 2.20) model. The Lund–Malmö 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 to −1.02; **Fig. 3**). As expected, the CamGFR v1, which was developed on the basis of 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 to −9.90 and −9.18; 95% CI, −10.61 to −7.60, respectively; **Fig. 3**; Supplementary Table S9).

Subgroup analyses in the validation cohort, stratified by age, sex, BSA, cancer diagnosis (i.e., solid, hematologic, 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 (**Fig. 4**; Supplementary Figs. S6–S10; Supplementary Tables S10–S14). 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 (Supplementary 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 (Supplementary Table S16), all comparisons with CamGFR v2 for both IDMS and non-IDMS creatinine were significant ($P = 0.006$ for the comparison with Lund–Malmö 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 underdosing of carboplatin using the Calvert equation (1), of each model in turn. This threshold was selected on the basis of the 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 hematologic 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 (**Figs. 3** and **4**; Supplementary Figs. S6–S10; Supplementary Tables S9–S14). CamGFR v2 was also the most robust model when the proportions of patients with estimates that would lead to >10% and >30% over- or underdosing were examined (Supplementary 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 Lund–Malmö, 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 article. Data were included from 1,605 patients across five centers. Using this external

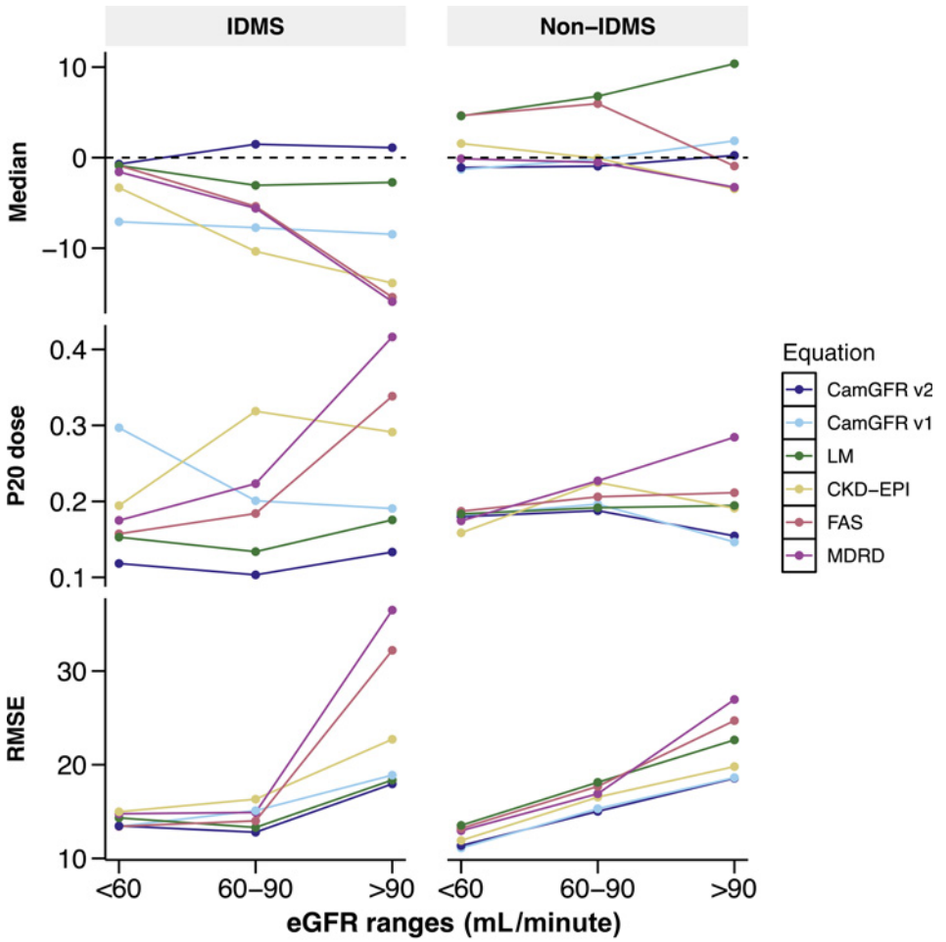

Figure 4.
Residual (measured GFR − eGFR) median, dose P20, and RMSE for the CamGFR v1, CamGFR v2, CKD-EPI, Lund–Malmö (LM), and FAS models, as well as the MDRD study equation, as stratified by eGFR. Source data is presented in Supplementary Table S14.

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 (Supplementary 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 (Supplementary 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 Lund–Malmö model (Supplementary 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 were more consistent between centers (5), but on average lower than those measured using non-IDMS–standardized assays (**Fig. 2**; ref. 17). 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 (**Figs. 3** and **4**; Supplementary Figs. S6–S10; Supplementary Tables S9–S14).

