Embracing the Complexity of Global Healthcare

2021 GLOBAL ANNUAL MEDICAL REPORT
Vol. 6

FRESENIUS MEDICAL CARE

FRESENIUS
MEDICAL CARE

MISSION

We provide the best possible care. Sustainably in diverse healthcare systems. For a growing number of patients around the world.

Fresenius Medical Care achieves optimal sustainable clinical, quality, and technological standards in patient care through our commitment to developing innovative products and therapies.

The unique position of Fresenius Medical Care builds on many years of professional experience and continual innovation. Accordingly, the focus of our research and development effort is to maintain the technological and clinical edge needed to create innovative products and enhanced therapies. Our employees are united in our commitment to providing high-quality products and services and bringing the optimal sustainable medical and professional practices to patient care.

“TAKING CARE IS A TEAM EFFORT.”

I’m proud to share Fresenius Medical Care’s 2021 Annual Medical Report. We have an incredibly unique opportunity to transform an area of medicine where we can have a global impact on patients’ lives in communities around the world.

The shared experience of COVID-19 has been very unusual for everyone. And the pandemic continues to pose considerable challenges for society and healthcare systems worldwide. As a leading healthcare provider for people living with kidney disease, we look after one of the most vulnerable patient populations, and our priority remains their safety and well-being.

As a leader in value-based care, we also understand that continuously delivering on this commitment means taking care delivery to a higher level. That requires interpreting science and medical practice patterns on a global basis and driving medical outcomes across the regions. With our Global Medical Office, we ensure that we harness the full potential of our vertically integrated approach to achieve the best clinical outcomes for the patients we serve, their families, and the payor community.

Our 2021 Annual Medical Report highlights the ongoing leadership and commitment of our Global Medical Office in advancing our company’s clinical and scientific strategy on behalf of the patients we serve around the world.

And taking care is a team effort. I am grateful to every Fresenius Medical Care employee who delivers on our promise to create a future worth living for our patients, worldwide, every day.

RICE POWELL
Chief Executive Officer
Chairman of the Management Board

25TH ANNIVERSARY

FRESENIUS MEDICAL CARE
GLOBAL ANNUAL MEDICAL REPORT

The Annual Medical Report is published by the Global Medical Office at Fresenius Medical Care.

FRESENIUS MEDICAL CARE
Global Medical Office

Global Medical Office Communications
+1 781-699-3900
GMOcommunications@fmc-na.com

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Please send questions and inquiries about editorial to GMOcommunications@fmc-na.com

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ADVANCING KIDNEY DISEASE CARE THROUGH SCOPE, SCALE, AND EQUITY

Franklin W. Maddux, MD, FACP
Global Chief Medical Officer
Member of the Management Board

The advances in kidney disease care that fundamentally transformed a fatal condition into a chronic, manageable illness are among the great achievements in modern medicine. Making high-quality, reliable healthcare available to individuals living with kidney disease has been our company's mission since its founding a quarter century ago.

Fresenius Medical Care began with a clear vision to address the global impact of kidney disease by combining medical device engineering expertise with comprehensive patient care knowledge, in a company that puts patients at the center of its thinking. Every year, millions of people with kidney failure die because treatment is not available, accessible, or affordable—and governments and ministries of health around the world are putting a necessary focus on this. The worldwide variability and disparities in kidney disease care also represent a highly complex and unique challenge. With a scope that is both meaningful and flexible, Fresenius Medical Care takes the best ideas, invests in their development, and implements and innovates those ideas at scale.

The ability to take healthcare innovations and learnings from one locale to another has helped Fresenius Medical Care make an impact in communities worldwide. By advancing standards of care through knowledge sharing and innovation in care delivery, the company has made a number of sentinel milestones for the field that have had significant impact on patient care, leading to both higher care quality and more availability of that care.

"The idea behind Fresenius Medical Care was that we could combine the deep knowledge of National Medical Care's clinical services with the Fresenius Product Technology to innovate new therapies to fit the specific needs of dialysis patients."

Ben Lipps
Former Chairman of the Management Board and Founding CEO, Fresenius Medical Care

FRESENIUS MEDICAL CARE CONTRIBUTIONS TO MAJOR HEALTHCARE ADVANCES

SINGLE-USE DIALYZERS	Fresenius Medical Care led the global effort to reduce or eliminate dialyzer reuse and to move the industry toward single-use dialyzers.
VOLUMETRIC CONTROL	The company invented volumetrically controlled machinery used to control the fluid removal during a dialysis treatment.
HOLLOW FIBER DIALYZERS	People in over 150 countries dialyze on a spun biocompatible hollow fiber dialyzer innovated by Fresenius Medical Care.
BICARBONATE-BASED ACID CONCENTRATES	Fresenius Medical Care developed bicarbonate dialysate mixtures to address symptoms during treatment.

A LEGACY OF LIFELONG LEARNING

Fresenius Medical Care is built on a legacy of learning and evolving the delivery of care and the tools to treat advanced kidney disease (Figure 1).

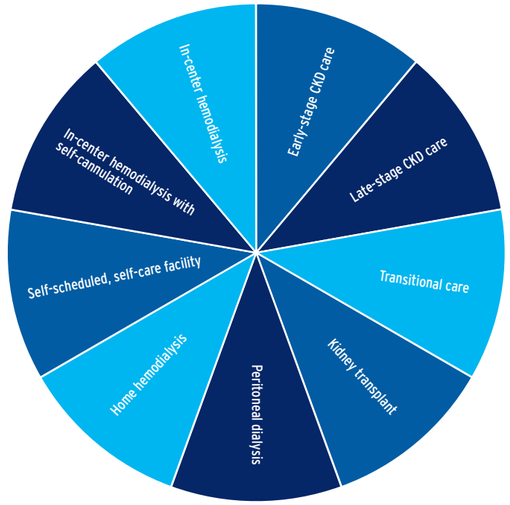
Each year, we care for more than 350,000 patients directly, with more than 50 million treatments. In fact, one in two dialysis machines used in the world are made by Fresenius Medical Care. The patients we serve range in age from infants to the elderly. We care for patients with diverse backgrounds and social circumstances, and all wish to live a life of meaning on their own terms. In addition to advancing medical science and our work in the field, we've learned a lot from being a trusted partner for patients:

- **Patients desire more choices for treatment options and the power to decide which best supports their personal goals.**
- **Patients desire the chance to receive treatment at a location that is convenient to them.**
- **They want to stay connected to their own health information and to their care teams.**
- **Patients want to be productive and empowered, and not let the disease overcome their wish to contribute to their family and community.**
- **They expect the safest care possible with a minimum of side effects.**
- **Patients and doctors want the option of a kidney transplant whenever it is deemed the best option for kidney replacement therapy.**
- **Undeniably, social determinants of health—such as food security, stable housing, and social justice—have substantial effects on patient outcomes.**

FIGURE 1 | Advancing the Kidney Care Model

Over the course of their lifetime, individuals living with kidney disease will desire different treatment options that fit with their personal goals. Treatment offerings represent various levels of patient participation and different sites of care, including in-center and at-home options, at both earlier and later stages in the disease (Figure 2).

FIGURE 2 | Treatment options for an individual living with kidney disease



Today, Fresenius Medical Care's clinical vision is to deliver the right treatment to the right patient at the right time—on the individual's own terms. This requires breaking down the barriers between CKD and ESKD care so the continuum of these stages of kidney disease are recognized as an integral part of the lifetime journey of the patient with kidney disease. We are compelled to develop new therapies that are accessible, are cost effective, improve cardiovascular health, and offer improved outcomes.

A FORWARD-LOOKING STRATEGY

Healthcare innovations have enabled patients to live more energetic, productive lives. What might we offer to patients in the future?

- **Dialysis treatments with a lower risk of bleeding?**
- **Surgical implantation of a blood vessel that becomes a patient's own tissue over time?**
- **A device that automates the control of fluid removal to protect the heart and adjusts to the hemodynamics of the patient?**
- **Access to medications and therapies that afford a better chance of receiving and maintaining a functioning kidney transplant or an engineered organ?**

Fresenius Medical Care is in the best position to move this clinical vision forward in the coming decade in the construct of our three-domain strategy: the **Renal Care Continuum**, **Critical Care**, and **Complementary Assets**. This three-domain strategy represents a path to transform delivery of healthcare and improve patient outcomes on a worldwide basis.

The company's Clinical and Quality Agenda is the foundation for our medical leadership and brings to life our strategy. The agenda articulates a focus for our clinical vision, the priorities for our field, and the dimensions of collaboration within the organization. The agenda's priorities help socialize the science of promising innovation, accelerate data-driven healthcare, expand research opportunities that advance medical practice, and support our partnership with physicians around the globe (Figure 3).

Together with our business partners, the Global Medical Office drives progress that is thoughtfully planned, driven by science, and rooted in evidence. This focused approach paves the way for Fresenius Medical Care to address some of humanity's most urgent healthcare needs.

For the past quarter century, this has been our history, and it is the basis of our future.

END-STAGE KIDNEY DISEASE | **A SHIFT IN FOCUS** | EARLY-STAGE CKD | LATE-STAGE CKD | END-STAGE KIDNEY DISEASE

"As an organization built like no other, the vision was to realize this incredibly unique opportunity to transform an entire area of medicine where we can have a global impact on the lives of the patients we serve."

Rice Powell
Chairman of the Management Board, Chief Executive Officer, Fresenius Medical Care

RENAL CARE CONTINUUM

The Renal Care Continuum addresses each stage of kidney disease and recognizes the diverse and changing needs across a patient's lifetime journey.

- **Our products enable therapeutic benefit and can serve as sensing platforms that provide greater insight into a patient's individual physiology.**
- **Our patient care services provide life-saving treatment and help sustain healthcare delivery systems throughout the world.**
- **Value-based care breaks down existing and artificial barriers between chronic kidney disease, end-stage kidney disease, and kidney transplant care.**
- **Analytics provides important insights to improve healthcare and make it more personalized.**

CRITICAL CARE

Critical Care is the second strategic domain and recognizes the impact of multi-organ support for those with acute critical illness. Our portfolio includes kidney, heart and lung support and we provide more organ replacement therapy than any other company on earth.

COMPLEMENTARY ASSETS

Complementary Assets is the third strategic domain and recognizes the importance of innovative technologies. Tissue-engineered blood vessels and bodily structures, cell-based therapies, and genetic engineering technologies are complementary capabilities with great potential to advance kidney disease care.

FIGURE 3 | The company's Clinical and Quality Agenda is built around core themes and provides a framework to realize the company's patient-centered mission.

CARDIOVASCULAR HEALTH
Improve patient outcomes and quality of life by optimizing cardiovascular health

Focus on kidney replacement therapy, the interdialytic interval, fluid/volume management, and cardiovascular medications

1

PRECISION MEDICINE
Rapidly evolve precision medicine for individuals with kidney disease by launching a worldwide genomics registry

Accelerate the development of individualized algorithms, artificial intelligence tools, and advance personalized prescribing

2

MEDICAL COMMUNICATIONS AND EDUCATION
Develop global communications infrastructure and processes to support efficient and impactful worldwide communication

Align medical education programs and develop new teaching programs and platforms

3

GLOBAL RESEARCH
Expand opportunities for individuals with kidney disease to participate in research

Focus on research that generates clinical evidence for product development and regulatory approval

4

PATIENT-CENTERED CARE
Promote care that includes a focus on quality of life and patient goals

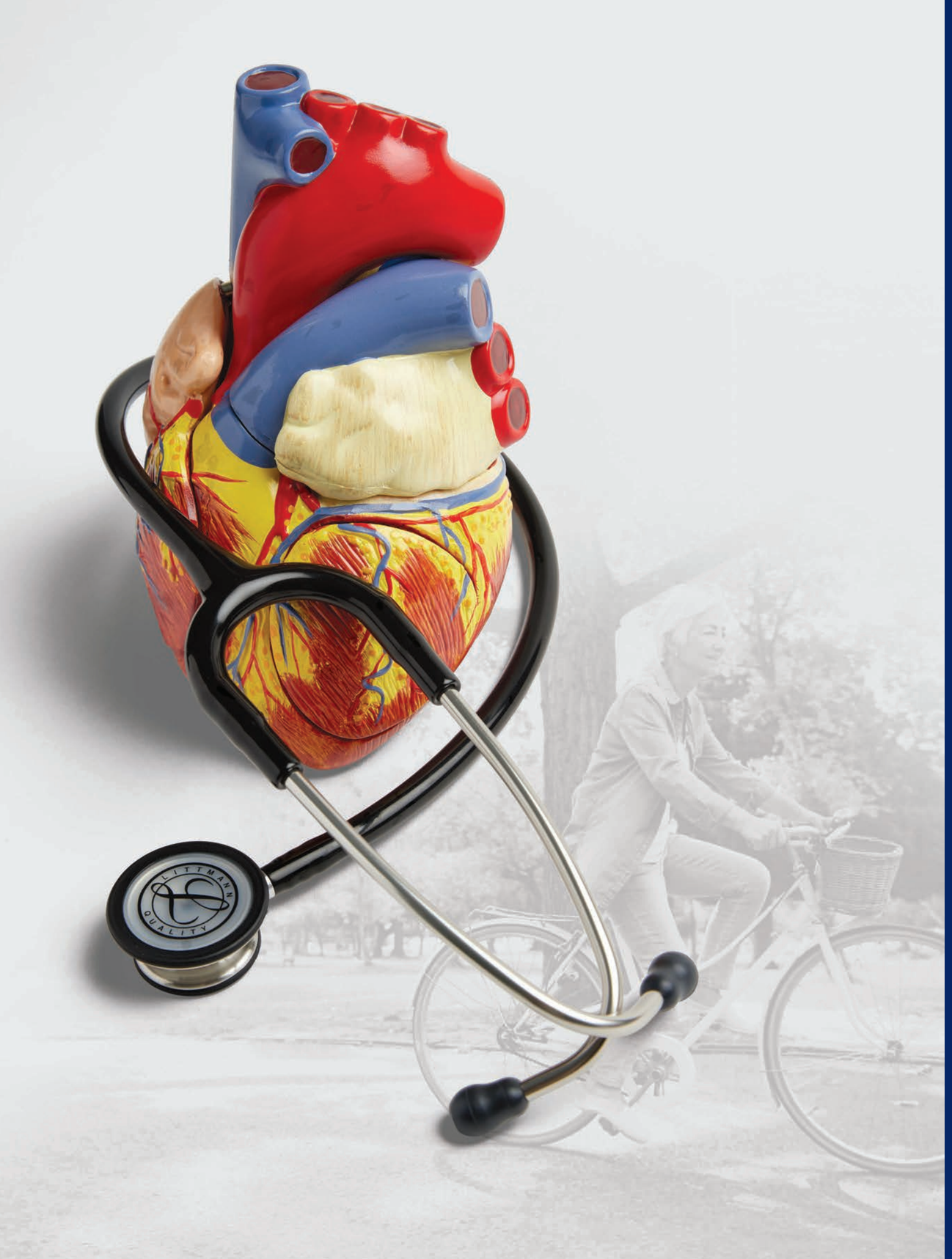
Improve the patient experience of care

5

INNOVATION AND TRANSFORMATION
Invest in innovative therapies

Expand the use of connected health

6



CARDIOVASCULAR HEALTH

Make cardioprotective strategies a standard component of dialysis. Reexamine our approaches to fluid/volume management, therapy intervals, cardiovascular medication choices, and other protocols to improve patient outcomes and quality of life.

FLUID MANAGEMENT: PAST, PRESENT, AND FUTURE

Sabrina Casper, MSc
Lemuel Rivera Fuentes, MD
Peter Kotanko, MD, FASN

Physicians now have an assessment toolkit to help them manage fluid balance in dialysis patients. Bioimpedance devices and relative blood volume (RBV) monitors are among the most noteworthy technical advances, but because attaining favorable RBV ranges requires constant adjustments to the ultrafiltration (UF) rate, these devices cannot do the job alone. To address this issue, Fresenius Medical Care developed its UF control algorithm. This innovation continuously compares the patient's RBV profile to the target curve and makes UF rate adjustments, resulting in a final UF removal within the prescribed UF goal range. In recognition of its potential to improve long-term patient outcomes, the US Food and Drug Administration granted a rare 21st Century Breakthrough Device designation to the company's UF controller.

Fluid balance is tightly regulated through a delicate and coordinated interplay of organs—most prominently the kidneys, but also the gastrointestinal tract, liver, skin, and nervous, circulatory, and endocrine systems. The intricate physiology responds in a highly coordinated way to changes in water, salt, and other nutrients to meet the body's demands. In healthy adults, the total body water (TBW), as a fraction of body weight, is about 50% in females and 60% in males. This fraction decreases slightly with age. Broadly speaking, TBW can be separated into intracellular (about two-thirds of TBW) and extracellular (about one-third of TBW) water compartments. Blood volume contributes approximately 70-75 mL/kg body weight to TBW.

Dysfunction of the organs and systems that regulate fluid balance can result in disturbed fluid status. Both fluid depletion (FD) and fluid overload (FO) come with acute and long-term consequences. Kidneys are a marvel and have a tremendous capacity to control TBW through regulating urine volume and composition. Consequently, most patients with impaired kidney function or end-stage kidney disease experience at some point either FO or FD.

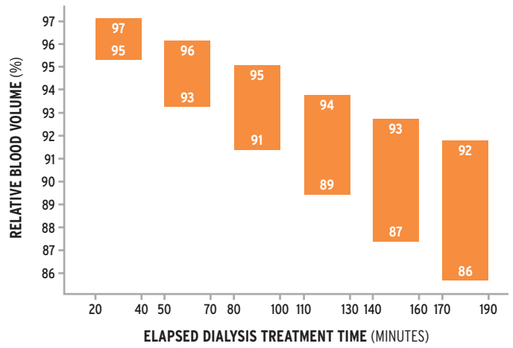
To quantitate fluid status and complement clinical judgment, several diagnostic tools have been developed. They can be broadly classified as either biochemical tests or technical devices. The former includes, for example, the measurement of natriuretic peptides—e.g., brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro-BNP)—which increase in response to several conditions such as heart failure, left ventricular hypertrophy, and FO. In individuals receiving dialysis, these conditions frequently coexist, rendering biochemical markers of fluid status unreliable.[1] In contrast, technical devices to assess fluid status are widely used in dialysis. The two most noteworthy tools are bioimpedance devices and relative blood volume (RBV) monitors.

Collaborating with Nephrocare in Fresenius Medical Care's Europe, Middle East, and Africa region, researchers studied the relationship of baseline and one-year cumulative FO exposure in 39,566 incident dialysis patients from 26 countries.[2] The researchers used the company's Body Composition Monitor, a whole-body multi-frequency bioimpedance spectroscopy device, to assess fluid status. Cumulative one-year FO exposure predicted a higher risk of death. In an international cohort study in 8,883 hemodialysis patients from the MONitoring Dialysis Outcomes (MONDO) initiative, both pre-dialysis FO and FD were associated with higher mortality.[3]

To quantitate fluid status and complement clinical judgment, several diagnostic tools have been developed. They can be broadly classified as either biochemical tests or technical devices.

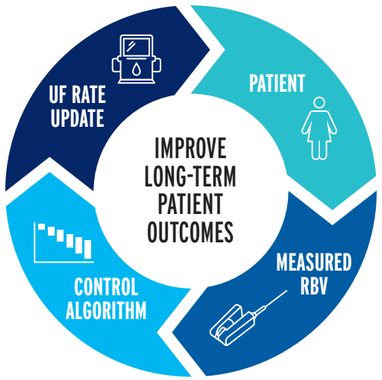
Less data exist regarding the association between RBV changes attained during hemodialysis (HD) and patient outcomes. In a study of 308 patients receiving hemodialysis and followed for a median of 30 months, FO was detected by relative plasma volume (RPV) monitoring.[4] The researchers discovered that a shallow intradialytic slope of RPV with a decline of less than 1.39% per hour was associated with higher mortality. A study of 842 patients followed for a median of 30.8 months corroborated these results directionally.[5] The authors identified what they termed "favorable" RBV ranges that were associated with improved survival (Figure 1). Approximately 32% of patients attained RBVs within the favorable ranges, while 65% had RBV trajectories above and 2.5% below.

FIGURE 1 | Relative blood volume ranges associated with significantly lower all-cause mortality. The hourly RBV ranges associated with improved survival: first hour, 93-96% [hazard ratio (HR) 0.58 (95% confidence interval (CI) 0.42-0.79)]; second hour, 89-94% [HR 0.54 (95% CI 0.39-0.75)]; third hour, 86-92% [HR 0.46 (95% CI 0.33-0.65)].



The Crit-Line® in a Clip (CLiC®) device allows real-time monitoring of a patient's RBV during hemodialysis. While possible in theory, active attainment of the favorable RBV ranges would require frequent manual adjustments of the ultrafiltration (UF) rate, an intervention that may not be feasible in routine clinical practice. To address that problem, Fresenius Medical Care has developed the so-called Adaptive UF Feedback Control algorithm, which directs a patient's RBV curve into the favorable ranges. The algorithm automatically raises and lowers the UF rate during HD in response to a patient's treatment-specific RBV trajectory, measured with the CLiC®. The general closed-loop flow is shown in Figure 2.

FIGURE 2 | Closed-loop flow of the Adaptive UF controller



Before the treatment, the physician prescribes a target UF volume together with a maximum- and minimum-allowed volume deviation tailored for each patient. The controller manages the UF rate adjustments, resulting in a final UF removal within the prescribed UF goal range. The controller not only aims at attaining favorable RBV ranges but also steers the entire RBV curve to abide by a population-validated ideal trajectory that passes through half-hourly RBV values associated with the best patient survival. By continuously comparing the patient's treatment-specific RBV profile to the target curve, UF rate adjustments are made every 10 minutes to direct the patient's RBV curve toward that trajectory while observing the prescribed UF goal range. At the end of 2018, Fresenius Medical Care submitted the UF controller concept to the US Food and Drug Administration and was granted 21st Century Breakthrough Device designation.

The UF controller was first tested through computer simulations ("in silico"), then in the laboratory setting using an analog model that allowed the adjustment of key components such as absolute blood volume, UF volume, plasma refill rate, and treatment time. After the successful bench testing, the first non-significant risk investigational device exemption clinical research study was initiated. In that study, the UF controller was carried out in an assisted setting ("nurse-in-the-loop") where it could not change the UF rate automatically. In the assisted setting, the controller's UF rate recommendations were evaluated by a dialysis nurse who either implemented or disregarded them. This "nurse-in-the-loop"

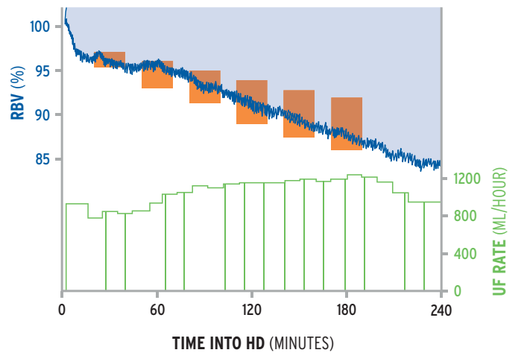
The UF controller was first tested through computer simulations ("in silico"), then in the laboratory setting using an analog model that allowed the adjustment of key components such as absolute blood volume, UF volume, plasma refill rate, and treatment time.

setting was accomplished by connecting a 2008T machine's CLiC to a laptop with the control algorithm embedded into a graphical user interface. This interface tracked the RBV curve in real time, UF volume, and UF rate, and displayed the favorable RBV ranges.

Fifteen subjects (63 dialysis sessions) were analyzed. In the depicted dialysis session example, the UF rate changed around every 10 minutes, steering the patient's RBV trajectory through the favorable RBV ranges. In this session, the prescribed UF goal was 3.5 L with an allowed deviation of ± 1 L (Figure 3).[6] The final UF volume eventually removed was 4.1 L, showing that the controller was able to attain the favorable RBV ranges while staying within the prescribed UF volume limits.

Considering all studied sessions, 63% of 300 RBV target timepoints were within the favorable RBV ranges (Figure 4). Out of 1,038 controller UF recommendations, 926 (89.2%) were accepted by dialysis nurses. The UF rates suggested by the controller were neither excessively high nor low. The frequency of intradialytic hypotension and muscle cramps was not increased, and there was no indication of adverse events related to the use of the UF controller.

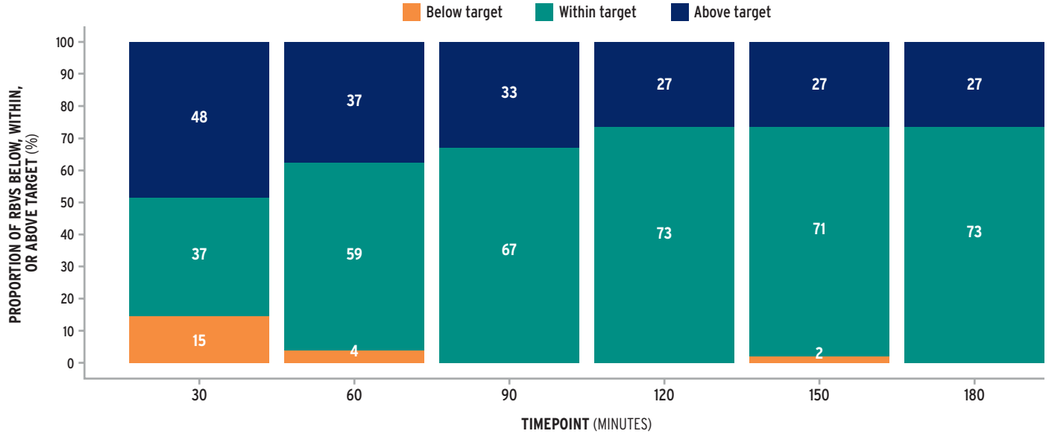
FIGURE 3 | Example of a "nurse-in-the-loop" study treatment. The UF rate was adjusted by a nurse based on the control algorithm recommendations during the treatment, successfully keeping the patient within the favorable RBV ranges.



In summary, the UF controller steered patients' RBV curves toward the predefined target ranges while strictly observing the prescribed UF goal range. Importantly, the authors who studied the 842 patients had reported that only about a third of them were able to achieve the favorable RBV ranges at three hours into a conventional HD treatment.[7] In contrast, with the use of the UF controller, over 70% of subjects were within the desired three-hour RBV target. While it is posited that outcomes will improve in patients who are actively steered into the favorable RBV ranges by the UF controller, well-designed and rigorously executed outcome studies are warranted. The next phase of the UF controller studies is being planned and will include intradialytic BP monitoring and use of a fully automated adaptive UF feedback design.

Fluid management in individuals receiving maintenance dialysis has come a long way, from exclusive reliance on physical examination and history taking, to quantitative assessment by bioimpedance and RBV monitoring, to an Adaptive UF Feedback Control algorithm. While each of these is valuable, the future of fluid management still lies in the wise and collaborative application of all the available tools.

FIGURE 4 | Proportion of RBV values below, within, and above the respective RBV target range for each of the RBV target timepoints. Underlying data: all subjects who contributed data (N=14), all RBV targets (N=300).



THE EXPERTS

SABRINA ROGG CASPER, MS

Senior Computational Scientist, Global Research and Development, Fresenius Medical Care

Sabrina Casper is a senior computational scientist on Fresenius Medical Care's Biomathematical Modeling team and works closely with the Renal Research Institute. She develops optimization and optimal control algorithms to improve and personalize therapy of dialysis patients. Her areas of experience range from design and implementation of new algorithms to in silico, laboratory, and clinical pilot testing. Sabrina holds a master's degree in mathematics from the University of Konstanz in Germany.

LEMUEL RIVERA FUENTES, MD

Supervisor, Clinical Research, Renal Research Institute

Lemuel Rivera Fuentes joined the Renal Research Institute in 2018 as a research scientist, and in 2021 became the supervisor of clinical research. His research interests include the design and execution of pilot studies for innovative therapies to manage volume and anemia in dialysis patients. Lemuel obtained his medical degree from Universidad La Salle in Mexico City, where he was awarded the Excellency in Medical Academic Achievement Grant by the Pfizer Scientific Institute. He completed his internal medicine residency at ABC Medical Center and a nephrology fellowship program at Salvador Zubirán National Institute of Medical Sciences and Nutrition in Mexico City. He went on to pursue a high specialization postgraduate course in transplant nephrology sponsored by the National Autonomous University of Mexico. He is board-certified by the Mexican Council of Internal Medicine and the Mexican Board of Nephrology.

PETER KOTANKO, MD, FASN

Research Director, Renal Research Institute
Senior Vice President, Research and Development

Noted researcher and scholar Peter Kotanko is research director of the Renal Research Institute (RRI). RRI's research aims to improve patient outcomes and quality of life. An adjunct professor of medicine and nephrology at the Icahn School of Medicine at Mount Sinai in New York City, he has authored and coauthored more than 350 research papers and book chapters, and is the former vice chair of a medical department at an academic teaching hospital in Graz, Austria.

CARDIOVASCULAR HEALTH IN CHRONIC KIDNEY DISEASE: IMPROVING OUTCOMES USING SGLT-2 INHIBITORS

Bernard Canaud, MD, PhD
Allan Collins, MD, FACP

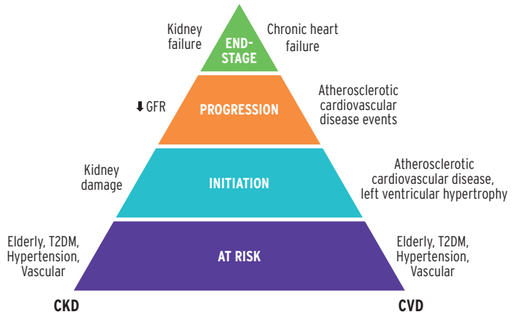
Cardiac disease is the leading cause of death for patients with chronic kidney disease (CKD). Because the risk of cardiovascular disease increases with the progression of CKD, cardiac care is an essential component of comprehensive CKD management. Sodium glucose-co-transporter 2 (SGLT-2) inhibitors are a new class of medication initially developed to control hyperglycemia in people with type 2 diabetes mellitus. In addition to helping patients achieve glycemic and overall metabolic control, SGLT-2 inhibitors have been shown to have cardio-protective benefits for high-risk patients with diabetes, and recent studies indicate they also hold promise for slowing CKD progression and for treating heart failure and other cardiovascular conditions.

Slowing the progression of kidney disease is a key focus in nephrology research.[1,2] The best results are achieved by combining dietary interventions, lifestyle modifications, and pharmacologic therapies with systemic and renal hemodynamic effects. Treatment optimization relies on a stepwise approach using several classes of medications to lower glomerular and vascular stress in addition to hypertension and proteinuria. In this context, anti-hypertensive drugs that block the renin angiotensin aldosterone system (RAAS) have been effective; however, more specific interventions based on the primary cause of kidney disease and/or the specific risk identified are also required.[3,4]

In the case of type 2 diabetes mellitus (T2DM), a leading cause of kidney disease, controlling hyperglycemia and related metabolic disorders remains important in slowing diabetic kidney disease (DKD) progression.[5,6] Comparatively, for hypertensive and vascular nephropathy, the optimal control of hypertension and correcting aggravating factors, such as severe renal stenosis by angioplasty and stenting, may preserve kidney function.[7] In addition to focusing on slowing kidney disease progression, comprehensive CKD management should also integrate cardiac health components.[8,9]

Cardiovascular disease (CVD) is the leading cause of death in individuals with CKD, accounting for between 40 and 60% of deaths in individuals with advanced kidney disease.[10] The risk for CVD develops as CKD progresses, representing a mutually aggravating process with the same risk factors and benefiting from the same management approach (Figure 1).[11] CKD is recognized as one of the most prominent cardiovascular risk factors.[12]

FIGURE 1 | Renal and cardiac burden in CKD patients follow the same pathways with mutual aggravation



Source: Sarnak MJ, et al. Cardiovascular disease and chronic renal disease: a new paradigm. Am J Kidney Dis. 2000 Apr;35(4 Suppl 1):S117-31.

POTENTIAL DISRUPTION: SGLT-2 INHIBITORS

SGLT-2 inhibitors are a new class of medication initially developed to facilitate glycemic control in T2DM by inducing glucosuria.[13] In less than a decade, they have become the first-in-class treatment for diabetes, with impressive results on glycemic and overall metabolic control and outcomes.[14,15] SGLT-2 inhibitors are associated with unexpected protective results on cardiac outcomes in this highly vulnerable population.[16] Recent studies have identified that SGLT-2 inhibitors are associated with positive clinical benefits in various chronic diseases, such as heart failure and CKD, even among individuals without T2DM.[17,18]

Gliflozins are specific glucoside-based inhibitors of sodium-glucose co-transporters (SGLT).[19,20] Sodium-dependent glucose transporters are a member of the protein family consisting of SGLT-2 and SGLT-1 located in the proximal kidney tubule. SGLT-2 proteins are mainly located in the initial part of the proximal tubule involved in 90% of glucose reabsorption filtered back to the systemic circulation (Figure 2). Inhibition of SGLT-2 increases the urinary glucose excretion with significant glucosuria (50 to 80 g per day in normoglycemic conditions, and up to 100 or 120 g per day in hyperglycemic conditions), facilitating glycemic control and inducing caloric loss and starvation adaptation. SGLT-2 inhibition increases urinary flow through its osmotic action but also natriuresis by blocking glucose-sodium protein cotransporters.[21] Increase of natriuresis delivery at the macula densa site results in a deactivation of the tubuloglomerular feedback mechanism mediated by vasoconstriction of the glomerular afferent arteriole. Therefore, glomerular hypertension and hyperfiltration decreases, contributing to reduced glomerular stress and proteinuria, a hallmark of kidney dysfunction in diabetes.

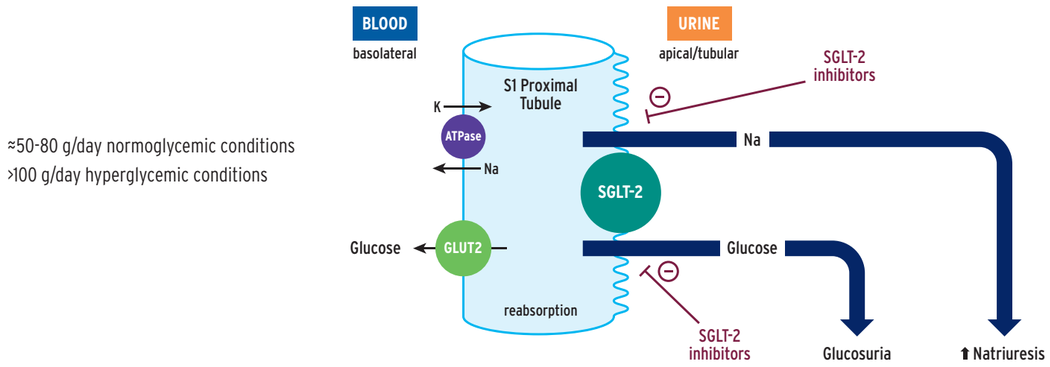
As of August 2021, dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin are approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of T2DM.

INNOVATION FOR T2DM PATIENTS WITH DIABETIC KIDNEY DISEASE

Four major randomized controlled trials revealed the clinical benefits of SGLT-2 inhibition in T2DM patients (Figure 3).[22]

In brief, dapagliflozin, empagliflozin, and canagliflozin have remarkable and consistent class effects on renal outcomes. Baseline renal filtration function and degree of proteinuria are the most significant indicators of risk for both renal and cardiovascular events.

FIGURE 2 | Tubular action of SGLT-2 inhibitors



BENEFITS FOR TREATING HEART FAILURE

Additional analysis of several SGLT-2 inhibitor trials shows a consistent benefit for treating patients with heart failure, in particular with reduced ejection fraction, and advanced kidney disease from DKD.[23,24,25,26,27,28, 29,30,31] In these studies, recruited patients were receiving optimal treatment for T2DM and cardiac disease with SGLT-2 inhibitors considered an add-on treatment. In all studies, primary cardiac outcomes of cardiac death and hospitalization for heart failure were improved, with 15% risk reduction on average (range 3 to 25%) in patients receiving SGLT-2 inhibitors.

The ongoing Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) study is assessing the effects of dapagliflozin versus placebo in managing heart failure patients with preserved ejection fraction, using the same primary endpoint as the Dapagliflozin and Prevention of Adverse Outcomes (DAPA) in Heart Failure trial.[32,33] This study will complement other cardiovascular outcome studies evaluating the benefits and risks of SGLT-2 inhibitors in various cardiac settings (e.g., acute decompensated heart failure, chronic reduced or preserved ejection fraction with and without T2DM). Findings of these studies may have enormous implications for future treatment approaches.[34]

TREATING NON-DIABETIC CHRONIC KIDNEY DISEASE

In the Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND) study, 58 CKD patients without diabetes (eGFR≥25 mL/min; m GFR 58 mL/min) with proteinuria (≥500-3500 mg/d, m 1110 mg/24h) receiving a renin-angiotensin system blockade agent were randomly assigned to receive dapagliflozin (10 mg/d) or a placebo.[35] eGFR declined by −6.6 mL/min at week six in the dapagliflozin group, but this reduction was fully reversible within six weeks after dapagliflozin discontinuation. Body weight was reduced by 1.5 kg with dapagliflozin, while changes in blood pressure did not differ significantly between dapagliflozin and placebo treatment.

In the subanalysis of the DAPA in Chronic Kidney Disease (DAPA CKD) trial, of the 270 participants with IgA nephropathy (94% confirmed by previous biopsy), 137 were randomized to dapagliflozin and 133 to a placebo.[36,37] In this IgA subgroup, mean eGFR was 43.8 mL/min and median urinary albumin-to-creatinine ratio was 900 mg/g. Composite renal outcomes consisted of sustained eGFR, proteinuria, ESKD, or renal death. Relative risk reduction in a 50% sustained decrease in eGFR, ESKD, or death from renal causes was 46%, 39% in death from cardiovascular causes, and 26% for proteinuria in patients receiving dapagliflozin.

In this perspective, the ongoing EMPA-KIDNEY study, exploring cardio-renal effects of empagliflozin in CKD patients irrespective of whether the individual has diabetes, will be of tremendous interest.[38] Potential risks of temporary or sustained eGFR decline associated with SGLT-2 inhibitors use in CKD with or without proteinuria deserve further trials to precisely assess the safety and renal protective effects of these drugs.[39]

PLEIOTROPIC EFFECTS OF SGLT-2 INHIBITORS

Effects of SGLT-2 inhibitors are well documented and largely encompass their effects on glycemic homeostasis and DKD.[40,41] SGLT-2 inhibitors facilitate glycemic control without stimulating insulin release, weight loss due to glucosuria and caloric loss, reduction of body fat facilitating insulin action, reductions of salt load and extracellular volume, lowering of systemic blood pressure, and reduction of glomerular pressure and filtration marked by a reduction of proteinuria.[42] Interesting findings have been observed with proteinuric glomerular disease and CKD that require further confirmatory studies to define new therapeutic options.

Beyond the scope of glycemic control and DKD, the use of SGLT-2 inhibitors is expanding with promising results in the treatment of other conditions such as heart failure and cardiorenal syndrome. Further studies are needed to validate safety of this approach in advanced kidney disease. SGLT-2 inhibitors are associated with sustained sodium removal facilitating restoration of the whole-body sodium homeostasis. Furthermore, SGLT-2 inhibitors induce profound metabolic changes including ketogenesis from liver and reprioritization of energetic oxidation metabolic pathways favoring cardiomyocytes activity and regenerative process. Interestingly, the common denominator and the main action point of SGLT-2 inhibitors seems to be a way of depleting total body salt excess, restoring sodium and water homeostasis that include sodium osmotically active (extracellular compartment) but also tissue sodium (third compartment of water-free sodium).[43]

SUMMARY

Despite significant progress in cardiovascular disease management for advanced CKD patients, cardiac health remains one of the main challenges in this highly vulnerable population. Therapeutic approaches to reduce cardiac burden and slow kidney disease progression have steadily improved over recent years by effectively addressing the deleterious mechanical effects of fluid excess and hypertension on cardiac and kidney end organ damage. In this context, RAAS blockade agents have slowed down this process, but they have not been sufficient to halt it. SGLT-2 inhibitors beyond glucosuria and throughout their pleiotropic actions, offer a new and complementary approach for improving cardiac health in CKD patients without T2DM.[44] Ongoing studies focusing on low eGFR patients are exploring the benefits and risks of these medications.[45]

Therapeutic approaches to reduce cardiac burden and slow kidney disease progression have steadily improved over recent years by effectively addressing the deleterious mechanical effects of fluid excess and hypertension on cardiac and kidney end organ damage.

