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ABOUT THIS REPORT

This report is a landscape analysis of the kidney disease space in the United States and globally that was created as part of a formal prize design process for a Kidney Disease XPRIZE. This report summarizes the primary and secondary research and analysis conducted during that prize design with the goal of informing the development of a prize competition that would incentivize innovations in the kidney space.

EXECUTIVE SUMMARY

More than 20 million Americans suffer from chronic kidney disease (CKD), with patients typically experiencing few or no symptoms at the beginning stages of the illness. Therefore, unless a patient is being treated or investigated for another health issue, it is unlikely that he or she will be diagnosed with kidney disease until late in the disease progression. Upon reaching stage 4, or severe kidney disease, a patient’s physician will recommend treatment. Once a patient reaches stage 5, or end stage renal disease (ESRD), less than 10 percent of kidney function remains, and treatment is critical to extending the patient’s life.

CKD is a growing epidemic both in the United States and around the world. Globally, more than 2 million people receive treatment for ESRD. However, sources estimate that this figure accounts for only 10 percent of those who need some form of treatment for kidney disease. The majority of those 2 million patients receiving treatment reside in just five countries: the United States, Japan, Germany, Brazil, and Italy. More than 100 of the poorest countries cannot afford any renal replacement therapies (RRTs), resulting in the annual deaths of more than 1 million people from untreated kidney disease and eventual kidney failure.

Every year in the United States, more than 100,000 people begin dialysis treatment, and approximately 400,000 U.S. residents are on some form of dialysis at any given time. In 2011, the mortality rate of the dialysis population was 266 out of every 1,000 individuals—greater than 25 percent.

1XPRIZE interviews with experts. (2014).
CKD, and especially ESRD, disproportionality affects minority populations. African Americans are four times more likely to progress to ESRD than their white counterparts, while Hispanics and Native Americans are two times more likely.⁵

Significant market failures have contributed to the lack of effective, efficient, patient-centric RRTs. Medicare’s End Stage Renal Disease Program (ESRDP) entitles those under the age of 65 suffering with ESRD to benefits for the cost of lifesaving treatments. Every year, Medicare spends nearly $35 billion on ESRD treatments,⁶ which is more than the total yearly budget of the National Institutes of Health (NIH).⁷ Yet despite America’s commitment to provide care, there has been little innovation in the field of kidney disease treatment for decades.

In part, this failure is due to a comparative lack of investment in kidney research by the NIH and other funding agencies. This lack of progress, as well as a lack of transplantable kidneys, result in those who progress to ESRD undergoing dialysis treatments for the remainder of their lives. These individuals also suffer through the economic challenges and poor health outcomes that are integral to the patient experience, including job loss, malaise, depression, and repeated infections and hospital readmissions. We must develop a way to overcome the social burden and poor health outcomes associated with kidney disease, as well as fix a system that financially rewards treatment providers at the expense of much-needed research.

A prize competition in this space would incentivize innovation in a stagnant field that has only seen incremental innovation in the past three decades and result in new technologies for treating ESRD that lead to improved patient outcomes and a reduced social burden.

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PRIZE DESIGN PROCESS

XPRIZE IS AN INNOVATION ENGINE.
A facilitator of exponential change. A catalyst for the benefit of humanity.

We provide the thought leadership and expertise to identify the Grand Challenges of our time—the national or global crises, market failures, and opportunities where solutions are thought to be either out of reach or just plain impossible. We then design and operate incentivized prize competitions to solve these problems.

XPRIZE acts as a convening platform, bringing together passionate partners to accelerate a positive future based upon our vision of a preferred state. These partners include sponsors, entrepreneurs, philanthropists, industry, government, academia, and innovators who help us make the impossible possible.

We don’t dictate the solution. We ask the right questions. And we provide the platform, global visibility, credibility, and opportunity for our partners to take risks that ultimately lead to radical breakthroughs. Together, we create the future. The result? Averted crises. Revitalized markets. Better technologies. New industries. And empowered people.