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 with other models (**Fig. 3**; Supplementary 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 nonseminomatous 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/minute; **Fig. 4**; Supplementary Table S14). It is also the only model other than CamGFR v1 that generates accurate prediction intervals for each GFR estimate (Supplementary Figs. S5 and S11). Applied to carboplatin, CamGFR v2 may therefore represent a new standard of care.

A challenge inherent to modeling non-IDMS creatinine values is the significant variation in calibration between centers (**Fig. 2**; ref. 17). However, as adoption of IDMS standardization becomes more widespread (6), this limitation will become less relevant to clinical practice. Currently, incorporation of either IDMS- or non-IDMS–standardized creatinine measurements best ensures robustness of CamGFR v2 to technical variation between centers and internationally (**Fig. 2**; refs. 5, 6, 17). Additional technical limitations to modeling 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 hematologic 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 (Supplementary Tables S1–S3) limit our conclusions for the relative accuracy of CamGFR v2 in this setting. While these 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 with 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 application for CamGFR v2 now has an analytic function whereby researchers can batch-analyze patient datasets from uploaded .csv files (ref. 38; Supplementary Fig. S11).

The Lund–Malmö 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 (**Fig. 3**; Supplementary Table S9), each of which were developed using data from patient populations enriched for patients with chronic kidney disease (CKD; refs. 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 (**Fig. 3**; Supplementary 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 (United States–based and CKD-enriched in CKD-EPI/MDRD vs. United Kingdom/Sweden-based and cancer-enriched in CamGFR v2), nonspecificity bias in IDMS-standardized assays (5), and the effects of intercenter 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, in contrast, is a 13 kDa 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 overdosing, is most immediately relevant in the context of carboplatin, and should be examined and prospectively validated by other groups to determine whether it presents a new standard of care.

Authors' Disclosures

C.M. Connell reports other from EMI Clinical Lectureship, University of Cambridge during the conduct of the study. E. Gablenz reports personal fees from Carl-Duisberg Scholarship, Bayer, and Studienstiftung des Deutschen Volkes outside the submitted work. H.V. Meyer reports grants from Simons Center for Quantitative Biology during the conduct of the study. S. Tavaré reports personal fees from Kallyope outside the submitted work. T. Janowitz reports grants from Cancer Research UK, Pershing Square Foundation, and NIH/NCI Cancer Center Support grant during the conduct of the study. No disclosures were reported by the other authors.

Authors' Contributions

E.H. Williams: Conceptualization, data curation, software, formal analysis, investigation, visualization, methodology, writing-original draft, writing-review and editing. **T.R. Flint:** Formal analysis, visualization, writing-original draft, writing-review and editing. **C.M. Connell:** Data curation, funding acquisition, investigation, writing-review and editing. **D. Giglio:** Resources, data curation, investigation, writing-review and editing. **H. Lee:** Writing-review and editing. **T. Ha:** Formal analysis, writing-review and editing. **E. Gablenz:** Data curation, writing-review and editing. **N.J. Bird:** Resources, data curation, investigation, writing-review and editing. **J.M.J. Weaver:** Funding acquisition, investigation, writing-review and editing. **H. Potts:** Data curation, investigation, writing-review and editing. **C.T. Whitley:** Data curation, investigation, writing-review and editing. **M.A. Bookman:** Writing-review and editing. **A.G. Lynch:** Formal analysis, writing-review and editing. **H.V. Meyer:** Formal analysis, writing-review and editing. **S. Tavaré:** Resources, formal analysis, writing-review and editing. **T. Janowitz:** Conceptualization, data curation, formal analysis, supervision, funding acquisition, validation, investigation, methodology, writing-original draft, project administration, writing-review and editing.

Acknowledgments

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 (to E.H. Williams, S. Tavaré, T. Janowitz, and A.G. Lynch), from CSHL (to T. Ha, H.V. Meyer, and T. Janowitz), from the Simons Center for Quantitative Biology (to H.V. Meyer), from the Pershing Square Foundation (to T. Janowitz), from The Experimental Medicine Training Initiative (to C.M. Connell), from the National Institute for Health Research UK (to J.M.J. Weaver), and from a Carl-Duisberg Scholarship and a German National Merit Scholarship (to E. Gablenz). S. Tavaré is a consultant for Kallyope, Inc. We thank all patients who participated in the study. We are grateful to the three anonymous reviewers for constructive feedback.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received August 15, 2020; revised October 27, 2020; accepted December 4, 2020; published first December 10, 2020.

