GENOMICS AND PRECISION MEDICINE: THE FRENOVA GENOMICS REGISTRY

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Through the My Reason® campaign, the registry is engaging individuals with chronic kidney disease (CKD) around the world and amassing the volume of data needed for meaningful gene sequencing and analysis. By creating genomic and phenotype data sets for more than 100,000 patients, researchers can begin to unlock the complexities of CKD, develop individualized therapies, and ultimately optimize patient outcomes.

Although the microscope was invented circa 1600, it wasn't until the late 19th century that it was used to discover that cancers actually had multiple cellular forms. Today, instead of characterizing malignancies based on their location, genomic sequencing is identifying genetic mutations that more specifically classify tumors based on the presence or absence of these mutations and guiding very specific therapies. For example, in chronic lymphocytic leukemia, the presence of a mutation in the TP53 gene means that the cancer won't respond to chemotherapy and those individuals are best treated with a stem cell transplant.[1] Given the success in this and other cancer treatments by utilizing similar genomic evaluation technologies developed over the past 10 to 15 years, kidney diseases are only beginning to be unraveled. Cases that were previously undiagnosed, labeled "chronic glomerulonephritis" or "hypertensive disease" without the true cause being known, or that have hypertension as a secondary phenomenon can be more precisely identified. This specific approach to disease management is often called precision medicine.

The ultimate goal of precision medicine is to tailor medical treatments to specific disease processes and thereby optimize patient outcomes.[2] Applied to kidney disease, precision nephrology combines clinical phenotypes, genomics data, and epidemiological information not only to best diagnose underlying kidney diseases that have been underdiagnosed or missed, but also to detect extrarenal manifestations of their systemic illnesses, all of which may potentially inform a tailored therapy.

Nephrology has been underrepresented in clinical research, even as rapid progress in gene sequencing and analysis has led to advances in precision medicine and individualized care in oncology, cardiology, and other medical areas. Against this backdrop, Fresenius Medical Care's Frenova Renal Research division announced in early 2021 the creation of a new genomic registry initiative that will contain genetic sequencing data from individuals living with chronic kidney disease (CKD) worldwide.

UNRAVELING THE MECHANISMS OF KIDNEY INJURY IN CKD

Although inherited kidney diseases are rare, they may account for about 10% of adult end-stage kidney disease (ESKD) and at least 70% of pediatric nephropathies.[3] There is compelling evidence for a genetic contribution across different forms of kidney disease, in addition to more widely known hereditary etiologies (like autosomal dominant polycystic kidney disease or Alport syndrome). The heritability of glomerular filtration rate (GFR) is estimated to be 30 to 60% in the general population, and other parameters such as tubular transport of electrolytes similarly show substantial heritability.[4,5] This means that not only is baseline eGFR and tubular transport often similar within family lines, but also the risk of abnormalities of these functions in CKD may be inherited as well. Between 10 and 29% of adults with ESKD report a positive family history across different ethnicities and etiologies.

Humans have 20,687 genes, which come in allele pairs, one on each chromosome. It only takes one to three base pair alterations from individual to individual to result in our differences, including predilection to various diseases. Human genes contain about three billion base pairs of DNA, and about 1.5% of the whole genome is called the exome, where all protein coding genes are located. The non-coding region, or intron, makes up the rest.[6]

Evaluation of gene aberrations may be approached with genome-wide association studies, used in associating single nucleotide polymorphisms (SNPs) with a disease or trait being studied. The limitation is that very large samples are needed because the thresholds of significance are far lower than in clinical studies (e.g., $p < 5 \times 10^{-8}$). This will often require the use of meta-analyses in which several cohorts are lumped together to be studied.[7] There are a variety of more specific genetic tests that can detect single nucleotide variants (SNVs). These potentially can be SNPs, but it cannot be determined from only one individual. SNPs mean that the nucleotide varies in a species' entire population.

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Common modalities for more targeted diagnostic genetic testing include Sangar sequencing, chromosomal microarray, and next-generation approaches including targeted next-generation sequencing, sequencing panels, whole exome sequencing, and whole genome sequencing. These vary in their ability to assess SNVs, chromosomal disorders, and variations in selected regions of the genome including just the exome or the entire genome itself. The determination depends on what disease state or specific abnormality is being evaluated.[8,9]

A CATALYST FOR INNOVATION

The development of the Frenova genomics registry at the intended scale is made possible through partnership with patients and providers. Frenova is collaborating with Ali Gharavi, MD, Professor of Medicine and Chief of the Division of Nephrology at Columbia University College of Physicians and Surgeons, who will serve as Senior Advisor to the project, along with Michael Anger, MD who will lead the study as Principal Investigator.

