

# KIDNEY FAILURE

A GIVING SMARTER GUIDE



MILKEN INSTITUTE  
CENTER FOR STRATEGIC PHILANTHROPY

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## PHILANTHROPISTS' FOREWORD

### *From the desk of Robert and Cynthia Citrone*

When Rob's father was first diagnosed with end stage renal disease (ESRD) we were devastated. How horrific is a disease that is named "end stage?" Where is the hope? I watched in despair as Rob sprung to action to help and comfort his father.

How could we not be donors? How do the best doctors in the world not have a plan? Rob has built his success on action and identifying opportunities, yet this process was an exercise in futility in this new ESRD terrain. It was then that we found The Milken Institute and its Center for Strategic Philanthropy (CSP). Mike, Melissa, and the entire CSP team worked with us to investigate the problem, mobilize our resources, and develop a call to action. Thanks to the Institute, we are enthused and invigorated to dedicate our time and resources to make an impact in the ESRD field. With its leadership, we are poised to give hope back to our father and so many others.

### *From the desk of Robert L. Citrone*

Chronic kidney disease, end stage renal failure, hemodialysis, peritoneal dialysis, major life changes, endless medications and tests, possible transplant; this is the life of a patient with renal disease. Like so many diseases, renal disease is not discriminating; it happens to all people from all walks of life, young and old alike.

When I was told that I would end up on dialysis within 6 to 12 months, I felt as though I had just been given a death sentence. Life, as I knew it, would never be the same again, for me or my family. As dialysis options were discussed, I made the decision to do hemodialysis. However, once home, I began to do my own research and, contrary to some members of my medical team, discovered that hemodialysis was not the right option for me or my lifestyle.

As a new peritoneal dialysis patient, with end stage renal failure, the focus then turned to the possibility of a kidney transplant. For me, this was one of the most heartbreaking and frustrating experiences of my life. Even though I am on a waiting list, I have basically been precluded by the government's guidelines. I have learned that, for the majority of transplant patients, finding a donor falls directly onto the shoulders of the patient and his or her family. Through the process of seeking a transplant, I have discovered that there is a real lack of knowledge, among the general population and even the medical world. Several years ago, I identified a few potential kidney donors. However, the donors themselves were dissuaded from donating. With better knowledge, there may have been a different outcome.

We all like to think we are unique—that our stories are ours alone. But that just isn't true. The longer I live the life of a renal patient, the more my life and story becomes intertwined with other renal patients who I have come to know, who are fighting for a longer and better life. I often think of the U.S. veteran, who is seeking a kidney donor by posting his plea on the windows of his car. The grandmother who refuses to go through the rigors of dialysis and dies much too young. The 41-year-old man who dies of cardiac arrest in his sleep. The young transplant woman who is given a second chance and gives birth to a healthy baby. The young athlete who received the gift of life 11 years ago from his sister. The 12-year-old daughter who lost her beloved father. Or the husband who just lost his wife to kidney failure, but continues his own battle with the disease, even if it means losing various limbs.

I have so many questions... Why should so many people have to die so young from such a disease? Why must it be the responsibility of individuals to find their own donors? Why doesn't the general population and medical field have a better awareness of kidney disease? Why isn't there better donor awareness? What will happen when, or if, the transplanted kidneys fail? Why are there no specific drugs for renal disease? What about artificial kidneys? Is it possible to have a better type of dialysis? And the list goes on and on. This is not a battle to fight alone.

And now, woven into our story is the Milken Institute's Center for Strategic Philanthropy. In the new chapter of our story, CSP has brought together the preeminent doctors and researchers in the renal disease field to discuss,

strategize, prioritize needs, and set goals. Meeting with this team of doctors and researchers, I once again discovered that I am not alone. They have the same questions and concerns. And how wonderful that, through their work, they are seeking to answer those questions.

As you review the Giving Smarter Guide, you will find that it is a powerful tool to guide us as we go forth to defeat kidney disease. I invite you to join our story. A story where hope is beginning to be intertwined into the pages. A story of hope that will continue for generations to come. A story of hope that will bring a longer and better life for renal disease patients.

Robert L. Citrone, March 2017



## EXECUTIVE SUMMARY

This Giving Smarter Guide is the culmination of a year-long effort to identify strategic philanthropic opportunities that can move the needle on unmet needs specific to kidney failure research and treatment. Kidney failure is an irreversible disease in which the kidneys can no longer support life on their own. To live, patients suffering from kidney failure must initiate treatment to replace kidney function through dialysis or kidney transplantation. According to the Centers for Disease Control and Prevention (CDC), more than 300 people begin treatment for kidney failure every 24 hours in the United States. The quality of life (QOL) for these patients is severely impacted because their lives are forever changed.

Approximately 17 percent of U.S. adults live with chronic kidney disease (CKD), the most common form of kidney disease characterized by a gradual loss in kidney function. Nearly 600,000 CKD patients have progressed to a state of kidney failure, the final stage of CKD. A person living with CKD may not be aware of the disease until it has progressed to the point of kidney failure. This lack of awareness is a major barrier with serious ramifications for patient health, research support, and cost.

The healthcare costs are staggering. In aggregate, Medicare spends about \$30 billion per year for kidney failure patient care—accounting for greater than 7 percent of Medicare fee-for-service spending. Aside from the economic burden, this disease takes an emotional toll on patients and families, as they navigate their new realities of a demanding dialysis treatment schedule, extreme resultant fatigue, as well as lost wages and high out-of-pocket costs.

Although the federal government provides nearly \$600 million in CKD/kidney failure research funding, it is less than 2 percent of care costs and woefully disproportionate to disease prevalence. The pharmaceutical industry has faced several drug development challenges, and there has never been a drug developed primarily for the prevention of kidney failure. Several barriers that plague the CKD/kidney failure field can be classified in the following categories:

- Lack of disease awareness and workforce challenges;
- Lack of innovation in transplantation and dialysis delivery; and,
- Limited disease understanding at the molecular level.

At the behest of the Citrone family, the Milken Institute Center for Strategic Philanthropy convened world-renowned kidney experts and stakeholders to identify transformative research and systems opportunities where philanthropy could accelerate progress in the CKD/kidney failure space. The primary opportunities are as follows:

- Channeling private investment to **spearhead public awareness campaigns** would be the first step to raise the national profile of the disease state, encourage policy reform, and attract funding dollars for research and improved therapies—similar to the experience for other high-profile diseases.
- Private giving can also transform the kidney disease and transplantation workforce by **endowing annual summits and creating a global network of faculty** to nurture the future generation of researchers and physician-scientists.
- Philanthropic giving can move the needle on organ scarcity by funding innovative efforts to **expand access to transplantation, increase living kidney donation** rates, and strategically invest in **artificial kidney development**.
- The catalytic potential of philanthropy can foster a culture shift regarding kidney disease, whereby patients are better informed and encouraged to participate in **clinical trials**.

This Guide was developed with the express purpose of empowering patients, supporters, and stakeholders to make strategic, informed decisions when directing their energy and philanthropic investments into research and development efforts aligned with their interests.

## OVERVIEW

Chronic kidney disease (CKD) is a condition characterized by a gradual loss in kidney function. The last stage of CKD, known as kidney failure (or end stage renal disease [ESRD]), is an irreversible disease in which the kidneys are no longer capable of supporting daily life. About 20 million American adults are living with CKD, and more than 600,000 have progressed to kidney failure, the fifth and final stage of CKD. Although there are several possible causes of kidney failure, high blood sugar (diabetes) and high blood pressure (hypertension) are the leading causes. In fact, approximately one in three adults with diabetes and one in five adults with hypertension currently have CKD. Early stages of CKD are asymptomatic, and therefore CKD patients can be unaware of their status—leading to a large proportion of patients learning of their kidney failure during emergency situations. A startling statistic is that greater than 50 percent of all dialysis patients end up receiving dialysis treatment during an emergency room visit, underscoring the need for disease awareness and early detection.

Several complications result from kidney failure, namely cardiovascular disease (CVD) and congestive heart failure (CHF), low red blood cell count (anemia), and bone and mineral disease. Treatment of these complications takes a severe toll on quality and length of life.

Treatment options for kidney failure patients are quite limited. There is a dire need for innovation in dialysis delivery and care, as well as increased access to kidneys for transplantation. Dialysis is widely accessible in the United States because it is a Medicare-covered condition, but dialysis treatment has not improved since its development more than 50 years ago, and mortality rates remain abysmally high. Kidney transplantation is by far the best option for kidney failure patients, but donor organs are in short supply. Consequently, preventing progression of CKD to kidney failure is of paramount importance, underscoring the need to develop novel treatment options for CKD.

## SOCIETAL IMPACT OF KIDNEY FAILURE

### POPULATION BURDEN

Kidney diseases are the ninth leading cause of death in the United States. According to the CDC, more than 1 in 10 Americans are currently living with CKD. Of those, more than 600,000 people are living with kidney failure.

CKD/kidney failure is more common in patients aged 60 or older, and this at-risk population is growing rapidly. Since 2011, “Baby Boomers” (people born between 1946 and 1964), who comprise more than 20 percent of the total U.S. population, began to turn age 65. The U.S. Census Bureau reports that all of the youngest Baby Boomers will be over age 65 by 2029. When the prevalence of diabetes and high blood pressure is considered, the outlook becomes even bleaker. Based on 2012 statistics, nearly 10 percent of the U.S. population is diabetic and nearly 30 percent is hypertensive and therefore at risk of developing CKD/kidney failure.

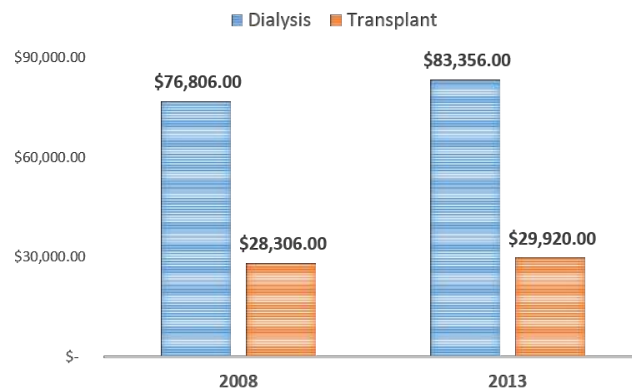
Furthermore, CKD and kidney failure disproportionately affect the U.S. population in terms of race, ethnicity, and socioeconomic status (SES). Black Americans are three times as likely to develop kidney failure as White

Americans, and Hispanics are 40 percent more likely to develop kidney failure compared to non-Hispanics. Similarly, low SES is associated with CKD incidence, progression to kidney failure, and poor health outcomes and reduced access to quality healthcare. Experts state that lapses in care quality are strongly associated with these disproportionate rates.

Although this Guide will focus on U.S. incidence of kidney failure, kidney disease is a global health crisis. According to the 2010 Global Burden of Disease study, CKD ranked 18th in leading causes of death worldwide—up from 27th in the 1990 rankings. Only HIV/AIDS had a larger ranking change. According to a 2015 report in *Lancet*, the estimated 2.6 million people who receive kidney replacement therapy globally is projected to double by 2030. Alarmingly, only half of kidney failure patients around the world receive life-saving kidney replacement therapy, effectively making kidney failure a death sentence in many countries. Indeed, there is work to be done to stem the tide of kidney disease incidence.

### ECONOMIC BURDEN

Since 1972, anyone with kidney failure (regardless of age or income) was granted Medicare eligibility to cover the cost of dialysis or kidney transplantation services. Kidney failure was, and still is, the only medical condition to receive universal coverage under this government program. At that time, only about 10,000 U.S. patients were receiving; however, this number swelled to more than 450,000 patients in 2013, according to data collected by the U.S. Renal Data System (USRDS [see page 32]). This increase is significant because treatment for kidney failure is costly. One year of dialysis treatment costs Medicare \$69,000 to \$85,000, and 1 year of transplant-associated treatment costs approximately \$30,000 (Figure 1). In aggregate, Medicare spends about \$30 billion per year for kidney failure patient care. Even though kidney failure patients comprise less than 1 percent of the total Medicare population, they account for greater than 7 percent of Medicare fee-for-service spending.



**Figure 1. Medicare costs for kidney failure patients.** Per person per year costs of prevalent kidney failure patients. Yearly costs to treat a patient on dialysis are nearly triple the costs to treat a transplant patient.

Patients and their caregivers suffer direct financial strain. Kidney failure often renders patients unable to work because of the extreme fatigue that often accompanies dialysis treatment, which translates into lost wages, loss of lifetime earning potential, and loss of retirement savings and security. In addition, kidney disease patients incur the most out-of-pocket expenses of any Medicare beneficiary.

Individuals that donate a functional kidney to a kidney failure patient are not exempt from financial strain. Although public or private insurance may cover their surgery, kidney donors will incur transportation and childcare costs, as well as lost income due to surgery and recovery. Currently, living donors do not have job protection under the Family and Medical Leave Act (FMLA) during the long recovery process. These financial risks disincentivize kidney donation, despite altruistic intention, which partially drives the shortage of kidneys donors. In turn, many patients have no alternative to dialysis, which is not only three times more expensive than kidney transplantation, but also limits QOL and life expectancy. A policy change that provides better support for living donation would save

the government an average of \$60,000 a year for every patient that received a kidney transplant rather than dialysis treatment, according to the [2013 Economic Report to the President](#).

As the prevalence of at-risk individuals continues to rise, so too will the impending costs. Now is the time to address these difficult issues by identifying key unmet needs that impede research progress and therapeutic innovation in CKD/kidney failure.

## POLICY AND REGULATORY INITIATIVES

This section will profile a series of legislative and regulatory matters significant to the CKD/kidney failure community pertaining to access to care, quality of care, and medical research.

