$$\frac{\partial \rho^{(X)}}{\partial t}(a,t) + \frac{\partial \rho^{(X)}}{\partial a}(a,t) = \Gamma_X\left(\rho^{(X_1)}(a,t), \ldots, \rho^{(X_n)}(a,t), a, t\right)$$

Predicting Population Trends in Kidney Health Using Advanced Mathematical Modeling

Dr. Doris Fuertinger
Dr. David Jörg

As more novel therapies are being developed, advanced quantitative tools are essential in evaluating and predicting their impact on future populations with kidney disease. To better understand the complex interplay of demographic and medical factors, Fresenius Medical Care has created the Population Impact Model. This proprietary methodology uses public health trends and clinical data to test a spectrum of hypotheses and provide insights into the potential impact of new therapeutic approaches.

The landscape of kidney disease is ever-changing. Globally, changes in lifestyle have led to a steady increase in obesity and diabetes, major drivers of chronic kidney disease (CKD). On the other hand, the last couple of decades have seen tremendous progress in the form of improved treatments for CKD such as new drugs to slow the progression and/or treat the underlying etiology of kidney disease such as SGLT2 inhibitors (SGLT2i)[1,2,3] and GLP-1 receptor agonists (GLP1ra).[4] In addition, innovative dialytic therapies, such as high-volume hemodiafiltration (HVHDF), have documented beneficial impact on clinical outcomes in people with end-stage kidney disease (ESKD) on dialysis.[5] Advanced epidemiological-type models are an invaluable tool to assess the integrated impact that novel therapies and demographic changes in the population may have on the size and characteristics of future populations with kidney disease.

The size and demographic composition of the CKD population depend on the complex interplay of various factors. Every year, hundreds of thousands of people develop ESKD around the world, many of them receiving kidney replacement therapy, mostly hemodialysis. At the same time, both the prevention and treatment of kidney disease are steadily improving, facilitated by new drugs and technologies. Novel therapies such as HVHDF have proven survival benefits for people with ESKD on maintenance hemodialysis.[5] GLP1ra—originally developed as a treatment for type 2 diabetes—gained much attention for their potential to reduce weight and delay kidney disease progression.[4] These are but a few examples. While life expectancy shows a general trend towards longer life expectancy, sudden global events like the COVID-19 pandemic can have a significant impact on the population.[6,7]

Advanced epidemiological-type models are an invaluable tool to assess the integrated impact that novel therapies and demographic changes in the population may have on the size and characteristics of future populations with kidney disease.

In this complex situation, several questions arise:

- **How will new therapeutic drugs like GLP1ra and SGLT2i affect the progression of kidney disease at the population level?**
- **Will the mortality benefits of HVHDF change the age structure of people on dialysis?**
- **When will the effects of the COVID-19 pandemic on the ESKD population diminish?**

Estimating the impact of these developments on populations with kidney disease is a challenging task, not least because different demographic groups, especially younger and older individuals, may be affected differently.

Quantitative Population Impact Modeling

This is where transparent mathematical models capturing the epidemiology of kidney disease can provide quantitative insights and make a decisive difference. By capturing ongoing public health trends and combining them with the latest clinical insights on the effect and efficacy of novel therapeutics, such models can provide valuable insights into what populations with kidney disease will look like in the future.

Fresenius Medical Care's Global Medical Office has developed a proprietary, science-based systematic modeling approach: the Population Impact Model. It provides a quantitative tool to test a spectrum of hypotheses about the future impact of novel therapeutic interventions and large-scale public health disruptions in the kidney space. The Population Impact Model is specifically designed to:

(a) understand how the sizes and age distributions of populations with kidney disease evolve over time, and

(b) generate predictions for various scenarios including the effects of disruptive therapeutic developments like new drugs and treatments on disease progression, mortality, and other relevant factors.

In a first step, the model specifically addresses developments in the United States, Fresenius Medical Care's largest dialysis services market, predicting the development of the U.S. population with kidney disease over the next decade.