FIGURE 3 | Four major randomized controlled trials studied SGLT-2 inhibition in type 2 diabetes mellitus

TRIAL NAME	STUDY POPULATION	OUTCOMES	RISK REDUCTION
DECLARE-TIMI 58 study (dapagliflozin)	17,160 T2DM patients with either one established atherosclerotic cardiovascular disease or multiple risk factors, and creatinine clearance ≥60 mL/min, were randomly assigned (1:1) to 10 mg dapagliflozin or placebo once daily	Sustained eGFR decline or end-stage kidney disease (ESKD) or death from renal or cardiovascular causes	HR 0.76 (95% CI, 0.67-0.87)
EMPA-REG OUTCOME trial (empagliflozin)	7,020 T2DM patients with eGFR ≥30 mL/min and overt cardiovascular disease were randomly assigned to receive either empagliflozin (10 mg or 25 mg) or placebo once daily	Incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease) and incident albuminuria	HR 0.61 (95% CI, 0.53-0.70)
CANVAS-R (Canagliflozin Cardiovascular Assessment Study Renal)	10,142 T2DM patients with diabetic kidney disease, or DKD (eGFR 76.5 mL/min, UACR 12.3 mg/g) were randomly assigned to receive either canagliflozin (100-300 mg/d) or placebo	Sustained doubling of serum creatinine, ESKD, and death from renal causes	HR 0.60 (95% CI, 0.47-0.77)
CREDENCE study (canagliflozin)	4,401 T2DM patients with DKD (eGFR30-90 mL/min, UACR >300 mg/g) were randomly assigned to receive canagliflozin (100 mg/d) or placebo	ESKD (<15 mL/min), dialysis or transplant, doubling of serum creatinine level, or death from renal or cardiovascular causes	HR 0.75 (95% CI, 0.59-0.95)

THE EXPERTS

BERNARD CANAUD, MD, PhD
Senior Chief Scientist, Global Medical Office

Bernard Canaud serves as senior chief scientist for the Global Medical Office and is the former chief medical officer for Fresenius Medical Care's Europe/Middle East/Africa region. Throughout his distinguished career, he has served on the editorial boards of nearly a dozen prestigious academic journals. He is the former president of the Société Francophone de Dialyse and has published over 400 referenced manuscripts, written chapters in more than 80 books, and contributed to nephrology congresses worldwide with more than 1,500 presentations. Dr. Canaud has contributed to the development of the European Best Practice Guidelines on dialysis fluid purity, vascular access, and anemia management and has been a coinvestigator of the international DOPPS study. He was an expert member of the French HAS (Haute Autorité de Santé) for renal replacement therapies. He headed the nephrology, dialysis, and intensive care departments at Lapeyronie University Hospital for 25 years. Dr. Canaud is currently emeritus professor of nephrology at the Montpellier University School of Medicine in France. He graduated with his doctor of medicine from Montpellier Medical School and received his master of science doctorate in nutrition from the University of Sciences, Montpellier. In addition, he has received several awards and distinctions throughout his career.

ALLAN J. COLLINS, MD, FACP
Senior Chief Scientist, Global Medical Office

Allan Collins has a distinguished career with more than 30 years of work in nephrology and ESKD treatment. He is the former chief medical officer for NxStage Medical, Inc. and served as director of the National Institutes of Health's/NIDDK's United States Renal Data System from 1999 to 2014. Dr. Collins has published more than 300 articles, 600 abstracts, and 20 book chapters, and has given more than 365 invited presentations. His clinical experience and research have focused on acute and chronic care of ESKD and chronic kidney disease patients, and prospective and retrospective clinical studies on dialysis techniques and associated outcomes. The former president of the National Kidney Foundation, Dr. Collins served on its scientific advisory board for six years, with the Kidney Dialysis Outcomes Quality Initiative, and on the International Society of Nephrology's Commission for the Global Advancement of Nephrology Committee. He graduated with his medical degree from Wayne State University in Detroit.

PROTECTING KIDNEY PATIENTS' HEARTS: HAS THE TIME COME TO RETHINK DIALYSIS TREATMENT CADENCE?

Franklin W. Maddux, MD, FACP

Cardiac disease prevention and management is one of the most important clinical targets in patients receiving maintenance dialysis. Cardiac disease is a leading cause of death in people receiving dialysis, and premature cardiomyopathy and the associated higher risk of fatal cardiac arrhythmias are well recognized. Cardiac dysfunction may result from subtle persistent volume overload and increased intracardiac pressures. Despite this understanding, the field has not made significant enough advances in the prevention of cardiovascular complications.

One of the areas for opportunities to advance care is the frequency of hemodialysis. Standard thrice weekly hemodialysis represents the dominant cadence of current dialysis delivery throughout the world. The vast majority of patients receiving in-center dialysis are treated three times per week, resulting in a pattern of long interdialytic intervals (LIDIs) of 72 hours without dialysis each week. This traditional pattern predestines a long interdialytic interval (LIDI) every week for patients receiving in-center hemodialysis.

What are the risks to patients without residual kidney function that can be attributed to the LIDI? Two-thirds of patients have demonstrated cardiac rhythm disturbances following a missed treatment or the LIDI.[1] In a large study in 2011, the investigators found that the first hemodialysis treatment after the LIDI is associated with increased cardiovascular-related hospital admissions and elevated death rates.[2] They concluded that "the long interdialytic interval is a time of heightened risk among hemodialysis patients." A Dialysis Outcomes and Practice Pattern Study suggests the dialysis treatment schedule affects day-of-week mortality.[3] In data from the United States, Japan, and Europe, in-center prevalent hemodialysis patients treated on Monday, Wednesday, and Friday have a higher risk of death on Mondays, and patients treated on Tuesday, Thursday, and Saturday have a higher risk of death on Tuesdays (Figure 1).

Cardiac dysfunction may result from subtle persistent volume overload and increased intracardiac pressures. Despite this understanding, the field has not made significant enough advances in the prevention of cardiovascular complications.

FIGURE 1 | In-center hemodialysis treatment schedule and mortality risk

These findings highlight the serious risks associated with the LIDI. Complications associated with the LIDI also include exacerbation of volume accumulation and cardiac re-modeling.[4] In addition, the first hemodialysis treatment following the LIDI is more likely to require a higher ultrafiltration rate. Higher ultrafiltration rates during hemodialysis have received significant attention as the understanding of the deleterious consequences, including myocardial stunning, have advanced.

As kidney care evolves to become more personalized and precise for every person, cardiovascular health and prevention of chronic volume overload and the associated long-term complications must be addressed. The field must advance to provide a treatment frequency that aligns with physiologic needs. Instead of focusing on treatment of cardiac complications, it is necessary to proactively prevent or slow the progression of cardiac disease and focus on cardiovascular health. It must be considered whether both active monitoring for rhythm disturbances and understanding the nervous system's input into arrythmias need consideration.

Examining how best to personalize the hemodialysis treatment frequency for each person's physiologic needs—with the prescription informed by residual kidney function, blood pressure control, and cardiovascular treatment goals—is critical. Such an endeavor will require the collaboration of stakeholders across the entire healthcare delivery system, from patients to providers to payors and policy makers, and has the potential to make a lasting impact on advanced kidney disease care worldwide.

The field must advance to provide a treatment frequency that aligns with physiologic needs. Instead of focusing on treatment of cardiac complications, it is necessary to proactively prevent or slow the progression of cardiac disease and focus on cardiovascular health.

FRANKLIN W. MADDUX, MD, FACP
Global Chief Medical Officer, Member of the Management Board

Franklin W. Maddux is global chief medical officer for Fresenius Medical Care, overseeing the delivery of high-quality, value-based care for the world's most expansive kidney care organization. His distinguished career encompasses more than three decades of experience as a physician, expert nephrologist, technology entrepreneur, and healthcare executive. Dr. Maddux joined Fresenius Medical Care's North America region in 2009 after the company acquired Health IT Services Group, a leading electronic health record (EHR) software company, which he founded. He developed one of the first laboratory electronic data interchange programs for the US dialysis industry and later created one of the first web-based EHR solutions, now marketed under Acumen Physician Solutions. He previously served as chief medical officer and senior vice president for Specialty Care Services Group and is the former president of Virginia's Danville Urologic Clinic, where he was a practicing nephrologist for nearly two decades. His writings have appeared in leading medical journals, and his pioneering healthcare information technology innovations are part of the permanent collection of the National Museum of American History at the Smithsonian Institution. An alumnus of Vanderbilt University, Dr. Maddux earned his medical degree from the School of Medicine at the University of North Carolina at Chapel Hill, where he holds a faculty appointment as clinical associate professor.

PRECISION MEDICINE

Rapidly evolve precision medicine for individuals with kidney disease by launching a worldwide genomics registry. Integrate data from across therapies to accelerate the development of algorithms, artificial intelligence tools, and precision/personalized treatments.

GENOMICS AND PRECISION MEDICINE: THE FRENOVA GENOMICS REGISTRY

Michael Anger MD, FACP, FASN
Jeffrey Carr

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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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.

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

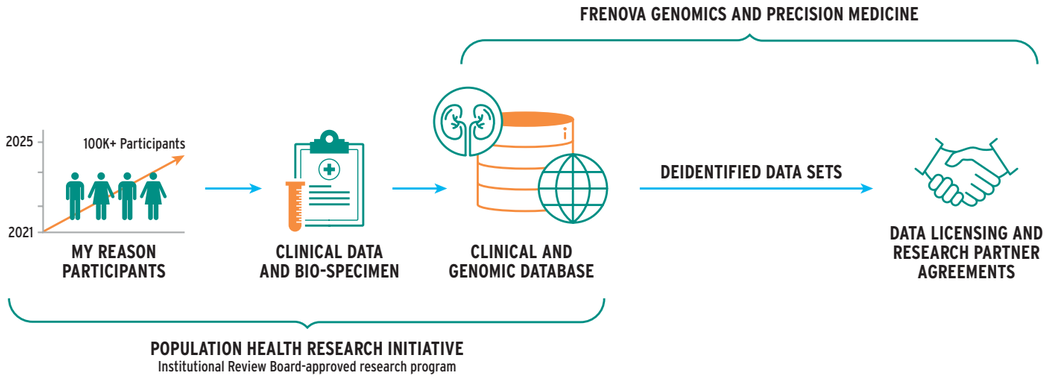
FIGURE 1 | The My Reason campaign is designed to raise awareness of genetic research in the patient community

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).

The development of the Frenova genomics registry at the intended scale is made possible through partnership with patients and providers.

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



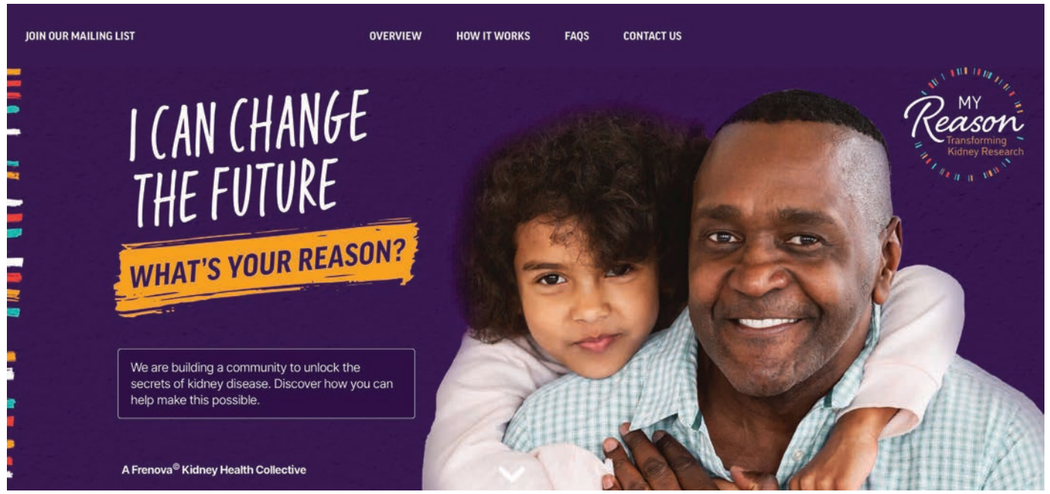
Frenova Research coordinators have begun consenting patients within the Frenova Site Management Organization network of US dialysis clinics. The program is now expanding to include Fresenius Kidney Care clinics throughout the US and will eventually expand to other global regions and include individuals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

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.

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.

PRECISION NEPHROLOGY:
UNDERSTANDING KIDNEY INJURY TO BRING THE RIGHT DRUG TO THE RIGHT PERSON

Ravi I. Thadhani, MD, MPH
Opeyemi A. Olabisi, MD, PhD

Precision medicine requires properly recognizing the "right patient," having the "right drugs," and knowing the right time to apply them.[1] A prerequisite for precision nephrology is a deep understanding of the mechanism(s) of kidney injury and a precise means to diagnose the injury. Kidney injury is a heterogeneous condition. Adequate diagnosis requires knowledge of the injured kidney cell types, the underlying causal mechanisms and temporal course involved, and knowledge about the injury's reversibility. All currently remain hurdles that must be successfully crossed for precision nephrology to become a reality.

Currently, kidney injury is classified by its temporal course as acute kidney injury (AKI) or chronic kidney disease (CKD).[2,3] Uniformity, not precision, is the goal of these clinical diagnostic criteria, which provide a standard approach to clinically diagnosing and staging severity of kidney injury based on serum creatinine, proteinuria, and urine output. These measures are indifferent to the precise mechanisms involved.

Kidney injury results in reduction in glomerular filtration rate (GFR). However, adaptation by non-injured nephrons could partially compensate for reduced GFR. Therefore, GFR may not reflect the true extent of kidney injury. Moreover, loss of GFR is a late marker of kidney injury, and a reduction in GFR by one mechanism can have a different outcome than a reduction by a different mechanism of injury. Consequently, these limitations preclude advances in precision nephrology.

THE RIGHT PATIENT

Cellular biomarkers of kidney injury temporally precede clinical biomarkers (e.g., serum creatinine, proteinuria). Therefore, cell-based biomarkers have the potential to uncover early injury and the underlying mechanisms involved. For example, analysis of glomerular cells of individuals with diabetic kidney disease (DKD) implicated upregulation of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway as a key step in DKD pathogenesis.[4] Follow-up studies confirmed that JAK-STAT upregulation in podocytes plays a causal role in DKD progression and that inhibition of this pathway reduced albuminuria in individuals with DKD.[5,6] Molecular biomarkers aid early diagnosis, identify underlying mechanisms, and suggest targets for pharmacologic therapies.

Furthermore, single-cell RNA sequencing (scRNA-seq) enables profiling of whole transcriptome of thousands of cells, thereby providing information at a single-cell level on what genes are expressed, in what quantities, and how the gene expression profile of one kidney cell type compares across thousands of other kidney cells. Single-cell assay for transposase accessible chromatin (ATAC-seq), in contrast, provides genome-wide profiling of chromatin states, revealing which chromatin regions are open and assessable to transcription factors. Therefore, a combination of scRNA-seq and scATAC-seq could reveal identity of kidney cells and genes involved in kidney injury. A recent scRNA-seq analysis found that cell type–specific changes in gene expression impacting ion transport, angiogenesis, and immune activation are early manifestations of DKD.[7] These gene expression changes may be leveraged as early biomarkers of DKD. The promise of these technologies is currently not realized because of the high cost of acquiring this information and the enormous bioinformatic analytics required to uncover meaningful results.

THE RIGHT DRUG

Development and use of the right drug is the second goal of precision medicine. There are no known safe and effective drugs targeting AKI. Until the recent discovery of the efficacy of sodium glucose co-transporter 2 inhibitors (SGLT-2i), there had not been a major new drug for CKD in decades. While multiple reasons underlie the AKI and CKD "drug drought," poor fidelity of model organisms in capturing important aspects of human kidney injury has been a limitation. Rodent models have their limitations: A recent scRNA-seq comparison of mouse and human glomeruli discovered remarkable species differences in gene expression profiles of defined glomerular cell types, questioning the suitability and translatability of mouse models of human glomerular injury.[8]

Human induced pluripotent stem cell (iPSC)-derived kidney organoids offer promising new ways to model human kidney diseases. Because iPSCs retain the genomic endowment of the individual, they are more likely to capture salient attributes that may be relevant for the person's susceptibility to disease, mechanism of injury, and response to specific therapies. Kidney organoids are particularly suitable for modeling diseases that originate from polymorphic human genes, which are absent in model organisms.

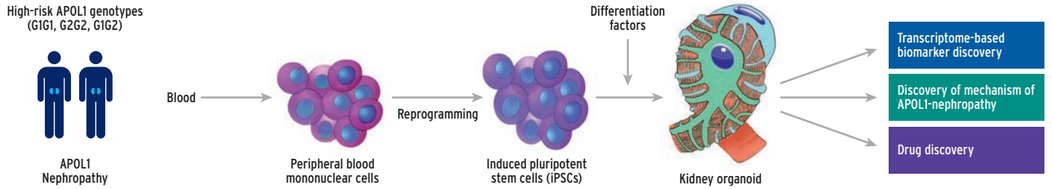
Carriage of two variants (G1 & G2) of the APOL1 gene is strongly associated with increased incidence and rapid progression of APOL1 nephropathy including COVID-19–associated nephropathy.[9,10,11,12] APOL1 variants explain approximately 70% of excess risk of non-diabetic kidney disease among African Americans, who constitute more than 35% of the ESKD population. The molecular mechanism of APOL1 nephropathy remains unknown. The APOL1 gene is naturally absent in all experimental animals, limiting their use to model APOL1 nephropathy. Patient kidney organoids, especially when combined with next-generation sequencing technologies, have the potential to illuminate the molecular pathomechanism of APOL1 nephropathy, leading to the discovery of pharmacologic targets and reducing racial kidney health disparities (Figure 1).

Another kidney disease that is likely to benefit early from human kidney organoid models is polycystic kidney disease (PKD). Kidney organoids from individuals with PKD develop large cysts that mimic kidney cysts seen in people with PKD, indicating that such organoids may be the ideal tool for drug discovery.[13,14]

Precision medicine, however, did not yield SGLT-2i, which has dramatically improved CKD management Therefore, why advocate for this cumbersome, costly approach? Because unlike in oncology, where precision medicine frequently guides drug discovery, the success rate of drug discovery in nephrology is abysmal. There has been over a 30-year gap between the approval of ACE inhibitors and recent approval of SGLT-2i for slowing CKD progression. At this rate, the next breakthrough kidney drug will be approved in 2050, after three million new people will have reached dialysis in the US alone.

Patient-derived kidney organoids may help accelerate the discovery of therapeutic targets and more efficiently identify potential toxicities of candidate drugs. Nephrology writ large is being transformed by a deeper understanding of biology, genetics, and novel technologies, all poised to set the stage for improving the understanding and treatment of kidney injury.

FIGURE 1 | Patient iPSC-derived kidney organoid captures an individual's unique genetic identity. The figure outlines how the technology could be applied specifically to APOL1-nephropathy.



RAVI I. THADHANI, MD, MPH
Chief Academic Officer, Mass General Brigham

Ravi Thadhani manages an approximately $2 billion research enterprise. He oversees several key system-wide departments at Mass General Brigham (MGB), including Human Subjects Affairs, the Clinical Trials Office, Research Management, the MGB Biobank, and Graduate Medical Education. Dr. Thadhani managed a research laboratory for about 25 years, with a focus on kidney disease and developing diagnostics and therapeutics for women with complications in pregnancy. He has published over 300 manuscripts and has been inducted into several honor societies. He is a standing member of the FDA's Cardio-Renal Division Advisory Panel. He has received several distinguished awards, including the Harold Amos Faculty Diversity Award from Harvard Medical School, the Alumni Award of Merit from the Harvard T.H. Chan School of Public Health, and the John P. Peters Award from the American Society of Nephrology. He is a Professor of Medicine at Harvard Medical School.

OPEYEMI A. OLABISI, MD, PhD
Assistant Professor of Medicine, Duke Department of Medicine, Division of Nephrology

Opeyemi Olabisi is a physician-scientist and assistant professor of medicine at Duke School of Medicine. He practices adult nephrology and conducts NIH-funded research that leverages patient-derived stem cell models to elucidate mechanisms underlying APOL1 nephropathy. He is a recipient of several awards, including the NIH Director's New Innovator Award, Duke Whitehead Scholars award, and the Albert Einstein College of Medicine Alumni's Rising Star–Scientific Investigator Award. Dr. Olabisi received his bachelor's degree in biology from The City College of New York and his MD-PhD from Albert Einstein College of Medicine. He completed both his residency training in internal medicine and his nephrology fellowship at Massachusetts General Hospital, and did a postdoctoral research fellowship at Harvard Medical School.

COMMUNICATION AND MEDICAL EDUCATION

Align global medical education programs and develop new teaching tools. Continue to expand content creation, enhance production, and widen distribution of medical information, compliance communication, and medical education on a worldwide basis.

GLOBALIZING MEDICAL INFORMATION AND EDUCATION

Corinne Zeller-Knuth, PhD
Amy Janik, BSN, RN
Rainer Himmele, MD, MSHM

The new Global Medical Information and Education Office (GMIE) is leveraging technology and worldwide expertise to drive best practices and deliver practical, flexible, and innovative programs. These include the Advanced Renal Education Program (AREP) and the Global Medical Education Webinar Series. Both of these platforms are expanding their offerings and support regional customization and greater virtual participation. The GMIE team is also creating a portfolio of interactive tools, prescription calculators, and games that simulate a clinical environment. All these developments are driving a significant increase in participation from across Fresenius Medical Care and from the larger nephrology community.

Fresenius Medical Care's ongoing focus on the importance of medical education for its worldwide community led to the creation of the Global Medical Information and Education (GMIE) Office at the end of 2020. This new group brings together the worldwide Medical Information and Education teams into one coordinated unit to drive best practices, deliver consistent communication, unite platforms, and eliminate redundancies.

The GMIE teams collaborate internally and externally to develop educational materials and provide medical and clinical expertise in support of the company's product portfolio, associated therapeutic areas, and research and development projects. To reach across the nephrology and critical care communities, specific educational programs have been developed for the spectrum of healthcare providers: physicians, nurses, dietitians, social workers, technicians, and others. This is done through two distinct platforms: the Advanced Renal Education Program (AREP) and the Global Medical Education Webinar Series.

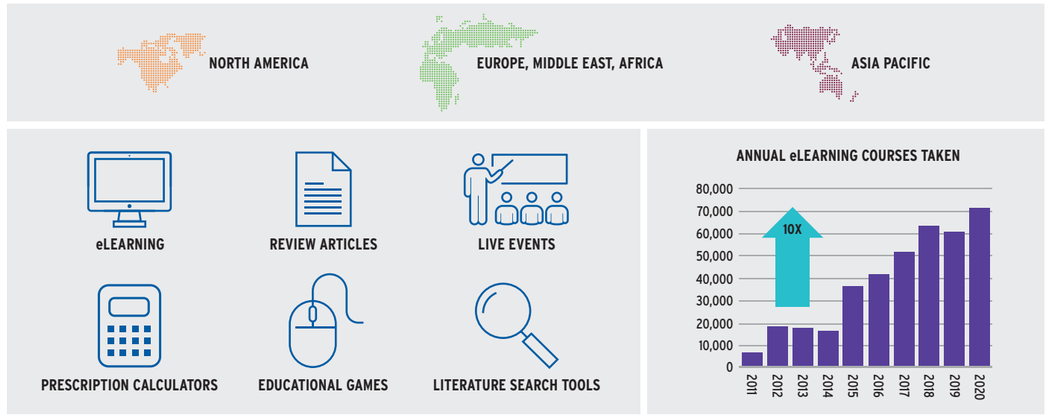
ADVANCED RENAL EDUCATION PROGRAM

Since its inception in 1996, AREP has evolved into a key educational platform for healthcare providers. It is endorsed by the International Society for Peritoneal Dialysis and the International Society for Hemodialysis and is accredited to provide continuing education credits. Historically, home dialysis in the United States has been AREP's major focus. Now, it has expanded offerings to include hemodialysis, on-line hemodiafiltration, and critical care, including heart and lung therapies (Figure 1).

The AREP platform disseminates education through two main avenues: regional websites and live events, both in-person and virtually. The three AREP websites have eLearning courses, short videos, educational games, literature search tools, and home therapy prescription tools. In 2020, there were nearly 680,000 pageviews for review articles, and over 71,000 eLearning courses were taken, which represents a tenfold increase in participation in the last decade (Figure 1).

Building on the traditional didactic presentations and eLearning courses offered by the AREP platform, the GMIE teams have been developing innovative and interactive educational tools in recent years that are designed for participant engagement and can be easily translated to the clinical environment for immediate application. These include case-based online educational games, like the Striving to Obliterate Peritonitis (STOP) Task Force where participants learn and apply the International Society for Peritoneal Dialysis guidelines on prevention and treatment of peritonitis; short, animated videos to introduce topics; educational simulators that allow users to practice their skills in a virtual environment; and home dialysis prescription calculators.

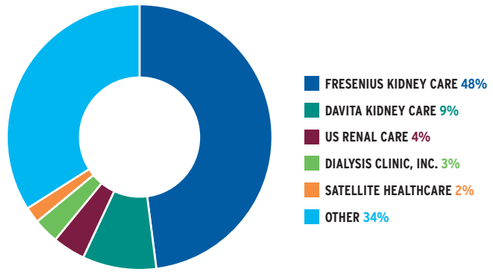
FIGURE 1 | Advanced Renal Education Program websites



The North America AREP website hosts two home dialysis prescription calculators, one for peritoneal dialysis (PD) and one for home hemodialysis (HDD) (Figure 2). Both tools allow users to predict prescription outcomes based on demographic and clinical data, with evidence-based guidance to support what may be most appropriate for an individual patient. The importance of fluid removal is reinforced with suggestions for ultrafiltration optimization highlighted for both modalities. As educational tools, these calculators are novel in that prescribers can change one variable at a time and easily see how the change affects the predicted outcome. As a testament to the need for, and simplicity of, the tools, nearly 1.4 million prescriptions have been modeled since the launch of the PD calculator. Interestingly, most PD prescriptions modeled in the calculator have an unknown transport type, suggesting that the tool is being utilized for customizing initial PD prescriptions, which was one of the original educational goals when the calculator was launched: to encourage the use of patient-specific prescriptions from the beginning. In January 2021, the HHD calculator was launched and is quickly gaining users.

In 2020, AREP live events quickly adapted to the virtual world and changed from live in-person symposia to live online webinars. To foster virtual engagement with participants, programs were adjusted from days-long traditional lecture programs to shorter interactive roundtable discussions with expert nephrologists, nurses, and individuals with end-stage kidney disease receiving dialysis. In 2020, there were 21 live events that drew over 6,200 participants from across dialysis providers, 14% of which were prescribers (Figure 3).

FIGURE 3 | AREP live event provider affiliation



21
PROGRAMS IN 2020

10,851
REGISTRANTS

6,254
PARTICIPANTS

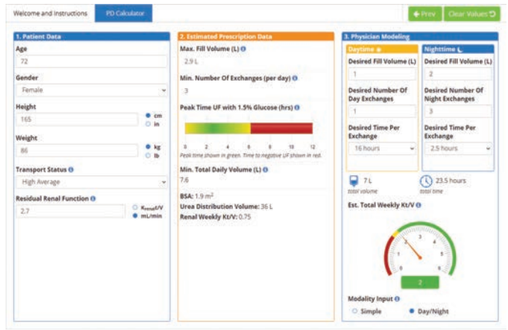
★★★★★
POSITIVE IMPACT ON CURRENT PRACTICE

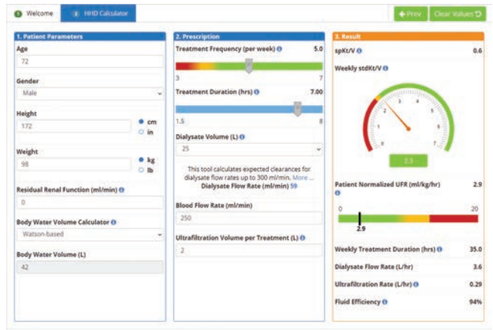
★★★★★
MORE CONFIDENT MANAGING PATIENTS

GLOBAL MEDICAL EDUCATION WEBINAR SERIES

The webinar series in the United States is a spin-off of the success@homeTM Clinical Resource Line, which provides nurse-to-nurse phone support on PD therapy and PD-related products; in 2020 nearly 1,000 questions were answered. In addition to the clinical phone support, the resource line has been hosting nurse-focused, live educational webinars since 2008. Webinar attendance in the last five years has grown from around 1,900 participants in 2016 to over 11,000 in 2020 (Figure 4). The growth in participation rate can be attributed to multiple factors: CE credit offering for nurses at the end of 2018, expanded promotion to DaVita Dialysis healthcare providers and delivering programs in Spanish in 2019; and communication campaigns, faculty expansion, and the COVID-19 pandemic in 2020. Like AREP, the webinar series was historically focused on home therapies, specifically PD, with product and disease state education. In recent years, webinars have expanded to include topics on HHD, anemia, hyperphosphatemia, and fluid management. Topics across the kidney disease spectrum are all well attended (Figure 4).

FIGURE 2 | PD and HHD calculators





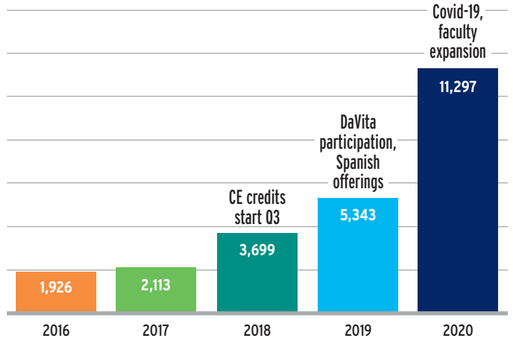
LOOKING FORWARD

The GMIE teams have already implemented ways to further extend their educational reach. For AREP, live programs are offering continuing medical education credits, increasing physician participation. Education will expand to more comprehensively address topics related to chronic kidney disease, home dialysis, in-center hemodialysis, on-line hemodiafiltration, and critical care nephrology, and extracorporeal membrane oxygenation (ECMO) therapies.

In March 2021, the Global Medical Education Webinar Series was expanded worldwide, with programs also being hosted by the Europe, Middle East, and Africa (EMEA) and Asia Pacific Medical Information teams. Sharing content, speakers, and webinar platforms, the GMIE collaboration includes shared hosting and promotion of the programs between North America and EMEA, and between EMEA and Asia Pacific. In the first half of 2021, nearly 12,000 participates attended the global programs.

Within the new GMIE group, a new matrix-based organizational structure includes regional leads in North America, EMEA, and Asia Pacific; and focused therapy workgroups for on-line hemodiafiltration, home dialysis, and critical care. This structure will further facilitate cross-regional and cross-topic collaboration as new educational content is developed; once developed, these educational programs can be adapted and/or translated to each region's specific needs.

FIGURE 4 | Medical education webinar growth



In the United States, the GMIE group includes a group of highly specialized, field-based medical support specialists (MSSs).

The MSS team was especially critical in supporting PD product training throughout the COVID-19 pandemic. Team members quickly adapted to the virtual environment and are all certified in Facilitating Virtual Training by the Association for Talent Development. At the beginning of the pandemic, the MSSs quickly developed and deployed virtual PD product training to over 200 participants across 15 hospitals in New York City so facilities could provide acute PD to patients with COVID-19 when resources for acute hemodialysis therapies were limited. In 2020, the MSS teams provided 11,100 hours of training to 11,712 nurses across the country. In 2021, they are already on track to exceed these numbers.

THE EXPERTS

CORINNE ZELLER-KNUTH, PhD
Director, Medical Information and Education

Corinne Zeller-Knuth has been with the FMCNA Medical Information and Education Office for over seven years, where her responsibilities include leading the development of home therapies education for the Advanced Renal Education Program. She also reviews and responds to medical information queries from healthcare professionals across the United States, provides medical and scientific expertise on promotional review committees, and serves as a core team member on global research and development–connected health and peritoneal dialysis modeling projects. She earned her PhD in biochemistry from the University of North Carolina at Chapel Hill, and after many years in academia studying the regulation of signal transduction and mRNA transcription, she transitioned to industry.

AMY JANIK, BSN, RN
Senior Manager, Medical Information Clinician

Amy Janik has been with FMCNA for 20 years, beginning as an in-center hemodialysis nurse and then transitioning to home therapies, where she focused primarily on peritoneal dialysis. After having many different roles over the years, Amy has been with the Medical Information and Education Office for the last six years. She works across the organization supporting peritoneal dialysis initiatives, and manages the success@home Clinical Resource Line and the Global Medical Education Webinar Series. Prior to transitioning to nephrology nursing, she worked for many years as a nurse in a post-operative surgical unit. Amy earned her BSN from Grand Valley State University in Allendale, Michigan.

RAINER HIMMELE, MD, MSHM
Vice President, Head of Global Medical Information and Education

As head of Global Medical Information and Education, Rainer Himmele leads a highly engaged medical team with the vision to align and provide state-of-the-art educational programs on dialysis best practices to all Global Medical Office regions. He received his medical training at the University of Heidelberg, Vienna, New York, and Zurich. He holds a research doctorate in molecular biology and genetics at the German Cancer Research Center, and a master of science in healthcare management from the University of Heidelberg and Mannheim Business School in Germany.

MANAGING CARDIOVASCULAR DISEASE IN DIALYSIS PATIENTS IN LATIN AMERICA

Juan Berbessi, MD
Maria Resk, MD
Alejandro Kohn Tuli, MD

Fresenius Medical Care teams throughout Latin America are implementing a range of strategies to improve cardioprotective strategies for patients with chronic kidney disease. Although initiatives vary from country to country, all are focused on developing more personalized and precise treatment options. Specific programs focus on the detection and management of fluid overload, assessment of drug interactions, consideration of home therapies, and thorough evaluation of cardiovascular risk.

Cardiovascular disease is the leading cause of death in individuals with chronic kidney disease (CKD) and is highly prevalent in individuals on maintenance dialysis.[1,2,3] Compared to the general population, the relative risk of a cardiovascular-related death is between 10 to 30 times higher in individuals with late-stage CKD.

Many of the people who begin dialysis do so with existing features of hypertension and fluid overload, which are major risk factors for cardiovascular disease.[4,5,6] To address this reality, Fresenius Medical Care in 2018 updated its Clinical and Quality Agenda to include cardiovascular health as one of the six core themes guiding the company's clinical outlook (Figure 1).

With the introduction of cardiovascular health as a core focus area, Medical Office teams throughout the company have begun integrating cardiovascular-related initiatives into clinical services to improve patient outcomes and make care more personalized and precise. While requiring adaptability to local healthcare frameworks and processes, cardiovascular-related strategies are aiding teams across the organization in improving patient care.

LATIN AMERICA

The company's Latin America region provides a strong example of how taking a more personalized approach to kidney replacement therapy (KRT) can reduce the high incidence of cardiovascular disease and death among individuals with kidney disease.

Fresenius Medical Care in Latin America has programs for advanced CKD prior to dialysis initiation for stage 3b to stage 5 CKD, including the CERCA (Cuidado de la Enfermedad Renal Cronica Avanzada) program in Argentina and the FMEPrever program in Colombia. The strategies implemented to improve cardiovascular health include medication management with prioritization of angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and sodium glucose co-transporter 2 inhibitors. These strategies have demonstrated a positive impact on the reduction of cardiovascular complications, early mortality, disease progression, and improvement in quality of life.

Frequently, individuals with advanced CKD are treated with multiple medications as reflected by the up to 19 to 25 pills taken per day. Polypharmacy and potential drug interactions that compromise cardiac function and/or lead to complex arrhythmias are a significant concern in the late-stage CKD population. In Colombia, the FMEPrever program includes comprehensive medication documentation, assessment of relevant drug interactions, strict pharmacovigilance, and adverse event monitoring related to prescribed medications.

Clinics in Peru and Colombia routinely assess the risk of developing cardiac arrhythmias due to QT interval prolongation based on potential drug-drug interactions at the time of clinic admission.

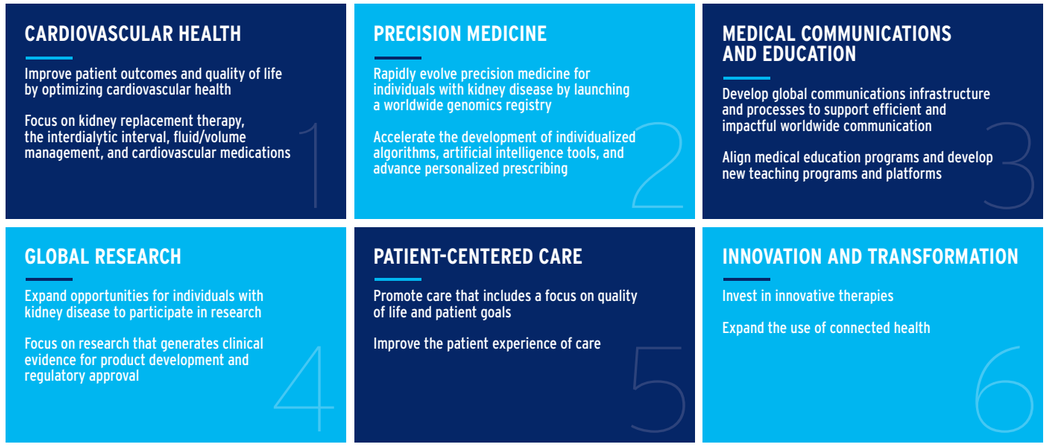
Among incident patients, the goal is to maintain hourly ultrafiltration rates less than 13 mL/kg/h and prevent intradialytic or post-dialysis hypotension, thus reducing the risk of myocardial, cerebral, and mesenteric ischemic events, myocardial stunning, and cardiac arrhythmias.

Other cardioprotective strategies focus on: appropriate volume management and nutritional optimization at admission; programs such as Hyper-Care in Brazil (daily in-center high-volume hemodiafiltration, or HDF, five to six times weekly); and using serial measurements of body composition from the first week on dialysis (Fresenius BCM™) in Chile, repeating the measurements with four-week intervals for at least the first three months of KRT.

In FME Ecuador, a prescribed sodium dialysate concentration of <138 mmol/L (99% of treatments) and an ultrafiltration rate between 10 and 12 mL/kg/h (99% of all treatments) have been implemented in addition to body composition monitoring and multidisciplinary support. Patients also undergo an annual mandatory cardiology assessment that includes chest x-ray, electrocardiogram, and echocardiogram, if indicated. By reducing the unnecessary overuse of beta-blockers and antihypertensive medications, a significant reduction of intradialytic hypotension has been observed.[7]

With the introduction of cardiovascular health as a core focus area, Medical Office teams throughout the company have begun integrating cardiovascular-related initiatives into clinical services to improve patient outcomes and make care more personalized and precise.

FIGURE 1 | Cardiovascular Health is one of the six core themes of the Fresenius Medical Care Clinical and Quality Agenda



Peru has developed a robust patient education program that covers important topics such as chronic volume overload and the consequences of high ultrafiltration rates, in order to improve understanding of the effect of fluid overload on cardiovascular health. Training for medical and nursing staff was developed in parallel, aimed at optimizing the management of volume status and the ultrafiltration rate, as well as the proper interpretation of the body composition monitor (BCM) results.

In Brazil, the in-center daily high volume (HV)-HDF protocol includes principal indications for HV-HDF and buttonhole vascular access cannulation to minimize the discomfort of frequent arteriovenous fistula cannulation. Our experience suggests that daily hemodialysis can be a good option for prevalent patients.[8]

In Argentina, HV-HDF was incorporated into clinical care with a strong implementation program, as HV-HDF may reduce cardiovascular complications. Currently, there are 2,830 patients using this therapy in our dialysis clinics—which represents 31.6% of those on hemodialysis—with excellent results and a significant reduction in mortality (Figures 2 and 3).

CONCLUSION

Cardiovascular disease poses significant risks for patients with CKD. Addressing these risks using a multidisciplinary clinical team and patient education approach and making care more personalized and precise could help lower the incidence of cardiovascular events among patients with kidney disease. Specific cardiovascular-related care strategies include thorough cardiac screening and risk assessment, evaluation of individual lifestyle factors, consideration of various treatment options such as home-based therapies, and ongoing management of dialysis complications. Detecting and controlling fluid overload, hypertension, cardiac arrhythmias, cardiac remodelling, and vascular calcification can likewise significantly improve cardiovascular health.