### LIVING DONOR PROTECTION ACT OF 2016 (H.R. 4616, S. 2584)

Representative Nadler (D-NY), Representative Burgess (R-TX), Senator Kirk (R-IL), and Senator Gillibrand (D-NY) introduced the [Living Donor Protection Act](#), which seeks to prohibit insurance companies from denying or limiting life, disability, and long-term care insurance to living donors and from charging higher premiums after donations. The bill also clarifies that living organ donors may use time granted through the Family and Medical Leave Act (FMLA) to recover from donation.

#### Key Takeaways

- ❖ One-third of all kidneys come from living donors; however, this has plateaued in recent years.
- ❖ This bill protects living donors by:
  - Prohibiting insurance companies from denying coverage to living donors and from raising premiums after kidney donation.
  - Providing job security under FMLA to allow donors to take ample time to recover from surgery following kidney donation.

### THE CKD IMPROVEMENT IN RESEARCH AND TREATMENT ACT OF 2015 (H.R. 1130, S. 598)

Representatives Tom Marino (R-PA), John Lewis (D-GA) and Peter Roskam (R-IL) and Senators Ben Cardin (D-MD), Mike Crapo (R-ID), and Bill Nelson (D-FL) introduced the [Chronic Kidney Disease Improvement in Research and Treatment Act of 2015](#) in February 2015. The bill seeks to improve access to quality care for patients, promote education and awareness, and increase efficiency in biomedical research in CKD.

#### Key Takeaways

- This bill addresses issues in both insurance coverage and research.
- ❖ Insurance coverage-related:
    - This bill would increase access to coverage by allowing kidney failure patients under 65 to enroll in Medicare Advantage plans.
  - ❖ Research-related:
    - Because of the lack of safe and effective treatments and disproportionate economic burden of the disease, CKD/kidney failure research is vital.
    - This bill mandates an assessment of current federal funding levels relative to CKD care expenditures and federal epidemiological studies to assess disease progression and treatment among minority populations.

Specifically, the bill augments access to care by allowing individuals under age 65 with kidney failure to enroll in Medicare Advantage plans. Furthermore, it proposes an expansion of patient access to kidney disease education programs and home dialysis treatment options. The bill also proposes a plan to more effectively manage and coordinate biomedical research in kidney disease.

The bill mandated an assessment of current federal funding levels relative to CKD care expenditures, the findings of which were recently published by the U.S. Government Accountability Office ([GAO-17-121](#)). The legislation also

mandates a federal study to better understand the progression of kidney disease and treatment of kidney failure in minority populations.

## QUALITY INCENTIVE PROGRAM

The Medicare Improvements for Patients and Providers Act of 2008 created a [Quality Incentive Program \(QIP\)](#) for Medicare's ESRD program. The QIP, which took effect in 2012, aims to promote high-quality services in outpatient dialysis care. The QIP links a portion of facilities' Medicare reimbursement directly to QIP performance standards and the quality of care that patients receive. For those facilities that do not meet or exceed certain standards, the QIP reduces payments.

### Key Takeaways

- ❖ Because of high mortality rates associated with dialysis, initiatives aimed at increasing QOL are needed.
- ❖ This bill would increase clinical quality across dialysis centers by tying funding to performance metrics.

## THE BASICS: THE KIDNEYS AND HOW THEY WORK

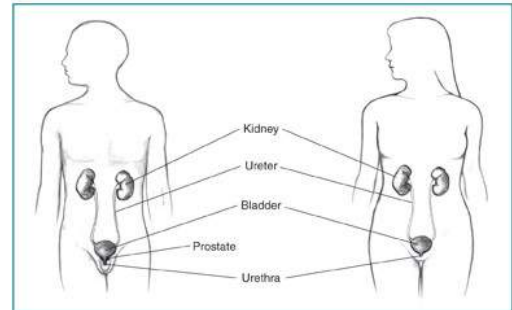
Kidneys are vital to everyday life because they are the central filtration system of the body. Below the basics of kidney anatomy and function are addressed through a series of questions:

### WHERE ARE THE KIDNEYS LOCATED?

The kidneys are two bean-shaped organs located directly opposite each other on the left and right side of the upper abdominal area pressed against the back muscles.

The kidneys are a key part of the urinary system. Figure 2 illustrates the urinary system components:

- Kidneys—These organs filter blood and produce urine.
- Ureters—These tubes carry urine from the kidneys to the bladder.
- Bladder—This hollow organ stores urine prior to excretion.
- Urethra—This tube expels urine.



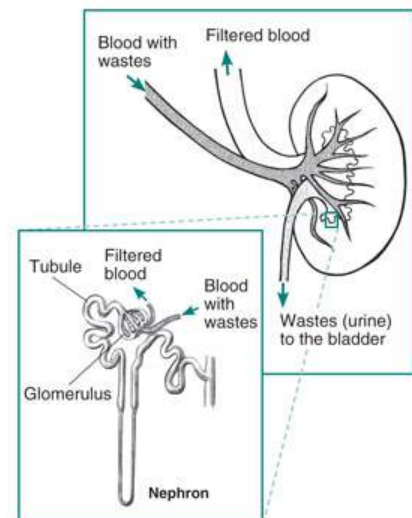
**Figure 2. The urinary system.**

Illustration of the male (left) and female (right) urinary system. Source: National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK).

### HOW DO THE KIDNEYS WORK?

The kidney's primary function is to filter waste products out of the blood. Waste is generated from the chemical reactions that are performed in cells all over the body. The kidney is composed of about 1 million filtering units, called nephrons. The nephron consists of two parts:

- Glomerulus—This is the filter component of the nephron. As blood passes through this filter, waste products from the blood are trapped and excreted through the urethra while blood cells and other large molecules (such as proteins) are retained.
- Tubule—This tube allows for the reabsorption of necessary minerals back into the blood and sends excess fluid and waste to the ureters.



**Figure 3. Path of blood through the kidney.**

Illustration of a kidney showing the vessels that carry blood into and out of the kidney, as well as urine to the bladder. Zoom-in: an illustration of a nephron, the kidney's filtering unit. Source: NIDDK.

#### Did you know?

*The kidneys filter the body's total blood content nearly 40 times per day.*

Quick Facts	Quarts	Gallons
Volume of blood in body	4 – 6	1 – 1½
Volume of blood filtered by kidneys per day	120 – 150	30 – 37½
Volume of urine produced per day	1 – 2	¼ – ½

The kidney performs other essential functions to maintain the following:

- Blood pressure and volume balance
- Bone health and mineral balance
- Red blood cell production

#### BLOOD PRESSURE AND VOLUME BALANCE

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Healthy kidneys maintain fluid balance by removing excess water and sodium from the blood. When the kidneys are damaged, the body retains fluid and swells, which results in high blood pressure.

Conversely, when a person experiences a sudden drop in blood pressure or decreased blood flow through the kidney, such as during periods of dehydration or hemorrhage, the renin-angiotensin-aldosterone system (RAAS) is activated. The RAAS is discussed in greater detail in the Molecular Biology of Disease section on page 26.

#### BONE HEALTH AND MINERAL BALANCE

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Phosphorus, calcium, and vitamin D are necessary for proper bone health. The kidneys play an active role in processing both phosphorus and vitamin D to maintain bone health and overall mineral balance. The kidneys remove excess phosphorus in the blood, which can induce calcium leakage from the bones, leaving them weak and brittle.

Vitamin D helps to maintain proper levels of calcium and phosphorus in the blood. The kidney plays a role in converting vitamin D into its active form (also known as vitamin D metabolism), which helps to control the amount of calcium and phosphorus that the body can absorb from ingested food. When its functioning is compromised, the kidney loses its ability to activate vitamin D, thus resulting in mineral imbalance.

#### RED BLOOD CELL PRODUCTION

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Red blood cells are produced in the bone marrow and are responsible for carrying oxygen to all tissues in the body. Healthy kidneys produce the hormone erythropoietin (EPO), which induces red blood cell production. A hormone is a chemical produced by the body and released into the blood to trigger or regulate particular body functions. Kidney damage leads to a lack of EPO production, resulting in anemia (a condition characterized by low levels of red blood cells). Anemia has pervasive effects throughout the body, because each organ receives less than the amount of oxygen needed to perform at optimal capacity.



## CAUSAL FACTORS, RISK FACTORS, AND PREVENTION

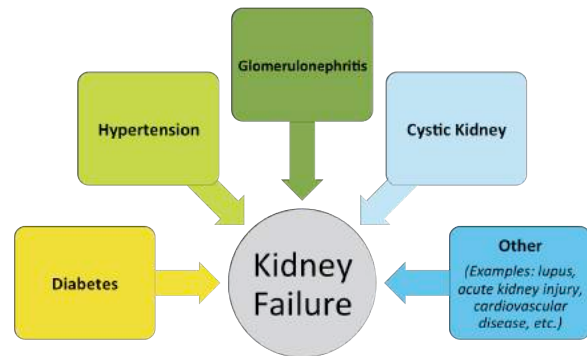
Several diseases and conditions can lead to kidney failure (Figure 4); however, the top two causes are diabetes and hypertension.

In addition, there are several risk factors associated with developing CKD/kidney failure. Both general and genetic risk factors are outlined in detail below.

### GENERAL RISK FACTORS

General risk factors include but are not limited to:

- *Medical conditions*—People living with diabetes, hypertension, other kidney diseases, and cardiovascular disease are at increased risk of developing CKD/kidney failure.
- *Family history*—Those with a family history of CKD/kidney failure are more likely to develop kidney failure.
- *Age*—The incidence and prevalence of kidney failure increases with age. CKD is most prevalent in patients age 60 or older.
- *Sex*—Men are more likely to develop kidney failure than women.
- *Race*—Blacks, Asians/Pacific Islanders, and Native Americans are more likely to develop kidney failure than Whites, at ratios of 3:1, 1.2:1, and 1.2:1, respectively.
- *Ethnicity*—Hispanics are 40 percent more likely than non-Hispanics to develop kidney failure.



**Figure 4. Primary causes of kidney failure.**

Kidney failure is the final outcome of several possible inciting conditions.

Source: Milken Institute Center for Strategic Philanthropy

### GENETIC RISK FACTORS

Recent discoveries indicate that patients who express both possible genetic variants of the apolipoprotein L1 (*APOL1*) gene—G1 and G2—are at increased risk of developing kidney failure due to hypertension and other conditions.

### PREVENTION

Preventing kidney failure is synonymous with preventing either onset or progression of CKD by controlling the diseases or other factors that lead to CKD:

- *Eat a balanced diet* to control blood sugar and cholesterol levels, thereby preventing or controlling the onset of diabetes, hypertension, and CVD.
- *Exercise* to prevent or control the onset of diabetes, hypertension, and CVD.
- *Stop smoking* to avoid development of atherosclerosis, which can decrease blood flow to the kidneys leading to sustained, increased blood pressure.

- *Control blood sugar* to prevent complications from diabetes.
- *Maintain blood pressure* below 130/80.

A significant barrier to effective prevention is a lack of early detection. Several factors contribute to this situation, such as a general lack of awareness by the public about CKD or its diagnosis, absence of symptoms that patients associate with kidney disease, and limited testing strategies to predict and detect declining kidney function. The Barriers to Research Progress and Key Philanthropic Opportunities section on page 33 highlights ways that strategic philanthropy could help move the needle on this pressing issue.

## SIGNS AND SYMPTOMS OF KIDNEY FAILURE

A person living with CKD may not be aware of the presence of disease until it has progressed to the point of kidney failure. This is because a person can lose up to 90 percent of kidney function before feeling any specific symptoms. Table 1 lists the kidneys' functions and the symptoms that result when the kidneys fail to perform these functions.

