

# GFR Measurement and Chemotherapy Dosing in Patients with Kidney Disease and Cancer

Blaithin A. McMahon<sup>1</sup> and Mitchell H. Rosner<sup>2</sup>

## Abstract

Chemotherapeutic agents require precise dosing to ensure optimal efficacy and minimize complications. For those agents that are removed from the body by the kidney, accurate knowledge of GFR is critical. In addition, GFR needs to be determined rapidly, easily, and, if possible, with little additional cost. The ability to easily measure GFR also allows for rapid detection of nephrotoxicity. Current methodologies include direct clearance measurement of an indicator substance or estimation of creatinine clearance or GFR through regression equations that use a serum marker, such as creatinine or cystatin C. These methodologies all have shortfalls and limitations, some of which are specific to the patient with cancer. Newer methodologies that directly measure GFR are in clinical trials and offer the ability to rapidly and noninvasively provide accurate estimates of drug clearance as well as detection of nephrotoxicity. These methods offer the opportunity to refine drug dosing and improve outcomes.

KIDNEY360 1: 141–150, 2020. doi: <https://doi.org/10.34067/KID.0000952019>

## Introduction

Chemotherapeutic agents used to treat cancer generally have narrow therapeutic indices along with potentially serious adverse toxicities. Accurate dosing is required to ensure optimal outcomes and to avoid toxicity. For those drugs excreted through the kidney, a precise understanding of kidney function is needed to ensure achievement of therapeutic levels and avoidance of these toxicities. In general, two pathways are involved in the excretion of drugs and their metabolites by the kidney: glomerular filtration and tubular secretion. Glomerular filtration is relevant for smaller, nonprotein-bound substances. Tubular secretion is a more common pathway for protein-bound compounds. In addition, tubular reabsorption of a drug can also occur, which can raise the concentration of the drug. In most cases, the best measure of kidney function is the GFR, which has generally been accepted as a measure of functioning kidney mass (1). In addition, measures to directly and indirectly measure GFR have been well validated, and there is extensive experience with their operational characteristics (1). Although measurement of tubular secretion can be performed, it is more laborious and of unclear clinical significance (1).

Some of the chemotherapeutic agents that are, at least partially, excreted through the kidney include capecitabine, etoposide, carboplatin, cisplatin, mitomycin, methotrexate, pemetrexed, pentostatin, topotecan, bleomycin, and others (2). In fact, carboplatin is unique among chemotherapeutic agents in that its dosing is largely on the basis of determination of eGFR (3). For many other drugs, dosing guidelines in the setting of impaired kidney function are either nonexistent or only loosely evidence based (4–6). Although in some

cases, drug levels can be measured and dosing can be adjusted to reach therapeutic levels (such as with methotrexate and cyclophosphamide), in other cases this is more difficult or is not feasible (7). An example of the benefit of more personalized dosing strategies on the basis of the measurement of drug levels was a study by McCune *et al.* (8) where personalized therapeutic drug monitoring of cyclophosphamide dosing parameters was used in patients undergoing hematopoietic stem cell transplantation. In those patients with personalized cyclophosphamide dosing, there was improved liver function, lower incidence of AKI (by 38%), and similar rates of nonrelapse and overall survival (8).

This article focuses on the various methodologies that are available to assess kidney function in patients with cancer, with the aim of leading to more accurate chemotherapeutic drug dosing as well as rapid detection of nephrotoxicity. Each methodology has limitations in the patient with cancer. For instance, the use of serum creatinine as a measure of GFR in patients with cancer may be influenced by poor dietary intake of protein, muscle wasting, malnutrition, changes in hydration, and liver disease that are prevalent in these patients (1). As an example of this, Launay-Vacher and colleagues (9,10) found that an abnormal serum creatinine was seen in <10% of patients with cancer, whereas an abnormal GFR was seen in a much higher percentage (approximately 50%). In fact, it may be the case that patients with cancer more often present with abnormal GFRs than normal levels of kidney function. For instance, only 38.6% of patients with breast cancer, 38.9% of patients with lung cancer, 38.3% of patients with prostate cancer, 27.5% of patients with gynecologic cancer, and 27.2% of patients with colorectal

<sup>1</sup>Division of Nephrology, Medical University of South Carolina, Charleston, South Carolina; and <sup>2</sup>Division of Nephrology, University of Virginia Health System, Charlottesville, Virginia

**Correspondence:** Dr. Mitchell H. Rosner, Division of Nephrology, Box 800133, University of Virginia Health System, Charlottesville, VA 22911. Email: [mhr9r@virginia.edu](mailto:mhr9r@virginia.edu)

cancer had a  $GFR \geq 90$  ml/min per  $1.73$  m<sup>2</sup> at the time of therapy initiation (9,11–13).

### The Effect of Impaired GFR on Chemotherapeutic Pharmacokinetics and Drug Toxicity

The effects of kidney disease may affect aspects of pharmacokinetics of cancer drugs that are unexpected and beyond simple urinary excretion. Recently, the Food and Drug Administration (FDA) published a guidance document for industry regarding the new requirements for pharmacokinetic studies in patients with impaired GFR. The FDA recommends that pharmacokinetic studies in kidney impairment models be conducted for medications that are not renally eliminated, recognizing the fact that nonrenal clearance mechanisms can be altered in patients with impaired kidney function (14).

As an example of this, a lower absorption rate of sunitinib was observed in patients with reduced kidney function compared with patients with normal function (15). In addition, the volume of distribution of a drug is significantly affected by serum protein binding. In patients with hypoalbuminemia (from nephrotic syndrome or poor nutritional status), the free fraction of some drugs may be increased, leading to altered kinetics and actions. Development of toxicity has been observed in patients receiving cisplatin plus paclitaxel chemotherapy in those patients with lung cancer who have malnutrition and low albumin levels (16). In those patients with significantly impaired kidney function, uremic toxins can compete with drugs for plasma protein-binding sites, also leading to altered pharmacokinetics (17). However, despite these established alterations in the pharmacokinetics of a cancer drug in patients with impaired kidney function, the single most important factor to understand in patients with kidney disease is the effect of a diminished GFR on the elimination phase for a cancer drug. As an estimation of the magnitude of this issue, in the Insuffisance Rénale et Médicaments Anticancéreux (Renal Insufficiency and Anticancer Medications) studies, 79.9% of the patients received at least one drug that required dose modification for kidney function, and 80.1% of the patients received at least one anticancer drug with significant nephrotoxicity risk potential (18,19).