FIGURE 2 | Number of patients on HV-HDF in Fresenius Medical Care Argentina over time

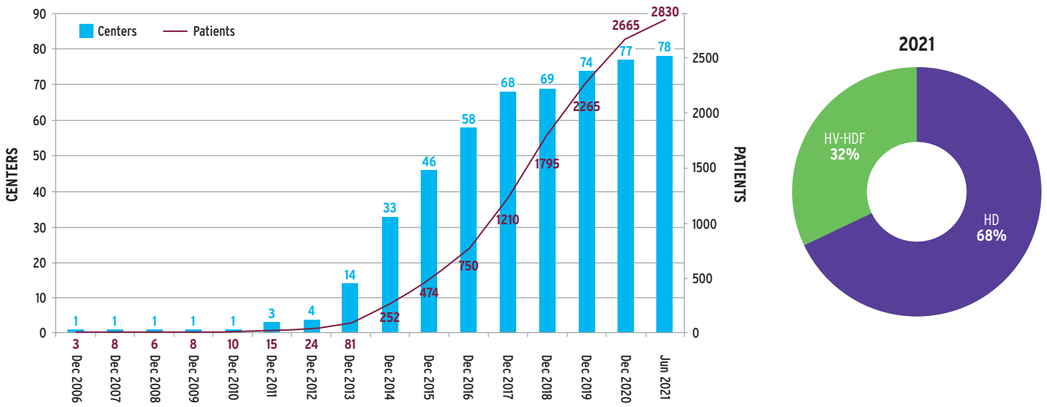
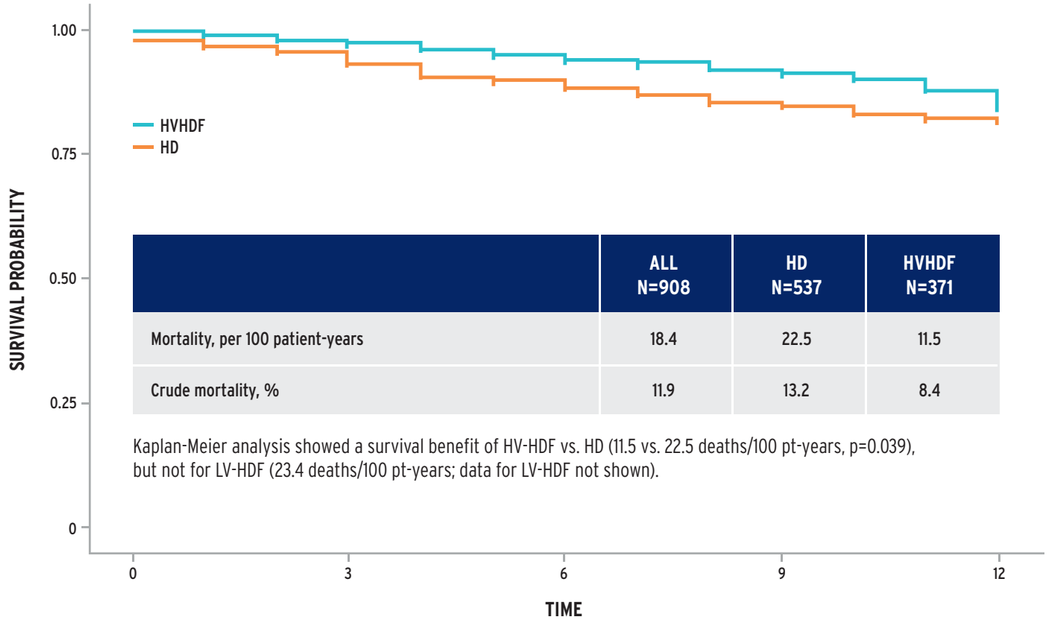


FIGURE 3 | Hemodiafilitation in Argentina demonstrated improved survival for patients



	ALL N=908	HD N=537	HVHDF N=371
Mortality, per 100 patient-years	18.4	22.5	11.5
Crude mortality, %	11.9	13.2	8.4

Kaplan-Meier analysis showed a survival benefit of HV-HDF vs. HD (11.5 vs. 22.5 deaths/100 pt-years, p=0.039), but not for LV-HDF (23.4 deaths/100 pt-years; data for LV-HDF not shown).

Source: Ferder M, et al. Improved survival with high-volume hemodiafiltration in Argentina: a propensity score-matched cohort study. Abstract. American Society of Nephrology, November 8, 2019. https://www.asn-online.org/education/kidneyweek/2019/program-abstract.aspx?controlId=3235721.

JUAN CARLOS BERBESSI, MD

Vice President, Global Head of Medical Office Compliance Operations, and Chief Medical Officer, Fresenius Medical Care Latin America

As chief medical officer for Fresenius Medical Care Latin America, Juan Carlos Berbessi leads delivery of all medical and scientific activities across the region. He joined Fresenius Medical Care as regional medical director in 2018. Previously, he served as medical affairs director, overseeing delivery of all medical and scientific activities across therapeutic areas in Colombia. Trained in epidemiology and molecular biology, Dr. Berbessi has served as spokesperson to external and internal bodies on medical and scientific issues related to medical products, and he integrates medical and scientific insight into affiliate, regional, and global strategies. His career spans nearly three decades with over 20 years of experience in the pharmaceutical industry across five multinational companies: Hoechst, GSK, Wyeth, AMGEN, and AbbVie. He obtained his medical degree from Universidad Libre, and trained in biomedical research at the Pontificia Universidad Javeriana and in microbiology and human genetics at the Universidad de los Andes in Colombia.

MARIA MERCEDES RESK, MD

Medical Director, Fresenius Medical Care CARICAM Region

As medical director for Fresenius Medical Care's CARICAM region, Maria Mercedes Resk leads all medical and scientific activities across the region. Prior to joining Fresenius Medical Care in 2018, she served as a medical affairs and therapeutic area head in Costa Rica and Argentina. She is trained in financial and pharmaceutical marketing, working with external and internal medical-related products and on local and global strategies. She has more than 12 years of experience in the pharmaceutical industry in two multinational companies: Novartis Argentina and CAC, Covance Argentina. She is a graduate of the Universidad Nacional de Cordoba in Argentina and obtained her medical degree from Argentina Cardiologist Society Universidad de Buenos Aires.

ALEJANDRO KOHN TULI, MD, FRCS

Medical Director, Fresenius Medical Care Argentina SA

As medical director for Fresenius Medical Care Argentina SA, Alejandro Kohn Tuli leads the delivery of all medical and scientific activities across the country. Prior to joining Fresenius in 2018, he served as medical director of hospitals in Qatar and, in his position as chief medical information officer for the Heart Hospital, supported the Nation-Wide eHealth Strategy at the Ministry of Public Health in Qatar. During his 30 years of clinical experience, he actively participated in clinical, research, education, and hospital administration activities. He has been a member of international medical societies and an active member of international clinical advisory boards for the pharmaceutical, device, medical equipment, and HER industries. Over the past 25 years, he practiced as a surgeon, intensivist, and hospital executive in the UK, Argentina, and Qatar. He graduated from the School of Medicine, Buenos Aires University, Argentina, and trained as a cardiothoracic and heart and lung transplant surgeon as a fellow of the Royal College of Surgeons of England.

GLOBAL RESEARCH

Make research a standard offering to patients, and prioritize research to improve patient outcomes. Focus on research that generates critical clinical evidence for product development and regulatory support.

IMPROVING CARE WITH REAL-WORLD EVIDENCE

Anke Winter, MD, MSc
Linda Hanna Ficociello, DSc

Real-world evidence (RWE) can help expand our understanding of the effectiveness of various interventions for people with end-stage kidney disease. Dialysis organizations are well-positioned to develop RWE based on analyses of real-world data (RWD) because of the extensive electronic health data generated by patients' frequent interactions with the healthcare system. Despite its methodological challenges, analyses of RWD could provide valuable insights that improve the care of individuals with kidney disease.

End-stage kidney disease (ESKD) is complex and often complicated by co-existing chronic conditions. It is vital for healthcare providers and individuals living with kidney disease to have all available evidence, including real-world evidence, to make informed treatment decisions.

Traditionally, randomized controlled trials (RCTs) have been the foundation of regulatory approval and treatment decision making. These trials are considered the gold standard for providing evidence on various types of interventions such as treatment and therapeutic approaches. RCTs are crucial in understanding the efficacy and safety of an intervention; however, when they are conducted in small, selected populations under ideal study settings, they may not reflect the intervention's effectiveness in broader populations in a real-world setting.[1]

Various systematic reviews evaluating the inclusion of diverse patient populations in clinical trials have found that the majority of RCTs rarely consider individuals with chronic conditions, including those with ESKD, and tend to exclude older people.[2,3,4] These exclusions limit our understanding of how these clinical trial findings may be generalizable to individuals with ESKD. In addition, the well-controlled study setting of an efficacy trial may not reflect the real-world healthcare settings.

For example, study-specific clinical assessments of treatment regimens or clinical outcomes may not represent how the treatment is administered or how treatment effects are monitored in routine practice. This could result in attenuated treatment effectiveness in the real world even though the well-controlled study setting shows treatment efficacy. Furthermore, not all clinical trial outcome measures, such as surrogate endpoints, reflect outcomes that matter to patients.[5]

These exclusions limit our understanding of how these clinical trial findings may be generalizable to individuals with ESKD. In addition, the well-controlled study setting of an efficacy trial may not reflect the real-world healthcare settings.

DATA IN THE REAL WORLD

There is an urgent need to have evidence that relates to the heterogeneity of patient populations and that examines outcomes that matter to people living with chronic conditions.[6,7] To date, there is no universally accepted definition of RWE, but several have been proposed. According to the Real-World Evidence Transparency Initiative, RWE is defined as: "Clinical evidence from RWD analysis on the use and potential benefits or risks of an intervention. RWE can be generated by different study designs or analyses including randomized trials (and large simple trials), pragmatic trials, and prospective or retrospective observational studies."[8] Furthermore, RWD is defined as: "Data on patient health status and/or routine healthcare. RWD can come, for example, from electronic health records claims and billing databases, product and disease registries, wearable devices, and electronic applications. Data can also be collected prospectively such as disease registries."[9]

There is an urgent need to have evidence that relates to the heterogeneity of patient populations and that examines outcomes that matter to people living with chronic conditions.

EXISTING DATA SOURCES

Dialysis organizations are uniquely positioned to develop RWE because of the extensive electronic health record (EHR) databases that are necessary to support the clinical care of people receiving dialysis. Extensive data is gathered from dialysis clinics and includes longitudinal and routine collection of vital signs, treatment parameters, biochemical measures, medications, and quality-of-life measures. In addition, in-center hemodialysis patients have many interactions with healthcare providers during their dialysis treatments, enabling frequent assessments over long periods of time. Outside of clinics, connected health incorporates data from sources such as home dialysis machines and patient care portals.[10]

There are advantages and disadvantages of using retrospective RWD (Figure 1). The potential benefits include the study of heterogenous, diverse, and large patient populations that reflect real-world delivery of care over a longer period of time. In addition, the use of existing records allows the examination of multiple exposures, outcomes, and patient subgroups due to large sample sizes. Compared with clinical trials, studies that use RWD may be associated with lower costs and produce results more quickly.

The potential disadvantages of retrospective studies that use RWD include the potential for selection bias and confounding because randomization is not possible.[11] In randomized controlled trials, the random allocation is intended to balance known and unknown factors that can potentially influence the observed treatment effects. If not well-controlled through study design, then these known and unknown factors can result in biased or confounded study results. Furthermore, the use of RWD sources can increase the likelihood that there is missing data or that not

Extensive data is gathered from dialysis clinics and includes longitudinal and routine collection of vital signs, treatment parameters, biochemical measures, medications, and quality-of-life measures.

all the desired information is collected as part of routine care. There are methodologies to help mitigate these challenges, including restriction of patients, selection of proper unexposed patients through direct matching or propensity score matching, instrumental variables, or proxy measures for variables of interest. Other mitigation strategies can be employed during analysis, including statistically controlling for confounding, stratification by covariates, or imputation methods.[12]

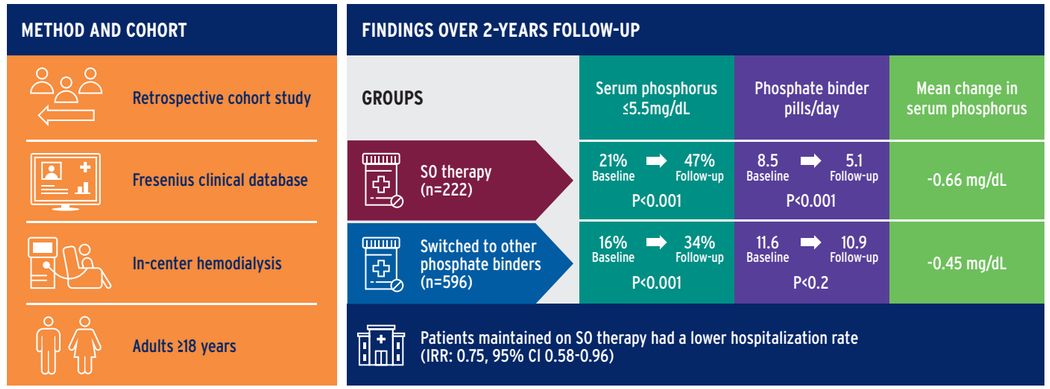
SUPPORTING REGULATORY DECISIONS

Real-world evidence studies based on RWD can support the regulatory decision-making process for medical devices and pharmaceuticals. In few and selected cases, such as rare or orphan diseases, studies including RWD have been considered in the pre-market approval process by regulatory authorities for new drug applications or line extensions.[13] After market approval, studies based on RWD can add to the understanding of the safety and effectiveness of the device or drug when utilized under real-world circumstances.[14]

FIGURE 1 | Advantages and disadvantages of real-world data

ADVANTAGES	DISADVANTAGES
Generalizability	Lack of randomization
Large sample sizes	Confounding
Long follow-up	Bias
Low cost	No study schedule
Quick results	Not all data of interest is available
Multiple exposures and outcomes	Missing data
Focus on how treatments are delivered	

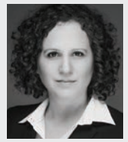
FIGURE 2 | RWE and RWD were vital in determining the effectiveness of combining phosphate binder therapy with sucroferric oxyhydroxide in hemodialysis.



Source: Coyne DW, et al. Sucroferric oxyhydroxide in maintenance hemodialysis: a retrospective, comparative cohort study. Kidney Medicine 2020 March;2(3):307-16.

Some RWD sources, such as product registries, are specifically developed and designed for post-market device or drug surveillance purposes. In contrast, other RWD sources, such as EHRs and claims data, are usually established for non-regulatory purposes. Therefore, it is important to ensure that the RWE study based on secondary RWD sources fits the regulatory purpose and meets data quality and regulatory standards.[15] In addition, there may be country-specific and product designation-specific differences in requirements and acceptance of RWE studies based on RWD in the context of the regulatory decision-making process.

RWE can expand the scientific understanding of the effectiveness and safety of interventions in individuals with ESKD such as determining the effectiveness of combining therapeutics (Figure 2). Despite the methodological challenges, secondary analyses of RWD can complement the existing evidence base and provide valuable insights that improve the care of individuals with kidney disease.



ANKE WINTER, MD, MSc
Senior Director, Epidemiology and Real-World Evidence
Applied Data Science, Biostatistics, and Epidemiology, Global Medical Office, Fresenius Medical Care

Anke Winter oversees epidemiology and real-world evidence activities in the Europe, Middle East, and Africa region. Her team provides support in assessing the value of Fresenius Medical Care products, therapies, and clinical strategies in real-world settings. She has over a decade of research experience in academic and industry settings, and has authored 32 scientific publications. Prior to joining Fresenius, she held faculty appointments at the Washington University School of Medicine in St. Louis. Dr. Winter completed her medical degree at the RWTH Aachen University in Germany, obtained her doctor of medicine from the University of Münster, and holds a master of science in epidemiology from the Harvard T.H. Chan School of Public Health.

LINDA HANNA FICOCIELLO, DSc
Senior Director, Epidemiology and Health Economics
Applied Data Science, Biostatistics, and Epidemiology, Global Medical Office, Fresenius Medical Care

Linda Ficociello leads a real-world evidence generation team that analyzes clinical and economic data using advanced analytics to demonstrate the clinical and cost effectiveness of Fresenius Medical Care products and services, with a primary focus on North America. She has 25 years of experience in chronic disease epidemiology and kidney disease research. Her research interests include epidemiologic methods, comparative effectiveness, fluid management in dialysis, home dialysis, and mineral bone metabolism. She has authored over 40 peer-reviewed manuscripts and more than 120 abstracts, posters, and invited presentations at scientific conferences. Before coming to Fresenius, she was an instructor in medicine at Harvard Medical School and a research associate at the Joslin Diabetes Center. Dr. Ficociello received her doctorate in epidemiology at Boston University School of Public Health and completed a postdoctoral fellowship at Harvard Medical School.

ENRICHING CLINICAL TRIAL DESIGN THROUGH THE USE OF PATIENT-REPORTED MEASURES

Krister Cromm, MA, MBA, MSc
Saynab Atiye, RPh

The addition of patient-reported outcomes (PROs) in clinical trials opens new and meaningful pathways for discovery. By combining clinical and patient-reported endpoints, trials featuring PROs can identify when and how a product can support improving patients' health status inside and outside the clinic; help clinicians and patients define treatment goals together; and demonstrate an intervention's value to multiple stakeholders in society. The Home Hemodialysis and CONVINCE consortium studies exemplify how an evolution from disease-centered to person-centered care can be integrated into clinical trial designs with digital solutions.

The development of medical devices, therapies, and pharmaceuticals relies on clinical research. Data on safety, efficacy, or performance of an intervention is collected to provide evidence to meet regulatory requirements and demonstrate potential benefit to payers and society, including information about the costs and expected use of the therapy.

Traditionally, biomedical clinical research has been conducted through quantitative research, focused on so-called "hard outcomes" and other measures that can be observed directly and are not prone to observer bias. While important, this quantitative research provides limited information about patient feelings, motivations, social or cultural values, or religious and cultural views, or the patient-physician relationship, all of which can greatly influence treatment success.

ENHANCING CLINICAL RESEARCH BY ADOPTING A BROADER APPROACH

Health outcomes that are directly evaluated by the patient and included in surveys are commonly referred to as patient-reported outcomes (PROs). Data about these characteristics can be captured through qualitative research that describes life experiences in a systematic manner, giving them meaning beyond individual, subjective observations. Once qualitative research has consistently identified underlying constructs such as pain, the ability to participate in social roles, or treatment-related fatigue, individual statements arising from these surveys are developed and tested so that they can be used as qualitative factors in quantitative research designs. The technique of converting personal statements into reliable and valid quantitative measurements makes it possible to analyze how changes in clinical endpoints precede or follow changes in PROs.

Combining PROs from various domains of well-being can form an instrument designed to measure overall health-related quality of life (HRQOL). Such instruments can be generic, such as the commonly used SF-36 survey, or disease-specific, such as the Kidney Disease Quality of Life survey. Examining HRQOL in clinical trials together with clinical endpoints results in a comprehensive view of health outcomes. The outcome model ahead shows pathways that patients and clinicians can follow to achieve better health and well-being while keeping clinical endpoints in view (see Figure 1).[1] In contrast to PROs, when psychological surveys measure health perceptions or views influencing patient experience, rather than the outcome of care, they are referred to as patient-reported experience measures (PREMS).

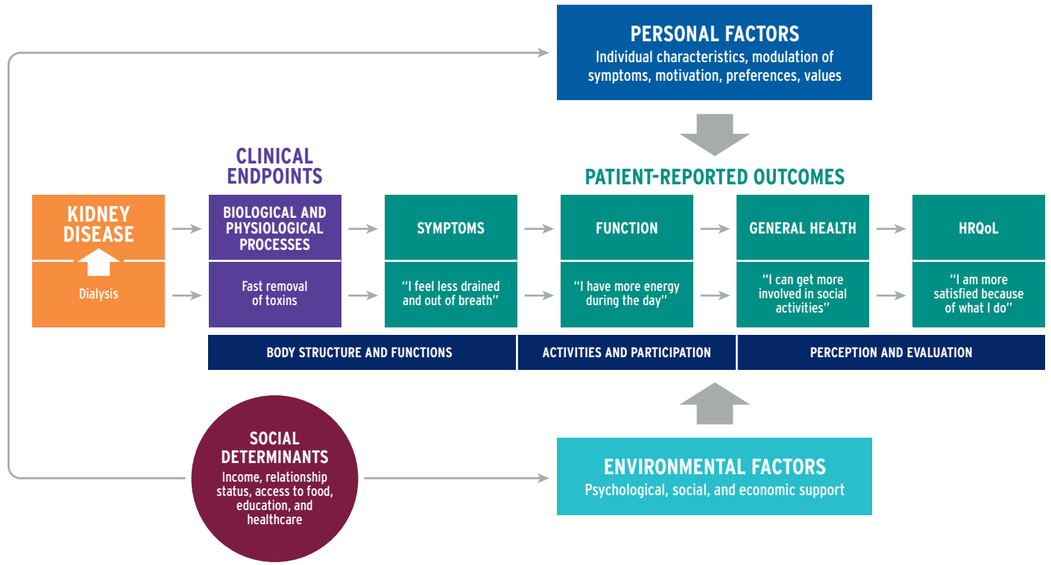
Ideally, patient-reported measures should be confirmed by qualitative methods in the beginning of a clinical trial, such as structured interviews with the relevant populations. In this way, such measures can be adapted or expanded to fit the patient-specific needs and circumstances. However, modern research methods follow different strategies that make it possible to choose from large sets of survey items to tailor-fit questionnaires to individual respondents. Computer-adaptive tests can be filled in via tablet computers or smartphones, such as the Patient-Reported Outcomes Measurement Information System (PROMIS®) surveys that were developed in the United States under a grant by the National Institutes of Health.[2]

In clinical trials, clinical and patient-reported endpoints are complementary. This is also emphasized by individuals with kidney disease, who consistently report that health-related quality of life is as important as established clinical outcomes, along with the fact that the alignment of these goals does not receive adequate attention. Practically, concerns with treatment priorities are more evident in clinical practice; therefore, numerous published articles over the last decade discuss improving PROs in clinical care only, rather than looking at the preceding clinical trial stage.

Very few individuals with kidney disease work in dialysis product development or are otherwise involved in decision making that leads to product purchasing decisions. Health-related quality of life has rarely been considered as the determining factor in dialysis product research. This has resulted in systematic limitations of research findings. Nonetheless, technological, social, and economic developments have led to increasing involvement of individuals in their healthcare and have led governments to take steps toward patient involvement in clinical trials. Thus, much can and must be done to adopt patient-centered approaches in product and research design early on, to improve health-related quality of life for those with kidney disease.

For kidney disease, combining outcomes holistically is notably reflected in the Standardised Outcomes in Nephrology (SONG) Initiative, launched in November 2014.[3] The initiative established a set of core outcomes and outcome measures across the spectrum of kidney disease for trials and other forms of research, many of which are PROs. The outcomes were developed based on the shared priorities of patients, caregivers, clinicians, researchers, policy makers, and relevant stakeholders. It is assumed that they will help to ensure research outcomes that are meaningful and relevant to patients with kidney disease, their families, and their clinicians, and to support decisions about treatment. The guidelines play an increasingly important role in peer review and article acceptance in scientific journals.

FIGURE 1 | Pathway to health-related quality of life, developed by Krister Cromm based on a conceptual model of patient outcomes by Wilson and Cleary



There are various other initiatives by patient organizations, researchers, international organizations, and regulators—such as the Organization for Economic Cooperation and Development's Patient-Reported Indicator Surveys initiative (PaRIS) or the Consensus-based Standards for the selection of health Measurement Instruments initiative (COSMIN)—to establish mechanisms to focus on patient-centered priorities or remove bias from clinical trials by advocating for patient participation starting in the design stage.[4,5]

Besides strengthening the consideration of PROs and PREMS that formalize the patient voice in the development of new therapies, the European Medicines Agency (EMA) generally fosters patient contributions to drug development. It also supports key initiatives like the European Patients' Academy on Therapeutic Innovation (EUPATI) to embed patient priorities into clinical trial designs.[6,7] Patients are experts in their disease area, so it is crucial that their input is reflected in decisions made by the regulator and embedded in all the work the regulators do. Therefore, the interaction should be as early as possible.

The EMA also aims to update relevant clinical guidelines to include reference to PROs addressing study objectives, design, and analysis.[8] Thus, the EMA has included the reinforcement of patient relevance in evidence generation in its "Regulatory Science Strategy to 2025" as one of the five main goals. The EMA is looking to further enhance its methods to enable greater input from the wider patient community in a systematic manner. There are also opportunities arising from new digital tools and the science of patient reporting. EMA is starting to see the use of various PROs as endpoints within submissions for marketing authorization applications for pharmaceuticals. Given other trends—such as eHealth, precision medicine, and the drive for outcome-based healthcare—the use of patient data will likely continue to grow. Understanding how to generate, analyze, and use relevant patient data will be key to EMA's regulatory science strategy.[9]

In the United States, the Food and Drug Administration's Center for Devices and Radiological Health equally strives to ensure patients and their care partners are the focus of the regulatory decision-making process by encouraging the inclusion of clinical outcome assessments such as PROs in the evaluation of medical devices.[10] In Australia, the Addendum to National Health Reform Agreement mandates the implementation of PROs for funding, emphasizing empowerment and health literacy as much as paying for value and outcomes.[11]

The EMA outlined guidance for the use of health-related quality-of-life measures in the evaluation of medicinal products. It describes how HRQOL measures may provide more insight into interpreting the effect on the primary endpoint in terms of consequences for daily life and social functioning. Any claims about HRQOL improvements must be supported by data collected with instruments validated for use in the corresponding health condition.[12]

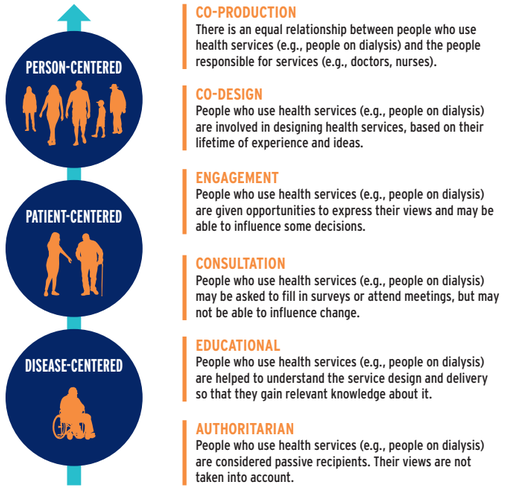
THE CONVINCE CONSORTIUM AND THE HOME HD STUDIES

Research initiatives at Fresenius Medical Care inspire and embrace the implementation of patient-centered care and patient-reported measures.[13] The company is actively reviewing where and how an evolution from the former disease-centered approach to the current patient-centered strategy can be developed toward holistic person-centered care through integration and leadership in clinical trial designs (Figure 2).

CONVINCE is a consortium that is performing an international, multi-center, prospective, randomized, controlled study—with 1,360 enrolled participants—comparing high-dose hemodiafiltration versus conventional guideline-based hemodialysis. Together with partners in industry and academia, Fresenius Medical Care has received 6.8 Mio € in funding from the EU's Horizon 2020 grant, the top funding authority in the European Union representing more than 447 million citizens in the EU's 27 member states. Across nine countries in Western, Southern, and Eastern Europe, the trial examines not only the effect of hemodiafiltration on hospitalizations and mortality, but also a wide range of physical, mental, and social outcomes using electronic PROMIS participant surveys. To support the comprehensive examination of PROs, the clinical trial surveys are translated into national languages. A specific dialysis recovery time module has been developed to understand how dialysis therapy increases or reduces fatigue before, during, and after treatment sessions and on the days following dialysis. The trial also examines psychosocial factors, including stress, social support, and self-efficacy. The CONVINCE study offers the opportunity to establish a valid and reliable measurement framework for PROs that allows comparing these outcomes in nephrology across treatment settings.

As we have already validated the questionnaire approach with the baseline assessment in CONVINCE, we are now building on this knowledge. In Turkey, the Home Hemodialysis (HHD) Study, a sponsor-initiated trial, plans to enroll 700 participants and examine how treatment at home affects their HRQOL until 2023. Prior to the main HHD study, a validation and pilot study of over 150 participants will be completed later in 2021. In that study, PROs will be examined in detail to establish a measurement base of what is important from the patient perspective—in particular, self-rated cognitive function and abilities, fatigue, sleep, depression, anxiety, and sexual function. This trial will also consider the economic aspects of care, which are markedly different for patients who perform treatment at home. This will render important information regarding how limited resources change healthcare outcomes and will help identify the circumstances where HHD patients experience better results, so that more patients can eventually enjoy the benefits of home therapies.

FIGURE 2 | Evolution of person-centered healthcare in end-stage kidney disease



Source: Morton RL, Sellars M. From patient-centered to person-centered care for kidney diseases. *Clin J Am Soc Nephrol* 2019;14(4):623-25.

CONCLUSION

PROs in clinical trials offer new ways to expand clinical trial design. Rather than limiting the focus of clinical trial outcomes to traditional clinical or biochemical measures, trials featuring PROs can identify when a product can support a patient in improving their health status or well-being. Transforming and improving clinical care requires a more thoughtful and comprehensive approach to clinical trial design. This will allow the development of the best treatment strategy together with and for the benefit of individuals with kidney failure. Fresenius Medical Care is committed to products that meet patients' needs, inspiring the development of new care strategies.

KRISTER CROMM, MA, MBA, MSc
Expert Director Patient Experience
Clinical Research, Europe/Middle East/Africa, Asia Pacific, and Latin America, Global Medical Office, Fresenius Medical Care

Krister Cromm provides leadership and guidance on patient-reported measures and person-centered care. In 2010, he joined the Asia Pacific Medical Office in Hong Kong before establishing the Patient Experience function in Bad Homburg, Germany, in 2015. He represents the company in the CONVINCE consortium and is active in the International Society for Quality of Life Research (ISOQOL) and the European Health Psychology Society (EHPS). Prior to joining Fresenius Medical Care, he worked for Bayer and Merck in various capacities. Krister holds a master's degree in Chinese studies from the School of Oriental and African Studies at the University of London, an MBA from the European School of Business, and a master's degree in psychology from City University of Hong Kong.

SAYNAB ATIYE, RPh
Director, Clinical Research Home/Critical Care
Europe/Middle East/Africa, Asia Pacific, and Latin America, Global Medical Office, Fresenius Medical Care

Saynab Atiye has been part of Fresenius Medical Care since 2015. Within the Department of Clinical Research in Bad Homburg, Germany, she is a focus team lead responsible for the home and critical care therapy areas. In this function, she and her team manage multiple national and international clinical studies from start to finish, including strategic concepts and detailed planning and execution. Before joining Fresenius, she worked for almost 10 years in clinical research and international regulatory affairs in the pharmaceutical industry, where she managed clinical studies for medicinal products and medical devices. Saynab is a pharmacist by profession and received her degree at the University of Heidelberg.

RETHINKING GLOBAL CLINICAL RESEARCH IN THE ERA OF DIGITAL HEALTH

Manuela Stauss-Grabo, PhD

This is an era of change. For the last five decades, computational power and capabilities have increased and evolved in an unprecedented manner. Clinical trials are the central mechanism for unbiased assessment of proposed advances in health, healthcare, and evaluation of approaches to prevention, diagnosis, and treatment of disease. The digital health era now offers tools for transforming clinical research through improved efficiencies of highly complex trials. Leveraging digital technologies will be instrumental in accelerating clinical evidence generation on a global level.

Clinical trials are a fundamental tool used to evaluate the efficacy and safety of new drugs, medical devices, and other therapeutic interventions. Today, the conduct of clinical trials continues to rely heavily on the use of paper documents. For example, participant recruitment, informed consent, and the collection of source data are still performed manually, often in paper format. Thus, it is time to fundamentally shift the traditional paradigm as the current methods for conducting clinical trials are no longer sustainable. New strategies for the future of clinical trials are needed, including the concept of digital clinical research. Digitally enabled tools will help to improve participant access, participant engagement, trial-related measurements, and interventions. More and more aspects of conducting clinical trials—e.g., remote patient monitoring via telemedicine—and other decentralized ways of collecting data will then be managed electronically and automatically.[1]

CLINICAL EVIDENCE GENERATION IN THE DIGITAL AGE

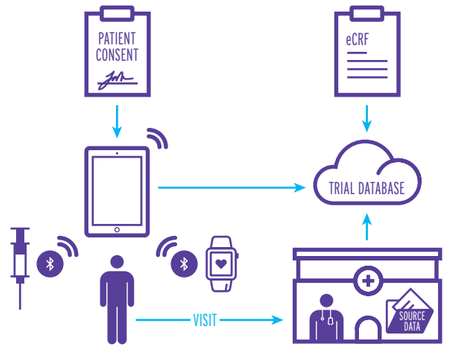
The digitization of modern life began with the personal computer, then accelerated with the emergence of the Internet and the rapid uptake of mobile devices. Initially, life science and healthcare industries were reluctant to embark on the transformative activities made possible by the rise of these technologies and what is now the backbone of what is called digital clinical evidence generation.[2] The hesitation to act on digitization and data stores had validity, particularly because of concerns relating to personal health information and regulations such as the Health Insurance Portability and Accountability Act and the European Union's legislation on data protection, such as the Data Protection Directive and the General Data Protection Regulation.[3,4]

Yet while privacy and security concerns must be addressed, in clinical research the use of new technologies like artificial intelligence that support the identification of meaningful relationships in raw data and the extraction of relevant insights must be increased. By supporting physicians to make more informed clinical decisions, digital clinical evidence generation provides unprecedented development opportunities for all fields of healthcare, including drug and medical device development. This will create significant benefits that will reshape not only processes relevant for Fresenius Medical Care's global clinical research but also—and most importantly—patient care in general.

mHEALTH

The rapidly accelerating adoption of mobile, self-serve diagnostic, monitoring, and treatment modalities (or mHealth) in both the healthcare and clinical trial arenas is already demonstrating a material impact on healthcare delivery.[5] By capturing timely and high-quality data remotely, at-home wearable devices provide the dual benefit of reducing both investigator and participant burden, for example, by reducing the frequency and duration of clinical visits (Figure 1).[6]

FIGURE 1 | As the use, reliability, and confidence in digital tools and electronic data management systems increase, such systems will be further introduced into clinical trials.



Taken a bit further, digital technology permits continuous real-time monitoring of participants' well-being during and after clinical trials. This will boost the process of collecting data and will drastically increase insights into patient health and compliance, as well as safety and effectiveness of the therapy in question. Digital mHealth tools enable the swift, secure collection of large volumes of accurate and consistent data on which further analysis can then be performed on the spot, such as comparing therapies and assessing efficacy.[7,8,9]

These days, many clinicians are dispirited by the numerous repetitive practices required in conducting clinical trials. If digital data sources were to be fully used, many of those repetitive practices would be unnecessary. It is important to note that all stakeholders, including health authorities, have a great interest in clinical trial optimization. As an example, consider the US Food and Drug Administration's (FDA) "Voice of the Patient" program, which aims to "systematically gather patients' perspectives on their condition and available therapies to treat their condition."[10]

While the adoption of mHealth will require transforming study teams to a new and different way of working, the digital technologies will improve trial efficiency by enhancing and supporting the role of investigators and study staff. Fresenius Medical Care will be moving toward a participant-centered clinical trial experience by minimizing geographic obstacles for participation and establishing a high level of connectivity with participants and investigators. This allows for the possibility of individual findings and overall results to be returned repeatedly to participating investigators throughout the duration of the study, thus fostering a true partnership in clinical research. mHealth will help shape a more personalized, more precise, and more supportive clinical research environment.

GLOBAL CLINICAL TRIALS: OPTIMIZING METHODS, DESIGN, AND THE REGULATORY ENVIRONMENT

Traditionally, Fresenius Medical Care's clinical trials have been largely limited to North America and certain countries in Western Europe. The introduction of global digital clinical trials represents enormous potential in various areas, including streamlining operational costs, increasing speed and agility, and enhancing the diversity of clinical participants. Today, there is an enormous opportunity to harness digital technology to expand research activities geographically and concurrently to accelerate the pace at which evidence through clinical trials can be generated.[11,12,13,14]

However, this cannot be accomplished by replicating the current research processes and simply transforming them from paper to digital form. Rather, a complete rethinking and reengineering of the clinical trial concept around the participant and the clinical site is needed. While some trials could be conducted digitally in a virtual environment, many will require a hybrid of virtual and clinical site-based activities. Future digital clinical trial concepts will use micro-randomization to build and optimize individual intervention components within just-in-time adaptive interventions. These mHealth technologies aim at delivering the right intervention components at the right time and location to optimally support individuals' health behaviors.[15,16,17,18,19,20,21]

Finally, the harmonization of pharmaceutical regulations is essential to transform the traditional concept of clinical trials. Significant progress on regulatory convergence has been achieved to date by agreements and close collaboration between regulators like the FDA and the European Medicines Agency. Much effort is still needed before a fully global harmonization can be realized.[22,23,24]

UTILIZING EMERGING TECHNOLOGIES FOR THE FUTURE

Medicine today primarily focuses on treating disease; in the future, it will increasingly be used to prevent disease. A dramatic transformation of the global clinical trial operational delivery model is under way, driven by ever improving digital clinical technology in a more harmonized regulatory environment. Fresenius Medical Care's global clinical research team is prepared to responsibly and creatively adopt digital technologies to create efficiencies in a way that preserves the strength of classical clinical trials. There is ample evidence of the benefits of mHealth.

Correspondingly, digital tools will improve clinical trial designs, yield data of higher quality at lower cost, and accelerate Fresenius Medical Care's product development cycle times. This will ultimately permit an accelerated release of new products and therapies that improve the health of individuals living with kidney disease and provide more advanced treatment options for healthcare professionals.

MANUELA STAUSS-GRABO, PhD
Vice President, Head Clinical Research, Europe/Middle East/Africa, Asia Pacific, and Latin America, FME Global Medical Office

Manuela joined Fresenius Medical Care in 2013. With more than 15 years of practical experience in clinical research, she currently leads the clinical research team for Europe, Middle East, and Africa, Asia Pacific, and Latin America regions. Utilizing her biology background and research expertise, Manuela is dedicated to generating clinical evidence aimed at better understanding kidney disease and improving the outcomes of renal patients worldwide. Located in Bad Homburg, Germany, the Global Medical Office's clinical research team manages numerous national, international, and multi-regional clinical studies from start to finish, including the development of strategic concepts on implementing and actively using state-of-the-art digital technologies. Manuela earned her biology degree from Julius-Maximilians-University Würzburg and her PhD in pharmacy from Philipps-University Marburg, both in Germany.

PATIENT-CENTERED CARE

Maximize outcomes across every patient's lifelong care journey. Address clinical inequities that compromise individual and community health. Focus on systemic social justice issues as drivers of inequality in global healthcare systems.

OPTIMAL DIALYSIS START: LESSONS LEARNED FROM THE UNITED STATES AND CANADA

Dugan Maddux, MD, PhD
Ted Toffelmire, MDCM, FRCPC, FACP

Over the past decade, programs that focus on helping people transition to dialysis with an "optimal start" have had limited success. This is true in both the United States and Canada, even though the cost of treatment is not a factor in Canada. These results underscore the fact that current education and care coordination efforts are not addressing the depth of patient feelings, concerns, and experiences or the impact of social determinants of health.

Research suggests people who start dialysis in a planned way with a permanent access have better early dialysis outcomes, improved quality of life, and lower healthcare costs compared to patients who have an unplanned dialysis start.[1,2,3,4] In order to improve early dialysis outcomes, chronic kidney disease (CKD) programs focus on helping people transition to dialysis with an "optimal start," which is often defined as starting treatment with either a permanent dialysis access, with home therapy, or with a preemptive transplant.[5,6,7] In the past decade, CKD programs have developed robust treatment options education, multidisciplinary care team approaches, and case management interventions to improve the likelihood that people will experience a planned and optimal dialysis start.[8,9,10,11] Such interventions have led to variable, incremental improvement in the percentage of people who achieve an optimal start.