References

1. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 1989;7:1748–56.
2. Chantler C, Garnett ES, Parsons V, Veall N. Glomerular filtration rate measurement in man by the single injection methods using 51Cr-EDTA. Clin Sci 1969;37:169–80.
3. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function - measured and estimated glomerular filtration rate. N Engl J Med 2006;354: 2473–83.
4. Coresh J, Astor BC, McQuillan G, Kusek J, Greene T, Van Lente F, et al. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. Am J Kidney Dis 2002;39:920–9.
5. Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem 2006;52:5–18.
6. National Institute of Diabetes and Digestive and Kidney Diseases. Creatinine standardization recommendations. Available from: https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate/creatinine-standardization/recommendations.
7. Matsushita K, Mahmoodi BK, Woodward M, Emberson JR, Jafar TH, Jee SH, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD Study equation for estimated glomerular filtration rate. JAMA 2012;307: 1941–51.
8. Foley RN, Wang C, Ishani A, Collins AJ. NHANES III: influence of race on GFR thresholds and detection of metabolic abnormalities. J Am Soc Nephrol 2007;18: 2575–82.
9. Beumer JH, Inker LA, Levey AS. Improving carboplatin dosing based on estimated GFR. Am J Kidney Dis 2018;71:163–5.
10. Williams EH, Connell CM, Weaver JMJ, Beh I, Potts H, Whitley CT, et al. Multicenter validation of the CamGFR model for estimated glomerular filtration rate. JNCI Cancer Spectr 2019;3:4–7.
11. McLean L, Whittle JR, Graham J, Ismail H, Lichtenstein M, Hicks RJ, et al. Carboplatin dosing in the era of IDMS-creatinine; the Cockroft-Gault formula no longer provides a sufficiently accurate estimate of glomerular filtration rate for routine use in clinical care. Gynecol Oncol 2020;157:793–98.
12. White-Koning M, Paludetto MN, Le Louedec F, Gladieff L, Chevreau C, Chatelut E, et al. Formulae recently proposed to estimate renal glomerular filtration rate improve the prediction of carboplatin clearance. Cancer Chemother Pharmacol 2020;85:585–92.
13. Murray B, Bates J, Buie L. Impact of a new assay for measuring serum creatinine levels on carboplatin dosing. Am J Heal Pharm 2012;69:1136–41.
14. Sørensen BT, Strömgren A, Jakobsen P, Jakobsen A. Dose-toxicity relationship of carboplatin in combination with cyclophosphamide in ovarian cancer patients. Cancer Chemother Pharmacol 1991;28:397–401.
15. Casal MA, Nolin TD, Beumer JH. Estimation of kidney function in oncology implications for anticancer drug selection and dosing. Clin J Am Soc Nephrol 2019;14:587–95.
16. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
17. Stevens LA, Manzi J, Levey AS, Chen J, Deysher AE, Greene T, et al. Impact of creatinine calibration on performance of GFR estimating equations in a pooled individual patient database. Am J Kidney Dis 2007;50:21–35.
18. Oliver RTD, Mead GM, Rustin GJS, Joffe JK, Aass N, Coleman R, et al. Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). J Clin Oncol 2011;29:957–62.
19. Jodrell DI, Egorin MJ, Canetta RM, Langenberg P, Goldbloom EP, Burroughs JN, et al. Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. J Clin Oncol 1992;10:520–8.
20. Childs WJ, Nicholls EJ, Horwich A. The optimisation of carboplatin dose in carboplatin, etoposide and bleomycin combination chemotherapy for good prognosis metastatic nonseminomatous germ cell tumours of the testis. Ann Oncol 1992;3:291–6.
21. Janowitz T, Williams EH, Marshall A, Ainsworth N, Thomas PB, Sammut SJ, et al. New model for estimating glomerular filtration rate in patients with cancer. J Clin Oncol 2017;35:2798–805.
22. Du Bois D, Du Bois EF. Clinical calorimetry: a formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916;XVII:863–71.
23. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Expressing the Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem 2007;53:766–72.
24. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999;130:461–70.
25. Davison AC, Hinkley DV. Bootstrap methods and their application. Cambridge, UK: Cambridge University Press; 1997.
26. van der Voet H. Comparing the predictive accuracy of models using a simple randomization test. Chemom Intell Lab Syst 1994;25:313–23.