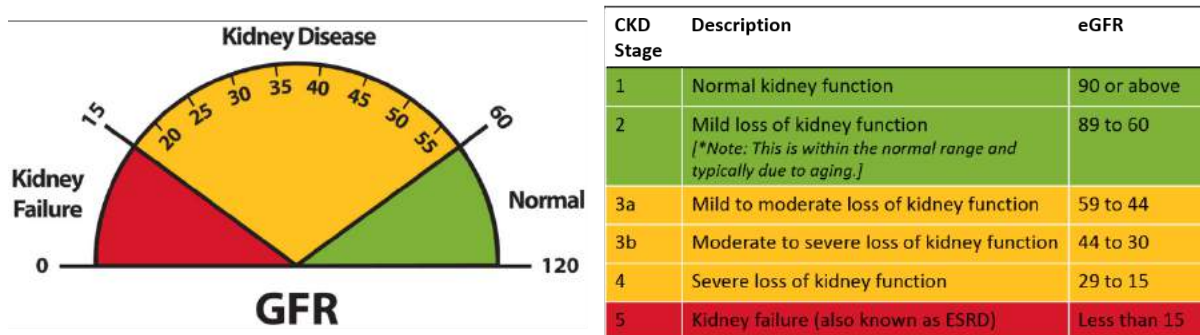
**Table 1. Kidney Function and Symptoms of Kidney Failure**

Kidney Function	Symptoms When Kidney Function Fails
<b>Filter waste products out of the blood (This is the primary function of the kidneys)</b>	Waste products (toxins) accumulate in the blood, possibly leading to the following symptoms: <ul style="list-style-type: none"> <li>• Problems urinating</li> <li>• Itchy, pale skin</li> <li>• Nausea and vomiting</li> </ul> If left untreated, toxin build-up could be fatal.
<b>Regulate blood pressure and volume balance</b>	Failing kidneys lack the ability to remove extra fluid from the blood, possibly leading to the following symptoms: <ul style="list-style-type: none"> <li>• Cardiovascular diseases</li> <li>• Swelling</li> <li>• Shortness of breath</li> </ul>
<b>Maintain bone health and mineral balance</b>	Failing kidneys lack the ability to regulate proper mineral concentrations, possibly leading to bone pain.
<b>Promote red blood cell production</b>	Failing kidneys lose their ability to produce a hormone necessary to make red blood cells. This possibly leads to the following symptoms: <ul style="list-style-type: none"> <li>• Anemia</li> <li>• Fatigue</li> </ul>

## DIAGNOSIS

Kidney failure is currently diagnosed based on the clinical presentation of protein in the urine (known as proteinuria) and the diminished filtration capacity of the kidneys, known as the estimated glomerular filtration rate (eGFR). Therefore, both proteinuria and eGFR are kidney disease biomarkers. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of disease state or treatment efficacy. A biomarker can be detected in biofluids (e.g., blood, urine) and tissues (e.g., kidney, skin). A nephrologist (physician who specializes in kidney diseases) typically diagnoses kidney failure using the following laboratory tests:

- *Urine albumin or protein*—This test analyzes the urine for the presence of protein. When the kidneys are failing, they are unable to reabsorb protein back into circulation, resulting in protein spilling into the urine. Albumin is a specific type of protein, and the tests to measure its abundance are more sensitive for detecting kidney disease.
- *Serum creatinine measurement*—This test is used to detect evidence of increased creatinine in the blood. Creatinine is a waste by-product of muscle metabolism. Healthy kidneys filter out creatinine from the blood into the urine. Elevated creatinine levels signal kidney damage.
  - eGFR calculation—eGFR is calculated using serum creatinine levels and certain formulas that factor in other risk factors such as age, gender, and race. The eGFR calculation is used to determine the stage of CKD as illustrated in Figure 5. It is important to use eGFR, rather than the serum creatinine measurement in isolation, to enable early detection of kidney disease.
  - Cystatin C measurement—This test is used to detect evidence of increased cystatin C in the blood. Cystatin C is an inhibitor of a class of proteins that break down other proteins (known as proteases). Healthy kidneys filter out cystatin c from the blood into the urine. Elevated cystatin c levels signal kidney damage as well. In certain circumstances, the combined measurement of



creatinine and cystatin C can improve the accuracy of eGFR estimation.

**Figure 5. eGFR meter and stages of CKD.**

Meter (left) and corresponding table (right) illustrating eGFR numbers that denote normal, diseased, and failed kidney conditions. Modified and adapted from [NIDDK](#).

A nephrologist may also order the following supporting laboratory tests:

- *Blood urea nitrogen (BUN) measurement*—This test is an indicator of kidney and liver health. Urea nitrogen forms after protein has been broken down. Healthy kidneys filter out urea nitrogen that has

traveled from the liver, into the bloodstream and through the kidney. Higher than normal circulating urea nitrogen levels may indicate kidney damage.

- *Blood pressure*—Elevated blood pressure, together with the other kidney damage indicators listed above, support the diagnosis of kidney failure.
- *Mineral panel*—Failing kidneys can lead to higher than normal circulating levels of calcium, phosphorus, and potassium; therefore, a blood test to detect these minerals can help to assess kidney health.
- *Hematocrit*—Hematocrit is the ratio of red blood cells to the total volume of blood. A low hematocrit score indicates decreased red blood cell content—a sign of anemia.
- *Hemoglobin*—This is the oxygen-carrying protein found in red blood cells. If anemia is present, hemoglobin content will be lower than normal.
- *Kidney biopsy*—In some cases, a biopsy (piece of tissue) is taken for further microscopic examination to determine the extent of kidney tissue damage as well as CKD stage. At a recent National Institutes of Health (NIH) workshop, the lack of kidney biopsies performed was highlighted as a key unmet need in the field. Investigators underscored the need for increased, standardized kidney biopsy practices to fuel research and development efforts in the quest for therapeutic innovation.

## TREATMENT

The only two treatment options available to kidney failure patients are dialysis or kidney transplantation. Although the use of medication to control blood pressure and/or blood sugar can slow the progression through CKD stages 1-4, the damage to the kidneys is permanent. Nevertheless, the patient's kidneys can still perform their key functions to support living. If the patient progresses to kidney failure (CKD stage 5), the kidneys can no longer support life on their own.

Although lifesaving, dialysis and transplantation are fraught with challenges. Regarding the former, the lack of innovation in dialysis care is a large unmet need for the kidney disease field. Regarding the latter, access to donor kidneys is extremely limited, which has motivated the White House to champion efforts to address the donor organ shortage. Both treatment options are described below.

## DIALYSIS

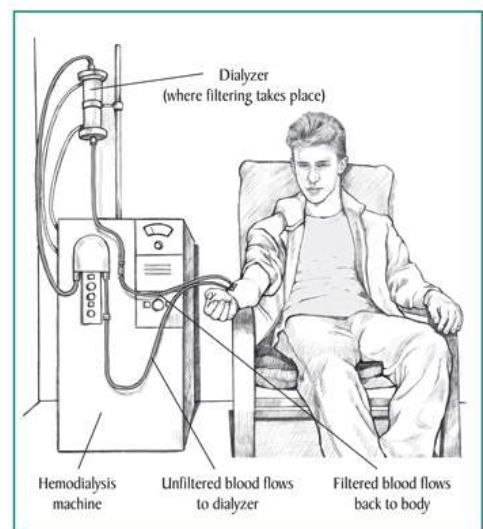
Dialysis treatment involves the use of specialized machinery to filter the blood when the kidneys can no longer do so. There are two types of dialysis: hemodialysis and peritoneal dialysis.

## HEMODIALYSIS

Hemodialysis treatment uses a dialysis machine to clean the total volume of the patient's blood (Figure 6). The patient's blood enters the dialysis machine, passes through the dialyzer (filter serving as the artificial kidney) to remove waste and excess fluid, and then re-enters circulation through a vein. Arteries and veins are two major blood vessels in the body. Arteries take blood away from the heart, and veins take blood back to the heart. About 1 pint (0.125 gallons) of blood flows through the dialysis machine per minute.

In practice, there are two methods of hemodialysis delivery:

- *In-center dialysis*—This method typically involves receiving dialysis treatment in a dialysis center. Treatment is administered three times per week for sessions lasting 3 to 4 hours each.
- *Home dialysis*—This method involves the patient and/or caregiver administering dialysis treatment at home, following thorough training sessions. This process can involve smaller, more portable machines.



**Figure 6. Depiction of hemodialysis process.**  
Source: [NIDDK](#).

Hemodialysis is the most common kidney failure treatment. In 2013, about 88 percent of newly diagnosed patients were treated using this modality. The success of hemodialysis depends on the surgically placed vascular access point from which the blood leaves and returns to the body.

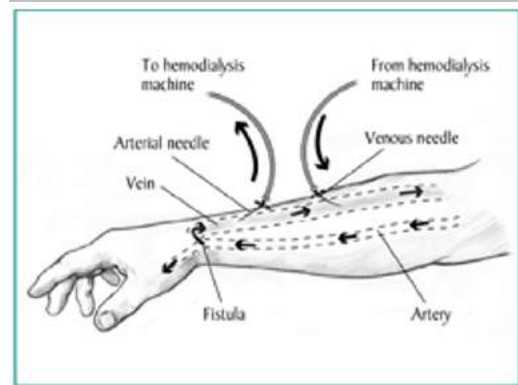
## VASCULAR ACCESS

Accessing the patient's vascular system is critical to dialysis because the vascular system is responsible for circulating blood. For dialysis to occur, the machine's tubes must be connected to the patient's vasculature, which is called vascular access. Figure 7 illustrates the three vascular access possibilities discussed below:

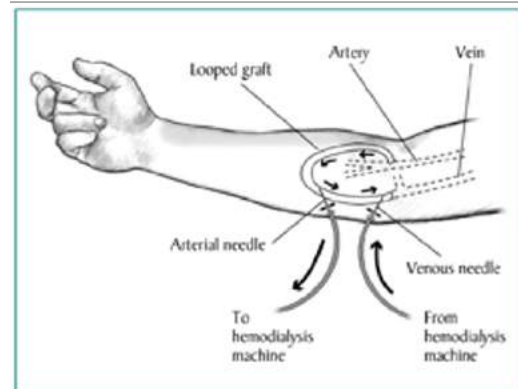
- *Arteriovenous (AV) fistula*—This surgical procedure creates a direct connection between an artery and vein in the forearm. This procedure must be performed 2 to 3 months in advance of use because the AV fistula needs time to develop. The AV fistula is designed for long-term use, typically lasting several years. This is the gold standard for vascular access; however only 17 percent of patients initiate dialysis with an AV fistula due to various contributing factors (e.g., age, vascular health).
- *Arteriovenous (AV) graft*—This tube is surgically inserted under the skin and connects an artery to a vein in the forearm. This procedure must also be performed in advance, about 2 to 3 weeks, of use. During dialysis, this tubing is punctured to connect the machinery to the vascular system. The AV graft is also designed for long-term use, typically lasting about 2 to 3 years. This method is used when a patient is not a good candidate for an AV fistula or when an AV fistula fails.
- *Venous catheter*—This flexible tube is surgically inserted into a vein in the neck, chest, or leg near the groin. The venous catheter is available for use upon insertion; however, it is only intended for short-term use (2 weeks

to a month). A venous catheter is typically used in emergency situations or when kidney disease has progressed more rapidly than expected.

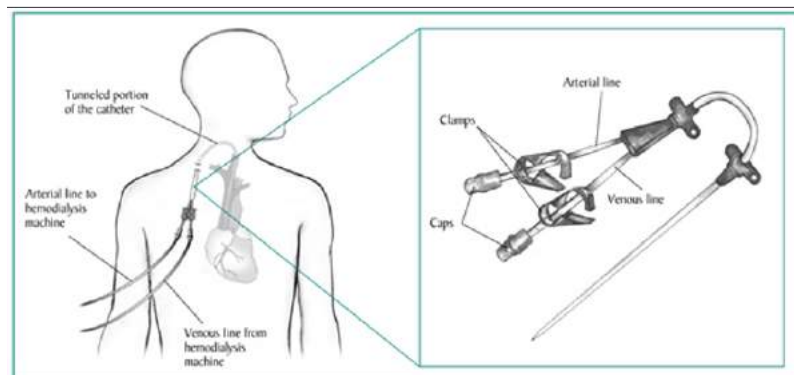
### AV Fistula



### AV Graft



### Venous Catheter



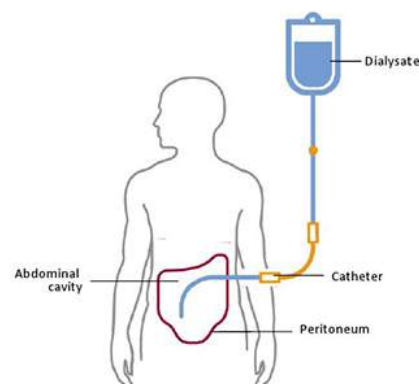
**Figure 7. Vascular access options.**

Depictions of vascular access options, showing common placement locations on the body. Adapted from [NIDDK](#).

## PERITONEAL DIALYSIS

Peritoneal dialysis uses the lining of the patient's abdomen (the peritoneum) as the filter for the patient's blood. This process is illustrated in Figure 8:

- The patient's abdominal cavity is filled with a saline and glucose solution, or the dialysate.
- Waste products and excess fluid are absorbed from the blood into the dialysate after about 4 to 6 hours, which is the dwell time.
- The used dialysate is drained and the stomach is re-filled with fresh dialysate; this exchange typically takes 30-40 minutes to complete.



**Figure 8. Peritoneal dialysis.**

Source: [NIDDK](#).

Most patients typically complete four to six exchanges daily. With continuous ambulatory peritoneal dialysis (CAPD), the exchange is performed manually. With peritoneal dialysis process, a machine (cycler) automatically performs three to five exchanges while the patient sleeps. This is known as automated peritoneal dialysis (APD). Peritoneal dialysis is not as common as hemodialysis. In 2013, a mere 9 percent of newly diagnosed kidney failure patients were treated with this modality. Patients report that CAPD and APD allow for greater flexibility and independence.

## COMPLICATIONS ASSOCIATED WITH DIALYSIS TREATMENT

Dialysis is a lifesaving therapy, in that kidney failure would be fatal without this intervention. Nevertheless, it is a very limited maintenance therapy. The yearly mortality rate is unacceptably high at 15-20 percent. The survival rate for dialysis patients is shockingly low—approximately 55 percent of hemodialysis patients and 66 percent of peritoneal dialysis patients are still living after 3 years of treatment. The dialysis treatment paradigm has improved only modestly over 30 years, and therefore innovation is desperately needed to benefit patients.

Several complications can arise with dialysis—all of which significantly impact QOL. AV grafts and catheters are prone to developing blood clots and infection, leading to hospitalization events. Other complications include narrowing of blood vessels, increased blood pressure, and loss of proper circulation to the arms and legs (extreme cases can result in amputation). AV fistulas are less prone to but not exempt from these complications.

As stated above, several secondary health conditions accompany kidney failure, namely anemia, bone and mineral disease, and CVD. Consequently, patients must undergo treatment for those diseases in addition to their dialysis treatment. Dialysis patients usually take many different medications to overcome these secondary conditions: erythropoietin-stimulating agents (ESA) that boost red blood cell production, intravenous (IV) iron to support oxygen binding to red blood cells, activated forms of vitamin D, blood pressure pills, and drugs that bind phosphorus in food to reduce toxic mineral buildup in the body. Some patients suffering from anemia also undergo blood transfusions; however this treatment can pose challenges for future transplant eligibility because of potential over-sensitization (see Barriers Associated with Kidney Transplantation section below on page 23).