The initiative is built around the My Reason® campaign (Figure 1). Patients who choose to participate in the study consent to provide their clinical data and access to their blood biospecimen, knowing that future generations might gain from advances in understanding various kidney diseases. Biospecimens are stored in ultra-low temperature freezers to potentially be used for future additional testing and to provide the opportunity for whole exome sequencing targeting the protein-coding region, which enables identification

FIGURE 1 | The My Reason campaign is designed to raise awareness of genetic research in the patient community

MY Reason Transforming Kidney Research

of many disease-causing variants. The combined genomic and patient phenotype data set (the observable characteristics of each individual) will be held in a cloud-based repository where the data can be retrieved for analysis and used to support research collaborations (Figure 2).

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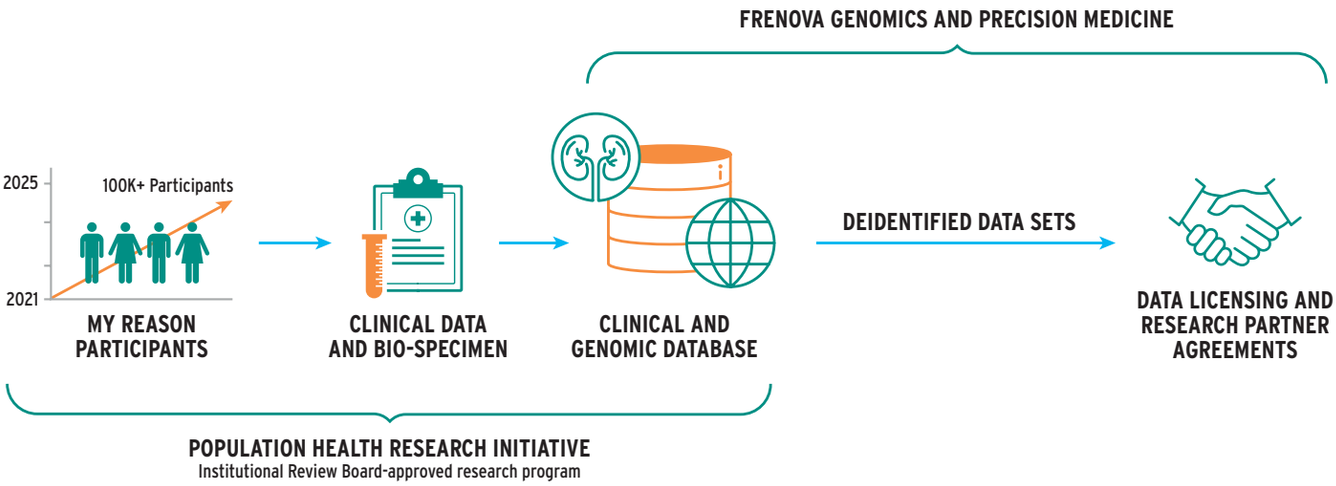
Innovative biopharmaceutical companies are making significant investments in the development and study of genotypic-driven therapies associated with known monogenetic disorders that predispose individuals to various kidney diseases. The creation of this large data set will be crucial to unraveling the complexities of CKD and enabling accelerated discovery and development of new therapies.

FIGURE 2 | A cloud-based repository will support research collaborations



Frenova Research coordinators have begun consenting patients within the Frenova Site Management Organization network of US dialysis clinics. The program is now expanding to include Fresenius Kidney Care clinics throughout the US and will eventually expand to other global regions and include individuals with earlier stages of CKD.

Information on the registry and the opportunity to consent to participate is available through the My Reason website at **www.whatsyourreason.com** (Figure 3).

The creation of the world's largest kidney genomics registry will require widespread engagement with the kidney community and the participation of individuals at all stages of CKD, along with their families, in My Reason.

