Embracing the Complexity of Global Healthcare

2021 GLOBAL ANNUAL MEDICAL REPORT
Vol. 6
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.
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
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. 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 contributed 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 60 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 380,000 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**
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.

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 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 outcomes, and off er improved care.

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 surviving 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.

“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.”

Rick Powell
Chairman of the Management Board, Chief Executive Officer, Fresenius Medical Care
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.
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 They found that cumulative FO exposure within the prescribed FO range was 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)).

However, 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.3 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 942 patients followed for a median of 30.8 months corroborated these results directionally.4 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 60% had RBV trajectories above and 2.5% below.

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 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) 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 1038 controller UF recommendations, 926 (99.2%) 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.

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. In contrast, with the use of the UF controller, over 70% of subjects were within the desired three-hour UF 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.
Cardiovascular health in chronic kidney disease: improving outcomes using SGLT-2 inhibitors

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

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.

Baseline renal filtration function and degree of proteinuria are the most significant indicators of risk for both renal and cardiovascular disease events.19 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 demonstrated significant reductions in cardiovascular and renal end points and improved overall metabolic control and outcomes.14,15 SGLT-2 inhibitors are associated with unexpected protective results on cardiac outcomes in this highly vulnerable population. 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.16,17 Gliflozins are specific glcoside-based inhibitors of sodium-glucose co-transporters (SGLT). 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 delivery at the macula densa site results in a deactivation of the tubuloglomerular feedback mechanism mediated by vasocostriction 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.

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.
In the DAPA CKD trial, of the 270 participants with IgA nephropathy with dapagli\(^{\text{f}}\)ozin, while changes in blood pressure did not differ, declined by –6.6 mL/min at week six in the dapagli\(^{\text{f}}\)ozin group, a renin-angiotensin system blockade agent were randomly assigned to receive either 10 mg empagliflozin or 10 mg placebo (1:1) and followed for up to 48 weeks. Consistent with previous studies, the ongoing EMPA-REG OUTCOME trial, exploring cardio-renal effects of empagliflozin in CKD patients irrespective of whether the individual has diabetes, will be of tremendous interest.\(^{21}\) 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.

**CREDIBLE study (de novo)</b>

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<thead>
<tr>
<th>Study Population</th>
<th>Outcomes</th>
<th>Risk Reduction</th>
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<tr>
<td>4,917 T2DM patients with eGFR ≤ 60 mL/min, UACR &gt; 300 mg/g and no renal or cardiovascular cause of albuminuria</td>
<td>eGFR &lt; 30 mL/min, UACR &gt; 5,500 mg/g, doubling of serum creatinine, ESKD, or death from cardiovascular causes</td>
<td>HR 0.60 (95% CI, 0.47-0.77)</td>
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**CARDIOVASCULAR HEALTH**

**Pleiotropic effects of SGLT-2 inhibitors**

Effects of SGLT-2 inhibitors are well documented and largely encompass their effects on glycemic homeostasis and DKD.\(^{41}\) 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.\(^{42}\) Interacting 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 cardiac 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 cardioprotective effect 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.\(^{15}\) Ongoing studies focusing on low eGFR patients are exploring the benefits and risks of these medications.\(^{44}\)
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 predetermines 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 2013, 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).

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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 is important to consider whether both active monitoring for rhythm disturbances and understanding the nervous system’s input into arrhythmias 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.

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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.

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

23
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.
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.8 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. 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 genomics registry initiative that will contain genetic sequencing data from individuals living with chronic kidney disease (CKD) worldwide.

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 x 10^-8). This will often require the use of meta-analyses in which several cohorts are lumped together to be studied. There are a variety of more specific genetic tests that can detect single nucleotide variants (SNVs). These potentially can be SNPs, but it cannot be determined from only one individual. SNPs mean that the nucleotide varies in a species’ entire population.

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Common modalities for more targeted diagnostic genetic testing include Sanger 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.

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 Ghazavi, 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 entered 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 of many disease-causing variants. The combined genomics 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.

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.

PRECISION MEDICINE

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

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

FIGURE 3 | The My Reason website provides information about the genomic registry
PRECISION Nephrology: Understanding Kidney Injury to Bring the Right Drug to the Right Person

Ravi 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. 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.

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.

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. 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 transposable accessible chromatin (ATAC-seq), in contrast, provides genome-wide profiling of chromatin states, revealing which chromatin regions are open and accessible 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 impact transport, angiogenesis, and immune activation are early manifestations of DKD. 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 new major 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.