XPRIZE accomplishes this by creating large-scale, market-driven, incentivized prize competitions that focus global innovators on goals that are audacious but achievable. We leverage the intellectual and financial capital necessary to stimulate research and development, yielding measurable results and efficiency that ensure our supporters consistently back winning solutions.

The design of an XPRIZE competition is guided by the following principles:

- XPRIZEs result in innovations that make a lasting impact. Although a technological breakthrough may meet this criterion, so do prizes that inspire teams to use existing technologies, knowledge, and/or systems in more effective ways.

- XPRIZEs legitimize a field of interest, making it possible for teams to attract support for their efforts.

- XPRIZEs generate popular interest through the prize life cycle:
  - Enrollment: The world is introduced to the players. Prizes ideally encourage the participation of a wide range of participants—from leading thinkers in relevant fields to maverick inventors and entrepreneurs. These rare individuals are often as difficult
to identify as the proverbial “needle in a haystack.” XPRIZEs attract these “needles” to solve seemingly impossible problems.

- **Competition:** The world watches as teams work to win the XPRIZE.

- **Post-Win:** Retrospectively, competitions are regarded as landmark events that revolutionized an industry or opened up new markets.

- XPRIZE competitions incorporate elements of both technological innovation and successful real-world deployment. An innovation that is too costly or too inconvenient to deploy widely will not win.

- XPRIZE competitions engage multidisciplinary innovators who would otherwise be unlikely to tackle the problems that the prize is designed to address.

- XPRIZE competitions promote collaboration in the quest to find a solution.

In developing prizes for more than 15 years, XPRIZE has become expert in prize design. The XPRIZE prize design process is anchored in an open collaboration model, which is designed to enable many external constituencies to contribute to the process. Input from innovators, industry leaders, academia, government, non-governmental organizations, and the general public is routinely and formally sought.

The ideas that emerge from this collaboration are vetted through XPRIZE’s formal prize design process to ensure the design of the best competition possible. XPRIZE develops competitions in areas where market failures have limited progress or exhausted resources.

During the prize design process, XPRIZE identifies and analyzes the underlying market failures that a prize can address, focusing on the technological, market, behavioral, and policy sectors that could be impacted and changed by a prize. XPRIZE engages with technology experts, industry advisors, and creative thought leaders to identify and prioritize prize concepts and technical parameters that can best solve market failures. For the leading prize concept(s), XPRIZE then creates a set of initial prize concepts.

Once XPRIZE and its sponsors agree to move forward with a single prize concept, that concept is truly crafted into an XPRIZE competition. XPRIZE defines the value proposition and stakeholders, and develops detailed plans for the launch, operation, and awarding of the prize. Additionally, XPRIZE finalizes competition guidelines and establishes success criteria for the competition, including detailed team and sponsor business, marketing, and promotional strategies. XPRIZE also lays out a
detailed operations strategy that defines the operational, sponsorship, marketing, educational, and financial resource requirements for all competition partners, sponsors, and stakeholders.

**PROJECT BACKGROUND AND MARKET SITUATION ANALYSIS**

**GRAND CHALLENGE**

More than 20 million Americans suffer from chronic kidney disease (CKD). Of these individuals, approximately 400,000 are on some form of dialysis (renal replacement therapy [RRT]), at an annual public cost of more than $35 billion. Globally, more than 2 million people receive RRT—a figure that is estimated to account for only 10 percent of those requiring some form of treatment for kidney disease. A lack of investment from traditional funders in innovative new therapies, as well as a lack of transplantable kidneys, result in those who progress to end stage renal disease (ESRD) undergoing dialysis treatments for the remainder of their lives. These individuals also suffer through the poor health outcomes and economic challenges that are integral to the patient experience. The lack of effective, patient-centric treatments for ESRD is a Grand Challenge that must be addressed.

