

Avoiding insufficient therapies and overdosing with co-reporting eGFRs (estimated glomerular filtration rate) for personalized drug therapy and improved outcomes – a simulation of the financial benefits

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ABSTRACT

Patients with impaired renal function are at high risk for morbidity and mortality. Chronic kidney disease (CKD) even in the early stages can be associated with significant side effects of drug therapy, longer length of stay, and high costs. Correct assessment of renal function in the hospital is important to detect CKD, to avoid further damage to the kidneys, and to optimize pharmacological therapy. Current protocols for renal function testing in drug dosing are only creatinine based, are not robust enough, and can wrongly classify certain patients.

Goal of our simulation study is to optimize noninvasive renal function estimates and to allow for optimal dosing of pharmacological treatment without further

renal damage. Co-reporting of creatinine- and of cystatin C-derived estimated glomerular filtration rates (eGFR) allows a personalized approach for patients with large discrepancies in eGFR and it enabled us in detecting patients at high risk for side effects due to incorrect drug dosing. This approach might be highly effective for patients as well as for clinicians. In addition, we simulated the efficiency by estimating savings for the hospital administration and the payor with a benefit cost ratio of 58 to 1.



INTRODUCTION

Renal function declines over time in a physiological fashion and an eGFR of 35 ml/min 1.73 m² surface area only can be physiologic in nonagenarians (1). However, for dosing of drugs which are cleared by the kidneys, drug approval regulatory offices ask for a normal renal function (i.e., an eGFR >60 ml/min) to allow a normal dosing scheme (2), some drugs may not be used in patients with severe CKD or even in moderate CKD. In addition, a reduced renal function can be present in patients of all ages, is mostly completely asymptomatic, and often not known by the patient. Reduced kidney function is seen in chronic diseases of the kidney but also in patients admitted to the hospital with acute kidney injury (AKI). Therefore, in many hospital patients, the situation can be complex and complicated by “acute on chronic kidney disease” as seen for example in patients with hypovolemia, acute cardiac insufficiency, or acute infection (3).

The GFR can be measured based on the clearance of exogenous filtration markers, but due to its impracticability for routine application as well as complex issues with biological variation (4-6), the eGFR is calculated based on the serum or plasma concentration of biomarkers such as creatinine, cystatin C or other biomarkers (7) in the combination of demographic