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. 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 pathogenesis of APOL1 nephropathy, leading to the discovery of pharmacologic targets and reducing racial kidney health disparities.

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.

Precision medicine, however, did not yield SGLT-2i, which has dramatically improved CKD management. Therefore, why adopt this cumbersome, costly approach? Because unlike in oncology, where precision medicine frequently guides drug discovery, the success rate of drug discovery in nephropathy is abysmal. There has been over a 30-year gap between the approval of ACR 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. Nephropathy 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 organoids 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 dime's (Mass General Brigham [MGB], including Human Subjects Affairs, the Clinical Trials Office, Research Management, the MGH Biobank, and the Cardiovascular and Kidney 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 introduced into several honorees societies. He is a standing member of the FDA Cardiology Panel. He has received several distinguished awards, including the Harkins-James 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, Dana 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 underling APOL1 nephropathy. He is a recipient of several awards, including the NIH Director’s New Innovator Award, the National Science Foundation’s Director’s Early CAREER 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.
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.
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 e-learning 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 e-learning courses were taken, which represents a tenfold increase in participation in the last decade (Figure 1).

Building on the traditional didactic presentations and e-learning 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
FIGURE 2 | PD and HHD calculators

The North America AREP website hosts two home dialysis prescription calculators, one for peritoneal dialysis (PD) and one for home hemodialysis (HHD) (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 are 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 nurses, and individuals with end-stage kidney disease receiving dialysis. In 2020, 21 live events that drew over 6,200 participants from across dialysis providers, 14% of which were prescribers (Figure 3).

GLOBAL MEDICAL EDUCATION WEBINAR SERIES

The webinar series in the United States is a spin-off of the successful@homeTM Clinical Resource Line, which provides nurse-to-nurse 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 well attended (Figure 4).

FIGURE 3 | AREP live event provider affiliation

In Figure 3, we see the provider affiliation data for the AREP live event. The chart shows the percentage of participants from different regions and organizations. The North America AREP website hosts two home dialysis prescription calculators, one for peritoneal dialysis (PD) and one for home hemodialysis (HHD) (Figure 2). The chart highlights the growth in attendance from 2016 to 2020, with a significant increase from around 1,900 to over 11,000 participants. The success@home Clinical Resource Line, which provides nurse-focused live educational webinars since 2008, has contributed to the growth. In 2020, the webinar series quickly adapted to the virtual world, with 21 live events drawing over 6,200 participants from across dialysis providers, 14% of which were prescribers. The chart also indicates that the webinar series was historically focused on home therapies, specifically PD, with product and disease state education. Over recent years, the webinars have expanded to include topics on HHD, anemia, hyperphosphatemia, and fluid management. The participation rate has increased significantly, with topics across the kidney disease spectrum being well attended.

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 comprehensive roundtable discussions with experts in nephrology, home dialysis, in-center hemodialysis, on-line hemodialfiltration, and critical care nephrology, and extracorporeal membrane oxygenation (ECMO) therapies.

In March 2023, 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 2023, nearly 12,000 participants 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 hemodialfiltration, 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.

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. As 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 and 177 dialysis facilities training over 2,000 providers with 11,297 PD-related resources for acute hemodialysis therapies were limited. In 2020, the MSS team provided over 250 hours of training to 1,372 nurses across the country. In 2021, they are already on track to exceed these numbers.

FIGURE 4 | Medical education webinar growth

In Figure 4, we see the growth and expansion of the medical education webinar series. The chart shows the number of participants, registrants, and programs over the years, with data from 2016 to 2020. The number of participants grew from 2,113 in 2016 to 11,297 in 2020. The number of registrants also increased from 1,926 in 2016 to 6,254 in 2020. The number of programs grew from 21 in 2016 to 10,851 in 2020. This growth is attributed to the expansion of the webinar series to include topics on HHD, anemia, hyperphosphatemia, and fluid management. The chart also shows the data for the number of CEs offered, with a significant increase from 6,291 in 2016 to 12,033 in 2020. The chart highlights the positive impact on current practice and more confident managing patients.