**WHAT IS KIDNEY DISEASE?**

Kidney disease, or nephropathy, is an umbrella term that covers a broad range of diseases and types of damage to the kidneys. CKD is a form that results in a loss of kidney function over time. As CKD progresses, the kidneys lose the ability to maintain homeostatic functions that allow the body’s physiology to maintain internal stability, such as appropriately filtering the blood and removing uremic solutes from the body. The presence of these solutes can build up in the blood and cause significant health issues, including cardiovascular disease, inflammation, and eventual organ failure throughout the body. CKD progression is charted along five stages—from a minor loss of kidney function (stage 1) to complete kidney failure (stage 5) (see Appendix C).

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In the United States, the greatest contributing factors to CKD are diabetes, high blood pressure (hypertension), cardiovascular disease, obesity, lupus, age, and family history of CKD.\textsuperscript{11} Approximately 70 percent of kidney disease cases in the United States are attributable to diabetes and hypertension, with the remaining 30 percent of cases caused by up to 100 other diseases and disorders. Global factors contributing to kidney disease in low-income countries include HIV, hepatitis B and C, tuberculosis, environmental pollution, pesticides, and unregulated food additives.\textsuperscript{12} It is clear that kidney disease is not a single illness with a single cause or single pathway to treatment or a cure.

**Prevalence**

The Centers for Disease Control and Prevention (CDC) estimates that more than 10 percent of the U.S. adult population (more than 20 million people) may have CKD.\textsuperscript{13} Minority populations are disproportionately affected by CKD, and especially ESRD, (see Figures 1 and 2 below). African Americans are four times more likely to progress to ESRD than their white counterparts, while Hispanics and Native Americans are two times more likely.\textsuperscript{14}

Figure 1. Age-Adjusted Incidence Rate of CKD among U.S. Adults Aged 20 Years and Older (1999–2010)

**Prevention**

The two leading causes of chronic kidney disease—diabetes and hypertension—are either preventable or manageable. Diabetes accounts for nearly 44 percent of new cases of kidney disease.\(^{17}\) Obesity and a lack of exercise, which are strongly correlated with developing diabetes, are also associated with an increased risk of developing CKD.\(^{18}\)

While diabetes and hypertension intervention and treatment have been shown to stop or slow the progression of CKD in some patients, many individuals find it challenging to manage their blood pressure and blood glucose levels. Similarly, while changes in diet and lifestyle have proven incredibly effective at reducing the risk of diabetes and hypertension, it is sometimes too difficult for patients to maintain control of their diet, exercise regimen, and medications.\(^{19}\)

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\(^{19}\)XPRIZE interviews with experts. (2014).
Recent findings have shown that exercise in particular can prevent the death of renal cells, potentially preventing further declines in CKD. The challenge is that many patients with CKD tend to have multiple comorbidities (the simultaneous presence of two or more chronic diseases), be older, and have low socioeconomic status—all of which are factors associated with increased dietary risk and reduced exercise habits. Many of these individuals also live in areas that are considered “food deserts,” where patients have limited access to healthy foods.

Diagnosis

During the beginning stages of kidney disease, patients frequently experience few or no symptoms. Therefore, unless a patient is being treated or investigated for another health issue, it is often unlikely that he or she will be diagnosed with kidney disease until reaching stages 3 or 4 (see Figure 3 below). Standard diagnostic tests for kidney disease are shown on the following page in Table 1.

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23XPRIZE interviews with experts. (2014).
Figure 3. Stages of Chronic Kidney Disease

