Every day, each employee at Fresenius Medical Care, along with our world-leading portfolio of dialysis machines, medical devices, pharmaceuticals and therapeutics create the foundation on which high-quality kidney care is built, around the globe.

The well-being of our patients is our priority, a focus that has been key to our worldwide success. As leaders in value-based care, we 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.

To achieve our goal of global care delivery, I announced earlier this year the creation of the Global Medical Office to enhance our patient-focused care delivery business model. This function, led by Dr. Franklin W. Maddux as our Global Chief Medical Officer, marks an important milestone in the company’s evolution. Dr. Maddux, and the team he leads, will ensure that we harness the full potential of our global, vertically-integrated approach to achieve the best clinical outcomes for our patients, their families and the payor community.

I am grateful to our caregivers, researchers, scientists and as well all other employees at Fresenius Medical Care. Together, they set the standard for what it means to deliver the highest possible quality of care for the more than 330,000 patients we serve around the world.

Rice Powell
Chief Executive Officer and Chairman of the Management Board, Fresenius Medical Care
It’s a privilege to share the inaugural volume of Fresenius Medical Care’s Global Annual Medical Report. The report began as a regional publication in North America five years ago and is now a feature of the newly formed Global Medical Office and one of the company’s key worldwide publications.

This annual volume of insights demonstrates our leadership in reimagining the future of renal care while still raising questions that demand better answers and highlighting areas we feel need specific focus. Since our company’s beginnings, the people of Fresenius Medical Care—our physicians, caregivers, researchers, scientists, and global employees—have been our greatest asset in transforming health care delivery systems throughout the world.

The 2019 Global Annual Medical Report explores the power of interconnected thinking, a core feature of the Fresenius Medical Care DNA and company culture. This more fulsome, collaborative vision results in exponentially greater capacity for understanding and innovation, setting us apart in our ability to effect positive change in the care of people with advanced kidney disease.

Thank you for your interest in our company. I’m grateful to my Fresenius Medical Care colleagues for their commitment to the shared purpose that interconnects us: the patients around the world, every day, who entrust us with their care.

Franklin W. Maddux, MD, FACP
Global Chief Medical Officer, Fresenius Medical Care
In 1912, Dr. Eduard Fresenius, proprietor of the Hirsch Pharmacy, started a fledgling company that his remarkable foster daughter—the pharmacist Else Kröner—would build into one of the world’s foremost healthcare organizations for people with chronic health conditions.

The medical-humanitarian spirit that motivated Else Kröner continues to inspire and guide the people of Fresenius Medical Care. Every day, in localities across the globe, our compassion and commitment to advanced therapies creates a future worth living for our patients.

Creating a future worth living. For patients. Worldwide. Every day.

About decades of experience in dialysis, innovative research, the global leader in dialysis services and products—that is Fresenius Medical Care. Patients with kidney disease can now look ahead with much more confidence thanks to our innovative technologies and treatment concepts. We give them a future, one that offers them the best-possible quality of life. We use the increasing demand for modern dialysis methods to our advantage and work consistently to enhance the company’s growth. Together with our employees, we focus on pursuing strategies that will enable us to uphold our technological leadership. As a vertically integrated company, we offer products and services for the entire dialysis value chain.

The highest medical standards are our benchmark. This is our commitment to our patients, our partners in the healthcare system and our investors, who trust in the reliable performance and the future of Fresenius Medical Care.
Kidney disease is a global epidemic that is straining health care systems and diminishing the quality of life for millions of people who are coping with obesity, cardiovascular disease, diabetes, and other related chronic conditions. The scope and complexity of the problem requires an unprecedented level of collaboration to attack root causes of kidney disease, galvanize diverse peer communities, and better identify innovation wherever it occurs worldwide. As a vertically integrated global health care company, Fresenius Medical Care is in the ideal position to harness the power of this interconnected intelligence and pioneer solutions that can have a large-scale impact on patient care. The 2019 launch of the Global Medical Office and the internal publication of the first global Clinical Quality Agenda not only encourage network-wide research and communication, but also underscore the company’s fundamental commitment to transformative health care.
Creating a future worth living, for patients, worldwide, every day. This global commitment unites the people of Fresenius Medical Care in our commitment to improving kidney care for people around the world.

With a global patient care footprint covering more than 150 countries, 986 languages, nearly every time zone, and myriad regulatory frameworks and geopolitical environments, Fresenius Medical Care is a unique collection of nearly 113,000 accountable people waking up every day to study, engineer, build, and serve people with chronic illnesses.

The ability to harness the collective and diverse ingenuity across this formidable network is one of the distinguishing characteristics of our vertically integrated care ecosystem. Our global purview and local sensitivity are key to our ability to drive medical outcomes across regions that make the greatest impact. At the heart of this thoughtful, carefully planned progress is the concept of interconnected intelligence.

Interconnected intelligence is more than merely being “connected,” which implies narrow, confined linkages, commonalities, and understandings within a limited group or community. In contrast, interconnectedness connotes something much broader: relationships not only within specific groups and communities, but also between diverse groups and communities. Interconnectedness enables a more fulsome vision that results in exponentially greater capacity for understanding, innovation, and progress—and the recognition that we are, indeed, stronger together, and that the free flow of information and ideas remains the greatest organizational catalyst to improving health care systems.

Through our interconnected global outlook, Fresenius Medical Care focuses on four key tenets:

• **Harmonizing values around kidney care**: Organize and expose harmonization of performance and market maturity, and understand variability in care delivery across geographies and economies

• **Identifying innovations for global transformation**: Harness the global potential of local insights through a robust pipeline of research, data, and collaborative discoveries

• **Organizing a global health care quality agenda**: Unlock global access to universal quality insights that can improve care outcomes across geographies

• **Building cornerstones of transformation through purposeful, connected communities of people**: Build communities with shared purpose, and use their collective knowledge, intelligence, and intent to drive health care transformation and progress

**A GLOBAL EPIDEMIC ON THE RISE**

In 2017, a study conducted by the University of Washington in conjunction with the Bill and Melinda Gates Foundation quantified the impact of over 300 major diseases and injuries around the world, showing “a growing and disturbing global public health crisis.” The Global Burden of Disease study found that 2.2 billion people—or 30 percent of the world’s population—are either overweight or obese, leading to burgeoning global health problems and rising deaths.

The United States reported the highest percentage of obese children and young adults—13 percent—while Egypt reported the highest number of obese adults, at 38 percent. The study also showed the frequency of obesity has doubled in more than 70 countries since 1980. The two leading causes of death were identified as cardiovascular disease and diabetes, with chronic kidney disease ranked as the second-leading cause of disability. The United States is a microcosm of this global epidemic, with more than 30 million Americans diagnosed with kidney disease as of 2019.
In the United States alone, Medicare, the federal health insurance for people age 65 or older, some young people with disabilities, and people with end-stage kidney disease, spent over $113 billion in 2016 in managing kidney disease, more than 20 percent of all Medicare spending (Figure 1). The numbers on a global scale are expected to increase substantially over the next decade.

As the global incidence of kidney disease rises, the burden on the world’s health care economies continues to grow. Unsustainable health care spending will result in government policy shifts in the kidney disease space to address patient needs (Figure 2). As an example, in the biggest US policy change since the 1972 Social Security Amendments that extended Medicare coverage to kidney failure patients regardless of age, the July 2019 presidential executive order announcing the Advancing American Kidney Health initiative pledges to address the impact of kidney disease by reducing end stage kidney disease, slowing CKD progression, increasing kidney transplants and focusing on home dialysis care.

BUILDING A GLOBAL COMMON GROUND: HARMONIZING VALUES AROUND KIDNEY CARE

In 2019, Fresenius Medical Care’s Global Chief Executive Officer Rice Powell announced the creation of the Global Medical Office as a key strategy to address kidney disease-related challenges of the global health care system. The Global Medical Office is charged with transforming care against the backdrop of an alarming worldwide public health epidemic, stressed ministries of health, radically diverse global regulatory frameworks, and unsustainable conditions in health care economies. This endeavor begins with finding common ground across global diversity.

Fresenius Medical Care concentrates on four distinct areas of harmonization:

1. Treating the full spectrum of chronic kidney disease (CKD)
   A full, contextual view of CKD is required to bring solutions that address the global epidemic and to develop effective risk and care coordination strategies. It is necessary to consider the spectrum of stages 1-5 CKD, end-stage renal disease (ESRD), and related comorbidities such as diabetes, hypertension, and cardiovascular disease (Figure 3).

2. Slowing CKD progression
   The global epidemic of kidney disease requires more than care interventions for patients in the final stages of illness. Fresenius Medical Care looks beyond ESRD to include the full range of complications that comprise CKD, focusing on efforts to slow disease progression through early detection, intervention, and addressing social determinants of health.

3. Coordinating patient-centered lifetime care
   Fresenius Medical Care is pioneering the concept of life span care coordination by considering the full patient care journey in the context of the full CKD spectrum and by considering both power and choice as key drivers of patient outcomes and experience. Priorities include identifying opportunities for improvement in local access to care and delivering evidence-based standards of care (Figure 4).

4. Protecting cardiac and vascular systems in CKD care
   Cardiovascular disease is the leading cause of death for late-stage and end-stage CKD patients. To minimize the chance of persistent or chronic injury to the cardiac and vascular systems during treatment, Fresenius Medical Care is focused on innovations, care coordination, and new technology that improves patients’ ability to receive treatments in a way that protects their cardiac and vascular systems.
Collectively, these values of kidney care provide a framework for powerful global CKD care delivery and improved patient outcomes and experiences. Harmonizing these values globally leverages local insights toward a greater good.

GLOBAL COLLABORATION: IDENTIFYING TRANSFORMATIVE INNOVATIONS

At the core, kidney disease care innovation relies on collaboration to foster an environment of change and progress. Innovation must advance medical science and translate that new science into daily patient care. This opportunity to bring emerging science into standard patient care is a unique, inherent value of a vertically integrated company whose domain includes science, product development, manufacturing, service provision, provider partnership, and insurance (Figure 5).

Delivering global innovations begins with generating ideas that lead to care delivery action. Key attributes of this innovative spirit include:

- Using interconnected intelligence for diverse idea generation
- Creating actions to follow commitment
- Focusing on innovations with high utility
- Being open to ideas and skills from inside and outside the corporate ecosystem
- Innovating for the future state of the science rather than where it is today
- Communicating internally and externally about innovation and vision
- Connecting with people across cultures and boundaries
- Promoting innovation that reflects patient and caregiver needs

This innovative spirit facilitates faster, more sensible, and sustainable changes to kidney disease care—so that all people, wherever they live in the world, will know that Fresenius Medical Care is present, listening, and responding with determination to help improve the lives of people living with kidney disease.

QUALITY ACROSS CONTINENTS

Prior to announcing the launch of the Global Medical Office, Fresenius Medical Care initiated a first-of-its-kind endeavor: the development and publication of the company’s first global Clinical and Quality Agenda (CQA). The CQA outlines areas of medical and clinical focus across the company’s businesses around the world and is a key part of our efforts to enhance the quality and safety of patient care across the enterprise.
This complex, collaborative, evaluative process is the result of an annual planning and review process with our chief medical officers, Global Medical Office leaders, and clinical and medical teams around the world. The agenda looks broadly across the company to identify areas that need greater attention and to articulate opportunities for deeper collaborations and synergies on local, regional, and global levels by considering a full spectrum of themes and concepts (Figure 6).

BUILD CORNERSTONES OF TRANSFORMATION: PURPOSEFUL, CONNECTED COMMUNICATION

As a global network of caregivers, creators, thought leaders, and innovators, Fresenius Medical Care seeks to build environments that are conducive to idea sharing, innovation, and progress. To unlock the global potential of shared purpose, we work with diverse communities to build robust pipelines of ideas and innovations.

With a view toward maximizing interconnected intelligence, Fresenius Medical Care considers the concept of “community” broadly, looking at communities through distinct lenses: knowledge communities, professional communities, and peer communities (Figure 7).

Knowledge communities are people and organizations with a common purpose who come together to share knowledge for the greater good. Whether a global data-sharing collaborative, a community-based research think tank, or a cross-industry initiative, the company and its thought leaders actively participate in collaborative endeavors that can make impacts on the science of kidney care as a whole.

There is great power in the ability to be understood by “someone like me.” Peer communities enable individuals with like circumstances to share their experiences, find solutions for shared challenges, and look toward improving the future. Fresenius Medical Care actively participates in and nurtures peer communities, whether they are support groups of kidney disease patients and their caregivers, kidney care advocates, or patient education professionals.

Across the span of kidney disease care are remarkable individuals who make that care possible: nephrologists, nurses, dietitians, social workers, clinic managers, care coordinators, pharmacists, and others. A commitment to professional development of both our colleagues and their professions is a hallmark of the company’s community focus and is one way we invest not just in our people but in the future of care itself (Figure 8).
CONCLUSION

The fast-growing global epidemic of chronic kidney disease demands immediate attention and a long-term strategy to cope with the implications of this worldwide challenge. I’m grateful to lead a group of people determined to harness the full potential of our interconnected intelligence to improve the lives of people with kidney disease by relieving their suffering and enabling them to lead productive and complete lives.

Fresenius Medical Care is transforming health care by addressing root causes of chronic kidney disease, slowing disease progression, enhancing global care quality, fostering idea sharing, and scaling innovations at both the local and global levels. By shifting from episodic, event-based, crisis-driven health care to continuous support models for patients across their life span journey of care, the company is changing the pattern of health delivery from reacting to health issues as they happen to predicting and intervening before a person is faced with a health crisis. This transformation will allow the global health system to recognize the importance of both medical and social support for patients living with a persistent illness, and to be a better partner to people around the world living with the challenges of chronic disease.

FIGURE 8 | Value-based care at work

Meet Our Expert

FRANKLIN W. MADDUX, MD, FACP
Global Chief Medical Officer, Fresenius Medical Care

Franklin W. Maddux’s distinguished career encompasses more than three decades of experience as physician, expert nephrologist, technology entrepreneur, and health care executive. He previously served as Executive Vice President and Chief Medical Officer for Fresenius Medical Care North America and joined Fresenius Medical Care in 2009 after the company acquired Health IT Services Group, a leading electronic health record (EHR) software company founded by Maddux. 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. A practicing nephrologist for nearly two decades, Dr. Maddux graduated with his baccalaureate in mathematics from Vanderbilt University and holds his MD from the School of Medicine at the University of North Carolina at Chapel Hill, where he holds a faculty appointment as clinical associate professor. His writings have appeared in leading medical journals, and his pioneering health care information technology innovations are part of the permanent collection of the National Museum of American History at the Smithsonian Institution.
As the world’s leading provider of kidney disease-related products and services, Fresenius Medical Care supports people living with kidney disease in a richly diverse, complex ecosystem. Caring for patients in over 50 countries, the company is a citizen of countless communities and cultures, effectively functioning across numerous geopolitical environments with regulatory frameworks, economies, and health care systems of varying maturities.

**NEARLY 113,000 EMPLOYEES AROUND THE GLOBE**

**DIALYSIS MACHINES WORLDWIDE IS MANUFACTURED BY FRESENIUS MEDICAL CARE**

**HEALTH CARE PRODUCTS**

- Hemodialysis machines
- Peritoneal dialysis cyclers
- Dialyzers
- Peritoneal dialysis solutions
- Hemodialysis concentrates, solutions, and granulates
- Bloodlines
- Systems for water treatment
- Renal pharmaceuticals
- Acute cardiopulmonary products
- Apheresis products
- Other equipment and medical devices
More than 333,000 patients worldwide

Every 0.6 seconds we provide a dialysis treatment somewhere in the world

More than 3,900 dialysis centers in over 50 countries

Health care services:
- Health plan services
- Urgent care services
- End stage renal disease-related laboratory testing services
- End stage renal disease-related treatments
- Pharmacy services
- Ambulatory surgery center services
- Ambulant treatment services
- Vascular, cardiovascular, and endovascular specialty services
- Physician nephrology and cardiology services
- Acute dialysis services

Fresenius Medical Care at a Glance:
- 42 production sites
- Nearly 113,000 employees around the globe
- 333,000 patients worldwide
- More than 3,900 dialysis centers in over 50 countries

Production sites:
- Bad Homburg
- Global Corporate Headquarters
- Hong Kong
- Waltham
- Rio de Janeiro
- Europe, Middle East, Africa
- North America
- Latin America
- Asia Pacific

Health care products:
- Hemodialysis machines
- Peritoneal dialysis cyclers
- Dialyzers
- Peritoneal dialysis solutions
- Hemodialysis concentrates, solutions, and granulates
- Bloodlines
- Systems for water treatment
- Renal pharmaceuticals
- Acute cardiopulmonary products
- Apheresis products
- Other equipment and medical devices
A highly diverse and culturally complex region covering more than 50 percent of the world’s population, with nearly 4.1 billion people speaking over 800 languages, the Asia Pacific region paints a colorful picture of health care challenges and opportunities.

**Geographic Complexity**
- Size (in sq. km): 24.1M
- Total region population: 4.1B
- Number of countries: 48
- Number of languages spoken: >800

**By the Numbers**
- Number of ESRD patients treated by Fresenius Medical Care: 31,476
- Number of dialysis treatments (HD and PD): 4.8M
- Total fluids removed (liters): 9.8M
- Total blood pumped (liters): 289M
- Total number of blood pressures taken: 33.6M
- Total number of dialyzers used: 3.6M
- Primary modality: In-center hemodialysis
- Percent of patients using home modality: 22
- Number of publications by regional authors: 3

**Regional Facts**
- Number of ESRD patients (HD, PD, transplant) in 2018: 1.6M
- Number of employees: 12,792

**Regional Headquarters**
- Hong Kong
- China

**Top 5 Pillars of Activity**
- Affordability
- Access to Care
- Quality of Care
- Guideline and Best Practices Implementation
- Local Regulatory and Reimbursement Policies

**EHR**
- NephroWeb and EuClid

**Meals Included with Treatment**
- Yes, variable
**EUROPE, MIDDLE EAST, AFRICA**

With the largest roster of countries, languages, and regulatory frameworks served by Fresenius Medical Care, the EMEA region faces enormous challenges to providing the best therapies to all patients in all countries.

**GEOGRAPHIC COMPLEXITY**

<table>
<thead>
<tr>
<th>SIZE (IN SQ. KM)</th>
<th>47.9M</th>
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<tr>
<td>TOTAL REGION POPULATION</td>
<td>2.5B</td>
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<tr>
<td>NUMBER OF COUNTRIES</td>
<td>109</td>
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<tr>
<td>NUMBER OF LANGUAGES SPOKEN</td>
<td>&gt;150</td>
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</table>

**BY THE NUMBERS**

| NUMBER OF ESRD PATIENTS TREATED BY FRESENIUS MEDICAL CARE | 66,938 |
| NUMBER OF DIALYSIS TREATMENTS (HD ONLY) | 9.7M |
| TOTAL FLUIDS REMOVED (LITERS) | 18.4M |
| TOTAL BLOOD PUMPED (LITERS) | 812M |
| TOTAL NUMBER OF BLOOD PRESSURES TAKEN | 45M |
| TOTAL NUMBER OF DIALYSEERS USED | 9.7M |
| PRIMARY MODALITY | IN-CENTER HEMODIALYSIS |
| PERCENT OF PATIENTS USING HOME MODALITY | 6.5 |
| NUMBER OF PUBLICATIONS BY REGIONAL AUTHORS | 26 |

**REGIONAL HEADQUARTERS**

- BAD HOMBURG, GERMANY

**REGIONAL FACTS**

- NUMBER OF ESRD PATIENTS (HD, PD, TRANSPLANT) IN 2018: 1.13M
- NUMBER OF EMPLOYEES: 21,038
- EHR: EuClid
- MEALS INCLUDED WITH TREATMENT: Yes, variable

**TOP 5 PILLARS OF ACTIVITY**

- CONTINUOUS IMPROVEMENT OF QUALITY OF CARE
- VALUE-BASED HEALTH CARE
- MEDICAL RESEARCH COLLABORATION AND STRATEGIES
- CARE AND PRODUCT INNOVATION
- ADVANCED ANALYTICS
**LATIN AMERICA**

Juan Carlos Berbessi, MD | Chief Medical Officer, Latin America

Latin America is a wonderfully diverse group of countries with challenging political and economic realities. Fresenius Medical Care understands the needs of patients from a multitude of cultures within the region and has established a value-based care approach to provide health care solutions to all people living with kidney disease.

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**GEOGRAPHIC COMPLEXITY**

- Size (in sq. km): 22.5M
- Total region population: 522M
- Number of countries: 33
- Number of languages spoken: 11

**BY THE NUMBERS**

- Number of ESRD patients treated by Fresenius Medical Care: 36,800
- Number of dialysis treatments (HD and PD): 5.5M

**BY THE NUMBERS**

- Total fluids removed (liters): 8.5M
- Total blood pumped (liters): 95M
- Total number of blood pressures taken: 20.2M
- Total number of dialyzers used: 4M
- Primary modality: In-center hemodialysis
- Percent of patients using home modality: 14
- Number of publications by regional authors: 3

**REGIONAL FACTS**

- Regional headquarters: Rio de Janeiro, Brazil
- Number of ESRD patients (HD, PD, transplant) in 2018: 432K
- Number of employees: 10,439

**TOP 5 PILLARS OF ACTIVITY**

- Enhanced educational activities
- Improved clinical care
- Enhanced research and publications activities
- Enhanced ability to support technology education
- Value-based care activities

**EHR**

- EuClid

**Meals included with treatment**

- Yes
The North America region includes some of the most mature health care systems in the world, along with some of the greatest population-based health challenges. Comprised of the United States, Puerto Rico, Canada, and Mexico, the North America region includes three primary languages: English, French, and Spanish. The region also boasts a mix of both public and private health care systems, with the United States leading the way in value-based care models.