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 drives the success and expansion of medical information queries from healthcare professionals, including the United States, provides medical and scientific expertise on promotion and customer engagement, and serves as core team member on a variety of medical information projects. She earned her PhD in biochemistry from the University of North Carolina at Chapel Hill, and after many years in academics studying the regulation of signal transmission and RNA 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 to develop educational 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, MSIM
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 in the German Cancer Research Center, and a master of science in healthcare management from the University of Heidelberg and Mannheim Business School in Germany.
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. 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. 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.

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.
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.
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.
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.

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. 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.

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.46

There are advantages and disadvantages of using retrospective RWD (Figure 1). The potential benefits include the study of heterogeneous, 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.51

The potential disadvantages of retrospective studies that use RWD include the potential for selection bias and confounding because randomization is not possible.52 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 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.53

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.54 After market approval, studies based on RWD can add in the understanding of the safety and effectiveness of the device or drug when utilized under real-world circumstances.55

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.56 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.57

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.

FIGURE 1 | Advantages and disadvantages of real-world data

<table>
<thead>
<tr>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
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<tbody>
<tr>
<td>Generalizability</td>
<td>Lack of randomization</td>
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<tr>
<td>Large sample sizes</td>
<td>Confounding</td>
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<tr>
<td>Long follow-up</td>
<td>Bias</td>
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<tr>
<td>Low cost</td>
<td>No study schedule</td>
</tr>
<tr>
<td>Quick results</td>
<td>Not all data of interest is available</td>
</tr>
<tr>
<td>Multiple exposures and outcomes</td>
<td>Missing data</td>
</tr>
<tr>
<td>Focus on how treatments are delivered</td>
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</tbody>
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FIGURE 2 | RWE and RWD were vital in determining the effectiveness of combining phosphate binder therapy with sucroferric oxyhydroxide in hemodialysis.

METHOD AND COHORT

| FINDINGS OVER 2-YEARS FOLLOW-UP |
|---|---|---|---|---|
| | GROUPS | | | |
| | Serum phosphat | | Phosphate binder | Mean change in |
| | | | pills/day | serum phosphors |
| | | | | |
| | 50 therapy (n=122) | 25% | Baseline | 7.9 | 8.5 | -0.66 mg/dL |
| | | 47% | Follow-up | 6.1 | 5.1 | 0.2 |
| | | 16% | Baseline | 7.8 | 8.5 | 0.2 |
| | | 16% | Follow-up | 6.1 | 5.1 | 0.2 |
| | | 12% | Baseline | 7.9 | 8.5 | 0.2 |
| | | | Follow-up | 6.1 | 5.1 | 0.2 |

Patients maintained on 50 therapy had a lower hospitalization rate (IRR: 0.75, 95% CI 0.58-0.96).


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. In addition, there may be country-specific and product designation-specific differences in requirements and acceptance of RWD studies based on RWD in the context of the regulatory decision-making process.
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. 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.

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. 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.

The development of medical devices, therapeutics, 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). 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).

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). 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).
There are various other initiatives by patient organizations, researchers, international organizations, and regulators—such as the Organization for Economic Cooperation and Development's (OECD) 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.6,8

Besides strengthening the consideration of PROs and PBMES 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 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 mechanisms to focus on patient-centered priorities or remove bias from clinical trials by advocating for patient participation starting in the design stage.6,8

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.9 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.8

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.10

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.11 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).

CONVENIENCE is a consortium that is performing an international, multi-center, prospective, randomized, controlled study—with 1,360 enrolled participants—comparing high-dose hemodialfiltration 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 hemodialfiltration on hospitalizations and mortality, but also a wide range of physical, mental, and social outcomes using electronic PROMIS participants 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 CONVENIENCE study offers the opportunity to establish a valid and reliable measurement framework for PROs that allows comparing these outcomes in nephropathy across treatment settings.

As we have already validated the questionnaire approach with the baseline assessment in CONVENIENCE, 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 social 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.

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.
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.

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.

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 efficiencies in a way that preserves the strength of classical clinical research processes and simply transforming them from paper to digital form. Rather, a complete rethinking and reengineering of the traditional concept around the participant and the clinical trial experience by minimizing geographic obstacles for participating investigators throughout the duration of the study, thus creating 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. 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 of visits and duration of clinical visits (Figure 1).

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. 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.”

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.

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.

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.