The Population Impact Model describes how the interplay of kidney disease incidence and progression, treatment, population aging, and mortality shape the size and age distribution of the CKD and ESKD populations over time (Figure 1). The mathematical principles underlying the model are the same as for widely established models of epidemiology, such as the ones used to predict COVID-19 incidence and prevalence during the pandemic.[8,9]

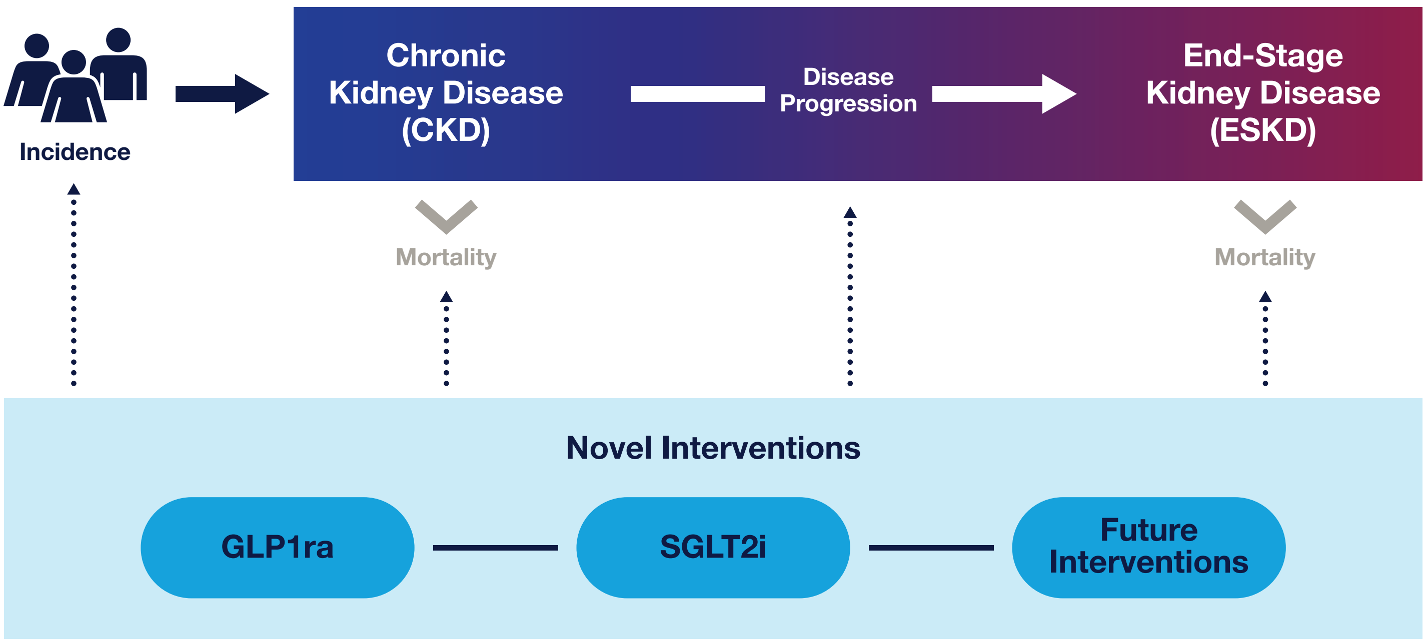
Public Health Trends in the United States

Any model prediction can only be as good as the data with which it is informed. Well-established publicly available databases like the United States Renal Data System (USRDS) and the National Health and Nutrition Examination Survey (NHANES) provide a wealth of data on the past and current state of populations with kidney disease in the United States.[10,11] However, to inform a systematic modeling approach and provide a basis for future predictions, the trends encoded in these datasets must be quantified:

- **How have ESKD incidence and mortality changed over the past decade, and how were they affected by the COVID-19 pandemic?**
- **Which proportion of people on dialysis received a kidney transplant, and how did this change over time for different age groups?**
- **How many persons developed CKD every year and at what age?**

By capturing ongoing public health trends and combining them with the latest clinical insights on the effect and efficacy of novel therapeutics, such models can provide valuable insights into what populations with kidney disease will look like in the future.

FIGURE 1 | SCHEMATIC OF THE POPULATION IMPACT MODEL



By applying advanced analytical methods, the data often reveal surprisingly robust temporal and aging patterns that encode systematic public health trends and shed light on the above questions for the past and present. These trends (and their disruptions) provide a robust foundation for predictions.