### By the Numbers

<table>
<thead>
<tr>
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<th>Value</th>
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<tbody>
<tr>
<td>Number of ESRD patients treated by Fresenius Medical Care</td>
<td>268K</td>
</tr>
<tr>
<td>Number of dialysis treatments (HD and PD)</td>
<td>32M</td>
</tr>
<tr>
<td>Total fluids removed (liters)</td>
<td>61M</td>
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<tr>
<td>Total blood pumped (liters)</td>
<td>2,429M</td>
</tr>
<tr>
<td>Total number of blood pressures taken</td>
<td>252M</td>
</tr>
<tr>
<td>Total number of dialyzers used</td>
<td>27M</td>
</tr>
<tr>
<td>Primary modality</td>
<td>HD, HHD, and PD, shifting to transplant and home dialysis-first policies</td>
</tr>
<tr>
<td>Percent of patients using home modality</td>
<td>15</td>
</tr>
<tr>
<td>Number of publications by regional authors</td>
<td>53</td>
</tr>
</tbody>
</table>

### Regional Facts

- **Regional Headquarters**
  - Waltham, Massachusetts (US)
  - Richmond Hill, Ontario (Canada)
  - Mexico City, Mexico

- **Regional Facts**
  - Number of ESRD patients (HD, PD, transplant) in 2018: 801K
  - Number of employees: 66,000+

### Top 5 Pillars of Activity

- Improved quality of care with cost containment
- Improved late-stage CKD management and transition to ESRD
- Increased patient access to dialysis home therapies
- Social determinants of health
- Skilled labor force
There are many reasons to embrace home therapies, and not just for the youngest and healthiest of the dialysis patient population. It’s time to expand our programs and even our concept of “home” to give patients more control over their lives, reduce hospitalizations, increase survival, and lower costs. To reach its 2022 goal of treating more than 15 percent of patients in a home setting, Fresenius Medical Care North America (FMCNA) is focusing on reducing patient burden through technological innovations, physician education, family support, transitional care dialysis units, and expanded telemedicine platforms.
In the United States, in-center hemodialysis has been the face of dialysis since the late 1970s. Even today, amidst a generational low in utilization of in-center hemodialysis, only 12 percent of patients dialyze at home. However, throughout the health care industry, person-centered care and empowered self-care is on the rise. In dialysis, technological advancements are bringing care home. Improvements in machine technology and connected health have made home dialysis simpler and more portable, thus increasing access for patients. Future device evolution will continue to increase safety, communication, and portability, and reduce burden while improving the care delivery process.

Fresenius Kidney Care (FKC) has embraced the move to the home. Compared to five years ago, the number of FKC patients on home hemodialysis (HHD) and peritoneal dialysis (PD) has increased by 90 percent and 39 percent, respectively (Figure 1).

**FIGURE 1 |** Relative growth of home therapies

![Graph showing relative growth of home therapies](image)

Home and self-care dialysis treatments are the quintessential path to empower patients and families, allowing patients the freedom to manage their treatments and disease. PD allows needleless daily dialysis, preserves residual renal function, and has early survival benefits. HHD eases delivery of more frequent dialysis (MFD) therapies in a cost-efficient manner. Studies show MFD of greater than 5 days per week improves blood pressure control with reduced medications and improves overall volume management. MFD can reduce the intradialytic volume complications of high ultrafiltration rates, cardiac stunning, prolonged recovery rates, and hypotension (Figure 2). In studies, MFD has been shown to address the interdialytic volume complications of left ventricular hypertrophy, hypertension, and congestive heart failure. Home therapies performed effectively address cardiac status and common complications of dialysis, reduce hospitalizations, increase survival, and lower costs. Most importantly, home therapies allow patients to succeed in living better lives with their families.
Chronic dialysis therapy has inherent burdens on patients, care providers, and families, often resulting in an unacceptable quality of life. Conventional hemodialysis has been called a “full-time job,” making work impossible and travel difficult and compromising family time. The time spent on dialysis, transportation to and from the treatment center, and recovery (greater than six to eight hours for many patients) can exceed 30 hours per week. Well-supported home dialysis may actually reduce these burdens (Figure 3).

WHERE IS HOME?

At present, the “home” in home dialysis is typically a single-family home or an apartment, but the definition is expanding to be anywhere the patient chooses: a private residence, a travel destination, a skilled nursing facility, or even a community center. While dialysis in the actual home will remain the primary site of home therapies, the concept of a home without walls will evolve.

Patients are frequently limited by storage space, so delivery systems will need to advance to require less storage space. As PD devices mature with online fluid generation, storage needs will markedly decrease. Industry may have to consider better, more frequent delivery systems to meet patient needs, perhaps even an Uber-like, as-needed delivery system.

Examples of potential changes needed to improve access to home therapies include community centers and paid care partners. Denmark, New Zealand, and the United Kingdom have already begun to study the use of community centers for home patients. Patients come to the community center for self-care on a desired schedule, either in place of or in addition to care in their home locations. A community center solves the problem of not enough storage space and could prevent social isolation of dialysis that is only provided in the home. One could envision community dialysis centers offering access during televised events or shows to provide a community of dialysis patients with socialization opportunities. Creating virtual community centers with telemedicine allows for the building of social connections, bonding together, and looking out for one another—in short, building homes without walls and communities without borders.

Home dialysis need not be relegated to only self-care in the private residence. Development of paid partner models can bring home therapies to those who need assistance. Programs have been initiated in Canada to demonstrate the benefits and costs with HHD. Assisted PD is available in many high-income countries using health care workers and in some lower income countries using extended family members or domestic help, increasing access to person-centered care.

While not truly a home therapy, self-care in-center dialysis units also empower and engage patients and can be a springboard to home therapies. Increasing in-center self-care should be a priority.

REMOVING BARRIERS AND IMPROVING RETENTION

There are very few contraindications to home therapy. Active drug or alcohol addiction and severe psychiatric illness without adequate support may make self-care impossible. Advanced age, low degree of education, significant comorbidities, language spoken, and illiteracy are perceived barriers that can be overcome with proper support and education tools. Given the right tools and support, patients can be empowered to control their own dialysis, medications, diet, and life.

Home dialysis access must be available for all patients, including those with a worse clinical prognosis. No longer can home therapies, particularly HHD, be offered to only the youngest and healthiest patients. PD and HHD, including MFD, improve the quality and quantity of life of the sickest and elderly patients. In fact, patients with more comorbidities can embrace home therapies. In the FREEDOM study, patients with the lowest quality of life at baseline exhibited the largest improvement during 12 months of frequent HHD. Given proper resources, these more challenging patients flourish on a home therapy.

Advancements in technology and telemedicine with both HHD and PD will improve access and decrease burden. Today, there are connected health platforms in use—including Baxter Sharesource™, Fresenius Medical Care connected health

FIGURE 2 | Ultrafiltration rates (UFR) and recovery time in dialysis and effect of more frequent dialysis

![Graph showing ultrafiltration rates and recovery time](image)


![Graph showing recovery time in the Freedom Study](image)


FIGURE 3 | Building blocks for successful growth in home dialysis

- **Teaching**: MD, RN, PCT, patients
- **Transitional Care**: Universal entry
- **Telehealth**: Reduce burden
- **Technology**: Reduce burden

Foundation

Adequate resources: home nurses, MSWs, dietitians, PCTs
platform, and the Nx2me™ platform from NxStage. These platforms have improved adherence, facilitated quicker training, and improved patient retention. Virtual clinic visits will decrease travel time for the patient and provide as-needed care. Telemedicine can improve adherence, reduce ER visits, and reduce hospitalization rates, resulting in lower costs and lower morbidity rates.

Growth of home therapies is dependent on the intake of new patients and improved patient retention. While technology changes and telemedicine will improve access and retention, patient and unit success depend on adequate resources in home dialysis units large enough to provide these resources at scale. In 2018, NxStage commissioned a survey of patients who had returned to in-center dialysis and a review of 10 large US centers to explore best practices in training and retention (NxStage data is on file). Together, these studies suggest patient drops could be mitigated by engaged professionals with adequate resources, prescription adaptability (frequency, solo dialysis, and nocturnal dialysis), and clinic adaptability to meet the patient and partner needs.

NxStage’s review of large home clinics found that the success of home dialysis programs varied by resources utilized. Successful units (measured as increased retention) invested in resources and caregiver engagement. Specifically, better results occurred when utilizing professional nurses with the desire to grow home therapies, engaged and available social workers, dietitians knowledgeable about the changes in home therapies, and patient care technicians (PCTs) in the home unit. Appropriate addition of PCTs to perform tasks consistent with local scope of practice rules allowed more time for nurses to focus on patient education, care, and retention. In short, successful units have nursing champions with a strong interdisciplinary team with time committed to home.

Likewise, it is imperative to support physician champions in the home therapies with additional education and streamlining processes to improve efficiencies in the intake, education, and delivery of home therapies. Academic training in home therapies is thought to be lacking. FMCNA will provide novel training techniques to support physicians through this culture change. There is a commitment to building teams of physician champions with imbedded nursing champions.

PATIENT TRANSITIONS

All patients with end-stage renal disease (ESRD) deserve adequate education on self-directed disease management, including:

- Disease education
- Dietary recommendations
- Medication management
- Modality options (transplant, peritoneal dialysis, home hemodialysis modalities, in-center care, and even hospice/palliative care)

While dialysis modality education is focused on CKD and in-center ESRD patients when they initiate therapy, there are special populations who need additional disease and modality education or reeducation to avoid immediate risks. Patients in transition have increased risk for hospitalizations, mortality, depression, and more outpatient care. These transitions include all transitions—the incident patient (new to ESRD), patients with failing PD or HHD therapy technique, patients losing transplant function, patients wanting to leave in-center, patients discharged from hospitals or transferred from/to skilled nursing facilities, and patients suffering from acute kidney injury requiring renal replacement. These pressure points are complicated by declining health, fear of transition, depression/grief, and, frequently, a lack of understanding of the illness and treatments.

Special attention is needed to help the PD patient transition to HHD as therapy technique fails. Nationally, 12,000 PD patients transitioned to hemodialysis in 2016, with less than 1 percent going to HHD. Education platforms need to be developed to help patients, physicians, and nurses understand the likelihood of transition and develop pathways of earlier transition to HD/HHD, which may reduce the increased morbidity seen with PD technique loss.

Transitional units, either in-center or free standing, will have the resources to educate on overall care and appropriate modality at the right time. They are more able to assist physicians with patients’ ongoing medical issues with weight, blood pressure, medications, and even appropriate frequency of dialysis daily rather than monthly, to improve outcomes. Transitional units offer distinct advantages over traditional in-center units for these patients. Existing transitional unit experience has seen improvement in modality selection, patient satisfaction, and even improved adherence with in-center dialysis prescription.

Throughout the patient journey, needs change and transitions occur. Growth will be dependent on the ability to ease patients through transitions, define proper timing of transitions, and provide the right prescription for the right therapy every day.

Meet Our Experts

**MICHAEL A. KRAUS, MD, FACP**

*Associate Chief Medical Officer, NxStage, Fresenius Medical Care*

Prior to working for NxStage, Michael Kraus held several positions and titles at Indiana University (IU) Health and Indiana University School of Medicine, including service line chief for IU Health Physicians, Kidney Diseases; and chief medical officer of IU Health Adult Dialysis Services. He is a leader in the field of short daily home hemodialysis and a well-published, internationally recognized invited speaker. He is a recipient of the Lifetime Achievement Award from the National Kidney Foundation of Indiana and of the Sagamore of the Wabash, the highest award presented to a citizen of Indiana.

**DINESH CHATOTH, MD**

*Associate Chief Medical Officer, Fresenius Kidney Care*

Dinesh Chatoth completed his fellowship in nephrology at the University of Texas Southwestern Medical Center in Dallas. He was an assistant professor of medicine and director of the dialysis program at the University of Arkansas for Medical Sciences. He has worked with the KDOQI workgroup for peritoneal dialysis and promotes home dialysis as a modality of choice for patients requiring renal replacement therapy. He oversees home therapy initiatives for the Medical Office and serves on the FKCK Pharmaceutical and Therapeutics Committee.
As the population of patients on dialysis continues to grow, the shortcomings of three, relatively brief in-center treatments per week are clear. Many patients experience chronic volume and pressure overload, which must be addressed with aggressive ultrafiltration and the use of multiple antihypertensive medications. More frequent hemodialysis, which is most readily delivered in the home setting, can be used to better manage volume status. More frequent home hemodialysis (HHD) reduces interdialytic volume load, pre-dialysis blood pressure, and the need for antihypertensive medication, and ultimately can improve cardiac structure.
The prevalent dialysis population rose to 511,000 patients at the end of 2016. With a forecasted annual growth rate of 2.5 percent, which is historically low, the size of the population in 2030 would nevertheless exceed 700,000. This projection is consistent with data reported in 2019 using different techniques.1

This growing population will stress the existing infrastructure with shortages in the numbers of nephrologists, nurses, dietitians, and social workers (Figure 1). In addition, the costs of care related to staffing and supplies will likely rise with inflation, making in-center care more expensive while revenue from payers may lag behind.

FIGURE 1  |  Prevalent dialysis population, actual (1996-2017) and projected* (2018-2030)

On top of these growth projections, recent data on trends in mortality and hospitalization rates show little improvement, suggesting that alternative approaches may be needed to advance value-based care (Figure 2).

FIGURE 2  |  Mortality and hospitalization rates 2014 to 2017

1. USRDS 2018 ADR Reference table D.6 with simple autoregression projection

* Medicare fee-for-service dialysis patients, 2014–2017: around 300,000 patients per week.

* Risk of death varies seasonally but is FLAT.

* Risk of hospital admission also varies seasonally but is likewise FLAT.
To continue to extend survival on dialysis, lower risks of hospitalization and emergent care, and improve the quality of life in dialysis patients, care delivery systems should aim for more stable dialysis treatments in lower-cost settings. Dialytic therapy, in particular, must address the primary sources of morbidity: cardiovascular death and infection. The reality is that three-times-per-week hemodialysis (HD) may not be effective for many patients in addressing chronic volume and sodium overload and underlying cardiovascular disease, including persistent hypertension (HTN), advancing left ventricular hypertrophy (LVH), heart failure (HF), and arrhythmia. While considerable attention has been given to the physiology of three-times-per-week HD with high ultrafiltration rates (UFRs), this therapy covers only 7 percent of the hours in a week. Little attention has been given to the remaining 93 percent, when volume and sodium loading of the cardiovascular system occurs.

Figure 3 illustrates the major differences in care for HTN, LVH, and HF in nondialysis and dialysis populations.

**FIGURE 3** | Management of chronic hypertension, left ventricular hypertrophy, and heart failure

The cornerstone of treatment for cardiovascular disease is control of salt and water throughout the day, seven days a week. Diuretic use is tailored to achieve diuresis throughout the day, but HD addresses fluid removal only three days a week and for just 3.5 to 4 hours on each of those days. The use of cardiac drugs to treat HF and HTN and to control volume-related LVH is limited; these drugs become ineffective when the vasculature is volume loaded, and the occurrence of intradialytic hypotension further complicates their use. Because no volume removal occurs in the time off HD, patient vasculature is cyclically loaded. This causes high pressures in the heart, increased stress on the myocardial walls, and dilatation of the heart chambers and fibrous structure of the heart and valves, which can lead to progressive LVH, HF, arrhythmia, and associated hospitalization and mortality.

Pressure profiles of the heart are shown in Figure 4. Normal pulmonary artery and right ventricular pressures are 20/10 mmHg systolic and diastolic. Between HD treatments, however, when volume loading occurs, pressures approach 40 mmHg systolic—pulmonary hypertension, essentially—demonstrating the direct impact on the heart of volume loading.

For a more complete look at the pathophysiologic causal pathway driving cardiovascular disease on three-times-per-week HD, the volume loading that occurs off dialysis needs to be viewed over the entire week of therapy (Figure 5).

**FIGURE 5** | Challenges with thrice-weekly hemodialysis

The top of the chart shows how volume loading with water and salt contributes to the evolution of chronic cardiac disease; the lower part synthesizes the intra-treatment consequences of volume removal, with higher UFRs leading to the now well-recognized phenomenon of cardiac stunning.

Volume loading off HD cannot be addressed by simply increasing the three-times-per-week treatment time. This was tested most recently in A Clinical Trial of Intensive (ACTIVE) Dialysis study, which compared thrice-weekly treatments totaling 12 to 15 hours to those totaling 24+ hours, looking at QOL and at secondary markers including biochemical data, BP, and left ventricular mass index (LVMi). There was no difference in primary QOL measures, and while the secondary outcomes showed fewer BP medications and phosphate binders, there was no statistical difference in BP control or LVMi. This study suggests that extending three-times-per-week treatment times may have limited effect given the off-dialysis volume loading that continues to drive up cardiac pressures.

The fundamental realities of cardiovascular pathophysiology and the inherent intermittency of in-center hemodialysis, even when session duration is extended, together provide the rationale for more frequent hemodialysis in the home setting.

The populations most vulnerable to these volume loading states are shown in Figure 6.

Patients with known HF and persistent fluid overload are potential candidates for more frequent HD therapy, as are those with persistent and resistant HTN, and those with evidence of abnormal LVH and persistent uncontrolled hyperphosphatemia. Additional populations that deserve consideration due to clinical challenges in care delivery are noted in Figure 7. While a patient may clinically benefit from more frequent dialysis, the decision to prescribe more frequent dialysis is a physician judgment based on medical necessity.

---

**TABLE 1** | Average rest values from first, second, and third nights (n = 16)

<table>
<thead>
<tr>
<th>Night</th>
<th>RV Systolic Pressure (mm Hg)</th>
<th>RV Diastolic Pressure (mm Hg)</th>
<th>Estimated PA Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First night</td>
<td>24.7 ± 4.4</td>
<td>19 ± 4.4</td>
<td>11.8 ± 4.3</td>
</tr>
<tr>
<td>(n = 555)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second night</td>
<td>24.7 ± 4.4*</td>
<td>3.6 ± 3.6*</td>
<td>13.9 ± 4.0*</td>
</tr>
<tr>
<td>(n = 555)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third night</td>
<td>29.3 ± 6.1*</td>
<td>4.8 ± 3.1*</td>
<td>15.3 ± 4.1*</td>
</tr>
<tr>
<td>(n = 165)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.

*p < 0.001 vs first night; †p < 0.005 vs second night.
Leading this list are patients transitioning from peritoneal dialysis (PD) to HD, a group with very high rates of death and hospitalization around the time of transition. A recent study compared PD patients transitioning to home hemodialysis (HHD) with those moving to in-center HD.\(^1\) The overall assessment of these groups is shown in Figure 8.\(^3\)

In this study, patients who moved from PD to HHD were hospitalized only 9.1 days during the three months before and three months after the transition, compared to more than double this rate among patients who moved from PD to in-center HD.

**FIGURE 6 |** Medical indications that are likely to clinically benefit from more frequent hemodialysis

- Persistent fluid overload, as measured by bioimpedance spectroscopy or lung ultrasonography
- Uncontrolled hypertension (systolic blood pressure >160 mmHg for 3-6 months, or systolic blood pressure >140 mmHg with concomitant use of 3+ medications)
- Left ventricular hypertrophy (left ventricular mass index >125 g/m2)
- Heart failure (New York Heart Association classes 2-4, with persistent elevation of NT-proBNP)
- Persistent hyperphosphatemia (serum phosphorus >5.5 mg/dL for 3-6 months)
- Intolerance to hemodialysis, as evinced by recurrent hypotension and cramping during treatment and/or long post-dialysis recovery time (e.g., >6 hours)

**FIGURE 7 |** Specific patient phenotypes that are targets for more frequent HD

- Patients transitioning from peritoneal dialysis to hemodialysis
- Patients in skilled nursing facilities for cardiac rehabilitation (e.g., after heart failure hospitalization) or long-term custodial care
- Patients on the kidney transplant waitlist (to maintain good cardiovascular health and mineral and bone metabolism in preparation for transplant)
- Patients who are pregnant
- Patients who require freely available daytime hours for education or work

Survival among HHD patients was significantly better, and their likelihood of a kidney transplant was 29 percent higher. This study provides insight into the possible advantages of a careful transition from peritoneal dialysis to HHD, with more frequent treatment and improved management of volume control and heart failure.

**THE SOLUTION**

Delivering hemodialysis five to six days per week has been shown in clinical trials to control volume, reduce blood pressure and the use of blood pressure medication, lower LVMi, reduce serum phosphorus and the use of phosphate binders, improve patient-related QOL measures, and shorten post-dialysis recovery time. The challenge in delivering more frequent therapy in the in-center environment, with fixed-run schedules and a lack of extra stations, is clear. The home setting in the best alternative; time is more flexible, and schedules can be better matched to patient and family lifestyles.

Published observational data have confirmed findings from clinical trials, demonstrating the efficacy of more frequent HD by daily treatments or on nocturnal schedules. More frequent HD addresses high UFRs and reduces volume loading of the heart by controlling interdialytic volume excess. Blood pressure control is achieved with fewer medications, and phosphate control is improved, also with fewer medications. More frequent HHD not only delivers the required stability of therapy in a lower-cost setting, but also improves the tolerability of the therapy and allows better control of cardiovascular disease.

**FIGURE 8 |** Reported outcomes in patients who transitioned from PD to HD

<table>
<thead>
<tr>
<th>Study Population</th>
<th>33,452 peritoneal dialysis patients transitioning to hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis Setting</td>
<td>521 patients to home HD (3.8%)</td>
</tr>
<tr>
<td>Hospitalization Days</td>
<td>9.1 hospitalization days during transition</td>
</tr>
<tr>
<td>Survival (4-year follow-up)</td>
<td>70.1% survived</td>
</tr>
<tr>
<td>Transplantation Incidence (4-year follow-up)</td>
<td>28.8% transplanted</td>
</tr>
</tbody>
</table>

Meet Our Experts

**ALLAN COLLINS, MD, FACP**
Senior Chief Scientist, Fresenius Medical Care

Allan Collins has a distinguished career with more than 30 years of work in nephrology and ESRD treatment. He is the former chief medical officer for NxStage Medical, Inc. and served as director of the National Institute of Health's NIDDK’s United States Renal Data System from 1999 to 2014. Dr. Collins has published more than 225 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 ESRD and chronic kidney disease patients, and prospective and retrospective clinical studies on dialysis techniques and associated outcomes. The former president of the National Kidney Foundation, Dr. Collins served on the NKF scientific advisory board for six years, with the Kidney Dialysis Outcomes Quality Initiative, and on the International Society of Nephrology’s Commission for the Global Advancement of Nephrology Committee. He graduated with his medical degree from Wayne State University in Detroit.

**ERIC WEINHANDL, PhD, MS**
Senior Director, Epidemiology and Biostatistics, Fresenius Medical Care

Eric Weinhandl has over 15 years of experience in dialysis-related research, including extensive experience with Medicare claims. Prior to joining Fresenius Medical Care, Eric was a clinical epidemiologist at NxStage Medical, where he led a team devoted to clinical research on the benefits and risks of frequent hemodialysis in the home setting. Earlier in his career, he worked at the Chronic Disease Research Group in Minneapolis, Minnesota, where he contributed to the United States Renal Data System, the Peer Kidney Care Initiative, and numerous industry-sponsored research projects on the comparative effectiveness of dialytic modalities and the pharmacoeconomics of chronic kidney disease. Eric holds a master of science in biostatistics and a PhD in epidemiology from the University of Minnesota, where he continues to serve as an adjunct professor in the College of Pharmacy. Eric has authored approximately 70 manuscripts and presented roughly 140 abstracts at scientific meetings.
Every year, more people are diagnosed with kidney disease than with cancer. In spite of this fact, research activity is overwhelmingly focused on new oncology treatments. As of Q2 2019, there is only one late-stage nephrology study for every 39 cancer studies, and the National Institutes of Health (NIH) provided 10 times more funding for cancer than for kidney disease. There are many reasons for this discrepancy, including the fact that the multiple comorbidities that affect kidney patients make investigations extremely complex. However, greater public awareness about kidney disease and the increased participation of clinicians and patients will have a demonstrable impact on the future of nephrology research and trials.
At least 20 percent of people between 65 and 74, and half of those over 75, have chronic kidney disease (CKD). Yet development pipelines for the 10 largest pharmaceutical companies contain fewer than 30 active nephrology clinical investigations compared with over 1,300 in oncology. In contrast with the vast number of research protocols cancer patients are encouraged to consider, inclusion in clinical studies is not a standard opportunity for people with kidney disease despite their eagerness to participate. Why is this? How can the industry be encouraged to think differently to advance renal research for the betterment of public health?