The effect of the failure to recognize impaired kidney function is critically important (20). In a study of patients with metastatic colon cancer receiving a combination of capecitabine and oxaloplatin, patients were dosed on the basis of their serum creatinine values that were in the “normal” range (20). Patients were then stratified on the basis of creatinine clearance as determined by the Cockcroft and Gault formula. In doing so, they identified 35% of patients with a creatinine clearance  $< 60$  ml/min (despite “normal” serum creatinine values). Drug toxicity, including cytopenias; stomatitis; diarrhea; and hand-foot syndrome were much more common in the group with unidentified kidney disease. Alternatively, in a recent trial of cyclophosphamide and doxorubicin or cyclophosphamide, methotrexate and fluorouracil over capecitabine in women with early stage breast cancer, the measurement of kidney function with the Cockcroft and Gault formula and subsequent dosing alterations led to equivalent outcomes and similar rates of complications in the groups with kidney disease and

those without (21). This highlights that the use of kidney function measurements and appropriate dose modifications can improve outcomes.

### Methodologies Using Exogenous Markers to Measure GFR

Measurement of GFR can be cumbersome and time consuming. Thus, in general, serum markers (such as creatinine and cystatin C) have been developed to be used in GFR estimating equations (see below). In some circumstances, more precise determination of GFR is needed, and then, urinary clearance of an ideal filtration marker can be measured. Clearance is the rate at which an indicator substance is removed from the plasma and specifies a volume from which all of a substance is removed per unit time: for a substance X, clearance = urinary concentration of X ( $U_x$ ) multiplied by the urine flow rate ( $V$ )/plasma concentration of X ( $P_x$ ). For an ideal substance that is freely filtered by the glomerulus undergoing no tubular reabsorption, excretion, or metabolism and thus, only excreted by GFR,  $GFR = (U_x) \times (V/P_x)$ . Thus, for indicator X, its plasma concentration is inversely related to GFR.

Typically, methodologies for the use of exogenous markers for the measurement of GFR rely on urine collections with time-averaged plasma concentrations of the exogenous marker. GFR can be determined by either a bolus or continuous infusion of the marker. There are several exogenous markers that can be used for determination of GFR. Inulin, with a molecular mass of 5000 D, is a freely filtered fructose polymer that is physiologically inert and meets many criteria for being an ideal marker for GFR measurement (1). However, timed collections are laborious, the compound is poorly soluble and is not readily available, and assays for its measurement are not widely accessible (22). Other markers include radionuclides and radiocontrast agents where clearance can be determined as the amount of indicator injected divided by the integrated area of plasma concentration curve over time (1). The most commonly used radionuclide agents include <sup>125</sup>I-iothalamate and <sup>51</sup>Cr-EDTA (detected by plasma levels) or <sup>99m</sup>Tcmercaptoacetyltryglycine and <sup>99m</sup>Tcdiethyl triamine penta-acetic acid (detected by  $\gamma$ -counter) (23). Radiocontrast markers include iohexol and diatrizoate meglumine, which are often determined by high-performance liquid chromatography (24). Radionuclide and radiocontrast methodologies, although accurate, are also not widely available, are time and labor intensive, and can be associated with adverse events, such as radiation exposure and risk for anaphylaxis. Thus, these methodologies are typically not used in daily patient-specific clinical decision making. Their role in oncology may be to provide confirmation of GFR values obtained through other techniques, to determine GFR in situations where there is clinical uncertainty (such as nonsteady-state conditions or at extremes of body mass), or in more formal research settings.

### Methodologies Using Endogenous Markers to Measure GFR

#### Creatinine

Serum creatinine has been used to estimate the GFR on the basis of several assumptions: (1) creatinine is freely

filtered at the glomerulus and thus, excreted by glomerular filtration, and (2) creatinine production and excretion are constant in the steady state. Although it is generally true that a rise in serum creatinine generally reflects a fall in GFR, due to a myriad of factors, serum creatinine levels only roughly track with GFR due to factors, such as age, muscle mass, meat intake, and race. Thus, either GFR estimation equations (which adjust for some of these confounding factors) or creatinine clearance must be used to best assess GFR. As described above, creatinine clearance can be calculated with a plasma measurement and timed urine collection (such as for 24 hours). When comparing a patient's creatinine clearance with normal values to assess for the presence of kidney disease, the value should be adjusted to body surface area (BSA). However, for the purpose of drug dosing, the unadjusted creatinine clearance is typically used. The lack of standardization around the utilization of clearance indexed to BSA or not is critically important, and clinicians and researchers need to pay special attention to the reporting of clearance values to ensure that they are comparing similar estimates of kidney function. However, creatinine clearance is not routinely used in clinical practice or clinical trials (due to difficulty in obtaining a 24-hour urine collection and lack of real-time results). Furthermore, creatinine clearance does not improve estimates of GFR over those provided by estimation equations using serum creatinine (see below). In addition to collection errors with capturing the timed urine collection, diurnal variation in GFR and day-to-day variation in creatinine excretion may also contribute to the errors in GFR estimation with timed urine collection (25,26).

Further compounding the accuracy of using creatinine for GFR measurements is that creatinine production is influenced by variables, such as age, sex, nutritional status, muscle mass, and intake of creatine supplements. In addition, a significant proportion (10%–40%) of creatinine excretion in the urine is due to proximal tubular secretion, which can lead to erroneous overestimation of GFR if only the serum creatinine is used (27). This is critically important early in the course of kidney disease, where the early fall in GFR and the rise in serum creatinine may be mitigated by rises in proximal tubular secretion of creatinine. Thus, clinically significant falls in GFR that may affect drug clearance may not be detectable by rises in serum creatinine. In fact, one study showed that, among patients with cancer and normal serum creatinine measurements, one of five patients had asymptomatic kidney insufficiency as assessed by a standard creatinine clearance method (28). This secretory pathway can also be inhibited by drugs, such as cimetidine, trimethoprim, dolutegravir, and others, which leads to false elevations in serum creatinine that do not reflect true falls in GFR. Importantly, many oncology patients may also not be in the steady state (where creatinine production and excretion are equalized) due to acute illness with fluctuations in their daily nutritional intake, changes in muscle mass due to cachexia, and alterations in body hydration.

Another confounding issue with the use of serum creatinine-based GFR measurements relates to variability in laboratory creatinine measurement (29). Currently, laboratories trace creatinine reference levels to isotope dilution mass spectrometry-assigned values to reduce interlaboratory variability and improve assay accuracy (30). Despite this, a recent study showed that the mean  $\pm$  SD of creatinine measurements was  $0.20 \pm 0.09$  mg/dl with the Jaffe assay,

yielding higher creatinine values than enzymatic assays (30). These variations should be considered in the assessment of GFR, and repeat measurements of creatinine should be obtained in unclear situations.