## BARRIERS ASSOCIATED WITH DIALYSIS TREATMENT

Kidney failure treatment exists at the nexus of medicine, clinical research, policy, and economics where there are competing interests and incentives to catalyze change and realize much needed progress. For example, challenges exist with the delivery and frequency of hemodialysis treatment. Scientific evidence indicates that patients fare better when they undergo more than three dialysis sessions per week (which is the current in-center regimen). Patients may receive more frequent dialysis, but they must pay for extra sessions out of pocket because Medicare will only reimburse for the current regimen. Because these patients already incur the highest amount of out-of-pocket costs of all Medicare beneficiaries, extra sessions are likely cost prohibitive for the clear majority of them.

## KIDNEY TRANSPLANTATION

As mentioned previously, the best treatment option for eligible patients with kidney failure is kidney transplantation. Kidney transplantation results in increased life expectancy, QOL, and cost savings for both patients and taxpayers. However, because of the scarcity of available donor kidneys, less than 30 percent of kidney failure patients receive a transplant.

Two types of donors provide kidneys for transplantation:

- A *living kidney donor* donates one functional kidney while still alive. Humans can live with one functional kidney.
- A *deceased kidney donor* has elected to have his or her organ(s) donated upon death.

Upon successful kidney transplantation, the patient must remain on immunosuppressive drugs as long as the transplant is working to ensure that the immune system does not attack the kidney as foreign tissue.

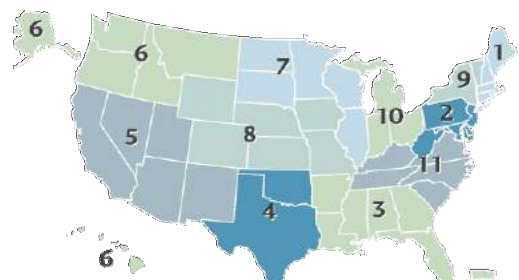
## ORGAN TRANSPLANT WAITLIST

Kidneys are the most transplanted organ in the United States. The organ transplant waitlist, managed by the [United Network for Organ Sharing \(UNOS\)](#), is divided into 11 geographic regions and is used to determine organ allocation throughout the country. Eligible kidney failure patients can elect to be placed on this waitlist and be notified once a kidney becomes available for which they are eligible. Just over 15 percent of all kidney failure patients (nearly 87,000 as of 2013) are listed for a kidney transplant.

The Kidney Allocation System (KAS) guides organ allocation through the United States. Several factors (medical and non-medical) weigh into the allocation of every donated organ, such as blood type, donor/recipient immune system compatibility, prior living donor status, length of time on waitlist, distance from donor hospital, survival benefit, and pediatric status.

Two central changes emerged from significant modification of the KAS in 2015:

- Kidney donors and recipients are now profiled using a different scoring system, and
- The concept of longevity matching of kidneys to transplant recipients was introduced.



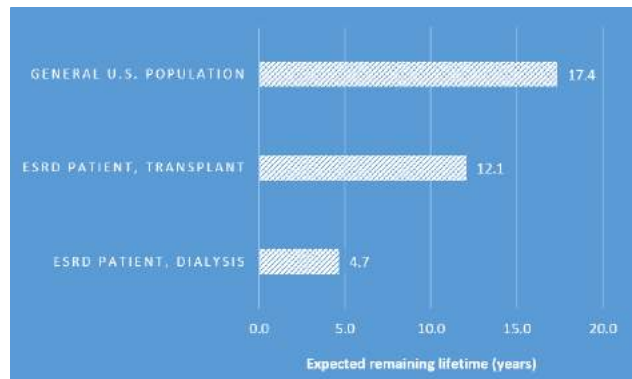
**Figure 9. UNOS regions.**

The U.S. is divided into 11 geographic regions. Source: [HRSA](#).

Deceased donors are assigned a score called the Kidney Donor Profile Index (KDPI). This numerical measure combines 10 donor factors into a single number—as opposed to four factors using the previous system—thereby making it a better predictor of donor quality. Every adult patient on the kidney waitlist is assigned a score called the Estimated Post Transplant Survival (EPTS). KDPI summarizes into a single number the quality of deceased donor kidneys relative to other recovered kidneys. KDPI is now used for the implementation of the “longevity matching,” in which candidates with longer estimated post-transplant longevity (EPTS score of 20 percent or less) will receive priority for kidneys from donors with KDPI of 20 percent.

## COMPLICATIONS ASSOCIATED WITH KIDNEY TRANSPLANTATION

Kidney transplantation is, by far, the best available option to kidney failure patients. In 2012, the probability of survival within 1 year post-transplant was 95 and 98 percent for deceased and living donor kidney transplant recipients, respectively. Furthermore, the remaining life expectancy of kidney transplant recipients ages 65-69 is nearly triple that of dialysis patients as illustrated in Figure 10. However, two major complications still exist with transplantation: the possibility of organ rejection and infection. For the period 2005-2008, survival of the transplanted kidney (called a graft) at 10 years (about 34-48 percent) was much lower than survival at 1 year (89-91 percent), which increases the likelihood of re-transplantation or dialysis. In fact, greater than 20 percent of transplant recipients return to dialysis after 10 years. The immunosuppressive drugs that transplant recipients must take for their remaining lifetime can leave the patient susceptible to infections and certain kinds of cancer. Philanthropy could play a role in efforts to improve transplant therapeutics.



**Figure 10. Expected remaining lifetime of kidney failure patients vs. general U.S. population, by treatment.**

This graph illustrates the remaining lifetime, in years, of kidney failure patients ages 65-69 by treatment modality of prevalent dialysis patients, prevalent transplant patients, and the general U.S. population (2012), based on USRDS data and the National Vital Statistics Report (2013).

## BARRIERS ASSOCIATED WITH KIDNEY TRANSPLANTATION

A record 17,878 kidneys were transplanted in 2015; however, this number pales in comparison to the number of patients awaiting a transplant. Each day, 144 people are added to the organ waitlist and 22 people die while waiting for a lifesaving transplant. For kidney failure patients, mortality on the transplant list is directly related to time on dialysis. Several challenges plague the kidney transplantation field, such as the following:

- *Lack of living donors*—Although living donation is widely accepted by the public, and several surveys suggest that 50-90 percent of people are willing to donate their kidney to a family member or stranger, this does not necessarily translate into organs donated. In 2013, about 5,000 people donated their kidney, which was less than one-third of all kidneys transplanted. Given that transplant recipients fare better with living donor kidneys, measures to facilitate living donation are needed.
- *Patient sensitization*—About 30 percent of transplant patients are sensitized, which affects access to transplantation. Sensitization means that the patient has developed proteins that will attack foreign tissue, like a transplanted organ. These proteins can develop through previous exposure to foreign tissue types, such as through blood transfusions, pregnancy, or previous organ transplants. According to Johns

Hopkins Medicine, sensitized patients may wait three to four times longer than unsensitized patients for a compatible donor kidney.

- *Lack of access due to racial, ethnic, SES, and geographic disparities*—As mentioned above, CKD disproportionately affects racial and ethnic minorities as well as individuals with low SES. Likewise, these individuals have less access to transplantation overall, are less likely to be added to the waitlist, and experience increased risk of transplanted organ failure. In addition, where one lives has a profound effect on transplant access.
- *Limited preservation capacity*—Currently, a kidney can be preserved for a maximum of 24-48 hours. Innovative solutions to increase the organ preservation time would expand access to available organs.
- *Lack of alternative tissue options*—Kidney transplantation is currently limited to organs provided by people; however, bioengineered cells and tissue would greatly expand graft options.
- *High discard rates*—Some of the 2,700 kidneys discarded in 2015 organs could have provided benefits to dialysis patients. Overall, the discard rate remains at about 20 percent.

As the number of patients in need of a kidney transplant continues to rise disproportionately to the number of donor kidneys available, breakthroughs in research and development are sorely needed. This is an area where strategic philanthropic investment could have significant impact—to support innovation in transplant therapeutics, organ preservation, as well as bioengineering of artificial cells and tissues, which may one day be able replace damaged kidney tissue.

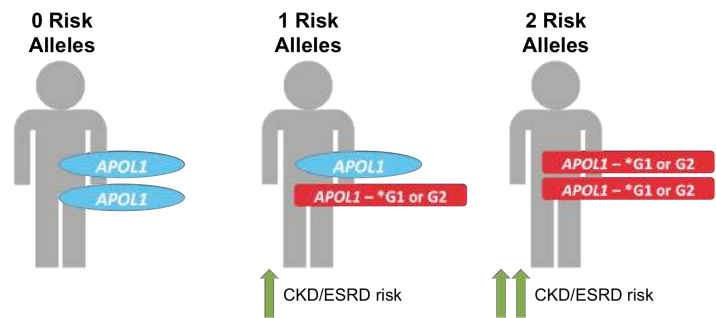
Organ transplantation is a national priority. The month of April was declared National Donate Life month by presidential order in 2015. On June 13, 2016, the Milken Institute Center for Strategic Philanthropy attended the [White House Organ Summit](#), which focused national attention on the current plight of organ donation and transplantation in the United States, as well as facilitated new initiatives, collaborations, and partnerships to aggressively reduce the organ waitlist. There is tremendous opportunity for philanthropy to leverage this national attention and momentum to catalyze change by supporting innovative solutions that reduce the waitlist and research efforts that explore innovative alternatives to conventional kidney transplants.

Surprisingly little is known about what causes kidney failure at a molecular level. As such, targeted therapies are currently nonexistent. There is a clear need to identify and address the challenges to research progress in CKD and kidney failure. Despite the apparent dearth of knowledge, one of the biggest breakthroughs in kidney disease biology exists at the level of genetics.

**APOL1—A KEY GENETIC RISK DETERMINANT IN KIDNEY FAILURE**

There are two copies of each gene in the body (except for the genes that determine sex)—referred to as alleles. Genes code for proteins, which in turn carry out cellular functions. The *APOL1* gene codes for the protein apolipoprotein L1, a component of high density lipoprotein (HDL, the “good” cholesterol).

Apolipoprotein L1 is also found in kidney cells. The two genetic variants of *APOL1*, G1 and G2, are associated with risk to kidney health. Recent scientific evidence indicates that a person who expresses one copy of either variant allele is at an increased risk of developing one of several kidney diseases, including kidney failure. Furthermore, a person who expresses two copies of either variant allele is at an even higher risk, nearly seven to eight fold, of progressing rapidly to kidney failure (non-diabetic, hypertension-associated type). Figure 11 conceptualizes the *APOL1* risk variants and the relative risk associated with their expression.



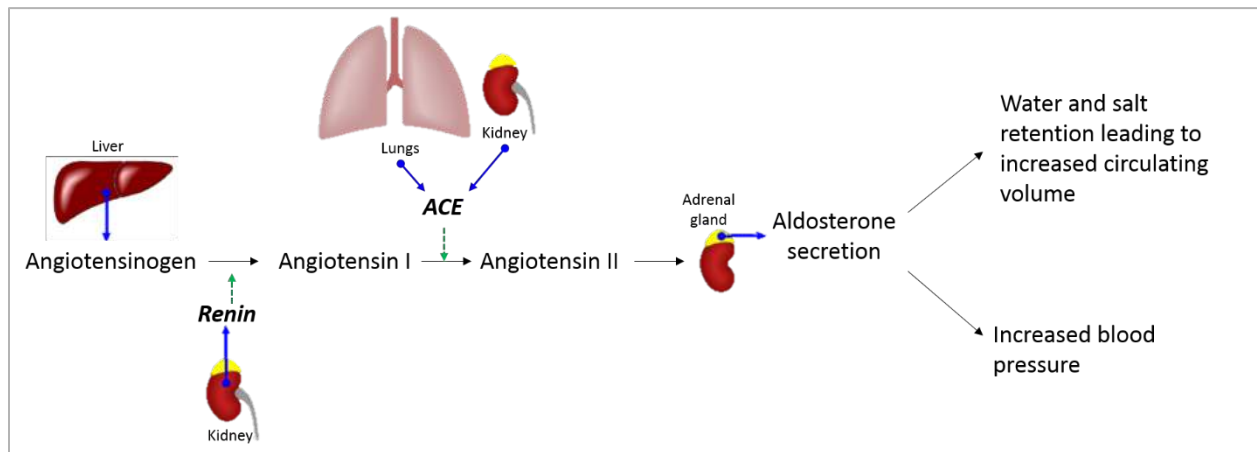
**Figure 11. *APOL1* risk variants and pattern of expression.**  
Source: Milken Institute Center for Strategic Philanthropy

Several experts have postulated that these genetic risk variants partially explain the racial disparity between Blacks and Whites because the G1 and G2 variants are most common in populations of recent African ancestry and occur very rarely in other populations. The field is working to understand this phenomenon at a mechanistic level to understand exactly how these variants contribute to kidney disease. In a recent article published in the *Proceedings of the National Academy of Sciences*, Olabisi and colleagues describe a potential mechanism for how *APOL1* gene variants cause toxicity within the cell, eventually leading to cell death. They demonstrate that *APOL1* risk variants overactivate certain proteins that are known to mediate kidney injury. This and other future discoveries may provide the field with potential therapeutic targets for future research and development efforts.

The science underlying kidney failure is unfolding; however, controversy and unanswered questions remain despite this intense study. In a 2013 article in the *Journal of Clinical Investigation*, Friedman and Pollak highlight that, although the relative risk of developing kidney failure is significantly higher in *APOL1* risk variant carriers, their presence is not sufficient to cause disease. It is highly likely that other genetic and environmental contributors modify the expression of the *APOL1* risk variant profile. Kidney failure is a complex disease caused by a myriad of conditions that affect total body metabolism. Therefore, it is likely that other molecular and environmental factors contribute to this disease. It is extremely difficult to isolate causal molecular interactions with so many comorbidities. However, identification of *APOL1* risk variants represents the greatest molecular discovery in the field to date.

## THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)—A THERAPEUTIC TARGET

The RAAS is a hormone system that regulates blood pressure, fluid volume, and sodium content in the body as illustrated in Figure 12. The kidneys produce renin and angiotensin-converting enzyme (ACE), proteins that catalyze complex biological reactions (enzymes). Renin and ACE drive the creation of angiotensin I, II, and aldosterone in the body. Together, angiotensin II and aldosterone work to raise blood volume, blood pressure, and sodium levels in the blood to restore the balance of sodium, potassium, and fluids. However, chronic overactivation of the RAAS can lead to hypertension. Blockade of the RAAS slows the progression of proteinuria-associated kidney disease. These important molecules in the RAAS represent therapeutic targets of currently used drugs (such as ACE inhibitors and angiotensin II receptor blockers [ARBs]) and experimental drugs in clinical trials.



**Figure 12. The renin-angiotensin-aldosterone system (RAAS).**

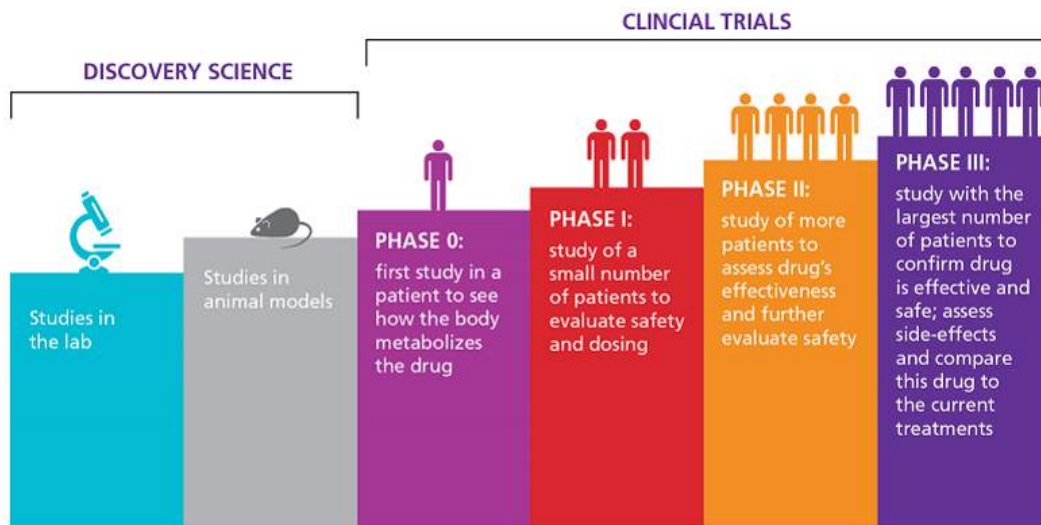
Renin and angiotensin-converting enzyme (ACE) are two key proteins that are secreted from the kidney to drive aldosterone secretion. Aberrant, chronic overactivation of this system can lead to high blood pressure and other deleterious effects. Drugs commonly used to target this system, such as ACE inhibitors and ARBs, are often used to treat CKD. Image modified from [Wikimedia Commons](#).

### CLINICAL TRIALS—OVERVIEW

Clinical research (also referred to as clinical development) is a branch of biomedical research involving human subjects. The goal of clinical research is to evaluate the safety and efficacy of drugs, medical devices, or diagnostics intended for use in human patients.

Clinical trials are an important component of clinical research because they are used to evaluate the safety and efficacy of an experimental drug or therapy in human subjects. Clinical trials are divided into phases as described in Figure 13. They can also be used to collect specimens from human subjects for further research. Importantly, information on potential side effects are gathered during the clinical trial period and weighed against the potential therapeutic benefit of the treatment under investigation.

The research and development (R&D) process—the process by which a laboratory discovery is developed into a commercial therapeutic, diagnostic or device—is very costly and time-intensive. It is estimated that 95 percent of new drugs tested in clinical trials fail to make it into the clinic. This is a high failure rate for a process that costs about \$1 billion in overall research costs and up to 15 years of time invested.



**Figure 13. Phases of clinical trials.**

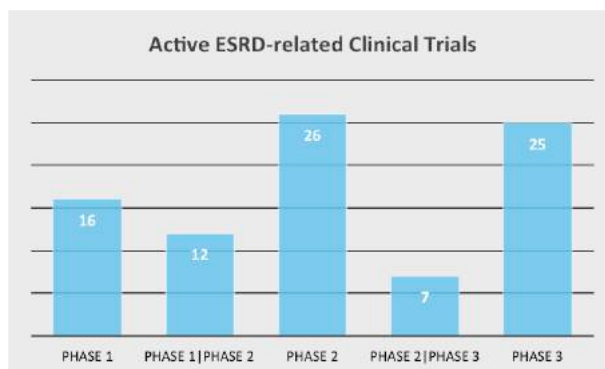
**During Phase I**, researchers test a new drug or treatment for the first time in a small group of people to evaluate its safety, determine a safe dose range, and identify potential side effects. **During Phase II**, proof-of-concept studies are performed as the drug or treatment is given to a larger group of people to determine the effective and optimal dose. **During Phase III**, the drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, and assess its impact compared to the current standard of care. Some clinical trials involve multiple phases to facilitate seamless transition from one to another and are written as **Phase I/II** or **Phase II/III**. These designations are also used in adaptive trials, wherein study parameters are modified with respect to ongoing trial results. Image courtesy of Dr. Jason Luke, University of Chicago School of Medicine.

## KIDNEY FAILURE CLINICAL TRIALS

As of July 2016, there are 90 active interventional clinical trials for kidney failure. Figure 14 illustrates the distribution of these trials by phase.

Kidney failure clinical trials are expensive and inherently risky for several reasons:

- **Time needed to complete a study**—Large patient populations, often numbering in the thousands, need to be followed for long periods of time to capture specific effects above conventional therapy.
- **Lack of reliable biomarkers to predict adverse safety events**—Investments in clinical trials could be more appropriately allocated if there was a reliable way to predict safety. According to experts, too many large trials have failed because of an inability to predict drug safety.
- **Heterogeneous nature of the disease**—Several disease paths lead to kidney failure, which in turn leads to remarkable heterogeneity in the presentation of CKD patients. However, the probability of success would increase if there were a reliable way to identify and selectively enroll CKD patients who are likely to progress to kidney failure (i.e., “strong progressors”). Patient heterogeneity can have negative effects on study results. Testing a uniform group of patients would prevent dilution of treatment effect and enable fast recognition of effective treatments. This issue highlights the need for better patient stratification to ensure that investigational treatments are applied to the right patients.



**Figure 14. Interventional clinical trials for kidney failure.**

Of the 90 active, interventional clinical trials, 25 (28%) are in Phase 3. Data obtained from [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Source: Milken Institute Center for Strategic Philanthropy

Despite the myriad of challenges, there are numerous opportunities for improvement in the kidney disease field. Philanthropy is uniquely poised to de-risk kidney disease research efforts and thereby attract industry investment to spur advances. Furthermore, strategic investment in critical resources and infrastructure will allow for acceleration of promising science from basic research, through the critical translational research phase, and into clinical development.

## INVESTIGATIONAL THERAPIES

The clinical development landscape is incredibly barren because of the paucity of clinically relevant molecules to target therapeutically. Most drugs were developed to treat other conditions, such as hypertension and diabetes, and adopted to treat kidney disease. Furthermore, the vast majority of kidney failure clinical trials test treatments of the complications associated with kidney failure and optimization of dialysis and transplant therapeutics.

The development of new drugs for kidney failure presents some interesting economic challenges as well. Medicare reimburses the cost of drugs as a bundled payment, defined as a reimbursement to healthcare providers “on the basis of expected costs for clinically-defined episodes of care.” Therefore, there is incentive for a pharmaceutical company to have its drug covered within the bundled payment system to realize any appreciable profits. However, the stakes to get a new drug covered in the bundled payment are high—the drug must have demonstrated efficacy



that far exceeds those for drugs already covered. Therefore, this high barrier of entry may disincentivize companies from innovating and creating new therapeutics.

The value proposition needs to be modified to align interests in search of better therapeutics to improve QOL for patients. Strategic philanthropic investment is uniquely poised to address these challenges because it is nimble enough to respond to dynamic changes within the kidney disease space.

Given the lack of innovation in pharmaceutical clinical development, the sections below provide the conceptual framework for a few new medical devices in development as well as highlight key initiatives presented at the White House Organ Summit that have potential for high impact.

## MEDICAL DEVICE DEVELOPMENT

Below are profiles of devices that aim to improve dialysis options by adding desired features (e.g., portability) or resolving vascular access complications (e.g., decreasing clot formation).

### WEARABLE ARTIFICIAL KIDNEY PROTOTYPE IN DEVELOPMENT

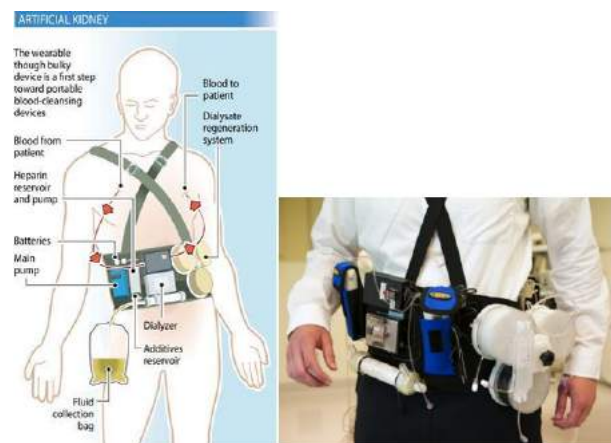
Standard dialysis generally involves attaching patients to an immovable dialysis machine (either at home or in a clinic) for sessions that range from 3 to 4 hours. Standard practice recommends dialysis three times per week. New research suggests that daily dialysis results in a considerable improvement in QOL, resulting in:

- Substantial reduction in complications such as anemia, hypertension, electrolyte abnormalities, and acid buildup in the body
- Attenuation of the need for additional medication to treat the aforementioned complications
- Fewer hospitalizations
- Fewer diet and fluid restrictions
- Increased appetite

A wearable artificial kidney (WAK) device, which would allow for daily dialysis, is currently in development and has passed an U.S. Food and Drug Administration (FDA)-approved proof-of-concept clinical trial involving seven patients. The FDA selected the WAK for a fast-track approval program in 2012. The present prototype (Figure )

is a 10-pound device, powered by 9V batteries and worn around the waist. The WAK prototype is being redesigned to decrease the size and improve efficiency and will undergo additional safety testing.

Transition to a daily dialysis model using a WAK device could lead to improved patient mobility and psychological well-being in addition to the benefits listed above. The WAK would provide a promising treatment option, in the face of low availability of kidneys for transplantation, ushering in a fundamental shift in care delivery. Apart from the clear medical benefits, this promising technology stands to substantially decrease the economic burden of dialysis treatment by reducing the number of hospitalization events.



**Figure 14. Wearable artificial kidney (WAK).** Left: Illustration ([Source](#)). Right: Person wearing the prototype ([Source](#)).

## IMPLANTABLE BIOARTIFICIAL KIDNEY—THE KIDNEY PROJECT PROTOTYPE IN DEVELOPMENT

Currently, the best treatment option for kidney failure is kidney transplantation; however, because of the limited availability of kidney donors, less than 30 percent of kidney failure patients receive a transplant. As the number of patients in need of a kidney transplant continues to rise disproportionately to the number of donor kidneys available, there is a tremendous need for an alternative medical solution.

The implantable bioartificial kidney represents a promising alternative to conventional kidney transplants that:

- Addresses the organ scarcity issue
- Eliminates the need for conventional dialysis
- Could attenuate the need for lifelong immunosuppression therapy that is required for conventional transplants to ensure that the body does not reject the kidney

This prototype device is designed to connect directly to the patient's blood supply and bladder (the other key components of the body's waste removal system), near the natural kidneys, which will not be removed (see depiction in Figure 15). Using novel silicon nanofilters and living kidney cells, the device is designed to operate based on the patient's blood pressure alone, without the need for a pump or an electrical power source. Government and private sources have funded the Kidney Project since its inception. Recently, the National Institutes of Health (NIH) awarded the project with a 4-year, \$6 million grant. The FDA also selected the Kidney Project for a fast-track approval program in 2012. If successful this device could dramatically change and save the lives of millions of patients and could become an integral part of the kidney care setting—similar to the pacemaker in the cardiology care setting.

## HEMOACCESS VALVE SYSTEM® (HVS) PROTOTYPE IN DEVELOPMENT

As discussed above, access to the patient's vascular system is critical to dialysis because the vascular system is responsible for pumping blood. For dialysis to occur, the machine's tubes must be connected to the patient's vasculature.

AV grafts are fraught with complications in addition to infection and blood clotting, such as narrowing of blood vessels, increased blood pressure, and loss of proper circulation to the arms and legs (extreme cases can result in amputation). These complications are due in large part to continuous blood flow through the graft. However, blood flow through a graft is only needed for dialysis purposes, which is, at most, 12 hours per week, as opposed to 24 hours a day.

