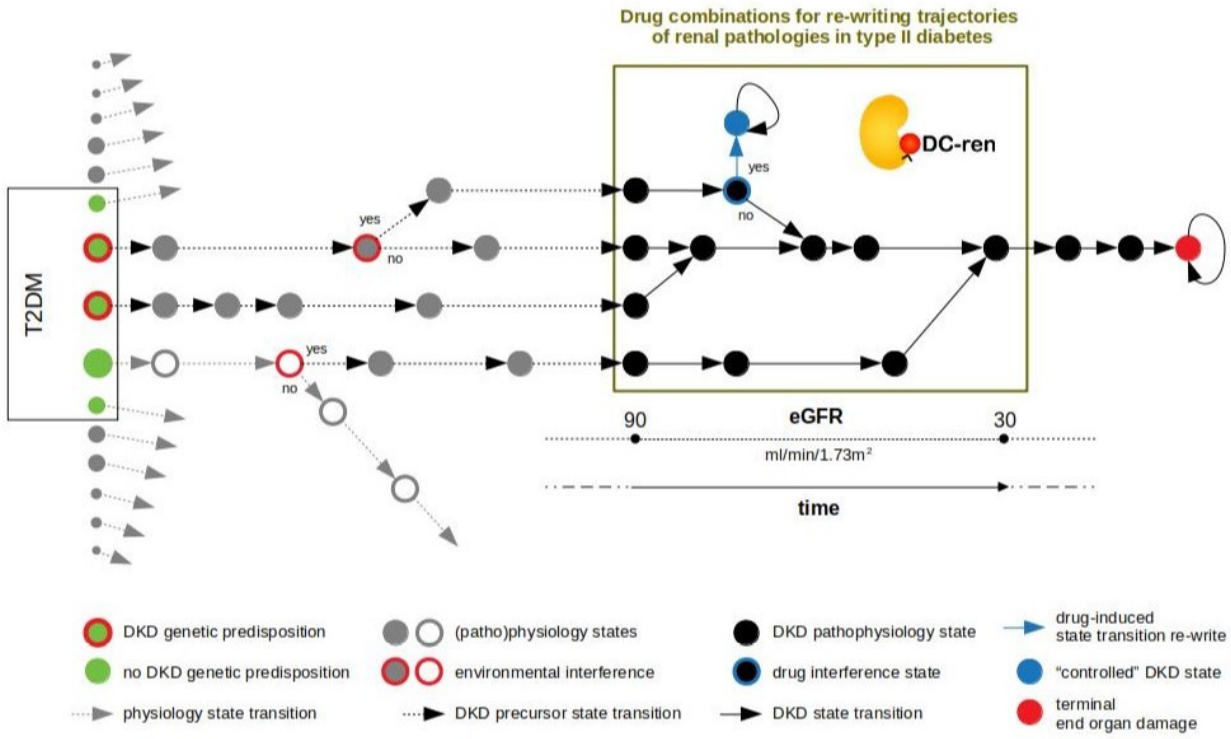
Summary of the context and overall objectives of the project

Diabetic Kidney Disease (DKD) is a serious clinical condition, and the incidence increases in parallel to the already epidemic prevalence of type 2 diabetes mellitus (T2DM). DKD is a chronic disorder, and the clinical course is currently captured by disease stages. This staging, derived from analysis of cohorts of DKD patients, allows an approximation of disease prognosis, but lacks accuracy on the level of individuals.
One purpose of assessing the prognosis is to provide guidance for treatment, and drugs for controlling various risk factors are at hand. On top, novel drugs demonstrating benefit on cardiovascular and renal outcome have been introduced to the clinics recently. However, while proving effective on a cohort level when using staging for deciding on prescription, also drug/drug combination therapy sees variance in response on the level of individuals.
Analysis of individual patients with DKD identifies inter-, but also intra-individual heterogeneity in disease evolution (prognosis) and drug response. Both, disease prognosis and the effect of a specific therapy are the direct consequence of an interaction between prevailing pathophysiology and drug mechanism of action. Hence, variability in prognosis and drug response is to be seen as variability in pathophysiology. Accordingly, personalized DKD treatment demands improved patient phenotyping for capturing this inter-individual (cross-sectional) and intra-individual (longitudinal) variability.

DC-ren follows a state-transition concept of disease evolution, a DKD state map:



A combination of genetic predisposition and environmental factors leads to individualized entry paths into DKD (triggering inter-individual heterogeneity). Further disease evolution follows trajectories of changing pathophysiology states (reflected as intra-individual heterogeneity).