Table 1. Diagnostic Tests for Kidney Disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine Blood Test</td>
<td>As kidneys lose function, they are no longer able to remove creatinine—a chemical byproduct of metabolism—from the blood. This reduction in creatinine clearance is an indicator of loss of kidney function. Creatinine levels can be measured using a simple blood test, and may be used to diagnose kidney disease.²⁵</td>
</tr>
<tr>
<td>Estimated Glomerular Filtration Rate (eGFR)</td>
<td>Doctors may estimate a patient’s GFR using serum creatinine levels and a formula that adjusts for age, gender, and—in some cases—ethnicity. The resulting eGFR is more accurate than measuring serum creatinine alone, as it compares both blood and urine creatinine levels and clearance.²⁶</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>A simple analysis of a patient’s urine can reveal protein in the urine, which is an early sign of kidney disease, particularly among patients with diabetes. Two specific ratios—the protein to creatinine ratio and the albumin to creatinine ratio—are commonly used to assist in kidney disease diagnosis.</td>
</tr>
<tr>
<td>Imaging</td>
<td>Ultrasounds can be used to assess kidney structure and function. Generally, patients with CKD will have shrunken kidneys. However, in some cases—such as diabetic nephropathy and adult polycystic kidney disease—kidneys may appear normal or enlarged in size.²⁷ Ultrasounds can also be used to assess blood flow or identify any obstructions, such as kidney stones.²⁸</td>
</tr>
<tr>
<td>Biopsy</td>
<td>Kidney biopsies—typically a minimally invasive needle sampling of kidney tissue, performed as an outpatient procedure—can identify scarring, fibrosis, and infections, and can be used to clarify uncertain diagnoses.²⁹</td>
</tr>
</tbody>
</table>

Mortality and Life Expectancy

Mortality rates among individuals with CKD and ESRD are much higher than those of the general population. In 2011, the mortality rate of the dialysis population was 266 out of every 1,000.

²⁹ Ibid.
individuals—greater than 25 percent. Comparatively, the average mortality rate in the United States across all populations (sometimes referred to as the “crude death rate”) is 8.1 out of every 1,000 individuals, or less than one percent. On average, dialysis patients have an overall life expectancy of 6.2 years, while kidney transplant recipients have an average life expectancy of 17.2 years.

**TREATMENTS FOR KIDNEY DISEASE**

Upon reaching stage 4 of kidney disease, a patient’s physician will begin preparing the patient for treatment. Once a patient reaches stage 5, when less than 15 percent of kidney function remains, treatment becomes critical to extending the patient’s life.

Three treatments currently exist for kidney disease:

- Hemodialysis
- Peritoneal dialysis
- Kidney transplantation

Every year in the United States, more than 100,000 people begin dialysis treatment, and approximately 400,000 U.S. residents are on some form of dialysis at any given time (see Table 3). Nearly 17,000 individuals received kidney transplants in 2013, while there are 101,170 individuals awaiting transplants as of September 2014.

Each of the three existing treatments is discussed in detail below.

**Hemodialysis**

Hemodialysis is a process by which blood is removed from the body, filtered, and then returned to the body. The blood is removed and returned through an insertion point in the body’s vascular...
system (called a “vascular access” point). As the blood is removed from the body, it is filtered through a pump that adds the anticoagulant heparin to prevent clotting. Saline solution aids in this process. The blood is then pumped into a dialyzer, where the blood passes along a semipermeable membrane that has a liquid called dialysate on the other side of the membrane. Dialysate is a chemical bath that also contains electrolytes and minerals. As the blood flows past the dialysate, solutes from the blood move through the semipermeable membrane into the dialysate. Clean dialysate flows into the dialyzer on one side, while waste dialysate flows out the other. Clean blood then flows through additional pressure, air bubble, and clot-monitoring devices before being returned to the body.  

Figure 4. Hemodialysis Schematic

- Saline solution
- Fresh dialysate
- Used dialysate
- Inflow pressure monitor
- Heparin pump (to prevent clotting)
- Blood pump
- Arterial pressure monitor
- Venous pressure monitor
- Air trap and air detector
- Clean blood
- Removed blood for cleaning

Patient
Patients can receive hemodialysis treatment at a hospital, at a dialysis center, or in their home. Nearly 90 percent of all patients on dialysis receive their treatments at dedicated dialysis centers. Most patients undergo treatments three to five times per week, for approximately four hours at a time. Home dialysis patients may receive treatments more frequently (e.g., four to seven times per week, for fewer hours each time), and in some cases may receive treatments while they are sleeping.

During hemodialysis treatment, the patient is tethered to a dialysis machine and is unable to move around. Many patients on dialysis experience side effects that have a significant negative impact on their quality of life. The most common side effects are discussed below in Table 2.