ALWAYS A POOR COUSIN

Since 1945, trials for renal indications have lagged other organ system categories. As clinical trial activity has increased, the gap between investigation of renal disease and other disease entities—notably, oncology and infectious disease—has widened (Figure 1).4,5

FIGURE 1 | Number of randomized controlled clinical trials registered in the United States annually, by organ system (reprinted with permission)
Not only is kidney disease often excluded from the focus of pharmaceutical companies’ studies, but patients with kidney disease are often excluded from other studies. For example, a systematic review of randomized trials for cardiovascular disease (CVD) interventions between 2006 and 2013 revealed that of 371 trials, 57 percent (212) excluded patients with kidney disease. Renal disease affects so many physiological systems that researchers are reluctant to include these patients for fear of adverse effects. Yet exclusion of this population seems imprudent. Kidney disease is extremely common in people with CVD, and they could benefit from tested interventions.7

HUMAN AND FINANCIAL COSTS
The number of people likely to be diagnosed with cancer in the United States is smaller than the number likely to be diagnosed with kidney disease. The NIH projects that by 2020, there will be 18.1 million cancer survivors with a projected annual cost of care of $187 billion (in 2010 dollars).4 While these numbers are staggering, the cost of kidney disease is also high, with more people affected by kidney disease than cancer. The Centers for Disease Control and Prevention estimates the prevalence of CKD in the general adult population to be 15 percent (37 million).9 The 2018 US Renal Data System (USRDS) Annual Report estimated the total Medicare spending on both CKD and end-stage renal disease (ESRD) patients is in excess of $114 billion.10 It is difficult to estimate the cost of CKD and ESRD in combination with concomitant diseases that typically complicate renal care.

A person can lose 90 percent of kidney function before experiencing symptoms, making kidney disease a hidden public health crisis.11 “There are many missed opportunities for (CKD’s) potential early detection and subsequent treatment implementation,” said Rajiv Saran, MD, professor of internal medicine at the University of Michigan and director of the USRDS coordinating center. “For example, the relatively low testing rates for urine protein even among those with diabetes or hypertension—both well-known risk factors for kidney disease—remains a concern.”12 The idea that this disease has been overlooked for so long is astounding.

PUBLIC AND INDUSTRY ENGAGEMENT
In 2018, 15 new oncology treatments were introduced and the number of drugs in late-stage development expanded by 19 percent, up 63 percent since 2013.13 As of Q2 2019, there is only one nephrology study for every 39 cancer studies in the pipeline.14 This difference is disproportional to the prevalence of these diseases in the population.

Many factors affect research and development investment decisions, such as potential commercial value, competition, therapy novelty, likelihood of approval, development cost and time, and public perception. The public demand for effective oncological treatments has driven the development of precision and immune-oncology therapies, offering hope to millions. However, nephrology is a completely different landscape. There is little public demand and urgency to create novel kidney-related therapies because many patients will expire due to associated comorbid conditions, such as CVD, before they even know they have kidney issues.

THE FUNDING DISCREPANCY
In 2018, with a budget of $39 billion, the NIH provided 10 times more funding for cancer than for kidney disease ($6.34 billion vs. $598 million), while Alzheimer’s research received $1.91 billion.15 The American Society of Nephrology (ASN) Research Advocacy Committee estimates that the NIH spent more than $500 annually per cancer patient but only $30 per CKD patient.16 Indeed, Kaiser’s annual “Hot 100” indications list—a gauge of global R&D investment in pharma—showed that in 2018, kidney transplant was listed at number 70, while epidermolysis bullosa, a genetic skin disorder with an incidence of 1 in every 50,000 live births, was number 41.17

Industry press has framed the $25 million KidneyX initiative—a partnership between the US Department of Health and Human Services and the ASN—as nephrology’s answer to the Cancer Moonshot program; however, funding for the Cancer Moonshot is $1.8 billion. That is 72 times the funding of KidneyX.18

It’s difficult to determine to what extent research generates sales through improved or novel offerings, or how pharmaceutical sales increase interest in research. But in 2017, the global CKD drug market was estimated at $2.7 billion.19 In contrast, the global oncology drug market was valued at $97.4 billion.20

Even with reasonable funding, investigator and patient barriers to successful renal research remain. Kidney failure patients’ low glomerular filtration rate may alter the safety profile of certain drugs and devices.21 Multiple comorbidities also make trials in renal patients risky and confound results.

Limited activity in kidney research has impacted the evidence base for CKD treatment, resulting in the lack of useful surrogate end points for progression from early-stage CKD hindered trials. Several costly phase III trials recently failed to achieve improved outcomes, further curtailing industry interest.22 At present, there are relatively few therapies in development for the treatment of CKD, and the global CKD drug market consists mainly of calcium channel blockers and ACE inhibitors—therapies that have hardly changed in the past 30 years; however, the sodium-glucose transport protein 2 (SGLT2) inhibitors have begun to show promise and the active early stage research for more drug targets seems to be growing.23

The number of people likely to be diagnosed with cancer in the United States is smaller than the number likely to be diagnosed with kidney disease.
In 2018, with a budget of $39 billion, the NIH provided 10 times more funding for cancer than for kidney disease.

THERE IS HOPE

A 2018 joint NKF, FDA, and European Medicines Agency massive data meta-analysis has begun to yield basic insight—for instance, the value of albuminuria for tracking early CKD disease progression. Current genetic techniques should uncover more sensitive biomarkers to help identify and follow patients with early-onset CKD.

Despite inadequate funding and scarce high-quality randomized trials, important clinical research studies do exist. For example, small-molecule drugs for the treatment of anemia in patients with CKD have been developed. A glucuretic proximal tubule transport inhibitor is also in trials to evaluate its effect on renal outcomes and cardiovascular mortality in patients with CKD.

The renal research and patient communities are resolved to change; however, only 22 percent of patients heard about clinical trial opportunities from their nephrologist, their most trusted source of information. This statistic is in stark contrast to patients with melanoma (45 percent) and lung cancer (58 percent) whose oncologists frequently shared information about clinical trial opportunities. Since patients and investigators are the bedrock of successful clinical trials, changing this pattern is key.

Within the nephrology and renal care ecosystem, building awareness of the potential economic and clinical benefits of trial participation should help recruit high-performing investigative sites. Clinically, study patients may be able to receive treatments otherwise unavailable, plus they can have the satisfaction of giving back, an important consideration for many renal patients. Because patients are seen by both clinical and research teams, they benefit psychologically and medically from the increased level of care. Although not confirmed in renal trials, study patients in other disease areas have shown increased engagement and better adherence with improved clinical outcomes.

Despite the benefits, physicians often avoid adding the complexity of clinical research to their patient practices; however, the industry is motivated to relieve the research burden to increase physician participation. Outsourcing services can be engaged to essentially manage administrative research tasks. Principal investigators can enjoy the benefits of participating in clinical studies, yet still have time to care for patients.

While kidney research faces challenges, the renal research community must mobilize to overcome them. Enlisting the help of front-line nephrologists and easing barriers for participation in clinical trials are important steps to make kidney research more attractive for prospective investigators.

Pointing to frenzied and redundant investments in oncological research and biotech, Jay Bradner, Novartis R&D president, questioned in a 2018 Forbes interview, “Can we as a society be over-invested in working to cure cancer?” In 2019, maybe investors should be asking the same question. It’s time to take a closer look at kidney research, an almost uncharted field with vast, hidden potential.

Meet Our Expert

KURT MUSSINA, MBA
President, Frenova Renal Research

Kurt Mussina is a chemist, global health care executive, and accomplished entrepreneur with a distinguished 30-year career spanning the research, development, and approval continuum for drugs and medical devices. Under his leadership, Frenova has expanded its focus from ESRD research to the full spectrum of CKD and renal impairment, growing the Frenova community of researchers into a world-class network of more than 550 principal investigators across 360 research sites. He previously held senior executive roles in client management and business development for international contract research organizations, including expatriate assignments in Denmark and the United Kingdom. Mussina began his career as an analytical chemist and R&D scientist for leading pharmaceutical companies, including Novartis. He graduated with a bachelor’s degree in chemistry from Montclair State University in New Jersey and holds his master of business administration from the Fuqua School of Business at Duke University in Durham, North Carolina.
In 2017, the Centers for Medicare and Medicaid Services (CMS) implemented a policy that allowed for outpatient end-stage renal disease (ESRD) facilities to provide care to Medicare beneficiaries with acute kidney injury requiring dialysis (AKI-D). Since that time, an increasing number of individuals with AKI-D have received dialysis in the outpatient setting. Fresenius Kidney Care (FKC) cared for more than 9,000 individuals with AKI-D in a one-year period following implementation of the new policy. Examination of the clinical course and outpatient management of AKI-D is necessary to further the understanding of the AKI-D population and to continue to optimize outcomes in this population.
In the United States, the incidence of AKI-D increased by more than two-fold from 2000 to 2009; in 2009, more than 160,000 hospitalizations included a diagnosis of AKI-D. In critically ill patients, the incidence of AKI-D increased nearly four-fold between 1996 and 2010. Among patients with AKI-D, the in-hospital mortality rate depends on a number of factors and ranges from 25 to 65 percent. The likelihood of ongoing dialysis following discharge from the hospital varies across studies and is influenced by a number of factors.

In the United States, the potential treatment settings for sustained AKI-D have changed over time. Prior to 2017, a number of considerations—including the payor, state regulations, outpatient dialysis facility policies, and contractual care arrangements—determined whether AKI-D could be managed in an outpatient dialysis center. On January 1, 2017, CMS implemented a policy that allowed for outpatient end-stage renal disease (ESRD) facilities to provide care to Medicare beneficiaries with AKI-D. This new policy heralded a shift in the care delivery for sustained AKI requiring ongoing dialysis. Given the change in CMS policy and evolving care systems, Fresenius Medical Care North America (FMCNA) undertook an initial examination of the clinical course of AKI-D in the outpatient dialysis facility setting.

**AKI-D POPULATION**

To examine the clinical course of AKI-D, FMCNA included individuals with a first admission to FKC clinics between April 1, 2017 and March 31, 2018 for treatment of AKI-D. The AKI-D population included 9,127 individuals who initiated care in 2,005 FKC facilities (Figure 1). During this one-year time frame, approximately 600 to 900 patients with AKI-D started outpatient dialysis therapy per month, and 20 percent of admissions for the initiation of in-center hemodialysis were for AKI-D (Figure 2).

**FIGURE 1** | Geographic distribution of AKI-D cohort
The AKI-D cohort had a mean age of 63.3 ± 14.7 years; 42 percent were female, and 98 percent initiated dialysis with a catheter for vascular access. The initial dialysis prescription was thrice weekly for the vast majority of patients (96 percent), and the mean dialysis treatment time was 223 ± 26 minutes.

FMCNA examined the first 90 days of AKI-D by 30-day treatment periods and followed the cohort for up to 90 days or until recovery of kidney function, transition to ESRD, withdrawal from dialysis, transfer to a non-FKC facility, loss to follow-up, or death. The number of individuals with AKI-D under observation at the beginning of each 30-day treatment period was as follows: 9,127 in days 1-30; 5,410 in days 31-60; and 2,702 in days 61-90. The number of individuals with at least one in-center hemodialysis (ICH) treatment during the treatment period was lower over the latter treatment periods (Figure 3), and accordingly the number of AKI-D observations was lower over time. The availability of data differed by clinical measure, and available data was used to estimate clinical parameters.

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**FIGURE 2 | Proportion of patients initiating in-center hemodialysis with AKI-D versus incident ESRD**

The AKI-D cohort had a mean age of 63.3 ± 14.7 years; 42 percent were female, and 98 percent initiated dialysis with a catheter for vascular access. The initial dialysis prescription was thrice weekly for the vast majority of patients (96 percent), and the mean dialysis treatment time was 223 ± 26 minutes.

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**FIGURE 4 | Bone and mineral metabolism labs**

Potential markers of inflammation, including the median albumin and neutrophil-to-lymphocyte ratio (NLR), differed by treatment period (Figure 5). Catheters remained the dominant vascular access in use over time, and 95 percent of the AKI-D population used a catheter for vascular access in days 61-90. Among patients who were using a catheter in the last 30 days of observation, only 4 percent had an arteriovenous fistula or arteriovenous graft present.

**FIGURE 5 | Markers of inflammation: albumin and neutrophil-to-lymphocyte ratio**

Mean hemoglobin concentrations ranged from 9.3 to 10.5 g/dL and were on average higher in later treatment periods (Figure 6). Among patients receiving Venofer, the mean total dose in the first 30 days was 612 mg followed by mean total doses exceeding 400 mg (Figure 7). The mean ferritin concentration and transferrin saturation among all patients with available laboratory measurements, regardless of IV iron administration, are shown in Figure 7. The percent of AKI-D patients who received an erythropoiesis stimulating agent (ESA) in days 1-28, 29-56, and 57-84 was 53 percent, 80 percent, and 87 percent, respectively. Four-week periods were reported for consistency with ESA dosing frequency. The majority of patients treated with an ESA received Mircera. Mircera dosing ranged from 15 to 17 mcg per hemodialysis treatment (equivalent to approximately 90 to 100 mcg every two weeks); however, doses had a broad distribution as reflected by the large standard deviation (Figure 8). The mean Mircera dose was higher in individuals with AKI-D as compared to incident ESRD patients initiated on in-center hemodialysis (Figure 8).

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**ANEMIA MANAGEMENT**

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**DIALYSIS ADEQUACY, BIOCHEMICAL MEASURES, AND VASCULAR ACCESS**

The mean spKt/V (a measure of dialysis adequacy) was 1.5 ± 0.4 in days 1-30 and 1.6 ± 0.4 in days 31-60 and 61-90. The mean potassium concentration was 4.3 ± 0.6 in days 1-30 and 31-60, and 4.4 ± 0.6 in days 61-90. The 30-day calcium and phosphorus concentrations ranged from 8.7 to 8.9 mg/dL and 4.5 to 4.8 mg/dL, respectively, depending on the time frame of observation (Figure 4). Mean intact parathyroid hormone (iPTH) concentrations ranged from 289 to 302 pg/mL with large standard deviations (Figure 4).
MEASURES OF RENAL FUNCTION AND VOLUME MANAGEMENT

Among individuals with measures of 24-hour urine urea clearance, the median urine urea clearance was 4.8 to 5.3 mL/min (Figure 9), whereas the median serum creatinine ranged from 4.0 to 4.3 mg/dL. The median 24-hour urine volume (and number of individuals with urine volume measured) in days 1-30, 31-60, and 61-90 was 1.1 L (N=2,164); 1.0 L (N=1,315); and 1.0 L (N=574), respectively. In the first 30 days, less than 50 percent of treatments resulted in a post-dialysis weight within 1 kg of the estimated dry weight (EDW), and 33 percent of treatments resulted in post-dialysis weights more than 1 kg below the EDW (Figure 10). The average percent of treatments below EDW was lower over time (Figure 10).
DISCUSSION

In conclusion, approximately 20 percent of patients admitted to FKC in-center hemodialysis facilities for the initiation of dialysis had a diagnosis of AKI-D. Among patients with AKI-D, 36 percent recovered kidney function and 37 percent transitioned to ESRD in the first 90 days. Late recovery of kidney function was also observed among individuals with prolonged AKI-D. Prior studies of in-hospital AKI-D transitioned to outpatient dialysis management have been single-center studies with cohorts ranging from approximately 100 to 200 AKI patients.12,13,14,15 These studies found that 25 to 43 percent of patients with AKI-D recovered kidney function in the outpatient setting, and in the first 90 days, 45 to 49 percent transitioned to ESRD and 9 percent died.15,16,17 Similar to published studies, this analysis found a high proportion of patients recovered kidney function, and a comparable mortality rate of 10 percent was observed in the first 90 days. FMCNA’s initial findings contribute to a broader understanding of outcomes in this population given the large and geographically diverse cohort examined post-implementation of the CMS policy.

Given the increasing incidence of AKI-D, decreasing mortality, variability in the need for dialysis following hospital discharge, and the changing care settings for AKI-D, estimating the number of individuals in the United States with AKI-D who will require outpatient dialysis support is challenging.19,20,21,22,23,24 Based on its experience, FMCNA estimates that more than 100,000 patients with AKI-D will be managed in an outpatient dialysis setting in the next five years in the United States. The changing care paradigm for AKI-D creates new opportunities to further study and understand sustained AKI-D, but significantly more research is needed to understand the optimal treatment strategies for patients with prolonged AKI-D.25,26

Importantly, the change in CMS policy has allowed more patients with AKI-D the opportunity to be treated outside of the hospital and receive dialysis support while recovering kidney function. In addition, it has presumably encouraged appropriate utilization of hospital resources—an anticipated benefit of the change in policy.27 With the experience gained over the past two years, there is an opportunity to evolve the care of AKI-D to continue to optimize outcomes in this medically complex population.

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Importantly, the change in CMS policy has allowed more patients with AKI-D the opportunity to be treated outside of the hospital and receive dialysis support while recovering kidney function.

Meet Our Experts

**LORIEN S. DALRYMPLE, MD, MPH**

*Vice President, Epidemiology and Research, Fresenius Medical Care*

Board certified in nephrology, Lorien 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 is co-chair of the National Quality Forum Renal Standing Committee and co-chair of the KHI ESRD Global Data Standard Workgroup.

**NORMA J. OFSTHUN, PhD**

*Senior Vice President, Data Governance, Fresenius Medical Care*

Norma Ofsthun leads FMCNAs data governance efforts and chairs the company’s Data Governance Program. She has collaborated with numerous Fresenius physicians and outside collaborators on a variety of research publications in the renal field. Over the past 20 years, Norma’s team has provided data and reports for key clinical initiatives such as the conversion from reuse to single-use dialyzers, the development of electronic algorithms for drug dosing, and the current AKI program. Norma holds her doctorate in chemical engineering from the Massachusetts Institute of Technology and holds numerous patents related to membrane-based medical devices.
Effective communication among diverse audiences, groups, communities, and constituencies is key to health care progress and transformation. Knowing this, Fresenius Medical Care embraced the image-rich power of video communications and enhanced the company’s ability to communicate nimbly—and at scale—by creating the Fresenius Medical Care Broadcast Network.

The visionary initiative was introduced in 2018 and sponsored by Frank Maddux, global chief medical officer, and led by Kate Dobbs, senior vice president of Marketing and Communications for Fresenius Medical Care North America (FMCNA). Working in partnership, the Medical Office and Corporate Communications teams created a master plan to build a professional-grade television studio at the FMCNA headquarters in Waltham, Massachusetts, capable of live broadcasts on local and global scales. A full studio production team was hired to manage the facility, and diverse programming was introduced—ranging from live global broadcasts to on-demand webinars and short- and long-form video segments.

“The future of communications is increasingly image-rich, and our emerging generations of physicians, patients, and clinicians are very attuned to consuming video content on multiple screens,” says Maddux. “Shifting toward video-based communications greatly enhances our ability to communicate complex clinical-medical themes and concepts in new and compelling ways. One well-produced video using the full power of visual storytelling—images, words, narration, animation, sound, people—can communicate more clearly and effectively than a flat, two-dimensional memo on a piece of paper.”

PROGRAMMING

The Medical Office designed and created the inaugural content for physician audiences. Following successful completion of these initial pilot programs, the studio went live as a full communications resource for the entire company and is used to engage not only physicians but also clinicians, employees, and public audiences around the globe.
MEDICAL OFFICE LIVE

To kick off the broadcast network and engage physicians in communities across North America, the Medical Office scheduled six live-broadcast symposia called Medical Office Live. Hosted by Frank Maddux and the Medical Office, these daylong events presented high-priority clinical topics:

JULY 2018  |  BOSTON, MA
Home therapies and the growing patient access to and adoption of this viable care modality

NOVEMBER 2018  |  NASHVILLE, TN
Social determinants of health outcomes and care disparities in chronic kidney disease

JANUARY 2019  |  LA JOLLA, CA
Acute kidney injury, artificial intelligence, and research in chronic kidney disease

MARCH 2019  |  CHAPEL HILL, NC
Value-based care for renal disease, including a groundbreaking discussion on renal transplantation featuring nationally recognized leaders from both the dialysis and transplant surgery spaces

MAY 2019  |  BOSTON, MA
Best-practices in running joint venture clinics, policy updates related to more frequent dialysis, and more

OCTOBER 2019  |  FT. LAUDERDALE, FL
Vascular access in dialysis care

ON-DEMAND PROGRAMMING

The Medical Office introduced a regular programming lineup, including Medical Office Studio, a series of interviews with clinical experts and thought leaders, as well as recorded clinical presentations much like TED Talks. Additionally, the Medical Office launched short-form video segments called Medical Office Minutes, one to two minutes long, designed to convey important information in a quick, concise, and easily digestible format.

Other special broadcasts were presented for associates, including:

MARCH 2019
Special live broadcast and webinar for Fresenius Medical Care social workers and dietitians regarding updates to the KDIGO bone and mineral disease guidelines and a related new binder optimization program in Fresenius Kidney Care.

MAY 2019
The first broadcast for all FMCNA employees was similar to a town hall and featured FMCNA Chief Executive Officer Bill Valle, who discussed company updates and answered questions from the audience.

The heart of the broadcast network is the video studio, constructed in the company’s North American headquarters, featuring professional-level television production capabilities.

Humacyte™, Inc. president Jeff Lawson, MD, PhD, discusses regenerative medicine and the health economic benefits of the company’s Humacyl™ human acellular blood vessel.
Improving fluid management is key to reducing patient deaths from cardiovascular causes. Two new innovations from Fresenius Medical Care represent a true breakthrough because together they combine more accurate measurement of fluid overload with data that guides an automatic and safe adjustment of the ultrafiltration rate during treatment. Because these tools are producing precise real-time information, Fresenius Medical Care can continually measure their impact on the health of patients.
Control of intravascular volume is a critical function of normal kidneys that is lost in end-stage renal disease (ESRD). The accumulation of excess fluid acutely leads to pulmonary edema and chronically causes hypertension with subsequent left ventricular hypertrophy, heart failure, and death. Fluid overload (FO) in both chronic kidney disease stages 3 to 5 and ESRD patients is associated with hypertension, anemia, proteinuria, arterial stiffness, inflammation, endothelial dysfunction, sleep apnea, impaired oxygenation, left ventricular hypertrophy, congestive heart failure, and other adverse cardiovascular complications and outcomes. In 2016, the US Renal Data System reported an adjusted mortality rate for prevalent hemodialysis patients of 166 per 1,000 patient-years. Cardiovascular causes, including arrhythmias, cardiac arrest, congestive heart failure, acute myocardial infarction, and atherosclerotic heart disease, were responsible for 48 percent of dialysis patient deaths.