DIALYSIS TRANSITION IN CANADA

Residents of Canada access healthcare without consideration of expense. On their own initiative, they access a primary care practitioner, walk-in clinic, or emergency room where they receive indicated care. About 85% of Canadians (including about 90% of females) have a regular medical doctor, but less than 50% of Canadians "regularly go to the doctor for complete physicals or checkups."[12,13] Rather, the decision to present for healthcare is often affected by symptoms, convenience, and perceived need.

Since progressive kidney diseases rarely exhibit symptoms early and general screening tests frequently omit serum creatinine, kidney disease is often not detected until late in the disease—unless the patient has a coexisting risk factor that prompts such specialty screening (especially diabetes). Thus, patients who have chronic diseases that heighten the risk of kidney disease or who have detected progressive kidney disease continue to receive medical care without the cost influencing their decisions. One might therefore consider that users of this healthcare system might have kidney disease detected, followed, and controlled earlier than users of a system where payment is required for each medical visit, test, or intervention.

In 2019, the incidence of patients requiring kidney replacement therapy was about 208 per million population, 62% male and 38% female.[14] Of these, 2.9% received a preemptive kidney transplant, 22% received home dialysis, and 75% began dialysis in an outpatient setting. Patients started dialysis with a mean eGFR of 9 mL/min/1.73m^2. Some 92.9% of patients on peritoneal dialysis (PD) and 69.7% of hemodialysis (HD) patients were followed by a nephrologist for 90 days or more, before starting treatment. Of those who started in-center hemodialysis, 84.7% began with a catheter as vascular access, 14.6% with a fistula, and 0.5% with a graft.

In Canada, during the transition to kidney replacement therapy, or among different therapies within the nephrology program, holistic support is provided to highly variable extents. In 2005, over 90% of the Canadian nephrologists surveyed stated they "always or usually used" a multidisciplinary team–based CKD care clinic. But the expertise available in these settings varied significantly among the centers, based to some degree on the individual interests and funding available to support such services.[15]

DIALYSIS TRANSITION IN THE UNITED STATES

In 2018, about 132,000 Americans (390 per million population) reached end-stage kidney disease (ESKD). Of these, about 113,000 (86%) started with in-center hemodialysis and about 15,000 (11%) started with either peritoneal dialysis or home hemodialysis. In the United States, uninsured individuals were less likely to receive pre-dialysis CKD care than people with Medicare or commercial insurance (Figure 1).[16] Lack of pre-dialysis nephrology care is associated with a poorer transition to dialysis start, with increased use of a central venous catheter (CVC), lower use of a home therapy, and increased risk of hospitalization at the time of transition to dialysis start (Figure 2).[17]

In Canada, during the transition to kidney replacement therapy, or among different therapies within the nephrology program, holistic support is provided to highly variable extents.

Despite more than a year of late-stage CKD nephrology care, over half of US patients still started dialysis with a CVC, a data point that has not improved significantly since 2005.[18,19] Kaiser Permanente published findings from a 2007 to 2014 "Optimal Start Initiative," which leveraged in-person CKD education, vascular access coordinators, and data tracking tools and only resulted in an increase in optimal starts from 57% to 68%.[20] Coordinated nephrology care, late-stage CKD management, and preparation for dialysis start improve the likelihood that people may start dialysis as an outpatient without hospitalization for urgent dialysis start. In the US, 54% of individuals transitioned to dialysis without hospitalization in 2018, an increase from 40% in 2013, but racial disparities in achieving an outpatient start persisted, suggesting unequal access to CKD care.[21]

FIGURE 1 | Approximate percent of patients starting ESKD with prior nephrology care based on insurance type in the US

TYPE OF INSURANCE	NO PRE-ESKD NEPH CARE	0-6 MONTHS OF PRE-ESKD CARE	6-12 MONTHS OF PRE-ESKD CARE	>12 MONTHS OF PRE-ESKD CARE
Uninsured	23%	16%	19%	26%
Medicare Primary	14%	15%	20%	36%
Medicare Secondary	11%	12%	22%	45%
Medicare Advantage	16%	15%	21%	35%

WORKING TOWARD AN OPTIMAL DIALYSIS START

Canada and the US have common goals for treating ESKD but some fundamentally different approaches.[22] Canada has national healthcare funding, and all dialysis facilities are in the public domain. The US functions with both federal and commercial insurance coverage, and most of the dialysis facilities are privately held. In general, individuals with ESKD in Canada are more often male (61% vs. 58%), less likely to be Black, and more likely to use a home therapy than individuals with ESKD in the US.

In both countries, lack of real improvement in optimal starts despite formal programs, robust education, and care coordination has spurred research in this area. In the US, use of a central venous catheter at dialysis start has been essentially unchanged over the past decade at 82% in 2010 and 81% in 2018, according to USRDS data.[23] Despite efforts to improve desirable home dialysis starts, only 14% of patients started kidney replacement therapy with either a preemptive transplant, PD, or HHD in 2018, a slight improvement from 9.4% in 2010. In Canada, the use of a central venous catheter at the start of dialysis may have increased slightly over the same period, from 78.6% to 83.9%, while the presence of a functioning AV fistula at the start of dialysis decreased from 16.3% to 14.6%.[24] During this same period, significant efforts to improve home therapy start resulted in an increase from 22.2% to 25.8%, buoyed largely by the increase in patients starting dialysis on APD from 6.3% to 9.9%.[25]

Studies have identified both system issues and patient issues that impact dialysis start.[26,27,28] System issues include fragmented care among nephrology practices, vascular access centers, surgeons, and sites of care delivery. These have led to delays and barriers to permanent access creation and contribute to unprepared and unplanned dialysis starts.[29] In addition, patient factors are now recognized as significant contributors to not achieving an optimal dialysis start.[30,31,32]

IMPACT OF PATIENT FACTORS

Researchers studying Kaiser's program found that whether or not an optimal dialysis start was achieved, most people preparing to start dialysis in the setting of coordinated nephrology care with education and case management still had feelings of fear, ambivalence, and denial.[33]

Qualitative nephrology studies demonstrate that patient feelings, experiences, concerns, and goals of care frequently diverge from—and surprise—providers who did not know or even imagine these feelings or expectations existed.[34] In kidney disease, this causes healthcare decisions that do not reflect the choices, desires, goals, and/or values of the patient, yielding a "values gap" that impedes achieving quality goals in nephrology care. Qualitative research suggests the current biomedical approach to patient care in nephrology, an approach rooted in quantitative measures, is limiting patient engagement in shared decision making and the opportunity to support patient autonomy.[35]

IMPACT OF SOCIAL DETERMINANTS OF HEALTH

In the US, late-stage CKD patients transitioning to dialysis start may have not only emotional needs that hinder the opportunity to start dialysis in an optimal way but also socioeconomic challenges that create major barriers to optimal care. An estimated 50% of patients starting dialysis each year are uninsured or are covered by Medicaid, and the majority are ethnic and racial minorities. These patients are challenged with social, economic, and environmental exposures that impact health behaviors, health care opportunities, and access to care.[36]

In the United States, CKD rates are the highest in the poorest neighborhoods, and socioeconomically challenged communities create CKD "hot spots."[37,38] Poor neighborhood residents with high rates of food insecurity and chronic disease have a greater risk of CKD and risk of progression of CKD to ESKD.[39,40,41] In addition, CKD and poverty appear to be bidirectional: Impoverished people have less access to healthy food, are more likely to have unstable housing, have more employment challenges, are less likely to be able to adhere to medical care, and have less access to healthcare, which increases the likelihood of CKD and CKD progression. Having a chronic disease often creates disability, missed work days, decreased employment income, and greater healthcare expenses, all leading to increased poverty.[42]

Studies show that poor education level, common in the socioeconomically disadvantaged population, is associated with a decreased likelihood to start dialysis with a home therapy. This group of patients has greater difficulty navigating the complex medical requirements to get a kidney transplant.[43]

FIGURE 2 | Type of vascular access at start of dialysis based on pre-ESKD nephrology care in the US

TYPE OF VASCULAR ACCESS AT DIALYSIS START	NO PRE-ESKD CARE	>12 MONTHS OF PRE-ESKD CARE
CVC only	81%	38%
CVC with maturing AVF or AVG	11%	14%
Usable AVF or AVG	3.5%	27%

Specifically, for CKD, addressing unmet social determinants of health (SDOH) needs for patients would involve:[44]

- **Nephrology providers and practices partnered with community and public health resources, to create more opportunity to connect patients and families to these resources**
- **Increased use of patient navigators and health coaches**
- **Increased screening for social needs and connecting screening with streamlined interventions**

IMPLICATIONS OF AN OPTIMAL DIALYSIS START

People who have access to care and are in a trusting partnership with a multidisciplinary nephrology team can navigate the complex steps to make a modality decision, pursue transplant and/or permanent access work-up, and obtain a usable permanent dialysis access. They are more likely to transition to dialysis in a planned way in an outpatient or home setting. Informing and educating patients is necessary for achieving an optimal dialysis start, which is a shared provider and patient goal.

Data suggests that many SDOH-related inequities result in a disproportionate number of socioeconomically challenged racial and ethnic minority patients starting dialysis in a suboptimal manner. CKD education alone or even in concert with standard nephrology care will improve the likelihood of an optimal start but may not be sufficient to overcome these barriers.

Additionally, research suggests that for many people experiencing major health crises or changes in treatment, emotional barriers may prevent the ability to achieve a desired outcome such as an optimal dialysis start. Late-stage CKD preparation for the transition to dialysis start should acknowledge and address personal emotional stress such as fear, guilt, isolation, and abandonment. Steps should be taken to ensure that the nephrology team and individual person have shared values and goals. Information and education may not be enough to achieve an optimal dialysis start until SDOH and emotional needs are addressed.

Qualitative nephrology studies demonstrate that patient feelings, experiences, concerns, and goals of care frequently diverge from—and surprise—providers who did not know or even imagine these feelings or expectations existed.

THE EXPERTS

DUGAN MADDUX, MD, PhD

Vice President, Kidney Disease Initiatives, Fresenius Medical Care North America

Nephrologist Dugan Maddux champions Fresenius Medical Care North America's clinical innovation endeavors across the continent and is co-founder of the Gamewood companies, including Acumen Physician Solutions. A blogger, writer, and essayist, she developed the Nephrology Oral History project chronicling early dialysis pioneers. She holds her bachelor's degree in chemistry from Vanderbilt University, her doctor of medicine from the University of North Carolina at Chapel Hill, and her PhD from the University of Maastricht in the Netherlands.

TED TOFFELMIRE, MDCM, FRCPC, FACP

Senior Manager, Clinical Research
Senior Director, Medical Affairs, Fresenius Medical Care Canada

Ted Toffelmire is emeritus professor of medicine (nephrology), pharmacology, and toxicology at Queen's University, where he began his practice in 1988. His scientific inquiry has largely focused on various aspects of patients with kidney disease, including anemia, pharmacology, quality of life, and exercise. He joined Fresenius Medical Care Canada in 2007. He holds degrees in life sciences (BSc, Queen's University), pharmacology (MSc, Queen's University), and medicine (MDCM, McGill University); completed residencies in internal medicine and nephrology (University of Western Ontario); and completed a fellowship in clinical pharmacology (University of California at San Francisco).

SHARED HAEMODIALYSIS CARE: TRANSFORMING PATIENT EXPERIENCE

Kolitha Basnayake, PhD, FRCP

The benefits of the shared haemodialysis care model for in-centre patients are significant and span multiple facets of overall experience. Patients who are active partners in their care report better physiological, psychological, and social outcomes compared to those in more traditional dialysis care environments where control lies primarily in the hands of healthcare staff. There are wider benefits to healthcare systems and organisations through efficient use of resources, reduction in avoidable hospital admissions, and improved staff morale. Quality improvement programmes must address barriers to shared haemodialysis care alongside the factors that support successful implementation.

End-stage kidney disease (ESKD) significantly impacts patient quality of life, morbidity, and mortality. Patients on in-centre dialysis spend many hours every week in clinics and in general tend to be passive recipients of their care, with limited involvement in their treatment.[1] There is a growing body of evidence to support the view that in patients with long-term conditions, those who take an active role in their care report better outcomes than those receiving more traditional models of care.[2] It is well recognized that lower health literacy levels among patients are also associated with worse outcomes. Therefore, targeting these areas has the potential to deliver meaningful changes in healthcare.

In shared haemodialysis care (SHC), a structured interventional approach is implemented that helps patients receiving treatment in-centre to learn about and become more involved in their own care. Partnership is the key to success, along with an individualised approach to education. Healthcare professionals adopt the role of facilitators, rather than purely that of caregivers to passive patients.[3] Each individual patient is helped to develop knowledge and skills about their treatment, including learning to perform it themselves, in a way that feels comfortable to them.

Haemodialysis is divided into 14 constituent tasks encompassing the key steps required for preparation, delivery, and discontinuation (Figure 1). Patients' levels of competence and progress, from beginner to fully independent, are recorded using standardised training and educational materials.[4] Well-being is optimised by minimising the emotional impact of haemodialysis and improving safety, timeliness, and effectiveness of treatment. Key goals are to improve health literacy, patient activation, safety, experience, and outcomes.

FIGURE 1 | Shared care tasks

1. **Hand and access hygiene**
2. **Observations** (including temperature, weight, blood pressure)
3. **Preparing the vascular access pack for dialysis**
4. **Lining the machine**
5. **Priming the machine**
6. **Programming the machine**
7. **Preparing the fistula or graft**
8. **Priming line access**
9. **Needling AVF/AVG starting dialysis**
10. **Caring for myself during dialysis, including problem solving**
11. **Discontinuing dialysis—fistula**
12. **Discontinuing dialysis—line**
13. **Complete dialysis** (strip down machine, clear away, record observations)
14. **Administration of any medications** (EPO, low molecular weight heparin, etc.)

HOME HAEMODIALYSIS

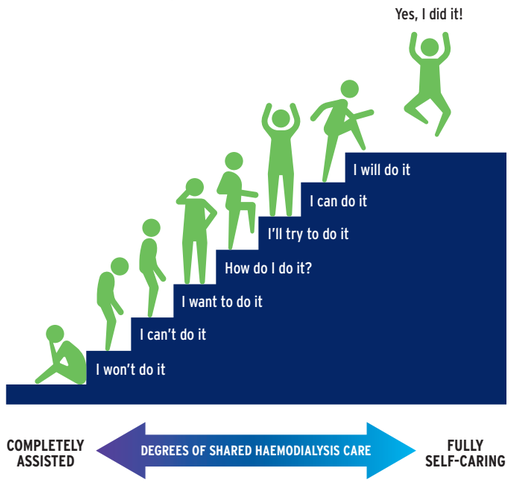
Patients performing haemodialysis at home are effectively fully self-caring. Home haemodialysis is associated with fewer complications, better survival, and improved quality of life compared to in-centre haemodialysis. These observations provide reassurance that in the in-centre setting, undertaking SHC and training patients to perform the treatment themselves are also safe.[5] Infection rates and mortality as a result of COVID-19 were significantly worse among in-centre patients compared to home patients. For some, being able to undertake more complex tasks, such as self-cannulation, may lift barriers to moving from the in-centre setting to home. Thus, SHC has the potential to increase opportunities for home haemodialysis uptake.[6]

PATIENT ACTIVATION

Patient activation is a modifiable measure of the degree of engagement and sense of control an individual has over their health. It is defined as "an individual's knowledge, skill, and confidence for managing their health and healthcare."[7] At the lowest level, patients may feel overwhelmed and disengaged, whereas through higher levels they take increasing control of their health. Lower patient activation is associated with poorer outcomes, including hospitalisation and loss of confidence in healthcare providers. In patients with kidney failure, characteristics associated with lower activation are older age, diabetes, and higher levels of deprivation.[8] Given that these characteristics are frequently observed, often in combination among in-centre haemodialysis patients, interventions that increase patient activation in this group may help improve outcomes.

SHC has the potential to increase activation by helping patients engage with their treatment at a pace that suits them, overcoming specific fears, promoting self-management, and reducing anxiety using small manageable steps (Figure 2).

FIGURE 2 | Small steps within shared care provide a framework to unlock potential



Source: Wilkie M, Barnes T. Shared hemodialysis care: increasing patient involvement in center-based dialysis. Clin J Am Soc Nephrol 2019;14(9):1402-4.

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SHC also offers benefits to healthcare organisations, as patient activation is recognised as a useful strategy for effective management of health resources and has been shown to improve the role of healthcare professionals (Figure 3).[9,10] Time saved performing routine tasks, for example, allows nurses to deal with more complex cases and to spend more time educating and supporting patients in a holistic manner.[11] Patient and professional satisfaction is also increased as the relationship is expanded to focus on the person, their life, and the patient's other health problems.[12]

HEALTH AND SOCIAL CARE POLICY AND GUIDANCE

The importance of patient involvement in their haemodialysis care has been increasingly recognised by the nephrology community and supported by policy makers. In the United Kingdom, the National Institute for Health and Care Excellence guidance has clearly indicated that patient choice and preferences must be considered throughout.[13] NHS England's service specification stipulates that dialysis providers must offer education about access to shared care training for patients and that this should include opportunities for self-care either in the dialysis facility or in the home.[14] At the clinical practice level, the UK Renal Association guidance recommends SHC, recognising the beneficial impact on all domains of health including enhanced safety that comes with education about infection control, equity of access, and patient experience.[15] The work of the SHC initiative in the United Kingdom has been adopted by Scarborough Health Network in Canada, who describes it as a change in their dialysis care philosophy.[16]

Getting It Right First Time (GIRFT) is a national initiative that undertook a comprehensive assessment of nephrology services in the UK to identify areas of unwarranted variation. The final report is expected to be released in 2021. Areas of need already highlighted include home dialysis. Prevalence averaged at 17%, but some renal units had up to 40% while nearly two-thirds of units were below 20% (Figure 4).[17] Given these findings, it is anticipated that clear recommendations will be made to increase SHC as a means of standardising and facilitating home dialysis uptake.

The National Kidney Federation has recommended that renal units in the UK reach a minimum prevalence of 20% of their dialysis population on home dialysis by the end of 2024.[18] Clearly, SHC will have to be central to any efforts to reach this target.

FIGURE 3 | Benefits of the SHC model for healthcare organisations

1. Provide patient choice through person-centred care, consistent with NICE guidelines
2. Improve patient experience through self-management and shared decision making
3. Enhance patient health literacy
4. Improve staff satisfaction, morale and retention and create new opportunities
5. Increase haemodialysis capacity through more effective resource use

SHAREHD

SHAREHD is a quality improvement collaborative of healthcare teams and patients designed to scale up shared haemodialysis care and includes 600 patients across 12 renal units in England.[19] Publication of results is expected in 2021. Baseline data revealed variation between units for the number of tasks undertaken by patients and complexity of tasks. A positive association between the number of tasks and patient activation was observed.[20] In addition, certain treatment-related tasks that have significant scope for increased uptake were key to becoming independent or transferring to home haemodialysis; one of these was self-cannulation.

One of the units involved in the original project was Hull Dialysis Centre, the largest NephroCare centre in the UK, caring for approximately 180 patients receiving dialysis. The programme enjoyed significant success and supported a thriving home haemodialysis programme.

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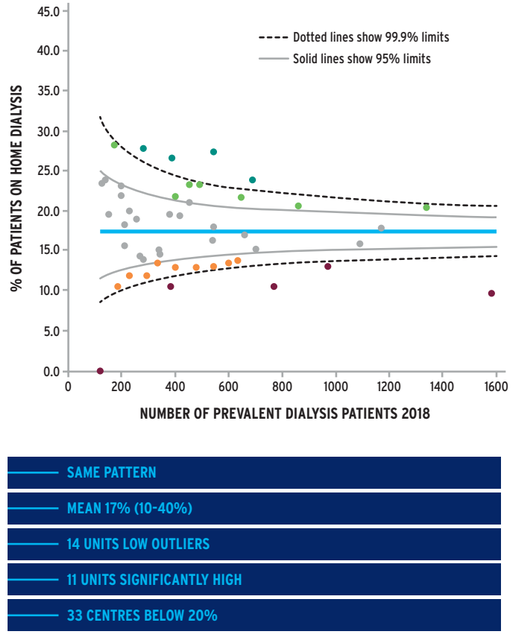
FIGURE 4 | Variation in prevalent home dialysis



Source: National Kidney Federation. Increasing home dialysis in the context of COVID-19 in the UK. Report. January 2021. kidney.org.uk/home-dialysis-campaign#Report.

Since 2018, significant efforts have been made to implement SHC throughout the NephroCare network in the UK. A benchmarking exercise in early 2021 (unpublished internal data) revealed that 76% of all NephroCare patients participated in their care at some level, with five clinics reporting over 10% of patients engaging with five or more tasks (Figure 5).

BARRIERS AND ENABLERS TO THE IMPLEMENTATION OF SHC

SHC is not currently standard practice. The reasons for this vary from centre to centre. Results of a study by SHAREHD identified key barriers and enablers to success from both a patient and healthcare professional perspective; our own experience indicates that organisational aspects also had an impact on uptake (Figure 6). Despite this, the importance of collaboration at all levels is clear. A culture of change involving patients and professionals working together is essential, along with a participative approach to education that considers patients' preferred learning styles. When confidence is low, or ambivalence and resistance are present, motivational interviewing techniques encourage patients to become active participants in the process by evoking their intrinsic motivations for participation.

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FIGURE 5 | Shared haemodialysis care participation

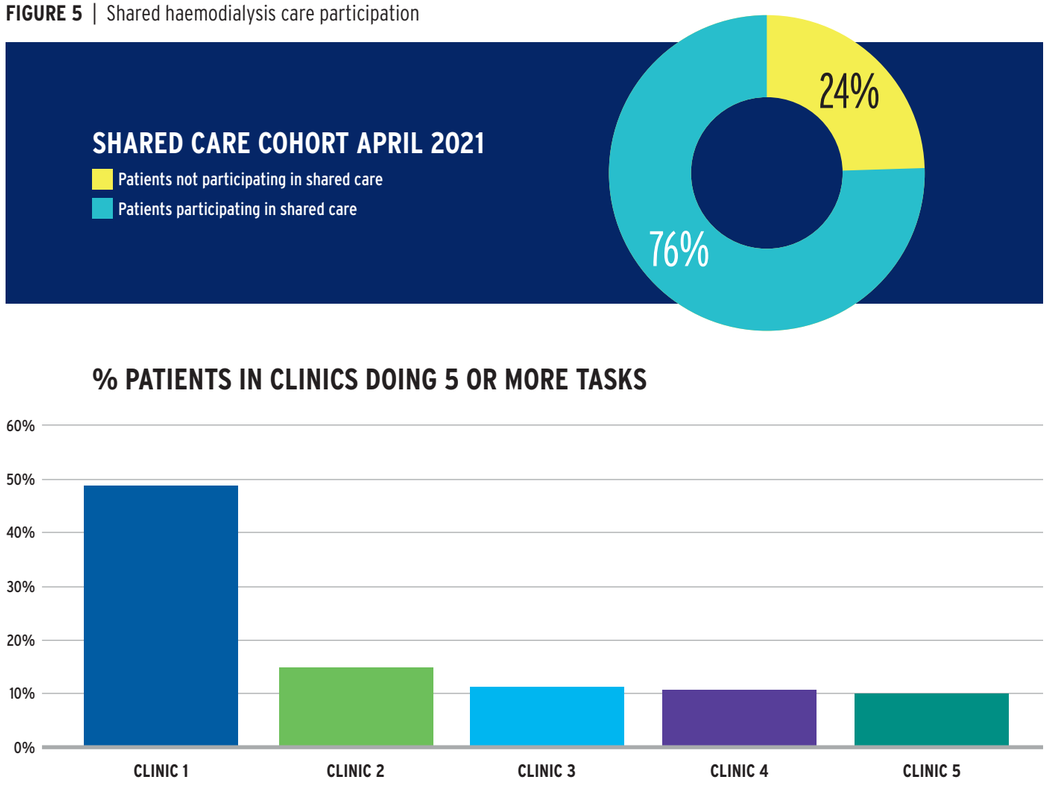


FIGURE 6 | SHC barriers and enablers of SHC

BARRIERS			ENABLERS		
PATIENT	HCP	ORGANISATIONAL	PATIENT	HCP	ORGANISATIONAL
Knowledge			Belief about capabilities	Belief in the patient's capabilities	Belief in the concept
Environmental context and resources			Goals	Training and support	Robust data
Perception of roles/identity			Optimism	Passion	Strategy
Emotions			Reassurance and reinforcement	Structure and process	Strong leadership culture

CONCLUSION

Empowering in-centre haemodialysis patients to become active participants in their care has the potential to enhance overall experience, increase patient activation, and therefore improve clinical, psychological, and social outcomes. There are also significant wider benefits to healthcare systems and organisations, including improved recruitment and retention through enhancing staff morale and job satisfaction, more effective use of resources, and reduction in costs associated with avoidable hospital admissions. Implementation is not without its challenges and requires commitment at all levels and a willingness to be flexible and innovative. Key success factors are collaboration between patients and healthcare professionals, and a paradigm shift from a traditional paternalistic model of care delivery to one of co-production and shared decision making.

KOLITHA BASNAYAKE, PhD, FRCP
Medical Director, UK and Ireland

Kolitha Basnayake is the country medical director for the United Kingdom and Ireland and is a practicing consultant nephrologist. He oversees clinical governance, with a strong focus on safety. Dr. Basnayake has led transformation and delivery of home dialysis and chronic kidney disease management services. His interests include improving quality in healthcare through patient choice, measuring patient-reported experiences and outcomes, and addressing variations in practice. His research background is in paraproteinaemic kidney diseases, for which he received his PhD from the University of Birmingham.

PATIENT-CENTERED VASCULAR ACCESS CARE

Milind Nikam, MBBS, MRCP, MD, FAMS, FRCP
Luca Neri, MD, PhD
Walead Latif, DO, MBA, CPE, FASDIN

Improving vascular access care is the Achilles' heel of hemodialysis; however, it is also the key to improving outcomes for individuals living with kidney disease. With a global community focused on identifying and evaluating potential advancements and innovation in vascular care and technology, Fresenius Medical Care is devoted to providing precise and personalized care.

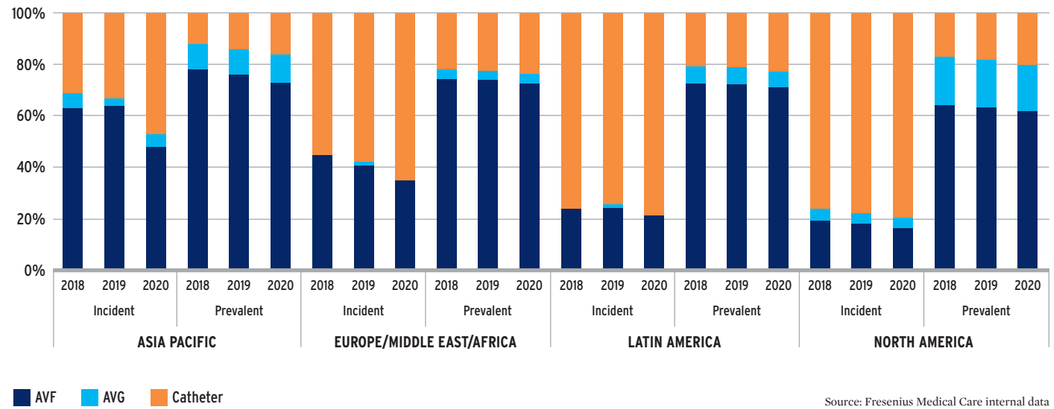
Vascular access is widely recognised as a critical aspect of dialysis care by all stakeholders, including individuals living with kidney disease and caregivers.[1] Unfortunately, challenges persist with vascular access care and outcomes, and significant interregional differences continue to exist.

Catheter use in incident patients is exceedingly high in both North America and Latin America, with over 75% of patients initiating hemodialysis (HD) with catheters. In the United States, HD initiation without a maturing arteriovenous fistula (AVF) or arteriovenous graft (AVG) increased from 60.2% to 65.2% between 2013 and 2018.[2] Catheter use is somewhat lower in incident patients in the Fresenius Medical Care Europe, Middle East, and Africa (EMEA) region, with over 60% initiating HD with a catheter in 2020. This practice is significantly lower in the Asia Pacific (AP) region, notwithstanding the economic challenges in many of the AP countries. However, even in AP, a steady increase in catheter use has been seen in incident patients since 2018 (Figure 1). Notably, AVG use is lower in the EMEA and Latin America regions even in the prevalent patients when compared with AP and North America. In 2020, there was a clear global impact of the COVID-19 pandemic on vascular access, with catheter use rising, especially in patients newly starting dialysis (Figure 1).

HIGH CATHETER USE IN HD PATIENTS

Catheter use is high, especially in incident patients, despite the knowledge that arteriovenous vascular acess are superior and despite initiatives focusing on increasing AVF use. USRDS and DOPPS data suggest that better transition (pre-HD) care planning that includes vascular access care improves arteriovenous access rates.[3,4] It is noteworthy that over 90% of AVFs are cannulated within one month in Japan, whereas only 70% of AVFs are cannulated within four months in the United States.[5] This observation may reflect the differences in success rates of AVF creation surgeries between these countries. Regardless of the high catheter rates, AVG usage remains low in incident patients, especially in the EMEA region.

FIGURE 1 | Catheter use in incident and prevalent patients



Source: Fresenius Medical Care internal data

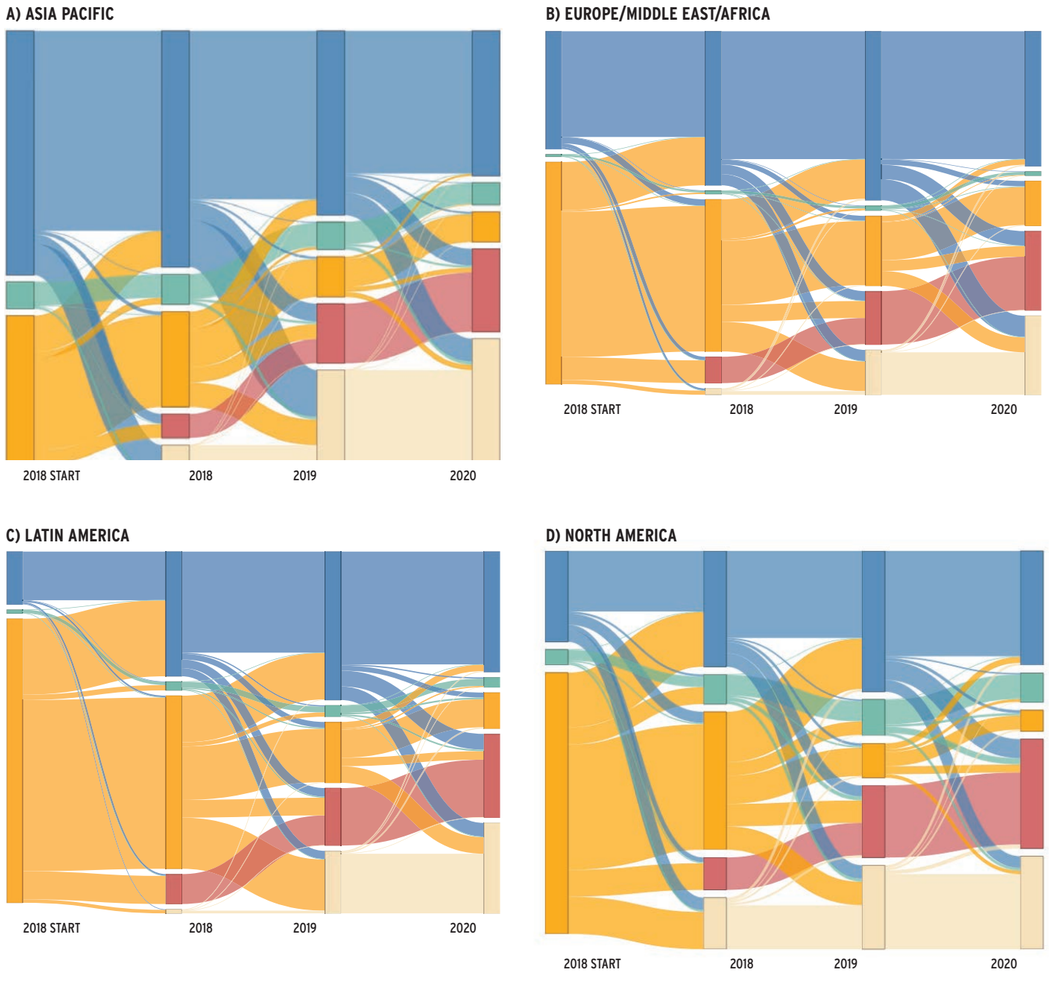
Regional variation is due to numerous factors including economic differences, patient characteristics, healthcare systems, and physician practice patterns. The Sankey diagrams (Figure 2) depict the outcomes of individuals who started HD in 2018 and serve as a stark reminder of the risks of initiating HD with a catheter.[6] Selection bias alone may not explain these findings.[7,8,9] The pandemic's impact on vascular access outcomes may have long-term effects on patient outcomes and healthcare costs.

EVOLVING APPROACHES TO VASCULAR ACCESS CARE

The high utilization of HD catheters, notwithstanding significant policy and practice changes, has prompted increased focus on catheter avoidance strategies, such as the catheter-last approach, which incorporates patient-centred and personalized care.[10,11,12,13]

Application of patient-centred care to minimise catheter burden requires, first, enhanced patient risk prediction algorithms that can more accurately predict end-stage kidney disease risk, timing, and arteriovenous vascular access success. Using these predictions and considering the healthcare systems, care approaches that allow treatment personalization by judicious and appropriate use of the available therapeutic armamentarium are needed, and those that are most suited to the patient's vascular access care needs considering their physical and biological characteristics. This should include consideration of AVGs, early cannulation graft materials, human-derived vascular conduits, percutaneous AVFs, and peritoneal dialysis (PD). As an example, an elderly individual who needs HD sooner and has high predicted AVF maturation failure risk may benefit from the use of AVGs, humanised vascular conduits, or indeed PD, depending on the goals and preferences of the individual.

FIGURE 2 | Sankey diagrams (A-D) demonstrating evolution of outcomes for those initiating HD in 2018 by vascular access type. Individual colours represent unique outcomes, and the width of the bands represents proportion of individuals with that access and/or outcome.



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Furthermore, it is important to prolong patency of arteriovenous access by more accurately predicting vascular access failure and having timely and effective interventions to maintain patency. In some circumstances, the approach may include creation of a new dialysis access, ideally prior to complete failure of the vascular access in use.

Timely referral for arteriovenous access creation is one of the critical steps needed to avoid the use of catheters for HD initiation. To this end, FME-EMEA has developed the Prognostic Reasoning System for Chronic Kidney Disease (PROGRES-CKD). PROGRES-CKD integrates 32 routinely collected clinical parameters into one summary risk score to predict kidney replacement initiation within six months with excellent accuracy (AUC=90%). PROGRES-CKD was deployed in the Czech Republic and Italy as an integral part of RenalSafeguard®, a holistic care programme aimed at preventing CKD progression, reducing cardiovascular risk, and improving transition management for NDD-CKD patients.

One additional pillar of decision making is accurate prediction of arteriovenous access success, pre- and post-creation, based on predictive algorithms that are able to incorporate broad data sources such radiological, physiological, sensor-based, metabolomics, and genomics data. FME-AP and the Renal Research Institute (RRI) collaborated with the UK-based Manchester Vascular Access (MANVAS) study to leverage the combination of metabolomics data with clinical, ultrasound, and laboratory information to predict AVF success, prior to creation.[14] Post-creation AVF maturation can be monitored with a non-invasive and semi-continuous monitoring approach developed by RRI that measures central venous oxygen saturation (ScvO2) and estimates upper body blood flow (eUBBF) using the Crit-Line® Monitor. The study demonstrated a clear relationship between AVF maturation and ScvO2 as well as eUBBF temporal dynamics, thus allowing for personalized cannulation and intervention plans.[15]

EVOLUTION IN ARTERIOVENOUS ACCESS CREATION

Innovative technologies introduced in recent years offer new options for vascular access care.[16] Foremost, several versions of early cannulation grafts are readily available and allow for cannulation within 72 hours of implantation. Early cannulation grafts may have primary and secondary patency and rates of infection, pseudoaneurysms, and thrombotic events that are comparable to polytetrafluoroethylene grafts.[17]

The latest advancement in the vascular access arena is the human acellular vessel (HAV) by Humacyte Inc.[18,19] The HAV is a bioengineered vessel cultivated and decellularized from antigens prior to implantation. The HAV can be readily shipped, refrigerated, and inserted when needed. After implantation, the HAV has been shown to adopt characteristics of native blood vessels (Figure 3). This is a first-of-its-kind technology and promises to provide patients with a truly personalised vascular access option lined by their own vascular cells, and is available off the shelf. In the right circumstances, the HAV may be considered a first-line vascular access option, one with no immune-reactivity and with low infection rates. The HAV is also being studied for other indications including vascular trauma, peripheral arterial disease, and paediatric cardiac surgery.

Lastly, the advent of percutaneous AVF creation has greatly enhanced and expedited AVF creation options for individuals on dialysis. Two such approaches are currently offered, and with the appropriate anatomy, a fistula can be created in an outpatient setting without the need for admission to the hospital. Current studies from percutaneous devices (Wavelinq by Bard and Ellipsys by Avenu) indicate high technical success rates, with primary patency rates equivalent to surgically created AVFs.[20,21,22] The advantages of a percutaneous AVF include the absence of surgical scars, early creation, and shorter time to surgery. However, AVFs created using percutaneous techniques may require specialised cannulation approaches.

EVOLUTION IN ARTERIOVENOUS ACCESS MAINTENANCE

Annually, 14% of AVFs and between 50 and 80% of AVGs fail acutely, primarily as a result of thrombosis associated with stenotic lesions.[23] Prevention of vascular access thrombosis is beneficial for many reasons, and thrombosis itself, regardless of other lesions, portends poor vascular access survival.[24]

Vascular access surveillance techniques such as access flow (Qa) measurements are commonly performed using dilution techniques. Despite the wide use of Qa measurements, these measurements have key limitations including the need for special equipment, insensitivity to haemodynamic changes during dialysis, and inaccurate detection of outflow stenosis.[25]

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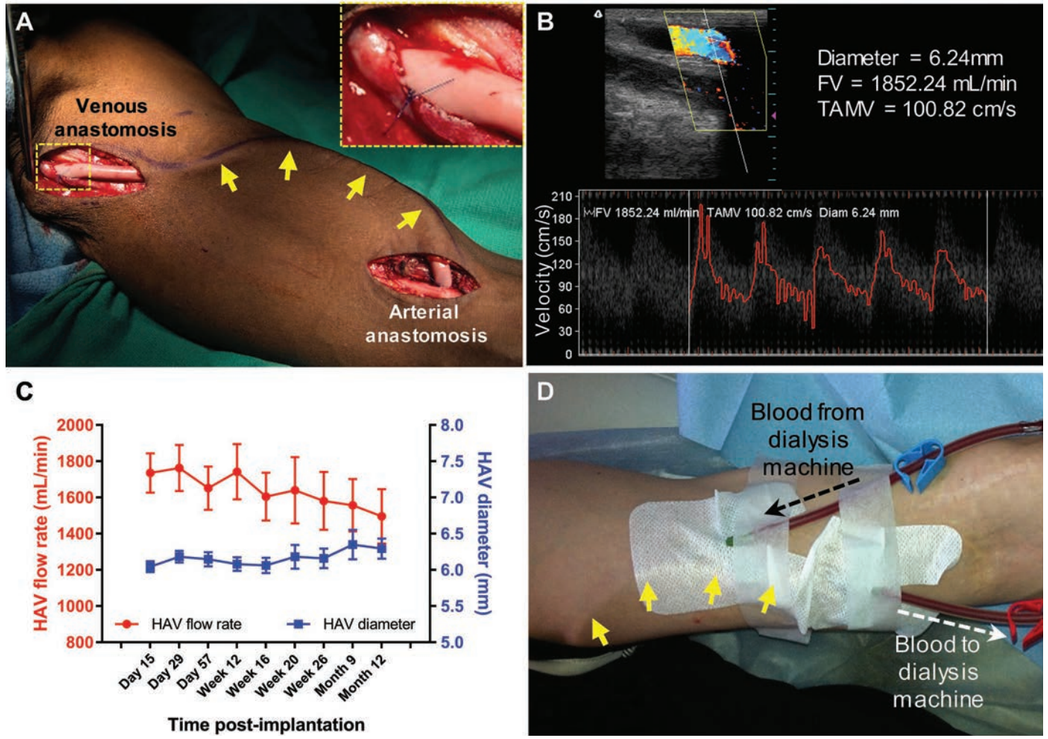
FIGURE 3 | Clinical implantation and hemodialysis access. (A) Intraoperative image of HAV implantation (tunneled under the skin; yellow arrows) in the upper arm for use as a dialysis access. (B and C) Postoperative Doppler ultrasound measurements of mid-HAV diameter, blood flow volume (FV), and time averaged mean velocity (TAMV) during follow-up within the patient population. (D) Photograph of cannulation of the subdermal HAV (yellow arrows) for hemodialysis.