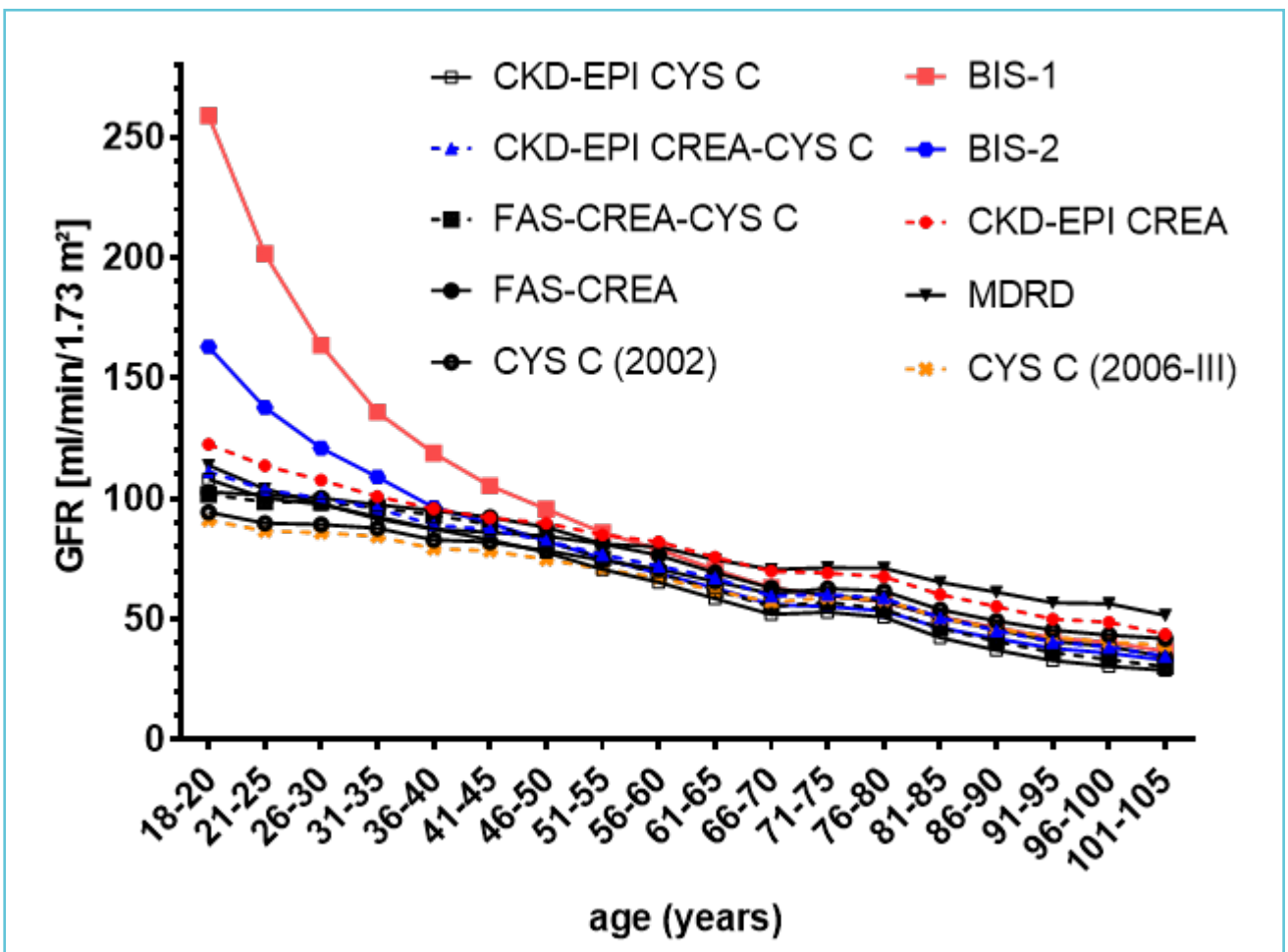
factors such as age, sex, and race. Several formulas are available for this calculation. The challenges with these formulas are several-fold: First, some of these formulas were derived from very selected populations (the formula used as standard for drug dosing, the creatinine-based Cockcroft-Gault equation, is based on 249 males only (8), and the Modification of Diet in Renal Disease (MDRD) equation is based on patients with renal disease only (9)). Like the newer Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, these formulas are creatinine-based and are interfered by all factors affecting creatinine values such as age, body mass, drug intake, dietary protein intake, muscle mass, and ethnicity. Therefore, the application of a certain formula should not be transferred to a general population or to all hospital patients. Second, the formulas have been developed by optimizing the mean distance between the actual measured GFR (as determined by invasive methods) and the eGFR among all study subjects. This averaging does not exclude high and even exceedingly high differences to the real GFR in certain study subjects and patients, respectively (10). Third, the parameters used in these formulas must be highly standardized and after restandardization, formulas must be adjusted accordingly. It is a matter of discussion whether it is sufficient - e.g., after the restandardization of creatinine testing with SRM967 (11) - to adjust the eGFR formulas by a fixed factor or whether new studies employing the “gold standard” are needed. These issues are peculiar for the Cockcroft-Gault equation since the (non-standardized) creatinine method used in the development of the Cockcroft-Gault equation is no longer in use and samples from the study are not available to evaluate how the results might compare to the current standardized creatinine values and there is no version of the Cockcroft-Gault equation for use with standardized creatinine results, unlike to the

MDRD formula (12). While in many patients, there are little differences between eGFR estimations obtained by different formulas, in some patients and in dosing of some drugs with a narrow therapeutic range, the Cockcroft-Gault equation was less reliable in assessing the risk of kidney damage (13). However, many drug approval regulatory offices still oblige the use of the Cockcroft-Gault equation, with no comments on the creatinine standardization having occurred in the meantime.