Finally, serum creatinine is an insensitive indicator of kidney function in that patients can lose significant amounts of GFR without changes in creatinine values and that the changes in serum creatinine can lag 24–72 hours after a kidney insult (28–30). Similarly, some patients with cancer and recovered AKI can have a “normal” serum creatinine after their AKI but now have diminished renal reserve. Renal functional reserve describes the capacity of the intact nephron mass to increase GFR from baseline in response to physiologic and noxious stimuli, and it can be calculated by using endogenous creatinine clearance corrected for BSA with the use of the Dubois method. Basal renal functional reserve can predict future risk of AKI in patients with stomach cancer (31), and it may provide an opportunity to risk stratify high-risk patients with AKI prior to future cancer treatments and to increase the frequency of laboratory monitoring of renal function during cancer treatment.

Important exceptions when timed 24-hour collections are useful may be the estimation of GFR in individuals with variations in dietary intake (vegetarian diet or creatine supplements) or muscle mass (amputation, malnutrition, or muscle wasting) because these factors are not specifically taken into account in prediction equations (see below). In these situations, collection of a 24-hour urine sample for measurement of creatinine clearance or measurement of clearance of an exogenous filtration marker may provide better estimates of GFR than prediction equations.

### Cystatin C

Cystatin C is 13,000-D cysteine proteinase inhibitor produced by all nucleated cells at a constant rate. It is freely filtered at the glomerulus, and then, it undergoes catabolism within the kidney tubules, resulting in no urinary excretion. Thus, the serum level of cystatin C depends on GFR, and it can be used as a measure of kidney function (32,33). Measurement of cystatin C is by particle-enhanced nephelometric immunoassay. It has been reported that cystatin C levels are not affected by sex, age, race, protein intake, or muscle mass, and thus, it may have enhanced accuracy over serum creatinine in determination of GFR (34–37). However, this is widely debated, and data from several studies have documented variations in cystatin C levels associated with sex, lean body mass, height, weight, thyroid disease, and other conditions (37–40). In addition, there are variations in the laboratory measurement and reporting of cystatin C levels that further confound its use (41). Within oncology, the use of isolated cystatin C measurements for the determination of GFR and detection of nephrotoxicity has been questioned because there seem to be independent effects of both the malignancy and chemotherapy on cystatin C levels, which confound its utility (42–44). Thus, cystatin C measurements alone are not appropriate for measurement of kidney function or for detection of nephrotoxicity.

### Estimation of GFR through Regression Equations

Estimation of GFR is typically through various regression equations that may include creatinine clearance estimation,

**Table 1. Estimation of GFR through regression equations in patients with cancer**

Formula	Equation	Reference
<b>Creatinine clearance</b>		
Cockcroft–Gault, ml/min	$(140 - \text{Age}) \times \text{Wt} \times (1 - 0.15 \times \text{Sex}) / \text{Cr} \times 0.814$	Cockcroft and Gault (47)
Jelliffe, ml/min	$(98 - 0.8 \times (\text{Age} - 20)) \times (1 - 0.1 \times \text{Sex}) \times (\text{BSA} / 1.73) / \text{Cr} \times 0.0113$	Jelliffe (48)
Wright, ml/min	$(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \text{Sex}) / \text{Cr}$	Wright <i>et al.</i> (49)
<b>eGFR measurements</b>		
Modification of Diet in Renal Disease	$\text{GFR} = 186 \times \text{Serum Cr}^{-1.154} \times \text{Age}^{-0.203} \times 1.212$ (if patient is black) $\times 0.742$ (if patient is a woman)	Levey <i>et al.</i> (53)
CKD-EPI creatinine	$\text{SCr} \leq 0.7$ (for women) and $\text{SCr} \leq 0.9$ (for men) $144 \times (\text{SCr} / 0.7)^{-0.329} \times 0.993^{\text{age}} \times (1.159$ if black) (if patient is a woman) $141 \times (\text{SCr} / 0.9)^{-0.411} \times 0.993^{\text{age}} \times (1.159$ if black) (if patient is a man) $\text{SCr} \geq 0.7$ (for women) and $\text{SCr} \geq 0.9$ (for men) $144 \times (\text{SCr} / 0.7)^{-1.209} \times 0.993^{\text{age}} \times (1.159$ if black) (if patient is a woman) $141 \times (\text{SCr} / 0.9)^{-1.209} \times 0.993^{\text{age}} \times (1.159$ if black) (if patient is a man)	Levey <i>et al.</i> (55)
CKD-EPI cystatin C	For all levels of Scys $\leq 0.8$ or $\geq 0.8$ $133 \times (\text{Scys} / 0.08) - 0.499 \times 0.996^{\text{age}} \times 0.932$ (if woman) $133 \times (\text{Scys} / 0.08) - 0.499 \times 0.996^{\text{age}} \times 1.0$ (if man)	Inker <i>et al.</i> (76)
<b>Cancer-specific GFR equations</b>		
Calvert formula	$\text{Dose (mg)} = \text{AUC (mg ml}^{-1} \text{ min}^{-1}) \times (\text{GFR (ml min}^{-1}) + 25)$	Calvert <i>et al.</i> (77)
Martin formula	$163 \times \text{ABW} (1 - 0.00496 \times \text{age}) \times (1 - 0.252 \times \text{sex})$	Martin <i>et al.</i> (66)

Wt, weight; Cr, creatinine; BSA, body surface area; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; SCr, serum creatinine; Scys, serum cystatin C; AUC, area under the curve; ABW, actual body weight.

eGFR measurements, or cancer-specific equations. Although the National Comprehensive Cancer Network and the International Society of Geriatric Oncology recommend an assessment of kidney function before the administration of chemotherapeutic drugs, even in patients with “normal” kidney function, there are no collective guidelines declaring which method of estimating kidney function is preferred in patients with cancer. Given their ease of use and extensive validation studies, regression equations (eGFR measurements, creatinine clearance estimations, and cancer-specific equations) are most commonly used, and they are highlighted in Table 1. These GFR estimating equations allow estimation of GFR (eGFR) with the use of endogenous filtration markers, such as serum creatinine and serum cystatin C, and they are accepted per current clinical practice guidelines (45).

### Creatinine Clearance Estimation

The estimation of creatinine clearance regression methodologies was first described in the 1950s. Estimated creatinine clearance is typically reported in milliliters per minute and is not equal to GFR (reported in milliliters per minute per 1.73 m<sup>2</sup>), although it is often used as a surrogate for GFR (46).