Source: Kirkton RD, et al. Bioengineered human acellular vessels recellularize and evolve into living blood vessels after human implantation. Science Translational Medicine 2019 March 27;11(485)

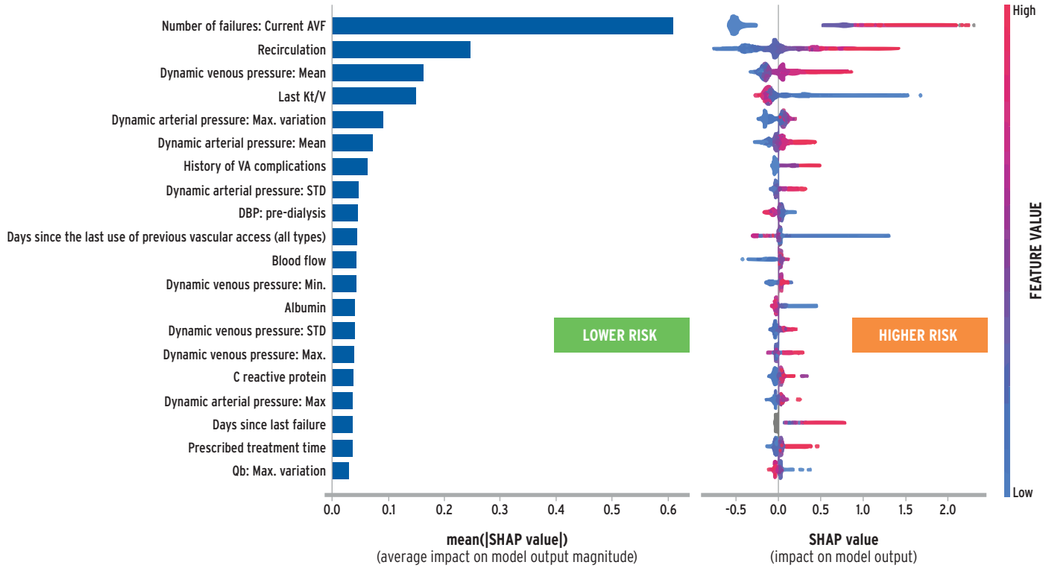
To enable personalized AVF management, Fresenius Medical Care is currently developing several applications of artificial intelligence to enhance surveillance and assist in medical decision making. FME-EMEA has trained and validated a risk stratification algorithm to predict AVF dysfunction. The AVF failure score (AVF-FS) has excellent discrimination properties (AUC=0.81) and is sensitive to changes in AVF functional parameters. The AVF-FS can be used to predict AVF failure based on routinely collected information and machine sensor data. In addition, the model may offer diagnostic clues based on ranking of variable risk impact (Figure 4). Additional advancements include stenosis detection by e-stethoscope and other sensor records and image recognition algorithms detecting and grading AVF aneurysms.[26]

Once detected, stenoses are primarily managed using endovascular techniques. Drug-coated balloons have shown promise in reducing re-stenosis rates in vascular access.[27,28] Newer drug coatings are also being evaluated.[29]

The calls for patient-centred and personalised vascular access care are welcome. The evolving approaches to vascular access decision making, creation, and preservation will contribute to a brighter future for individuals living with kidney disease.

To enable personalized AVF management, Fresenius Medical Care is currently developing several applications of artificial intelligence to enhance surveillance and assist in medical decision making. FME-EMEA has trained and validated a risk stratification algorithm to predict AVF dysfunction.

FIGURE 4 | An example of AVF-FS model output depicting the ranking of variable importance and its association with the failure risk



THE EXPERTS

MILIND NIKAM, MBBS, MRCP, MD, FAMS, FRCP

Vice President, Global Clinical Affairs, Fresenius Medical Care Global Medical Office
Head of Medical Governance and Digital Health, Global Medical Office, FME-Asia Pacific

Milind Nikam is a vice president in Global Clinical Affairs within the Fresenius Medical Care Global Medical Office. He leads medical governance and digital health in Asia Pacific. His interests are vascular access including device development, hemodialysis medical program management, and application of digital health, including AI for improving dialysis care. He joined Fresenius Medical Care in 2017 as a medical director for the Singapore office. Prior to that, he successfully set up one of the first interventional nephrology programs in Singapore. Dr. Nikam graduated in medicine from Mumbai with a prestigious gold medal and obtained his subsequent post-graduate training in internal medicine and nephrology in the United Kingdom, earning a doctorate in dialysis vascular access from the University of Manchester. Additionally, he is trained in endovascular interventional nephrology, one of the first in the UK.

LUCA NERI, MD, PhD

Director, Clinical and Data Intelligence Systems Advanced Analytics, Fresenius Medical Care Europe/Middle East/Africa

Luca Neri had led the Advanced Analytics Division at Fresenius Medical Care for the EMEA region since 2019. He joined Fresenius Medical Care as a medical data analyst in 2016. Dr. Neri has 15 years' experience in epidemiology and outcomes research, and has acquired a broad range of analytical and methodological skills in the field of outcomes research and advanced analytics. Before joining Fresenius, he held a postdoctoral position at the St. Louis University Center for Outcomes Research and was later appointed adjunct instructor of health management and policy at the same institution. Before joining Fresenius Medical Care, he served as scientific consultant and advisory board member for several commercial, science, and industry clients and academic institutions. His research interest focused on the epidemiology and outcomes of chronic kidney disease and other chronic medical conditions. He earned his medical degree at the University of Milan School of Medicine, where he also earned a specialty degree and a PhD in environmental and occupational medicine.

WALEAD LATIF, DO, MBA, CPE, FASDIN

Senior Consultant to the Chief Medical Officer, Fresenius Medical Care North America
Medical Director, Azura Vascular Care

Walead Latif leads FMCNA vascular access initiatives and is a member of the American Society of Nephrology and the American Society of Diagnostic and Interventional Nephrology. He graduated with honors from the University of Medicine & Dentistry Osteopathic School of Medicine at Rutgers University, and completed both an internal medicine residency and a nephrology fellowship at Beth Israel Medical Center in New York City. He is board-certified in internal medicine and nephrology.

IMPROVING ACCESS TO KIDNEY TRANSPLANTATION: A GLOBAL PERSPECTIVE

Benjamin Hippen, MD, FASN, FAST

Throughout the world, the need for kidney transplantation far outstrips the supply. Structural inequalities in allocation, risk-averse organ acceptance, poor care coordination, and waitlisting impediments are among the complex issues that hinder access. As part of its comprehensive vision for patient care, Fresenius Medical Care is taking a multifaceted approach to advancing transplantation. This includes a focus on patient care across the entire continuum of kidney disease and the development of novel organ preservation and regeneration technologies to expand the pool of kidneys available for transplant.

It is uncontroversial that for many patients with advanced chronic kidney disease (CKD) and end-stage kidney disease (ESKD), transplantation remains a preferred therapy, conferring better quality and longer life for patients compared with other kidney replacement therapies (KRTs), at considerably lower cost. Regnant immunosuppression regimens, conferring excellent long-term graft survival, have changed little over the last two decades.

Persistent challenges facing the global transplant community include impediments to waitlisting, fewer transplants among marginalized populations, barriers to communication, suboptimal care coordination, insufficient development of cost-effective care delivery models, and risk-averse organ acceptance behaviors.[1,2,3] The use of novel organ preservation and regeneration technologies to expand the pool of available organs is also needed. Finally, kidney transplantation is only successful if recipients are cared for in a manner that positions them to enjoy many years of graft survival.

Strategies permitting extended patient monitoring and novel therapeutic targets to prolong patient and graft survival are paramount to maximizing the "gift of life."[4] It is no accident that these goals are consonant with Fresenius Medical Care's vision to provide comprehensive care to patient populations across the entire continuum of kidney disease.

ABATING STRUCTURAL INEQUALITIES IN ACCESS TO TRANSPLANTATION

For vulnerable populations in the United States, equitable access to kidney transplantation has remained stagnant for two decades, despite record year-over-year improvements in organ procurement and transplantation, including during the COVID-19 pandemic.[5] Insufficient waitlisting rates have led some commentators to recommend an "opt-out" approach to transplant referrals: unless individual patients refuse or have an absolute contraindication, all would be referred for transplant by default.[6] Others recommend revisions to an allocation system that currently privileges "preemptive" waiting time. While the revision to this system in 2014 went some distance in reducing unequal rates of deceased donor kidney transplantation in Black Americans, preemptive waiting time is often not available to those who "present late" with ESKD, which in turn may recapitulate structural inequalities in waiting list prioritization.[7]

Revisions to the kidney allocation system designed to bring precision to assessments of organ quality (in the form of the Kidney Donor Profile Index, or KDPI)—in order to direct high-quality kidneys to young recipients—has not fully ameliorated access disparities.[8] Unintentionally, this same scoring system often resulted in "high" KDPI kidneys (suggesting a worse long-term outcome) being discarded more frequently compared to organ acceptance trends before the implementation of the KDPI system.[9] A study comparing organ acceptance and discard behaviors in the US and France showed that >17,000 kidneys discarded in the US would likely have been transplanted in the French transplant system.[10] Even an ostensibly positive development like the elimination of the three-year limit on Medicare coverage for 80% of the expenses of immunosuppression medications will still require recipients to find funding for the remaining 20% of the cost.

A recent shift toward a "geographic" allocation of kidneys to recipients within 250 nautical miles of the donor hospital may abate long-standing disparities in median waiting times for kidneys in areas of high population density. In essence, however, this solution is likely to extend median waiting times for all patients and increase the costs of organ procurement by causing more kidneys to be shipped longer distances. Whether the new allocation system effectively alleviates the structural inequalities in access to transplantation, or simply extends the waiting time for all candidates on the list without alleviating access disparities, remains to be seen.

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To improve access and increase the total number of kidney transplants performed, and to improve access to kidney transplantation for patients around the world, Dr. Hippen and his team will focus on:

- Designing care models to improve communication and care coordination between general nephrologists, dialysis providers, and transplant centers
- Implementing workflow streams to improve the efficiency and timeliness of the multidisciplinary transplant evaluation, while bringing transparency to the process for patients and healthcare providers
- Identifying best practices in organ acceptance processes and patient care models from transplant centers around the world, and developing a toolbox suitable for transplant programs globally
- Integrating kidney transplantation into value-based care arrangements with private payors to improve patient access to transplantation, while reducing healthcare expenditures for public and private payors
- Identifying, codifying, and promulgating novel innovations in organ procurement, including developing freestanding organ procurement centers, exploring new technologies in organ preservation and organ regeneration, and supporting the mission of organ procurement organizations through regulatory and policy reforms
- Identifying pharmaceutical and medical device innovations that render kidney transplantation safer for patients and prolong allograft survival

Novel allocation schemata will only be of theoretical interest for the far too many patients who remain on the outside of the waitlisting system looking in. In many countries, living donor kidney transplantation is a mainstay, reflecting a limited infrastructure to accommodate organ procurement from deceased donors, often compounded by the absence (or relatively recent enactment) of a legal and policy framework governing organ procurement and allocation. For example, India passed the Transplantation of Human Organs Act in 1994, a response in part to reports of India serving as a global nidus of organ trafficking. Twenty-five years later, nearly 90% of all kidneys and almost three-quarters of transplanted livers in India are still procured from living donors. For the most part, organ transplantation is only available to those in the private healthcare system, underscoring that policy reforms are necessary but not sufficient conditions for success.[11]

The need for kidney transplantation far outstrips the available supply around the world. For patients enduring the worst vicissitudes of the social determinants of health, addressing insecurities in food, water, housing, and transportation, as well as bridging the digital divide, is far more salient than novel organ preservation technologies or organ allocation debates. Australia boasts an impressive five-year patient and graft survival rate, which has been attributed to multidisciplinary teams devoted to long-term care, a robust single-payor system, and an outcomes tracking system that feeds back to transplant programs; however, even Australia struggles to equitably serve the Aboriginal population with ESKD.[12,13]

It is too heavy a lift to rely on care coordination to address inadequate social infrastructure, but a reasonable place to begin is to design, scale, and implement technologies to enable virtual assessments and patient tracking technologies that meet and provide clinical services to patients "where they live" rather than "where the doctors work." The value of expanding "telemedicine" capabilities and artificial intelligence tracking tools is in advancing primary and secondary efforts to delay the progression of CKD, provide early-warning systems for clinical deterioration, and provide an efficient means of tracking entire populations of patients who are hoping to keep their transplant for as long as possible.

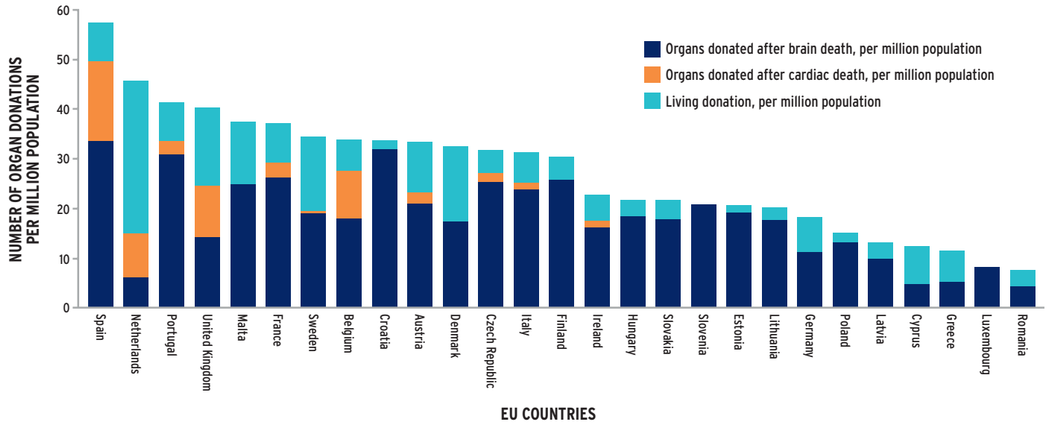
To improve access to transplantation, population-level health management and patient tracking tools can identify clinically appropriate candidates early, provide comprehensive education about the benefits of transplantation, target subpopulations for assistance in identifying living donor candidates, schedule needed testing in a rational manner that avoids unneeded repetition and redundancy, provide an efficient means of tracking the progress and ongoing clinical suitability of waitlisted patients, and ensure that no viable candidates "get lost" in the evaluation process, as too many often do. The key to ameliorating access disparities is to ensure no transplant candidate is consigned to the shadows. As with all such technologies, implementation will need to be guided and checked by an ethical framework that safeguards autonomy and privacy and foregrounds close attention to patients' treatment preferences, efforts that will inexorably be a process and not a single event.[14]

IMPROVING ORGAN PROCUREMENT RATES AND ORGAN ACCEPTANCE BEHAVIORS

As a recent "road map" for improvement published by the European Kidney Health Alliance showed, ample opportunities remain to improve organ procurement rates between and within countries (Figure 1).[15] The COVID-19 pandemic exposed the resilience of organ procurement regimens in some parts of the world and the vulnerability of many others. Conspicuously, after a brief pause in March to April 2020, organ procurement rates in the US rebounded to record levels by the end of 2020. In France and elsewhere, the pandemic had a catastrophic effect on organ procurement rates.[16] It is believed that similar depressions in organ procurement have transpired globally, and a systematic accounting of this trend across multiple countries is a focus of ongoing study.[17] Learning the lessons of how the US managed to recover and remain successful in procuring organs during the pandemic will be instructive for organ procurement systems globally. One approach is to procure organs and tissues outside the traditional hospital system, increasing capacity for needed intensive care unit beds and operating rooms.[18,19] This could prove important not only for future pandemics, but for the future of organ and tissue procurement around the world.

Learning how to successfully expand access to organ transplantation will be for naught unless more organs are procured. In the US, a 15-year regulatory regime requiring transplant centers to achieve a high threshold for patient and graft survival under threat of decertification from Medicare finally came to an end. This regulatory policy likely led to demonstrable risk aversion regarding candidate listing practices and organ acceptance behaviors, possibly contributing to a durable 20% rate of organ discard in the country.[20] While not all the discarded

FIGURE 1 | Organ procurement comparison for European countries



Source: Vanholder R, et al. Organ donation and transplantation: a multi-stakeholder call to action. *Nat Rev Nephrol* 2021;17(8):554-68.

kidneys were likely viable, prudent and targeted regulatory reform is needed to encourage transplant surgeons to accept and transplant ostensibly "higher risk" kidneys without risking regulatory or financial jeopardy.

So-called "presumed consent" or "opt-out" policies in Europe, in which consent to organ procurement after brain death is "presumed" for policy purposes, are variably defined and enforced, and have not been shown to improve organ procurement rates compared to the traditional "opt-in" consent model extant in the US.[21]

One promising avenue is to build on the success of the European Union's European Senior Program (ESP), which improved access to transplantation for elderly recipients by explicitly allocating kidneys from older donors (which might otherwise have been discarded) to them.[22] While expanding the organ pool is an important strategy, it will not be a wholesale panacea: a recent analysis from Europe suggests that extending elderly donors after circulatory death may not routinely confer survival versus maintenance dialysis.[23]

In addition, identifying key demographic differences in high-KDPI kidneys will be key to learning the right lessons about more aggressive organ procurement. A recent retrospective review of utilization of and outcomes from using high-KDPI kidneys in the UK showed that high-KDPI scores in UK donors were often driven more by advanced age, rather than the combination of advanced age and comorbidities such as hypertension and diabetes.[24] Given the limitations of the KDPI score as a predictive tool (the KDPI only has a c-statistic of 0.6 for predicting graft survival), the need for more sophisticated prognostic tools to make distinctions between subcategories of "high risk" kidneys is urgent.[25]

STEWARDSHIP OF THE "GIFT OF LIFE": EXTENDING LONG-TERM PATIENT AND GRAFT SURVIVAL

Improving access is also for naught without longevity. In the US, a conflagration of quality metrics focused on one-year outcomes, a culturally bound sharp separation of duties between transplant centers and general nephrologists, and a payment model that rewards procedures more than longitudinal care all conspire to make the long-term care of transplant recipients no one's dedicated responsibility. Given a recent analysis that showed the burden of premature graft failure in the US in 2017 resulted in $1.37 billion of additional costs and a reduction of nearly 30,000 additional quality-of-life years, implementing population health interventions to extend patient and graft survival harmonizes good patient care with return on public investment.[26]

Happily, there are new potential therapeutic targets for extending allograft survival, including some early data suggesting that sodium glucose co-transporter 2 inhibitors (SGLT-2i) may be of benefit in transplanted patients.[27] Providing this end-to-end care for patients across the continuum is integral to the future of integrated patient care models that will be pioneered by Fresenius Medical Care.

BENJAMIN HIPPEN, MD, FASN, FAST
Senior Vice President, Global Head of Transplant Medicine, Global Medical Office

Benjamin Hippen, MD, FASN, FAST, is clinical professor of medicine at the University of North Carolina at Chapel Hill School of Medicine. Prior to joining Fresenius Medical Care, Dr. Hippen was a general and transplant nephrologist with Metrolina Nephrology Associates, P.A., a 38-nephrologist private practice in Charlotte, North Carolina, where he served as a medical director of a large in-center dialysis facility, and previously served as medical director of a large home therapies unit. He currently serves on the board of directors of InterWell Health, a nephrology-focused population health management company. He previously served on the board of managers for the Carolinas Physician Alliance, an accountable care organization operated by Atrium Health. The author of more than 50 peer-reviewed manuscripts focused on ethics and public policy issues in nephrology and transplantation, Dr. Hippen previously served as an associate editor for the *American Journal of Transplantation* and on the editorial board of the *Journal of Medicine and Philosophy*.

PATIENT-CENTERED CARE: CREATING A FRAMEWORK FOR GLOBAL QUALITY MEASUREMENT

Jeffrey L. Hymes, MD
Katrin Köhler, MSc, MBA

The treatment of end-stage kidney disease is complex and resource intensive. The patient population is among the most fragile, with multiple comorbid conditions that complicate kidney replacement therapy. Across the world, Fresenius Medical Care must meet this challenge of regions and locales with widely differing financial resources, languages, healthcare systems, and information technology maturity. A core function of the Global Medical Office (GMO) is to identify opportunities for improvement of care. To that end, the GMO has initiated a global program to understand regional factors affecting quality performance and reporting, identify successes, and organize for further improvement.

KEY PERFORMANCE INDICATORS

Key performance indicators of quality in end-stage kidney disease (ESKD) care are made public by a variety of authorities, including Kidney Disease: Improving Global Outcomes (KDIGO), the Kidney Disease Outcomes Quality Initiative (KDOQI), the Centers for Medicare and Medicaid Services (CMS), the European Dialysis and Transplant Association (EDTA), and others. Within Fresenius Medical Care, there has been substantial progress in adopting uniform definitions of quality care. These are embodied in the clinical quality score (CQS) in the United States and the balanced scorecard (BSC) in the Asia Pacific (AP), Latin America (LA), and Europe, Middle East, and Africa (EMEA) regions. Included in both sets are considerations of patient experience.

While these have traditionally focused on measurement of intermediate outcomes (e.g., dialysis adequacy, hemoglobin levels, central venous catheter rates), increased attention is now being paid to patient-centered outcomes, a model of care that respects the patient's experience, values, needs, and preferences in the planning, coordination, and delivery of care. Additionally, social determinants of health have significant influence on patient outcomes. These factors include access and quality of healthcare and education, economic stability, neighborhood and environment, and the social and community context in which our patients live.

IMPACT OF SOCIAL DETERMINANTS OF HEALTH

Access to healthcare has a profound influence on health and well-being. The availability of care, the frequency and duration of dialysis treatment, and therapy for the complications associated with ESKD are determined by payment models that vary greatly around the world. Even when universal healthcare coverage is available, the included services can vary widely. Mexico, for example, provides funding for dialysis through the Mexico Social Security Institute but limits treatment time to three hours. In India, the absence of affordable insurance may cause patients to elect to only dialyze twice a week. Social and political policies in South Africa limit public payment for dialysis to those suitable for transplant. Similar disparities exist in payment for treatment of associated conditions like anemia and metabolic bone disease.

In response to these restrictions, Fresenius Medical Care encourages longer treatments, the use of high flux dialyzers, and hemodiafiltration to maximize delivered dialysis. Conversations are held with payment authorities to emphasize the need for adequate treatment. To further reduce the cost of care, less complicated but effective dialysis systems are in development. Attention to fluid removal, guided by Fresenius Medical Care devices like the Body Composition Monitor, can reduce hospitalization for volume overload and lessen the impact of untreated anemia.

Trained nephrologists are essential to the provision of excellent care, and Fresenius Medical Care contracts with or employs these qualified experts as medical directors in most countries. In some regions, limited training in the specialty makes this more challenging, with the number of nephrologists per 1 million population ranging from 13 in Thailand to 45 in Italy. The best qualified nephrologists continue to be identified and recruited to supervise care directly.

DATA ANALYTICS AND QUALITY IMPROVEMENT

The components required to monitor and improve quality include common standards, uniform definition of patient inclusion, robust data collection, sophisticated analytics, and effective communication of outcomes. Like dialysis technology itself, these capabilities have evolved over time. The variable evolution of these capabilities in different countries can pose a challenge to quality assessment and comparison. Fresenius Medical Care continues to make progress in the use of electronic medical records (EMR) in all regions. This includes EuCliD and myCompanion (EMEA, AP, LA) and eCube Clinicals, PatientHub, and PhysicianHub (US).

Disparities in interfaces between automated dialysis machines and databases, as well as disparities in the ability to download laboratory results, still exist but are rapidly declining. Currently the performance data generated by these systems is used to direct quality improvement activities specific to each region and country. In the next year, it will also serve as the basis for uniform education and training in Clinical Quality Improvement (CQI) for all medical directors and nursing leaders.

To take advantage of the enormous data accumulated through Fresenius Medical Care's IT systems, clinical data analytics capability has been aggregated and includes experts across all regions. Not only are outcomes evaluated to guide quality improvement, but predictive modeling is being adopted to anticipate and avoid events like hospitalization and vascular access failure. The combined impact of consistent data collection expert analysis was demonstrated in a recent publication describing improved patient survival utilizing the BSC in NephroCare in Italy.[1]

MANAGING QUALITY PERFORMANCE EXPECTATIONS

Given the disparities in resources and regional maturity, it is logical to ask how quality performance should be measured. The answer lies in a sensitive assessment of each country's current ability to achieve the internationally recognized key performance indicators embedded within all Fresenius Medical Care clinical systems and a determination of a path to incremental change. As an example, in places where twice weekly dialysis is common, we should expect data collection to be complete, the calculation of dialysis adequacy to be appropriate to the actual frequency of dialysis, and all modifiable aspects of the prescription to be optimized. This path requires completion of electronic medical record and interface deployments, recruitment and education of the best nephrologists, consistent appraisal of business priorities, uniform training in CQI, and open communication and support among regions. The GMO is committed to this course and will continue to advance the global alignment toward quality improvement and sustainable patient-centered care in collaboration with internal and external partners.

JEFFREY L. HYMES, MD

Executive Vice President, Global Head of Clinical Affairs
Chief Medical Officer, Fresenius Kidney Care North America

Jeffrey Hymes joined FMCNA in 2007 after three decades in nephrology practice and governance. He co-founded REN Corporation in 1986 and National Nephrology Associates (NNA) in 1998. He served as NNA's president and chief medical officer from 1998 to 2004. He served as president of Nephrology Associates, a 32-physician nephrology practice in Middle Tennessee, from 1989 to 2012. Dr. Hymes is a former member of the Renal Physician Association's board of directors. He is a graduate of Yale College and the Albert Einstein College of Medicine, completed his medical internship and residency at Yale New Haven Medical Center, and did subspecialty training in nephrology at Boston University. Dr. Hymes is board certified in internal medicine and nephrology, and previously certified in critical care.

KATRIN KÖHLER, MSc, MBA

Vice President, Global Medical Office Strategy and Operations, Fresenius Medical Care

Affiliated with Fresenius Medical Care since 2003, Katrin Köhler leads Global Medical Office Strategy and Operations for the Global Medical Office, driving cross-regional medical strategies and synergies on a global level. She formerly served as director of Strategic Medical Development and Medical Innovation and Portfolio Management for Fresenius Medical Care Europe/Middle East/Africa. She has worked closely with the company's global business and medical leaders on key strategic initiatives, and has broad experience across the company's business regions. She graduated with her master of science degree, specializing in innovation and business creation with a major in business administration, from Sweden's Jönköping International Business School. She holds dual master's degrees in international management and economics from the European School of Business at Reutlingen in Germany and the Lancaster University Management School in the United Kingdom. Katrin is the global program lead of the Sustainability Area "Patients—Quality of Care," which has been assigned to the Global Medical Office by Fresenius Medical Care's Management Board.

INNOVATION AND TRANSFORMATION

Encourage technologies that support our patients, including connected devices for home use, monitoring and communications apps, telehealth, and health records integration.

CRITICAL CARE AT FRESENIUS MEDICAL CARE

Michael Etter, MD, MBA, MPH, PhD

Fresenius Medical Care has established critical care as a key pillar for strategic growth. To help realize the company's long-term vision, the Global Medical Office has created an interdisciplinary critical care therapy team to guide the development new diagnostic tools, advanced data analytics and AI capabilities, innovative devices, and other critical care delivery improvements.

Critical care, or intensive care, is the medical specialty that treats life-threatening conditions, which are often accompanied by organ and/or central nervous system dysfunction. Critical illness necessitates highly complex medical care and may require the need for multi-organ support. The primary goal of critical care is to provide physiologic support while the underlying disease or injury is treated and, in that regard, may be considered by some as "bridging" rather than "healing."

Despite significant improvements in critical care medicine over the past decades, the number and utilization of critical care beds is still on the rise.[1] Multiple factors may contribute to the observed increase, including aging populations, higher prevalence of coexisting chronic illnesses, broader use of immunosuppressive therapies, higher utilization of medical procedures and devices, and the spread of multi-drug-resistant pathogens. Despite the increasing numbers of critically ill patients, the overall mortality associated with critical illness has declined—e.g., age-standardised sepsis mortality decreased by 52.8% from 1990 to 2017.[2] This may be related to a better understanding of pathophysiology, improvements in ICU management (e.g., acute respiratory distress syndrome protocols, prevention of bloodstream infections), innovations in treatment, and advances in extracorporeal organ support.

CRITICAL CARE: STRATEGIC VISION FOR THE RENAL CARE CONTINUUM

In 2020, the company established critical care as one of three strategic pillars for the company's successful long-term growth (Figure 1). This vision also includes the renal care continuum, the critical care space; and complementary assets, innovations that can advance the company's work in kidney and critical care. Critical care as a core domain recognizes the importance of multi-organ support as a key component of care for those with critical illness. Today, the Fresenius Medical Care portfolio includes extracorporeal kidney, heart, and lung support. Kidney replacement therapies for acute kidney injury in the ICU include the company's multiFiltratePRO CRRT device and the NxStage System One. Integration of the Xenios company into the Fresenius Medical Care portfolio in 2016 expanded extracorporeal support to include heart and lung therapies such as extracorporeal membrane oxygenation (ECMO) and decarboxylation (extracorporeal CO2 removal, or ECCO2R) systems. In addition to providing critical care services in selected countries, Fresenius Medical Care also provides a portfolio of critical care products throughout the world (Figure 2).

FIGURE 1 | Critical Care is one of Fresenius Medical Care's three strategic pillars

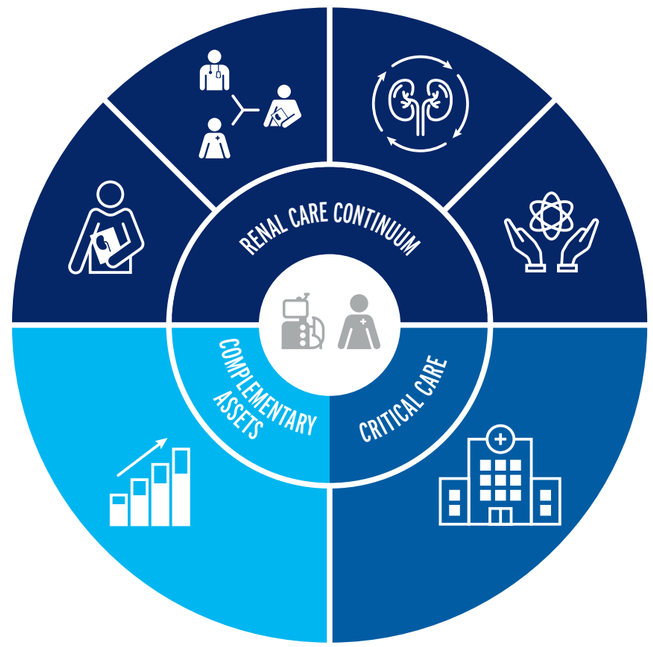


FIGURE 2 | Critical Care Portfolio Offered by Fresenius Medical Care

Fresenius Medical Care multiFiltratePRO

The multiFiltratePRO is a state-of-the-art CRRT platform that offers advanced therapy functions like regional citrate anticoagulation and therapeutic plasma exchange.

CURRENT AVAILABILITY:
Asia Pacific | EMEA | Latin America | North America

NxStage System One

NxStage System One is designed to provide simplicity and versatility that allows the delivery of kidney replacement therapy throughout the continuum of patient care, with a focus on prolonged intermittent kidney replacement therapy.

CURRENT AVAILABILITY:
North America | EMEA (indicated for home therapy only)

Xenios Console

The Xenios Console offers therapies for those suffering from cardiac and pulmonary insufficiency. This dedicated technology combines both heart and lung support on one single platform offering applications from effective CO2 removal (ECCO2R) to complete oxygenation (ECMO).

CURRENT AVAILABILITY:
Asia Pacific | EMEA | Latin America | North America (branded as Novalung Console)

ExThera Medical Seraph 100

The Seraph 100 Microbind® Affinity Blood Filter contains ultrahigh molecular weight polyethylene beads with end point-attached heparin and is approved for the reduction of pathogens from the bloodstream.

CURRENT AVAILABILITY:
EMEA | Latin America

CytoSorbents CytoSorb

This extracorporeal cytokine filter contains innovative porous polymer beads that are able to remove cytokines and many other inflammatory mediators, such as free hemoglobin, bacterial toxins, myoglobin, and activated complement.

CURRENT AVAILABILITY:
EMEA | Latin America

Critical care as a core domain recognizes the importance of multiorgan support as a key component of care for those with critical illness. Today, the Fresenius Medical Care portfolio includes extracorporeal kidney, heart, and lung support.

CRITICAL CARE OPPORTUNITIES

Fresenius Medical Care has identified the following opportunities to further improve critical care therapies: the development of innovative devices; automation of processes related to the function and operation of medical devices; optimization of medical device usability; access to intensive therapy expertise (e.g., continuous kidney replacement therapy, ECMO, apheresis support); expansion of ICU point-of-care testing; and enhanced clinical decision support.

To lead these efforts, the Global Medical Office at Fresenius Medical Care has established a critical care therapy team whose medical expertise spans multiple specialties including cardiac surgery, surgical and medical critical care, and anaesthesiology. With its comprehensive and diverse views on the various disease pathologies and therapeutic approaches within the ICU, the team will provide medical guidance for the development and execution of the critical care strategy and collaborate with a network of external advisors around the globe.

Initial areas of focus include the development of less invasive ECCO2R for treatment of acute exacerbation of chronic lung disease and pulsatile flow during ECMO therapy (i-COR) to support cardiac conditions that may benefit from synchronized cardiac support. One of the key challenges for multi-organ extracorporeal support is vascular access: support systems that can use a single vascular access are an important area of development within the company. The critical care team plans to explore opportunities to improve diagnostic and patient surveillance at the point of care and advanced data analytics and artificial intelligence capabilities to improve medical decision making.

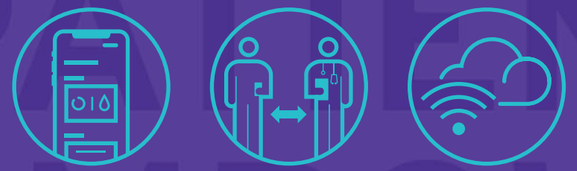
In summary, the development of critical care therapies will include the continuous strengthening and expansion of the company's current extracorporeal organ support technologies and has the potential to improve critical care in communities around the world.

Initial areas of focus include the development of less invasive ECCO2R for treatment of acute exacerbation of chronic lung disease and pulsatile flow during ECMO therapy (i-COR) to support cardiac conditions.

THE EXPERT

MICHAEL ETTER, MD, MBA, MPH, PhD
Senior Vice President, Global Head of Critical Care Therapies
Chief Medical Officer, Fresenius Medical Care Asia Pacific

Michael Etter joined Fresenius Medical Care Asia Pacific in 2009, leading the Medical Office and the Medical Affairs departments. As chief medical officer, Dr. Etter oversees all medical aspects of the medical device and pharmaceutical business segments as well as the healthcare services provided in dialysis clinics, hospitals, and other medical institutions within Asia Pacific. In addition to his medical support related to CKD and ESKD across the portfolio of healthcare services and products provided in Asia, Dr. Etter's clinical focus is on critical care medicine and related extracorporeal therapies. He holds board certifications in surgery, emergency medicine, and medical quality management. He is a graduate of the Technical University Munich Medical School in Germany and holds dual master's degrees in business administration and public health.



CONNECTED HEALTH AT FRESENIUS MEDICAL CARE

Stefano Stuard, MD, PhD
Claudia Amato
Shelly Nash, DO, FACOOG

Fresenius Medical Care's connected health platforms are designed around patient needs to support care in the most proactive and efficient manner possible. These platforms empower patients and clinical staff through a digital ecosystem enabling connections among patients, healthcare professionals, medical devices, technical operations, and customer service. Keeping patients and care teams connected, with access to recent treatment data, is vital in order to continuously improve medical outcomes, user experience, and effectiveness of care.

The COVID-19 pandemic advanced an era in which nearly every activity of life went digital. In healthcare, the increased availability of new technologies has allowed for better delivery of quality of care at lower costs, creating value for all stakeholders involved. Digital transformation has helped healthcare providers streamline operations to understand patient needs and deliver required services. Technological devices provide vast amounts of data that can be analyzed to facilitate real-time decisions for more personalized medical care. With the rise of technological innovations, patients are becoming active decision makers in their medical care process and healthcare operations and processes are improved.

In the Europe, Middle East, and Africa (EMEA), Asia Pacific (AP), and Latin America (LA) regions, Fresenius Medical Care has three main elements that form the connected health platform in over 20 countries: the well-established EuCliD clinical quality data warehouse, the PD Patient Monitoring solution, and the MyCompanion patient app. In the near future, all elements of the digital ecosystem in EMEA, AP, LA will be summarized under the umbrella brand theHub.

EUCLID CLINICAL QUALITY DATA WAREHOUSE

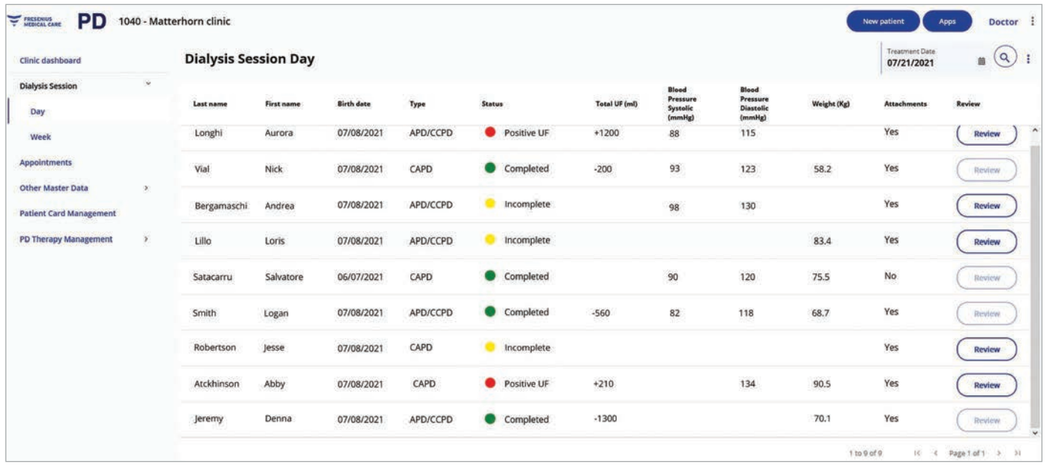
In the EMEA region, Fresenius Medical Care implemented EuCliD®, a central digital warehouse for clinical data across the company's NephroCare network of dialysis clinics.[1] EuCliD allows data management processes to be standardized into a consolidated and unified source of evidence while reducing the costs for evidence generation.[2]

EuCliD availability in EMEA clinics was a key factor for the development of efficient and effective continuous quality improvement (CQI) programs. The clinical quality improvements generated by combining digital transformation, new medical governance strategies (medical patient review, or MPR), and clinical target achievement are associated with better quality of life among dialysis patients.[3] Moreover, a large historical cohort study showed that the CQI-MPR programs, leveraged by digital transformation, enhanced the intermediate clinical endpoints and patient rate of survival in Fresenius Medical Care NephroCare clinics in the EMEA region.[4]

THE PD MONITORING SOLUTION

The PD Patient Monitoring Solution is a cloud-based solution for home dialysis designed to keep patients connected to their care teams, with better access to recent treatment data. By making this data more easily accessible to clinicians, care teams can resolve treatment issues earlier and reduce unnecessary hospitalizations. The platform enhances clinical workflows with advanced therapy programs that are designed to improve patient outcomes and nurse productivity. Using a connected health platform such as the PD Patient Monitoring Solution can reduce hospitalizations and minimize technique failure.[5] Evidence also suggests that connected health is associated with a 15% reduction in patient dropout and increased longevity on peritoneal dialysis (PD) by 3.5 months (Figure 1).[6]

FIGURE 1 | The PD Patient Monitoring Solution HCPs portal



Fictionalized patient information

The PD Patient Monitoring Solution ensures uninterrupted communication between patients at home and healthcare professionals (HCPs) in the clinic (Figure 2).