Fluid removal using ultrafiltration at hemodialysis sessions is prescribed to control fluid balance. Clinically, an estimate of the patient’s optimal volume status is made and referred to as estimated dry weight (EDW). However, there are multiple challenges with this approach:

- EDW is established using clinical findings (blood pressure, edema, lung sounds), which may be inadequate, as evidenced by the near universal presence of hypertension and left ventricular hypertrophy in hemodialysis patients.
- Since ultrafiltration can only remove fluid from the intravascular space, the rate and amount of fluid removal is limited by the volume and rate of fluid movement from tissues into the vascular compartment. When this rate is exceeded, patients experience intradialytic hypotension (IDH) and stunning or shock injury to the heart, brain, and gut.
- Due to IDH, shortening of prescribed treatments, noncompliance, and incorrect clinical assessment, as many as 30 percent of hemodialysis treatments end over a liter of fluid different from the prescribed EDW. This disparity is associated with a higher rate of hospitalization.
- Retention of excess fluid at the end of a dialysis session is compounded by the two-to-three-day interval between hemodialysis treatments, during which additional fluid accumulates.
- Post-dialysis FO and even moderate pre-dialysis FO and fluid depletion (FD), as well as rapid changes in fluid status, are incrementally associated with increased mortality.

Cardiovascular causes, including arrhythmias, cardiac arrest, congestive heart failure, acute myocardial infarction, and atherosclerotic heart disease, were responsible for 48 percent of patient deaths.
Two technological innovations have been developed by Fresenius Medical Care to address these challenges and improve fluid management in hemodialysis. The Body Composition Monitor (BCM) uses electrical impedance to determine the absolute amount of excess fluid in the patient and is used in Fresenius Medical Care Europe, Middle East, and Africa (EMEA). The Crit-Line Monitor (CLM), used in Fresenius Kidney Care (FKC), serially measures hematocrit to guide the rate of fluid removal.

**BODY COMPOSITION MONITOR**

In Fresenius Medical Care EMEA NephroCare clinics, BCM is the exclusive method used to measure the degree of patient FO. The BCM gives valuable information that helps the practitioner to correct FO and develop effective ultrafiltration strategies in patients receiving both hemodialysis and peritoneal dialysis. The peritoneal fluid is largely isolated from the circulation, and the BCM measurement is not influenced by the filling of the peritoneum in peritoneal dialysis patients.

BCM measures fluid status by multiple-frequency whole-body bioimpedance spectroscopy. Based on a fluid model using 50 discrete frequencies, the extracellular water, the intracellular water, and the total body water are calculated.7 BCM determines FO in absolute liters independent of body composition by use of a physiologic model of normal tissue hydration. FO is estimated in proportional terms relative to extracellular water (FO percentage). The BCM gives valuable information that helps the practitioner to correct FO and develop effective ultrafiltration strategies in patients receiving both hemodialysis and peritoneal dialysis.

Of the approximately 67,000 hemodialysis patients treated in Fresenius Medical Care EMEA NephroCare clinics, 70.3 percent of them (approximately 47,100 patients) are quantitatively assessed for fluid status every 13 weeks.

The Fresenius Medical Care EMEA Balanced Scorecard is used to measure medical outcomes. Hydration status is one of 10 key performance indicators in the scorecard. The hydration status score is based on the last available BCM measurement within 13 weeks of the month of analysis and on a quality indicator value (Cole fit) ≥70 percent. The relative hydration score is the result of the following formula: (Pre-dialysis body weight – Normohydration weight)/Extracellular water. Patients are considered to be overhydrated when their relative FO (=FO/extracellular volume) is >15 percent in men and >13 percent in women, which coincides with an absolute FO of about 2.5L.9

**CRIT-LINE MONITOR**

Blood consists of a fluid portion (plasma) and a solid phase made up of cells (red and white blood cells and platelets). The proportion of red cells found in the total volume of blood is termed the hematocrit. The Crit-Line consists of a small chamber attached to the dialysis machine blood line, an infrared light source that illuminates the chamber, and a sensor that captures the light signal after it has passed through the patient's blood. The electronics in the device interpret this signal and derives the hematocrit. Additionally, oxygen saturation of the red blood cells is also measured. Readings are taken as often as one per second, and the results are displayed on an LCD screen.

When fluid enters the vascular space, the hematocrit is diluted and falls. Conversely, as fluid is removed from circulation, the hematocrit increases. These changes indicate intravascular volume minute by minute. If fluid removal by dialysis exceeds the rate at which excess tissue fluid reenters the circulation, blood pressure may fall. By monitoring the hematocrit with CLM, too-rapid rises in hematocrit can be noted as the rate of ultrafiltration increases.

In practice, the changes in hematocrit can be charted over the course of dialysis and generally characterized as too slow profile, too rapid profile, or correct profile, although the best hematocrit rate of change may vary by patient. Attention to these curves allows the dialysis technician to guide the rate of fluid removal to maximum tolerated levels without hypotension. Mortality rates are higher in patients who have lower degrees of volume reduction in each hour of dialysis. When used with the 2008T hemodialysis machine, a type C curve will cause ultrafiltration to cease. The FDA has granted Breakthrough Device Designation Status to ongoing work at FMCNA to use CLM data to automatically raise and lower the ultrafiltration rate during a treatment, making it a smart device.

In the Fresenius Medical Care EMEA dialysis network, due to the mandatory BCM evaluation and the implementation of hydration status management in medical routine, we have observed a progressive reduction in the number of patients with FO.
Oxygen saturation of hemoglobin (SaO2) can be measured by the Crit-Line device using different wavelengths of light transmitted through a chamber in the dialysis line and applying mathematical algorithms. Depending on the type of vascular access, either the mixed venous/arterial or mixed central venous (using a central venous dialysis catheter) can be measured. While it is well known that hypoxemia is common during hemodialysis, there is little published research on the clinical and therapeutic implications of this finding.

Using CLM, an association has been shown between peripheral mixed arteriovenous oxygen levels (SmvO2) and markers of inflammation. Also, low SaO2 is associated with intradialytic hypotension. Low mixed central venous oxygen saturation (ScvO2) is associated with evidence of inflammation. Additionally, since ScvO2 can be used as a representation of cardiac output, further hemodynamic implications can be seen. Declines in ScvO2 are seen with high rates of ultrafiltration in dialysis, suggesting that cardiac output declines in that circumstance.

Sleep apnea is common in dialysis patients. Decreases in O2 saturation during hemodialysis measured via the Crit-Line are seen in patients with sleep apnea. Such observations could suggest the need for referral for formal sleep studies in these individuals.

While the presence of a central venous catheter allows for the study of ScvO2, this type of vascular access is associated with higher cost and an increased risk of infection, hospitalization, and death. Thus, the replacement of a central line with a peripheral arteriovenous fistula (AVF) and monitoring of its maturation is necessary. The AVF, accomplished by surgically connecting an artery and vein, creates a shunting of blood from the arterial system into the venous system. Since arterial blood is better oxygenated, this results in an increase in the ScvO2 and cardiac output measured with Crit-Line. As the AVF matures and enlarges, ScvO2 rises. Should the vessel fail to mature or become occluded, a plateau and decrement in ScvO2 is seen. This can be an indication that an intervention to revise the AVF is needed.

Fresenius Medical Care is in a unique position to improve the management of fluid overload in ESRD patients using the combination of BCM and CLM. While BCM provides the objective measurement of the magnitude of the fluid excess carried by a patient, CLM guides the removal of the fluid at a rate that is safe and well tolerated. Further investigation using these devices will provide insight into the role of changing oxygenation status during dialysis. Importantly, these complementary technologies provide reportable key performance indicators to assess treatment improvement.

Fresenius Medical Care is in a unique position to improve the management of fluid overload in ESRD patients using the combination of BCM and CLM.
Improving vascular access and reducing catheter contact time not only improve the health and lives of patients, but also can save the health care system millions of dollars each year. However, achieving this important goal requires significant coordination among all stakeholders, as well as a focus on best practices, data-driven metrics, and transformative technologies. Azura Vascular Care’s free-standing access centers are modeling this comprehensive approach by providing patients with a “one-stop shop” for all their vascular needs. Pilot studies indicate that creating access and caring for patients in this ambulatory setting can reduce catheter exposure time by 29 percent, and can lower infection rates, hospitalizations, and costs. As part of its commitment to innovation, Azura is also looking to utilize percutaneous fistula creation and, potentially, the Humacyte™ human acellular vessel—both of which hold promise for improving clinical outcomes.
Dialysis access type is among the most important determinants of the future health of the patient with end-stage renal disease (ESRD). It is well known that hemodialysis catheters are fraught with deleterious sequelae that negatively impact the ESRD patient. Vascular access complications and higher prevalence of catheter contact time add up to poorer quality of life, higher mortality rates, and higher cost of care. A recent study found that patients who initiate hemodialysis with an arteriovenous fistula (AVF) have a 35 percent lower mortality rate than those who initiate with a catheter.1 Another study identified that the annual cost of care for a patient initiating hemodialysis with a catheter was $36,180 higher than initiating it with an AVF.2 Every hour that a patient is not transitioned from a catheter significantly increases the risk of death to the patient and costs the health care system an additional $4—adding up to many millions of dollars over the course of a year.

Vascular access quality improvement is a complex process requiring the coordinated effort of all stakeholders in order to reduce catheter contact time. Catheter avoidance now requires an understanding of new technologies like percutaneous fistula creation, the Humacyte™ human acellular vessel (HAV) for dialysis access, early cannulation grafts, and percutaneous placement of peritoneal dialysis (PD) catheters to facilitate urgent start PD. Additionally, existing technologies have improved to facilitate access salvage and sustainability with procedures such as fistula thrombectomy, treatment of high flow fistulae and steal, and treatment of central venous occlusions.

Avoiding the use of catheters and timely catheter removal are more important than whether a particular access modality might be considered a “gold standard.” Instead, each patient represents a unique and complex clinical state and therefore requires a thoughtful plan tailored to their specific needs.

**CATHETER REDUCTION STRATEGIES**
- Use of early stick grafts
- Humacyte™ human acellular vessel
- Percutaneous access creation
- Percutaneous PD catheter placement to facilitate urgent start PD
- One-stop shop for vascular access placement and management

**ACCESS SALVAGE PROCEDURES**
- Fistula thrombectomy
- Sharp needle recanalization
- Superficialization
- Aneurysm reduction
- Infection excisions
- Treatment of central vein occlusion
- Resistant, symptomatic breast swelling treated with embolization

**LONG-TERM ACCESS MAINTENANCE**
- Treatments for steal syndrome
- Heart failure and high flow access
- Use of covered stents
- Management of cardiac rhythm devices
- Management of the “out of access” patient
- Access and kidney transplant patients
Currently accepted vascular access quality measures lack sufficient sensitivity and specificity to contribute meaningfully to improving vascular access outcomes. As part of the Centers for Medicare and Medicaid Services (CMS) quality initiative, the 5-star rating system directly addresses the percent of patients with an AVF and those with a central venous catheter (CVC) for greater than 90 days. While these are important measures and relatively easy to track, they do not provide direction for catheter elimination or for the rapid creation of the ideal access for an individual patient.

Azura proposes a comprehensive quality improvement program using the following nine touch points (Figure 1).

Although three of the nine touch points are listed under the dialysis clinic, the success of the clinic’s outcomes is directly related to the access management team’s dedication to catheter reduction. Many of the catheter removal delays can be eliminated by focusing on providing prompt service to reduce scheduling times. This focus on time metrics, coupled with promptly identifying access dysfunction prior to thrombosis through surveillance and monitoring, will pave the way for improving total catheter contact time and access vintage and reducing missed treatments. To ensure informed decisions and facilitate collaboration, the quality measures for vascular surgeons and access center interventionalists could be provided to dialysis centers and nephrologists.

**ONE-STOP SHOP**

Providing the ESRD patient with a “one-stop shop” for all their access needs (from creation to maintenance and salvage) allows for improved care coordination for timely catheter removal. Pilot studies performed in collaboration with Fresenius Kidney Care have shown that providing access creation in the access center setting can reduce catheter contact time by up to 29 percent. In addition, providing access care in a freestanding access center reduces infection rates, hospitalizations, and mortality, as well as the total cost of care. This is one of the leading reasons Azura is converting most of its access centers to Ambulatory Surgery Centers (ASC).

Incorporating vascular surgeons into Azura’s ASC structure means the patient will navigate fewer providers and clinic locations to achieve timely catheter removal. The ASC model will also allow Azura to utilize two exciting and transformative technologies: percutaneous fistula creation and, potentially, a human acellular vessel named Humacyl®.

**PERCUTANEOUS FISTULA CREATION**

Percutaneous anastomosis devices were approved in June 2018 for use as an alternative to surgical fistula creation in the United States. Early studies suggest these percutaneous fistulas are comparable to surgically created fistulas on measures such as technical and clinical success; however, they may require maturation procedures. Additionally, the limited acceptable anatomical locations may preclude the use of this technique in many patients requiring an access.

Demonstrated advantages of endovascular fistula creation include the ability to perform AV access creation in an outpatient setting utilizing a minimally invasive technique, thus widening the group of physicians able to create functional AV fistulas. In addition, access creation in the vascular access center will improve access to care while reducing patient wait times.

These advantages may contribute significantly to patient satisfaction as well as increasing AVF prevalence and reducing CVC contact time for ESRD patients.

Seven Azura centers have been designated pilot sites for this exciting and important project. More than a half dozen physicians are currently being trained on the use of these devices. Between Azura centers in San Antonio, Texas, and Woodland Park, New Jersey, 50-plus successful percutaneous fistulas have already been placed. Furthermore, the transition to the ASC model will allow Azura interventional physicians and vascular surgeons to create fistulas on an outpatient basis.

**HUMACYTE™ HUMAN ACCELLULAR VESSEL**

Fresenius Medical Care North America has partnered with Humacyte, the developers of the novel bioengineered human acellular vessel named Humacyl®. Humacyl® has been designated a biologic that offers off-the-shelf availability and, potentially, superior clinical efficacy and safety as compared with polytetrafluoroethylene grafts (pending the results of investigative trials), with the regenerative properties of a fistula. Humacyl® is grown in vitro from banked human aortic smooth muscle cells. These smooth muscle cells are placed on a tubular scaffold made of biodegradable material (Figure 2). Cells on the scaffold multiply, generating extracellular matrix proteins during the culture in a closed bioreactor system. Material from original donor cells

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**FIGURE 1 | Touch points of vascular access quality improvement**

<table>
<thead>
<tr>
<th>DIALYSIS CLINIC</th>
<th>Total catheter time</th>
<th>Reductions in catheter contact time are directly related to reductions in morbidity and mortality.</th>
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<tbody>
<tr>
<td>Access vintage</td>
<td>Expert cannulation and successful interventions will increase access vintage across a population of patients.</td>
<td></td>
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<tr>
<td>Missed treatments due to access issues</td>
<td>Healthier accesses lead to fewer emergent access procedures, which lead to fewer missed dialysis treatments.</td>
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<tr>
<th>VASCULAR SURGEON</th>
<th>Proportion of AVFs created</th>
<th>Functioning AVFs have the lowest complication rates.</th>
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<tbody>
<tr>
<td>AVF and AVG 30-day failure rates</td>
<td>Benchmarking vascular surgeons identifies superior access creators and mitigates failure rates.</td>
<td></td>
</tr>
<tr>
<td>AVF maturation rates with and without interventions</td>
<td>Superior maturation rates reduce catheter contact time.</td>
<td></td>
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<tr>
<th>ACCESS CENTER</th>
<th>Interventions per patient / per year</th>
<th>Use of best practices and best technologies will lead to fewer interventions.</th>
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<tbody>
<tr>
<td>Fistula and graft thrombectomy success rates</td>
<td>The most skilled physicians will consistently salvage over 98% of thrombosed accesses, both grafts and fistulas.</td>
<td></td>
</tr>
<tr>
<td>30-day re-thrombosis rates</td>
<td>Use of best practices and best technologies will lead to superior patency and fewer interventions.</td>
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that can trigger an immune response is then removed from the HAV matrix. The result is the Humacyl® human acellular vessel (Figure 3). Early patient data indicates that once implanted, the HAV is remodeled by the host patient to create a vascular structure similar to native vascular tissue.

Investigational studies have demonstrated that the Humacyl® can be cannulated four weeks after placement. With this early cannulation, CVC contact time can potentially be reduced—in turn, reducing complications of CVC, such as infection and central venous stenosis. Since the HAV is acellular and created from biologic human smooth muscle cells, Humacyl® is not immunogenic. This essentially eliminates the risk of rejection. In addition, Humacyl® has a decreased risk of infection, in comparison with traditional grafts, reducing the potential for catheter reinsertion.

ECONOMIC IMPACT OF CATHETERS

The economic impact of hemodialysis catheter use is considerable. In a study based on CMS data and hospital costs reported by the Kaiser Family Foundation and American Hospital Association, for “urgent start” hemodialysis patients (those requiring either temporary or tunneled hemodialysis catheters immediately and typically in a hospital-based setting), total inpatient and outpatient costs were $19,352 per patient for the first 90 days, plus an additional $8,053 per patient for the first 90 days of dialysis services. Considering 80 percent of the estimated 124,675 incident ESRD patients begin treatment with HD catheters, the cost impacts are truly staggering, at approximately $3.4 billion for the first 90 days and an additional estimated $800 million for dialysis services. When adding prevalent ESRD patients to these estimates, it becomes clear that HD catheter-based dialysis represents an unacceptably large percentage of the $114 billion annual Medicare ESRD/chronic kidney disease spending.

Azura is committed to reducing this economic burden through a variety of pathways, including outpatient PD catheter placement, which is a more patient-centered, more comfortable, and more efficient way to begin dialysis. It also represents a significant cost savings, with potential decreased costs of approximately $3,000 per incident patient in the first 90 days and $200 per incident patient for dialysis services over the same period of time. Of course, this thought experiment assumes that all of the 80 percent incident ESRD patients beginning dialysis with a hemodialysis catheter change to PD. This assumption is somewhat unrealistic for a variety of medical, anatomic, and patient- and physician training-related reasons, but it still underscores the cost savings that may be recognized by Azura’s determination to expand PD catheter placement options nationally.

To succeed at reducing catheter contact time, vascular access management requires coordinating multiple complex processes. These processes must be continually monitored and enhanced through data-driven analytics, best practices, and evidence-based quality improvement initiatives, thereby allowing all stakeholders to make informed decisions. Implementing the nine touch points of vascular access quality improvement, coupled with improved care coordination and adoption of new technologies in the “one-stop shop” ASC model, will help Azura achieve the vision of one access for a lifetime.

Meet Our Experts

MURAT SOR, MD
Chief Medical Officer, Azura Vascular Care
A graduate of the University of Pennsylvania, Murat Sor is certified by the American Board of Radiology, with subspecialty certification in interventional radiology. He is an assistant professor at Georgetown University Hospital’s Interventional Radiology Fellowship program. Since 2015, he has served as the CMO of Azura Vascular Care and on the Fresenius Medical Care corporate medical advisory board. In addition, he is the medical director of HealthQare Associates, an Azura affiliated center, where he continues his clinical practice in interventional radiology.

NORMA J. OFSTHUN, PhD
Senior Vice President, Data Governance, Fresenius Medical Care
Norma Ofsthun leads FMCNA’s data governance efforts and chairs the company’s Data Governance Program. She has collaborated with numerous Fresenius physicians and outside collaborators on a variety of research publications in the renal field. Over the past 20 years, Norma’s team has provided data and reports for key clinical initiatives such as the conversion from reuse to single-use dialyzers, the development of electronic algorithms for drug dosing, and the current AKI program. Norma holds her doctorate in chemical engineering from the Massachusetts Institute of Technology and holds numerous patents related to membrane-based medical devices.
Renal Support Network
Renal Support Network (RSN) provides support groups, conferences, and nonmedical programs for people living with kidney disease. Fresenius Medical Care contributes resources and thought leadership content for RSN to encourage connection between end-stage renal disease, dialysis, and transplant patients and the kidney community at large.

Medical Education Institute
Medical Education Institute (MEI) develops and distributes, at little or no cost, informational materials to patients with chronic diseases and conducts research on patient experience and interaction with health care teams. FMCNA sponsored MEI’s KidneySchool.org, which offers a free online program to help patients learn to manage and live with late-stage CKD, and offers continuing education credits for dialysis nurses and care technicians.

Renal Support Network

Medical Education Institute

Communities as Hubs of Interconnected Intelligence and Drivers of Innovation

Health care transformation and innovation on local and global scales would not be possible without the free exchange of information and ideas. Recognizing the unlimited potential that comes when people join together with shared purpose, Fresenius Medical Care embraces community as a vital source of interconnected intelligence and takes its place as a global citizen committed to lifelong learning by viewing the concept of community through three broad lenses: peer, professional, and knowledge.

PEER COMMUNITIES

National Kidney Foundation
In 2018, Fresenius Medical Care formalized its relationship with the National Kidney Foundation (NKF), the largest organization in the United States dedicated to the awareness, prevention, and treatment of kidney disease, to sponsor NKF’s National Kidney Walks. Fresenius Medical Care North America (FMCNA) Chief Executive Officer Bill Valle served as the inaugural national corporate chair, and over 5,600 FMCNA employees were among the 85,000 walkers in 90 North American cities.

Kidney Care Partners
Kidney Care Partners (KCP), a coalition of more than 30 organizations, is dedicated to expanding patient choice and access to care, improving quality of care, developing enhanced therapies, and furthering innovative research for individuals with chronic kidney disease (CKD). Fresenius Medical Care partners with KCP to support its research and development and to help individuals living with kidney diseases.
PROFESSIONAL COMMUNITIES

ERA-EDTA

European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) is one of the largest nephrology-focused organizations in Europe and the Mediterranean area, promoting clinical advances in nephrology, dialysis, renal transplantation, hypertension, and related subjects. Fresenius Medical Care actively partners with ERA-EDTA on knowledge-sharing symposia and events.

American Nephrology Nurses Association

The American Nephrology Nurses Association (ANNA) is committed to advancing the nephrology nursing specialty. FMCNA funds ANNA’s scholarship program; assists FMCNA nurses with membership dues, conference fees, and certification expenses for member nurses; and helped produce a video that showcases the nephrology nursing profession.