Creatinine clearance estimates have evolved to include the Cockcroft and Gault (47), Jelliffe (48), and Wright *et al.* (49) formulas. These formulas use patient characteristics, such as weight, age, sex, and serum creatinine (Table 1), but fail to incorporate several other non-GFR determinants of serum creatinine, including diet, race, tubular secretion, and extrarenal elimination of creatinine, and they may no longer

provide accurate estimates (50). In addition, these equations were developed before standardization of creatinine assays, overestimating GFR up to 10%–20% and therefore, predisposing many patients with cancer to unnecessary toxicities. Therefore, these estimates run the risk of misassigning a patient to an incorrect category of GFR, resulting in potential therapeutic management errors. Of note, some chemotherapeutic drugs are dosed not by dose modification for changes in kidney function but instead, on the basis of threshold kidney function values below which the drug should not be dosed. For example, recommendations for pemetrexed preclude administration if the kidney function is <45 ml/min. Thus, misassigning a GFR value to a patient may result in that patient either not being given an effective chemotherapy or being given an effective chemotherapy inappropriately (51). Despite this fact, almost half of all active clinical trials involving chemotherapeutic drugs use kidney function thresholds defined by serum creatinine alone or a composite of serum creatinine or creatinine clearance. In one comprehensive study of all active phases 1–3 cisplatin trials obtained from the [www.clinicaltrials.gov](http://www.clinicaltrials.gov) website, 212 of 465 studies (46%) used serum creatinine alone or a composite of serum creatinine or creatinine clearance, and many trials had inadequate information on kidney function thresholds (52).

### eGFR Measurements

In an effort to improve kidney function measurement and address some of the shortfalls in creatinine clearance estimation, the Modification of Diet in Renal Disease (MDRD)



**Table 2. Some factors that may influence serum creatinine and cystatin C measurements**

Factors	Serum Creatinine	Serum Cystatin C
Filtration marker generation	Body mass	Increased by corticosteroids Increased in hyperthyroidism Decreased in hypothyroidism
	Race/ethnicity	
	Diet	
	Nutritional status	
	Catabolic states	
Nonrenal elimination	Ingestion of cooked meats	None
	Rhabdomyolysis	
	Clearance by RRT	
	Decreased by inhibition of gut creatininases by antibiotics	
Inhibition of tubular secretion	Increased by insensible losses	None
	Cimetidine, ranitidine	
	Fenofibrate	
	Trimethoprim	
	Albumin	
	Dolutegravir	
Assay interference	Cisplatin	None
	Flucytosine	
	Drugs (flucytosine, barbiturates, some cephalosporins, N-acetylcysteine, some catecholamines [such as dopamine], dobutamine)	
	Others (bilirubin, ketones, glucose)	

(53) and more recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations (53) were developed. The CKD-EPI equation is currently recommended by the National Kidney Foundation–Kidney Disease Outcome Quality Initiative and the Kidney Disease Improving Global Outcomes (KDIGO) guideline groups (KDIGO guidelines CKD 2012). In comparison with estimates of creatinine clearance, such as the Cockcroft and Gault equation, the MDRD and CKD-EPI equations estimate GFR and incorporate race (black versus other) and sex but not weight (Table 2). The CKD-EPI and MDRD study equations are designed for use with a standardized serum creatinine assay and have been validated in cohort studies of patients with cancer (54).

The CKD-EPI equation is more accurate than the MDRD study equation, especially at higher GFRs (>60 ml/min per 1.73 m<sup>2</sup>), and this accounts for the preference in its use over the MDRD equation (55). Various CKD-EPI equations can be used with serum creatinine, serum cystatin C, or combination of both values. Of note, patients with cancer were not well represented in the patient cohorts from which these eGFR equations were derived, and thus, some caution in extrapolation of these equations to this patient population should be exercised. However, over the past 3 years, several publications have shown superior performance of the CKD-EPI equation in the population of patients with cancer over other methodologies (51,55). In addition, the MDRD equation has been shown to be superior to the performance of the Cockcroft and Gault equation when applied to patients receiving chemotherapy (56,57). This was nicely demonstrated in one study of 455 adult oncology patients whose GFR was measured using <sup>99m</sup>Tc-DPTA and compared with renal function estimates using the four-variable MDRD, the CKD-EPI, the Cockcroft and Gault, the Wright, and the Martin formulas (56). Assessment of concordance with chemotherapy dose was determined. All bedside formulas result in similar levels of concordance in dosage of carboplatin when

compared with a direct measure of renal function. All formulas resulted in carboplatin dosing of more than ±20% of target dose in a fifth of all patients. However, the Cockcroft and Gault equation (with ideal body weight) was the least concordant, and it was significantly discordant in obese patients (body mass index >30 kg/m<sup>2</sup>), resulting in underdosing of carboplatin (56). This explains the superiority of the MDRD and CKD-EPI equations over the Cockcroft and Gault formula; it is significantly less accurate in patients with extremes of body mass, a situation that is not uncommon in many patients with cancer (10,50,54). Furthermore, many chemotherapeutic drugs are routinely dosed according to BSA, despite a growing body of evidence that there are significant limitations regarding BSA-based dosing of chemotherapeutic drugs. BSA dosing is associated with high pharmacokinetic variability, and it is a poor indicator of optimal drug exposure (58). The BSA indexing of estimated creatinine clearance (milliliters per minute per 1.73 m<sup>2</sup>) can alter dose classification of patients, and it can have implications for patient groups with BSAs that are significantly different from 1.73 m<sup>2</sup>, ultimately resulting in inappropriate dose reductions or dose escalations (59,60).

More recent studies have compared the CKD-EPI equation with the MDRD and Cockcroft and Gault equations and found that use of the CKD-EPI equation adjusted for surface body area was more accurate, demonstrated less bias (54), and may describe an eGFR that is more precise to true measured GFR compared with Cockcroft and Gault equations. As with measured GFR, there are limitations to use of these equations to estimate GFR. There are various non-GFR parameters that affect filtration marker production, tubular reabsorption/secretion, nonrenal elimination, and assay interference that might contribute to a source of error in estimation of GFR in the general population. These issues are likely even more common in the patient with cancer (Table 2) (61) and include variable tubular creatinine secretion (59).

Furthermore, patients with cancer who are ill may be in a nonsteady-state condition where estimating equations are less likely to be accurate. These changes in GFR over time were demonstrated in a large retrospective evaluation of patients with solid tumors without CKD. Patients had an average decline in GFR of 7 ml/min per 1.73 m<sup>2</sup> after 2 years of diagnosis or a CKD stage decline from stage 2–3 or 4 (62). In another study, the risks of AKI were 17.5% and 27% in the first and fifth years of cancer diagnosis, respectively (63), demonstrating that GFR is changing in a substantial number of patients with cancer. Finally, estimating equations have been assessed in both adult and pediatric populations. In adults, all eGFR estimating equations gave reasonable estimates of GFR and can replace measured creatinine clearance with 24-hour urine collections (64). However, in a very limited number of pediatric studies with small study numbers, cystatin C–based equations outperformed creatinine-based equations in estimating GFR in children before hematopoietic stem cell transplant. However, all GFR estimating formulas had decreased sensitivity to detect impaired GFR and may suggest measurement of kidney function in children and young adults who need an accurate assessment of kidney function before HCT (65).