The PD Patient Monitoring Solution is a cloud-based digital ecosystem. With a simple Internet connection, users can store and access their data online in a fast, easy, and safe way. HCPs have a single place to manage all PD patients, track progress, and monitor prescribed therapies: the PD Patient Monitoring Solution HCPs portal. The PD Patient Monitoring Solution also relies on hardware devices—the Cycler, the Card Reader, and the Gateway—that enable bidirectional connectivity between the Cycler at home and The PD Patient Monitoring Solution HCPs portal in the clinic . Patients are empowered to track their daily treatment data and vitals to self-manage their chronic kidney disease using the PD Health Tracking App, which is also connected to the cloud via Wi-Fi, enabling communication between patients and healthcare professionals.

The PD Patient Monitoring Solution is an innovative, paperless, digital solution that provides access to detailed, organized patient data in a timely manner. It allows healthcare professionals to focus on delivery of high-quality care for patients who choose home-based treatment.

MYCOMPANION APPLICATION

The myCompanion app is Fresenius Medical Care's health solution for in-center hemodialysis patients. It allows patients to access their treatment data, track values of critical lab results, and access medication information. The app provides patients with additional information about their condition, treatment plan, and

The PD Patient Monitoring Solution is an innovative, paperless, digital solution that provides access to detailed, organized patient data in a timely manner. It allows healthcare professionals to focus on delivery of high-quality care for patients who choose home-based treatment.

treatment results, and facilitates more informed discussions with their healthcare team. myCompanion empowers individuals living with kidney disease to take a more active role in their disease management. The app also provides a holistic learning curriculum that includes engaging content to help patients learn about kidney disease (Figure 3).

Ultimately, improved data sharing will provide healthcare professionals with constant updates on the health of their patients, even before the next contact occurs. This establishes and supports a trusting, collaborative relationship between patients and their care team.

FIGURE 2 | The PD Patient Monitoring Solution ecosystem ensures communication between patients and healthcare professionals

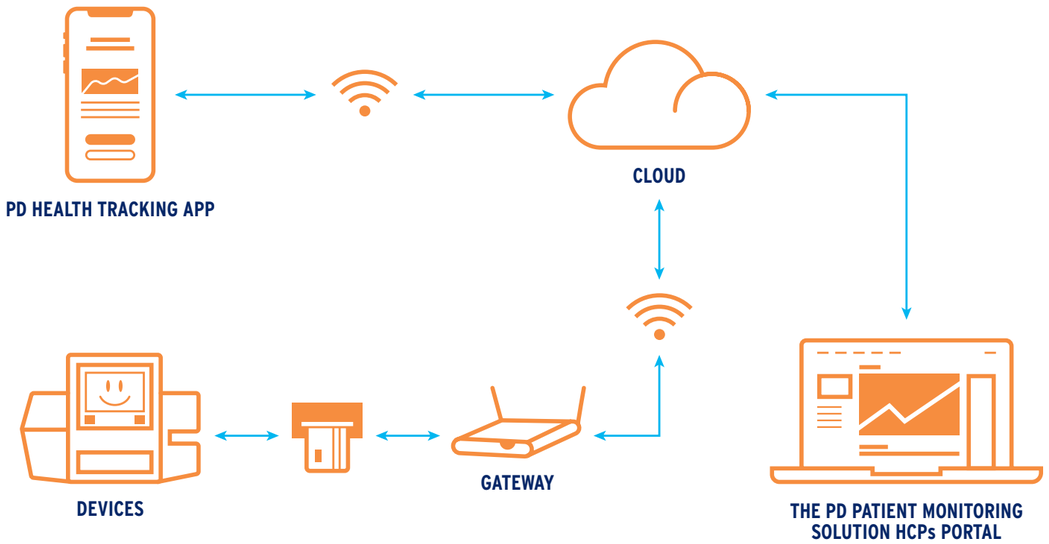
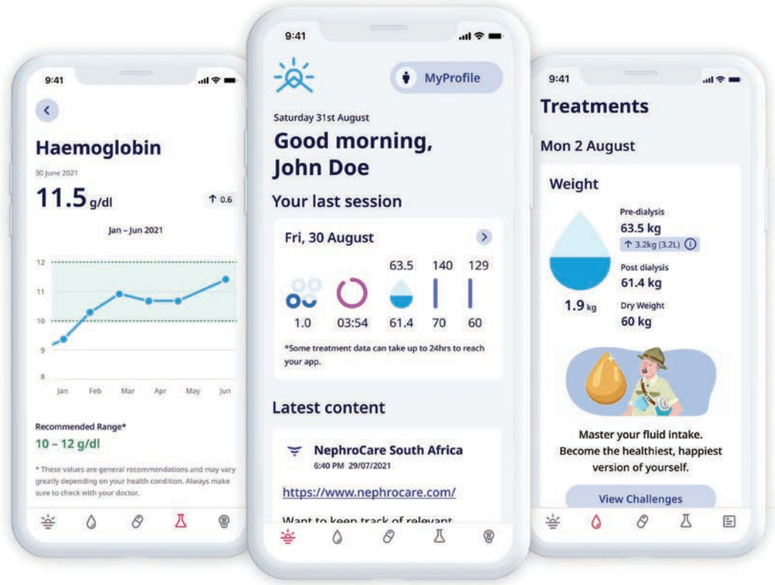


FIGURE 3 | myCompanion application



Fictionalized patient information

STEFANO STUARD, MD, PhD

Senior Vice President, Chief Clinical Officer, Fresenius Medical Care Europe/Middle East/Africa

Stefano Stuard supports the NephroCare medical leadership in his role as chief clinical officer for the EMEA region. He previously served as vice president and head of the EMEA Center of Excellence for Clinical and Therapeutic Governance, and continues as the operational medical counsel for the company's services business in EMEA. Dr. Stuard's distinguished career includes more than a decade with Fresenius Medical Care in clinical governance roles for the company's EMEA and Latin America regions. He has served as a director/consultant for nephrology and dialysis departments in Italian public and private hospitals. He has published over 150 manuscripts in peer-reviewed journals. Dr. Stuard received his PhD in nephrology from the University of Bologna (Italy), his doctor of medicine and surgery, and a post-graduate specialization in nephrology magna cum laude, both from the University of Chieti (Italy). He received an award from the European Society of Artificial Organs for his contribution in the field of artificial organs.

CLAUDIA AMATO

Vice President, Head of Digital Innovation, Fresenius Medical Care Europe/Middle East/Africa

Claudia Amato is the head of Digital Innovation EMEA, in the Operations and Digital Strategy department. Her department focuses on constantly enriching the Fresenius Medical Care portfolio with innovative and holistic digital solutions and bringing them to the market. She has worked at Fresenius Medical Care since 1997 in different roles, with responsibilities mainly related to IT and the management of digitalization programs. She was responsible for the development and deployment of EuCliD in EMEA, Latin America, and Asia Pacific. Claudia received her degree in computer science from the Italian Università degli Studi di Milano in 1993.

SHELLY NASH, DO, FACOOG

Senior Vice President, Chief Medical Information Officer, Fresenius Medical Care North America

Shelly Nash is a physician, informaticist, senior vice president, and chief medical information officer for FMCNA. Prior to joining Fresenius, Dr. Nash served in a similar role for AdventHealth as its vice president, chief medical information officer, and chief of quality physician enterprise. She was previously employed as a physician executive for GE Healthcare, worked as a physician in private practice, and taught at Michael Reese Hospital and Midwestern University in Chicago. Dr. Nash graduated from the University of Illinois with a bachelor of science in biology and received her doctor of osteopathic medicine from the Chicago College of Osteopathic Medicine. She is board certified in both obstetrics and gynecology and in clinical informatics by the American Board of Preventive Medicine.

INNOVATION AND TRANSFORMATION THROUGH PARTNERSHIPS

Robert J. Kossmann, MD, FACP, FASN
Jan Walter, MBA, MSc

Fresenius Medical Care is driving innovation and transformation in kidney care. The company's strategy embraces both internal research and external investment in regenerative medicine, organ transplant, and organ recovery/revitalization. By working with partners that include Humacyte, eGenesis, and Unicyte, Fresenius Medical Care is increasing the potential for meaningful change and a dramatically improved quality of life for patients with chronic kidney disease and end-stage kidney disease.

Healthcare delivery and operations are constantly evolving, but meaningful change and improvement require innovation and transformation. As the leading provider of dialysis products and services, Fresenius Medical Care has an obligation to continuously improve the standard of care for the treatment of chronic kidney disease (CKD) and end-stage kidney disease (ESKD). Fresenius Medical Care approaches innovation through the dual pathways of original research and third-party collaborators and investments.

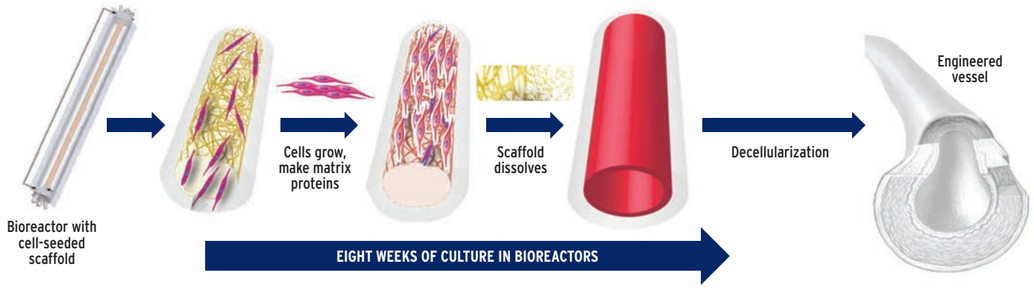
Some of Fresenius Medical Care's most promising external investments are in new and evolving areas such as regenerative medicine, organ transplant, and organ recovery/revitalization. Each of these technologies has the potential to substantially transform the care of individuals with ESKD, ultimately holding the promise to significantly change and improve kidney replacement therapies. Examples of Fresenius Medical Care's promising partnerships include Humacyte, eGenesis, and Unicyte.

Humacyte is developing a universally implantable regenerative human acellular vessel (HAV), which can be used for the creation of a dialysis access, for the treatment of peripheral arterial disease, and for emergency vascular repair and reconstruction following traumatic injury. Humacyte uses a proprietary manufacturing process to grow the HAV from human smooth muscle cells in a bioreactor over a period of three months, with decellularization at the end of the process. Once surgically implanted, the HAV's regenerative characteristics permit repopulation and recellularization of the HAV with the recipient's own cells. Host cell repopulation of the HAV re-creates living tissue, fully a part of the individual, without complications associated with rejection.

For individuals undergoing maintenance dialysis, this means that complications related to conventional vascular access types (e.g., poor maturation of AVFs, infection of arteriovenous grafts) may be significantly reduced. Furthermore, the HAV provides an alternative vascular access option, which may be advantageous for home- or self-cannulation due to its subcutaneous, easily accessible positioning.

Imagine, a patient in urgent need of a permanent vascular access for hemodialysis has no remaining vasculature that can be used for the creation of a fistula. An off-the-shelf organic vessel can be implanted, which will become a new part of the patient's own vasculature and can be cannulated for dialysis within four weeks.

FIGURE 1 | Humacyte process for generating universally implantable regenerative human acellular vessel



Imagine, organ supply would be sufficient so that instead of being on a perennial waiting list, an individual with ESKD could get a kidney via a xenotransplant within a few days, reducing the need for dialysis altogether.

Xenotransplant technology developed by eGenesis, a company in which Fresenius Medical Care has also invested, is another potentially disruptive technology. For most patients, kidney transplantation is often the preferred treatment for ESKD. Unfortunately, the need for kidneys for transplantation far exceeds the available organ supply. While policy makers and communities around the world are focusing more on increasing the availability of donated kidneys, that is unlikely to address the need. Xenotransplantation, transplanting kidneys from one species to another (e.g., a pig donor organ transplanted into a human), may offer a solution to overcome the shortage of transplantable human kidneys.

eGenesis has developed a technology that promises to transform the field of transplantation by offering reliable and effective organs. The company utilizes cutting-edge gene editing technologies to address the key issues—immune response and viral infection risk—that have impeded xenotransplantation to date. eGenesis's development pipeline includes programs for kidney and islet cell transplantation as well as earlier-stage programs focused on other solid organs.

Producing compatible and highly available xenogeneic organs could transform the field of transplantation.

Unicyte is a company with three established technology platforms: allogeneic human liver stem cells, nano-extracellular vesicles/exosomes, and organoids (islet-like structures). Pre-clinical and preliminary clinical data indicate a curative effect of the platforms. Potential therapeutic applications are promising and broad, spanning the fields of nephrology, endocrinology, hepatology, and oncology. Specific diseases that may be treated using this innovative therapy include CKD, acute kidney injury, diabetes (type 1 in particular), nonalcoholic steatohepatitis, urea cycle disorders, inherited metabolic liver disorders, hepatocellular carcinoma, and renal clear-cell carcinoma. Pre-clinical work is ongoing, and clinical development is starting in 2021.

For the treatment of kidney disease, nano-extracellular vesicles are of particular interest as they may potentially delay disease progression and may even partially regenerate the organ and revitalize its original function. Unicyte has the potential to provide breakthrough medical therapies.

Imagine, shortly after a patient is diagnosed with early-stage CKD, an injection can regenerate the organ and completely revitalize its function.

LOOKING AHEAD

Each of the above-showcased investments has the potential to transform the current standard of care for CKD and ESKD and beyond. Humacyte will be the first to market, proving that an in-vitro manufactured organ can be implanted without triggering an immune response and, once implanted, can evolve into the patient's own vascular structure based on its regenerative capabilities. eGenesis is exploring the concept of xenotransplantation to create sufficient global supplies for not only kidneys but also a variety of organs. Unicyte's approach is illustrating the potential to stop disease progression and possibly regenerate a kidney or liver.

FIGURE 2 | Unicyte manufacturing process based on standard platforms established in regenerative medicine and biologics

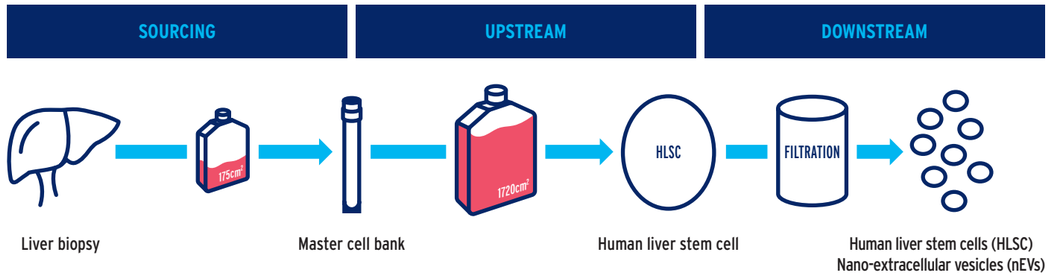
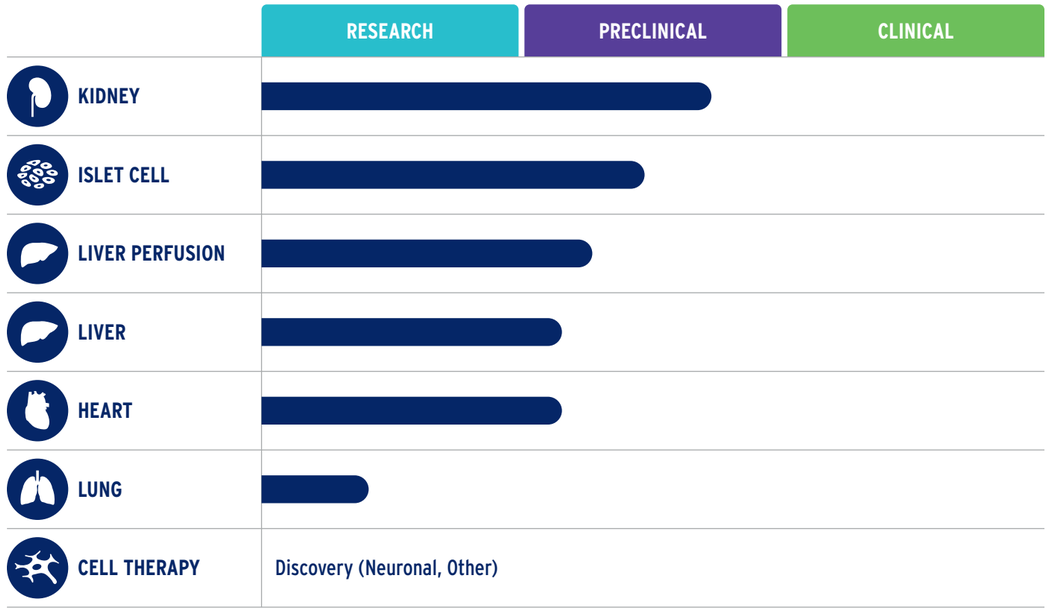


FIGURE 3 | eGenesis conducts research into solid organ xenotransplantation; kidney and islet cell transplantation; and liver, heart, lung, and cell therapies.



It is often a long and uncertain path from an idea to an approved product. But to constantly rethink, reimagine, and reinvent its business, products, and services itself are key cultural aspects of a true industry leader. It is Fresenius Medical Care's strategic mandate to remain the driver behind an ever evolving and improving standard of care for the treatment of CKD and ESKD. Whether it's through continued incremental technical improvements or disruptive innovation—or through thoughtful optimization of the organizational structure or fundamental transformation of "care enablement" and "care delivery" models—Fresenius Medical Care is embracing constant change as a core cultural aspect. Furthermore, staying ahead of the curve requires visionary choices backed by long-term funding, a deep entrepreneurial talent pool, and strong governance.

This forward-looking culture combined with the ability to act as a catalyzer for breakthrough technologies and consequently shorten their time to market makes Fresenius Medical Care's approach to innovation and transformation unique.

THE EXPERTS

ROBERT J. KOSSMANN, MD, FACP, FASN

Executive Vice President, Chief Medical Officer, Fresenius Medical Care North America

Robert (Rob) Kossmann is executive vice president and chief medical officer for FMCNA. From 2014 to 2019, he served as senior vice president and chief medical officer for Fresenius Medical Care's Renal Therapies Group, the company's medical equipment and renal pharmaceuticals division. Dr. Kossmann has been instrumental in helping guide the nephrology field through leadership roles, including formerly serving as president of the Renal Physicians Association (RPA); a founding member of RPA's Nephrology Coverage Advocacy Program (now Policy Advocacy Leadership program); a nephrology advisor to the American Medical Association's Relative Value Scale Update Committee; and founder of the New Mexico Renal Disease Collaborative Group. A practicing nephrologist for two decades, Dr. Kossmann trained in nephrology at the University of Washington in Seattle and holds his bachelor's and doctor of medicine degrees from Case Western Reserve University in Cleveland, Ohio.

JAN WALTER, MBA, MSc

Senior Vice President, Regenerative Medicine Commercialization, Fresenius Medical Care

Jan Walter leads worldwide commercialization efforts for regenerative medicine opportunities, with a focus on the Humacyte product portfolio. He previously served as senior vice president for Fresenius Medical Care in central Asia Pacific with commercial and legal responsibilities for a mix of mature and emerging markets, including Korea, India, the Philippines, Afghanistan, Bangladesh, Bhutan, Maldives, Nepal, and Pakistan. He is the former managing director for Fresenius Kabi in Southeast Asia, and began his career with Fresenius SE and CO KGaA as assistant to the chief executive officer. Jan graduated with dual master's degrees in business administration and economics from the University of Leipzig in Germany and holds his MBA from Binghamton University in New York.

SUBSTANTIAL CLINICAL IMPROVEMENT: OPTIMIZING CMS GUIDELINES FOR NEW PRODUCTS

Michael Anger, MD, FACP, FASN

Despite the growing incidence and prevalence of kidney disease on a worldwide basis, there have been fewer nephrology-themed randomized controlled trials than any other internal medicine subspecialty, less funding from public and private sources, and fewer innovative devices or medications developed than all other diseases combined.[1,2,3] In response to increasing demand to address this inequity, the Centers for Medicare and Medicaid Services (CMS) established the end-stage renal disease (ESRD) Prospective Payment System (PPS) Transitional Add-on Payment Adjustment for New and Innovative Equipment and Supplies (TPNIES). Its purpose is to facilitate beneficiary access to certain qualifying new and innovative renal dialysis equipment and supplies, by providing an add-on payment adjustment to support ESRD facilities in the uptake of new and innovative equipment and supplies under the ESRD PPS.

The TPNIES program began in 2020, and in its inaugural year had two applicants: a dialyzer that was touted to improve several aspects of the life of someone receiving dialysis, and a home dialysis machine cartridge that was to encourage greater use of home hemodialysis. Neither of these were successful in their TPNIES quest.

In the case of the dialyzer, CMS opined that the studies and data presented (by the applicant) either were low powered, did not provide statistical significance in their results, and/or did not include a control population. In addition, they cautioned that the studies provided signaled that albumin might be filtered by the product, resulting in low levels of albumin for some individuals receiving dialysis.[4] In the case of the home dialysis machine cartridge, CMS clarified that capital-related assets were not covered in the first version of TPNIES and that the stand-alone cartridge (without the home dialysis machine) could not be evaluated on its own. In the Final Rule, published in the Federal Register on November 9, 2020, CMS modified the original criteria to expand the dates a device would be eligible and included capital-related assets that include home dialysis machines when used in a home for a single person.

What are the criteria and how does CMS make a decision? Although the details are lengthy and complex, the main determinant is evidence that the renal dialysis device shows substantial clinical improvement for Medicare beneficiaries in at least one of the following:

- **It must offer a new treatment option for people who are unresponsive to or ineligible for current treatments.**
- **It must offer the ability to diagnose a medical condition earlier in the disease course or one that is currently undetectable.**
- **It must significantly improve clinical outcomes relative to services or technologies previously available.**
- **The totality of information must otherwise demonstrate substantial improvement relative to renal dialysis services previously available.**

How does one determine what constitutes significant improvement of clinical outcomes? The relative and absolute risks of mortality in dialysis have fallen in the past several decades in the United States.[5] Despite this, mortality remains very high. Does prolonging life on dialysis constitute substantial clinical improvement? Individuals report fatigue, insomnia, cramps, depression, anxiety, and frustration as their major concerns, so wouldn't alleviating symptoms or improving quality of life be as or even more important?

How does one determine what constitutes significant improvement of clinical outcomes? The relative and absolute risks of mortality in dialysis have fallen in the past several decades in the United States. Despite this, mortality remains very high.

Although CMS has created a framework for defining substantial clinical benefit, is the framework optimal and how should substantial clinical benefit be defined? Advances that significantly impact quality of life should be of the highest priority. Imagine a therapy that eliminated the need for phosphate binders, stopped cramping completely, prevented any post-therapy fatigue, or reduced the number of days dialysis was needed (yet provided comparable or even better clearances and ultrafiltration). Think of the factors that contribute to the morbidity on dialysis: cardiovascular complications, infections, bleeding, and cognitive changes. Let's really spur thought, investigation, and the creation of changes that would provide new meaning to "substantial."

New products ideally should have rigorous, well-designed, large randomized controlled trials to clearly demonstrate substantial clinical improvement, including careful study design and endpoints. Support of investigator-initiated research studies needs to be promoted to address potential data gaps. There should be attempts to generate health economic data from these trials and studies to demonstrate product value. Finally, publications and meta-analysis supporting the new device will be critical in helping establish a network of advocates including key opinion leaders, individuals receiving dialysis, and healthcare organizations.

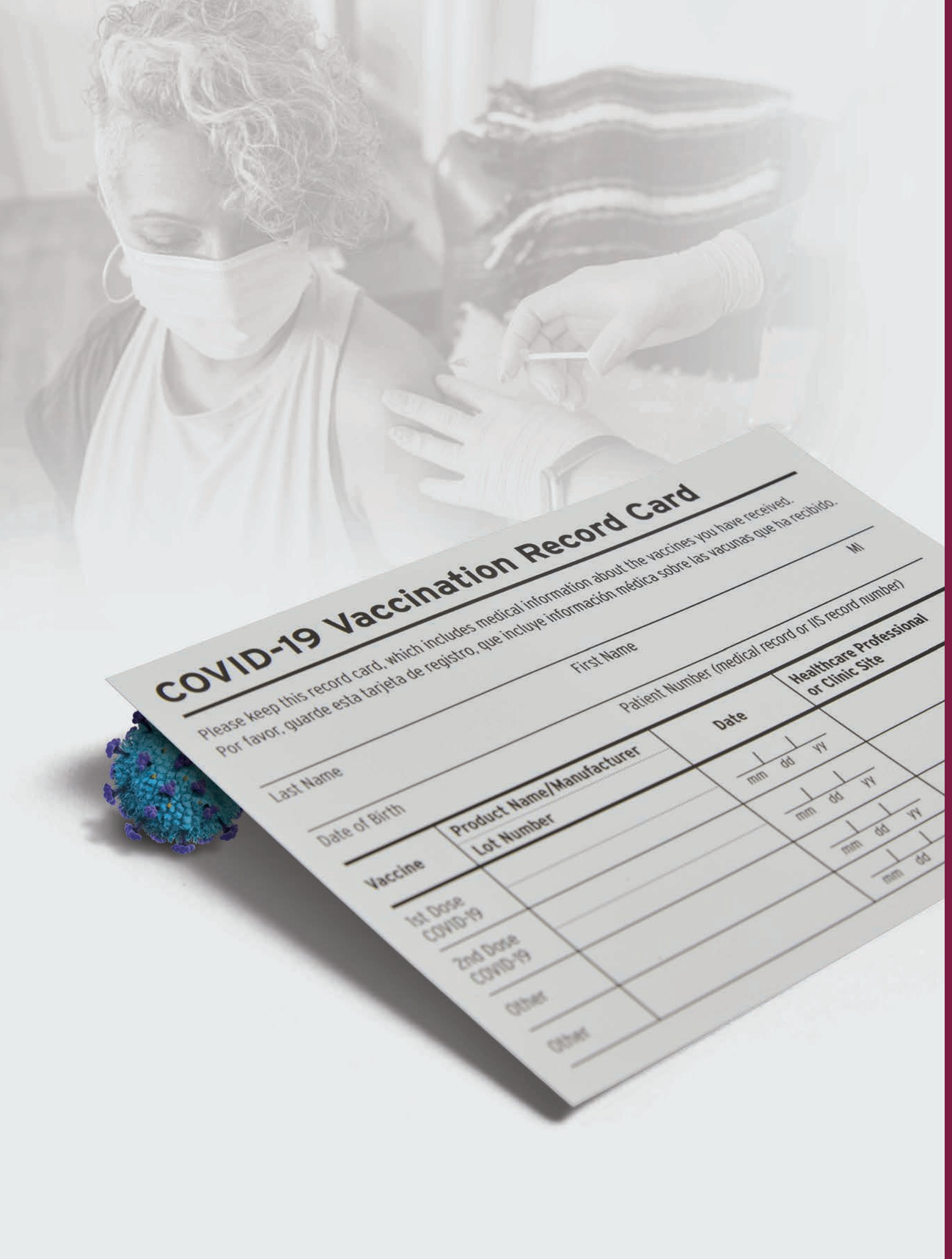
With this approach, great advances may be realized to better all aspects of the lives of those who suffer with the spectrum of kidney ailments.

CMS OUTLINED SEVEN POTENTIAL OUTCOMES TO DEMONSTRATE SUBSTANTIAL CLINICAL IMPROVEMENT:

- ☑ Reduction in at least one clinically significant adverse event, including a reduction in mortality or a clinically significant complication
- ☑ Decreased rate of at least one subsequent diagnostic or therapeutic intervention
- ☑ Decreased number of future hospitalizations or physician visits
- ☑ More rapid beneficial resolution of the disease progression including, but not limited to, a reduced length of stay or recovery time
- ☑ Improvement in one or more activities of daily living
- ☑ Improved quality of life
- ☑ Greater medication adherence or compliance

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.



COVID-19 PANDEMIC

Lead rapid response, including deployment of equipment and volunteer staff to hospitals. Develop protocols that set the highest standards for care. Prioritize safety, successfully protecting patients, families, caregivers, and front-line staff. Advocate for all kidney patients worldwide. Advance knowledge about COVID-19, and incorporate learning into future crisis response plans.

COVID-19: GLOBAL OVERVIEW OF COVID-19 IN END-STAGE KIDNEY DISEASE

Fatih Kircelli, MD
Dixie-Ann Sawin, MS, PhD

Global COVID-19 data confirms that dialysis patients experienced a much higher rate of hospitalization and death than the general population. However, there has been insufficient research into many issues surrounding the immediate risks and long-term impact of COVID-19 on individuals with end-stage kidney disease. This has created a knowledge gap on many topics, including testing, vaccine efficacy, therapeutic options, prolonged positivity rates, reinfection, and the incidence and severity of "long-hauler" symptoms.

Identification of a novel ß-coronavirus in Wuhan, China, in December 2019 marked the beginning of the global COVID-19 pandemic. As of June 5, 2021, SARS-CoV-2 has infected approximately 173 million people, resulting in over 3.7 million deaths in 220 countries and territories.[1,2] The COVID-19 pandemic fostered greater global collaboration in science, allowing robust COVID-19 research and almost 142,000 peer-reviewed publications indexed on PubMed.gov (by June 5, 2021). However, COVID-19 data on individuals with end-stage kidney disease (ESKD) has been slow to emerge, with only 511 publications identified (as of June 6, 2021) that discuss topics such as epidemiology, clinical outcomes, diagnosis, testing, disease management, and therapeutic options for this high-risk population.

EPIDEMIOLOGY AND CLINICAL OUTCOMES IN ESKD

The incidence of COVID-19 in individuals with ESKD on maintenance dialysis has varied between countries (Figure 1). The noted differences are likely due to numerous factors, including: the time frame of observation and associated population rates of COVID-19, the method of identifying and ascertaining COVID-19, and differences in patient comorbidities and age.

In a cohort of 365 hemodialysis patients, 22.2% were symptomatic and were tested by reverse transcriptase polymerase chain reaction (RT-PCR); 36.2% were seropositive.[4] Of the seropositive individuals on dialysis, 40.3% (52 out of 129) were found to be asymptomatic or undiagnosed. Thus, undiagnosed asymptomatic disease in dialysis patients can be high and may serve as an additional source of infection within the clinics. In the general population, at least 20% of SARS-CoV-2–infected patients experienced severe or critical illness with respiratory failure, septic shock, multiorgan failure, or neurological issues.[5,6,7] Among individuals with ESKD on maintenance dialysis, rates of hospitalization associated with COVID-19 have been high and generally exceed 50%; mortality ranges from 10% to 30% depending on the study (Figure 1). The notable variability is presumably due to a number of factors, including the inclusion of individuals with asymptomatic and more mild disease. Comparatively, the risk for severe infection and hospitalization has been estimated to be two- to seven-fold higher for individuals with ESKD.[8,9,10]

Individuals on dialysis have also been observed to experience shorter duration from symptom onset to intensive care unit admission than other groups.[11] A higher percentage of dialysis patients (25%) also showed symptoms of altered mental status versus non-dialysis-dependent patients with CKD (12%).[12] Critically ill SARS-CoV-2–positive dialysis patients had a higher likelihood of developing thromboembolic complications than those without COVID-19. These individuals also had a higher probability of requiring mechanical ventilation or extracorporeal life support.[13,14]

Some individuals on dialysis may not fully recover from COVID-19 and suffer from fatigue and neurologic, cardiac, gastrointestinal, and respiratory symptoms.[15] Contributing factors to this "long-hauler" phenomenon in the general population—including age, female sex, obesity, asthma, neurologic deficits, and persistent inflammation—may also apply in ESKD.[16] The incidence of long-haul for individuals with ESKD is not known.

DIAGNOSTIC TESTING

Common methods for detecting SARS-CoV-2 in infected individuals include RT-PCR and serological tests that primarily recognize the spike (S) protein.[17,18,19,20] Sampling typically occurs by saliva, nasopharyngeal, or nasal swabs from the respiratory track for RT-PCR, or blood for antibody or serology testing.[21] Many individuals infected with COVID-19, including those on dialysis, have positive RT-PCR tests that persist for weeks after recovery. However, it is not known if these individuals are more immunocompromised/immunosuppressed than the general population, or whether prolonged RT-PCR positivity is indicative of delayed clearing of infectious virions.[22] It has been proposed that ESKD patients, with typically altered immune responses, could harbor live virus longer. Such prolonged SARS-CoV-2 positivity could obscure cases of still-active virus and reinfection, impacting treatment options, clinical care, duration of hospital stay, discharge planning, and hospital capacity.[23,24,25]

Seroconversion typically occurs between 7 and 11 days from exposure and can persist after recovery.[26] A UK study found detectable immunoglobulin G (IgG) in 100% of COVID-19-positive HD patients after seven months.[27] In contrast, 26% of critically ill ESKD patients could not elicit antibody responses, indicating that HD patients may be immunocompromised.[28,29] Despite limitations, serological testing in ESKD may be a valuable tool to determine seroprevalence, monitor exposure, and guide improvements for infection prevention and control.

FIGURE 1 | The incidence of COVID-19 and associated clinical outcomes in ESKD populations[3]

COUNTRY	TIME FRAME	STUDY DESIGN; ASCERTAINMENT OF COVID-19	STUDY POPULATION	INCIDENCE	COVID-19-ASSOCIATED OUTCOMES
United Arab Emirates (UAE)	March 1- July 1, 2020	- Retrospective cohort study - Routine RT-PCR testing every 14 days and if symptoms	1,180 adults with ESKD receiving IHD or PD	13% (41% of cases asymptomatic)	Mortality 9%
France	March 16- May 4, 2020	- Documented COVID-19 in the French Renal Epidemiology and Information Network (REIN) registry - COVID-19 diagnosis based on clinical presentation or RT-PCR testing	48,669 dialysis patients receiving care in 1,245 dialysis units (HD in the hospital, outpatients center, self-care unit) or home dialysis	3.3% (2% of cases asymptomatic) Incidence varied 0-10% by geography and incidence in facilities with ≥1 case: 6%	Mortality 21%
United Kingdom	March 11- May 10, 2020	- Retrospective cohort study - RT-PCR testing if symptoms and asymptomatic testing as of April 15, 2020	746 patients receiving hemodialysis in 4 dialysis facilities in London	22% (7% of cases asymptomatic)	Hospitalization 63%* Mortality 24%*
Europe	February 1- April 30, 2020	- ERA-EDTA Registry - Clinical diagnosis or based on testing results and reported to registry		2.9%†	28-day mortality 21% (95% CI, 19.8%-22.7%) 28-day unadjusted mortality ranged from 8.5% to 29.7% depending on the country
China	Through February 28, 2020	- Retrospective cohort study - Clinical presentation and imaging features or positive RT-PCR; all patients underwent chest CT	627 patients receiving chronic hemodialysis in Wuhan hospital-based dialysis center	12% (22% of cases asymptomatic)	Mortality 19%
China	January 1- March 10, 2020	- Retrospective cohort study - RT-PCR confirmed COVID-19; RT-PCR testing performed based on clinical presentation or imaging findings, universal chest CT screening	7,154 patients receiving hemodialysis, hemodiafiltration, or hemoperfusion in 65 centers in Wuhan, China	2% (21% of cases asymptomatic‡)	Mortality 31%‡
Germany	February - April 2020	- Retrospective cohort study - RT-PCR testing if symptoms or if COVID-19 close contact	755 patients receiving chronic hemodialysis in 5 dialysis centers	7%	Hospitalization 77% Mortality 27%
Canada	March 12 - August 20, 2020	- Ontario Renal Network surveillance - Positive NAAT; testing generally done for symptoms or if COVID-19 close contact	12,501 adults receiving IHD or home dialysis in Ontario	1.5%	Hospitalization 63% Mortality 28%
United States	January 1-31, 2021	- Cross-sectional study - Receptor binding domain (RBD) total antibody (IgM and IgG) chemiluminescence assay (RT-PCR data not available)	21,464 adult, unvaccinated dialysis patients	18.9%§	
United States	February 17- June 20, 2020	- Retrospective cohort study - RT-PCR testing routinely, or if symptomatic, or based on screening	7,948 adults on maintenance dialysis	5.5%	Mortality 25%

* Outcomes assessed in a subset of 148 of the 164 COVID-19 cases
† COVID-19 diagnosis through May 1, 2020, as a percentage of the prevalent HD or PD population as of December 31, 2017
‡ Symptoms and outcomes assessed in a subset of 131 of the 154 COVID-19 cases
§ Cross-sectional prevalence

To better understand duration of seropositivity and acquired immunity, combined testing for the S and nucleocapsid proteins is currently being developed and tested in vitro.[30] This approach allows for differentiation between vaccinated and infected individuals. High-quality, quantitative methodologies that evaluate persistent positivity post-infection, reinfection, potential antibody titer reduction over time, and effect of variants in ESKD patients are needed.

COVID-19 TREATMENT OPTIONS AND CHALLENGES IN ESKD

As of July 2021, COVID-19 therapeutic options for individuals living with ESKD are still limited as clinical trials often excluded this population.[31,32,33,34,35,36,37]

Several monoclonal antibody (mAb) therapies were granted EUA by various global authorities. Bamlanivimab plus etesevimab, casirivimab plus imdevimab, or sotrovimab, as single or combination therapy, are recommended for non-hospitalized or mild-to-moderate COVID-19.[44] No dose adjustments are needed in patients with mild-moderate renal impairment. The recombinant anti-IL-6 receptor antibody, tocilizumab, was also granted EUA in the US and was successfully used to treat non-critical hemodialysis patients with COVID-19-related pneumonia or cytokine release syndrome; no dose adjustment was needed in these patients.[45] EUA status (US) for hospitalized COVID-19 patients with high convalescent plasma titers early in disease course has been given. Antiviral agents, including remdesivir, are not approved or recommended in ESKD.[46,47,48]

High-quality, quantitative methodologies that evaluate persistent positivity post-infection, reinfection, potential antibody titer reduction over time, and effect of variants in ESKD patients are needed.

Remdesivir evaluation in ESKD has been inadequate, and it is not recommended in individuals with eGFR <30 mL/min/1.73 m2.[38,39] A case series of hospitalized COVID-19-positive HD patients suggests good tolerance of standard doses of remdesivir resulting in a 52.2% discharge rate.[40] In another study, administration within 48 hours of hospital admission shortened the duration of stay for dialysis patients by 5.5 days.[41] Remdesivir was not significantly associated with early treatment termination due to abnormal liver function tests in patients with creatinine clearances <30 ml/min versus ≥30 ml/min., and in a separate study, plasma concentrations were 45 to 49% lower post-dialysis as compared to pre-dialysis.[42,43]

Worldwide, COVID-19 vaccine campaigns have focused on those at highest risk for severe disease, and a number of countries have prioritized vaccination of individuals with kidney disease. Early reports found vaccine-derived antibody responses in 96% of dialysis patients, but IgG levels were lower than controls (median: 2900 mg/L versus 7401 mg/L).[49] Although more data is needed, and reported vaccine hesitancy among dialysis patients ranges from 20% to 51%, global authorities consider COVID-19 vaccines safe for individuals with ESKD and believe differences in side effects compared with the general population should be insignificant.[50,51]

LOOKING AHEAD

As the COVID-19 pandemic continues to evolve, there are several gaps in knowledge regarding the dialysis population that need to be addressed, as these patients have been excluded from major trials. Future research should focus on how often dialysis patients should be tested and whether the currently available tests are optimal for this population. Data is also needed on whether antibodies produced in recovered individuals with ESKD are as effective as in the general population. Research into "long COVID" in ESKD should be a priority. Transitioning more patients to home therapies now and post-COVID-19 should also be explored.

COVID-19 therapeutic options for individuals living with ESKD are still limited as clinical trials often excluded this population.

Vaccine safety and efficacy in this population are also not well understood. Results from the prospective, multicenter RECOVAC-IR study (ClinicalTrials.gov NCT04741386)—which aims to evaluate immunogenicity, safety, and antibody longevity in CKD, ESKD, and transplant patients up to 12 months post-vaccination with Moderna's mRNA-1273 vaccine—are eagerly awaited.[52] ESKD patients are immunocompromised and exhibit reduced or insufficient vaccine responses compared to healthy individuals, and strategies to overcome such impaired responses—e.g., appropriately timed booster shots or a mix of different COVID-19 vaccines—need to be determined. Whether vaccine-induced antibody formation reflects antiviral immunity in these patients is also not clear.[53] For instance, absence of seroconversion may not reliably indicate a lack of protection from severe COVID-19. Cellular immunity may still be present and afford some protection against infection or severe disease. Importantly, the benefits of vaccination outweigh the potential risks. However, discussion on the safety profiles of approved vaccines in these patients is essential to reducing vaccine hesitancy, improving vaccine penetration, and controlling the pandemic.