American Society of Nephrology

The American Society of Nephrology (ASN) educates health professionals and scientists, advances research and innovation, and communicates new knowledge. Fresenius Medical Care is a frequent exhibitor at major ASN conferences and supports ASN’s Ben J. Lipps Fellowship program, which awards 10 fellows $50,000 annually for up to two years to conduct original, meritorious kidney biology and disease research.

Renal Physicians Association

The Renal Physicians Association (RPA) advises and educates policymakers on issues impacting kidney disease patients and nephrology practices. Fresenius Medical Care nephrologists have served as past presidents of the RPA, and Fresenius Medical Care leaders and physicians actively participate in RPA knowledge-sharing events.

KNOWLEDGE COMMUNITIES

The MONDO Initiative

Dialysis providers collect volumes of detailed, longitudinal, and standardized patient data, resulting in valuable registries of routine patient care information on thousands of dialysis patients worldwide. Fresenius Medical Care and others providers contribute certain anonymized patient data to the MONDO (MONitoring Dialysis Outcomes) research consortium, which is a global outreach initiative that provides a platform for joint data analysis and outcome studies.

International Conference on Dialysis Advances in Kidney Disease

Nephrologists, renal researchers, and kidney experts from across the globe gather annually for the International Conference on Dialysis Advances in Kidney Disease, presented by FMCNA’s Renal Research Institute. Featuring expert presenters from numerous organizations, the three-day conference draws nearly 400 top physicians, researchers, and scholars from nine countries.

School Communities

With CKD more common in Taiwan than anywhere in the world, Fresenius Medical Care Asia Pacific introduced a novel awareness campaign for children. Because superhero characters are popular role models throughout Asia, the Fresenius Medical Care team created “The Kidney Kid” campaign designed to provide basic kidney education to children, regardless of cultural or social background. At school, children watched a video about this new “superhero” and received a cape, mask, stickers, adventure book, and educational material.

INTRODUCING THE FRESENIUS MEDICAL CARE FOUNDATION

In 2018, FMCNA launched the Fresenius Medical Care Foundation, a nonprofit addressing the environmental, social, and economic conditions that increase the risk for CKD. Its initial grant focus will be on partnership programs that ensure everyone who needs a kidney can pursue a transplant. The foundation will: make investments in the NKF’s Big Ask/Big Give program, to educate patients and donors about living donor transplant options; and, through Donate Life America, build innovative initiatives to simplify the process of linking recipients with living donors.
There are several promising new treatments for managing anemia in patients with chronic kidney disease. These treatments harness the positive elements of hypoxia-inducible factors (HIFs), proteins that help stimulate red blood cell production. Although each of the three oral agents now in clinical trials acts somewhat differently, all block the enzyme that degrades HIF in the body. Preliminary results also indicate that these drugs help patients better use their own stores of iron, and further study may reveal additional benefits for patients at all stages of kidney disease.
Every day, over 100 billion blood cells are produced in a complex, tightly regulated process. The pool of stem cells responsible for this is remarkably small—estimated at 11,000—and it maintains this production level throughout life. Groundbreaking research in the field of hematopoietic medicine, which is focused on understanding the hematopoietic microenvironment and the repopulation of blood cell types in the body at the gene level, is ongoing.

Several early reports demonstrated that hematopoietic stem cells (HSCs) were present in “regions of presumed hypoxia” within the bone marrow. Those in hypoxic areas showed greater hematopoietic repopulating capability than those in more perfused areas. New imaging techniques with endogenous markers have also allowed better oxygen mapping and further understanding of specific cellular and anatomical locations of stem cell niches in the bone marrow. Essentially, studies suggest that HSCs reside in settings of low oxygen, and their activities depend on signaling and gene regulation from the surrounding niche. Hypoxia and anemia are well-documented issues for patients with chronic kidney disease (CKD) as well as for end-stage renal disease (ESRD) patients already on dialysis.

One of the new areas of exploration in hematopoietic medicine is hypoxia-inducible factors (HIFs). HIF is a protein expressed under low oxygen (or hypoxic) conditions in the body. There are multiple, unique HIFs in the body, but they belong to the same superfamily structure of proteins exhibiting a basic helix–loop–helix Per–Arnt–Sim (bHLH-PAS) pattern manifesting in a heterodimer of an oxygen-sensitive α-subunit and a constitutively expressed β-subunit. HIF stimulates the body’s production of the hormone erythropoietin (EPO), which enables the bone marrow to produce red blood cells. Chronic hemodialysis (CHD) treatment is, more often than not, also associated with decreased levels of red blood cells and circulating iron, reducing availability of iron for erythropoiesis. Erythropoiesis requires approximately 30 mg of iron per day, which is mainly provided by the recycling of iron from red blood cells via macrophages. This process is adversely affected in CHD patients, and can promote resistance to EPO and erythropoiesis-stimulating agents (ESAs) in many hemodialysis patients.

Chronic inflammation is par for the course in CHD and ESRD and has also been suggested as an independent predictor of EPO and ESA hyporesponsiveness. Thus, in the setting of kidney disease and dialysis, chronic inflammation—in combination with typical blood losses—might magnify subtle alterations in cellular iron handling that would not necessarily be observed in nondialysis patients. As a result, anemic states develop in ESRD dialysis patients.

Regulation of HIF proteins impacts erythropoiesis. Prolyl hydroxylase domain (PHD) enzymes change HIF activity according to oxygen tension and regulate its cellular content. HIF-prolyl hydroxylase (HIF-PH) is the primary enzyme for degrading HIF, resulting in inhibition or slowing of erythropoiesis. Therefore, HIF-PH inhibitors/HIF stabilizers can be used to treat anemia.

HIF stimulates the body’s production of the hormone erythropoietin (EPO), which enables the bone marrow to produce red blood cells.
HIF-PH inhibitors (HIF-PHIs), also known as hypoxia-inducible factor stabilizers (HIF-stabilizers), are designed to inhibit enzymatic degradation of HIF—i.e., they increase the HIF protein’s half-life and stabilize the HIF protein. This action prolongs the effects of HIF, stimulates endogenous production of erythropoietin and erythropoiesis, and ensures that the body produces enough red blood cells.

**NEW THERAPY OFFERS PROMISE**

Several HIF-PHIs are at various stages of clinical development for use in the treatment of CKD with anemia. As of Q2 2019, at least three drugs have progressed to phase 3 clinical trial: roxadustat, daprodustat, and vadadustat. Early safety data from phase 2 analysis indicate these drugs are performing well for anemia treatment.

For instance, roxadustat (FG-4592) was recently approved in China for the treatment of anemia in CKD patients on dialysis. It is also being tested for treatment of anemia in non-dialysis patients. It is an orally bioavailable HIF-PHI that promotes coordinated erythropoiesis through HIF-mediated transcription. Roxadustat also inhibits production of the hormone hepcidin (high hepcidin results in reduced dietary absorption of iron and inhibits iron release from cellular storage). This reduction in hepcidin, in turn, increases iron levels. Phase II and III studies have shown high responder rates (79 to 96 percent) for a dose range of 1-2.5 mg/kg in patients on thrice weekly HD (mean Hb have shown high responder rates (79 to 96 percent) for a dose range of 1-2.5 mg/kg in patients on thrice weekly HD (mean Hb increased by ≥ 1 or 2.0 g/dL). The protein sequence for HIF-1 alpha is shown in Figure 1.

**FIGURE 1 | HIF-1 alpha protein sequence**

As of Q2 2019, at least three drugs have progressed to phase 3 clinical trial: roxadustat, daprodustat, and vadadustat.

Daprodustat (GSK1278863) is an oral HIF-PHI that is being developed for treatment of anemia associated with CKD in patients receiving or not receiving dialysis. In the hemodialysis study, the effects on hemoglobin coincided with expected elevations in endogenous erythropoietin but were markedly lower than those in the recombinant human erythropoietin control arm. Importantly, clinically significant elevations in plasma vascular endothelial growth factor (VEGF) concentrations, a potentially concerning off-target effect, were not seen.

Vadadustat, an oral agent also known as AKB-6548, is in development for the treatment of anemia in both nondialysis-dependent and dialysis-dependent CKD patients. In early clinical studies, vadadustat was well tolerated in healthy volunteers and patients with CKD, where it increased reticulocytes, plasma EPO, and Hb levels in a dose-dependent manner. Patients with ESA-resistant renal anemia, who account for 10 percent of ESA users, would be among the biggest beneficiaries of therapy with this class of drugs.

Trial reports demonstrate a notable additional benefit of HIF-PHIs: The drugs reduce or block the inflammatory response that keeps the body from using its own iron stores (e.g., reduction in hepcidin, an inflammatory inhibitor of iron uptake and utilization in the body). Furthermore, there have been no off-target effects reported to date. Although the early data is promising, larger longitudinal phase 3 studies already under way will yield further important therapeutic and safety data. Potential adverse events with these products could, however, include hypertension, acute pancreatitis, nausea, and diarrhea.

As with HIF proteins, HIF-PHIs vary in structure; therefore, they may have “off-target effects” with unintended consequences in the body beyond erythropoiesis. This is a source of potential concern. For example, HIFs can stimulate synthesis of VEGF, a protein that stimulates the growth of new blood vessels. Although the growth of new blood vessels is beneficial in appropriate circumstances, in the presence of malignancy (cancer), VEGF not only increases the spread of the malignancy but can also potentially facilitate the spread of the malignancy. It is crucial that HIF-PHIs developed to treat anemia be specifically targeted for the individual substrate target, enabling the response (i.e., stimulating red blood cell production) to be singular.

HIF-PHIs represent a promising, novel therapeutic approach to the management of anemia. Roxadustat is anticipated to obtain FDA approval and be available for clinical use within the next 12 months; daprodustat and vadadustat are expected to follow suit in subsequent years. To the field of nephrology, the prospect of such a class of oral agents as HIF-PHIs is exciting, as it may provide expanded benefit in the management of anemia in patients with CKD both on dialysis and those not requiring dialysis (Figure 2).

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**HIF-1 ALPHA SEQUENCE:**

1 meqagqand kikiserrke karsardaersk sesevvel ahalplphhv sshikasvnm
dl ritstiyrv kildagldi edemkaqicm fylkalldvnt mvltdqdgdi yisdvynskm
121 qifatfehig svolhtpcd heemmretthi rngkkkege onterstfrir iclitbigrn
181 tmikastati vhlctphihv ydtnsnqgegy kqymctegi vilcpeqihq snipqgdak
241 tftrshodm lksyderit eimgyepel gralvqegvsh latsblbt khhlfkggy
301 ttqyrmnak rgyvgvenq aherinyknk ocppcicveny vsgqyqgdh iffgetcvc
361 ikvessdmk mtcjftkves edtssigfili kkegdloit apagodtis idlgstddet
421 ddqgelevd yndvimpnpn ekqinlmm spiptaetpl plrsadapl nqeqalikpe
481 npeisfiet mnpqjhtqds pslqstrqgs pepsnqyec fyyssdmvne kltcvekfit
541 aedtakrif stqpdoe mlrapymal dfrisfird splesssasp esasqstv
601 xqetoeqci tanattnt kdektrot mdekkil riqytihke tskalqgcy
661 dtqstapn radqyvepl ekstgwpvn lvalqgrit vptsqkpl ialgpdqskr
721 kmehdpqilq avgii
ROBERT J. KOSSMANN, MD, FACP, FASN
Executive Vice President, Chief Medical Officer, Fresenius Medical Care North America
Robert (Rob) Kossmann is executive vice president and chief medical officer for Fresenius Medical Care North America. 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.

DIXIE-ANN SAWIN, PhD, MS
Senior Director, Medical Information and Communications, Fresenius Medical Care Renal Therapies Group
With over 15 years of basic science research in neuroscience, genetics, molecular biology, and immunology, Dixie-Ann Sawin leads the Medical Information team for the Fresenius Medical Care Renal Therapies Group. She and her team are responsible for responding to all medical information queries from health care providers across the United States, providing medical and scientific expertise on promotional review committees as well as business and core development teams. Her team also supports pre- and post-market launch education, compiles regulatory and pharmacovigilance reports and publications for peer-reviewed journals, and develops educational content for the renal community through the Advanced Renal Education Program. She also serves as director for the Fresenius PharmD Fellowship and Internship Program.

FIGURE 2 | HIF mediates responses to hypoxic conditions

Acute ambient hypoxia
HIF-1α/HIF-2α

Chronic ambient hypoxia
?K1.5
?endothelin1

Constriction of dermal blood vessels
Increased blood flow to liver and kidneys

HIF-1α/HIF-2α

Decreased blood flow to liver and kidneys

EPIDERMIS

DERMIS

Nitroglycerin treatment
Dilation of dermal blood vessels

NO

EPO

RED BLOOD CELLS

Systemic O2 delivery

VHL

HIF-1α/HIF-2α

HIF-1α/HIF-2α

O2

NOS2

NO

EPO

BONE MARROW

Acute ambient hypoxia
HIF-1α/HIF-2α

?K1.5
?endothelin1

Constriction of dermal blood vessels
Increased blood flow to liver and kidneys

HIF-1α/HIF-2α

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HIF-1α/HIF-2α

HIF-1α/HIF-2α

O2

NOS2

NO

EPO

BONE MARROW

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RED BLOOD CELLS

Systemic O2 delivery

VHL

HIF-1α/HIF-2α

HIF-1α/HIF-2α

O2

NOS2

NO

EPO

BONE MARROW
The complex metrics and practices that govern the transplant waiting list are undergoing significant change. There are many factors driving this evolution in selection criteria, including reforms in Medicare regulations and the kidney allocation system. However, in spite of these major changes, dialysis providers, nephrologists, transplant centers, regulators, and payors still have too many competing interests. Better transplant access requires a vision and framework that mandates open communication and active collaboration between all stakeholders.
Many nephrologists and patients with end-stage renal disease (ESRD) may be forgiven for thinking of the transplant waiting list as a fairly simple concept rendered mysterious by layers of complexity. For patients referred for transplant (or clinicians tracking such referrals), it can be a surprise to discover that being listed is an ongoing process, rather than a discrete event. Staying “active” on the waiting list involves frequent reevaluations, virtual and in-person check-ins, and retesting. In addition, the patient must provide a series of updates on physical issues, social support, and financial health.

A nephrology clinic or dialysis facility has little insight into the transplant surveillance system. It is often difficult to discern exactly what is tracked, how it is tracked, or when a patient status is changed due to a variance from the prevailing wait-list criteria. The ability of the dialysis facility or nephrology practice to reliably communicate with a transplant center about referred and wait-listed patients is often piecemeal at best. Why?

In most markets, nephrology practices, dialysis providers, and transplant centers operate independently of each other. The historically siloed division of labor between these three stakeholders yielded separate institutions, regulatory frameworks, technology platforms, and, ultimately, different organizational cultures. Put simply: Dialysis providers and transplant centers do not fully understand each other, and in today’s regulatory framework, they do not have a stake in each other’s success. Recently, the regulatory milieu has shifted toward apportioning some regulatory risk on dialysis facilities for transplant-related quality metrics. However, unless the barriers between dialysis providers, nephrologists, and transplant centers are deliberately lowered, each stakeholder will advocate for their own quality metrics processes, which may not yield a positive impact on care coordination or meaningfully expand access to transplantation.

**REGULATORY RISK**

Historically, kidney transplant centers were held to narrowly defined risk-adjusted Medicare benchmarks for patient and graft survival rates. In the event a center failed to meet regulatory requirements, the failure could result in penalties such as public sanctions, being required to enter into an expensive Systems Improvement Agreement to continue to qualify for Medicare reimbursement, and losing private payor contracts for all solid-organ transplants in their program. Medicare’s methodology employed to adjust risk was the subject of significant debate and criticism at the time of implementation.1 With ongoing concerns about regulatory sanctions by Medicare, some transplant centers elected to limit exposure to regulatory risk by

- Limiting acceptance of higher-risk organs
- Intensively surveilling active wait-listed candidates, while implementing lower thresholds for wait-list inactivation and removal
- Instituting more conservative candidate selection criteria, effectively excluding higher-risk transplant candidates from the waitlist

**Dialysis providers and transplant centers do not fully understand each other, and in today’s regulatory framework, they do not have a stake in each other’s success.**
Transplant centers following a risk-averse approach often achieved high patient and graft survival rates; however, the approach also resulted in the unintended consequences of reducing patient access to the wait list and increasing organ discard rates.

To address these concerns, Medicare liberalized the thresholds for regulatory sanctions based on outcomes. A first step in that direction was raising the flagging thresholds for patient and graft survival. Most recently, in September 2018, Medicare proposed the organization substantially step back from the regulatory oversight of transplant centers, shifting that role back to the Organ Procurement and Transplantation Network (OPTN), under the supervision of the Department of Health and Human Services. Whether this regulatory shift will improve access to the waiting list or reduce rates of organ discard remains to be seen.

But, even as Medicare appears to be de-escalating its regulatory presence in transplant as of Q4 2018, individual private payors continue to administer Center of Excellence criteria, which is essentially a series of patient and graft survival outcome metrics like Medicare. In addition, the private payor Center of Excellence program also benchmarks transplant centers using unique metrics such as a transplant rate. The transplant rate is the number of transplants performed at a center per 100 patient-years on the waiting list. The significance of the measure is that centers with a higher transplant rate ostensibly deliver beneficiaries to transplant faster than centers with a lower rate. The catch is that patients who are listed “inactive” count toward the total number of patient-years in the denominator. Centers with a high number of patients listed “inactive” will have an artificially lower transplant rate. Private payors view lower transplant rates unfavorably, and transplant centers might have a reason to adjust their wait-list policies to avoid misinterpretation of the result of the transplant rate methodology.

New to the policy landscape is a quality metric that is designed to hold dialysis facilities accountable for increasing access to transplantation. After much discussion and public comment, Medicare will hold facilities accountable for the Percentage of Prevalent Patients Waitlisted (PPPW). There are several notable features of PPPW as a quality metric:

1. PPPW measures rates of wait-listing, not rates of referral. A unit that refers many patients but lists (too) few will fall afool of the PPPW metric.
2. Referral is within the power of the medical director and attending physician of the dialysis unit, but the decision to wait-list is not.
3. Transplant centers, under pressure to improve their transplant rate metric, may choose not to list medically appropriate candidates for transplant until they have accrued sufficient waiting time to be close to the top of the list.

In short: The PPPW is a quality metric that is not wholly within the control of the facility and its medical leadership. The PPPW conflicts with competing pressures on transplant centers to improve their transplant rate metric by reducing waiting lists to include just those patients likely to be transplanted in a short period of time after listing.

New to the policy landscape is a quality metric that is designed to hold dialysis facilities accountable for increasing access to transplantation.

A BETTER WAY FORWARD

An article published in the American Journal of Transplantation outlined a vision for a reimbursement model that would align the interests of dialysis providers, nephrologists, transplant centers, regulators, and payors. While the proposal was framed around the ESRD Seamless Care Organization (ESCO) shared-savings model, the article identified ways in which Fresenius Medical Care North America (FMCNA) can break down clinical care silos, expand access to transplantation for patients, and ensure current and future transplant candidates remain medically, socially, and financially positioned to succeed after transplantation (Figure 1).
The vision includes:

- **Implementing a common information technology platform**: Provide all stakeholders real-time tracking of the status of transplant referrals, patient progress in the transplant evaluation process, wait-list activity status, and status updates once a patient is active on the list.

- **Supporting quality metrics that expand patient access to transplant and improve wait-list management, rather than box-checking**: Private payors and regulators should abandon the transplant rate and PPPW metrics in favor of metrics that reward collaborative, integrated wait-list management programs between transplant centers and dialysis facilities.

- **Inviting transplant personnel into FKC dialysis facilities**: Facilitate chart review, chairside in-person transplant education, and participation in monthly multidisciplinary continuous quality improvement (CQI) meetings. Doctors, nurses, social workers, and patient care technicians know FKC patients and have the tools and insights to position patients to succeed with transplant.

- **Using system solutions to identify and overcome surmountable barriers to transplant**: Many FKC patients are medically suitable but not socially, psychologically, or financially ready for transplant. Building on FKC experience operating ESCOs in more than 30 markets around the country, FMCNA is committed to partnering with local transplant centers to create support programs for patients to find novel ways to bridge gaps in social support, transportation, and medication adherence.

- **Pressuring transplant centers to do their part**: High rates of organ discard do not serve patients well. Transplant centers must be encouraged and supported to do their part to increase access to transplantation by transplanting higher risk organs.

Effective wait-list management can increase the number of patients with access to kidney transplantation. Only with active, transparent collaboration between nephrologists, transplant programs, dialysis providers, and patients can a rational, consistent, and scalable delivery system be designed.

**FIGURE 1 | New model puts patient at center of care**

Meet Our Experts

**BENJAMIN HIPPEN, MD, FASN, FAST**

*Medical Director, Fresenius Kidney Care; Partner, Metrolina Nephrology Associates, P.A.*

Benjamin Hippen is a general and transplant nephrologist with Metrolina Nephrology Associates, P.A., and is a Clinical Professor of Medicine at the UNC Chapel-Hill School of Medicine. Dr. Hippen serves as the associate medical director of the kidney and kidney-pancreas transplant program at Atrium Health, and he serves as medical director of a Fresenius Kidney Care in-center hemodialysis and home therapies facility in Charlotte, NC.

**FRANKLIN W. MADDUX, MD, FACP**

*Global Chief Medical Officer, Fresenius Medical Care*

Dr. Franklin W. Maddux’s distinguished career encompasses more than three decades of experience as physician, expert nephrologist, technology entrepreneur, and health care executive. He previously served as Executive Vice President and Chief Medical Officer for Fresenius Medical Care North America and joined Fresenius Medical Care in 2009 after the company acquired Health IT Services Group, a leading electronic health record (EHR) software company founded by Maddux. 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. A practicing nephrologist for nearly two decades, Dr. Maddux graduated with his baccalaureate in mathematics from Vanderbilt University and holds his MD from the School of Medicine at the University of North Carolina at Chapel Hill, where he holds a faculty appointment as clinical associate professor. His writings have appeared in leading medical journals, and his pioneering health care information technology innovations are part of the permanent collection of the National Museum of American History at the Smithsonian Institution.
Our increased knowledge of how salt is stored in the skin is changing our view of how to measure and treat salt loading in kidney patients. We now understand that skin sodium storage is not passive but governed by intricate physiological mechanisms. The Renal Research Institute is using these insights to develop more advanced ways to measure and precisely quantify the amount of sodium stored in the skin. If this type of measurement can be introduced as part of routine clinical testing, it will be a valuable tool in helping patients better manage salt overload, a known contributor to hypertension and other comorbidities.
Salt is indispensable for life. Throughout most of human history, salt (sodium chloride, NaCl) was an extremely precious article. Salt was a symbol of purity and loyalty (e.g., contracts were sealed with salt) and of trust (e.g., guests were greeted with bread and salt). In ancient Rome, the amount of money allotted to a Roman soldier to buy salt (sal in Latin) was called salarium, the root of the English word ‘salary’. The immense economic importance of salt is illustrated by the numerous place-names linked to salt, such as Salzburg, Austria (Salz is German for “salt”) and in England, where place-names with the ending “wich”—e.g., Sandwich—point to past saltworks. Taxes on salt ignited the Salt War between Perugia and the Papal States (1540), compounded unrest in pre-revolutionary France (18th century), and sparked Gandhi’s Salt March (1930) in defiance of the British rule.