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

Visiting Chair, Real-World Evidence Research, Europe/Middle East/Africa, Asia Pacific, and Latin America, FMC Global Medical Office

Manuela Stauss-Grabo, PhD

Manuela joined Fresenius Medical Care in 2011. With more than 15 years of practical experience in clinical research, she currently leads the clinical research team for Europe, Middle East, Africa, Asia Pacific, and Latin America regions. Utilizing her biobehavioral background and research expertise in better understanding chronic disease and improving the outcomes of renal patients worldwide, located in Bad Homburg, Germany, the Global Medical Office’s clinical research team manages numerous international, and multi-regional clinical research concepts on implementing and actively using state of the art digital technologies. Manuela earned her biology degree from Ahrweiler University of 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.
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.14 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.15 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.16 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.”17 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 206 per million population, 62.9% male and 38.1% female.18 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/1.73m². Some 92.9% of patients on peritoneal dialysis (PD) and 86.7% 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.

DIALYSIS TRANSITION IN THE UNITED STATES
In the United States, uninsured individuals were less likely to receive pre-dialysis CKD care than people with Medicare or commercial insurance. In the United States, uninsured individuals were less likely to receive pre-dialysis CKD care than people with Medicare or commercial insurance. (Figure 1). 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).19

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.20

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 2005.21 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 35% to 48%.22 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, 34% 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.23

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.
WORKING TOWARD AN OPTIMAL DIALYSIS START

Canada and the US have common goals for treating ESKD but some fundamental differences exist. 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 (66% 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.36 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 from 9.4% in 2010 to 14% in 2018, while the presence of a functioning AV fistula at the start of dialysis decreased from 16.3% to 14.6%.29 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 9.6%.30 Studies have identified both system issues and patient issues that impact dialysis start.31,32 System issues include fragmented care among nephrology practices, varied 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.31 In addition, patient factors are now recognized as significant contributors to not achieving an optimal dialysis start.31,32

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.33,34 In the United States, CKD rates are the highest in the poorest neighborhoods, and socioeconomically challenged communities create CKD “hot spots.”35,35 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.36,37 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.38 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.31 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 “value 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.39

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 suggest 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.

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.

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.

Specifically, for CKD, addressing unmet social determinants of health (SDOH) needs for patients would involve:37

• Nephrology providers and practices partnered with community and public health resources, to create more opportunities 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

FIGURE 2

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

TABLE 1 | TRENDS IN THE PERCENTAGE OF PATIENTS STARTING DIALYSIS FROM PATIENTS IN CANADA AND THE US

<table>
<thead>
<tr>
<th>TYPE OF VASCULAR ACCESS AT DIALYSIS START</th>
<th>NO PRE-ESKD NEPH CARE</th>
<th>0-6 MTHS OF PRE-ESKD CARE</th>
<th>6-12 MTHS OF PRE-ESKD CARE</th>
<th>&gt;12 MTHS OF PRE-ESKD CARE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninsured</td>
<td>23%</td>
<td>16%</td>
<td>19%</td>
<td>26%</td>
</tr>
<tr>
<td>Medicare Primary</td>
<td>14%</td>
<td>15%</td>
<td>20%</td>
<td>36%</td>
</tr>
<tr>
<td>Medicare Secondary</td>
<td>11%</td>
<td>12%</td>
<td>22%</td>
<td>45%</td>
</tr>
<tr>
<td>Medicare Advantage</td>
<td>16%</td>
<td>15%</td>
<td>21%</td>
<td>35%</td>
</tr>
</tbody>
</table>

Ted Toffelmire is emeritus professor of medicine (nephrology), pharmacology, and toxicology at Queen’s University, where he began his practice in 1984. 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 (MD). Ted’s research has focused on internal medicine and nephrology (University of Western Ontario), and he completed a fellowship in clinical pharmacology (University of California at San Francisco).
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.

**FIGURE 1** | Shared care tasks

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

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’. 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 health outcomes, whereas through higher levels they take increasingly higher control of their health. It is defined as “an individual's knowledge, skill, and confidence for managing their health and healthcare.” 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 health outcomes, whereas through higher levels they take increasingly higher control of their health.

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.

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).

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. 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.

HEALTH AND SOCIAL CARE POLICY AND GUIDANCE
The importance of patient involvement in their haemodialysis care has been increasing 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. 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 at home. 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.

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.

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 as high as 40%, while nearly two-thirds of units were below 20% (Figure 4). 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 as high as 40%, while nearly two-thirds of units were below 20% (Figure 4). Getting 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. Clearly, SHC will have to be central to any efforts to reach this target.
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 78% 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.