FATIH KIRCELLI, MD
Vice President, Medical Information and Education, Fresenius Medical Care Europe/Middle East/Africa

Fatih Kircelli leads the medical information and education team throughout Fresenius Medical Care's Europe/Middle East/Africa region. His team provides medical expertise to all related departments on the company's product portfolio and therapies. Over his eight years with Fresenius Medical Care, he has served as a country medical director as well as marketing and renal pharma business unit director for Turkey. He is a nephrologist with over 60 publications in peer-reviewed journals. He received his associate professor degree in nephrology in 2012.

DIXIE-ANN SAWIN, MS, PhD
Senior Director, Medical Information and Communication, Global Medical Office

With over 15 years of basic science research in neuroscience, genetics, molecular biology, immunology, and neuro-immunology; three post-doctoral fellowships; and multiple first author publications, Dixie-Ann Sawin leads the medical information team for FMCNA. Her team is responsible for responding to all medical information queries from healthcare providers across the US and providing medical and scientific expertise on promotional review committees as well as business and core development teams. Her team also supports pre- and post-market launch education, compiles regulatory and pharmacovigilance reports, prepares publications for peer-reviewed journals, and develops educational content for the renal community through the Advanced Renal Education Program. She also serves as director for the Fresenius PharmD Fellowship and Internship Program. She obtained her PhD in neuroscience and genetics from Duke University and a master's degree in molecular genetics from the University of Central Florida.

COVID-19 EMERGING VARIANTS

Frank Laukhuf, MD
Chance Mysayphonh, PharmD

Containing the COVID-19 pandemic requires monitoring the rapidly emerging variants of the virus. As of spring 2021, there were more than a dozen variants being evaluated by the World Health Organization and the Centers for Disease Control and Prevention. Fortunately, none of these is a variant of high consequence, a classification that would indicate that prevention measures or medical countermeasures have significantly reduced effectiveness. Although current vaccines are very effective, manufacturers are focused on developing strategies to ensure that new and booster vaccines can keep pace with the rapid rate of mutation and maintain the highest level of protection.

INTRODUCTION TO CORONAVIRUSES

Coronaviruses are a diverse family of positive-sense single-stranded RNA-enveloped viruses. The virus infects mammals, including humans, avian, and other animal species. The *Coronaviridae* consist of four genera: *alphacoronavirus*, *betacoronavirus*, *gammacoronavirus*, and *deltacoronavirus*. Infection in mammalian species is exclusively by *alphacoronaviruses* and *betacoronaviruses*.[1] Sequencing of the full-genome and phylogenetic analysis reveal that COVID-19 is caused by a *betacoronavirus* within the same subgenus as the severe acute respiratory syndrome virus (SARS). Early on, the *Coronaviridae* Study Group designated the novel virus that emerged from Wuhan, China, late in 2019 as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2]

REPLICATION CYCLE

Like other infectious coronaviruses, the initial sequence of infection from SARS-CoV-2 involves binding of the spike (S) protein to the cellular entry receptors of the host. The expression and distribution of these entry receptors influence viral pathogenicity. Three receptors are commonly associated with coronavirus to human infectivity and pathogenesis: human aminopeptidase N (APN; HCoV-229E), angiotensin-converting enzyme 2 (ACE2; HCoV-NL63, SARS-CoV and SARS-CoV-2), and dipeptidyl peptidase-4 (DPP4; MERS-CoV).[3]

The receptor of interest associated with SARS-CoV-2 is the ACE2 receptor, which is ubiquitous and found virtually in all organs; there is abundant surface expression of ACE2 receptors on lung alveolar epithelial cells and enterocytes of the small intestine.[4] Once the SARS-CoV-2 virus binds to the host ACE2 receptor, intracellular fusion is assisted by the TMPRSS2, a surface serine-protease. The intracellular viral replication cycle begins by uncoating and releasing the >30 kb mRNA strand, where the genetic sequence containing 10 genes is immediately translated to the viral replication and transcription complex and further produces a total of 26 proteins. The result is virions secreted from the infected cells by exocytosis (Figure 1).[5]

MUTATIONS AND VARIANTS

Mutations are defined as changing a gene, resulting in a variant form transmitted to subsequent generations. Mutations are common in viruses. The capacity of viruses to adapt to the host and environment is dependent on the ability of the virus to generate diversity in a short period of time. In terms of viral mutation rates among the different types of viruses, RNA viruses can mutate faster than DNA viruses, and there is a negative correlation in mutation rate versus the size of the genome. These viral mutation rates are normally represented as the rate of substitution per nucleotide per cell infection cycle (s/n/c).[6] Coronaviruses are the exception to the rapid viral mutation rate seen in other smaller RNA viruses such as influenza.

Coronaviruses such as SARS-CoV-2 contain within their large (>30 kb) genome a region to encode for an RNA-dependent RNA-polymerase, a proofreading mechanism to reduce the mutation rate and stabilize the genome. Betacoronaviruses accumulate around 10^{-6} (s/n/c) mutations in each round of replication compared to the 14 kb influenza virus, which has a mutation rate of approximately 10^{-5} (s/n/c) or ten times the mutation rate for coronavirus.[7]

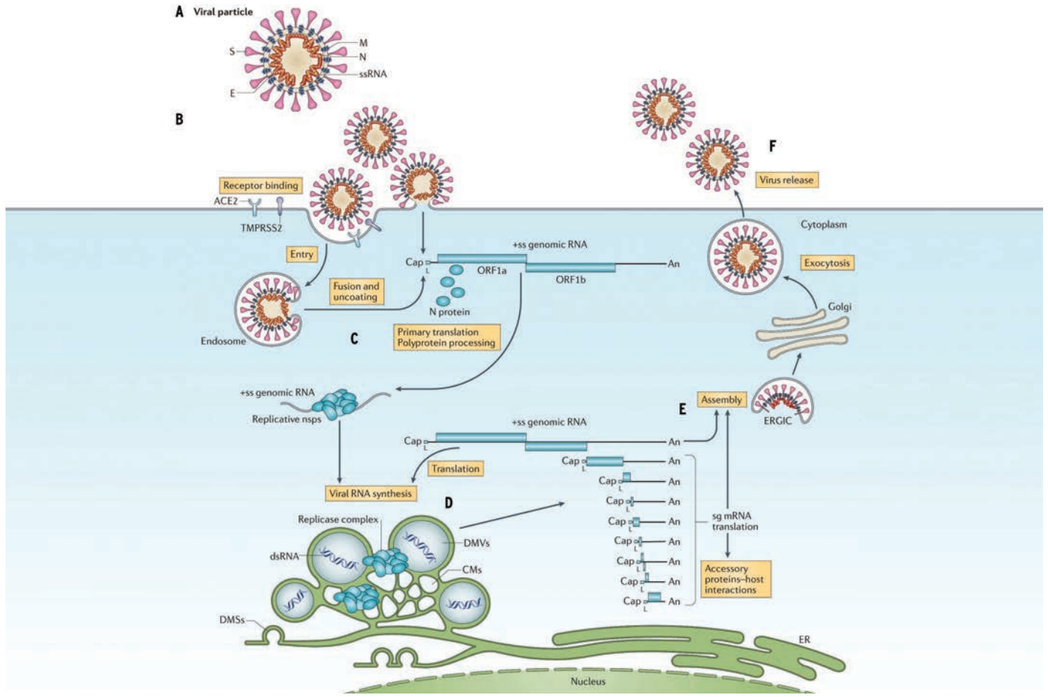
Although most of the mutations found on the SARS-CoV-2 virus are benign, specific mutations on the spike protein can enhance the adaptability and transmissibility of the virus. More importantly, mutations on the spike protein can be concerning considering that this region houses the receptor-binding domain (RBD)—the contact region to the host cellular entry receptor. Mutations are represented by an amino acid residue number indicating the location of the amino acid sequence. The location for the RBD for SARS-CoV-2 is between amino acid residues 319 and 541, with the receptor-binding motif located between amino acid residues 437 and 508.[8]

The first recognized mutation that altered the fitness of the SARS-CoV-2 virus was the D614G mutation found on the spike protein, which enhanced the infectivity and stability of the virions. Before May 2020, the D614G mutation was rare but quickly became the dominant circulating strain of SARS-CoV-2, occurring in more than 74% of all published sequences by June 2020. Nearly all specimens sequenced today contain the D614G mutation.[9]

VARIANTS OF INTEREST AND VARIANTS OF CONCERN

Monitoring variants is essential to containing the COVID-19 pandemic. As an example, the genomic database GISAID is an international collaboration of genetic data aggregation and identification. The most significant value is the ability of these databases to identify and monitor emerging variants with criteria from organizations such as the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC). Unfortunately, the sharing of SARS-CoV-2 genome data continues to lag. As an example, the United States only uploaded 1.6% of COVID-19 cases to GISAID in March 2021.[10]

FIGURE 1 | SARS-CoV-2 Replication Cycle



(A) SARS-CoV-2 viral particle **(B)** SARS-CoV-2 spike protein bind to ACE2 surface receptor and TMPRSS2 prime viral spike protein for cellular entry **(C)** Uncoating of viral particle in the cytosol and translation of proteins required for viral replication and transcription complex **(D)** Biogenesis of viral organelles replication complex that translate viral mRNA to structural protein that translocate into the Endoplasmic Reticulum **(E)** From the ER, the protein translocate to Golgi for post-processing to a mature viral particle before exocytosis

Source: V'kovski P, et al. Coronavirus biology and replication: implications for SARS-CoV-2. *Nat Rev Microbiol* 2021 Mar;19(3):155-70.

As of spring 2021, there were more than a dozen circulating variants of SARS-CoV-2. Three classifications of these variants are closely monitored by the CDC and WHO. Variants of interest are variants with genetic markers associated with changes in the RBD, reduced neutralization by antibodies, reduced efficacy of treatments, predicted increase in transmissibility or disease severity, or potential diagnostic impact. Variants of concern demonstrate significant increase in transmissibility, more severe disease, reduction in neutralization by antibodies, reduced effectiveness of vaccines, or diagnostic failure. Fortunately, none of the current variants meet criteria for the third classification, variant of high consequence. The variant of high consequence classification is reserved for viral variants with clear evidence that prevention measures or medical countermeasures have significantly reduced effectiveness.

Globally, per the WHO, in May 2021, there were four primary variants of concern: B.1.1.7, B.1.351, P.1, and B.1.617.2 (Figure 2). The variant B.1.1.7 was initially detected in the United Kingdom in September 2020. The B.1.351 and P.1 variants are similar but have different origins. B.1.351 emerged from South Africa around September 2020, and P.1 was detected in early December 2020 in travelers from Brazil to Japan. The B.1.351 and P.1 have three mutations on the RBD (N501Y, E484K, and K417N/T). Of note, the mutation at the E484K position appears in three of the SARS-CoV-2 variants of concern—a pattern of convergent evolution where the trait emerges in different independent lineages over time as the virus adapts to similar environments; there is evidence that the mutation improves the virus fitness in some way by either evading neutralizing antibodies or reducing the efficacy of vaccines.

The other emerging variant of concern, B.1.617.2, was first discovered in India in December 2020 and quickly spread throughout the country. It contains two key mutations, L452R and T478K. These two mutations were not discovered together before being identified in the B.1.617.2 variant. The L452R mutation is the same mutation found in the B.1.427 and B.1.429 strains, which demonstrate an approximately 20% increase in transmissibility compared to the original Wuhan strain, along with a twofold increase in viral shedding.[11] The B.1.617.2 variant has mutations associated with an increase in transmissibility and ability to evade the immune responses. Early studies suggest that convalescent sera from patients infected with SARS-CoV-2 was 50% less effective against B.1.617.2. Antibodies from participants vaccinated with the Pfizer vaccine were 67% less potent against the B.1.617.2.[12] Figure 2 summarizes the WHO variants of concern and important mutation characteristics.

VACCINE EFFICACY ACROSS DIFFERENT VARIANTS

The adenovirus-vector vaccine ChAdOx1 from AstraZeneca only found 10% protection against mild-to-moderate disease from the B.1.351 variant, but demonstrated 75% protection against the B.1.1.7 variant, demonstrating the importance of understanding vaccine

efficacy with respect to circulating variants.[13] Another adenovirus-vector vaccine from Janssen also showed differing efficacy based on the region and associated circulating variants.[14]

Moderna and Pfizer vaccines are both authorized mRNA vaccines with greater than 90% efficacy against SARS-CoV-2 observed in the clinical trials.[15,16] However, SARS-CoV-2 variants have changed over time, and the currently circulating predominant variant differs compared to the time period of the phase 3 clinical trials; in vitro studies suggested a four- to sixfold reduction in neutralizing antibody response against variants with the E484K mutation.[17,18,19]

VACCINE DEVELOPMENT AND VARIANTS

Public health and nonpharmaceutical interventions remain two of the most effective ways to control the spread of the SARS-CoV-2 virus and its variants. Vaccines remain the greatest hope at stopping the pandemic, and booster vaccination will likely be required to help protect against emerging variants.

Vaccine manufacturers are employing different strategies to evaluate booster doses of COVID-19 vaccines. Pfizer-BioNTech is evaluating a booster dose of the same vaccine against the variants, hoping that the increase in antibody production and associated immune system priming will be effective at preventing infection from the variants, while Moderna is exploring booster vaccine candidates based on the B.1.351 genetic sequence.

Unlike the traditional vaccine platforms, the mRNA vaccines are agile in terms of adaptability and speed of development. Additionally, mRNA vaccines have inherent adjuvant properties that enhance the response of the antigen-presenting cell. Once the target vaccine antigen is identified, the genetic information is sequenced and converted to an mRNA sequence that encodes the target antigen. The process from antigen identification to mRNA vaccine candidate can occur in just eight days.[20]

Indeed, several questions remain on the first-generation COVID-19 vaccines and their efficacy against the variants. The immune response, along with which elements are associated with protection against infection, remains incompletely understood. The correlates of protection from the different vaccines still need to be determined.

The WHO recently proposed a framework for expediting new vaccine development. One intriguing proposal is using pooled safety data on products sharing the same platform, to avoid the need for lengthy, costly, and challenging clinical studies. The proposal is in line with European Medical Association guidance on adapting the second generation of vaccines to the variants.

FIGURE 2 | WHO variants of concern as of May 2021

LINEAGE + ADDITIONAL MUTATIONS	COUNTRY FIRST DETECTED	SELECT SPIKE MUTATIONS OF INTEREST	YEAR AND MONTH FIRST DETECTED	EVIDENCE FOR IMPACT ON TRANSMISSIBILITY	EVIDENCE FOR IMPACT ON IMMUNITY	EVIDENCE FOR IMPACT ON SEVERITY
B.1.1.7	United Kingdom	N501Y, D614G, P681H	September 2020	Yes	Unclear	Yes
B.1.1.7+E484K	United Kingdom	E484K, N501Y, D614G, P681H	December 2020	Yes	Neutralization	Yes
B.1.351	South Africa	K417N, E484K, N501Y, D614G, A701V	September 2020	Yes	Escape	Yes
P.1	Brazil	K417T, E484K, N501Y, D614G, H655Y	December 2020	Yes	Neutralization	Yes
B.1.617.2	India	L452R, T478K, D614G, P681R	December 2020	Yes	Escape	

THE EXPERTS

FRANK LAUKHUF, MD

Senior Vice President, Head of Medical Affairs Products for Europe/Middle East/Africa, Asia Pacific, and Latin America; Chief Medical Officer, Fresenius Medical Care EMEA

Frank Laukhuf is head of the medical office throughout Europe, the Middle East, and Africa. At the cross-regional level, he leads the Medical Affairs Products team that medically manages the entire product portfolio of Fresenius Medical Care, both medical devices and drugs, around the globe except for the United States. Frank is a board-certified internist and nephrologist. He spent 15 years in direct patient care and several years in hospital management, allowing him to gain extensive insights in the healthcare systems of Germany and Switzerland in particular. After joining Fresenius Medical Care in 2011, Frank led the development and expansion of the medical product governance function in EMEA before taking over as chief medical officer of EMEA. He holds a doctor of medicine from Heidelberg University in Germany as well as a postgraduate diploma in health economics.

CHANCE MYSAYPHONH, PharmD

Director of Clinical and Therapeutic Initiatives, Fresenius Kidney Care

Chance Mysayphonh serves as regional clinical pharmacist for Fresenius Kidney Care, overseeing the Antibiotic Stewardship Program and kidney disease initiatives. Prior to Fresenius, in 2018 he served as clinical systems analyst for TwelveStone Health Partners, where he supported multiple clinical teams by utilizing data to improve outcomes and led the Accreditation and Certification Committee. Dr. Mysayphonh also served as clinical infusion pharmacist for Vanderbilt HC/Walgreens Infusion, where he provided post-acute care to prevent rehospitalization, led the clinical team for all chemotherapy patients, and worked closely with the Vanderbilt Infectious Disease Clinic regarding antibiotic drug protocols and therapy management. Dr. Mysayphonh received his doctor of pharmacy from the University of Tennessee, with graduate training at Vanderbilt University.

COVID-19 VACCINES: CRITICAL NEW TOOLS IN THE FIGHT AGAINST THE GLOBAL PANDEMIC

Teresa Portela, PhD
Phaneth Keo, PharmD

As several different COVID-19 vaccines are authorized for emergency use and/or approved around the world, the race to contain the pandemic has been given a new weapon. This chapter explores the COVID-19 vaccine landscape—based on data available as of May 31, 2021—the various strategies for vaccine rollout, and the opportunities and challenges concerning equitable vaccine access.

With COVID-19 being a highly infectious disease, vaccine development is key to protecting the global populations against SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) and preventing its viral transmission. Generally, it takes a vaccine up to 10 years to go from laboratory and clinical testing to receiving country regulatory approval (see Figure 1).[1,2]

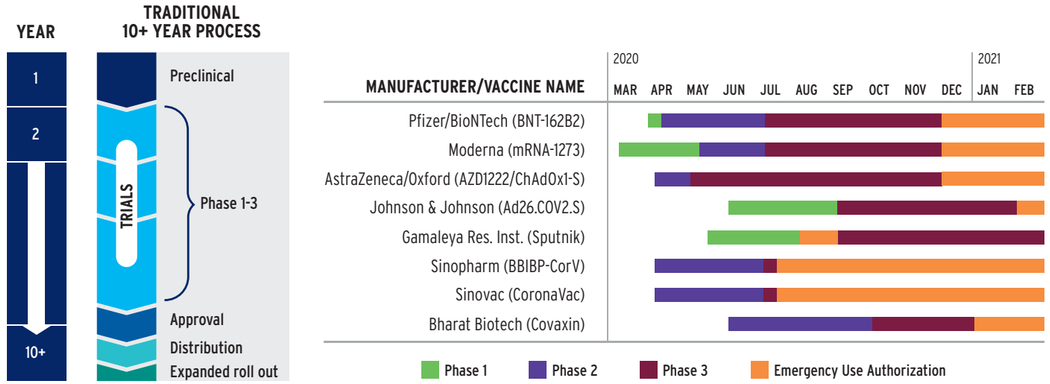
For the COVID-19 vaccines, there are several factors that allowed these timelines to be accelerated without skipping any steps in the development process while ensuring their safety and efficacy. Unprecedented funding from private and public sources allowed vaccine developers to run multiple clinical trials at the same time and manufacture product prior to country regulatory approval. For some vaccines, researchers used existing national or global clinical trial networks to rapidly recruit participants and conduct the trials. Even though some vaccine technologies may appear new, they actually leverage decades of research and experience against various infectious diseases (e.g., influenza, severe acute respiratory syndrome or SARS). Finally, vaccine developers closely collaborated with country regulators who expedited the pathway for vaccine authorization and/or approval. By the end of 2020, within one year of the initial outbreak, the world had multiple vaccines available for use.

Even though some vaccine technologies may appear new, they actually leverage decades of research and experience against various infectious diseases (e.g. influenza, severe acute respiratory syndrome or SARS).

Vaccines train the immune system to build a response by producing antibodies to protect people from contracting or developing severe COVID-19 disease and transmitting it to others. These are critical steps to controlling the spread of the virus.[3,4]

Of the COVID-19 vaccines authorized (as of April 30, 2021), four main vaccine platforms or technologies are utilized (see Figure 2 for a detailed overview).

FIGURE 1 | COVID-19 vaccine development compared to traditional vaccine development



mRNA vaccines contain synthetic strands of genetic material called mRNA that provide instructions for immune cells to produce harmless spike proteins, which are also found on the surface of SARS-CoV-2.[5,6] Once the spike proteins are produced, immune cells break down and remove the mRNA, preventing it from entering the nucleus of the cell. Thus, mRNA vaccines cannot alter DNA. Immune cells display the vaccine-generated spike proteins on their surface to generate an immune response and make antibodies similar to what happens during a COVID-19 infection. Although mRNA vaccines are now being used for the first time in humans for COVID-19, the technology has been studied for over 20 years against various diseases (e.g., influenza, rabies).

Viral vector vaccines developed for COVID-19 use a modified version of adenoviruses as vectors.[7,8] Adenoviruses are common viruses that infect humans, causing mild respiratory and gastrointestinal tract infections. When adenoviruses are used as a vaccine vector, they are modified to be unable to reproduce and cause infection. Once inside the cell, the adenovirus vector delivers instructions to make harmless spike proteins. Since the adenovirus vector vaccines do not contain the live virus, recipients cannot get COVID-19 disease from the vaccine. Prior to using the adenovirus vector vaccines for COVID-19, the platform was used in Europe for an Ebola vaccine.

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Protein subunit vaccines use specific parts of the virus, spike proteins or peptides, to stimulate the immune system. Protein subunit vaccines do not contain the entire virus pathogen.[9,10] Protein subunit vaccines have been successfully used to protect people from various diseases (e.g., hepatitis B, pertussis).

Inactivated virus vaccines use the entire virus, which has been killed or modified using chemicals, heat, or radiation to make it unable to replicate and cause infection.[11,12] Most non-COVID-19 vaccines available today use this platform (e.g., influenza, polio) since it can induce strong antibody response. However, these vaccines require special laboratory facilities to safely grow the virus, have a relatively long production time, and require booster shot(s) for ongoing protection—not ideal in a global pandemic where time is of the essence.

FIGURE 2 | COVID-19 vaccine platforms (as of April 30, 2021)

PLATFORM/TYPE	MANUFACTURER/SUPPLIER	VACCINE NAME	EFFICACY	APPROVAL OR AUTHORIZATION FOR EMERGENCY OR LIMITED USE	DOSE SCHEDULE
mRNA	Pfizer-BioNTech	Comirnaty Tozinameran	95%	85 countries	2 doses (separated by 21 days)
	Moderna	mRNA-1273	94%	46 countries	2 doses (separated by 28 days)
Viral vector non-replicating adenovirus	Oxford-AstraZeneca	Vaxzevria Covishield	79%	98 countries	2 doses (separated by 28 to 56 days)
	Johnson & Johnson/Janssen	Ad26.COV2.5	67%	41 countries	1 dose
	CanSino Bio Beijing	Ad5-nCoV Convidecia	65%	5 countries	1 dose
	Gamaleya Research Centre	Sputnik Gam-COVID-Vac	92%	65 countries	2 doses (separated by 21 days)
Inactivated virus	Sinovac Biotech	CoronaVac	51%	24 countries	2 doses (separated by 14 days)
	Sinopharm Beijing	BBIBP-CorV	79%	40 countries	2 doses (separated by 21 days)
	Sinopharm Wuhan	Vero Cells	86%	2 countries	2 doses (separated by 28 days)
	Bharat Biotech	BBV152 Covaxin	81%	9 countries	2 doses (separated by 28 days)
Protein-based	Vector State Research Center	EpiVacCorona	100%	2 countries	2 doses (separated by 21 days)

Sources: US National Library of Medicine, ClinicalTrials.gov; COVID 19 Vaccine Tracker, https://covid19.trackvaccines.org; and the European Medicines Agency, ema.europa.eu

THE RACE TO VACCINATE

Each country has developed its own strategy for protecting its population, influenced by the vaccine platform authorized, supply, and the regional epidemiology of the pandemic (e.g., number of and change in new cases, severity of disease, circulating variants).

As shown in Figure 2, the majority of authorized or approved vaccines require a two-dose schedule.[13,14] For countries that follow the manufacturers' guidelines or clinical trial evidence, this strategy is ideal if vaccine supply is relatively adequate. However, the vaccine rollout may slow down as the countries need to reserve supply for the second dose.

The United Kingdom and Canada have implemented a strategy to delay the second dose, contrary to the manufacturers' guidelines, in order to protect the largest number of individuals in the population as early as possible with a single dose while optimizing limited supply.[15,16] An exploratory analysis of the Oxford-AstraZeneca vaccine showed vaccine efficacy (VE) against symptomatic COVID-19 after one dose was 76% during the first 90 days.[17] Additionally, VE after the second dose was higher (81%) with a dosing interval of 12 weeks or more compared to a dosing interval of less than 6 weeks (55%). This is not the first vaccine to demonstrate greater protective efficacy with wider dosing interval—influenza, Ebola, and malaria vaccines have also demonstrated similar effects.

Although there are clear advantages with this strategy, there are some uncertainties. It is unclear if partial vaccination would increase the risk of viral mutations, which may lead to the emergence of new variants. As for the recipients, there are concerns some may forget to return for their second dose, have confusion with vaccination schedule, and/or believe one dose provides adequate protection.[18]

For the vulnerable, at-risk populations (e.g., people who are older, are immunocompromised, or have end-stage kidney disease, or ESKD), the duration of vaccine protection may be different, which raises the question of whether they should be exempt from this strategy and may require an additional (booster) dose to achieve the same level of protection as the general population.

Most countries have created a vaccine strategy based on age, with priority given to older people who are at higher risk for severe COVID-19 disease and death. Some countries have also prioritized healthcare workers, to ensure they are protected while they help sustain the healthcare system. As vaccine supply increases, some countries have expanded their prioritization lists to include people with chronic medical conditions who are highly vulnerable to COVID-19 (e.g., immunocompromised, ESKD). Emerging evidence has demonstrated that individuals with ESKD do develop and maintain an immune response after an infection or vaccine, and implementation of full vaccination protocols optimizes their protection.[19]

Emerging evidence has demonstrated that individuals with ESKD do develop and maintain an immune response after an infection or vaccine, and implementation of full vaccination protocols optimizes their protection.

Recently, some countries have been evaluating or have approved combining different vaccines for the two-dose regimen.[20] Mixing vaccine doses may be attractive in countries where there is supply shortage with the first-dose vaccine; using another vaccine for the second dose would overcome this issue as well as help people get vaccinated faster. Mixing vaccines may also be used when safety issues arise after the first dose that cause the recipients to be unable or unwilling to get a second one (e.g., severe allergic reactions, rare blood clots). Experts are evaluating if mixing two different vaccine platforms (e.g., adenovirus vector with mRNA) could enhance protection. Some uncertainties associated with this strategy include its impact on the efficacy of future booster dosing (if needed) and whether side effects are increased.

Regardless of what vaccine strategy/strategies a country adopts, the goal is to achieve a high vaccination rate to help people build immunity against COVID-19, a very contagious disease. During the early phase of the global vaccine rollout, there were hopes that once enough people were immunized, herd immunity could be achieved and viral transmission reduced. Based on experience from past infectious disease control, there are many barriers that can impact vaccine uptake, some of which have been identified in Figure 3.[21] Any of these factors, alone or in combination, will make it challenging to eliminate SARS-CoV-2 globally. In fact, is it realistic to expect to eliminate such a contagious virus over a short period? Despite discovering a vaccine for smallpox in 1796, this contagious disease was not globally eradicated until 1980, following almost 30 years of a coordinated WHO global campaign.[22]

Experts are evaluating if mixing two different vaccine platforms (e.g., adenovirus vector with mRNA) could enhance protection.

FIGURE 3 | Potential barriers to vaccination

EXAMPLES OF COMMON STRUCTURAL BARRIERS	
BARRIERS	**DESCRIPTION**
Cost	Price of vaccine or medical visit to receive the vaccine that is incurred by the individual
Convenience	The time someone has to take to get vaccinated, easy physical access, and geographic proximity to vaccines
Supply chain issues	Disruptions to or constraints on the manufacture, distribution, and delivery of vaccines

EXAMPLES OF COMMON ATTITUDINAL BARRIERS	
BARRIERS	**DESCRIPTION**
Complacency about the disease being prevented	Low perceived risk of contracting or severity of the disease being prevented
Perceived risks of vaccines	Belief that vaccines are harmful (i.e., they cause the disease they claim to prevent or cause other conditions)
Lack of trust	Mistrust toward vaccines, regulatory agencies that monitor vaccine development and distribution, healthcare workers who deliver vaccines, and companies that develop and produce vaccines
Misinformation	Belief in false information that is produced and distributed to create fear and uncertainty around vaccines
Misconceptions	Lack of knowledge about vaccines and recommendations to get vaccinated

If COVID-19 cannot be eradicated, then it is likely the virus will become an endemic disease, similar to influenza and four human coronaviruses that cause the common colds.[23] Through vaccination, acquired immunity from infection, and non-pharmacological interventions, some regions may be able to eradicate or substantially contain the virus; in other regions, COVID-19 will continue to circulate, but the annual number of infections, impact of the virus (severity and death), and need for social isolation will lessen. With the future of COVID-19 being unknown, it is critical for people to continue to adhere to public health mitigation measures (e.g., vaccinations, maintaining good hand hygiene) to reduce the spread of the virus.

THE IMPORTANCE OF EQUITABLE VACCINE ALLOCATION

The rapid development of COVID-19 vaccines has brought hope of potentially controlling this pandemic. However, this is only possible if everyone around the world has access to the vaccines. Despite the fact that many countries have accelerated the authorization or approval of different vaccines, some of these countries still do not have access to them. The following identifies several potential reasons why inequalities in vaccine allocation exist:[24]

- **Higher income countries have secured the available vaccine supply.**
- **Manufacturers are unable to provide vaccine supply despite efforts to ramp up production.**
- **The geographical landscape of a country may challenge vaccine distribution and/or storage requirements.**
- **Lower- and medium-income countries are unable to afford the cost of vaccines.**
- **There is limited access to vaccine intellectual property.**
- **There are restrictions or bans on exporting vaccines and/or raw materials needed to produce vaccines.**

To help ensure equitable global access to vaccines, tests, and treatments regardless of a country's wealth, a global initiative named COVAX, co-led by the Coalition for Epidemic Preparedness Innovations (CEPI), Gavi and the World Health Organisation (WHO), alongside a key delivery partner UNICEF was created. COVAX helps to develop, manufacture, and distribute vaccines in bulk while ensuring that the ability to pay is not a barrier to access.[25]

If COVID-19 cannot be eradicated, then it is likely the virus will become an endemic disease, similar to influenza and four human coronaviruses that cause the common colds.

FIGURE 4 | Vaccine doses purchased by income level compared with share of global adult population (as of July 7, 2021)

INCOME LEVEL	PERCENTAGE OF GLOBAL POPULATION 18 YEARS AND OLDER	SHARE OF POPULATION THAT HAS RECEIVED AT LEAST ONE DOSE
High income	19%	51%
Upper middle income	37%	31%
Lower middle income	37%	14%
Low income	7%	1%

As of July 7, 2021, 51% of individuals in high-income countries have received at least one dose, even though they account for 19% of the global adult population (Figure 4).[27] As for low income countries, only 1% of their population have received at least one dose, followed by 14% in low middle income countries. Additionally, disparities in vaccines is further impacted by region, with Europe having 40% of their population having received at least one dose, followed by the Americas (39%), while the African region has the lowest rate (2%) followed by Eastern Mediterranean region (9%). Critical to closing the disparities between countries, vaccine supply needs to be accessible and vaccination rates need to be increased. Therefore, it is imperative that high-income countries lead by example and assist in making vaccines accessible to everyone, which may require they share their existing or excess supply.

CONCLUSION

The future of COVID-19 vaccines is promising. In addition to the list of authorized vaccines already identified, over 90 vaccines are in clinical development and over 190 vaccines are in pre-clinical development.[28] The ease and success of the global vaccination program will be enhanced if these newer vaccines are available as a single dose, have easy storage and transport requirements, and offer novel forms of delivery (intranasal, subcutaneous, oral, etc.).

51% of individuals in high-income countries have received at least one dose, even though they account for 19% of the global adult population.

For the world to return to a "new normal" where people can safely socialize and travel again, a planned and phased approach to reopening and continued support of various public health measures (e.g., optimizing vaccinations, non-pharmaceutical interventions) will be critical. As COVID-19 evolves from being a pandemic to endemic disease, it is hoped that the virus will primarily cause mild to moderate disease and be less likely to cause severe disease and deaths in vaccinated individuals, especially in vulnerable populations.

THE EXPERTS

TERESA PORTELA, PhD

Head of Regional Crisis Situation Center and Medical Science Liaison Community, Fresenius Medical Care Europe/Middle East/Africa

Teresa Portela has broad healthcare experience acquired from her various positions within Fresenius Medical Care. Prior to joining Fresenius in 2008, she worked in the field of laboratory diagnostics for Siemens Healthcare for the North America region. In her current role, she helps individuals with kidney disease receive optimized care, diagnosis, and treatment in line with highest code of conduct standards. Her knowledge of the market's healthcare structure and medical regulations, combined with experience gained from her Crisis Response Team work in 2017-2021, has helped her support countries' structures to mitigate pandemic-related strategies and reshape them into new ways of engaging with healthcare providers across EMEA and globally. Teresa received her PhD in biochemistry and biotechnology from Rheinische Friedrich-Wilhelms-Universitat Bonn, Germany.

PHANETH KEO, PharmD

Vice President, Medical Science Liaisons and Medical Strategies for Innovative Therapies, Fresenius Medical Care, Renal Therapies Group

Since joining the Medical Affairs Department at Renal Therapies Group in 2007, Phaneth has managed the activities of the US Medical Science Liaison team. Additionally, Phaneth has been involved in various strategic initiatives involving the RTG portfolio, Global Research and Development predevelopment projects, and FMCNA. Phaneth received her doctorate from the Medical College of Virginia School of Pharmacy and completed a postdoctoral fellowship with Rutgers University Ernest Mario School of Pharmacy and Bristol Myers Squibb.

COVID-19–ASSOCIATED ACUTE KIDNEY INJURY: MANAGING PANDEMIC DEMAND SURGE FOR KIDNEY REPLACEMENT THERAPY IN THE UNITED STATES

Dinesh Chatoth, MD
David Thompson, DO

During the COVID-19 pandemic, 30-40% of patients admitted to hospitals developed acute kidney injury (AKI). The number of patients requiring kidney replacement therapy (KRT) increased dramatically, putting overburdened hospitals under even further strain. To help meet the needs of patients throughout the US, Fresenius Medical Care North America (FMCNA) deployed its Disaster Relief Team, which included 600 volunteer staff members and contract nurses. In addition, FMCNA created a pool of dialysis equipment and supplies that could be quickly routed to hospitals around the country. FMCNA's well-coordinated response underscores the need for a frequently updated surge plan that is always ready for the next healthcare emergency.

Kidney involvement in patients with COVID-19 infection has been commonly observed throughout the pandemic and varies from mild asymptomatic hematuria and proteinuria to acute kidney injury (AKI) requiring kidney replacement therapy (KRT). Initial reports from Wuhan, China, indicated that AKI rates related to COVID-19 infection were insignificant.[1,2] However, very soon, growing evidence from Europe and New York showed that AKI from COVID-19 developed in 30-40% of patients admitted to the hospital and is associated with a considerable number of in-hospital deaths.[3,4]

AKI associated with COVID-19 can result from intrinsic renal pathology—including vascular thrombosis, viral mediated renal tubular injury, and glomerulonephritis—and from acute tubular necrosis resulting from fluid depletion, cytokine mediated systemic inflammatory syndrome, multiorgan failure, and rhabdomyolysis. Kidney biopsies are essential in understanding the pathogenesis of COVID-19–associated AKI. However, there are only a few series of kidney biopsies reported in COVID-19–associated AKI patients, with the majority of them showing acute tubular injury. Risk factors for COVID-19–induced AKI are shown in Figure 1.

A meta-analysis showed that among critically ill patients with COVID-19 the pooled prevalence of AKI was 46% and 19% of patients in the ICU required KRT.[5] Patients with COVID-19–associated AKI have higher mortality rates than those with COVID-19 without AKI. The mortality rate increases with severity of AKI and need for KRT.[6,7] A retrospective study found that 68% of people with COVID-19 AKI requiring KRT died during hospitalization.[8]

A different study came to similar conclusions. When compared to patients without COVID-19, AKI associated with COVID-19 was more severe, including necessitating KRT and being associated with lower in-hospital kidney recovery.[9,10] In a single center experience in New York, there was a high incidence (23%) and peak prevalence (29%) of severe AKI requiring KRT among critically ill patients. Although half of these patients died, the majority (84%) of those who survived had sufficient recovery of kidney function to allow cessation of KRT.[11]

FRESENIUS MEDICAL CARE NORTH AMERICA'S RESPONSE TO AKI ASSOCIATED WITH COVID-19

Over the past year, the COVID-19 pandemic was associated with regional surges and global hot spots worldwide; the United States saw at least three distinct waves of COVID-19 cases by June 2021. The pandemic's ebbs and flows put severe strain on hospital resources, including staffing, and availability of dialysis equipment and supplies (Figure 2).[12] In New York City, the KRT demand for AKI patients was four to five times higher during the pandemic. Fresenius Medical Care North America's (FMCNA) vertically integrated network was extremely valuable in meeting the needs of patients throughout the US. FMCNA's Disaster Response team, which typically responds to natural disasters like earthquakes and hurricanes, played a critical role. Its relationships with emergency operation centers, federal and state governments, and hospital systems have been instrumental in the effective coordination and response to the pandemic.

MANAGING KRT DEVICES, DISPOSABLES, AND SUPPLIES

Demand for dialysis machines needed to manage cases of AKI increased 279% over baseline during the spring of 2020 in New York City.[13] Increased regional demand required the ability to deliver KRT equipment where it was needed while simultaneously avoiding a surplus of unused equipment elsewhere. To coordinate distribution of equipment in a fair and informed manner, a team was formed that included members of sales, operations, logistics, supply chain, customer service, and contracts departments. Additionally, an inventory tracking tool was created to provide real-time orders, demand, and machine availability.

FIGURE 1 | Risk factors for COVID-19-associated AKI

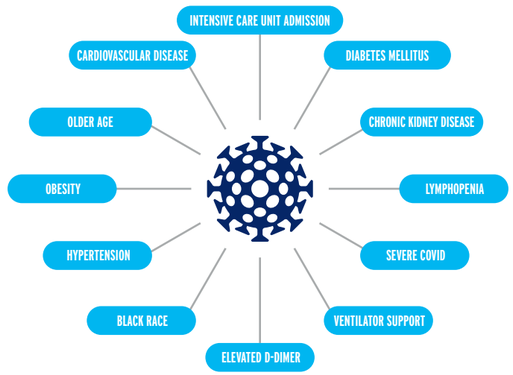
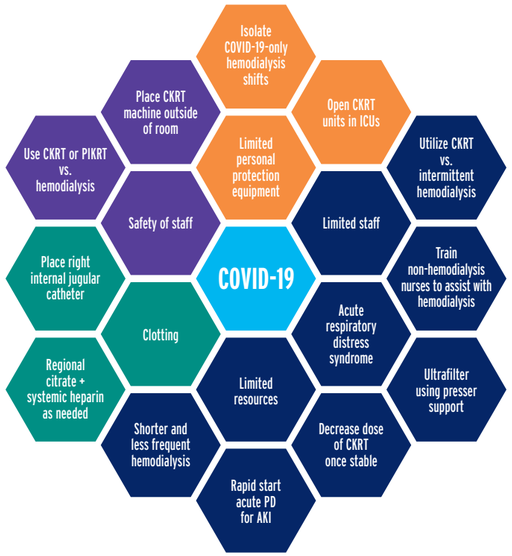


FIGURE 2 | Special challenges and strategies for KRT delivery in patients with COVID-19-associated AKI



To meet the increasing demand, several operational and manufacturing adaptations were implemented:

- **Increased the bagged dialysate solutions, including increasing the production of bicarbonate**
- **Expanded lactate-based home solutions for use in hospitals**
- **Received Emergency Use Authorization for Multifiltrate PRO device and MultiBic/MultiPlus Dialysis bagged solutions**
- **Doubled the manufacturing capacity for tubing sets and filters**
- **Increased the availability of supplies and expanded training to support acute peritoneal dialysis (PD)**

FMCNA formed a National Intensive Renal Care reserve to provide dialysis machines and related equipment for the US hospitals that were reeling under the pressure of the pandemic. The team created a pool of more than 150 pieces of dialysis equipment that were ready for rapid deployment to hospitals, to manage the three to five times increase in regional demand for KRT. This included partnering with the NxStage team to redeploy existing NxStage critical care machines to areas of need with one week's notice, allocating a pool of NxStage system one cyclers to provide additional capacity in ICUs, and increasing the premixed dialysate supply by 75%. The equipment and supplies were housed for rapid deployment and efficiently managed by the local Fresenius Kidney Care (FKC) Inpatient Services team, working closely with the NxStage team.