Over the course of evolution, a powerful machinery comprised of hormones, the kidneys, the liver, the skin, and muscles has emerged to adapt water and salt balance to the subject’s needs, with the kidneys playing a central role. In patients with kidney failure, the ability to excrete ingested salt and to maintain sodium balance declines. This excess salt has several consequences. First, a larger sodium mass is stored in the extracellular fluid, and this compartment expands in most kidney patients. Second, an increased amount of sodium is stored in the skin and muscles. While it had been known that salt can be stored in the skin, novel insights into the physiology and pathophysiology of “skin sodium storage” have substantially changed and expanded our view of sodium metabolism in health and disease. These novel insights have immediate consequences for kidney patients.

THE PHYSIOLOGY OF SALT: THE “TRADITIONAL”

Previous textbook knowledge taught that salt intake results in thirst, increased fluid intake, expansion of the extracellular volume, increased blood pressure, and so-called pressure natriuresis, which is the increased urinary excretion of salt at the expense of high blood pressure. This traditional picture has undergone substantial modifications over the past 10 to 15 years.

While it had been known that salt can be stored in the skin, novel insights into the physiology and pathophysiology of “skin sodium storage” have substantially changed and expanded our view of sodium metabolism in health and disease.
THE PHYSIOLOGY OF SALT: THE “NEW”

Several nontraditional aspects of salt metabolism and loading have been elucidated (Figure 1). They can be broadly categorized as:

• Salt storage without commensurate water retention in the skin and muscle interstitium
• Pro-inflammatory effects of salt
• Catabolic effects of salt

Originally, it was thought that sodium storage in the skin is a passive process, but recently it became clear that it is regulated by several intricate physiological mechanisms. Studies have shown that high-salt feeding can increase the content of particularly negatively charged GAG species in the skin and thus increase its Na⁺ binding capacity. Also, a high-salt diet increases the osmolarity in the skin, and this is sensed by local immune cells that “patrol” the interstitium, primarily macrophages. In response to increased osmolarity, the vascular endothelial growth factor C (VEGF-C) is released. VEGF-C is the primary lymphatic vessel growth factor, and its release results in hyperplasia of the lymph capillary network that facilitates Na⁺ (and chloride) clearance from the interstitium.

WHERE AND HOW IS SODIUM STORED?

It is now clear that sodium (Na⁺) is stored in at least four locations:

1. Osmotically active in the extracellular fluid such as plasma. This is the Na⁺ concentration that is reported in clinical laboratory results and is normally between 135 to 145 mmol/L.
2. Inside cells, at a concentration of around 10 mmol/L.
3. In bones and connective tissue. This compartment shows very little turnover.
4. In skin and muscle—more specifically, in the room between cells, the so-called interstitial space. This compartment is highly dynamic.

It is the interstitial Na⁺ storage that has received great attention in the past decade, because it has been associated with important comorbidities, such as hypertension, left ventricular hypertrophy, inflammation, and insulin resistance.

In the interstitium, Na⁺ associates non-osmotically with negatively charged glycosaminoglycan (GAG) via electrostatic interactions. GAGs are unbranched polyanionic polysaccharide chains of variable lengths made up of repeating disaccharide units; each of these disaccharide units carries one to three negatively charged side groups. GAGs are covalently bound to a protein backbone; the combined macromolecule is called proteoglycan. The proteoglycan is part of a “gel” that resides in the interstitial space. GAGs attract Na⁺ into this interstitial “gel” so that the resulting Na⁺ concentration may surpass the plasma concentration by 100 mmol/L.

HOW SODIUM DRIVES INFLAMMATION

Tissue Na⁺ also affects the immune system in several ways. First, a high-salt diet reduces the activation of innate immune cells that attenuate tissue inflammation. These cells are called alternatively activated (M2) macrophages. The reduced M2 activation may result in a pro-inflammatory response. Second, T-cells exposed to high salt conditions morph into a highly pro-inflammatory autoimmune Th17 phenotype that produces interleukin-17 (IL-17). There is evidence that IL-17 may be involved in the pathogenesis of hypertension. Taken together, these pro-inflammatory transformations may result in an interstitium that is in a chronic inflammatory state, resulting in vascular stiffness, target organ damage, and elevated blood pressure.

It is the interstitial Na⁺ storage that has received great attention in the past decade, because it has been associated with important comorbidities, such as hypertension, left ventricular hypertrophy, inflammation, and insulin resistance.
**THE CATABOLIC EFFECTS OF SODIUM**

Sodium loading decreases aldosterone levels and increases the production of cortisol, a steroid hormone. Through a series of steps, these hormonal changes result in an increased production of urea in the liver, whereby some of the substrates required for urea generation come from muscle breakdown. In other words, the increased urea production in the liver occurs at the expense of muscle catabolism. The goal of the increased urea production is to enhance the water retention by the kidneys and avoid excessive water loss following salt intake. In addition, the increased muscle metabolism results in increased water production in liver and muscle mitochondria. RRI’s hypothesis is that this increased water production in patients with kidney failure may contribute to the hyponatremia seen in some of them.

**WHY IS THIS ALL RELEVANT FOR KIDNEY PATIENTS?**

Patients with kidney disease, especially those on dialysis, are particularly prone to the untoward effects of salt because they have a reduced ability, or no ability, to excrete salt by their failing kidneys. In patients without residual kidney function, the only way to remove salt is through dialysis. Importantly, hemodialysis can sometimes load the patients with salt, especially in situations where the dialysate sodium concentration exceeds that in the patient’s plasma. In addition, patients may receive salt during hemodialysis—e.g., saline used for priming and rinsing or in the event of muscle cramps or hypotension.

Based on physiological reasoning, it is likely ideal that the sodium ingested between hemodialysis sessions should be removed. This goal can be achieved by adjusting the dialysate sodium level in such a way that it parallels the patient’s plasma Na⁺ level using a novel technology called electrolyte balancing control. This technology measures the conductivity, a proxy of sodium concentration, in the dialysate inlet and outlet streams, and adjusts dialysate inlet concentration so that diffusive sodium loading is avoided (Figure 2). This technology, developed by Fresenius Medical Care, also opens the way to a personalized removal of sodium, for example in patients with high sodium intake or in those with hyponatremia.

A major and fundamental problem is the quantitation of tissue sodium, since the only currently available noninvasive way to do so is by ²³Na magnetic resonance imaging (²³NaMRI). ²³NaMRI scans are only done in a few centers in the United States, are expensive, and are logistically challenging. Because of these limitations, the Renal Research Institute is currently exploring alternative methods, including novel measurement technologies. The vision is to make measurement of skin Na⁺ available to patients even beyond those on dialysis and to have this information become part of the routine clinical decision-making process.

**FIGURE 2** | The electrolyte balancing control. Conductivity is measured by meters in the dialysate inflow and outflow streams. The data are sent to the central processor unit, where this information is used to calculate the dialysate sodium concentration.

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**Meet Our Expert**

**PETER KOTANKO, MD, FASN**

*Research Director, Renal Research Institute*

Noted researcher and scholar Peter Kotanko heads research initiatives to improve patient outcomes and quality of life. An adjunct professor of medicine and nephrology at the Icahn School of Medicine at Mount Sinai in New York City, he has authored and co-authored more than 300 research papers and book chapters, and is the former vice chair of a medical department at an academic teaching hospital in Graz, Austria.
cytometry to support in-depth cell analysis research. It has an extensive list of validated assays to support high-throughput measurements of routine clinical markers, pharmaceutical compounds, uremic toxins, disease-specific biomarkers (especially kidney disease), bone mineral metabolism markers, and biomarkers related to neurocognitive disorders.

The RRI think tank is also part of an informal network that includes academic institutions in the US, Asia, Europe, Latin America, and Africa. This network is supported by a fellowship program providing MDs and PhDs the opportunity to spend one to two years conducting research at RRI. As of Q2 2019, RRI has hosted fellows from over 30 countries.

Much of the work at RRI centers on developing advanced mathematical models to improve dialysis patient care. RRI mathematicians, statisticians, and epidemiologists collaborate with Fresenius Medical Care’s Global Research and Development (GRD) division to spearhead the concept of virtual clinical trials (VCTs). Treatment algorithms are developed and tested in large-scale VCTs using mathematical simulations of patients’ physiology. In collaboration with the Fresenius Medical Care Global Medical Office, VCT-derived algorithms have been implemented at Fresenius Kidney Care (FKC) clinics throughout North America, potentially benefiting over 160,000 FKC patients.

RRI's sophisticated renal research laboratory, leadership in computational biomedicine, data analytics, and access to large patient population have made on-site discoveries of the highest levels possible.

“We strongly believe that the problems and questions posed by today's medicine are too complex to be seen through one lens only,” said Peter Kotanko, MD, FASN, RRI's research director and internationally renowned renal researcher. “The heart of RRI's capacity for innovation is our highly diverse team, individuals from around the globe who represent some of the brightest minds. Together, they are imagining the undiscovered and translating scientific discoveries into applied medicine.”

RRI’s two divisions—research and operations—collaborate seamlessly to conduct most clinical studies at its Manhattan dialysis facility. In addition, RRI operates 20 dialysis facilities in six states in the US, including two stand-alone home programs. The research lab provides services such as comprehensive biobanking, performs exploratory biomedical engineering, and develops nonstandard, cutting-edge, highly customized assays for in-house use as well as for third parties. Among other features, the lab performs liquid chromatography-mass spectrometry for both targeted and untargeted analysis and comprehensive flow cytometry to support in-depth cell analysis research. It has an extensive list of validated assays to support high-throughput measurements of routine clinical markers, pharmaceutical compounds, uremic toxins, disease-specific biomarkers (especially kidney disease), bone mineral metabolism markers, and biomarkers related to neurocognitive disorders.

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RRI’s diverse team represents leading minds from around the world, including clinicians, physician-scientists, engineers, mathematicians, statisticians, epidemiologists, biochemists, research coordinators, and specialists well versed in research administration.

### MILESTONE RRI INNOVATIONS

#### Virtual clinical trials

RRI and Fresenius Medical Care GRD created realistic simulations of large clinical trials—providing valuable safety information, revealing possible treatment protocol limitations, and predicting potential patient benefits. At their core, virtual trials are comprehensive mathematical models that simulate actual patient physiology. RRI applies advanced mathematical and computational techniques to adapt essential characteristics of individual patients using real-life dialysis clinical data, producing a model referred to as an avatar. Thousands of avatars are generated to build the virtual trial.

#### Dialysis-related hypoxic episodes

Recording and acting upon instantaneous bio-signals is important to create smoother dialysis treatments, minimizing patient physiological stress. RRI researchers were the first to analyze high-frequency recordings of arterial oxygen saturation to detect sleep-associated hypoxic episodes during dialysis.

#### Predictive analytics

Arteriovenous fistula (AVF) and arteriovenous graph (AVG) complications are frequent in chronic hemodialysis patients, resulting in compromised dialysis efficiency, increased hospitalization, higher costs, and mortality. RRI researchers developed a predictive model to identify patients at risk of AVF or AVG failure and to allow timely interventions to reduce conversions from AVF or AVG to central venous catheters.

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### RRI WINS KIDNEYX AWARD

In 2019, RRI’s novel concept for “displacer-enhanced dialysis” was one of 15 winners of the Kidney Innovation Accelerator (KidneyX) Redesign Dialysis competition, a public-private partnership between the US Department of Health and Human Services and the American Society of Nephrology. RRI’s proposal aims to develop a new displacer substance that can rid the blood of protein-bound uremic toxins that can negatively impact patient health and are difficult to remove by hemodialysis.

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### RRI BY THE NUMBERS

<table>
<thead>
<tr>
<th># OF RESEARCHERS</th>
<th># OF MDS AND PhDs</th>
<th>PUBLICATIONS SINCE INCEPTION</th>
<th>STUDIES CONDUCTED SINCE INCEPTION</th>
<th>RRI RESEARCH FELLOWS</th>
<th>LABORATORY CAPABILITIES</th>
<th>PATIENTS IMPACTED BY RRI RESEARCH</th>
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<td>24 (these are included in the 24 researchers)</td>
<td>17</td>
<td>Around 500 papers and book chapters, referenced over 25,000 times</td>
<td>100+</td>
<td>50+ fellows from over 30 different countries across 5 continents</td>
<td>The RRI laboratory can detect over 3,000 molecules using cutting-edge technologies</td>
<td>160,000+</td>
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Internationally renowned scholar and physician-scientist Peter Kotanko, MD, FASN, is research director for RRI and one of the world’s leading authorities on renal research.

Smartphone-based point-of-care diagnostics

Swift diagnosis and reduced time-to-treatment are essential for peritonitis therapy. Increased white blood cell levels in spent peritoneal dialysis (PD) dialysate results in cloudiness, which is a significant indicator of peritonitis. Early detection of cloudy dialysate often relies on patient judgment, which may be compromised due to poor visual acuity or cognitive difficulties. RRI scientists are developing a smartphone-based tool using the device’s built-in light sensors to objectively measure turbidity in spent PD fluid and automatically report the results to the care provider.
How can value-based care (VBC) better serve patients with kidney disease? Fresenius Medical Care North America (FMCNA) is leveraging its expertise to help design programs that balance the needs of patients, providers, and payors. Next-generation programs will most likely encompass a greater range of the disease, from chronic kidney disease (CKD) through end-stage renal disease (ESRD) and kidney transplant. This longitudinal model can offer patients less fragmented and episodic care, a broader choice of treatments, and improved outcomes over the course of many years.
FMCNA became a pioneer in population health management in 2006 by extending a VBC contract to ESRD patients in an early Centers for Medicare and Medicaid Services (CMS) demonstration. FMCNA continues to lead in this space and is preparing for the next generation of VBC.

VBC programs continue to mature across the US health care landscape, driven by the insurance providers (payors) and the Center for Medicare and Medicaid Innovation (CMMI). One of the most successful of these programs, the Comprehensive ESRD Care (CEC) Model, commonly referred to as the ESRD Seamless Care Organization (ESCO) demonstration, is in its fourth year of a five-year program, with FMCNA operating nearly two-thirds of all ESCOs and caring for 80 percent of the beneficiaries. Because the ESCOs create financial savings and improve care, CMMI is developing the next generation VBC program modeled on the successful ESCO program to continue beyond 2020.

CMMI has indicated that the next generation renal program will likely encompass a greater range of the disease, from CKD through ESRD and kidney transplant. The US government’s July 2019 announcement of the Advancing American Kidney Health initiative proposes to increase transplantation, home dialysis, and value-based models including the introduction of voluntary and mandatory payment models beginning in January 2020. ESRD Treatment Choices (ETC) is a required model that adds new financial incentives to encourage dialysis at home and intends to enroll half of the nation’s Medicare ESRD beneficiaries by randomly aligning beneficiaries using a specified geographic framework. To avoid penalizing ESRD providers with sicker patients, the model would risk adjust the home dialysis and transplant rates used for purposes of the performance payment adjustments. The administration is rolling out additional optional payment models through the CMMI.

**EXPANDING THE NUMBER OF PATIENTS IN VBC CONTRACTS**

Most renal patients never progress to dialysis, yet CKD is often overlooked in many VBC programs. Based on the US government’s kidney-focused policy announcement, the successes of the ESCO program and public comment from CMMI and Health and Human Services (HHS) officials, FMCNA anticipates that most future renal VBC programs will encompass CKD care, in-center dialysis, home dialysis, transplant, and post-transplant care, removing many of the artificial boundaries that kidney disease and treatment modalities traditionally have been segmented into and managed independently. Beyond improvements in more holistic patient care, a more expansive VBC program solves one of the age-old dilemmas of health insurance: beneficiary turnover. It can be challenging for payors to invest in long-term outcomes when beneficiaries may leave the plan before such investments yield financial results. A broader kidney program covering a larger spectrum of the disease state creates a consistency with patients and gives organizations like FMCNA increased financial incentive to invest in patient care and improved health outcomes by providing population health management over the course of years. After all, kidney disease is a longitudinal chronic illness, with dialysis only one part of the care continuum.
Based on the National Health and Nutrition Examination Survey (NHANES) conducted by the United States Renal Data System (USRDS), 14.8 percent of patients surveyed have stages 1-5 and 6.9 percent have stages 3-5. There were 124,675 new dialysis patients in 2016. Less than half of 1 percent of adults are receiving dialysis, and fewer than 1 in 30 patients with CKD receive dialysis (Figure 1). Because there are many more patients with CKD than ESRD at any given point in time, an expanded VBC model that includes CKD would provide FMCNA the opportunity to improve outcomes for a greater number of people than just those with ESRD.

Delaying renal disease progression can save the payor—and, in some cases, the taxpayer via Medicare contributions—as much as $48,000 per year per patient.²

**FIGURE 1 | Prevalence of chronic kidney disease**

<table>
<thead>
<tr>
<th>Stages</th>
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<td>Stages 3-5</td>
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<td>Stage 5</td>
<td>724K</td>
<td>0.36%</td>
</tr>
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</table>

**MORE INTEGRATED CARE ACROSS THE RENAL DISEASE CONTINUUM**

It is well established that starting dialysis is very difficult for patients socially, emotionally, and financially. Planning and preparation can not only help patients address and mitigate these challenges but also improve outcomes during this transition. FMCNA’s Renal Care Coordinator (RCC) program engages patients by providing care coordination prior to the initiation of dialysis and during a patient’s first 120 days receiving dialysis. In 2017, this intensive care coordination resulted in:⁴

- A 23 percent reduction in hospital admissions
- 9 percent more patients selecting home dialysis modalities
- Fewer dialysis treatments missed
- A 10 percent reduction in spending on total health care compared to non-RCC patients

Specific benefits of VBC programs that include the full renal disease spectrum are:

1. Development of longitudinal care plans. According to Cerner, a health information technology company, longitudinal care planning is not provided to patients because of a lack of incentives to the health care organizations.⁶ A single model for care coordination may eliminate fragmentation and episodic care. One example of an opportunity for improvement is diabetes care. According to USRDS, 36 percent of CKD patients have diabetes. Using longitudinal health plans and additional care coordination to manage common comorbidities should improve outcomes.

2. Management of CKD progression. Slowing or delaying the progression of CKD and reducing the frequency that patients crash (start urgently without ideal preparation) into dialysis are the goals or are desirable.⁶ Under a VBC care program, earlier intervention may result in disease progression delays thanks to:

- A centralized monitoring and tracking program
- Referrals for improved nutrition and diet management
- Improved medication management and monitoring to help avoid nephrotoxic drugs
- An expanded care team’s coordinated focus on mitigating conditions that worsen renal disease, such as diabetes and hypertension
- Preemptive transplantation

Such care coordination would focus closely on efforts to control blood pressure, reduce proteinuria with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, and reduce some cardiovascular risks by providing enhanced support to stop tobacco use.

3. Vascular care coordination. There is more opportunity to align and coordinate with vascular access care. The RCC program resulted in a 15 percent reduction in patients who started dialysis with a catheter.² Permanent access is correlated with reduced admissions, less chance for infection from a temporary catheter, and a reduction in the total cost of care.

4. More patient choice. More emphasis on transplant, conservative care (no dialysis), and modality selection should result in increased treatment options with proven better outcomes for patients, including peritoneal dialysis and home hemodialysis. Enhanced education and earlier and more frequent discussions create the opportunity to choose a modality that best suits an individual’s lifestyle and needs. Coordinating the competition and aggregation of the prerequisite transplant screening evaluations would result in more patients successfully completing this process and ultimately being listed as a candidate for transplant.

5. Mitigation of external influences. Stressing conservative care or transplant in a CKD VBC program mitigates potential bias of treatment recommendations. A study of CKD patients over 80 years of age with severe comorbidities found there was no difference in physical or mental function, but the conservative group spent fewer days in the hospital with lower overall cost of care.⁴ Yet some patients are not offered the option of getting a transplant or foregoing dialysis due to the way the current delivery system rewards providers. The next generation of VBC should incorporate more options, including conservative care without starting dialysis in patients who would experience a negative quality of life impact, such as the frail and elderly. Additionally, better education about palliative care and hospice care, as well as closer alignment of the palliative care provider network with the Accountable Care Organization (ACO), will be commonplace.

**A single model for care coordination may eliminate fragmentation and episodic care.**
6. Post-transplant management. Post-transplant care requires attention to detail and coordination among caregivers and the patient. In 2018, there were 21,166 transplants, with 94,892 patients listed as waiting for transplant. In the next generation of VBC programs, incentives are aligned to offer patients the necessary support to ensure that transplants are effective and lasting. As of Q1 2019, there are gaps in post-transplant care and confusion between roles of the transplant center, nephrologist, and primary care physicians. The National Kidney Foundation lists 17 areas of care that a transplant patient needs to consider—several are well beyond renal function and immunosuppression-related care. In a VBC care program, the care team is incentivized to ensure all aspects of the renal transplant patient’s needs are addressed and that the transplant remains viable for as long as possible. The care and care coordination needs are complex. Additional post-transplant care would include better preparation for failing transplants, including establishing permanent vascular access for anticipated return to dialysis.

7. Improved patient satisfaction. This is possible with additional support provided to the patient in the VBC program. Activities could be driven using data and a population health approach to allow for better and more targeted care. FMCNA—with its value-based care team (Fresenius Health Partners), aligned nephrologists, clinics, vascular access centers, vascular access care providers, transplant specialists, partnerships with transplant centers, and health systems—is perfectly aligned and well prepared to coordinate and manage the care of the renal patient.

EFFECTIVE FINANCIAL ALIGNMENT OF ACCOUNTABLE CARE ORGANIZATIONS

The next generation of VBC will have enhanced financial alignment. Payors seek to reduce the total cost of care and improve patient outcomes and lifestyles by having VBC programs designed to delay the progression to ESRD, facilitate more transplants, and encourage patients to seek home dialysis as their dialysis modality. The at-risk patient cohort must expand beyond ESRD to include pre- and post-ESRD to achieve these goals.

Stronger connections between payor (or CMS) and the participants (FMCNA and partners) with more financial transparency and increased flexibility will deliver innovative care by eliminating barriers to renal care inherent in a fee-for-service delivery system.