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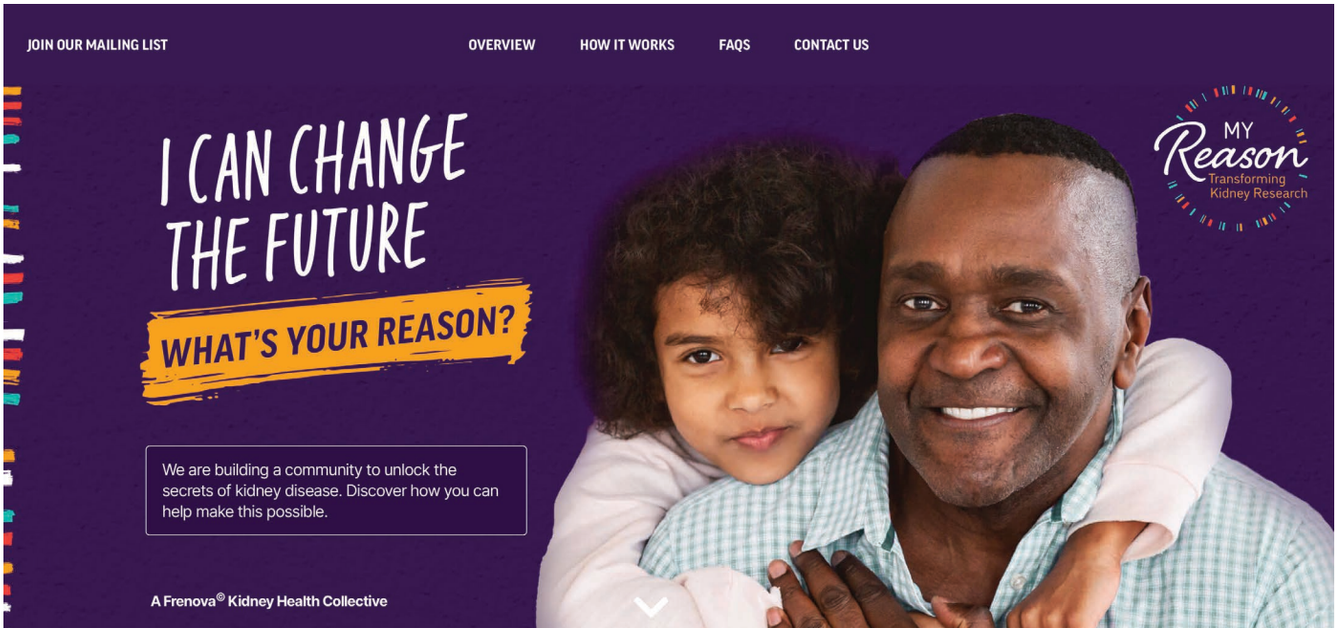
FIGURE 3 | The My Reason website provides information about the genomic registry



THE EXPERTS

MICHAEL ANGER, MD, FACP, FASN

Senior Vice President and Chief Medical Officer, Renal Therapies Group, Fresenius Medical Care North America
Chief Medical Officer, Frenova Renal Research

Michael Anger is senior vice president and chief medical officer of the Renal Therapies Group of FMCNA and chief medical officer of Frenova. He is clinical professor of medicine at the University of Colorado School of Medicine, a fellow of the American College of Physicians, a fellow of the American Society of Nephrology, and a member of the honor medical society Alpha Omega Alpha. Prior to joining Fresenius, Dr. Anger was the chief medical officer of American Renal Associates, as well as president and senior partner of Western Nephrology in Denver, Colorado, where he led the research division and interventional nephrology. He received his medical training at Hahnemann University, where he also did his internal medicine residency, and he completed his adult and pediatric nephrology fellowships at the University of Colorado School of Medicine.

JEFFREY CARR

Vice President, Operations and Business Development, Frenova Genomics and Precision Medicine

Jeff Carr is a global healthcare executive whose 25-year career has been committed to innovation in medical technologies and driven by a passion for pursuing solutions in areas of unmet need in healthcare. Jeff currently heads the Frenova Genomics and Precision Medicine program, an effort to catalyze greater investment in kidney health innovation through the development of the world's largest renal registry. Since joining Fresenius Medical Care in 2016, he has held leadership roles within the company—in business development with the Renal Therapies Group and as a lead member of the Global Efficiency Program. Jeff's previous positions include a management role with Alere, a global leader in point-of-care diagnostics (later acquired by Abbott Laboratories), where his focus was development and deployment of chronic disease management platforms with an emphasis on resource-limited settings. He earned his bachelor's degree from the University of Maine and pursued graduate studies at Northeastern University's D'Amore-McKim School of Business.