27. Chancharoenthana W, Wattanatorn S, Vadcharavivad S, Eiam-Ong S, Leelahavanichkul A. Agreement and precision analyses of various estimated glomerular filtration rate formulae in cancer patients. Sci Rep 2019;9:19356.
28. Garner AE, Barnfield MC, Waller ML, Hall GD, Bosomworth MP. Comparing glomerular filtration rate equations and the impact of different creatinine assays on the assessment of renal function in cancer patients. Ann Clin Biochem 2019; 56:266–74.
29. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150: 604–12.
30. Björk J, Grubb A, Sterner G, Nyman U. Revised equations for estimating glomerular filtration rate based on the Lund-Malmö Study cohort. Scand J Clin Lab Invest 2011;71:232–9.
31. Pottel H, Hoste L, Dubourg L, Ebert N, Schaeffner E, Eriksen BO, et al. An estimated glomerular filtration rate equation for the full age spectrum. Nephrol Dial Transplant 2016;31:798–806.
32. Duffull SB, Robinson BA. Clinical pharmacokinetics and dose optimisation of carboplatin. Clin Pharmacokinet 1997;33:161–83.
33. Levey AS, Inker LA. GFR as the "gold standard": estimated, measured, and true. Am J Kidney Dis 2016;67:9–12.
34. Levey AS, Coresh J, Tighiouart H, Greene T, Inker LA. Strengths and limitations of estimated and measured GFR. Nat Rev Nephrol 2019;15:784.
35. Bird NJ, Peters C, Michell AR, Peters AM. Reproducibilities and responses to food intake of GFR measured with chromium-51-EDTA and iohexol simultaneously and independently in normal subjects. Nephrol Dial Transplant 2008;23: 1902–9.
36. Delanaye P, Mariat C, Maillard N, Krzesinski JM, Cavalier E. Are the creatinine-based equations accurate to estimate glomerular filtration rate in African American populations? Clin J Am Soc Nephrol 2011;6: 906–12.
37. Praditpornsilpa K, Townamchai N, Chaiwatanarat T, Tiranathanagul K, Katawatin P, Susantitaphong P, et al. The need for robust validation for MDRD-based glomerular filtration rate estimation in various CKD populations. Nephrol Dial Transplant 2011;26:2780–5.
38. CamGFR v2 live app: Available from: https://sites.google.com/site/janowitzwilliamsgfr/. A screenshot of the interface is presented in the supplemental materials (Figure S11).
39. Lees JS, Welsh CE, Celis-Morales CA, Mackay D, Lewsey J, Gray SR, et al. Glomerular filtration rate by differing measures, albuminuria and prediction of cardiovascular disease, mortality and end-stage kidney disease. Nat Med 2019; 25:1753–60.
40. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20–9.
41. Pricker M, Wiesli P, Brändle M, Schwegler B, Schmid C. Impact of thyroid dysfunction on serum cystatin C. Kidney Int 2003;63:1944–7.
42. Okura T, Jotoku M, Irita J, Enomoto D, Nagao T, Desilva VR, et al. Association between cystatin C and inflammation in patients with essential hypertension. Clin Exp Nephrol 2010;14:584–8.
43. Jones M, Denieffe S, Griffin C, Tinago W, Fitzgibbon MC. Evaluation of cystatin C in malignancy and comparability of estimates of GFR in oncology patients. Pract Lab Med 2017;8:95–104.
44. Decock J, Obermajer N, Vozelj S, Hendrickx W, Paridaens R, Kos J. Cathepsin B, cathepsin H, cathepsin X and cystatin C in sera of patients with early-stage and inflammatory breast cancer. Int J Biol Markers 2008;23:161–8.

45. Bodnar L, Wcislo GB, Smoter M, Gasowska-Bodnar A, Stec R, Synowiec A, et al. Cystatin C as a parameter of glomerular filtration rate in patients with ovarian cancer. Kidney Blood Press Res 2010;33:360–7.
46. Kume M, Yasui H, Yoshikawa Y, Horinouchi M, Higashiguchi K, Kobayashi Y, et al. Transient elevation of serum cystatin C concentrations during perioperative cisplatin-based chemotherapy in esophageal cancer patients. Cancer Chemother Pharmacol 2012;69:1537–44.
47. Kos J, Stabuc B, Cimerman N, Brünner N. Serum cystatin C, a new marker of glomerular filtration rate, is increased during malignant progression. Clin Chem 1998;44:2556–7.
48. Aydin F, Tezcan G, Gungor O, Cengiz AK, Hazar V, Akman S, et al. Can serum cystatin C reflect the glomerular filtration rate accurately in pediatric patients under chemotherapeutic treatment? A comparative study with Tc-99m DTPA two-plasma sample method. Nucl Med Commun 2010;31:301–6.