Some specifics of the next generation of VBC programs will hopefully include:

- A monthly capitated cost trend established in advance
- A robust risk adjustment program similar to the Medicare Advantage program
- Stable patient alignment into the program (movement in and out of a program can make it extremely difficult to effectively manage care over longer periods of time)

Further improvements to VBC programs will likely include payor-supported enhanced benefits and, within CMMI demonstrations, the use of waivers, deviating from the established limitation of fee-for-service in Medicare. These will include:

- Allowance for spending on patient engagement technology and monetary incentives
- Enhanced home visits and care
- Telehealth
- Abolishment of the three-day hospital admission rule before being admitted to a skilled nursing facility
- Open shared savings distributions to a wider group of participants
- Developing exceptions to the Anti-Kickback Statute and Stark Law for aspects of care that benefit from integration
- Allowance for spending on nonmedical care and services

Having a VBC model that includes CKD, dialysis, and post-transplant care allows for patient participation over a greater duration of their renal disease state. This results in improved care continuity, slower disease progression, better ESRD care choices, higher home dialysis modalities selection, more transplant options, better post-transplant care, and a reduction in the total cost of care. The next generation of renal value-based programs will include more patients, participating for a longer period, and they will benefit from longitudinal care integration. FMCNA is poised to help design and deliver the next generation of programs to benefit patients, payors, and providers alike.
As part of a program to identify clinics that need additional support, Fresenius Kidney Care (FKC) is using sound to develop predictive models. Specific sounds create acoustic fingerprints that can signal what is happening in an environment. Using these fingerprints and a machine learning algorithm, Fresenius Medical Care North America (FMCNA) data scientists have converted sound into non-discernible numerical data that can potentially be used to classify clinic-level quality outcomes.
For several years, FKC has been experimenting with various predictive models in an attempt to identify dialysis clinics that are “at-risk” or in need of additional support. Those predictive models have consisted of data points that appear to correlate with patient safety and/or regulatory compliance risk areas.

Once “at-risk” clinics are identified, FKC sends expert dialysis nurses there to review clinical practices as well as various operational and process flow tasks that the clinic is performing. The expert nurses identify areas of risk or noncompliance, making best practice-based recommendations to the clinical staff for changes.

This process has proven effective. Clinics visited by expert nurses have seen a 13 percent improvement in septicemia rates over their counterparts. In addition, clinics that have been visited by expert nurses have a 48 percent lower chance of receiving a serious citation from a state health department auditor.

Nonetheless, the process can be improved upon. The data used to create this predictive model is from the previous year. If “live” clinic environment information could be captured, it might be possible to develop near real-time predictive models to support the effectiveness of expert nurse visits as well as potentially prevent patient adverse events.

**SOUND**

People rely on sound in daily life. In fact, it is one of the five essential senses (together with sight, taste, smell, and touch). Sound serves two main functions: communication and signaling.1

Signaling can advise that an event or an object is approaching without knowing through any other sense that the object is close. For example, someone sitting in their apartment might hear an airplane overhead and know that’s what it is even though they don’t see it. Signaling is an essential component of sound.

Clinics that have been visited by expert nurses have a 48 percent lower chance of receiving a serious citation from a state health department auditor.
Another critical component of sound is communication. Communication is a complex form of signaling. Humans developed a very complex form of signaling through communication called language. Although it's certainly not the only method of communication, it is the most frequently used.

There are applications of sound in daily life, but are there applications of sound in health care? Absolutely. A very early technology using sound in health care was the invention of the stethoscope. René Laennec invented the stethoscope in 1816 at the Necker-Enfants Malades hospital in Paris. Today, it is still routinely utilized by doctors to ascertain cardiac abnormalities, something that often cannot be noted with any other observation. A 2012 research paper claimed that the stethoscope had the highest positive impact on the perceived trustworthiness of the practitioner seen with it (Figure 1). Discerning heart sounds is not the only application of sound in health care. Sound can also help with assessing dangerous atherosclerotic plaques, monitoring chronic liver disease, and helping deliver drugs to particular locations within the body.

FIGURE 1 | First stethoscope

Source: https://en.wikipedia.org/wiki/Stethoscope

In addition to health care, sound can be used to determine something about every environment. Sound can provide a signaling mechanism about what may be happening in the environment. If you walk into a Starbucks with your eyes closed, you would be able to decipher if it is busy based on the level of noise. You could discern if it is the Christmas season based on the type of music playing. The loudness of voices may suggest whether customers are frustrated with wait times.

In fact, every environment carries its own unique specific noise, or "acoustic fingerprint."

FIGURE 3 | Taking the acoustic fingerprint

ACOUSTIC FINGERPRINT

An acoustic fingerprint is a condensed digital summary generated from an audio signal. It can identify audio samples or locate similar sounds in an audio database. Typically, acoustic fingerprinting is used to identify songs, melodies, tunes, or advertisements. However, it has the potential to also be used in the clinic environment (Figure 2).

FIGURE 2 | Acoustic fingerprinting

One challenge of using acoustic fingerprinting in a clinical setting is determining how to detect sound without recording identifiable information about the people or interactions in the clinic. To address this challenge, FMCNA developed an acoustic fingerprinting sensor, a device designed to collect the unique audio signature of an environment without collecting any discernible or interpretable sound such as individual voices or conversations. The device converts the acoustic fingerprint of a geographic location into an unidentifiable digital stream of numbers at the point of “impact” as the sound is recorded on the device, so that the numbers can never be reversed to identify individual sounds.

The acoustic fingerprinting device was developed in Node.js, a JavaScript run-time environment. It uses “aubio,” a library written in the C programming language, to perform audio processing. The software associated with the technology can be loaded on a Raspberry Pi or another computer, and the device can be installed in any environment. The device will turn itself on at a predefined time interval and “listen” for a user-defined duration. For example, every 30 minutes, the device turns itself on and listens for 30 seconds. Then the device summarizes the findings in 21 sound-specific numeric elements (Figure 3).

These 21 data elements are:
- Mean volume
- Centroid
- Slope
- Spread
- Skewness
- Kurtosis
- Decrease
- Rolloff
- 13 mel-frequency cepstral coefficients (numbered 0 to 12)

Article continues on page 68
**BRIEF OVERVIEW OF WHAT IS SOUND**

Sound is a pressure wave created by a vibrating object, such as a musical instrument, a person speaking, an airplane flying, or a variety of sounds coming from a dialysis clinic. The resulting vibrations set particles in the surrounding medium, which is usually air, in a vibrational motion. Since the particles are moving in parallel to the wave movement, the sound wave is referred to as a longitudinal wave. The result of longitudinal waves is the creation of compressions and rarefactions within the air. These compressions and rarefactions are typically described by the graph of a sine wave.

The frequency of a wave is measured as the number of complete back-and-forth vibrations of a particle in the air per unit of time, while the amplitude is the fluctuation or displacement of a wave from its mean value (Figure 6). The human eardrum vibrates in response to air vibrations, and the brain translates these different waves into a comprehensible sound.

However, if two different musical instruments make sound waves with the same amplitude and frequency, why do they sound so different? It’s because an instrument (or a human voice, for that matter) produces a whole mixture of different waves at the same time. These different sine waves are overlaid on top of each other simultaneously.

![Sample sound waves](image)

**FIGURE 6 | Sample sound waves**

To translate different waves occurring at the same time, a mathematical technique called “spectrum analysis” is used. Spectrum analysis is the technical process of decomposing a complex signal into simpler parts. One of the most common approaches to decompress complex sound waves into simpler components is a Fourier analysis, named for Joseph Fourier, a French mathematician and physicist who lived from 1768 to 1830.

An example of these complex sound waves is shown in Figure 7, along with the three individual pure tones that constitute this sample. Fourier analysis is used to determine which sine waves constitute a given signal, i.e., to deconstruct the signal into its individual sine waves. The result is expressed as sine wave amplitude as a function of frequency. This is what the acoustic fingerprinting sensor uses to transform sound data into numeric data streams.

![Fourier analysis](image)

**FIGURE 7 | Fourier analysis (complex wave at the bottom and series of individual sine waves on top)**

**ACKNOWLEDGMENTS**

We wish to thank our data scientists, Tommy Blanchard and Andy Long; our IT experts, Mike Ryder and Mehran Fattahy; and Scott Ash from the Fresenius Kidney Care Strategic Analytics team for the extensive work they put into the creation of the acoustic fingerprinting sensor and regulatory risk model, as well as the staff at the Stoneham Dialysis Clinic for allowing us to use this device in their clinic.
The data that comes out as a result of this process can be used in a variety of analytics. These frequently collected data points create a numeric fingerprint of a given environment that can be used for artificial intelligence—specifically, machine learning-based algorithms. These algorithms can be used to classify clinics into those with potential real-time patient safety concerns and considerations.

Thanks to the clinicians at the FKC Stoneham Dialysis Clinic, the development team has been able to get a first glimpse of what the typical acoustic fingerprint of a dialysis clinic looks like. The acoustic fingerprinting sensor was installed in the clinic for a period of 24 hours starting at 3 p.m. on day one and finishing at 3 p.m. on day two. The device collected numeric data reflecting the acoustic fingerprint of the environment every 10 minutes, in 10-second intervals (Figure 4).

Using this acoustic fingerprint of the dialysis clinic and XGBoost, a machine learning algorithm, FMCNA data scientists were able to predict when patients leave their dialysis chairs.

Using this acoustic fingerprint of the dialysis clinic and XGBoost, a machine learning algorithm, FMCNA data scientists were able to predict when patients leave their dialysis chairs.

While FMCNA is in the early stages of determining whether acoustic fingerprinting can assist with ascertaining if a clinic has a higher risk of patient safety issues, this technology can have other implications. For example, the ability to convert sound data into non-discernible numeric data can potentially be used to classify various heart sounds or sound waves associated with arteriovenous (AV) fistula generated thrill. Some artificial intelligence-based sound-processing algorithms already exist to identify heart murmurs and even gastrointestinal issues. Image-based artificial intelligence algorithms have also been used in radiation oncology and diabetic retinopathy classification. Identifying a wide range of artificial intelligence-based cardiac abnormalities may help reverse the problem of “forgetting the art of listening to the patient.”

**FIGURE 4 | Acoustic fingerprint of the Stoneham Dialysis Clinic**
In addition to sound data, physicians rely on other senses to understand the patient's condition. They rely on visual data for patient physical evaluations. They may use touch and skin pressure to ascertain if patients are having peripheral edema. Uremic breath has been reported to be associated with reduction in kidney function.\textsuperscript{13}

Converting these senses into numeric data streams will allow for application of artificial intelligence and machine learning algorithms to help deliver truly precise personalized care to patients. This technology may allow FMCNA to obtain unique signatures of dialysis patients—as unique as the DNA or microbiome of each patient.

The ability to convert sound data into non-discernible numeric data can potentially be used to classify various heart sounds or sound waves associated with arteriovenous (AV) fistula generated thrill.

**FIGURE 5** Predictive model to determine patient changeover using acoustic fingerprint

![ROC Curve](image)

**TABLE 1** Variables for predicting patient changeover

<table>
<thead>
<tr>
<th>Variable</th>
<th>ROC</th>
<th>AUC</th>
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<tr>
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Meet Our Experts

**LEN USVYAT, PhD**
*Vice President, Applied Advanced Analytics, Fresenius Medical Care*

Len Usvyat chairs Fresenius Medical Care’s Advanced Analytics Steering Committees and works closely with the global MONitoring Dialysis Outcomes (MONDO) initiative, an international consortium of dialysis providers. His team provides analytical support and functions in the liaison capacity with Fresenius’s integrated care assets, such as its pharmacy, vascular care centers, urgent care facilities, and the Fresenius health plan. Globally, he is responsible for connecting various advanced analytics partners inside and outside Fresenius Medical Care to the Medical Office Clinical Agenda and building out FMC’s capabilities in applied advanced analytics endeavors. These efforts vary and include activities such as routine and custom reporting, predictive modeling, outcomes analysis, and research. Len has published over 70 manuscripts in peer-reviewed journals. He holds a master’s degree from the University of Pennsylvania and a doctorate from the University of Maastricht in Netherlands.

**WENDY MILLETTE**
*Vice President, Regulatory Affairs, Fresenius Kidney Care*

Wendy Millette oversees the Regulatory Affairs Department for Fresenius Kidney Care, which assists Fresenius clinics in maintaining compliance with state and federal regulations and staying apprised of new and developing policies. Prior to her role in Regulatory Affairs, Wendy managed litigation in the Fresenius Legal Department from 2007 to 2014 after a career as a litigation attorney with a Boston law firm.
Can a large health care organization tackle a complex issue more quickly and successfully by assembling a “tiger team” of experts? Fresenius Medical Care North America (FMCNA) modeled this approach to look at the many issues surrounding hyperphosphatemia. In late 2018, a diverse group of subject matter specialists spent four days together exploring a wide range of treatment alternatives and recommendations. Through intense focus and open collaboration, this newly formed team was able to design a specific list of recommendations for Fresenius Kidney Care (FKC) clinics to optimize phosphate binder selection and patient adherence to treatment.
Hyperphosphatemia is associated with increased morbidity and mortality in the end-stage renal disease (ESRD) population (Figure 1). In addition to the modest removal of phosphorus via dialysis, the therapeutic approach to hyperphosphatemia includes dietary phosphorus restriction and the prescription of phosphate binders.

**FIGURE 1** | Hyperphosphatemia is associated with poor outcomes

**MORTALITY**

<table>
<thead>
<tr>
<th>RELATIVE RISK</th>
<th>INCREASED RISK OF HOSPITALIZATION</th>
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<tr>
<td>1</td>
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<tr>
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<td>8-9</td>
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<td>2.02</td>
<td>&gt;9</td>
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</table>

**HOSPITALIZATION**

<table>
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<tbody>
<tr>
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<tr>
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<td>18%</td>
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<td>20%</td>
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<td>31%</td>
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</table>

Recently, in the face of scientific evidence demonstrating an association between calcium-based binder use and poor outcomes, the global organization Kidney Disease: Improving Global Outcomes (KDIGO) updated its related clinical practice guideline by stating the dose of calcium-based binders should be restricted in both ESRD and late-stage chronic kidney disease patients. Today, there are four non-calcium-based binders available for use.

Availability of non-calcium-based binders alone is not sufficient. Medication adherence is a challenge for patients, especially given the large number of pills they are expected to take each day to manage their comorbid conditions. Patients face many barriers to phosphate binder adherence, including out-of-pocket expense, gastrointestinal (GI) side effects, and the growing body of evidence supporting the fact that pill burden plays a detrimental role to medication adherence. Unfortunately, hyperphosphatemia is a persistent problem for many patients with ESRD.

How does a large organization tackle a complex problem like hyperphosphatemia and treatment adherence in a short period of time? Every type of health care organization, including dialysis services organizations, is experiencing significant market changes. Concurrently, the dialysis industry is grappling with additional challenges that are altering business-as-usual practices, such as the shift from fee-for-service to fee-for-value, and the transition of patient volume and revenue from acute care to home and in-center hemodialysis clinic endpoints. Given the uncertainty and rapid change in the dialysis services space, along with FMCNA’s desire to enhance the value provided to patients, a more proactive and nimble approach to solving the problems faced by the organization is necessary. One approach is to employ a “tiger team.”

A tiger team is a diverse group of subject matter experts assembled to rapidly solve a problem. The technique has been around for years, but it was perhaps best exemplified by NASA’s rapid response to the Apollo 13 disaster in 1970. Fifty-six hours after it launched, an explosion in the service module put the lives of the three Apollo 13 astronauts in jeopardy. NASA quickly assembled a team of experts to focus on solving the complexities necessary to ensure the safe return of the astronauts. Assembling this team of experts, permitting them to focus solely on the problem at hand, and providing them with the support they needed allowed that team to succeed—leading many to call the event NASA’s finest hour.

The tiger team process requires the alignment of tenacious subject matter experts to quickly solve the organizational problem that is posed. While tiger teams are typically created to solve technical problems, they can be formed to develop solutions in any industry. Teamwork is a crucial element of the process. Tiger team participants must have the ability to collaborate, share ideas openly, and solve problems together so they maximize the combined power of their skill sets.

The tiger team assembled in Nashville in late 2018 was tasked by executive leadership with solving the clinical problem of phosphorus control by creating new ideas, spanning organizational boundaries, and optimizing critical decision making (Figure 2).

The week following the tiger team’s engagement, the BOP was rolled out to all FKC clinics nationally.

The BOP included the generation of recommendations based on the KDIGO update and a final recommendation generated in consultation with each patient’s registered dietitian, to ensure appropriate consideration of well-established barriers to phosphorus control. Every other week, each clinic received a list of patients, prioritized according to six clinical scenarios. The BOP recommendations were brought to the local care team’s attention, providing the care team with a useful tool as they strived to control the patient’s phosphorus.

By design, this team was not shackled by a formal agenda or a predetermined set of requirements. The intent was to function as an agile team, recognizing this might be uncomfortable for some of the participants. The tiger team quickly and openly identified challenges, which they solved with open minds. The camaraderie of the team exceeded expectations, particularly given the fact that many did not know each other well prior to the meeting. A diverse group of subject matter experts was recruited, their schedules cleared, and the team assembled in a large conference room. With egos and titles checked at the door, over the span of four days, the team brainstormed ideas, discussed options, and analyzed how to assist the local care team with optimization of binder selection for all FKC dialysis patients. To address the challenge, the tiger team designed the Binder Optimization Program (BOP).

The tiger team accomplished several things during the face-to-face meeting, including:

- **Established and prioritized six clinical scenarios**
- **Generated updates to existing reports received by FKC**
- **Designed a BOP assessment form for eCube and made updates to several existing eCube assessments**
- **Established an oversight structure to provide national support for the program**
- **Developed a series of key performance indicators (KPI) for the program**
- **Drafted an agreement between FKC and FreseniusRx to support the program**

Tiger team participants must have the ability to collaborate, share ideas openly, and solve problems together so they maximize the combined power of their skill sets.
KATHLEEN BELMONTE, MS, RN, FNP-BC, MBA
Vice President of Clinical Services, Fresenius Kidney Care

Kathleen Belmonte brings 20 years of health care experience to her role in leading clinical services for FMCNA’s kidney care division. She is the former chief operating officer for Immediate Care, LLC and served in senior executive roles in the diabetes medical supply and pharmaceutical space. A certified family nurse practitioner and diabetes educator, she holds a master of business administration from Babson College.

TERRY KETCHERSID, MD, MBA
Senior Vice President, Chief Medical Officer, Integrated Care Group, Fresenius Medical Care

Terry Ketchersid has clinical oversight of FMCNA’s Integrated Care Group, which includes value-based care and pharmacy initiatives. He received his bachelor’s degree in chemistry from Austin College, his executive master of business administration from Duke University’s Fuqua School of Business, and his doctor of medicine degree from the University of Texas Southwestern Medical School.

The basis of the team’s effectiveness is motivated by the problem at hand and the commitment to solve it.
For many patients with chronic kidney disease (CKD), food insecurity is a persistent threat to their health. Combating this issue is an association called the Food Is Medicine Coalition (FIMC), whose members provide medically tailored meals that meet the nutritional needs of kidney patients. Coalition members are also examining the positive impact that specific programs have on patient outcomes, health care utilization, and the cost of care. Recent studies reveal practical opportunities for health care providers and payors to collaborate with community groups and to integrate medically tailored meals into comprehensive treatment programs.
Food insecurity is a global problem affecting an estimated 1 billion people. There is enough food in the world for everyone, but issues with local food availability, food access, and food utilization result in over 800 million undernourished people worldwide. Asia Pacific and sub-Saharan Africa are most heavily impacted. Previously, global efforts to increase food production of grain staples prevented millions of deaths. But this “calories-first” approach has resulted in the emergence of obesity and related chronic diseases, such as diabetes mellitus and hypertension. Today, the focus of food security solutions has shifted to producing nutritionally rich fruits and vegetables. The World Health Organization, along with science and health advocates, supports new guidelines to encourage people to “eat a variety of real foods, mostly plants” to optimize health.

Social determinants of health such as housing, community, kinetics, intellectual purpose, and food security are central to Fresenius Medical Care North America’s innovative clinical programs. In the United States, social determinants of health are key drivers in health outcomes and cost. Proportionally, direct health care is estimated to impact only 10 percent of outcomes compared to behavioral patterns, social circumstances, and environmental exposures, which impact 60 percent. This is especially true in kidney disease where the majority of patients starting dialysis represent racial and ethnic minorities who lack access to adequate health care resources. Disparities in CKD incidence, progression, and treatment are associated with social determinants including socioeconomic status and home neighborhood. Albuminuria, low estimated glomerular filtration rate, and end-stage renal disease (ESRD) rates are highest in the poorest neighborhoods.
In 2013, an estimated 14.3 percent of American households faced economic instability resulting in food insecurity.\textsuperscript{10} Low income and food insecurity are associated with chronic diseases including diabetes mellitus, hypertension, and obesity as well as CKD and ESRD. Poor access to food increases the risk of not only CKD, but also CKD progression.\textsuperscript{11} Studies show that food insecurity in America results in the intake of calorie-dense foods with high starch, added sugar, and added saturated fats, leading to overnutrition (an overabundance of nutrients that don’t support normal growth and development).\textsuperscript{12}

The type of food matters. The Dietary Approaches to Stop Hypertension (DASH) diet intervention, which is rich in fruits and vegetables and low in saturated fats, lowers blood pressure and decreases CKD progression.\textsuperscript{13} Patients with CKD have higher survival rates when adhering to a diet high in fiber and polyunsaturated fats and low in salt, phosphorus, and acid load.\textsuperscript{14} A diet with a high acid load (less fruits and vegetables) increases CKD progression risk.\textsuperscript{15}

Can dietary intervention for CKD patients with food insecurity be a treatment to slow CKD progression and decrease the incidence of ESRD?

**EVIDENCE BASE FOR MEDICALLY TAILORED MEALS**

FIMC is an association of nonprofit medically tailored food and nutrition service providers. Agencies within FIMC have partnered with external researchers to develop rigorous evidence demonstrating that medically tailored meals improve health outcomes, reduce total medical expenses, and improve quality of life for individuals facing complex chronic illnesses, including CKD.

Medically tailored meals—an evidence-based nutritional intervention—are custom-made for an individual’s specific medical condition(s) and delivered to that person’s home. Registered dietitian nutritionists customize these meals to address the primary condition, co-occurring illnesses, and medication considerations. For example, the meal could address diabetes, cardiovascular disease, and CKD. Patients who stand to gain the most from medically tailored meals are those with one or more complex chronic conditions, and who typically face food insecurity and other challenges gaining access to or preparing nutritious meals.

Two clinical research studies published in 2018—led by the nonprofit Community Servings of Boston, a leading member of FIMC, in partnership with Dr. Seth Berkowitz, formerly of Massachusetts General Hospital and now at the University of North Carolina Medical School—evaluated the impact of medically tailored meals on health outcomes, health care utilization, and costs. Researchers found that medically tailored meals improve diet quality, while reducing health care utilization and costs, for individuals with complex chronic illnesses and poverty.