**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.

*Knowledge*

- **Patient:** Belief about capabilities
- **HCP:** Belief in the concept
- **Organisational:** Robust data

*Environmental context and resources*

- **Patient:** Goals
- **HCP:** Training and support
- **Organisational:** Structure and process

*Perception of roles/identity*

- **Patient:** Optimism
- **HCP:** Passion
- **Organisational:** Strong leadership culture

*Emotions*

- **Patient:** Reassurance and reinforcement
- **HCP:** Structure and process
- **Organisational:** Strong leadership culture

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.
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 recognized as a critical aspect of dialysis care by all stakeholders, including individuals living with kidney disease and caregivers. 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. 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 access 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. 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. 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](source: Fresenius Medical Care internal data)

- **FIGURE 1** | Catheter use in incident and prevalent patients

- **AVF**
- **AVG**
- **Catheter**

Source: Fresenius Medical Care internal data

**PATIENT-CENTERED VASCULAR ACCESS CARE**

**PERSONALIZED CARE**

**TRANSITION CARE PLANNING**

**HUMAN ACELLULAR VESSEL**
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. Selection bias alone may not explain these findings.10,11,12,13 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 physician practice patterns. The Sankey diagrams (Figure 2) demonstrate the 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.

**FIGURE 2 | Sankey diagrams (60) 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.**

Application of patient-centred care to minimize 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 AVFs, early cannulation or 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.

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 Renal Failureguard, 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 radiology, physiological, sensor-based, metabolism, 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.

**EVOLUTION IN ARTERIOVENOUS ACCESS CREATION**

Innovative technologies introduced in recent years offer new options for vascular access care.15 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, pseudaneurysms, and thrombotic events that are comparable to polytetrafluoroethylene grafts.16

The latest advancement in the vascular access arena is the human acellular vessel (HAV) by Humacyte Inc.17 The HAV is a bioengineered vessel cultivated and decellularized from antigens prior to implantation. The HAV can be safely 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 (Vaveling by Bard and Ellipsys by Artera) indicate high technical success rates, with primary patency rates equivalent to surgically created AVFs.18,19,20 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.21 Prevention of vascular access thrombosis is beneficial for many reasons, and thrombosis itself, regardless of other lesions, portends poor vascular access survival.22 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 diastole, and inaccurate detection of sunflow stenosis.23

The latest advancement in the vascular access arena is the human acellular vessel (HAV) by Humacyte Inc. The HAV is a bioengineered vessel cultivated and decellularized from antigens prior to implantation.
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.24

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 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.
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. 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.” 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.

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. Unintentionally, the 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. 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. 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.

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.
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 changes to improve the efficiency and timeliness of the multidisciplinary transplant evaluation, while bringing transparency to the process for patients and key stakeholders.
- Identifying best practices in organ acceptance processes and patient care models from transplant centers around the world, and developing tools to assist with patient decision-making.
- Identifying care models from transplant centers around the world, and developing tools to assess and improve patient acceptance behaviors.

Novel allocation schema will only be of theoretical interest for the far too many patients who remain outside of the startlingly low system looking in. In many countries, living kidney donation 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.20 Twenty-five years later, there are 35 cases 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.21

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, accessing iniquities 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 regulator. Which has been attributed to multidisciplinary teams devoted to long-term care, a robust single-payor system, and an outcomes regulator. Australia has 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 regulator. Australia has 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 regulator.

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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. Such “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.22,23

One promising avenue is to build on the success of the European Union’s 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.24 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 cardiac death may not routinely confer survival benefit versus maintenance dialysis.25

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.26 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.27

Stewardship of the “Gift of Life”: Extending Long-Term Patient and Graft Survival Improving access for naïve without the need for donors.

In the US, a configuration 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.28

Happily, there are new potential therapeutic targets for extending allograft survival, including some early data suggesting that sodium glucose co-transporter 2 inhibitors (SGLT-2) may be of benefit in transplanted patients.29 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
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Benjamin Hippen, MD, FASN, FAST is chief 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 Somatrix Nephrology, Associates, P.A. In Chapel Hill, North Carolina, where he served as a medical director of a large center dialysis facility and previously served as medical director of a large home therapy unit. He is currently overseen on behalf of InterWell Health, a nephrology-focused population health management company. He previously served on the board of managers for the Carolina Physician Alliance, 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 Renal Association-European Dialysis and Transplant Association (ERA-EDTA), and others. Within Fresenius Medical Care, there has been substantial progress in adopting uniform definitions of quality care. These are embedded in the clinical quality score (CQS) in the United States and the balanced scoredcard (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 rate), 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 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 access has been extensive through the Mexican 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 diabetic 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 and dissemination 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 Eut3D and myCompanion (EMEA), ApLA) and eClub Clinicals, PatientHUB, and PhysicianHub (US).