### Cancer-Specific GFR Equations

Because of the potential errors in the estimation of eGFR in patients with cancer listed in Table 2, investigators have developed patients with cancer–specific eGFR formulas and drug-dosing equations from small cohorts of patients with cancer (2,49) (Table 1). One cancer-specific eGFR equation is the Martin formula, which was assessed in 123 patients with mixed tumor types (66). This study used <sup>51</sup>Cr-EDTA plasma clearance concentrations versus the time data of 80 patients. The formula was generated using a population pharmacokinetic approach using the nonlinear mixed effects model program (Table 1), and the formula was then validated in a separate group of 45 patients with cancer. Actual body weight was the most predictive factor, and it was more accurate than the Cockcroft and Gault equation (66). Similarly to the Martin formulas, the Wright formula was also developed *via* a population pharmacokinetic method of <sup>51</sup>Cr-EDTA (clearance) GFR to evaluate the influence of each covariate using nonlinear mixed effects model in 62 oncology patients receiving targeted dosing of carboplatin and validated in an additional 38 patients (49).

The Wright formula estimates of GFR were less biased (mean prediction error =−3%) and more precise (mean absolute prediction error =12%) than Jelliffe (−15% and 19%, respectively) or Cockcroft and Gault (−8% and 16%, respectively) estimates.

An example of a dose-determining formula that is on the basis of GFR is the Calvert formula. This formula uses the rate of drug elimination (clearance) and overall systemic drug plasma concentration over time (AUC) to prevent drug toxicity. This formula uses GFR as the measurement of clearance to achieve a target AUC. This approach has been well documented for carboplatin dosing, especially in patients with ovarian or seminoma cancer, whereby a target AUC of 4–6 mg/ml per minute was determined to be the most appropriate therapeutic range. Importantly, increasing the AUC above this range increases the risk of myelotoxicity

without improving drug efficacy, and doses below this range can result in higher relapse rates (67,68). The National Comprehensive Cancer Network recommends using the Calvert calculation for carboplatin dosing on the basis of specific AUC targets (such as 4–6 mg/ml per minute). However, taken together, the cancer-specific equations are inferior in performance to the conventional aforementioned equations, such as the CKD-EPI equation, and have not gained wide acceptance or use.

### Use of These Measures in Drug Dosing of Chemotherapeutic Drugs

Given the limitations of both measured GFR and eGFR as well as their specific issues in the patient with cancer, how might we incorporate such methods into determining dosing of chemotherapy? In the cancer and noncancer populations, the CKD-EPI equation has proven to have superior performance over other GFR estimating equations and should be recommended as the more accurate estimating equation (57,69).

In addition, both oncologists and nephrologists need to determine the degree of error that is acceptable in the assessment of GFR for clinical decision making for the patient with cancer. If even a moderate degree of error is unacceptable as in the case of carboplatin dosing, then a combination of filtration markers with cystatin C and creatinine should be encouraged together with a measure of GFR, typically with using plasma clearance of iohexol or newer methodologies (see below). Furthermore, repeated assessments of both measured GFR and eGFR should be considered, especially in patients with changes in body mass and composition that can occur with cancer or in the determination of nephrotoxicity. Repeat assessments of both measured GFR and eGFR were highlighted in a recent paper by Rowe *et al.* (70) and demonstrated that biologic variability is larger for measured GFR than eGFR but also exists for eGFR.

Consider the following scenario in a 62-year-old white woman with ovarian cancer who weighs 62 kg, and her height is 167.6 cm. She is being considered for chemotherapy with carboplatin (Table 2). Her serum creatinine was 1.1 mg/dl, and serum cystatin C was 1.2 mg/L. eGFR<sub>cr</sub> was 64 ml/min per 1.73 m<sup>2</sup>, eGFR<sub>cys</sub> was 47 ml/min per 1.73 m<sup>2</sup>, and eGFR<sub>cr-cys</sub> was 56 ml/min per 1.73 m<sup>2</sup>, all determined by the CKD-EPI equation. This wide variation in eGFR may be explained by inherent errors with the use of creatinine or cystatin C as described above and in Table 2. In this scenario, a more accurate assessment of kidney function was needed, and measured GFR using plasma clearance of iohexol was found to be 49 ml/min.

### Real-Time GFR Assessment

The ability to directly measure GFR at the point of care with a rapid, accurate, and reproducible methodology is clearly needed. This ability would allow for adjustment of drug dosing on the basis of accurate assessment of measured GFR that removes many of the problems associated with other measures of GFR previously discussed. In addition, nephrotoxicity can be detected early and even before changes in serum creatinine become manifest. There are



**Figure 1. | FAST BioMedical methodology for GFR determination.** The FAST BioMedical technique to measure both GFR and plasma volume (PV) consists of injecting two fluorescent markers of different molecular mass: a small freely filtered 5-kD FITC-labeled carboxymethyl dextran and a large 150-kD rhodamine-labeled carboxymethyl dextran that is not filtered across the glomerulus. At three time points, a blood sample is drawn, and fluorescence is detected using a fluorometer. The raw data are converted using a software package to PV from the 15-minute sample and to measured GFR from all three samples. Plasma volume can be followed for up to 6 hours after one injection with repeated blood samples. IV, intravenous. Reprinted from FAST Biomedical, with permission.

now two methodologies in development that allow for direct quantitative GFR measurement.

The first technology uses a novel exogenous biomarker consisting of a 150-kD rhodamine derivative (which is confined to the vascular space) and a smaller, 5-kD fluorescein carboxymethylated dextran (rapidly filtered by the kidney). Together, these compounds form a visible fluorescent injectate, and concentrations of both compounds can be rapidly measured in plasma using a fluorimeter (71). After a bolus injection of these compounds, the measurement of fluorescence intensity decay can be used to measure kidney function (72,73). In addition, the use of the larger rhodamine derivative, which is retained in the vascular space, allows for determination of volume status. Three low-volume

(<1-ml) blood samples are taken over 120 minutes, with the first sample, at 15 minutes, allowing for determination of volume status. In a recent study, this technique showed close linear correlation with iohexol-based measured GFR measurements, including in patients with normal GFR and stages 3 and 4 CKD (71) (Figure 1).

The second technology is a transdermal GFR measurement system (Figure 2) (74). With this methodology, a small light sensor is placed on the patient's skin, and a biocompatible tracer is administered. The fluorescent tracer (MB-102 or relmapirazin) is removed from the blood exclusively by GFR, and measured fluorescence decreases over time as the substance is cleared by the kidney (75). The removal rate is dependent on GFR, and the measured fluorescence time-

- Patented fluorescent tracer agent



- Device

- Transdermal fluorescence detection sensor
  - LED light source
  - Photodetector
- Display monitor
  - Data acquisition software
  - GFR calculation software



**Figure 2. | MediBeacon transdermal GFR measurement system.** The patient is administered a fluorescent tracer agent that is removed from the blood exclusively by GFR, and measured fluorescence decreases over time as the substance is cleared by the kidney through GFR. A display monitor used algorithms to calculate GFR. LED, light emitting diode. Reprinted from MediBeacon, with permission.

dependent curve is converted to a measured GFR using algorithms embedded in the device monitor.