Any approach to optimize a single eGFR formula suffers from mutual exclusive adjustments

either in relation to the GFR range or to the patients' age (14). Finally, most of the studies used for the development of these calculation were performed in patients of 65 years of age or younger. This patient group, however, is not representative of the patients treated in the hospital and the applicability of these formulas for the general hospital population is questionable (15). When different calculations are used to demonstrate the age-dependent decline in eGFR, all formulas can detect the decline by age but the differences among these formulas, even when only comparing the means, are huge (Figure 1).

Figure 1 Mean age-dependent decline of eGFR calculated by different estimations. Total number of patients n=63,383*



* For details of the formulae see CKD EPI CYS (21), FAS-CREA-CYS (26), BIS-I and II (40).

While creatinine is established for many decades (16), cystatin C has been used widely only after the standardization with ERM-DA471/IFCC in 2010 (17). Cystatin C is regarded to be more accurate than creatinine, with a reciprocal function between cystatin C and GFR. Some non-renal conditions such as high doses of glucocorticoids (18) or inflammation (i.e., increased C-reactive protein) have been shown to affect cystatin C concentrations (19). Effects of certain thyroid conditions on cystatin C concentrations were reported but could not be verified by other studies (20).

Aim of our study was to assess the feasibility of parallel reporting GFR estimates based on two independent biomarkers (creatinine and cystatin C) with automatic alerts in patients with significant discrepancies between both biomarkers followed by an individually-tailored approach employing a multidisciplinary team to adjust the drug doses in patients with certain chemotherapies (proof of principle). The study also included a simulation of the calculated monetary savings.

PATIENTS AND METHODS

In our hospital, cystatin C tests can be ordered for all patients. For eGFR requests in patients of 75 years of age and older, cystatin C testing is added automatically since the MDRD formula is less adequate in older persons.

The approach and the estimated benefits of dual reporting of creatinine and cystatin C derived eGFR was retrospectively validated in our chemotherapy patient cohort from 2018. Therefore, all patients from January 1, 2018 to December 31, 2018 treated at the Marienhospital Stuttgart which had requests for eGFR were included in the simulation.

Patients receiving certain chemotherapies (containing trastuzumab, cisplatin, carboplatin, oxaliplatin, or nivolumab) were identified according

to their prescriptions by the staff of the hospital pharmacy. We used the total mass (in grams) of the chemotherapy applied since the dosing in patients is rather individual during the repetitive administration (affected by weight, renal function, results of the blood count, number of repetitions). For the simulation, the average dose of a single drug was estimated by the total mass of the respective drug divided by the total number of patients receiving this drug. Drug prices were obtained by the "Rote Liste".

BIOMARKERS

Serum cystatin C (calibrated to ERM-DA471/IFCC, turbidimetric method), creatinine (Jaffé method), albumin and urea were measured on Architect ci8200 (Abbott GmbH, Wiesbaden, Germany) using Abbott reagents and Bio-Rad controls (Bio-Rad, München, Germany).

Biomarker data and demographics were captured from the laboratory information system (LIS) (LabCentre, i-Solutions, Bochum, Germany). Calculations and simulations were performed using IBM SPSS Statistics, Version 24 (IBM Corp., Armonk, N.Y., USA). To estimate the financial benefit, it was assumed that the renal function of patients receiving chemotherapy is comparable to the overall renal function of our hospital patients.

AUTOMATIC ALERTS

EGFR was calculated from cystatin C results by the CKD-EPI formula (21) and from creatinine, urea, and albumin by the modified MDRD formula, both without race adjustments in our predominantly Caucasian patients (9) (22). Patients were classified according to their eGFRs to the respective CKD stages. Patients with significant discrepant classification only according to the cystatin C- and creatinine-derived eGFR (such as CKD3a by creatinine-derived GFR and CKD4 by cystatin C-derived eGFR) receive an automatic

alert in the LIS. This alert triggers a personalized, individual adjustment of chemotherapy dosing by the pharmacists, the clinical pathologists and the nephrologists. Since the eGFR is mandatory in all patients receiving these chemotherapies, the pervasion of this personalized approach was complete.