Limiting blood flow through an AV graft to only the times when needed for dialysis treatment can benefit the patient by extending the life of the blood vessels near the graft site and preventing vein collapse at the patient's primary access point for dialysis. The HVS in development (Figure 16) allows for selective blood flow control through an AV graft only when needed for dialysis and then turns off the blood flow to the graft between dialysis

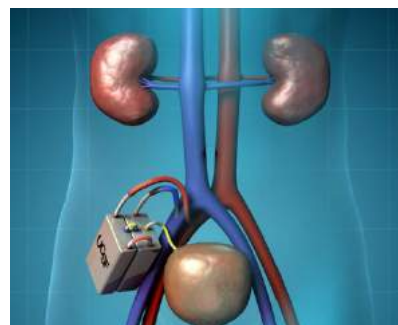


Figure 15. Implantable bioartificial kidney.

Source: [UCSF](#).

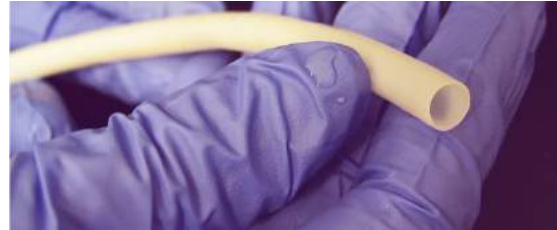


Figure 16. Hemoaccess Valve System®.  
Source: [Source](#).

sessions. The HVS was also selected by the FDA for a fast-track approval program in 2012 and is currently in clinical trials.

### **TISSUE-ENGINEERED VASCULAR GRAFT—HUMAGRAFT™** *PROTOTYPE IN DEVELOPMENT*

The repetitive complications associated with AV grafts result in increased hospitalization events and decreased overall QOL. The synthetic materials used to make AV grafts, such as Teflon® or polytetrafluoroethylene (PTFE), are often blamed for the repetitive infections associated with traditional AV grafts. Use of a human tissue platform could eliminate the adverse reaction to synthetic materials but could introduce issues with tissue matching. HumaGraft™ is a human bioengineered blood vessel that could deliver a tissue-based graft that does not require tissue matching, resulting in the following:



**Figure 17. HumaGraft™.**  
Source: [Humacyte](#).

- Longer graft life
- Low risk of infection and blood clots
- Low risk of adverse immune responses

The HumaGraft™ prototype is a bioengineered vein composed of human smooth muscle cells (Figure 17), which are decellularized to reduce immunogenicity and eliminate the need for tissue matching. These bioengineered veins demonstrated excellent blood flow and resistance to blood clots in early lab testing, and they could be refrigerated for up to 12 months—making them viable for long-term storage at hospitals. The HumaGraft™ was selected for fast-track approval status by the FDA in 2014 and is currently in Phase III clinical trials.

## **PUBLIC HEALTH MEASURES**

### **PUBLIC HEALTH INITIATIVES**

In response to the substantial impact of CKD and kidney failure on health, QOL, and healthcare costs, a variety of public health initiatives are in place to help reduce the prevalence of CKD and kidney failure in the U.S. population and promote access to quality care.

### **ESRD NETWORKS**

The [ESRD Networks](#) of the Centers for Medicare & Medicaid Services (CMS) were created by statutory mandate in 1978 to improve cost-effectiveness, ensure quality of care, encourage kidney transplantation and home dialysis, provide assistance to ESRD beneficiaries and providers, and increase ESRD Network Program accountability.

In 2015, the CMS awarded \$110 million in ESRD Network funding to 7 of the 18 ESRD Networks. These 7 entities will work over a 5-year contract period to continue efforts to improve quality of care and access to care for individuals with irreversible kidney disease who require dialysis or transplantation to sustain life.

## HEALTHY PEOPLE 2020

[Healthy People](#) is a national program to provide science-based, 10-year national objectives for improving the health of all Americans. This program has been in place for 30 years, with the most recent launch in 2010.

CKD claims 14 objectives in this ambitious program, one of which is specifically dedicated to reducing deaths in persons with ESRD (objective CKD- 14). The initiative seeks to accomplish this objective by reducing the:

- Total number of deaths for persons on dialysis
- Number of deaths in dialysis patients within the first 3 months of initiation of renal replacement therapy
- Number of cardiovascular deaths for persons on dialysis
- Total number of deaths for persons with a functional kidney transplant
- Number of cardiovascular deaths in persons with a functional kidney transplant

## CKD SURVEILLANCE SYSTEM

In collaboration with the University of California at San Francisco and the University of Michigan, the CDC implemented the national [CKD Surveillance System](#). The system tracks national trends in the number of cases, risk factors, and care practices that affect CKD prevention and control, evaluate quality improvement efforts, and monitor kidney disease objectives for Healthy People 2020 (described above). Systematic monitoring would inform efforts to prevent, detect, and manage CKD and its complications. These data also inform evaluations of the efficacy and impact of various government quality improvement programs.

Organizations involved in this effort include University of California at San Francisco, the University of Michigan, American Association of Kidney Patients (AAKP), American Association of Pediatric Nephrology (AAPN), National Kidney Disease Education Program (NKDEP), National Kidney Fund (NKF), Veteran's Health Association (VHA) National Program, Medical Education Institute, and the American Society of Nephrology (ASN).

## CKD HEALTH EVALUATION AND RISK INFORMATION SHARING (CHERISH)

In collaboration with NKF, the CDC established CHERISH to identify individuals at high risk for CKD, assess the participant's access to follow-up care, and examine disease progression in those with CKD.

Using national datasets such as the United States Renal Data System (described below), the CDC studies the epidemiology of CKD in the U.S. population. Under this program, the CDC also collaborates with the VHA to study health outcomes and the national history of CKD among various subsets of the population.

## UNITED STATES RENAL DATA SYSTEM (USRDS)

The [USRDS](#) is a national data system that collects, analyzes, and distributes information about ESRD in the United States. The USRDS is funded directly by the NIDDK. USRDS staff collaborate with members of CMS, UNOS, and the ESRD networks by sharing datasets and actively working to improve the accuracy of ESRD patient information.

## BARRIERS TO RESEARCH PROGRESS AND KEY PHILANTHROPIC OPPORTUNITIES

In October 2016, the Milken Institute Center for Strategic Philanthropy convened world-renowned kidney experts to discuss the state of science relevant to CKD and kidney failure, as well as the challenges currently impeding progress toward improved therapeutics and care. The ultimate goal of the retreat was to identify high-impact research and systems opportunities where philanthropic investments could accelerate progress in the CKD/kidney failure space.

Key challenge areas include the following:

DISEASE AWARENESS AND WORKFORCE CHALLENGES	TRANSPLANTATION AND DIALYSIS INNOVATION NEEDS	LIMITED DISEASE UNDERSTANDING
<i>Lack of disease awareness and education by physicians, systems, and patients</i>	<i>Scarcity of donor organs</i>	<i>Lack of molecular disease biomarkers</i>
<i>Kidney disease research workforce shortfall</i>	<i>Inadequate long-term transplant outcomes</i>	<i>Operational challenges to conducting successful clinical trials</i>
	<i>Lack of innovation in kidney replacement therapy</i>	

The sections below discuss each of the key challenges along with potential solutions and corresponding philanthropic opportunities to address these challenges and accelerate research progress. *Please note that these opportunities are high-level representations and should be considered carefully with respect to your philanthropic goals and discussed in detail with a philanthropic advisor.*

## DISEASE AWARENESS AND WORKFORCE CHALLENGES

### LACK OF DISEASE AWARENESS AND EDUCATION

#### THE PROBLEM

**Most patients are not diagnosed with CKD until the disease reaches advanced stages (kidney failure), even though relatively simple tests to detect earlier stages of kidney disease exist** (e.g., measuring creatinine levels in the blood to estimate GFR and/or albumin levels in the urine). This problem partially results from a general lack of awareness of the importance of monitoring kidney health because of the asymptomatic nature of CKD. Many patients with CKD risk factors may not be screened at early stages of CKD when progression may be slowed or prevented, or referred in a timely manner to specialty care. In some cases, patients may have had kidney tests performed (see the Diagnosis section on page 17); however, the physician or patient may be unaware. The lack of awareness and inequities in education disempower patients as well as providers, resulting in a lack of engagement and suboptimal QOL.

#### PROPOSED SOLUTIONS TO ADDRESS THE CHALLENGE

Facilitating efforts to educate the public on CKD risk factors, disease course, early diagnosis, and available treatment options would encourage a shift from being reactive to proactive about CKD diagnosis and treatment. Likewise, providing primary care physicians (PCPs) with the tools to proactively monitor kidney health and educate patients will further encourage a shift, thereby empowering both patients and providers.

## CORRESPONDING PHILANTHROPIC OPPORTUNITIES

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- **Fund targeted public awareness campaigns**—Raising awareness of CKD/kidney failure is the first step toward raising the national profile of the disease state, which fuels policy reform and attracts funding dollars for research and therapeutic development. Various disease communities (e.g., heart disease, HIV/AIDS, diabetes, cancer) have successfully implemented this lesson and offer several examples and lessons learned from which the kidney disease community can benefit. With evolving social media and gaming technologies, these campaigns could utilize novel approaches to promote awareness.
- **Engage patients to advocate for improved, patient-centered services at all stages of CKD—analogue to other high-profile diseases (e.g., HIV/AIDS, breast cancer, diabetes, ALS)**—Increasing patient engagement and advocacy is the second step toward raising the national profile of the disease state. Again, there are key lessons to be learned from disease communities that have robust advocacy programs. Intentionally engaging disproportionately affected minority groups, as other successful communities have done, is a necessary step forward. In addition, successfully engaging patients may require use of more accessible terms (e.g., use of “kidney” rather than “renal”) as well as terms that carry less stigma (e.g., use of “kidney failure” rather than “end stage renal disease”).
- **Support bioinformatics infrastructure that will enable innovative use of electronic medical records (EMRs)**—EMRs contain valuable, extractable information that can be utilized to create tools for early detection of kidney disease and identify patients at increased risk for kidney failure. Leveraging of this wealth of data would provide an invaluable tool for providers. However, lack of EMR database interoperability across hospitals and the lack of bioinformatics tools to easily and effectively mine EMR data pose challenges to successful data aggregation, harmonization, and standardization. Funding an infrastructure platform to address these challenges would facilitate creation, evaluation, and dissemination of new CKD decision aids for providers, even in low-resource settings.
- **Support a resource development consortium**—To avoid duplicative efforts and to better utilize existing resources, this consortium would be charged with standardizing and disseminating existing educational tools for trainees, providers, insurers, and patients. This process of resource development would clarify treatment options and clinical trial applicability based on patient needs. Likewise, it would encourage earlier discourse between patients and providers, allowing for more informed decision-making.

## KIDNEY DISEASE RESEARCH WORKFORCE SHORTFALL

### THE PROBLEM

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***The growth of the nephrology workforce has not kept pace with the global incidence of CKD/ESRD.*** A confluence of factors disincentivize physicians and scientists from pursuing a nephrology specialty, including but not limited to its perceived difficulty, lack of innovation in treatment paradigms, polarizing payer and policy dynamics (that are perceived to stifle creativity), and a lack of interest from the pharmaceutical and biotech industries. Despite the complex nature of the disease and ecosystem dynamics, a new influx of ideas would create the innovative culture necessary to move the field forward.

## PROPOSED SOLUTIONS TO ADDRESS THE CHALLENGE

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Investment in human capital that will foster a culture of innovation, facilitate new ideas and knowledge sharing, collaborate in research activity, and improve care practices is desperately needed to propel the field forward. Together these outcomes can lay the groundwork for the development of new treatments. This culture shift would also encourage other stakeholders to invest in the field as innovative solutions begin to bear fruit.

## CORRESPONDING PHILANTHROPIC OPPORTUNITIES

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- **Endow an annual Kidney Disease Summit**—Establishing an annual summit of leading multidisciplinary experts to create a vision for future renal therapies would facilitate more cross-talk within the various nephrology communities (e.g., dialysis, transplantation, basic and translational science, R&D), outline critical paths for the field, and galvanize the community to develop innovative solutions.
- **Endow a network of professorships in kidney disease and transplant innovation**—This global network of faculty would use these endowed professorships to focus on mentorship and novel kidney disease or transplant research. A built-in mentorship component would foster community-building and career development for junior faculty, thus preparing them to serve as future leaders and mentors.
- **Fund training fellowships in kidney disease to attract physician-scientists**—Grants to support fellowship stipends or provide bridge funding for young investigators would encourage them to enter and continue working in the nephrology space.

## TRANSPLANTATION AND DIALYSIS INNOVATION NEEDS

### SCARCITY OF DONOR ORGANS

#### THE PROBLEM

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**Kidney transplantation is, by far, the best available treatment for kidney failure.** Not only does transplantation correlate with better survival rates and improved QOL compared to dialysis, but also it reduces costs for insurance providers. Despite these obvious benefits, several limitations hinder innovation in kidney transplantation (listed in detail in the Barriers Associated with Kidney Transplantation section on page 23). Key barriers include:

- **Access to transplant**—Multifactorial and systemic issues contribute to disparities in transplant access, such as low SES, race, ethnicity, and geographic location.
- **Barriers to living donation**—There are approximately 100,000 ESRD patients on the transplant waitlist, but only about 6,000 live donor transplants per year. Living donors could help fill the organ shortage gap. Barriers to donation include biological incompatibilities of donors with their intended recipient, financial burdens of donation, and concern for donor health risks.
- **Variable high-risk protocols across clinics**—Great strides have been made in desensitization protocols, which allow for successful transplants of previously incompatible kidney donor-recipient matches, thereby expanding transplant options. However, these procedures vary from clinic to clinic, which leads to variable success rates.



## PROPOSED SOLUTIONS TO ADDRESS THE CHALLENGE

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Funding innovative, nontraditional efforts to expand access to transplantation, increase living kidney donation, and invest in artificial kidney development could address the organ scarcity issue. The potential for short- and long-term gains exist because a range of mechanisms are available to address this challenge. In addition, improved transplant outcomes can be achieved by standardizing the desensitization protocols. This standardization can lead to more efficient outcomes tracking and support iterative protocol improvement, thereby reducing the disparities in success rates across centers nationwide.