DC-ren aims at combining improved patient phenotyping in a state map representation of DKD: Assignment of individual patients to specific states (in contrast to more coarse-grained stages) shall offer improved estimation of prognosis. In addition, assignment to states shall inform on respective pathophysiology, in turn allowing rational selection of drugs and drug combinations promising to be effective on the level of individual patients.

The central objective of DC-ren is to transfer the state map concept into a software solution, the DC-ren toolbox, tailored at decision support for predictive statements, to be evaluated in a (virtual) clinical trial to answer the question: Shall an individual DKD patient presenting at the clinic stay on current therapy, or change to a different drug combination for stabilization of kidney function.

Work performed

Work in the first reporting period (01/2020-06/2021) focused on establishing the DC-ren data space and developing analytic methods serving the decision support logic of the DC-ren toolbox.
Available clinical data repositories and biobanks were utilized to establish a data space covering inter- and intra-individual variability in disease evolution and response to relevant drug classes.
The PROVALID study offers longitudinal patient visit sequences, allowing to select archetypical disease evolution trajectories under varying drug treatment (“learning from the individual”) within the spectrum of DKD from predisposition to advanced disease (represented by eGFR as measure for kidney filtration capacity in the range of 90-30 ml/min/1.73m2). A definition of “controlled” and “uncontrolled” disease was introduced as a measure of disease evolution and drug response, using cutoff values of change in eGFR in 12month time intervals. Close to 500 patients with in total 1600 individual visits were included in the DC-ren data space. A dedicated database was established serving controlled exchange of demographic, clinical and laboratory data.

A biobank was prepared for additional molecular phenotyping of all visits, including targeted proteomics (CE-MS), multiplexed assays (Luminex, Mesoscale) and extension of routine clinical laboratory parameter quantitation. The biomarkers to be measured were defined by extensive systems biology-motivated analysis for capturing causal involvement in disease progression and potential for seeing change upon drug effect.

Analytical methods development has followed complementary approaches: (i) machine learning, including Q-learning with Random Forests as predictive model, Support Vector Machines and Dynamical Clustering (ii) including prior knowledge on the variable level is driven forward by the PRE score approach, prior knowledge on the level of variable dependencies follows Bayesian Networks (iii) respecting constraints from dynamical systems foundations aims at aggregating patient state evolution trajectories into an aggregate graph of disease evolution using a Metropolis Monte Carlo approach. For gaining insight into the molecular mechanistic basis of state transitions, Boosted Trees and first order logic statement induction is pursued.
The current status allows effective methods evaluation on the upcoming DC-ren data space (being fully available by the end of 2021).

Progress beyond the state of the art, expected results until the end of the project and potential impacts

Cohort-centric approaches have been the gold standard for improving disease diagnosis as well as drug development, testing and prescribing. According to certain stratification means a homogeneous

cohort is defined, followed by one-size-fits-all prognosis and treatment guidelines using the stratification criteria as basis. Depending on the nature of the disease such cohort approaches naturally see limits. Specifically for complex, age-associated disorders improved stratification is needed, and cross-sectional segmentation has become a widely accepted strategy. However, cross-sectional segmentation may not be sufficient. Even individuals assigned to subgroups with improved cross-sectional homogeneity may still see episodes of slow and fast disease progression, and periods with excellent but also with limited response to a certain drug. This finding rests in longitudinal (intra-individual) variance caused by changing pathophysiology. Hence, an improved assessment of patients with respect to disease prognosis but also predictive statements on response to drugs needs an underlying model covering intra- and inter-individual variability of disease evolution grounding in pathophysiology. Correct stratification of patients into states demands predictive biomarkers serving as proxy for i) molecular mechanistic aspects of disease evolution and ii) informing on effect of drug mechanism of action.

State maps promise to serve the task. States are defined by proper biomarkers, the specific expression for individual patient allows state assignment. State transition information approximates a deterministic disease evolution process and covers the prognostic aspect, and prediction of drug effect indicates if a clinically detrimental state transition “re-writes” to an alternative state coming with an improved clinical situation by addition of a new drug.

DC-ren develops and exemplifies this approach for DKD, a complication seen with T2DM and concomitant significant socio-economic impact. Methods development will be integrated into a Technology Readiness Level 6 software solution (demonstration) with the promise to contribute to the wider area of personalization strategies and precision medicine.