Both of these methods would allow for a new paradigm of care where patients might be expected to get measured GFR levels just prior to drug dosing. The measured GFR would be used to adjust the dose of chemotherapy to ensure maximal efficacy and minimal toxicity. In addition, measured GFR could be measured at various time intervals postdrug infusion to detect toxicity and potentially alter treatment plans (for instance, early detection of drug nephrotoxicity may lead to postponing administration of radiocontrast agents or other nephrotoxic agents). Thus, measured GFR allows for both precision and personalized medical care with the hope for better outcomes.

### Summary

Effective therapy use of chemotherapeutic agents that have some degree of kidney clearance requires an understanding of kidney function that is typically determined by measurement of eGFR through a regression formula. However, clinicians and pharmacists need to be vigilant in understanding the limitations of this approach and supplement eGFR with more detailed and direct measurement of GFR when needed. These measurements should be taken repeatedly, especially if the patient may not be in a steady-state situation. Newer, real-time measurements of GFR may dramatically improve our ability to more precisely dose chemotherapies, detect early signs of injury, and improve outcomes.

### Author Contributions

B. McMahan and M. Rosner wrote the original draft and reviewed and edited the manuscript; M. Rosner conceptualized the study and was responsible for investigation and methodology.

### Disclosures

B. McMahan reports other from Sentien Biotechnology, a stem cell research company, outside the submitted work. M. Rosner reports personal fees from Baxter and personal fees from the American Society of Nephrology outside the submitted work.

### References

- Rosner MH, Bolton WK: Renal function testing. *Am J Kidney Dis* 47: 174–183, 2006
- Holweger K, Bokemeyer C, Lipp HP: Accurate measurement of individual glomerular filtration rate in cancer patients: An ongoing challenge. *J Cancer Res Clin Oncol* 131: 559–567, 2005
- Graciano Vera N, Pino Villarreal L, Ureña Vargas J: Carboplatin dosing accuracy by estimation of glomerular filtration versus creatinuria in cancer patients. *Chemotherapy* 63: 137–142, 2018
- The North London Cancer Network. Dosage adjustment for cytotoxics in renal impairment. 2009. Available at: <http://www.londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-cytotoxics.pdf>. Accessed September 16, 2019
- Hendrayana T, Wilmer A, Kurth V, Schmidt-Wolf IGH, Ulrich J: Anticancer dose adjustment for patients with renal and hepatic dysfunction: From scientific evidence to clinical application. *Sci Pharm* 85: 8, 2017
- Krens SD, Lassche G, Jansman FGA, Desar IME, Lankheet NAG, Burger DM, van Herpen CML, van Erp NP: Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 20: e200–e207, 2019
- Bardin C, Veal G, Paci A, Chatelut E, Astier A, Levêque D, Widmer N, Beijnen J: Therapeutic drug monitoring in cancer—are we missing a trick? *Eur J Cancer* 50: 2005–2009, 2014
- McCune JS, Batchelder A, Guthrie KA, Witherspoon R, Appelbaum FR, Phillips B, Vicini P, Salinger DH, McDonald GB: Personalized dosing of cyclophosphamide in the total body irradiation-cyclophosphamide conditioning regimen: A phase II trial in patients with hematologic malignancy. *Clin Pharmacol Ther* 85: 615–622, 2009
- Launay-Vacher V, Janus N, Deray G: Renal insufficiency and cancer treatments. *ESMO Open* 1: e000091, 2016
- Janus N, Launay-Vacher V, Byloos E, MachielsJ-P, Duck L, Kerger J, Wynendaele W, Canon JL, Lybaert W, Nortier J, Deray G, Wildiers H: Cancer and renal insufficiency results of the BIRMA study. *Br J Cancer* 103: 1815–1821, 2010
- Launay-Vacher V, Gligorov J, Le Tourneau C, Janus N, Spano JP, Ray-Coquard I, Oudard S, Pourrat X, Morere JF, Deray G, Beuzeboc P; Renal Insufficiency and Anticancer Medications (IRMA) Study Group: Prevalence of renal insufficiency in breast cancer patients and related pharmacological issues. *Breast Cancer Res Treat* 124: 745–753, 2010
- Launay-Vacher V, Etessami R, Janus N, Spano JP, Ray-Coquard I, Oudard S, Gligorov J, Pourrat X, Beuzeboc P, Deray G, Morere JF; Renal Insufficiency Anticancer Medications (IRMA) Study Group: Lung cancer and renal insufficiency: Prevalence and anticancer drug issues. *Hai* 187: 69–74, 2009
- Launay-Vacher V, Ayllon J, Janus N, Spano JP, Ray-Coquard I, Gligorov J, Pourrat X, Morere JF, Beuzeboc P, Deray G, Oudard S; Renal Insufficiency and Anticancer Medications (IRMA) Study Group: Drug management of prostate cancer: Prevalence and consequences of renal insufficiency. *Clin Genitourin Cancer* 7: E83–E89, 2009
- Paglialunga S, Offman E, Ichhpurani N, Marbury TC, Morimoto BH: Update and trends on pharmacokinetic studies in patients with impaired renal function: Practical insight into application of the FDA and EMA guidelines. *Expert Rev Clin Pharmacol* 10: 273–283, 2017
- Khosravan R, Toh M, Garrett M, La Fargue J, Ni G, Marbury TC, Swan SK, Lunde NM, Bello CL: Pharmacokinetics and safety of sunitinib malate in subjects with impaired renal function. *J Clin Pharmacol* 50: 472–481, 2010
- Arrieta O, Michel Ortega RM, Villanueva-Rodríguez G, Serna-Thomé MG, Flores-Estrada D, Diaz-Romero C, Rodríguez CM, Martínez L, Sánchez-Lara K: Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel-cisplatin chemotherapy: A prospective study. *BMC Cancer* 10: 50, 2010
- Bowmer CJ, Lindup WE: Decreased drug binding in uraemia: Effect of indoxyl sulphate and other endogenous substances on the binding of drugs and dyes to human albumin. *Biochem Pharmacol* 31: 319–323, 1982
- Launay-Vacher V, Oudard S, Janus N, Gligorov J, Pourrat X, Rixe O, Morere JF, Beuzeboc P, Deray G; Renal Insufficiency and Cancer Medications (IRMA) Study Group: Prevalence of Renal Insufficiency in cancer patients and implications for anticancer drug management: The renal insufficiency and anticancer medications (IRMA) study. *Cancer* 110: 1376–1384, 2007
- Janus N, Launay-Vacher V, Byloos E, MachielsJ-P, Duck L, Kerger J, Wynendaele W, CanonJ-L, Lybaert W, Nortier J, Deray G, Wildiers H: Cancer and renal insufficiency results of the BIRMA study. *Br. J. Cancer Br. J. Cancer*. 10.1038/sj.bjc.6605979. Available at:
- Chen J, Wang XT, Luo PH, He QJ: Effects of unidentified renal insufficiency on the safety and efficacy of chemotherapy for metastatic colorectal cancer patients: A prospective, observational study. *Support Care Cancer* 23: 1043–1048, 2015
- Lichtman SM, Cirrincione CT, Hurria A, Jatoi A, Theodoulou M, Wolff AC, Galow J, Morganstern DE, Magrinat G, Cohen HJ, Muss HB: Effect of pretreatment renal function on treatment and clinical outcomes in the adjuvant treatment of older women with breast cancer: Alliance A171201, an Ancillary Study of CALGB/CTSU 49907. *J Clin Oncol* 34: 699–705, 2016
- Gutman Y, Gottschalk CW, Lassiter WE: Micropuncture study of inulin absorption in the rat kidney. *Science* 147: 753–754, 1965