MANAGING STAFFING AND SERVICES DURING SURGE IN COVID-19 AKI CASES

Early in the pandemic, FKC mobilized over 600 staff members who volunteered to travel to hospitals and in-center programs across the country. Nurses and technicians were deployed to areas designated as hot spots. Additionally, contract nurses were deployed to acute dialysis programs in Tacoma, New York City, Chicago, and other cities due to the significant increase in demand for dialysis staff.

The FKC in-patient services team responded to the increased demand for KRT in the hospitals by:

- **Creating amendments to acute dialysis agreements with hospital systems to provide extended KRT—i.e., prolonged intermittent KRT, sustained low-efficiency dialysis, or continuous KRT—to critically ill patients in the ICU**
- **In select markets, supporting acute PD in ICUs by providing supplies, equipment, and nursing assistance**
- **Following state-specific executive orders and board of nursing guidance around licensure and emergency privilege for staff**
- **Adjusting staffing ratios of patient care technicians and licensed practical nurses to manage surge-related staffing needs**
- **Creating various care delivery models specific to the pandemic to increase the RNs' ability to safely oversee more patients receiving KRT**
- **Assisting nephrologists and dialysis administrators with triaging care and allocating valuable dialysis resources, which included expanding the options for KRT**
- **Working closely with hospital systems to manage the influx of patients in alternative locations across many hospital campuses and newly created COVID-19 units**
- **Partnering with outpatient dialysis units to discharge stable patients into COVID-19–positive treatment shifts**

COVID-19–ASSOCIATED AKI-D IN OUTPATIENT DIALYSIS FACILITIES

Many COVID-19 survivors with AKI do not recover baseline kidney function at the time of discharge from the hospital. A study from New York showed that 32% of all hospitalized patients had not recovered baseline kidney function at a median of 21 days after hospital discharge.[14] Another cohort study of 1,612 patients with COVID-19–associated AKI found that these patients experienced greater decreases in estimated glomerular filtration rate independent of comorbidities and severity of the AKI episode compared with patients with AKI not associated with COVID-19. The subgroup of COVID-19–associated AKI patients who had not recovered baseline kidney function at discharge were less likely to achieve complete kidney recovery during outpatient follow-up.[15]

A substantial number of COVID-19–associated AKI patients requiring dialysis (AKI-D) were discharged from the hospitals to FKC outpatient facilities. During the pandemic, the number of new patients with AKI-D receiving outpatient dialysis at FKC facilities increased from approximately 1,000 patients per month to 1,350 patients per month. Additionally, the total number of patients with AKI-D treated per month at FKC outpatient facilities increased from approximately 3,200 patients to 3,700 patients. This increase in AKI patient volume at outpatient dialysis facilities during the pandemic placed additional strain on the operations and management of the facilities, which were already stretched for resources. Importantly, approximately one-third of individuals with AKI-D following COVID-19 recovered enough kidney function to discontinue outpatient dialysis within 90 days of starting outpatient dialysis.

PREPARING FOR FUTURE PANDEMICS

The COVID-19 pandemic provides an opportunity to prepare for the provision of KRT in future pandemics.[16] To be better prepared, the healthcare system needs to develop a surge plan that is routinely updated. A coordinated response to an increase in KRT, at both the regional and national levels, is critical and must include expanding the options for KRT, including acute PD, intermittent HD, prolonged intermittent kidney replacement therapy (PIKRT), and continuous kidney replacement therapy (CKRT). In addition, the plan must address the potential for unforeseen shortages of KRT devices, disposables, and fluids, as well as manufacturing and supply chain issues.

The lessons learned from managing COVID-19–associated AKI during the pandemic are shown in Figure 3.

ACKNOWLEDGMENTS

The authors thank Gina Sharkey, vice president for Inpatient Services, and Tana Waack, vice president for Inpatient Services at Fresenius Kidney Care, for their editorial assistance and for sharing their valuable experience during this unprecedented pandemic.

FIGURE 3 | Lessons learned from managing COVID-19-associated AKI

CHALLENGE	LESSONS LEARNED (PREPARATIONS FOR FUTURE SURGES IN DEMAND)
Shortage of HD disposables and solutions	• Initiate rapid patient census tracking • Provide routine hospital communications to assess demand • Increase inventory and material tracking • Develop a team to manage pandemic demand
Shortage of HD machines	• Create and maintain a machine reserve • Refurbish traded hemodialysis machines to add to reserve • Develop new and unique business agreements for use in emergency situations • Quickly deploy PIKRT training to treat >1 patient with 1 machine during a 24-hour period
Staffing (including volunteers)	• Activate processes and workflows to address pandemic staffing needs, including volunteers • Develop vetting process for staff and volunteers • Provide extended KRTs in hospitals
Staff training	• Immediately train staff on new KRT modalities utilizing educators • Improve processes for credentialing and approving staff to assist during public health emergencies
Policies and procedures	• Continuously update infection control policies to care for patients with novel transmissible infections • Provide ongoing updates to operational policies to address pandemic-related changes
Market level surge reports	• Create and maintain surge reports to prioritize resources
Triaging and allocation of KRT	• Share disaster and pandemic response plans with hospitals and nephrologists • Maintain daily communication with nephrologists, hospitals, and other key stakeholders to determine KRT needs

THE EXPERTS

DINESH CHATOTH, MD

Associate Chief Medical Officer, Fresenius Kidney Care

Dinesh Chatoth oversees home therapy initiatives for the Medical Office and serves on the FKC Pharmaceutical and Therapeutics Committee. He has worked with the KDOQI workgroup for peritoneal dialysis and promotes home dialysis as a modality of choice for patients requiring kidney replacement therapy. Dr. Chatoth was an assistant professor of medicine and director of the dialysis program at the University of Arkansas for Medical Sciences. He is the former president and CEO of Georgia Nephrology, a 16-member physician practice in Atlanta, and has also served in different leadership roles at a health system in Georgia, including chair of the Department of Medicine. Dr. Chatoth completed his fellowship in nephrology at the University of Texas Southwestern Medical Center in Dallas.

DAVID THOMPSON, DO

Vice President and Medical Director, Critical Care, Fresenius Medical Care, Renal Therapies Group

David Thompson joined FMCNA's Renal Therapies Group in 2019 after 15 years of clinical practice in nephrology and critical care nephrology in Oklahoma City, Oklahoma. While in practice, he served as president and vice chief of staff of Integris Edmond Medical Center and held other leadership positions in the health system, including establishing and chairing the Sepsis Committee. He has served as director and regular lecturer for the Fundamental Critical Care Support course. He received his bachelor's degree in physiology and his medical degree from Oklahoma State University. He completed his postgraduate training with board certification in internal medicine, nephrology, and critical care medicine at the prestigious Mayo Graduate School of Medicine in Rochester, Minnesota.

GLOBAL INSIGHTS: HOW FRESENIUS MEDICAL CARE INCREASED THE UNDERSTANDING OF COVID-19

Peter Kotanko, MD, FASN
Caitlin Monaghan, PhD

During the early days of the COVID-19 pandemic, Fresenius Medical Care responded quickly. As the world's largest provider of care for people with end-stage kidney disease, the company took the lead in developing effective strategies to protect patients, families, caregivers, and clinical staff. It also focused its scientific and research expertise on increasing the global body of knowledge about COVID-19. The depth and breadth of peer-reviewed papers, research grants, and awards attest to the contributions of Fresenius Medical Care researchers and their associates.

The COVID-19 pandemic sparked an unprecedented surge in biomedical research and demonstrated what can be achieved when working toward a joint goal. As the world's largest provider of care for individuals with end-stage kidney disease (ESKD), Fresenius Medical Care swiftly pivoted resources to address pandemic-related knowledge gaps for individuals with kidney disease, contributing to the global body of knowledge (Figure 1). The goal of these activities was to provide insights to improve care for individuals with ESKD receiving dialysis and further understand potential innovative diagnostic strategies. The following is a summary of peer-reviewed publications that associates of and scientists within Fresenius Medical Care contributed to, along with federal funding awards.

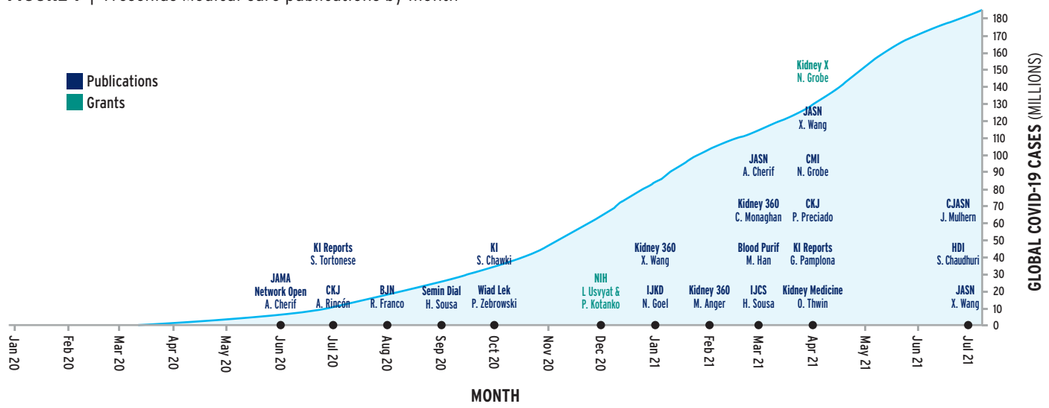
Early on during the crisis, it became apparent that individuals with COVID-19 were at significantly higher risk of developing acute kidney injury (AKI), leading to the need for dialysis, mechanical ventilation, vasopressor use, and other critical care interventions, summarized in a review by Goel et al.[1] The pandemic created a surge in hospitalized patients requiring dialysis and resulted in a shortage of continuous renal replacement therapy (CRRT) machines across the United States. Anger et al. detailed the many steps Fresenius Medical Care North America (FMCNA) took to ensure the care of individuals with AKI.[2]

THE CHALLENGE OF DIAGNOSING COVID-19

At the beginning of the pandemic, testing resources for SARS-CoV-2 were limited. To address this pressing problem, a test strategy called "pool testing" was proposed by Cherif et al.[3] Pool testing strategies combine samples from multiple people and test them as a group. This approach can shorten the screening time and increase the test rate and reporting speed. The authors put pool testing on a sound mathematical basis. The paper was widely referenced, and in July 2020, shortly after its publication, pool testing for COVID-19 received emergency use authorization from the US Food and Drug Administration (FDA). In their extensive narrative review, Grobe et al. described practical aspects and current experience with pool testing.[4] In April 2021, the FDA announced a streamlined approach to include pooled serial screening to testing protocols. Additionally, several communities—such as universities, hospitals, and long-term care homes in Asia, Europe, South America, and Africa—implemented pool testing strategies.

Fresenius Medical Care explored how innovative devices and artificial intelligence may potentially improve identification of individuals with COVID-19. Using Fresenius Medical Care's Crit-Line® device, Preciado et al. explored arterial blood oxygen saturation (SaO2) levels before the diagnosis of COVID-19 and discovered that SaO2 declined sharply during the incubation period in patients who were later either hospitalized or passed away.[5] Monaghan et al. built a machine-learning model to identify COVID-19 infections days before symptoms occurred.[6] Their predictive model identified subtle patterns in changes in treatment and laboratory measurements indicating an active infection. The authors proposed using this model to augment screening currently in place to identify pre-symptomatic and potentially asymptomatic individuals receiving hemodialysis. In their research, Chaudhuri et al. identified trajectories of clinical and laboratory characteristics associated with COVID-19 in hemodialysis patients.[7]

FIGURE 1 | Fresenius Medical Care publications by month



PERITONEAL DIALYSIS

There were early concerns in 2020 that SARS-CoV-2 may infect peritoneal fluid, rendering spent peritoneal dialysate potentially infectious. Collaborating with the FMCNA Medical Office, Wang et al. collected 26 spent peritoneal dialysis (PD) dialysate samples from 11 patients at 10 Fresenius Kidney Care (FKC) and Renal Research Institute (RRI) dialysis centers.[8] The research indicated the absence of SARS-CoV-2 in spent peritoneal dialysate collected 10 or more days after the onset of COVID-19 symptoms; however, SARS-CoV-2 in spent dialysate in the early stage of COVID-19 could not be ruled out. Subsequently, Wang et al. pioneered the identification of SARS-CoV-2 antibodies in spent peritoneal dialysate.[9] This is important, as PD effluent antibody testing could complement serum serology testing. Whether post–COVID-19 or vaccinal antibodies in PD effluent indicate immunity is a topic of ongoing research. As the world is accelerating vaccination efforts, a point-of-care test (e.g., lateral flow assay) will allow individuals on PD to quickly and frequently check for SARS-CoV-2 antibodies in spent dialysate and monitor the antibody response between clinic visits.

HEMODIALYSIS

Fresenius Medical Care clinics reacted swiftly to the pandemic by implementing strict protective measures for patients and clinic staff, such as universal masking and entrance controls. It is of greatest interest to understand if and to what extent these efforts have translated into lower infection rates in individuals receiving dialysis. Cherif et al. analyzed aggregated daily counts of confirmed COVID-19 cases from March 1 to July 29, 2020, in the general US population and FKC, and then computed the time-varying reproduction number Rt, which represents the expected number of secondary cases arising from each new infectious individual.[10] They demonstrated that for most US states, the lifestyle of in-center hemodialysis patients and interventions to prevent SARS-CoV-2 spread were effective in reducing risk. These results were directionally corroborated by Thwin et al., who conducted a seroprevalence study in New York City and compared the prevalence of SARS-CoV-2 antibodies in dialysis clinic staff and in-center patients with publicly available seroprevalence data.[11]

Fresenius Medical Care clinics reacted swiftly to the pandemic by implementing strict protective measures for patients and clinic staff, such as universal masking and entrance controls. It is of greatest interest to understand if and to what extent these efforts have translated into lower infection rates in individuals receiving dialysis.

An early report by Tortonese et al. highlighted the severity of COVID-19 infections in 44 individuals on maintenance dialysis who were referred to an in-patient hospital dialysis center in the Paris, France, region from March 11 to April 11, 2020.[12] In comparison to non-dialyzed patients admitted to the hospital, the mortality rate of individuals receiving dialysis was over twice as high and in-ICU mortality was almost three times higher. Additionally, they found that cough, thrombopenia, higher LDH concentrations, and higher blood CRP concentrations were independently associated with higher mortality in individuals receiving dialysis.

Chawki et al. reported on associations between elements within medical treatment histories and mortality risk in almost 250 individuals affected by COVID-19 and receiving hemodialysis.[13] Along with widely reported risk factors such as age, facility living, and dyspnea, they also found that previous immunosuppressive treatment was associated with increased mortality. However, previous treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was associated with decreased mortality. Rincón et al. reported retrospective analyses after a COVID-19 outbreak in a hemodialysis clinic prompted clinic-wide COVID-19 testing.[14] After testing the entire clinic for COVID-19 infection, the authors discovered that asymptomatic cases accounted for almost 40% of all infections. Key risk factors included living in a nursing home or being homeless, hospital admission in the previous two weeks, and sharing healthcare transportation with a future positive patient—none of which differed significantly between those who were symptomatic and asymptomatic.

Early in the pandemic, elective surgeries were postponed in many countries worldwide. Initially this included vascular access procedures as well. After an outcry from the nephrology community at large and, for example, from Franco et al. in Brazil, it was ultimately clarified that vascular access procedures should not be considered elective.[15] Żebrowski et al. argued that infection control measures necessary to contain and prevent outbreaks should drive adoption of home therapy in healthcare systems, especially in countries such as Poland where home therapy rates are very low.[16]

Using activity trackers worn by 42 individuals receiving in-center hemodialysis, Han et al. were the first to report the impact of lockdown on physical activities.[18] After a national emergency was declared in the United States, the average number of daily steps in this small cohort decreased sharply. Most interesting, compared to those who were COVID-19 negative, five out of six individuals who tested positive exhibited significantly higher physical activity in the two weeks prior to developing COVID-19 symptoms.

The pandemic took a toll on individuals in ways unrelated to infections, as reported by Sousa et al.[17] A quantitative and qualitative analysis of changes in patient characteristics from pre-outbreak (February 2020) to lockdown (April 2020) in Portugal revealed that both dialysis adequacy and serum albumin levels decreased significantly, while phosphorus levels increased. While no changes to dialysis prescriptions were reported during this time, treatments were significantly shorter during the lockdown, which could contribute to this finding. The authors also proposed an additional explanation based on associations with qualitative findings from semi-structured interviews with individuals receiving dialysis who reported decreased physical activity and increased difficulties with managing dietary and fluid restrictions.

It is important to keep in mind the pandemic's impact not only on patients and clinicians, but family caregivers as well. Sousa et al. performed a qualitative study interviewing family caregivers and identified four major themes surrounding additional caregiver burdens: emotional distress, changes in caregiving responsibilities, educational and supportive needs, and coping strategies to deal with the outbreak and lockdown.[19]

VACCINATION AGAINST SARS-COV-2: A SILVER LINING

It is undisputed that comprehensive vaccination is key to overcoming the pandemic. Pamplona et al. were the first to report on vaccination acceptance and hesitancy in staff from four RRI dialysis clinics located in New York City.[20] Out of 157 staff members, 42 (26.8%) were not vaccinated for various reasons, such as leave of absence (4; 2.6%), pregnancy or breastfeeding (8; 5.1%), past COVID-19 (24; 15.3%), and explicitly expressed vaccination hesitancy (6; 3.8%). In the authors' opinion, the low rate of vaccination hesitancy was due to transparent information and unanimous support of vaccination by all levels of leadership, among other factors. Mulhern et al. compared antibody response of mRNA-based vaccine with an adenovirus vector-based vaccine (Ad26.COV2.S) in dialysis patients. The authors found that markedly fewer dialysis patients vaccinated with Ad26.COV2.S had an adequate antibody response to SARS-COV2 when compared to patients vaccinated with mRNA vaccines.[21]

RESEARCH GRANTS AND AWARDS

Funding agencies around the world swiftly issued requests for research proposals in response to the pandemic. A research network composed of the FMCNA Medical Office, RRI, the University of California Santa Barbara, and the University of Pennsylvania was awarded a three-year research grant by the US National Institutes of Health for the project "Early Detection, Containment, and Management of COVID-19 in Dialysis Facilities Using Multi-Modal Data Sources." The goal of this project is to predict COVID-19 by using advanced statistical methods on routinely collected data.

The US Department of Health and Human Services and the American Society of Nephrology joined forces to establish the KidneyX COVID-19 Kidney Care Challenge. This effort seeks solutions to reduce the transmission of SARS-CoV-2 among people with kidney diseases and/or reduce the risk of kidney damage among people who contract the virus. Grobe et al. from RRI were awarded a grant to support their innovative proposal, "Pool Testing of Used Masks for Timely Diagnosis of SARS-CoV-2." Because face masks must be worn by all in-center patients and staff, testing of spent face masks may be a novel method to diagnose SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR). In a proof-of-concept research study, Wang et al. have implemented face mask testing in RRI clinics located in New York City. The researchers were able to detect SARS-CoV-2 RNA on worn face masks and identified a hitherto undiagnosed patient with COVID-19.[22]

Mask testing may lend itself to pool testing, a strategy that is particularly efficient in settings with a low disease prevalence.[23,24] This approach will require the development of setting-specific workflows to optimize mask collection and processing.

CONCLUSION

While social distancing required during the COVID-19 pandemic has kept many apart, it could not contain the flourishing of ideas, analytics, or drive to keep individuals with kidney failure and their providers safe, which is apparent in the number of peer-reviewed publications from and awards received by Fresenius Medical Care and associates. Through a strong commitment to providing the best care and collaboration, Fresenius Medical Care has advanced knowledge across a wide spectrum of topics surrounding COVID-19 across the globe.

Mask testing may lend itself to pool testing, a strategy that is particularly efficient in settings with a low disease prevalence.

THE EXPERTS

PETER KOTANKO, MD, FASN
Research Director, Renal Research Institute
Senior Vice President, Research and Development

Noted researcher and scholar Peter Kotanko is research director of the Renal Research Institute (RRI). RRI's research aims to improve patient outcomes and quality of life. An adjunct professor of medicine and nephrology at the Icahn School of Medicine at Mount Sinai in New York City, he has authored and coauthored more than 330 research papers and book chapters, and is the former vice chair of a medical department at an academic teaching hospital in Graz, Austria.

CAITLIN MONAGHAN, PhD
Senior Data Scientist, Applied Data Science, Biostatistics, and Epidemiology, Fresenius Medical Care

Caitlin is a senior data scientist whose focus is on designing, building, and implementing predictive analytics machine learning models to improve patient care and provide support to groups across the Fresenius Medical Care enterprise. Since joining Fresenius in June 2019, Caitlin has contributed to and presented conference abstracts, given talks on data science, and published manuscripts in peer-reviewed journals. Caitlin holds a master's degree in psychology from the University of Oregon and a PhD in neuroscience from Boston University.

ABOUT THE GLOBAL MEDICAL OFFICE

Led by Dr. Franklin W. Maddux, the Global Medical Office translates science into actionable medicine and facilitates the exchange of knowledge and collaboration among the company's medical-clinical, scientific, and business leaders. By focusing on common strategic priorities, teams across the network are fostering the most promising ideas, accelerating data-driven precision healthcare and research, and advancing the application of clinical science for the benefit of patients worldwide.

GLOBAL MEDICAL OFFICE LEADERSHIP

Franklin W. Maddux, MD, FACP

Global Chief Medical Officer, Member of the Management Board

Franklin W. Maddux is global chief medical officer for Fresenius Medical Care, overseeing the delivery of high-quality, value-based care for the world's most expansive kidney care organization. His distinguished career encompasses more than three decades of experience as a physician, expert nephrologist, technology entrepreneur, and healthcare executive. Dr. Maddux joined Fresenius Medical Care's North America region in 2009 after the company acquired Health IT Services Group, a leading electronic health record (EHR) software company, which he founded. He developed one of the first laboratory electronic data interchange programs for the US dialysis industry and later created one of the first web-based EHR solutions, now marketed under Acumen Physician Solutions. He previously served as chief medical officer and senior vice president for Specialty Care Services Group and is the former president of Virginia's Danville Urologic Clinic, where he was a practicing nephrologist for nearly two decades. His writings have appeared in leading medical journals, and his pioneering healthcare information technology innovations are part of the permanent collection of the National Museum of American History at the Smithsonian Institution. An alumnus of Vanderbilt University, Dr. Maddux earned his medical degree from the School of Medicine at the University of North Carolina at Chapel Hill, where he holds a faculty appointment as clinical associate professor.

Juan Carlos Berbessi, MD

Vice President, Global Head of Medical Office Compliance; Chief Medical Officer, Latin America

As chief medical officer for Fresenius Medical Care Latin America, Juan Carlos Berbessi leads delivery of all medical and scientific activities across the region. He joined Fresenius Medical Care as regional medical director in 2018. Previously, he served as medical affairs director, overseeing delivery of all medical and scientific activities across therapeutic areas in Colombia. Trained in epidemiology and molecular biology, Dr. Berbessi has served as spokesperson to external and internal bodies on medical and scientific issues related to medical products, and he integrates medical and scientific insight into affiliate, regional, and global strategies. His career spans nearly three decades with over 20 years of experience in the pharmaceutical industry across five multinational companies: Hoechst, GSK, Wyeth, AMGEN, and AbbVie. He obtained his medical degree from Universidad Libre, and trained in biomedical research at the Pontificia Universidad Javeriana and in microbiology and human genetics at the Universidad de los Andes in Colombia.

Michael Etter, MD, MBA, MPH, PhD

Senior Vice President; Global Head of Critical Care Therapies; Chief Medical Officer, Asia Pacific

Michael Etter joined Fresenius Medical Care Asia Pacific in 2009, leading the Medical Office and the Medical Affairs departments. As chief medical officer, Dr. Etter oversees all medical aspects of the medical device and pharmaceutical business segments as well as the healthcare services provided in dialysis clinics, hospitals, and other medical institutions within Asia Pacific. In addition to his medical support related to CKD and ESKD across the portfolio of healthcare services and products provided in Asia, Dr. Etter's clinical focus is on critical care medicine and related extracorporeal therapies. He holds board certifications in surgery, emergency medicine, and medical quality management. He is a graduate of the Technical University Munich Medical School in Germany and holds dual master's degrees in business administration and public health.

Robert J. Kossmann, MD, FACP, FASN

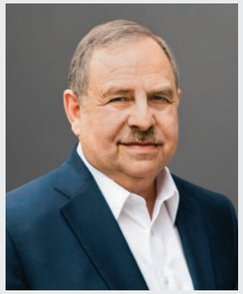
Executive Vice President; Global Head of Renal Therapies; Chief Medical Officer, North America

Robert (Rob) Kossmann is executive vice president and chief medical officer for FMCNA. From 2014 to 2019, he served as senior vice president and chief medical officer for Fresenius Medical Care's Renal Therapies Group, the company's medical equipment and renal pharmaceuticals division. Dr. Kossmann has been instrumental in helping guide the nephrology field through leadership roles, including formerly serving as president of the Renal Physicians Association (RPA); a founding member of RPA's Nephrology Coverage Advocacy Program (now Policy Advocacy Leadership program); a nephrology advisor to the American Medical Association's Relative Value Scale Update Committee; and founder of the New Mexico Renal Disease Collaborative Group. A practicing nephrologist for two decades, Dr. Kossmann trained in nephrology at the University of Washington in Seattle and holds his bachelor's and doctor of medicine degrees from Case Western Reserve University in Cleveland, Ohio.

Frank Laukhuf, MD

Senior Vice President; Head of Medical Affairs Products for Europe/Middle East/Africa, Asia Pacific, and Latin America; Chief Medical Officer, Europe/Middle East/Africa

Frank Laukhuf is head of the medical office throughout Europe, the Middle East, and Africa. At the cross-regional level, he leads the Medical Affairs Products team that medically manages the entire product portfolio of Fresenius Medical Care (both medical devices and drugs) around the globe except for the United States. Frank is a board-certified internist and nephrologist. He spent 15 years in direct patient care and several years in hospital management, allowing him to gain extensive insights into the healthcare systems of Germany and Switzerland in particular. After joining Fresenius Medical Care in 2011, Frank led the development and expansion of the medical product governance function in EMEA before taking over as chief medical officer of EMEA. He holds a doctor of medicine from Heidelberg University in Germany as well as a postgraduate diploma in health economics.



Jeffrey L. Hymes, MD

Executive Vice President; Global Head of Clinical Affairs; Chief Medical Officer, Fresenius Kidney Care North America

Jeffrey Hymes joined FMCNA in 2007 after three decades in nephrology practice and governance. He co-founded REN Corporation in 1986 and National Nephrology Associates (NNA) in 1998. He served as NNA's president and chief medical officer from 1998 to 2004. He served as president of Nephrology Associates, a 32-physician nephrology practice in Middle Tennessee, from 1989 to 2012. Dr. Hymes is a former member of the Renal Physician Association's board of directors. He is a graduate of Yale College and the Albert Einstein College of Medicine, completed his medical internship and residency at Yale New Haven Medical Center, and did subspecialty training in nephrology at Boston University. Dr. Hymes is board certified in internal medicine and nephrology, and previously certified in critical care.

Stefano Stuard, MD, PhD

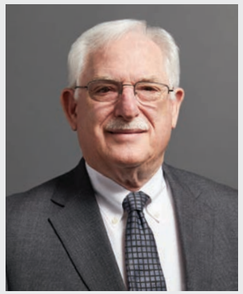
Senior Vice President; Chief Clinical Officer, Europe/Middle East/Africa

Stefano Stuard supports the NephroCare medical leadership in his role as chief clinical officer for the EMEA region. He previously served as vice president and head of the EMEA Center of Excellence for Clinical and Therapeutic Governance, and continues as the operational medical counsel for the company's services business in EMEA. Dr. Stuard's distinguished career includes more than a decade with Fresenius Medical Care in clinical governance roles for the company's EMEA and Latin America regions. He has served as a director/consultant for nephrology and dialysis departments in Italian public and private hospitals. He has published over 150 manuscripts in peer-reviewed journals. Dr. Stuard received his PhD in nephrology from the University of Bologna (Italy), his doctor of medicine and surgery, and a post-graduate specialization in nephrology magna cum laude, both from the University of Chieti (Italy). He received an award from the European Society of Artificial Organs for his contribution in the field of artificial organs.

Bernard Canaud, MD, PhD

Senior Chief Scientist

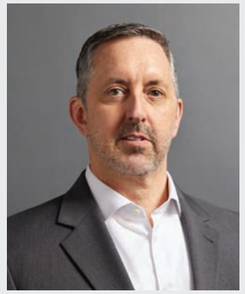
Bernard Canaud serves as senior chief scientist for the Global Medical Office and is the former chief medical officer for Fresenius Medical Care's Europe/Middle East/Africa region. Throughout his distinguished career, he has served on the editorial boards of nearly a dozen prestigious academic journals. He is the former president of the Société Francophone de Dialyse and has published over 400 referenced manuscripts, written chapters in more than 80 books, and contributed to nephrology congresses worldwide with more than 1,500 presentations. Dr. Canaud has contributed to the development of the European Best Practice Guidelines on dialysis fluid purity, vascular access, and anemia management and has been a coinvestigator of the international DOPPS study. He was an expert member of the French HAS (Haute Autorité de Santé) for renal replacement therapies. He headed the nephrology, dialysis, and intensive care departments at Lapeyronie University Hospital for 25 years. Dr. Canaud is currently emeritus professor of nephrology at the Montpellier University School of Medicine in France. He graduated with his doctor of medicine from Montpellier Medical School and received his master of science doctorate in nutrition from the University of Sciences, Montpellier. In addition, he has received several awards and distinctions throughout his career.



Allan J. Collins, MD, FACP

Senior Chief Scientist

Allan Collins has a distinguished career with more than 30 years of work in nephrology and ESKD treatment. He is the former chief medical officer for NxStage Medical, Inc. and served as director of the National Institutes of Health's/NIDDK's United States Renal Data System from 1999 to 2014. Dr. Collins has published more than 300 articles, 600 abstracts, and 20 book chapters, and has given more than 365 invited presentations. His clinical experience and research have focused on acute and chronic care of ESKD and chronic kidney disease patients, and prospective and retrospective clinical studies on dialysis techniques and associated outcomes. The former president of the National Kidney Foundation, Dr. Collins served on the NKF scientific advisory board for six years, with the Kidney Dialysis Outcomes Quality Initiative, and on the International Society of Nephrology's Commission for the Global Advancement of Nephrology Committee. He graduated with his medical degree from Wayne State University in Detroit.



Kurt Mussina, MBA

Senior Vice President; President, Frenova Renal Research

Kurt Mussina is a chemist, global healthcare executive, and accomplished entrepreneur with a distinguished 30-year career spanning the research, development, and approval continuum for drugs and medical devices. Under his leadership, Frenova has expanded its focus from ESKD research to the full spectrum of CKD and renal impairment, growing the Frenova community of researchers into a world-class network of more than 550 principal investigators across 360 research sites. He previously held senior executive roles in client management and business development for international contract research organizations, including expatriate assignments in Denmark and the United Kingdom. Mussina began his career as an analytical chemist and R&D scientist for leading pharmaceutical companies, including Novartis. He graduated with a bachelor's degree in chemistry from Montclair State University in New Jersey and holds his master of business administration from the Fuqua School of Business at Duke University in Durham, North Carolina.

Jan Walter, MBA, MSc

Senior Vice President, Regenerative Medicine Commercialization

Jan Walter leads worldwide commercialization efforts for regenerative medicine opportunities, with a focus on the Humacyte product portfolio. He previously served as senior vice president for Fresenius Medical Care in Central Asia Pacific with commercial and legal responsibilities for a mix of mature and emerging markets, including Korea, India, the Philippines, Afghanistan, Bangladesh, Bhutan, Maldives, Nepal, and Pakistan. He is the former managing director for Fresenius Kabi in Southeast Asia, and began his career with Fresenius SE and CO KGaA as assistant to the chief executive officer. Jan graduated with dual master's degrees in business administration and economics from the University of Leipzig in Germany and holds his MBA from Binghamton University in New York.

Benjamin Hippen, MD, FASN, FAST

Senior Vice President, Global Head of Transplant Medicine

Benjamin Hippen is senior vice president and head of Transplant Medicine, leading the company's worldwide efforts to expand access to and understanding of transplant medicine. He is a clinical professor in the Department of Medicine at the University of North Carolina at Chapel Hill School of Medicine, and serves on the board of directors of InterWell Health in North America, a nephrology-focused population health management company. A general and transplant nephrologist, Dr. Hippen served as physician partner with Metrolina Nephrology Associates, Physicians Alliance, a 38-nephrologist private practice in Charlotte, N.C., and served as medical director of both a large in-center dialysis facility and large home therapies unit. He is the author of more than 50 peer-reviewed manuscripts focused on ethics and public policy issues in nephrology and transplantation. He received his bachelor's degree in philosophy from Rice University and his doctor of medicine from Baylor College of Medicine. He completed his fellowship in nephrology and renal transplantation at the University of Alabama at Birmingham.

Lorien Dalrymple, MD, MPH

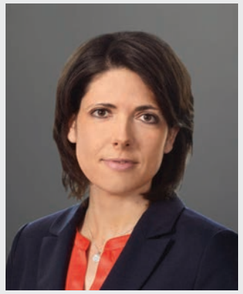
Vice President, Global Head of Population Health

Lorien Dalrymple was appointed global head of Population Health and member of the Global Medical Office leadership team after serving as vice president of Epidemiology and Research for the company's North America region. She co-chairs the National Quality Forum Renal Standing Committee, co-chaired the KHI ESKD Global Data Standard Workgroup, and has served on CMS Technical Expert Panels. Dr. Dalrymple has co-authored more than 50 publications, including peer-reviewed original research and editorials. She is a member of the Kidney Medicine editorial board. Prior to joining Fresenius Medical Care, she was an associate professor of medicine at the University of California Davis. Dr. Dalrymple received her bachelor's degree from Duke University, her medical degree from the University of Colorado, and her master of public health from the University of Washington. She completed her internal medicine residency and nephrology fellowship at the University of Washington and is board certified in nephrology.

Len Usvyat, PhD

Vice President, Applied Data Science, Biostatistics, and Epidemiology

Len is responsible for supporting data-driven functions—including data science, biostatistical, and epidemiologic efforts—within Fresenius Medical Care, advancing the agenda of the Global Medical Office. Len's team also provides support to these functions through data analytics, data engineering, research, and publications, as well as project management and administrative efforts. The team's main goals are to integrate advanced analytics into the clinical care of kidney disease patients, to support the generation of clinical evidence to meet regulatory requirements and post-market surveillance of the Fresenius Medical Care products portfolio, and to use real-world data to examine the clinical and cost-effectiveness of the products. Len chairs Fresenius Medical Care's Predictive Analytics Steering Committee, co-leads Global Advanced Analytics Alignment days, and works closely with the MONitoring Dialysis Outcomes (MONDO) initiative, an international consortium of dialysis providers. Len has published over 80 manuscripts in peer-reviewed journals. He holds a master's degree from the University of Pennsylvania and a doctorate from the University of Maastricht in Netherlands.



Katrin Köhler, MSc, MBA

Vice President, Global Medical Office Strategy and Operations

Affiliated with Fresenius Medical Care since 2003, Katrin Köhler leads Global Medical Office Strategy and Operations for the Global Medical Office, driving cross-regional medical strategies and synergies on a global level. She formerly served as director of Strategic Medical Development and Medical Innovation and Portfolio Management for Fresenius Medical Care Europe/Middle East/Africa. She has worked closely with the company's global business and medical leaders on key strategic initiatives, and has broad experience across the company's business regions. She graduated with her master of science degree, specializing in innovation and business creation with a major in business administration, from Sweden's Jönköping International Business School. She holds dual master's degrees in international management and economics from the European School of Business at Reutlingen in Germany and the Lancaster University Management School in the United Kingdom. Katrin is the global program lead of the Sustainability Area "Patients — Quality of Care," which has been assigned to the Global Medical Office by Fresenius Medical Care's Management Board.

Ryan A. Jimenez, EdM, APR

Senior Vice President, Global Head of Medical Office Communications

Ryan Jimenez leads worldwide medical communications for Fresenius Medical Care and is a member of the Global Medical Office executive leadership team. He joined Fresenius Medical Care corporate communications in 2016 as vice president of Medical Office Communications for North America, where he led the development of the region's medical and scientific communications strategies and capabilities, including serving as executive producer leading the company's *Medical Office Live* series of broadcast events across the continent. He is the former senior producer and communications director for CNN's *Larry King Live* and former communications director for First Lady Maria Shriver in the Office of Governor Arnold Schwarzenegger. He began his career in hospital communications at Catholic Healthcare West in the United States. He graduated from the Annenberg School of Communications and Journalism at the University of Southern California with his bachelor's degree in public relations and holds his master's degree in organizational behavior from Harvard University.

Fluid Management: Past, Present, and Future
by Sabrina Casper, MSc; Lemuel Rivera Fuentes, MD; and Peter Kotanko, MD, FASN

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Cardiovascular Health in Chronic Kidney Disease: Improving Outcomes Using SGLT-2 Inhibitors
by Bernaud Canaud, MD, PhD, and Allan Collins, MD, FACP

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Protecting Kidney Patients' Hearts: Has the Time Come to Rethink Dialysis Treatment Cadence?
by Franklin W. Maddux, MD, FACP

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Genomics and Precision Medicine: The Frenova Genomics Registry
by Michael Anger, MD, FACP, FASN, and Jeffrey Carr

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Precision Nephrology: Understanding Kidney Injury to Bring the Right Drug to the Right Person
by Ravi I. Thadhani, MD, MPH, and Opeyemi A. Olabisi, MD, PhD

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Managing Cardiovascular Disease in Dialysis Patients in Latin America
by Juan Carlos Berbessi, MD; Maria Resk, MD; and Alejandro Kohn Tuli, MD

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Improving Care with Real-World Evidence
by Anke Winter, MD, MSc, and Linda Hanna Ficociello, DSc

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Enriching Clinical Trial Design Through the Use of Patient-Reported Measures
by Krister Cromm, MA, MBA, MSc, and Saynab Atiye, RPh

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by Manuela Stauss-Grabo, PhD

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Optimal Dialysis Start: Lessons Learned from the United States and Canada
by Dugan Maddux, MD, PhD, and Ted Toffelmire, MDCM, FRCPC, FACP

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Shared Hemodialysis Care: Transforming Patient Experience

by Kolitha Basnayake, PhD, FRCP

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Patient-Centered Vascular Access Care

by Milind Nikam, MBBS, MRCP, MD, FAMS, FRCP; Luca Neri, MD, PhD; and Walead Latif, DO, MBA, CPE, FASDIN

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Patient-Centered Care: Creating a Framework for Global Quality Measurement

by Jeffrey L. Hymes, MD, and Katrin Köhler, MSc, MBA

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Improving Access to Kidney Transplantation: A Global Perspective

by Benjamin Hippen, MD, FASN, FAST

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COVID-19-Associated Acute Kidney Injury: Managing Pandemic Demand Surge for Kidney Replacement Therapy in the United States
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Franklin W. Maddux, MD, FACP
Global Chief Medical Officer
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