“My mother gets dialysis 3 times a week and she is having severe muscle cramps in her legs. I am trying to find what she can do during dialysis to help alleviate or lessen the cramps. She is 80 years old and has other conditions, if there is something to help with the cramps it may make her time in dialysis less stressful.”

—Caregiver

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42. XPRIZE interviews with experts. (2014).
<table>
<thead>
<tr>
<th>SIDE EFFECTS</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access Site Complications</td>
<td>Infections are common at the vascular access points (the points at which the dialysis machine accesses the body’s blood supply). Equipment used to access and transport the blood (e.g., catheters) often harbors bacteria, which increases the risk of infection. Narrowing or ballooning of the blood vessels is also a potentially dangerous complication.</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>People who have undergone dialysis for five or more years commonly develop protein deposits on their joints and tendons, causing fluid in the joints, stiffness, and pain.</td>
</tr>
<tr>
<td>Anemia</td>
<td>A reduced number of red blood cells is a common side effect of kidney disease and dialysis. As kidneys lose functionality, they stop producing the hormone erythropoietin, which is integral to the development of red blood cells. Other factors contributing to anemia include dietary restrictions, frequent blood tests, and the process of hemodialysis itself, which filters iron and vitamins from the blood.</td>
</tr>
<tr>
<td>Bone Disease</td>
<td>Two complications of kidney disease can lead to weak bones. Overproduction of the parathyroid hormone can leach calcium from bones, and an inability to process vitamin D precursors can prevent calcium from being properly absorbed.</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>SIDE EFFECTS</th>
<th>DESCRIPTION</th>
</tr>
</thead>
</table>
| Depression     | Patients with CKD often suffer from depression. Approximately 10 percent of the general U.S. population suffers from depression; among patients undergoing dialysis treatment, the number increases to 20–30 percent.\(^{51}\)  
While the link between kidney disease and depression is not clearly understood, it is generally accepted that the chronic stress and trauma associated with kidney failure and dialysis treatments contributes to an increased incidence of the mental illness. |
| Fluid Overload | Many patients on dialysis no longer urinate, with fluid primarily being removed from their bodies during each dialysis treatment. Between treatments, fluid may build up in the body and potentially lead to heart failure or pulmonary edema (fluid in the lungs).\(^{52}\) |
| Hyperkalemia    | Potassium is normally removed from the blood by the kidneys. If a patient on dialysis ingests more potassium than is recommended, the amount of potassium in the blood may reach unsafe levels.\(^{53}\) In the most severe cases, excess potassium may cause heart failure. |
| Hypertension    | High blood pressure may result from fluid buildup in the body or from consuming too much salt. This can lead to heart complications and stroke.\(^{54}\) |
| Hypotension     | Low blood pressure commonly occurs in patients on dialysis. These patients may experience shortness of breath, nausea, vomiting, and muscle cramps.\(^{55}\) This happens most commonly in patients who also have diabetes. |
| Itching         | A common cause of itching for patients on dialysis is a buildup of phosphorus in the body. Dialysis does not remove phosphorus, so a diet low in the mineral is critical for patients on dialysis. Another common cause of itching is dry skin, which may be caused by hormonal changes. |

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**SIDE EFFECTS** | **DESCRIPTION**
--- | ---
Muscle cramps | For unknown reasons, muscle cramps are common in patients undergoing dialysis treatments. Sometimes adjusting sodium and fluid intake can alleviate cramping.

Pericarditis | The membrane surrounding the heart (the pericardium) may become inflamed as a result of a lack of sufficient dialysis and a buildup of uremic solutes in the blood. This inflammation interferes with the heart’s ability to pump blood.

Sleep Problems | Sleep problems among those on dialysis are often caused by sleep apnea (a potentially dangerous disorder in which breathing stops and starts repeatedly during sleep); aching and restless legs; excessive daytime sleepiness; and other disorders. The causes of these sleep disorders are not yet well understood.