23. Fawdry RM, Gruenewald SM, Collins LT, Roberts AJ: Comparative assessment of techniques for estimation of glomerular filtration rate with <sup>99m</sup>Tc-DTPA. *Eur J Nucl Med* 11: 7–12, 1985
24. Frennby B, Sterner G: Contrast media as markers of GFR. *Eur Radiol* 12: 475–484, 2002
25. Bauer JH, Brooks CS, Burch RN: Clinical appraisal of creatinine clearance as a measurement of glomerular filtration rate. *Am J Kidney Dis* 2: 337–346, 1982
26. Levey AS: Measurement of renal function in chronic renal disease. *Kidney Int* 38: 167–184, 1990
27. Perrone RD, Madias NE, Levey AS: Serum creatinine as an index of renal function: New insights into old concepts. *Clin Chem* 38: 1933–1953, 1992
28. Launay-Vacher V, Izzedine H, Rey JB, Rixe O, Chapalain S, Nouridine S, Paci A, Bourget P, Deray G: Incidence of renal insufficiency in cancer patients and evaluation of information available on the use of anticancer drugs in renally impaired patients. *Med Sci Monit* 10: CR209–CR212, 2004
29. Lee E, Collier CP, White CA: Interlaboratory variability in plasma creatinine measurement and the relation with estimated glomerular filtration rate and chronic kidney disease diagnosis. *Clin J Am Soc Nephrol* 12: 29–37, 2017
30. Killen AA, Ashwood ER, Ventura CB, Styer P: Recent trends in performance and current state of creatinine assays. *Arch Pathol Lab Med* 137: 496–502, 2013
31. Yavas G, Elsurer R, Yavas C, Ata O: Basal renal function reserve and mean kidney dose predict future radiation-induced kidney injury in stomach cancer patients. *Support Care Cancer* 22: 445–451, 2014
32. Grubb AO: Cystatin C—properties and use as diagnostic marker. *Adv Clin Chem* 35: 63–99, 2000
33. Nilsson-Ehle P, Grubb A: New markers for the determination of GFR: Iohexol clearance and cystatin C serum concentration. *Kidney Int Suppl* 47: S17–S19, 1994
34. Roos JF, Doust J, Tett SE, Kirkpatrick CM: Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adults and children—a meta-analysis. *Clin Biochem* 40: 383–391, 2007
35. Laterza OF, Price CP, Scott MG: Cystatin C: An improved estimator of glomerular filtration rate? *Clin Chem* 48: 699–707, 2002
36. Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S: Performance of serum cystatin C versus serum creatinine as a marker of glomerular filtration rate as measured by inulin renal clearance. *Clin Exp Nephrol* 15: 868–876, 2011
37. Knight EL, Verhave JC, Spiegelman D, Hillege HL, de Zeeuw D, Curhan GC, de Jong PE: Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. *Kidney Int* 65: 1416–1421, 2004
38. Groesbeck D, Köttgen A, Parekh R, Selvin E, Schwartz GJ, Coresh J, Furth S: Age, gender, and race effects on cystatin C levels in US adolescents. *Clin J Am Soc Nephrol* 3: 1777–1785, 2008
39. MacDonald J, Marcora S, Jibani M, Roberts G, Kumwenda M, Glover R, Barron J, Lemmey A: GFR estimation using cystatin C is not independent of body composition. *Am J Kidney Dis* 48: 712–719, 2006
40. Stevens LA, Schmid CH, Greene T, Li L, Beck GJ, Joffe MM, Froissart M, Kusek JW, Zhang YL, Coresh J, Levey AS: Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int* 75: 652–660, 2009
41. Eckfeldt JH, Karger AB, Miller WG, Rynders GP, Inker LA: Performance in measurement of serum cystatin C by laboratories participating in the College of American Pathologists 2014 CYS Survey. *Arch Pathol Lab Med* 139: 888–893, 2015
42. Cavalcanti E, Barchiesi V, Cerasuolo D, Di Paola F, Cantile M, Cerece SC, Pignata S, Morabito A, Costanzo R, Di Maio M, Perrone F: Correlation of serum cystatin C with glomerular filtration rate in patients receiving platinum-based chemotherapy. *Anal Cell Pathol (Amst)* 2016: 4918325, 2016
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* 8: 95–104, 2017
44. He L, Li J, Zhan J, Yi F, Fan X, Wei Y, Zhang W: The value of serum cystatin C in early evaluation of renal insufficiency in patients undergoing chemotherapy: A systematic review and meta-analysis. *Cancer Chemother Pharmacol* 83: 561–571, 2019
45. Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members: Evaluation and management of chronic kidney disease: Synopsis of the kidney disease: Improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* 158: 825–830, 2013
46. Fernandez-Prado R, Castillo-Rodriguez E, Velez-Arribas FJ, Gracia-Iguacel C, Ortiz A: Creatinine clearance is not equal to glomerular filtration rate and cockcroft-gault equation is not equal to CKD-EPI collaboration equation. *Am J Med* 129: 1259–1263, 2016
47. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16: 31–41, 1976
48. Jelliffe RW: Letter: Creatinine clearance: Bedside estimate. *Ann Intern Med* 79: 604–605, 1973
49. Wright JG, Boddy AV, Highley M, Fenwick J, McGill A, Calvert AH: Estimation of glomerular filtration rate in cancer patients. *Br J Cancer* 84: 452–459, 2001
50. Hudson JQ, Nolin TD: Pragmatic use of kidney function estimates for drug dosing: The tide is turning. *Adv Chronic Kidney Dis* 25: 14–20, 2018
51. Casal MA, Nolin TD, Beumer JH: Estimation of kidney function in oncology: Implications for anticancer drug selection and dosing. *Clin J Am Soc Nephrol* 14: 587–595, 2019
52. Wang E, Paulus JK, Hackenjos D, Inker LA, Levey AS, Mathew P: Imprecise kidney function thresholds in cancer clinical trials and the potential for harm. *JNCI Cancer Spectr* 2: pky060, 2018
53. 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. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130: 461–470, 1999
54. Janowitz T, Williams EH, Marshall A, Ainsworth N, Thomas PB, Sammut SJ, Shepherd S, White J, Mark PB, Lynch AG, Jodrell DI, Tavaré S, Earl H: New model for estimating glomerular filtration rate in patients with cancer. *J Clin Oncol* 35: 2798–2805, 2017
55. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration): A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150: 604–612, 2009
56. Dooley MJ, Poole SG, Rischin D: Dosing of cytotoxic chemotherapy: Impact of renal function estimates on dose. *Ann Oncol* 24: 2746–2752, 2013
57. Ainsworth NL, Marshall A, Hatcher H, Whitehead L, Whitfield GA, Earl HM: Evaluation of glomerular filtration rate estimation by Cockcroft-Gault, Jelliffe, Wright and Modification of Diet in Renal Disease (MDRD) formulae in oncology patients. *Ann Oncol* 23: 1845–1853, 2012
58. Beumer JH, Chu E, Salamone SJ: Body-surface area-based chemotherapy dosing: Appropriate in the 21st century? *J Clin Oncol* 30: 3896–3897, 2012
59. Takimoto CH, Remick SC, Sharma S, Mani S, Ramanathan RK, Doroshow J, Hamilton A, Mulkerin D, Graham M, Lockwood GF, Ivy P, Egorin M, Schuler B, Greenslade D, Goetz A, Knight R, Thomas R, Monahan BP, Dahut W, Grem JL; National Cancer Institute Organ Dysfunction Working Group Study: Dose-escalating and pharmacological study of oxaliplatin in adult cancer patients with impaired renal function: A National Cancer Institute Organ Dysfunction Working Group Study. *J Clin Oncol* 21: 2664–2672, 2003
60. Murray PT, Ratain MJ: Estimation of the glomerular filtration rate in cancer patients: A new formula for new drugs. *J Clin Oncol* 21: 2633–2635, 2003
61. Samra M, Abcar AC: False estimates of elevated creatinine. *Perm J* 16: 51–52, 2012
62. Launay-Vacher V, Spano JP, Janus N, Gligorov J, Ray-Coquard I, Oudard S, Pourrat X, Morere JF, Beuzebec P, Deray G; Renal Insufficiency and Anticancer Medications (IRMA) Study Group: Renal insufficiency and anticancer drugs in elderly cancer patients: A subgroup analysis of the IRMA study. *Crit Rev Oncol Hematol* 70: 124–133, 2009
63. Christiansen CF, Johansen MB, Langeberg WJ, Fryzek JP, Sørensen HT: Incidence of acute kidney injury in cancer patients: A Danish