RESULTS

The prevalence of impaired renal function in inpatients and patients treated as outpatients at a hospital is remarkably high: In our institution with about 35,000 inpatients per year and about 200,000 outpatients, ~33% have severely impaired renal function (CKD stages 3b, 4 and 5) (Figure 2).

The focus of the co-reporting approach is on patients with impaired renal function (CDK stage

3a and 3b). For patients with mildly decreased renal function (CKD 1 and 2) little challenges are expected by dosing drugs which are (partially) cleared by the kidneys. Patients with CKD stage 4 or 5 are found rather rarely and essentially all these patients are already aware about their severely impaired renal function.

32.9% of all patients in our hospital are in CKD stages 3A and 3B and of these, 18.6% have a significant (i.e., >15 ml/min) discrepancy between creatinine- and cystatin C-based eGFRs. This corresponds to 6.2% of the whole hospital population. In general, creatinine-based eGFRs overestimate the GFR compared to cystatin C-based GFRs (Figure 3). The difference between both GFR estimates in patients with CKD stages 3A and 3B was +4.5 mL/min (95% range -18.3 - +22.3 mL/min).

Figure 2 Number of patients according to the CKD stages in 2018.
Total number of patients n=63,383

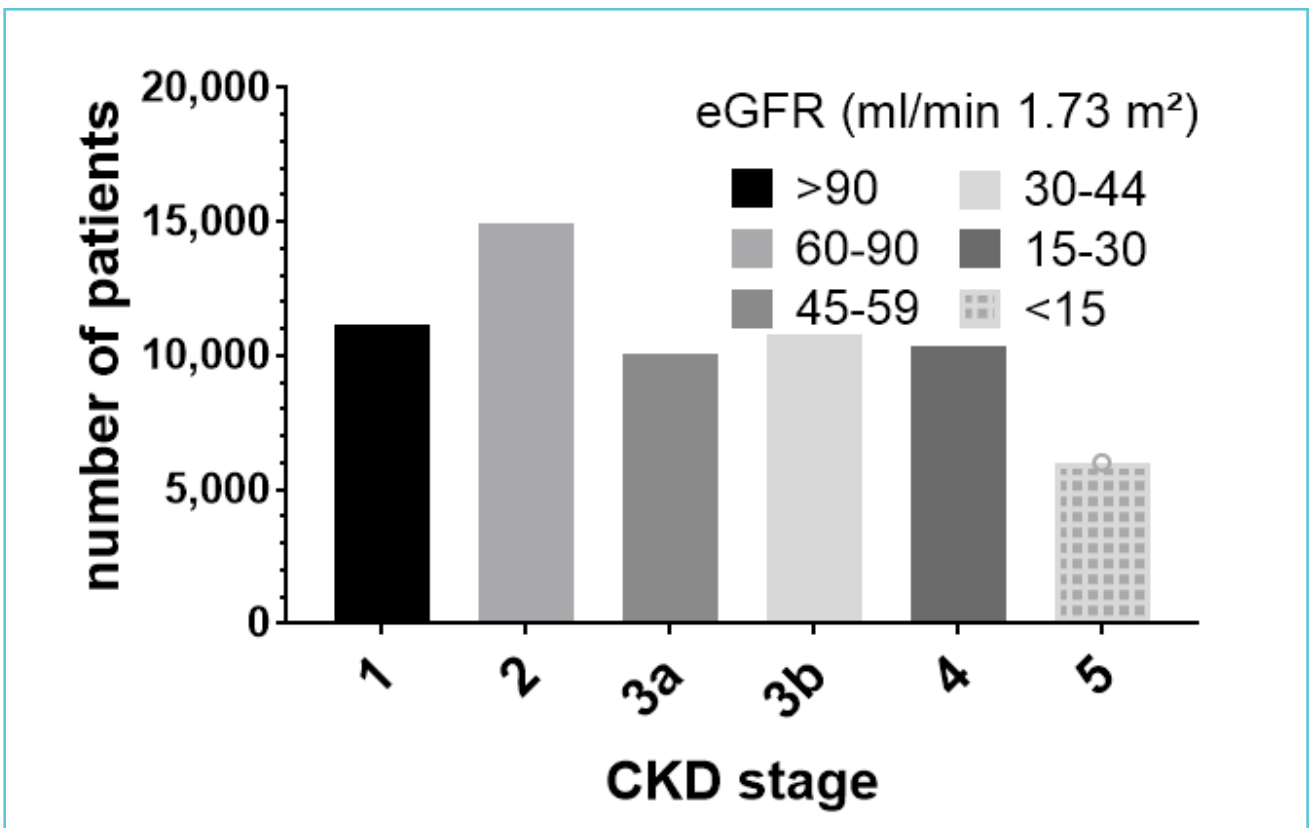
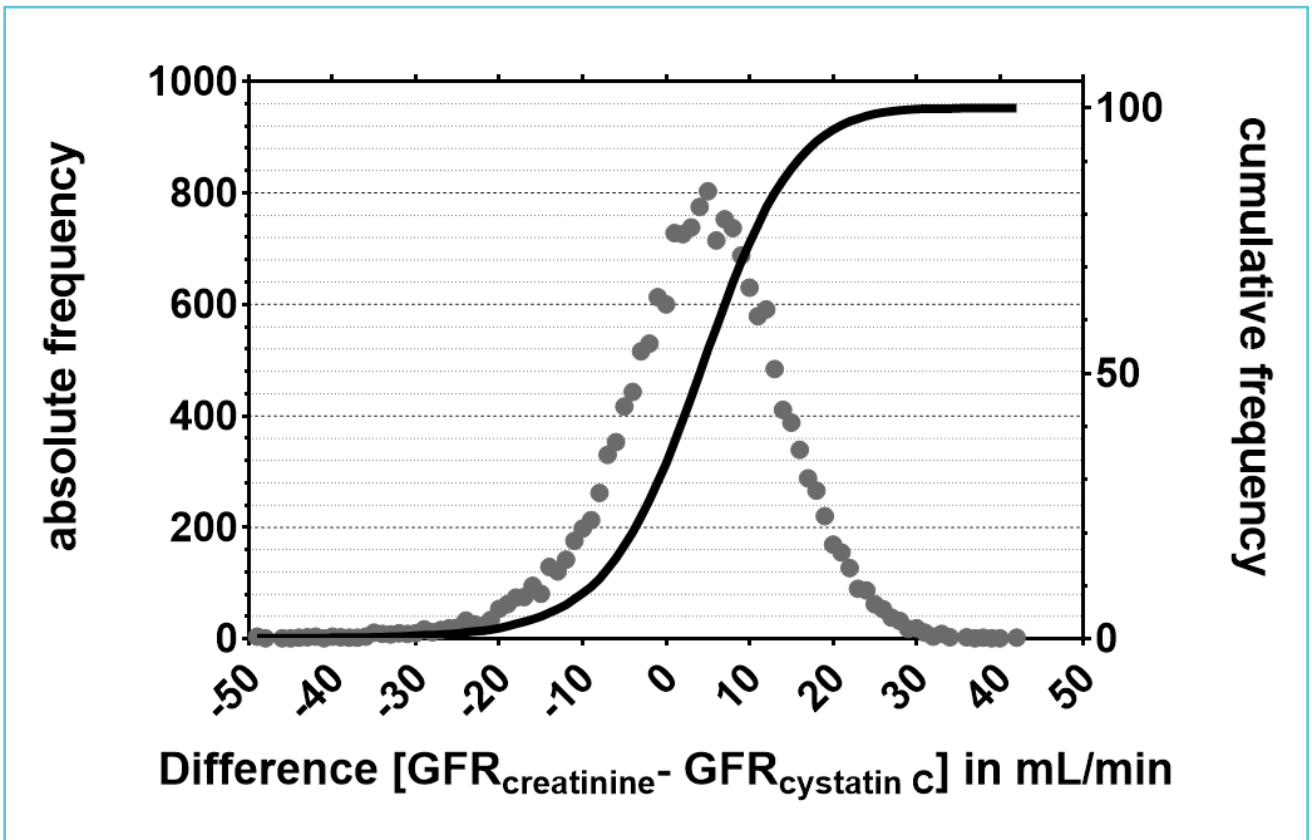


Figure 3 Individual difference and cumulative frequency between creatinine- and cystatin C-derived eGFR in patients with CKD stages 3A and 3B (as determined by creatinine-derived eGFR)



When these numbers are calculated in patients receiving chemotherapy in 2018, 193 of the total 606 patients were in CKD stages 3A and 3B and consequently 38 of these patients were at risk and could benefit from the dual reporting approach which avoids overdosing based on creatinine-based eGFRs only.