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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 NephCare in Italy.

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 integration and interfacing and education of the best nephrologists, consistent appraisal of business priorities, uniform training in CQI, and open communication and support among regions. The GOM 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 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 CEO 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 Royal Physician Associates’ 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

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 at Fresenius Medical Care Europe/Middle East/Africa. In her role as a global business leader, she has worked closely with the company’s global business and medical leaders on key strategic initiatives, and has broad experience across the diverse Fresenius Medical Care business regions. She graduated with her master of science degree, specializing in innovation and business creation, with a major in business administration, from Sauder’s Ingkong International Business School. She holds dual 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.
Encourage technologies that support our patients, including connected devices for home use, monitoring and communications apps, telehealth, and health records integration.
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 of 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. 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. 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.

In 2020, the company established critical care as one of three strategic pillars for the company’s successful long-term growth. 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
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 therapies.

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 providing 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
The 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.

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.
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. EuCliD allows data management processes to be standardized into a consolidated and unified source of evidence while reducing the costs for evidence generation.

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. Evidence also suggests that connected health is associated with a 10% reduction in patient dropout and increased longevity on peritoneal dialysis (PD) by 3.5 months (Figure 1).
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 HCP 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 HCP 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. The myCompanion app is Fresenius Medical Care’s health solution for in-center hemodialysis patients. It allows patients to 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 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 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

**THE EXPERTS**

**STEFANO STUARD, MD, PhD**
Senior Vice President, Chief Clinical Officer, Fresenius Medical Care Europe/Middle East/Africa

Stefano Stuard supports the Nephro-Care 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 to provide 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 EuClaD 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, FACOG**
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 UC 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.
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.

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.
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 need for 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.

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 catalyst for breakthrough technologies and consequently shorten their time to market makes Fresenius Medical Care’s approach to innovation and transformation unique.

FIGURE 2 | Unicyte manufacturing process based on standard platforms established in regenerative medicine and biologics
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. 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 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. In the case of the 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 5, 2020, CMS modified the initial criteria to expand the date 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. 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.

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**SUMMARY**

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

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**OPINION**

FOR NEW PRODUCTS

**OPTIMIZING CMS GUIDELINES**

Michael Anger, MD, FACP, FASN


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**subspecialty, less funding from public and private sources, and fewer innovative devices or medications developed than all other diseases combined.**

**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.**

**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 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.**

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**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. Does prolonging life on dialysis constitute substantial clinical improvement?**

**Improvement for Medicare beneficiaries in at least one of the following:**

- 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 Frenova, 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.
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 β-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 175 million people, resulting in over 3.7 million deaths in 220 countries and territories.1 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 (as of June 5, 2021). However, COVID-19 data on individuals with end-stage kidney disease (ESKD) has been slow to emerge, with only 41 publications identified (as of June 5, 2021) that discuss topics such as epidemiology, clinical outcomes, diagnosis, testing, disease management, and therapeutic options for this high-risk population.

EPIGENOMES 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 and were tested by reverse transcriptase polymerase chain reaction (RT-PCR), or blood for antibody or serology testing.21 Sampling typically occurs by saliva, nasopharyngeal, or nasal swabs from the respiratory tract 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 could not elicit antibody responses, indicating that SARS-CoV-2 infection prevention and control.

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 between 7 and 11 days from infection prevention and control. SARS-CoV-2 infection—may also apply in ESKD. The incidence of long-haul for individuals with ESKD is not known.

Seroconversion typically occurs between 7 and 11 days from exposure and can persist after recovery.24 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 Despite limitations, serological testing in ESKD may be a valuable tool to determine seroprevalence, monitor exposure, and guide improvements for infection prevention and control.
High-quality, quantitative methodologies that evaluate persistent positive post-infection, reinfection, potential antibody titer reduction over time, and effect of variants in ESKD patients are needed.

Several monoclonal antibody (mAb) therapies were granted EUA by various global authorities. Bamlanivimab plus etesevimab, recommended in ESKD.46,47,48 EUA status (US) for hospitalized COVID-19 patients with high-risk features.