- population-based cohort study. *Eur J Intern Med* 22: 399–406, 2011
64. Hahn T, Yao S, Dunford LM, Thomas J, Lohr J, Arora P, Battiwalla M, Smiley SL, McCarthy PL Jr: A comparison of measured creatinine clearance versus calculated glomerular filtration rate for assessment of renal function before autologous and allogeneic BMT. *Biol Blood Marrow Transplant* 15: 574–579, 2009
  65. Laskin BL, Nehus E, Goebel J, Furth S, Davies SM, Jodele S: Estimated versus measured glomerular filtration rate in children before hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 20: 2056–2061, 2014
  66. Martin L, Chatelut E, Boneu A, Rostaing L, Roussilhes C, Caselles O, Canal P: Improvement of the Cockcroft-Gault equation for predicting glomerular filtration in cancer patients. *Bull Cancer* 85: 631–636, 1998
  67. Jodrell DI, Egorin MJ, Canetta RM, Langenberg P, Goldbloom EP, Burroughs JN, Goodlow JL, Tan S, Wiltshaw E: Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. *J Clin Oncol* 10: 520–528, 1992
  68. Bosl GJ, Patil S: Carboplatin in clinical stage I seminoma: Too much and too little at the same time. *J Clin Oncol* 29: 949–952, 2011
  69. KDIGO: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 3: 1–150, 2013
  70. Rowe C, Sitch AJ, Barratt J, Brettell EA, Cockwell P, Dalton RN, Deeks JJ, Eaglestone G, Pellatt-Higgins T, Kalra PA, Khunti K, Loud FC, Morris FS, Ottridge RS, Stevens PE, Sharpe CC, Sutton AJ, Taal MW, Lamb EJ; eGFR-C Study Group: Biological variation of measured and estimated glomerular filtration rate in patients with chronic kidney disease. *Kidney Int* 96: 429–435, 2019
  71. Rizk DV, Meier D, Sandoval RM, Chacana T, Reilly ES, Seegmiller JC, DeNoia E, Strickland JS, Muldoon J, Molitoris BA: A novel method for rapid bedside measurement of GFR. *J Am Soc Nephrol* 29: 1609–1613, 2018
  72. Wang E, Sandoval RM, Campos SB, Molitoris BA: Rapid diagnosis and quantification of acute kidney injury using fluorescent ratiometric determination of glomerular filtration rate in the rat. *Am J Physiol Renal Physiol* 299: F1048–F1055, 2010
  73. Wang E, Meier DJ, Sandoval RM, Von Hendy-Willson VE, Pressler BM, Bunch RM, Alloosh M, Sturek MS, Schwartz GJ, Molitoris BA: A portable fiberoptic ratiometric fluorescence analyzer provides rapid point-of-care determination of glomerular filtration rate in large animals. *Kidney Int* 81: 112–117, 2012
  74. Available at: <https://www.medibeacon.com/products/nephrology/renal-function-system/>. Accessed September 20, 2019
  75. Dorshow RB, Bugaj JE: Next tier in vitro and in vivo nonclinical studies further elucidating the safety and toxicity profile of MB-102, a novel fluorescent tracer agent for measurement of glomerular filtration rate. *Regul Toxicol Pharmacol* 107: 104417, 2019
  76. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS; CKD-EPI Investigators: Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 367: 20–29, 2012 <https://doi.org/10.1056/NEJMoa1114248>
  77. Calvert AH: Dose optimisation of carboplatin in adults. *Anticancer Res* 14: 2273–2278, 1994