The monetary benefits of the adapted dosing scheme in 2018 were estimated by the total costs of the respective chemotherapies and the assumption, that co-reporting will lead to an overall lower dosage in 6.2% of patients. This value was estimated from the percentage of misclassification and the effects of the misclassification on the dosing of the chemotherapies of selected patients (n=20). The calculated monetary benefits are summarized in Figure 4. In total, the

savings would account to 105,000€ in direct drug costs alone in 2018.

DISCUSSION

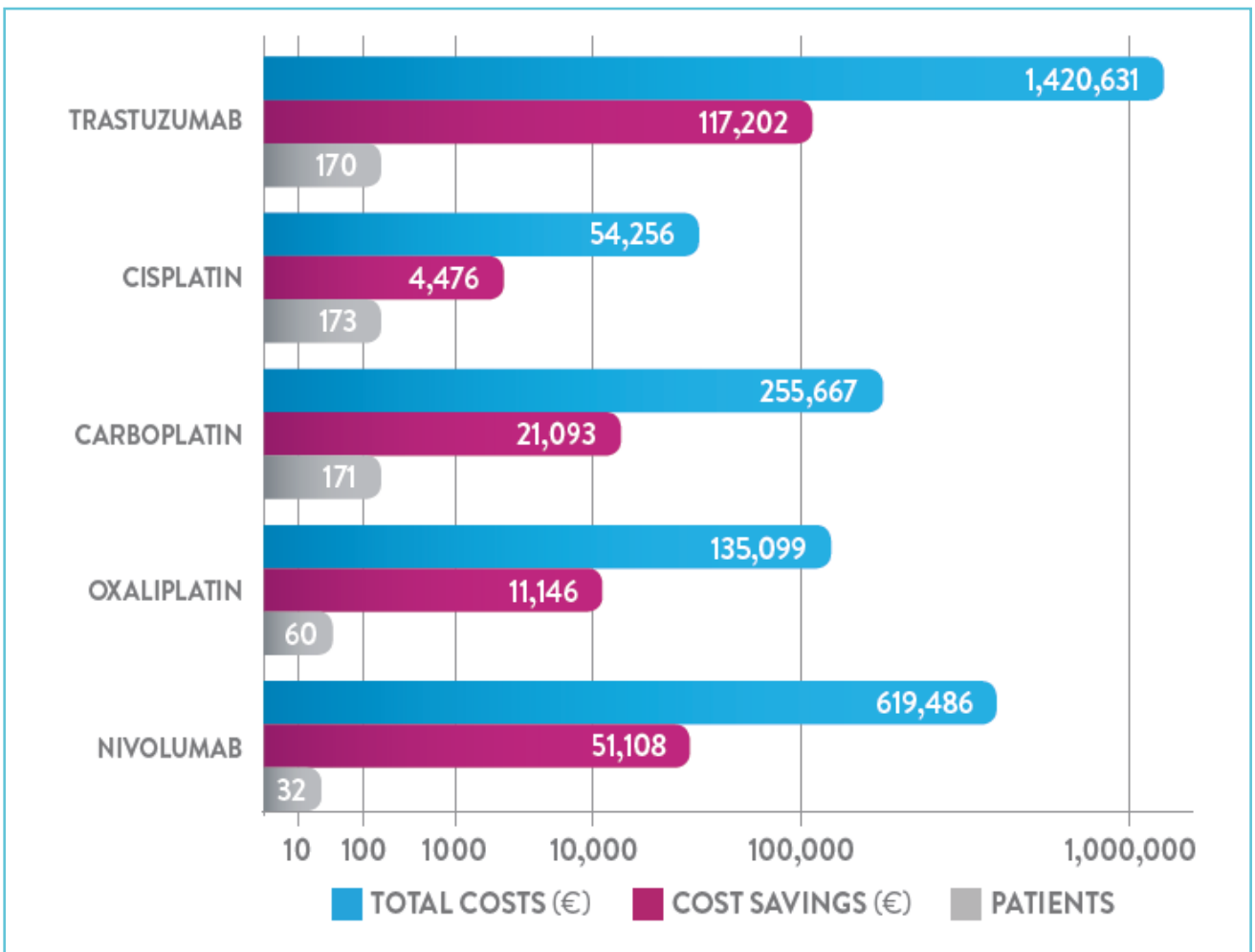
For drugs with a narrow therapeutic range like the chemotherapeutic drugs widely used, eGFR calculation can over- or underestimate renal function in patients with mild impaired renal function. The strong dependence on a single serum creatinine concentration in conventional dosing schemes poses several challenges such as significant (systematic) deviation from the true GFR (22, 23), significant biological variation (4), and unsuited dosing recommendation by the manufacturer of the drugs. In our simulations, parallel reporting of creatinine- and cystatin C-based eGFRs risk can mitigate false CKD

