Predictive Biomarkers in Nephrology Around the Corner

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Next to a drug’s safety profile, its efficacy is the main criterion determined in randomized clinical trials. Ultimately the applicability and success in clinical practice of a drug will dictate its widespread use. With sodium-glucose cotransporter-2 (SGLT2) inhibitors there is now a new class of drugs available in the armamentarium of nephrologists, as the beneficial impact on renal outcome has been shown in a number of clinical trials, with Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation (CREDENCE) being one of the most recent success stories.¹ Although the beneficial impact of SGLT2 inhibitors on renal outcome has been shown, not all patients respond equally to SGLT2 inhibitors. Unlike trials in infectious disease in which treatment can be clearly judged by the presence of the infectious agent after treatment, most trials assume that all patients similar to the entry criteria of a trial should be treated. CREDENCE, like most clinical trials, was set up as a case-control design with 1 treatment arm and a placebo control arm with the analysis focusing on mean differences of outcome parameters between the 2 groups. This approach by no means guarantees that each individual benefits from the therapy even if the trial is positive and a statistically significant difference has been detected between placebo and the active treatment.

Difference in drug response is a major issue and often not widely considered. Of the 10 drugs with the highest gross income in the United States, the number needed to treat to show benefit in 1 patient ranges from 4 up to 25, based on an analysis conducted in 2015.¹¹ Interestingly, most drugs in this list are targeting chronic diseases with oncological indications being absent from the list. In oncology, it is becoming the norm to profile patients on a molecular level or use companion diagnostic assays to guide therapeutic intervention with targeted therapies. Most companion diagnostic devices approved by the Food and Drug Administration are oncology-related and the assays test for tumor gene mutations or expression levels of individual genes that are either direct drug targets or within the pathway of the drug’s mechanism of action.

Predictive biomarkers indicate which patients will derive the most benefit of a given therapy. Baseline predictive biomarkers are measured before therapy. Dynamic predictive biomarkers indicate whether a change in marker levels after treatment as compared with marker levels at baseline will have value in predicting long-term responses. Predictive biomarkers should ideally be linked to disease pathophysiology, and in some cases also will have value as prognostic markers. In targeted tumor therapy, often a single biomarker is enough to educate whether a certain therapy should be administered or not. Treatment with the monoclonal antibody trastuzumab, for example, is preceded by determination of the HER2 receptor expression status. In chronic diseases, a single biomarker is often not enough to capture the full spectrum of dysregulated molecular processes at the molecular level. Computational strategies have been derived and applied to search for predictive markers and construct biomarker panels holding value in predicting drug response in chronic diseases.² Using information from Omics datasets, as well as information from scientific literature, molecular models of disease pathophysiology, as well as drug mechanism of action, can be constructed to guide selection of predictive biomarker candidates at the interference of disease mechanisms and drug mechanism of action. In a recent study, Heerspink and

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colleagues used such an approach to select biomarkers with the potential of predicting drug response for the class of SGLT2 inhibitors. Markers were selected capturing molecular mechanisms of inflammation, extracellular matrix deregulation and cell growth and differentiation and measured in blood samples from patients of the CANagliflozin Treatment And Trial Analysis-Sulfonylurea (CANTATA-SU) clinical trial investigating the SGLT2 inhibitor canagliflozin. Canagliflozin significantly reduced marker levels of tumor necrosis factor-R1, interleukin-6, matrix metalloproteinase 7, and FN1 with changes in tumor necrosis factor-R1 levels being significantly associated with renal outcome. In a separate study, Mulder and colleagues demonstrated that urine metabolites linked to diabetic kidney disease were responsive to dapagliflozin and correlated with changes in estimated glomerular filtration rate. Thus, there is excitement in the predictive biomarker field that biomarkers will be responsive to novel therapies and could guide which patient would benefit most from the new agent.

In the current issue of *KI Reports*, 2 studies, by Agrawal and colleagues and Gooding and colleagues, report on plasma proteomics and metabolomics profiles, respectively, being associated with steroid resistance in pediatric nephrotic syndrome and being capable of predicting drug response before treatment start. Only approximately every second adult patient with nephrotic syndrome benefits from glucocorticoid treatment, with nonresponders being at risk of suffering side effects and faster disease progression. The authors used a case-control setup and compared plasma proteomics and metabolomics profiles being differentially regulated between the steroid-resistant and the steroid-sensitive group in a discovery cohort. Mass spectrometry proteomics measurements and nuclear magnetic resonance metabolomics measurements were performed before glucocorticoid treatment start as well as 7 weeks after treatment initiation. A difference in plasma concentration levels of 13 proteins was found when comparing the steroid-resistant and the steroid-sensitive group of patients. With metabolites apart from creatinine, glutamine and malonate concentrations had value in predicting drug-resistance at baseline before treatment start. Glutamine also was one of the metabolites that was responsive to steroid treatment. However, the study was somewhat limited in that 45 subjects who were steroid-naive before obtaining the first sample and a validation group were not evaluated. In addition, urine metabolomics may be of higher yield than plasma metabolomics for renal diseases.