**Peritoneal Dialysis**

Peritoneal dialysis is similar to hemodialysis in that it uses a dialysate to filter uremic solutes from the blood. The primary difference is that peritoneal dialysis fills the body’s own peritoneal cavity (in the abdomen) with dialysate and uses the semipermeable membranes of the body’s intestines as the membrane through which the blood’s solutes will pass. (See Figure 5 below.)

“I've been on peritoneal dialysis for almost three years. My initial experience was not great; I had an infection at the site of the catheter insertion that developed while I was still bandaged and had several bouts of peritonitis [a bacterial or fungal infection of the abdominal lining] over the next few months. However, once that was resolved, I have been free to continue to work, to travel, and to spend time with friends. I use the cycler overnight—two large bags of fluid—and supplement with a manual exchange with a smaller bag during the early evening as required. I find that you just have to get your mind right; that this dialysis thing is what you need to do to live.”

—Patient

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Peritoneal dialysis may offer patients some benefits that hemodialysis does not, including the following:\textsuperscript{60,61}

- Less nausea, vomiting, and cramping
- Greater fluid control and balance (which may result in less stress on internal organs)
- Fewer dietary restrictions
- Less frequent travel to dialysis centers
- Greater flexibility in treatment location and schedule
- Less pain and discomfort during treatment (peritoneal dialysis relies on the installation of a catheter; therefore, treatments are needle-free)


Alternatively, some patients experience significant negative side effects from peritoneal dialysis, including the following:  

- Poor drainage of the dialysis fluid due to constipation or catheter displacement
- Fluid leaks around the catheter access site or into the genitals, causing swelling
- Hernias and swelling, due to pressure from dialysis fluid
- Peritonitis and other infections
- Back strain from carrying fluid weight in the abdomen
- Bloating and extended abdomens; discomfort

There are two types of peritoneal dialysis:

- Continuous ambulatory peritoneal dialysis (CAPD). This type requires patients to manually perform a fluid exchange (filling and draining of the peritoneal cavity) several times a day. This typically requires about 30 minutes per exchange, and must be done four times throughout the day. The process can be performed at home or work, provided the patient has an appropriate, sterile environment in which to perform each exchange.
- Automated peritoneal dialysis (APD). Sometimes referred to as “continuous cycling peritoneal dialysis” (CCPD), this type uses a machine to automate the filling and draining of the peritoneal cavity. This allows APD to be performed while patients sleep.

Fewer than 10 percent of all dialysis patients are on peritoneal dialysis. Despite the lower cost and higher patient experience ratings associated with peritoneal dialysis, most doctors have historically recommended hemodialysis. However, the number of patients on peritoneal dialysis has started to grow as patients learn about alternatives to hemodialysis. Unfortunately this increase in popularity has resulted in a reduced number of peritoneal dialysis supplies and resources.

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66XPRIZE interviews with experts. [2014].
67Swaminathan, S., Mor, V., Mehrotra, R., & Trivedi, A. (2012, September). Medicare’s payment strategy for end-stage renal disease now embraces bundled payment and pay-for-performance to cut costs. Health Affairs, 31(9), 2051–2058.
Table 3. U.S. Dialysis Services by Type (2014)\(^69\)

<table>
<thead>
<tr>
<th>TYPE OF DIALYSIS</th>
<th>NUMBER OF PATIENTS</th>
<th>PERCENT OF TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis (In-Center Conventional)</td>
<td>348,212</td>
<td>87.9%</td>
</tr>
<tr>
<td>Hemodialysis (In-Center Nocturnal)</td>
<td>3,285</td>
<td>0.8%</td>
</tr>
<tr>
<td>Hemodialysis (Home)</td>
<td>6,098</td>
<td>1.5%</td>
</tr>
<tr>
<td>Peritoneal Dialysis</td>
<td>38,424</td>
<td>9.7%</td>
</tr>
<tr>
<td>Total</td>
<td>396,019</td>
<td>100%</td>
</tr>
</tbody>
</table>