The first 2018 study, published in *Health Affairs*, a leading health policy journal, examined the impact of home-delivered meals on adults who were dually eligible for Medicaid and Medicare; the meals were reimbursed by a community-based health plan (Commonwealth Care Alliance). The study focused on two meal programs: medically tailored meals provided by Community Servings and a non-tailored food program provided by a Meals on Wheels vendor. Researchers demonstrated an average monthly net reduction (factoring in the cost of the meals) of 16 percent in medical costs for individuals receiving medically tailored meals versus a matched control group. It showed that the average monthly medical cost for patients receiving medically tailored meals was $843 versus $1,463 for the control group, a gross savings of $540 per month—factoring in the cost of the meals, a net savings of $220 per month. Medically tailored meal participants also experienced statistically significant reductions in emergency room visits, inpatient admissions, and emergency transportation services.\textsuperscript{16}

The second study, published in the *Journal of General Internal Medicine* in November 2018, tested whether the receipt of medically tailored meals improved dietary quality for food-insecure patients with advanced diabetes (A1C >8). The study was designed as a crossover trial in which participants were randomly assigned the order of “on meals” (home delivery of 10 meals per week for 12 weeks) and “off meals” (12 weeks of usual care). After 12 weeks, the “on meal” and “off meal” groups crossed over. Researchers utilized the Healthy Eating Index (HEI) as a measure to assess whether individuals experienced improvements in dietary quality, an essential factor in diabetes management. A clinically meaningful difference in the HEI is 5 points. The average “on meal” HEI score was 71.3 while the average “off meal” HEI score was 39.9, a difference of 31.4 points. The “on meal” group also reported lower food insecurity, less hypoglycemia, and fewer days where mental health was an issue in daily life than the “off meal” group.\textsuperscript{17}

**INTEGRATING MEDICALLY TAILORED MEALS INTO HEALTH CARE PAYMENT AND DELIVERY MODELS**

Since the publication of these two studies, there have been emerging opportunities to integrate medically tailored meals into health care payment and delivery systems. For example, beginning in 2020, accountable care organizations within the Massachusetts Medicaid (MassHealth) program will have access to funds through the Flexible Services Program to spend on nutrition and housing support services to qualifying members. Similar opportunities to integrate medically tailored meals into treatment plans for individuals on Medicaid are emerging in New York, California, Colorado, North Carolina, and other parts of the country that are moving toward models of value-based payments. Also beginning in 2020, Medicare Advantage Supplemental Benefits will reimburse for nutrition services for individuals coping with complex chronic illnesses.

Medically tailored meals—an evidence-based nutritional intervention—are custom-made for an individual’s specific medical condition(s) and delivered to that person’s home.
In preparation for meeting these changes, providers of medically tailored meals must overcome operational, logistical, and financial challenges. Community Servings recently invested in its infrastructure in order to contract with a leading Medicare Advantage plan. Because Community Servings receives patient information, it had to develop processes compliant with HIPAA and other data privacy requirements. To potentially partner with the MassHealth Flexible Services Program, Community Servings also developed the capacity to ship meals. It is now able to provide meals to any individual in Massachusetts, a requirement of Medicaid.

Community Servings is somewhat unique in its ability to invest in its infrastructure to meet new challenges in partnership with health care payors. Payors should consider investing in the community by joining community-based organizations that are typically resource-challenged but have the expertise to provide needed social services. The most successful social determinants programs—which comprehensively and equitably address patients’ social needs—will emerge from a fully collaborative process in which health care payors and providers work with community-based organizations on all aspects of program design and execution, such as:

• Assessing the need for investment in the community-based organization and agreeing to a fair rate of reimbursement for the service, to ensure there is capacity to generate maximum impact
• Reaching consensus on program eligibility criteria
• Identifying the screening and referral process
• Providing education and outreach to the individuals on the care team making the referrals
• Evaluating program impact
• Discussing future opportunities for replication and scaling of the model

Medically tailored meals and family food security may improve outcomes for patients with CKD. Interconnecting providers, payors, and community resources is complex, but it creates an innovative partnership to improve the lives of CKD patients (Figure 1).

**FIGURE 1 | Impact of diet on the risk of developing CKD and progression from CKD to ESRD**

<table>
<thead>
<tr>
<th>Food insecurity in minority populations in poorer socioeconomic neighborhoods</th>
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<tbody>
<tr>
<td>Persons without CKD but with increased risk of developing CKD</td>
</tr>
<tr>
<td>Consume higher levels of salt, calories, and saturated fats</td>
</tr>
<tr>
<td>Persons with CKD</td>
</tr>
<tr>
<td>Consume fewer fruits and vegetables</td>
</tr>
<tr>
<td>Increased onset of hypertension and diabetes</td>
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<tr>
<td>Increased risk of faster progression to ESRD</td>
</tr>
<tr>
<td>Increased risk of developing CKD</td>
</tr>
</tbody>
</table>

Meet Our Experts

**DUGAN MADUX, MD, PhD, FACP**
*Vice President, Kidney Disease Initiatives, Fresenius Medical Care*

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

**DAVID B. WATERS**
*Chief Executive Officer, Community Servings*

David Waters, an advocate for integrating medically tailored meals into the health care system, has formed partnerships with leading health care payors and providers to better link clinical care and social services, designing some of the country’s first health insurance contracts for prescription meals. He is the former board chair of the Association of Nutrition Service Agencies and is a leading member of the national Food Is Medicine Coalition as well as the Root Cause Coalition. In recognition of his leadership at Community Servings and within the Greater Boston community, David was named a Barr Foundation Fellow in 2017. A resident of Cambridge, he holds graduate degrees from Middlebury College and Boston University.
Advancing Interoperability to Reduce Provider Burden and Improve Patient Care

Ahmad Sharif, MD, MPH, SCPM | Fresenius Medical Care
Sam Gopal | Acumen Physician Solutions

When patient data is fragmented across many providers, it is challenging to coordinate effective care, from both a quality and a cost perspective. The advent of value-based care systems has made information sharing a more important metric of success. However, it is true interoperability—the ability for large networks to communicate with one another—that will deliver on the promise of “interconnected intelligence.” Fresenius Medical Care North America (FMCNA) is working with a consortium of other health care organizations to develop common standards and a practical framework for seamless data exchange.
With patient data coming from multiple venues of care, nephrologists are challenged with “connecting the dots” as well as coordinating across diverse providers to deliver quality patient care. There is a pressing need to advance interoperability and data sharing across information silos to reduce the provider burden. Acumen 2.0 powered by Epic Systems, in conjunction with FMCNA’s broader interoperability program, is providing one version of “interconnected intelligence” to meet this need.

Timely and relevant access to patient data is a key requirement in providing quality care for chronic kidney disease (CKD) and end-stage renal disease patients. Early CKD stage identification and progression management rely on accurate and relevant lab data. Empowering patients to make informed decisions on modality choice requires monitoring CKD progression and referral for patient education. Optimal dialysis starts at home or with an arteriovenous (AV) fistula instead of central venous catheter (CVC) and is predicated on timely referral of CKD patients for vascular access.

Looking ahead, the transition to value-based care is dependent on the ability to aggregate and analyze population-level data to improve quality outcomes with smarter spending. The promise of personalized, precise renal disease care with targeted interventions tailored to individual patient needs requires the ability to manage clinical data sets longitudinally. Simply put, current and future goals for patient care require a holistic view of the records that “follow the patient,” offering a comprehensive view of the patient journey as well as support for the nephrologist. To do this, we need to design and deliver data sets that transcend the physical walls of care venues—be it the CKD clinic, the patient’s home, the dialysis unit, or an inpatient facility.

The promise of personalized, precise renal disease care with targeted interventions tailored to individual patient needs requires the ability to manage clinical data sets longitudinally.
Acumen 2.0 is a single instance of Epic with logical separation across independent nephrology practices within the system. By connecting with Epic's industry leading CareEverywhere network, Acumen 2.0 allows for interoperability with other Epic instances and provides several value propositions:

• Meeting CMS quality metrics for Promoting Interoperability: This is achieved through consuming outside records; supporting electronic referral loops by receiving and incorporating health information; and reconciling problems, allergies, and medications. Figure 1 shows the range of interoperability options and value delivered by Acumen 2.0.

• Presenting a unified patient chart in workflow context: Doctors can look up a patient's chart anywhere in the country with seamless integration into clinician workflow. There is automated connectivity with Epic hospitals and connectivity with non-Epic providers via CommonWell/Carequality. Figure 2 shows an example of patient data from multiple venues of care presented within the Acumen 2.0 workflow context.

• Offering patient benefits: Information is available electronically on demand to/from Acumen providers and external providers, which eliminates duplicate or redundant labs and diagnostic studies.

• Helping to transition to value-based care: Data from care networks and interoperability help networks improve quality performance and cost. Registries and robust population management tools identify patients with gaps in care for timely intervention and give new insights into high-risk populations.

Interoperability occurs when information flows appropriately across organizational, vendor, and geographic barriers and is retrievable and consumable by clinicians for patient care.
FIGURE 2 | Acumen 2.0 reconciling patient data into chart

Presenting a unified patient chart in the context of provider workflow makes interoperability actionable in advancing patient care.
What if you had a cell phone plan that only allowed you to call other customers within your carrier's network? That's the situation for most health care providers today as they are constrained within data-sharing networks with membership limited by geographic or technology (EHR vendor) lines (Figure 3). Epic's leading CareEverywhere network only works with other Epic instances. CommonWell is a competitive vendor collaborative that works with other EHR vendors that incorporate CommonWell standards into their technology. eHealth Exchange is the largest public-private network anchored by large federal agencies, educational institutions, and leading private participants such as Kaiser Permanente. Other regional HIEs and exchanges have geographic membership limitations.

The Sequoia Project is a nonprofit, independent, trusted advocate for national health information exchange initiatives. It stewards existing programs, provides education, and incubates new programs. In 2018, the Sequoia Project recognized that it was unlikely any single network could serve the needs of the entire country, given the history of health IT. The Sequoia Project partnered with health IT leaders in public and private sectors to create Carequality. Carequality is a collaboration of the entire health care community formed to address the fragmented data-sharing network challenge. It is not a network—instead, it is a national-level, consensus-built, common interoperability framework. Carequality is designed to enable data exchange between and among health data-sharing networks. (By contrast, CareEverywhere and CommonWell are networks.) It brings together EHR vendors, record locator service providers, and other types of existing and disparate networks from the private sector and government to determine technical and policy agreements that will enable the data flow.

The most significant accomplishment of the Carequality framework is the “Golden Spike agreement” between the Epic Carequality and CommonWell consortium to implement this framework. Collectively, this agreement represents 90 percent of the acute EHR market and 60 percent of the ambulatory EHR market (Figure 4).

- CommonWell has agreed to offer an implementation of the Carequality “directed query” connectivity to its members.
- Epic has implemented Carequality for nearly 100 percent of its customer base.
- Carequality has agreed to support access to CommonWell's record locator service.
- Carequality has dramatically lowered friction for widespread "query" interoperability across all major EHR systems.
- CommonWell EHR vendors offer Carequality query at no charge to providers.

Fresenius Kidney Care (FKC) is developing core information technology capabilities to facilitate bi-directional data exchange between its dialysis facilities and external care providers. Using the Continuity of Care Document recognized standard, FKC clinical data can be exchanged and ingested by an external system. FKC is also establishing connections with the national CommonWell, Carequality, and eHealth Exchange networks. This will enable data originating from external patient care providers to be displayed in eCube Clinicals, a Cerner product, and FKC’s system in the dialysis units, to facilitate care coordination. This addition will allow illustration of FKC’s benefit from the Golden Spike agreement.

FKC’s initiatives with CommonWell, Carequality, and eHealth Exchange are advancing interoperability and data sharing with external care providers, resulting in a longitudinal record of care accessible by the dialysis patients’ diverse care teams. Acumen 2.0 reconciles patient information directly into the nephrology practice EHR systematically, eliminating the need to fax information or log into external care portals. Collectively, these efforts by FMCNA aim to deliver on the promise of interoperability and workflow integration to provide interconnected intelligence.

![TABLE: Fragmented data-sharing networks](image)

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**TABLE:** Fragmented data-sharing networks

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<thead>
<tr>
<th>NETWORK</th>
<th>ADOPTION</th>
<th>UTILIZATION*</th>
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<tbody>
<tr>
<td>CareEverywhere</td>
<td>Epic only</td>
<td>3.6B documents shared</td>
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<tr>
<td>CommonWell Health Alliance</td>
<td>80+ members; founded by vendor consortium</td>
<td>57k documents shared</td>
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<tr>
<td></td>
<td>of Allscripts, AthenaHealth, Cerner,</td>
<td>9.4M patients</td>
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<td></td>
<td>ChangeHealthcare, Evident, and Greenway</td>
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<tr>
<td>eHealth Exchange</td>
<td>Anchor participants include CMS, VA,</td>
<td>Largest public-private network</td>
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<td>DOD, SSA, educational institutions, and</td>
<td>120M patients</td>
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<td>large integrated delivery networks</td>
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*Utilization data represents transactions from the January 2014 inception of CommonWell through September 2017*
Carequality is a collaboration of the entire health care community formed to address the fragmented data-sharing network challenge.

**FIGURE 4** | Carequality “Golden Spike agreement” implications

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**Meet Our Experts**

**AHMAD SHARIF, MD, MPH, SCPM**  
**Senior Vice President, Chief Medical Information Officer, Fresenius Medical Care North America**

Ahmad Sharif oversees clinical IT systems for FMCNA and formerly served as chief medical information officer for a Tenet Health market. He was awarded a full scholarship to attend classes at Harvard University, holds an advanced project management certification from Stanford University, and completed his master's degree in public health and management from the University of North Texas.

**SAM GOPAL**  
**President, Acumen Physician Solutions**

Sam Gopal received his bachelor's degree in mechanical engineering from the Indian Institute of Technology, master's degree in industrial engineering from Purdue University, and master's degree in management from Harvard University Extension School. Prior to joining FMCNA, he held technology consulting, strategy, and product innovation roles in various industries including information management, defense logistics, semiconductor, and automotive supply chain distribution.
The rise of interoperability and interconnected technologies has fundamentally changed health care through systems integration—connecting caregivers and patients and improving access to longitudinal patient data.

“Connected health” thinking, the core of the Fresenius Medical Care technology agenda, centers on three main areas of the patient and provider needs: integrating and connecting clinical care systems and applications; enhancing data collection during treatments by reimagining the medical devices as a sensing platform; and expanding global analytics capabilities to drive personalized, precision patient care.

Fresenius Medical Care’s suite of connected health technologies enable care at home and beyond, providing real-time connection between patients and care teams, improving access to health care in remote areas, and providing clinical decision support to avoid potentially negative health care events. Fresenius Medical Care is also exploring biosensing wearables—such as digital blood pressure monitors and glucose sensors—as ways connected health technologies can empower patients to become more active participants in their care.

**CONNECTED HEALTH PORTFOLIO**

**Provider Hub**

Provider Hub is a mobile rounding tool for physicians that sits on the primary electronic health record (EHR) system and offers providers easy access to intuitively arranged patient data. Provider Hub is accessible from handheld and desktop devices.

**Clinician Hub**

Clinician access to real-time patient data is key to improving health care quality. Clinicians at Fresenius Kidney Care (FKC) use the Clinician Hub to view home-based and remote patient dialysis treatment data collected by devices such as the Liberty Cycler. Staying connected to patient treatments, regardless of location, allows real-time intervention to help improve patient care.

Provider Hub is a Fresenius Medical Care mobile rounding solution designed to put vital patient information at the physician’s fingertips.
**Patient Hub**

Patient access to their care team during home and remote treatments is essential for a sense of security—and success. Through the Patient Hub, FKC patients can connect with their entire care team, including nurses, physicians, and supply specialists. The Hub also manages schedules and offers a remote monitoring feature so patients can enter their daily weights.

**eCube Clinicals**

FKC’s primary dialysis information system, eCube Clinicals, is the holistic foundation that supports all applications and devices throughout the care ecosystem for care delivery, documentation, and clinical decision support.

**Health Information Exchanges**

Health Information Exchange (HIE) allows the clinician to electronically access and confidentially share patient’s vital medical history no matter where patients are receiving care. FKC has partnered with Cerner to join the national HIE CommonWell® Health Alliance Exchange as well as the largest HIE framework Carequality to facilitate real-time patient data sharing. This partnership will allow for bi-directional data exchange between provider participants. FKC is working to ensure that presentation of the HIE data fits well into the clinician’s workflow and that it is presented in a form that can be cognitively processed by the clinician for decision making. Timely access to vital patient clinical information will improve the quality, safety, and efficiency of patient care.

**Acumen 2.0 powered by Epic**

Systems interoperability, data sharing, and care coordination are increasingly important for effective population health management, especially for patients participating in risk-based care models. Acumen 2.0 powered by Epic is the industry’s leading nephrology focused EHR and is connected to Epic’s CareEverywhere global information backbone. It is accessible by most of the largest integrated health systems in the world, creating a broad, connected community for patient information sharing. The community is comprised of 405 health care organizations covering 41,200 clinics, 1,980 hospitals, and over 336,000 physicians. This extensive network ensures that nephrologists have improved access to important patient data to assist with informed and timely decisions.

**Nx2me Connected Health**

NxStage Medical’s Nx2me Connected Health is a state-of-the-art telehealth platform designed to make it easy to collect and share treatment information with clinics and care teams. Automated flowsheets ensure that tracking and recording treatment information is simple, eliminating the need to retain paper flow sheets for clinic visits. With the Nx2me application, patients can electronically send treatment information to their dialysis centers and care teams.

**Virtual Patient Communities**

A support network and community are important aspects for success in patients on home dialysis. Fresenius Medical Care North America piloted a virtual communities project to help home dialysis patients feel more connected to peers and others going through similar health challenges. Patients can interact with each other as well as learn and share insights through an online community.
The Global Medical Office was created in 2019 by Rice Powell, chief executive officer for Fresenius Medical Care, as a strategic endeavor to harness the full potential of the company’s worldwide vertical integration to interpret science and medical practice patterns on a global basis. Led by Dr. Franklin W. Maddux, the Global Medical Office is an important benchmark in the company’s history and comprises a team of distinguished clinical and business leaders working together on behalf of patients around the world.
Franklin W. Maddux, MD, FACP
Global Chief Medical Officer

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 physician, expert nephrologist, technology entrepreneur, and health care 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 founded by Maddux. 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. 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. His writings have appeared in leading medical journals, and his pioneering health care information technology innovations are part of the permanent collection of the National Museum of American History at the Smithsonian Institution.
Frank Laukhuf, MD
Chief Medical Officer | Fresenius Medical Care Europe/Middle East/Africa

Frank Laukhuf leads the medical office for Fresenius Medical Care throughout Europe, the Middle East, and Africa, and heads the region's three subunits: Clinical and Epidemiological Research, Medical Affairs/Medical Devices and Drugs, and Medical Information and Education. A board-certified internist and nephrologist with over 25 years of experience in both direct patient care and hospital management in Germany and Switzerland, he joined Fresenius Medical Care in 2011 where he led the development and expansion of medical product governance function in EMEA. Dr. Laukhuf holds a postgraduate degree in health economics and graduated magna cum laude with his doctor of medicine from Heidelberg University in Germany.
Bernard Canaud, MD, PhD
Senior Chief Scientist | Fresenius Medical Care

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

Allan J. Collins, MD, FACP
Senior Chief Scientist | Fresenius Medical Care

Allan Collins has a distinguished career with more than 30 years of work in nephrology and ESRD treatment. He is the former chief medical officer for NxStage Medical, Inc. and served as director of the National Institute of Health’s/NIDDK’s United States Renal Data System from 1999 to 2014. Dr. Collins has published more than 225 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 ESRD and chronic kidney disease patients, and prospective and retrospective clinical studies on dialysis techniques and associated outcomes. The former president of the National Kidney Foundation, Dr. Collins served on the NKF scientific advisory board for six years, with the Kidney Dialysis Outcomes Quality Initiative, and on the International Society of Nephrology’s Commission for the Global Advancement of Nephrology Committee. He graduated with his medical degree from Wayne State University in Detroit.

Kurt Mussina, MBA
President, Frenova Renal Research | Senior Vice President, Fresenius Medical Care

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

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

Len Usvyat, PhD
Vice President, Applied Advanced Analytics | Fresenius Medical Care

Len Usvyat chairs Fresenius Medical Care’s Advanced Analytics Steering Committees and works closely with the global MONitoring Dialysis Outcomes (MONDO) initiative, an international consortium of dialysis providers. His team provides analytical support and functions in the liaison capacity with Fresenius’s integrated care assets, such as its pharmacy, vascular care centers, urgent care facilities, and the Fresenius health plan. Globally, he is responsible for connecting various advanced analytics partners inside and outside Fresenius Medical Care to the Medical Office Clinical Agenda and building out FMC’s capabilities in applied advanced analytics endeavors. These efforts vary and include activities such as routine and custom reporting, predictive modeling, outcomes analysis, and research. Len has published over 70 manuscripts in peer-reviewed journals. He holds a master's degree from the University of Pennsylvania and a doctorate from the University of Maastricht in Netherlands.

Katrin Köhler, MSc, MBA
Vice President, Global Medical Office Operations and Strategies | Fresenius Medical Care

Affiliated with Fresenius Medical Care since 2003, Katrin Köhler leads strategy and operations for the Global Medical Office, driving cross-regional medical strategies and synergies on a global level. She formerly served as director of Strategic Medical Development and Medical Innovation and Portfolio Management for Fresenius Medical Care Europe/Middle East/Africa and has worked closely with the company’s global business and medical leaders on key strategic initiatives, with broad experience across the company’s business regions, also including locations in Germany, Canada, and France. 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 Reutlingen in Germany and the Lancaster University Management School in the United Kingdom.

Ryan A. Jimenez, EdM, BA, APR
Vice President, Global Medical Office Communications | Fresenius Medical Care

Ryan Jimenez joined Fresenius Medical Care in 2016, most recently serving as vice president of Medical Office Relations for North America, where he led the development of the region’s Medical Office communications strategies and capabilities. With FMCNA corporate communications, he led the development of FMCNA’s video broadcast network, including the creation of the Medical Office Live series of broadcast events across North America as executive producer. He previously served as regional communications director for Four Seasons Hotels and Resorts, leading global communications campaigns in North America, EMEA, Latin America, and Asia; and is the former senior producer and global communications director for CNN’s Larry King Live. He was appointed by California Governor Arnold Schwarzenegger as communications director for the office of First Lady Maria Shriver and began his career in hospital communications at Catholic Healthcare West in California. Ryan received his bachelor's degree from the Annenberg School of Communications and Journalism at the University of Southern California and holds his master's degree in organizational behavior and ethics from Harvard University.


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Rapidly Solving Complex Problems
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The Fresenius Medical Care Annual Global Medical Report is published by the Global Medical Office. We extend our deep gratitude to the various authors, contributors, and individuals who made this volume possible.

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“We are moved by the Power of Ideas, conceived by individuals, molded by collective intelligence and brought to life by investment in a higher purpose that is dedicated to improving the lives of people.”

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Global Chief Medical Officer