classification, and can improve accuracy of CKD staging and drug dosing for chemotherapeutic drugs as demonstrated in our simulation and applied as a routine approach in our hospital. According to our analysis for 2018, approximately 25% of the patients might benefit from this more accurate approach to determine GFR estimates as shown by the percentage of patients receiving altered dosing by an individualized approach.

The obvious benefits of this improved dosing regimen can be several-fold. First, we estimate that 1 out of 12 patients receiving chemotherapy

will avoid potentially lethal side effects by an optimized dosing regimen. Second, patients are more likely to comply with their treatment regimen containing highly toxic drugs when they are confident with the individual, patient-tailored dosing. When patients experience severe nausea or prolonged myelosuppression, their quality of life becomes further compromised and hinders sustained compliance. It is conceivable that the number of patients experiencing side effects of chemotherapy is decreased with corrected CKD classification and chemotherapy dosing. This concerns both the well-being of

Figure 4 Simulation of monetary benefits of adjusting chemotherapies by the individualized approach triggered by co-reporting of eGFRs*



* Please note the logarithmic scale.

the patients as well as the optimization of the time of the care givers since they must care less about treating unwanted side effects of chemotherapy such as heart failure, neuropathy, and renal failure (24). However, the calculation of the frequencies as well as the (additional) financial benefits of avoiding these detrimental side effects were far beyond the scope of this study. Fourth, most chemotherapeutic drugs (and their metabolites) have a narrow therapeutic range only. When a tool such as the Cockcroft-Gault equation is used for drug dosing, an inaccurate dosing is expected to occur in a substantial percentage of the patients and there is only little confidence by the care givers that the critical chemotherapy drugs are dosed correctly (13). An additional tool such as the co-reporting allows optimizing of patient treatments, and this leads to the expectation of less side effects in the patients (and their families) as well as less frustration in the care givers. Again, the calculation of the monetary benefits of the probably better confidence by the care givers and better adherence to the therapy by the patients was not performed during our study.

The implementation and governance of co-reporting is quite easy: Cystatin C testing can be performed by turbidimetry or nephelometry on essential all Clinical Chemistry analyzers (25) from serum samples already obtained before chemotherapy. The cost benefit analysis performed in 2018 in our hospital involving 606 patients showed that 1,800 € in Cystatin C testing (estimated costs for one test ~3,00 €) would account for savings of ~105,000 € in reduced chemotherapy drugs, which translates to a benefit:cost ratio of ~58:1. Co-reporting is not only highly effective but also extremely efficient. The benefits of the attending oncologists (such as higher confidence in producing less harm in their patients) and the benefits of the patients (such as less fear of unwanted side effects) are even not included in this monetary calculation.