Analysis of the proteomics profiles resulted in the identification of 66 proteins showing significantly different trends of regulation when comparing concentration changes from baseline to week 7 in the 2 patient groups under study. An independent cohort was used to validate the proteomics findings of the discovery cohort. The vitamin D-binding protein was identified as the most promising predictive marker also showing significance in the validation cohort. Mechanistic markers showing different patterns of regulation in the steroid-resistant group as compared with the steroid-sensitive group in the discovery and the validation cohorts included matrix metallopeptidase 2, adiponectin, sex hormone binding globulin, hemopexin, vitamin D-binding protein, and apolipoprotein L1.

These 2 studies shed light on the underlying molecular differences between steroid-resistance and steroid-sensitivity forming the basis for tailoring therapy to patients. Predictive marker performance is not yet high enough for actual use in clinical practice, and the number of patients analyzed can be expanded in subsequent studies. Combining proteomics and metabolomics datasets to increase predictive power might be an additional option for subsequent analyses, although there is no guarantee that the combination of different Omics datasets really leads to improved results, as was recently shown in a multi-Omics study in the context of diabetic kidney disease prognosis. In this study, those proteins that have been preselected based on prior knowledge showed the best performance in predicting disease progression in the early stages of disease. Untargeted metabolomics or lipidomics profiles did not significantly add to marker performance, although these platforms hold the potential to get a better understanding of disease pathophysiology. The degree of coverage for proteomics is clearly not all-encompassing, as there is almost a limitless number of post-translational protein modifications and the technology to capture all modifications is currently not available. Similarly with metabolomics, the degree of coverage is limited by the ability to identify every molecular species in a bio-sample with sufficient sensitivity and accuracy. Nevertheless, there is a tremendous amount of potential insights that can be obtained with existing proteomics, metabolomics, and lipidomics platforms. Before such Omics profiles or biomarker panels will enter clinical use, they probably first will be used to optimize clinical trial design either via identifying fast progressors who might have the largest benefit from drug treatment or via identifying responders based on matched
disease pathophysiology and drug mechanism of action. A better understanding of disease pathophysiology and the availability of predictive biomarkers would pave the way for platform trials in nephrology assigning patients based on molecular profiles to the best-suited treatment arm. S3

Different EU and US consortia are currently pursuing the identification of predictive biomarkers for different nephrological disease entities. In the EU Proteomic Prediction and Renin Angiotensin Aldosterone System Inhibition Prevention of Early Diabetic Nephropathy in Type 2 Diabetic Patients With Normoalbuminuria (PRIORITY) study, for example, the urinary proteomics CKD273 classifier is currently being evaluated to identify fast progressors being the prime target of drug therapy. S4 The Innovative Medicine Initiative project Biomarker Enterprise to Attack Diabetic Kidney Disease (BEAt-DKD) is using multi-Omics profiling to identify predictive molecular biomarkers for major drug classes being used for the treatment of patients with diabetic kidney disease, among them SGLT2 inhibitors or endothelin receptor antagonists. The Juvenile Diabetes Research Foundation and the Chronic Renal Insufficiency Cohort (CRIC) study initiatives have used several multi-Omics platforms to identify biomarkers linked to disease progression for diabetic and nondiabetic chronic kidney disease. The Kidney Precision Medicine Project in the United States is using similar approaches of characterizing patients with chronic kidney disease but also acute kidney injury on the molecular levels with the ultimate aim of identifying better biomarker and novel drug targets to enhance drug efficacy in the end.

It remains to be seen how long it will take before the use of companion diagnostics also becomes the norm in nephrological clinical trial design and drug development pipelines, as is already the case in the area of oncology. Studies like the 2 in the current issue of KI Reports on the identification of predictive biomarkers are first steps in the development of novel tools being available in the armamentarium of clinicians to better tailor therapies to the individual patient.

DISCLOSURE
KS is on the safety monitoring committee for Sanofi and CARA Therapeutics Inc. The other author declared no competing interests.

SUPPLEMENTARY MATERIAL
Supplementary File (PDF)
Supplementary References.

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