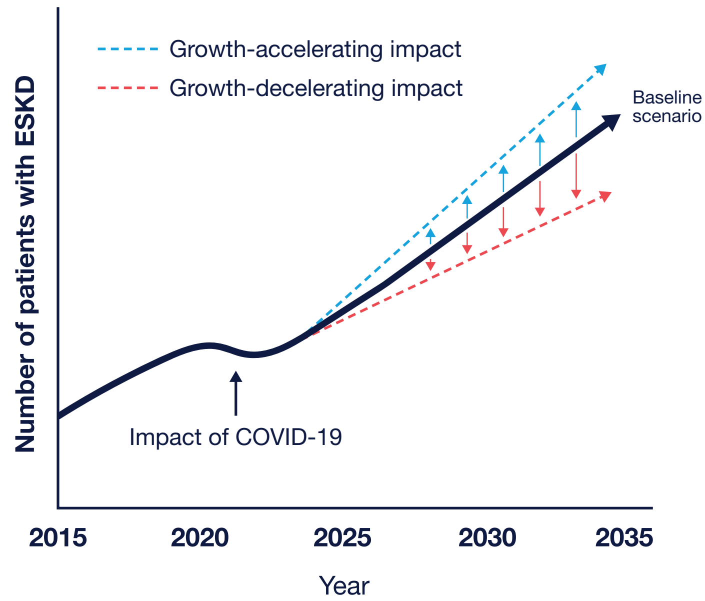
Assessing the Impact of Novel Drugs and Therapies

Once one understands current populations with kidney disease and the recent trends in kidney disease, then the crucial question is how these trends might be impacted by novel therapies. Clinical trials remain the primary source of knowledge about their safety and efficacy. They provide quantitative insights on how a therapeutic intervention changes the probability of kidney disease progression, death, and possibly other relevant clinical events for an individual. These insights can then be used to extrapolate an intervention's impact on the population scale (Figure 2). This, of course, also depends on how many and which patients are anticipated to have access to such novel interventions. Here, a modeling approach allows us to test different hypotheses (e.g., different anticipated prescription rates for a new drug in the coming years) and quantify how they affect the population.

Conclusions

Advanced epidemiological-type models provide a systematic and transparent tool to assess the population impact of current and future therapeutic innovations and public health megatrends. In particular, they help to disentangle the impacts of several concomitant developments in the kidney space, including the market introduction of new antidiabetic drugs and new kidney replacement therapies, pandemics, and other disruptions. Fresenius Medical Care is at the forefront of population impact modeling to inform medical, clinical, and business decisions. Continuous monitoring of therapeutic developments allows for regular updates to model assumptions and access to the latest predictions.

FIGURE 2 | ILLUSTRATION OF HOW EPIDEMIOLOGICAL MODELS CAN GENERATE PREDICTIONS ABOUT HOW NOVEL INTERVENTIONS CHANGE THE TRAJECTORY OF PATIENT POPULATIONS WITH KIDNEY DISEASE, DEPENDING ON THE RELATIVE IMPACT OF DIFFERENT INTERVENTIONS.



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Dr. Fuertinger is Head of the Computational Medicine Team within Fresenius Medical Care's Global Medical Office. She is an applied mathematician with an extensive background in physiology-based mathematical modeling, optimization and advanced computational methods. She has authored and co-authored multiple research papers and book chapters and is inventor on a number of international and U.S. patents held by Fresenius Medical Care.

Since joining Fresenius Medical Care in 2013 she had various roles at the Renal Research Institute, the Global Research and Development Department and the Global Medical Office. She pioneered concepts of in-silico clinical trials (i.e., computer based trials) that helped to shape and adjust clinical treatment protocols in the area of anemia and bone mineral metabolism. Dr. Fuertinger and her team further developed several state-of-the-art clinical decision support and automated therapy systems.

Dr. David Jörg
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Dr. Jörg is a Principal Scientist with Fresenius Medical Care's Computational Medicine Team within the Global Medical Office. He is a theoretical physicist by training and has a keen interest in bringing advanced mathematical modeling approaches to biomedical and healthcare applications.

Prior to joining Fresenius Medical Care in 2018, he conducted research at the intersection of biology and physics at the University of Cambridge, U.K., and the Max Planck Institute for the Physics of Complex Systems, Germany. He also served as an Organizer and turn-based Speaker of the Theory of Living Matter Group, a Cambridge-based researcher network.

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