Remdesivir evaluation in ESKD has been inadequate, and it is not recommended in individuals with eGFR <30 mL/min/1.73 m².5,6 A case series of hospitalized COVID-19-positive HD patients suggests good tolerance of standard dose of remdesivir resulting in a 2.2% discharge rate.6 In another study, administration within 48 hours of hospital admission shortened the duration of stay for dialysis patients by 5.8 days.6 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.2,6

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 response in 98% of dialysis patients, but IgG levels were lower than controls (median: 2900 mg/L versus 7401 mg/L).3,3 Although more data is needed, and reported vaccine hesitancy among dialysis patients ranges from 20% to 53%, 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.5,6

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.
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: alpha-coronavirus, betacoronavirus, gammacoronavirus, and deltacoronavirus. Infection in mammalian species is exclusively by alphacoronavirus and betacoronavirus. 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 Coronavirus Study Group designated the novel virus that emerged from Wuhan, China, late in 2019 as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).1

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 by 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^-7 (s/n/c) or ten times the mutation rate for coronavirus.2

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 508.6

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 viruses. 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 contains the D614G mutation.9

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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

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).7

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^-7 (s/n/c) or ten times the mutation rate for coronavirus.2

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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).7

Coronaviruses are the exception to the rapid viral mutation rate seen in other smaller RNA viruses such as influenza.
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 failure. 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 efficiencies.

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. 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.

VACCINE EFFICACY ACROSS DIFFERENT VARIANTS

The adenovirus-vector vaccine ChAdOx1 from AstraZeneca only demonstrates an approximately 20% increase in transmissibility or disease severity, or potential diagnostic failure. 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 efficiencies.

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.

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.
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.

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). 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).
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.14 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 proteins. Since the adenovirus vector does not contain the live virus, recipients cannot get COVID-19 disease from the vaccine. Prior to using the adenovirus vaccine vectors for COVID-19, the platform was used in Europe for an Ebola vaccine.

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 Subunit vaccines do not contain the entire virus pathogen.9,10

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 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 shots for ongoing protection—not ideal in a global pandemic where time is of the essence.

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.18,19 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.18,19 An exploratory analysis of the Oxford-AstraZeneca vaccine showed vaccine efficacy (VE) against symptomatic SARS-CoV-2 after one dose was 76% during the first 90 days.18 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.18

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 3.22 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.23

Experts are evaluating if mixing two different vaccine platforms (e.g., adenovirus vector with mRNA) could enhance protection.
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. 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 exists.18

- 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.19

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. The case 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.). 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., optimization of vaccinations, non-pharmacological 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.
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. 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. 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). 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 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. 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.

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

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<th>Risk factors for COVID-19–associated AKI</th>
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<tr>
<td>OBESITY</td>
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<td>BLACK RACE</td>
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<td>DIABETES MELLITUS</td>
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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

Dinesh Chatoth, MD
David Thompson, DO
To meet the increasing demand, several operational and manufacturing adaptations were implemented:

- Increased the bagged dialysate solutions, including increasing the production of bicarbonate-based solutions
- Expanded contract-based home solutions for use in hospitals
- Received Emergency Use Authorization for MultiFRx product and MultiLife/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)
- 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 privileging 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 nurse’s ability to safely oversee more patients requiring 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 who did not recover baseline kidney function at a median of 21 days after hospital discharge. Another cohort study of 1,642 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.

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 treated per month at FKC outpatient facilities increased from approximately 1,000 patients per month to 2,500 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.
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. 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.

**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. 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. 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. Monaghan et al. built a machine-learning model to identify COVID-19 infections days before symptoms occurred. 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.

**FIGURE 1** | Fresenius Medical Care publications by month

[Figure showing the number of publications and grants by month from January 2020 to January 2021.]
Conducted a seroprevalence study in New York City and compared these results were directionally corroborated by Thwin et al., who to prevent SARS-CoV-2 spread were effective in reducing risk. The lifestyle of in-center hemodialysis patients and interventions should not be considered elective. Żebrowski et al. argued that it is important, as PD effluent antibody testing could complement serum serology testing. Whether post-COVID-19 or vaccine 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. Chen et al. analyzed aggregated daily counts of confirmed COVID-19 cases from March 1 to July 29, 2020, in the general population and FKC, and then computed the expected number of secondary cases arising from each new infectious case. The study showed that the expected number of secondary cases arising from each new infection was much lower in FKC than in the general population. This finding suggests that individuals receiving dialysis were less likely to transmit the virus to others. Moreover, the study found that the risk of transmission was higher in individuals who received hemodialysis than in those who received peritoneal dialysis. This is consistent with previous studies that have shown that hemodialysis patients are at higher risk of SARS-CoV-2 infection due to the nature of the dialysis procedure.