## CORRESPONDING PHILANTHROPIC OPPORTUNITIES

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- **Fund start-up costs for a centralized national kidney exchange program**—Kidney paired donation programs facilitate exchanges between incompatible donor-recipient pairs. These efforts are currently decentralized, which can lead to different kidney-exchange chains competing for potential donors, thereby decreasing the donor pool. Centralizing the kidney exchange platform would help maximize the number of swaps that could be made within a given chain.
- **Fund start-up costs for a living donor registry**—The creation of a data-rich, technologically advanced live donor registry would inform understanding of the long-term risks and outcomes associated with kidney donation and would facilitate early recognition and interventions when a donor is at increased risk for kidney failure. Current tracking systems lack the robustness to facilitate the desired level of detection, analysis, and engagement.
- **Fund a pilot program that covers lost wages and other uncompensated expenses for living donors**—Although travel, lodging, and dining expenses may be covered for prospective live donors under the government-funded program called National Living Donors Assistance Center (NLDAC), this program is limited to patients who qualify based on income criteria for both the donor candidate and the intended recipient. Financial burdens, including lost wages, remain an important disincentive to expanding live kidney donation. Pilot studies testing this hypothesis would provide the cost-benefit analysis to substantiate increased funding for the NLDAC program or establish similar programs through nonprofit foundations.
- **Fund wide dissemination of novel donor engagement programs**—Social media apps have emerged as a creative tool to engage potential kidney donors; however, these apps are often decentralized and usually confined to one transplant center. Support for widespread dissemination and adoption could have a substantial impact by facilitating donor engagement, sharing education, and emphasizing the need for living donation.
- **Support the development of a master desensitization protocol to improve donor compatibility**—The development of a master protocol would accelerate dissemination of procedures among transplant centers, promote higher success rates nationwide, and provide a platform to foster development of future improved protocols.
- **Invest in research and development of bioartificial kidneys**—There is great promise in a future when bioengineered kidney tissue and/or organs are a viable reality, because they would lessen the reliance on donated kidneys, attenuate the need for lifelong immunosuppression therapy, and eliminate the need for conventional dialysis. This work remains in the early stages of development, so philanthropic capital would accelerate the timeline and spur innovation in this space.

## INADEQUATE LONG-TERM TRANSPLANT OUTCOMES

### THE PROBLEM

**Although the 1-year transplant success rate is about 90 percent, the 10-year success rate is much lower at 34-48 percent.** Several factors contribute to this disparity, including the challenge of appropriate tailoring of immunosuppression to maintain efficacy and reduce morbidity, and the financial burdens for transplant recipients post-procedure. Overall, immunosuppression is largely administered in a “one-size fits all approach,” such that some patients face risk of rejection and immunological graft loss, while others suffer complications of over-immunosuppression (e.g., infection, cancer). Novel approaches are needed to identify markers for transplants that are “at risk,” to better personalize immunosuppression to avoid irreversible injury and excess immunosuppression. Furthermore, for many patients, Medicare pays for immunosuppression medications for only the first 3 years, after which patients must pay for the medications out of pocket. This financial burden can cause patients to discontinue their medications or take them inconsistently, which dramatically compromises long-term success rates for transplant patients. Overall, measures to address these and similar factors may bolster long-term success rates.

### PROPOSED SOLUTIONS TO ADDRESS THE CHALLENGE

Better long-term transplant outcomes would lead to improved QOL for transplant recipients and overall savings to the healthcare system—potentially more than the estimated \$50,000 cost savings of transplant over dialysis. Piloting long-term immunosuppression support programs that are hypothesized to increase long-term success rates would provide the needed evidence to attract Congressional support.

### CORRESPONDING PHILANTHROPIC OPPORTUNITIES

- **Support a pilot study assessing the cost-benefit analysis for extended tolerance medications coverage**—Payers currently cover tolerance medications for only 3 years post-transplant. This study would investigate whether long-term coverage does in fact increase long-term graft survival and reduce the overall cost of care (as a return to dialysis treatment is a costly procedure). Such evidence would inform payers and provide support for expanded coverage options.
- **Support exploration of new markers of “at-risk” organ transplants before irreversible injury**—Serum creatinine is crude marker of transplanted organ function; however, it is not sensitive to subtle organ injury, which can lead to chronic rejection. Supporting the development of new biomarkers for early rejection may facilitate better immunosuppression personalization to maintain efficacy and reduce morbidity.

## LACK OF INNOVATION IN KIDNEY REPLACEMENT THERAPY

### THE PROBLEM

Dialysis treatment is in dire need of innovation as the technology has not improved significantly over the past thirty years. Although dialysis is a life-saving option in the short-term, it has negative long-term impact with an annual mortality rate of 15-20 percent. Treatment delivery and venous access are two main challenge areas to be addressed.

- *Treatment delivery* – Standard hemodialysis generally involves patients being attached to an immovable dialysis machine (either in a clinic or at home) for sessions that range between 3-4 hours, three times per week. This practice often leaves patients too tired to live fully productive, independent lives. Research suggests that more frequent dialysis may be beneficial to patients, however this is impractical within the current paradigm.
- *Venous access* – Achieving long-term vascular access (e.g. fistula or graft) is central to hemodialysis, however the primary failure rates leave several patients using short-term alternatives (e.g. central venous catheters [CVCs]). Prolonged use of short-term venous access options lead to complications, such as infection and hospitalization, which compromise successful dialysis treatment.

## POTENTIAL SOLUTIONS TO ADDRESS THE CHALLENGE

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Device innovation to support more frequent ambulatory dialysis and long-term venous access patency would drastically improve dialysis treatment. Further, fostering a community for innovation would provide the momentum necessary to bring novel, bold ideas to fruition.

## CORRESPONDING PHILANTHROPIC OPPORTUNITIES

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- ***Endow an annual Kidney Replacement Summit***—Efforts to radically re-imagine and re-invent dialysis machinery and conceive of completely novel alternatives will require collaboration across disparate disciplines (e.g., nephrology, bioengineering, cell biology). An annual summit specifically dedicated to this purpose will provide the space to create a vision and encourage creativity for revolutionizing renal replacement therapy.
- ***Fund device development***—Supporting efforts to (1) build a technologically-advanced wearable or implantable dialysis unit (see [Prize Challenge](#) opportunity co-developed by the American Society of Nephrology and XPrize) or (2) develop novel venous access technologies would expand options for patients. In addition to adding portability, these advancements could allow for daily blood filtering and possibly lower the yearly mortality rate. Lastly, supporting efforts to (3) develop remote medical monitoring devices designed to allow real-time dialysis monitoring, targeted adjustments to treatments, and real-time updates to EMRs. This advancement would empower patients to be more informed about their care and facilitate discussions with care providers.

## LIMITED DISEASE UNDERSTANDING

### LACK OF MOLECULAR DISEASE BIOMARKERS

#### THE PROBLEM

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***Currently the kidney disease field lacks tissue-based molecular biomarkers to diagnose disease, predict disease progression to kidney failure, or track treatment efficacy.*** This apparent lack severely hampers efforts to develop new drugs. The field lacks the measures to test whether the drug is engaging its intended target or having the desired effect, which ultimately contributes to the high cost and failure of clinical trials. This biomarker challenge is, in part, due to insufficient mechanistic understanding of CKD progression to kidney failure. To further complicate this landscape, the field lacks the tools to study kidney disease *in vivo*, making it difficult to develop imaging biomarkers or visualize putative biomarker localization.

## PROPOSED SOLUTIONS TO ADDRESS THE CHALLENGE

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Promoting team science will be a central component to supporting novel biomarker discovery efforts as the skills necessary to address this heterogeneous disease requires a multi-disciplinary and multi-stakeholder effort to increase efficiency and avoid duplication.

## CORRESPONDING PHILANTHROPIC OPPORTUNITIES

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- **Fund a centralized data exchange platform**—This would be a go-to resource platform, which houses EMR data, patient-reported data, as well as biofluids and tissues conducive to large-scale analysis. Ideally, this platform would link to a national patient registry (described in the next section). Such a platform would facilitate efficient data sharing as well as enrich basic, translational and clinical research with its wealth of biological and clinical patient data.
- **Fund consortia charged with developing a regulatory path towards biomarker registration**—Once a biomarker has been proposed within the kidney community, a regulatory path needs to be outlined to assess the validity and utility of these biomarkers for clinical practice. Proving a roadmap that outlines the process would help disseminate the incorporation of new biomarkers as best-practices throughout the community.

## OPERATIONAL CHALLENGES TO CONDUCTING SUCCESSFUL CLINICAL TRIALS

### THE PROBLEM

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**There has never been a drug developed primarily for the prevention of kidney failure.** We need therapies to stop people with kidney disease from worsening and being required to start dialysis. Pharmaceutical companies expend more than the entire NIH budget in drug development but have largely ignored kidney disease. Major companies which have tentatively ventured into developing CKD treatments often quickly exit due to both scientific and operational challenges. These challenges include, identifying patients who are unaware that they have the disease and encouraging participation from caregivers who may have a fatalistic view that the disease will inevitably progress to dialysis. Recruitment rates for CKD are less than 20-40 percent of those for other major diseases like diabetes, heart disease and Alzheimer's. This results in lengthy, overly costly trials yielding underpowered results due to the smaller target enrollment sizes. In concert with awareness efforts outlined in the first section of this document, the CKD patient community can be mobilized to more actively seek out trials testing new therapies. Opportunities to surmount these barriers would significantly de-risk industry investment to develop new therapeutic options and help leverage their substantial resources for bringing therapeutics to the market.

### POTENTIAL SOLUTIONS TO ADDRESS THE CHALLENGE

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Fostering a culture of patient and provider engagement could dramatically improve clinical trial participation. Successful examples to be emulated can be seen in various disease communities such as cancer, HIV/AIDS, and muscular dystrophy. In tandem, creating a global clinical trials network would expand the patient pool available for recruitment and build capacity for more efficient clinical trial practices.

## CORRESPONDING PHILANTHROPIC OPPORTUNITIES

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- ***Fund the creation of a national and/or international CKD patient registry***—Patient registries inform natural history studies, assist in clinical trial recruitment, facilitate safety monitoring, encourage patient participation in research and can serve as a site for patient education resources. Linking each patient’s anonymized health record to the registry would provide a critical new capability for doctors to better understand the spectrum of kidney disease progress. Such a registry could enable real-time feedback to support evidence-based guidelines for quality care and house trial ready cohorts and health systems. Establishing a CKD registry could also better connect the CKD patient community with caregivers and policy makers to have a voice in kidney research and care.
- ***Support administrative costs to facilitate a global clinical trials network***—As low clinical trial enrollment rates have resulted in terminated or inconclusive trials, leveraging the global community for patient enrollment could speed up the enrollment process and reduce costs for a clinical trial. In this network, enrolled academic and non-academic clinical centers would be able to conduct different trials at the same time. Supporting a central coordinating center for patient recruitment that would allow multiple international centers to interact would be key to facilitating this process.
- ***Fund a patient-reported outcomes (PRO) consortia***—Supporting the consortia by facilitating patient and professional meetings to spur development and validation of PROs for dialysis and transplantation would encourage PRO inclusion in regulatory assessments for future therapeutic options.

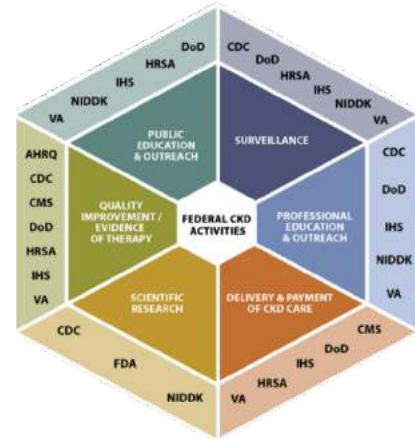
## KEY STAKEHOLDERS IN THE KIDNEY DISEASE COMMUNITY

### GOVERNMENT

Federal agencies and federally-mandated institutes are the largest funders of CKD/kidney failure-related research, totaling more than \$580M in aggregate (FY 2015). Table 2 displays federal agencies whose research expenses meet or exceed \$500K and Figure X provides a visual overview of federal activity surrounding CKD/kidney failure.

**Table 2. Federal Funding for Kidney Disease Research for FY 2015**

Agency or Institute	Research Expenses	Total Budget
National Institutes of Health (NIH)	\$564M	\$30B
Department of Veterans Affairs	\$20.9M	\$163.9B
Patient-Centered Outcomes Research Institute (PCORI)	\$14M	\$462.8M
Department of Defense (DOD)	\$7.1M	\$495.6B
Centers for Disease Control and Prevention (CDC)	\$2M	\$11.1B
Agency for Healthcare Research and Quality (AHRQ)	\$1.3M	\$440M
Food and Drug Administration (FDA)	\$500K	\$4.7B



**Figure 18. Federal CKD Activities**  
[Source.](#)

### DOMESTIC RESEARCH GRANT-MAKING ORGANIZATIONS

There are several nonprofit organizations specifically focused on charitable giving to support kidney failure and other kidney diseases. This section provides a brief overview of the nonprofit organizations involved in CKD/kidney failure-related research. This section only includes U.S.-based kidney disease organizations that include kidney failure (commonly referred to as ESRD) as a specific research focus. Organizations that are solely involved in patient support, advocacy, awareness or whose mission is to fund one specific research center are excluded. Table 3 displays the top nonprofit funders of CKD/kidney failure-related research whose research expenses meet or exceed \$500K. Additional information regarding their mission, key research funding mechanisms and clinical trials support activities is also provided below.

