Chronic Kidney Disease (CKD) is a large and growing clinical problem with increasing economic and organizational concerns as renal replacement therapy consumes a considerable proportion of health care resources\textsuperscript{1-3} and any medical intervention that may help to prevent the progression of CKD towards end-stage renal disease is extremely beneficial.\textsuperscript{4,5} Many drugs are cleared by the kidneys and dosing has to be tailored to the current renal function. Renal function decreases physiologically by age but is also affected by many diseases and drugs. The Modification of Diet in Renal Disease (MDRD) Study equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation are the two most widely used IDMS-traceable Creatinine-based estimates for glomerular filtration rate (eGFR) in adult patients so far. However, these estimates can be grossly inaccurate in certain patients.\textsuperscript{5} This inaccuracy in eGFR can lead to wrong drug dosing, resulting in increased complications, insufficient drug effects and expanded length of stays, reduced patient compliance, and also further long-term damage to the kidneys. Adding Cystatin C-based methods to eGFR estimation can overcome some of these disadvantages.\textsuperscript{6} In the Marienhospital Stuttgart, the parallel reporting of creatinine as well as of cystatin C-based eGFR calculation has lead to an integrated clinical care team initiative that identifies patients at increased risk for erroneous GFR estimation and allows optimal drug dosing leading to improved patient outcomes.
HYPOTHESIS

Providing two GFR estimates using both a creatinine-based equations and a Cystatin-C based equation will enable better recognition of:
1. Patients with possible renal function impairment
2. Patients with wrong GFR estimation
Discrepancies will drive improved implementation of therapeutic interventions for optimized treatment and improved patient outcomes.

DISCOVERY

Estimated Glomerular Filtration Rate (eGFR) is a crucial parameter for the assessment of renal function and drug dosing. Data from over 63,000 patients treated in the Marienhospital have shown severe discrepancies (i.e., differences >15 ml/min/1.73m²) using different GFR estimates. Creatinine-based eGFR over-estimates renal function, in particular in the elderly, compared to cystatin C-based eGFR. In patients with eGFR within the critical range of 30–60 ml/min/1.73m², up to 23.8% of CKD patients could have de-classification of disease with substantial consequences on drug dosing.

SITUATION

Correct renal function testing in the hospital is important to detect CKD, to avoid further damage to the kidneys, and to obtain an optimized pharmacological therapy.

Optimizing noninvasive renal function testing is a candidate for improving pharmacological treatment and avoiding further renal damage without consuming additional resources.

Avoiding insufficient therapies and overdosing with co-reporting eGFRs for personalized drug therapy and improved outcomes

AVOIDING INSUFFICIENT THERAPIES AND OVERDOsing WITH CO-REPORTING eGFRs FOR PERSONALIZED DRUG THERAPY AND IMPROVED OUTCOMES

PARTNERS

An integrated clinical care team initiative led by laboratory medicine developed a standardized process for dual reporting of eGFR to better detect and treat patients at increased risk for complications due impaired kidney function. All stakeholders were educated on the pharmacological practice uses of the different formulas for the estimation of eGFR. Key departments included laboratory medicine, pharmacy, nephrology and oncology.

COCKCROFT GAULT EQUATION (CREATININE-BASED)
- Standard for drug trials
- Derived from 249 men only

MDRD* OR CKD-EPI** (CREATININE-BASED)
- Historical standard
- Age-dependency
- Influenced by ethnicity
- Height, weight
- Liver cirrhosis
- Muscle mass
- Drugs
- Dietary protein intake

CYSTATIN C-BASED
- High accuracy in elderly patients
- High accuracy across ethnic groups
- High accuracy irrespective of diet
- High accuracy independent of drug intake
- Inaccurate in some thyroid patients
- Inaccurate under glucocorticoid treatment

*Modification of Diet in Renal Disease (MDRD). **Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).
AVOIDING INSUFFICIENT THERAPIES AND OVERDOSING WITH CO-REPORTING eGFRs FOR PERSONALIZED DRUG THERAPY AND IMPROVED OUTCOMES

EXECUTION

Renal adverse events is a major issue in oncological treatment. Gross misclassification by creatinine testing alone can occur in about 20% of all patients with slightly impaired renal function which could:

1. Erroneously trigger the replacement of an essential drug
2. Put the patient at a very high risk for severe side effects

In addition, correct dosing (i.e., using an appropriate eGFR estimation) will avoid severe side effects of chemotherapy.

To overcome these risks at the Marienhospital, dual methods for estimated GFR are calculated by the clinical laboratory with parallel reporting of creatinine based eGFR [MDRD] as well as of cystatin C-based eGFR calculations. An automated alert was established to flag patient records with a significant difference of greater than 15 ml/min/1.73m² in estimated GFRs based on discrepancies observed from the creatinine and cystatin C-based equations.

The alerts trigger a re-assessment of patients including a personalized approach for dosing of substances cleared by the kidney (antineoplastic drugs, antibiotics and contrast agents) for maximized patient care and outcomes.

PROOF OF VALUE

Side effects based on traditional dosing (creatinine based GFR) compared to improved GFR estimates were simulated using 606 patients receiving chemotherapy (Trastuzumab, Platin derivatives or Nivolumab) in 2018.

Results indicate that 19.4% of patients in CKD stages 3A and 3B were misclassified, reflecting 6.4% of total patients. Avoiding falsely high or low treatment in those patients with corrected chemotherapy dosing would lead to ~105,000 € savings in direct drug costs alone.
33% of patients at Marienhospital Stuttgart have severely impaired renal function. Parallel reporting of Creatinine and Cystatin C-based eGFRs risk mitigates wrongful CKD classification, and improves accuracy of CKD staging and dosing in 25% of these patients.

1 out of 14 patients receiving chemotherapy will avoid potentially lethal side effects.

“Patients are more likely to comply to their treatment regimen that avoid highly toxic drugs. When patients experience severe nausea or prolonged myelosuppression, their quality of life becomes further compromised and hinders sustained compliance.”
— Sr. Karin-Johanna Haase, pharmacist

“eGFR with Cystatin C enables me to optimally direct treatment for all my patients with confidence. I only start effective, but highly-toxic antineoplastic drugs if we also have the information on renal function based on Cystatin C-based GFR.”
— Manfred Hofmann, MD, PhD, gynecological oncologist

“A clear benefit of optimizing patient treatments involves maximizing my time on patient care. There is nothing more frustrating for me or the patient (and their families), than to waste valuable time with side effects that could have been avoided with different dose regimens.”
— Sebastian Maus, MD, nephrologist

No reimbursement challenges for patient treatment regimens involving innovative, expensive oncological drug treatment costs based on refined inclusion criteria in conjunction with this integrated care initiative.

A 2018 cost benefit analysis involving 606 patients involved 1,800 € in Cystatin C testing for a savings of ~105,000 € in reduced chemotherapy drugs.

Correct dosing of chemotherapy also avoids expenses associated with the side effects of over and under dosing. The cost avoidance in 2018 for reduced expensive chemotherapeutic dosing was 59,604 € for Trastuzumab alone.

Reduced primary and secondary prevention of heart failure, neuropathy, and renal failure based on optimized therapy in CKD stages 3A/3B (32% of patients with impaired renal function) with reduced serious short-term and long-term side effects.