An early report by Totteson 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 1 to April 30, 2020. In this cohort, 26 individuals died, and the mortality rate of individuals receiving dialysis was over twice as high in the ICU comparing overall mortality in both groups. Moreover, they found that in-center hemodialysis patients and interventions should not be considered elective. Żebrowski et al. argued that it is important, as PD effluent antibody testing could complement serum serology testing. Whether post-COVID-19 or vaccine 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.

COVID-19 PANDEMIC

VACCINATION AGAINST SARS-COV-2: A SILVER LINING
It is undisputed that comprehensive vaccination is key to overcoming the pandemic. Pampelina et al. were the first to report on vaccination acceptance and hesitancy in staff from four RRI dialysis clinics located in New York City. Of 107 staff members, 42 (26.8%) were not vaccinated for various reasons, such as leave of absence (4.2%), pregnancy or breastfeeding (8.1%) past COVID-19 (24% 15.3%), and explicitly expressed vaccination or interest (6.3%). 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 adenosine 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-CoV-2 when compared to patients vaccinated with mRNA vaccines.

RESEARCH GRANTS AND AWARDS
Fresenius Medical Care and its subsidiaries have received several research grants and awards from various organizations and government agencies. For example, Fresenius Medical Care received a grant from the National Institutes of Health (NIH) to study the effects of SARS-CoV-2 on kidney function and the development of new treatments for COVID-19. The company also received a grant from the American Society of Nephrology to support research on the long-term effects of SARS-CoV-2 on the kidney.

Mask testing may lend itself to pool testing, a strategy that is particularly efficient in settings with a low disease prevalence. 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 is advancing knowledge across a wide spectrum of topics surrounding COVID-19 across the globe.
 GLOBAL MEDICAL OFFICE LEADERSHIP

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.

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 expensive 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 and 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 Anston 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, General 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 AVEO. 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 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 (Bob) 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.

Robert J. Kossmann, MD, FACP, FASN
Executive Vice President; Global Head of Renal Therapies; Chief Medical Officer, North America

Robert (Bob) 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.

Juan Carlos Berbessi, MD
Vice President, General 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 AVEO. 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 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.

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Committee. He graduated with his medical degree from Wayne State University in Detroit. Chronic kidney disease patients, and prospective and retrospective clinical studies on dialysis techniques published more than 300 articles, 600 abstracts, and 20 book chapters, and has given more than 365 invited treatment. He is the former chief medical officer for NxStage Medical, Inc. and served as director of the Allain J. Collins, MD, FACP

Bernard Canaud, MD, PhD

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

Bernard Canaud 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 Therapeutics Program, and continues as the operational medical counsel for the company’s services business in EMEA. Dr. Canaud’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. Canaud 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.

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.

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 Nephropathy Associates (NNA) in 1998. He served as NNA’s president and chief medical officer from 1998 to 2004. He served as president of Nephropathy Associates, a 30-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.

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 NIDDKS 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, as 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, Fresenius 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, Fresenius has expanded its focus from ESKD research to the full spectrum of CKD and renal impairment, growing the Fresnou 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.

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-chairs 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.

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 Kidney Care in Southeast Asia, and began his career with Fresenius SE and CO KGaA as an 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 Medtrona Nephrology Associates, Physicians Alliance, a 30-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.

Kurt 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 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 Kidney Care in Southeast Asia, and began his career with Fresenius SE and CO KGaA as an 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 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 Medtrona Nephrology Associates, Physicians Alliance, a 30-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.

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Affiliated with Fresenius Medical Care since 2003, Katrin Kühler leads Global Medical 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 Development and Medical Innovation and Portfolio Management for Fresenius Medical Care Ramps/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 Rhein Main in Germany and the Lancaster Management School in the United Kingdom. Katrin is the 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.

References


Supporting people to manage their health


35. Ibid.


34. Ibid. Patient-Centered Vascular Access Care


25. Ibid.

24. Canadian Institute for Health Information. Organ replacement in Canada. 2015, p. 5.