**Table 3. Top Nonprofit Organizations Funding CKD/ESRD Research for FY 2014**

Organization	Founding Year	Research Expenses	Total Expenses
American Society for Nephrology (ASN)	2012	\$3M	\$3M
American Urological Association (AUA)	2005	\$3M	\$3.4M
National Kidney Foundation (NKF)	1950	\$1M	\$34.5M
American Society of Transplantation (AST)	1982	\$900K	\$4M

## AMERICAN SOCIETY FOR NEPHROLOGY (ASN)

### MISSION:

ASN leads the fight to prevent, treat, and cure kidney diseases throughout the world by educating health professionals and scientists, advancing research and innovation, communicating new knowledge, and advocating for the highest quality care for patients.

### RESEARCH FUNDING MECHANISMS:

ASN provides support across the entire research pipeline. Their grant-making is divided roughly into three categories: career development for new investigators, research fellowships, and travel grants for fellows, residents and students to attend Kidney Week, the organization's annual conference. Since ASN began funding grants in 1996, the society and the foundation have awarded more than \$35 million to support research and travel awards. In FY 2014, ASN dedicated \$3M to research-related expenses.

For more information about available awards, please visit ASN's [website](#).

## AMERICAN UROLOGICAL ASSOCIATION (AUA)

### MISSION:

AUA's mission is to promote the highest standards of urological clinical care through education, research and the formulation of health care policy.

### RESEARCH FUNDING MECHANISMS:

AUA provides support to basic, translational, and clinical research. The AUA is committed to supporting urologic research through funding, advocacy and scholarly exchange. The AUA is a leader in helping to identify gaps in knowledge and communicating urology research needs to key constituents at the federal level. The AUA's Research Scholars Program has provided support to young urology researchers for more than 35 years. AUA also administers a data grants program to support population-based, data-driven, specialty generalizable studies using electronic health records, data maintained by the AUA or other data sources already available to investigators. In FY 2014, AUA dedicated \$3M to supporting urology research.

For more information about available awards, please visit AUA's [website](#).

## NATIONAL KIDNEY FOUNDATION (NKF)

### MISSION:

The National Kidney Foundation is the leading organization in the U.S. dedicated to the awareness, prevention and treatment of kidney disease for hundreds of thousands of healthcare professionals, millions of patients and their families, and tens of millions of Americans at risk.



## RESEARCH FUNDING MECHANISMS:

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NKF supports translational, early clinical research as well as large-scale epidemiologic research regarding CKD risk factors, progression and prognosis. Since 1968, the National Kidney Foundation has provided more than \$100 million in research grants to the field. In FY 2014, NKF allocated about \$1M to their research program, which supported four young investigators and one clinical investigator. The organization also publishes peer-reviewed medical journals, including American Journal of Kidney Diseases, Advances in Chronic Kidney Disease, Journal of Renal Nutrition, and Journal of Nephrology Social Work.

For more information about available awards, please visit NKF's [website](#).

## AMERICAN SOCIETY OF TRANSPLANTATION (AST)

### MISSION:

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The American Society of Transplantation is an organization of professionals dedicated to advancing the field of transplantation and improving patient care by promoting research, education, advocacy, and organ donation.

### RESEARCH FUNDING MECHANISMS:

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The AST Transplantation and Immunology Research Network (TIRN) research grants program seeks to support fellows, junior faculty, and allied health professionals by funding innovative research in basic, clinical, and translational science. In FY 2014, AST dedicated about \$900k to supporting research.

For more information about available awards, please visit AST's [website](#).

## COLLABORATIVE INITIATIVES

### GOVERNMENT SPONSORED PROGRAMS

## ADVANCED TISSUE BIOFABRICATION MANUFACTURING INNOVATION INSTITUTE (ATB-MII)

The [ATB-MII](#) was announced in June 2016 and will receive \$80M in federal funding. It will bring together for-profit and nonprofit organizations, institutions of higher education, and federal and state agencies to accelerate innovation by investing in industrially relevant manufacturing technologies with applications in the Tissue Biofabrication Ecosystem. This effort will provide support to help bridge the gap between basic/early research and product development by advancing and scaling critical technologies in the manufacturing readiness level 4 to 7 range. The ATB MII will provide shared assets to help entities—particularly small manufacturers—access cutting-edge capabilities and equipment, creating an unparalleled environment to educate and train students and workers in Advanced Tissue Biofabrication skills.

## KIDNEY HEALTH INITIATIVE (KHI)

Recognizing both the lack of clinical trials and the huge unmet clinical need in kidney disease, the American Society of Nephrology (ASN) and the U.S. Food and Drug Administration (FDA) established the [Kidney Health Initiative \(KHI\)](#) in September 2012. KHI's mission is to advance scientific understanding of the kidney health and patient safety implications of new and existing medical products and to foster development of therapies for diseases that affect the kidney by creating a collaborative environment in which FDA and the greater nephrology community can interact to optimize evaluation of drugs, devices, biologics, and food products.

Member organizations include patient advocacy organizations, professional organizations, regulated industry (including both pharmaceutical and device companies), dialysis providers, academic research organizations, contract research organizations, research institutes, and other government agencies. To more fully incorporate patient stakeholder concerns across all KHI clinical and policy discussions, KHI formed the Patient and Family Partnership Council (PFPC).

## KIDNEY INTERAGENCY COORDINATING COMMITTEE (KICC)

The [Kidney Interagency Coordinating Committee \(KICC\)](#) is a program under the NIDDK. The committee consists of federal representatives involved in CKD programs and activities. KICC's purpose is to encourage communication and collaboration to shape a more coordinated federal response to CKD. Figure 18 outlines KICC member agencies.

## VETERANS ADMINISTRATION NATIONAL KIDNEY PROGRAM

VA partnered with the Medical Education Institute in 2012 to develop an interactive web-based learning system, known as the [VA eKidney Clinic](#), to help guide Veterans through the process of managing CKD and making treatment related decisions. The eKidney Clinic is available to the public in addition to VA patients and providers via the [VA National Kidney Program](#).

The VA has been actively collaborating with NIDDK and the Centers for Disease Control in the review of patient education materials pertaining to chronic kidney disease (CKD). These materials are available to VA providers for patient dissemination within the clinic and are directly available to patients via VA's eKidney Clinic, as well as through the Department of Defense's clinical practice guideline.

## CONSORTIA

Consortia are temporary associations of stakeholders from various sectors—academia, industry, government, nonprofits, etc. —that share resources in order to achieve a common goal. According to *FasterCures' Consortia-pedia Catalogue* (a database of biomedical research consortia) there are several consortia focused on kidney diseases. Described below are select consortia that are underway for kidney failure-related research and therapeutic development. For a full list, please visit [Consortia-pedia Catalogue](#).

### BIOLOGICAL SUPPORT FOR KIDNEY PATIENTS (BIOKID)

Biological Support for Kidney Patients (BioKid), is a bioreactor of kidney cells to remove toxins that remain after hemodialysis. BioKid is an outstanding aid in improving the quality of hemodialysis treatments and in reducing the risk of complications, such as cardiovascular problems, resulting from the accumulation of toxic waste products. The BioKid project was active from 2009-2014 and is now currently continued within the European Union Marie Curie Innovative Training Network (ITN) project called BioArt. In April 2015, researchers reported the creation of a living kidney membrane—a highly sought after goal within the kidney disease field.

### CHRONIC KIDNEY DISEASE PROGNOSIS CONSORTIUM (CKD-PC)

Chronic Kidney Disease Prognosis Consortium (CKD-PC) is a research group composed of investigators representing cohorts from around the world. Investigators share data for the purpose of collaborative meta-analyses to study prognosis in CKD.

CKD-PC was established in 2009 by Kidney Disease: Improving Global Outcomes (KDIGO) (sponsored by the U.S. National Kidney Foundation). Originally tasked with compiling and meta-analyzing the best available data on kidney measures and clinical outcomes, the CKD-PC currently consists of over 70 cohorts, which arise from general, high-risk, or CKD populations. To date, the CKD-PC has published over 15 high impact papers with important implications for the definition, staging, and management of CKD.

### CKD BIOMARKERS CONSORTIUM (BIOCON)

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) established the CKD Biomarkers Consortium (BioCon) to promote the discovery and validation of biomarkers to advance the field of chronic kidney disease (CKD) research. The NIDDK CKD Biomarkers Consortium brings together investigators whose expertise includes clinical nephrology, epidemiology, molecular biology, genomics, proteomics, metabolomics, systems biology, laboratory medicine, biostatistics, and laboratory test verification and qualification. BioCon is a collaborative effort involving numerous investigators from multiple institutions working together to pursue the development and validation of novel biomarkers for CKD by assaying biological specimens and utilizing data from the nation's largest epidemiological studies of kidney disease.

### (RE)BUILDING A KIDNEY CONSORTIUM

(Re)Building a Kidney is an NIDDK-funded consortium of research projects working to optimize approaches for the isolation, expansion, and differentiation of appropriate kidney cell types and their integration into complex structures that replicate human kidney function.

The ultimate goal of this consortium is to coordinate and integrate research to support the development and implementation of strategies such as *de novo* repair of nephrons, the re-generation of nephrons, and the *in vitro* engineering of a biological kidney to enhance renal repair and promote the generation of new nephrons in the postnatal organ.

#### **SYSTEMS BIOLOGY TOWARDS NOVEL CHRONIC KIDNEY DISEASE DIAGNOSIS AND TREATMENT (SYSKID)**

The Systems Biology towards novel chronic kidney disease diagnosis and treatment (SysKid) consortium is focused on expanding the basic science of chronic kidney disease. The project paves the way for progress in prevention, new diagnostic strategies, and treatment options for declining kidney function, which affects millions of patients suffering from diabetes and hypertension. SysKid was launched by the European Commission Seventh Framework Programme in 2010.

## GLOSSARY

<b>ALLELES</b>	Two copies of each gene in the body
<b>ANEMIA</b>	Low red blood cell count
<b>APOL1 GENE</b>	The gene that encodes for the protein apolipoprotein L1
<b>APOLIPOPROTEIN L1</b>	A component of high density lipoprotein
<b>ARTERIOVENOUS (AV) FISTULA</b>	A surgical procedure that creates a direct connection between an artery and vein in the forearm
<b>ARTERIOVENOUS (AV) GRAFT</b>	A tube surgically inserted under the skin that connects an artery to a vein in the forearm
<b>ATHEROSCLEROSIS</b>	Hardening of the arteries, which can decrease blood flow to the kidneys
<b>BIOMARKER</b>	A characteristic that can be objectively measured and evaluated as an indicator of disease state or treatment efficacy
<b>BIOPSY</b>	Tissue removed from a living body
<b>BLADDER</b>	Hollow organ that stores urine prior to excretion
<b>BLOOD UREA NITROGEN</b>	Indicator of kidney and liver health. Urea nitrogen forms after protein has been broken down.
<b>CLINICAL RESEARCH</b>	Branch of biomedical research involving human subjects
<b>CREATININE</b>	Waste byproduct of muscle metabolism
<b>DIALYSIS TREATMENT</b>	Involves the use of specialized machinery to filter the blood when the kidneys can no longer do so
<b>EGRF CALCULATION</b>	Calculation using serum creatinine levels and certain formulas that factor in other risk factors such as age, gender, and race
<b>ENZYME</b>	A protein that catalyzes complex biological reactions
<b>ERYTHROPOIETIN-STIMULATING AGENTS (ESA)</b>	Medication that boosts red blood cell production
<b>ESTIMATED GLOMERULAR FILTRATION RATE (EGFR)</b>	The estimated filtration rate capacity of the kidneys
<b>GLOMERULUS</b>	The filter component of the nephron
<b>GRAFT</b>	A transplanted organ
<b>HEMATOCRIT</b>	The ratio of red blood cells to the total volume of blood
<b>HEMODIALYSIS</b>	Treatment that a dialysis machine to clean the total volume of the patient's blood
<b>HEMOGLOBIN</b>	The oxygen-carrying protein found in red blood cells
<b>HUMAGRAFT™</b>	A human bioengineered blood vessel that proposes to deliver a tissue-based graft lacking the need for tissue matching
<b>HYPERTENSION</b>	High blood pressure

<b>KIDNEYS</b>	Organs that filter blood and produce urine
<b>NEPHROLOGIST</b>	Physician who specializes in kidney diseases
<b>NEPHRON</b>	The kidney's filtering unit
<b>PERITONEAL DIALYSIS</b>	Treatment that involves using the lining of the patient's stomach (the peritoneum) as the filter for the patient's blood
<b>PROTEINURIA</b>	Clinical presentation of protein in the urine
<b>RAAS</b>	A hormone system that regulates blood pressure, fluid volume, and sodium content in the body
<b>RESEARCH AND DEVELOPMENT (R&amp;D)</b>	The process by which a laboratory discovery is developed into a commercial therapeutic diagnostic or device
<b>SENSITIZATION</b>	A state in which the patient has developed proteins that will attack foreign tissue, like a transplanted organ
<b>SERUM CREATININE MEASUREMENT</b>	Test used to detect evidence of increased creatinine in the blood
<b>TUBULE</b>	Tube allows for the reabsorption of necessary minerals back into the blood and sends excess fluid and waste to the ureters
<b>URETERS</b>	Tubes that carry urine from the kidneys to the bladder
<b>URETHRA</b>	Tube that expels urine
<b>URINE ANALYSIS</b>	Analyzes the urine for the presence of protein
<b>VENOUS CATHETER</b>	A surgically inserted flexible tube inserted into a vein in the neck, chest, or leg near the groin
<b>WEARABLE ARTIFICIAL KIDNEY (WAK)</b>	A device currently in development, which would allow for daily dialysis

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