Besides setting up the automatic alert in the LIS, some additional resources might be needed for the education of the benefits and caveats of using cystatin C for dosing of drugs in addition or as substitution of creatinine. It is obvious that GFR calculations based on more than one biomarker (7, 12) can diminish the rate of gross errors. However, given the legal background with the official approval of certain drug with a certain (only creatinine-derived) GFR, switching to a combined creatinine- (urea)-cystatin C-based eGFR (26) as a substitute for the creatinine-derived formula seemed to be too revolutionary. Therefore, we chose the co-reporting of creatinine- (urea)- based and cystatin C based eGFRs instead (27). This allows to focus on the subset of patients with very discrepant eGFRs and apply clinical knowledge and experiences in these selected patients for dosing of chemotherapeutics. In fact, this approach will use the cystatin C-derived GFR for dosing in essentially all patients: In most of the patients, both formulas (creatinine- and cystatin C-derived) do not differ significantly. When significant discrepancies are observed between both formulas, clinical expertise will be used to dose chemotherapy accordingly.

It is of particular interest, that cystatin C does not only allow dosing in patients with severely impaired creatin metabolism (such as myopathies, severe malnutrition) but is also a good marker for the shrunken pore syndrome (SPS) (28). SPS is characterized by a large difference between creatinine-derived GFR and cystatin C-derived GFR estimates (29) with a selective impairment of the glomerular filtration of 12- to 29 kDa molecules. Filtering of small molecules such as creatinine is not impaired but cystatin C and drugs and metabolites of drugs with a higher molecular weight are cleared less effectively in patients with SPS.

Improving the dosing of drugs by co-reporting is not restricted to patients with chemotherapy:

other drugs, in particular those which are markedly affected by renal function such as certain anticoagulants (30), antibiotics (31), or antidiabetic drugs (32) will also benefit from a dosing scheme reflecting closer the patients' renal function (33). The monetary benefit by saving drug doses will be smaller in these patients compared to patients with chemotherapy (due to the lower cost of a single dose) but the non-calculated benefits of avoiding side effects and the increase in quality of life (such as less bleeding events, no amelioration of renal function, fewer events of lactate acidosis) will compensate the costs (34) for cystatin C testing.

The limitations of these studies are the unavailability of a gold standard for glomerular function testing such as invasive GFR testing in our patients and no proof, that the optimized dosing of drugs has in fact benefited the patients. However, it is conceivable that chemotherapeutic drugs should be administered tailored to the individual patient characteristics as detailed as possible including weight and size (body surface), renal function, and liver function. This dosing is of particular concern in patients receiving an array of highly effective drugs and the complex interaction during co-administration of several drugs suggests that the optimized dosing regimen will reduce side effects and improve the expected effects of chemotherapy. One might argue that the registration of a drug such as by FDA or EMA restricts the use of a certain GFR-formula. However, it is highly conceivable that drug dosing is affected by renal function and that a certain GFR estimate is only a somehow inaccurate approximation of the real renal function (35, 36). The pharmacokinetics of some chemotherapeutic drugs are only moderately affected by renal function except in the case of a severe decrease of GFR (GFR <45ml/min). It is of certain interest that creatinine-derived GFR overestimate renal function in patients with a GFR <45 ml/min while cystatin C

underestimate GFRs in patients with normal renal function (37). Therefore, the benefits of co-reporting will be particular in patients with an impaired renal function – this patient population has the highest risk of side effects and of overdosing. We used the most frequently used method, the blanked Jaffé method, for creatinine testing. This method is known to be less reliable than enzymatic creatinine methods (38) but both creatinine methods suffer from significant discrepancies in many patients to the true GFR (39) even when the overall correlation between both methods is excellent.

Coreporting of creatinine and cystatin C testing can be introduced in essentially every clinical laboratory and programming these calculation and rule-based comments with standard IT tools is very straightforward. The detection of patients with large discrepancies is automatically triggered by the LIS or by middleware and is fully reliable.

Taken together, co-reporting of creatinine and cystatin C-derived eGFR may circumvent the known inaccuracies of creatinine only-derived GFR calculations, the use of which is mandatory by regulatory agencies. We suggest adding cystatin C-derived GFRs to the conventional creatinine-derived calculation with automatic alerts and use an interdisciplinary team when dosing chemotherapy.



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