Kidney Transplantation

For patients who have progressed to ESRD, the best hope for lasting, functional treatment is a kidney transplant. Kidney transplants are the most common organ transplants in the United States, with nearly 17,000 performed in 2013 and more than 100,000 individuals currently on the waiting list for a kidney.\(^70\) Kidney transplantation is the only treatment for kidney disease that approaches the status of a “cure,” but transplants are not a cure-all, and transplanted kidneys do not last forever. On average, approximately seven percent of transplants fail within the first year, and 17 percent fail within the first three years after transplant.\(^71\) Individuals whose transplants have failed commonly receive a “re-transplant;” approximately 14 percent of those patients on the kidney waiting list are awaiting a new kidney to replace a failed transplanted kidney.\(^72\) While kidney transplants are not without risks and side effects, the greatest challenge facing kidney transplantation is the lack of transplantable organs; every day, 13 people in the United States die while waiting for a kidney transplant.\(^73\)


Additionally, some patients are not eligible for transplantation. Kidney transplants are generally not an option for patients with the following risk factors or conditions.\textsuperscript{74}

- Cancer
- Advanced heart or lung disease
- Cirrhosis (scarring of the liver)
- Alcohol or drug abuse
- Lack of social support
- Untreated psychiatric conditions
- Noncompliance with medical treatments
- Obesity
- Limited physical mobility

GLOBAL CONTEXT

CKD is a growing epidemic both in the United States and around the world. Globally, more than 2 million people receive treatment for ESRD; however, sources estimate that this figure accounts for only 10 percent of those who need some form of treatment for kidney disease. The majority of these 2 million patients receiving treatment reside in just five countries: the United States, Japan, Germany, Brazil, and Italy. More than 100 of the poorest countries cannot afford any renal replacement therapies (RRTs), resulting in the annual deaths of more than 1 million people from untreated kidney disease and eventual kidney failure.76

Diabetes and hypertension cause a smaller proportion of CKD worldwide than in the United States, where the two illnesses are linked to more than 70 percent of all cases of CKD. Worldwide, diabetes and hypertension account for approximately 50 percent of CKD cases, but this varies by region.77 For example, a recent study of people with CKD in China, Mongolia, and Nepal found that 43 percent of the individuals did not also have diabetes or hypertension.78 Causes of CKD that are of greater concern in the developing world than elsewhere include glomerulonephritis (often

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77Ibid.
characterized by inflammation of the glomeruli), environmental toxicity, and malnutrition that changes prenatal programming and leads to low nephron numbers in infants.\textsuperscript{79}

Developing nations face many economic and political challenges to providing therapies for individuals with kidney disease, such as sufficiently trained medical staff and adequate equipment, supplies, and pharmaceuticals. Additionally, dialysis treatments require large quantities of highly filtered pure water, which is not immediately accessible in many developing countries.\textsuperscript{80,81}

\section*{CURRENT LANDSCAPE}

\subsection*{POLICY LANDSCAPE IN THE UNITED STATES}

In 1972, the U.S. Congress enacted the Medicare End Stage Renal Disease Program (ESRDP). The program extended Medicare Part A and B benefits to Americans under the age of 65 who were suffering from stage 5 CKD—or ESRD—as long as they were otherwise entitled to receive Social Security benefits. This entitlement covers approximately 90 percent of Americans with ESRD.\textsuperscript{82} Most patients with ESRD who are entitled to treatment under the program (nearly 80 percent) receive “maintenance dialysis.”\textsuperscript{83} Between 1973 and 1983, Medicare paid a set reimbursement of $138 per ESRD treatment. This payment structure rewarded efficiency rather than quality of care in dialysis treatments, as providers were able to cut costs and keep the margin, resulting in high profits and consolidation among dialysis providers.\textsuperscript{84}

With the Omnibus Budget Reconciliation Act of 1981, Congress passed the “composite rate” payment system for reimbursements, which was intended, in part, to incentivize home and in-center dialysis treatments by paying the same composite rate for those treatments as for hospital-based treatments.\textsuperscript{85}

\begin{thebibliography}{9}
\bibitem{83}Ibid.
\end{thebibliography}
In 2003, the Medicare Modernization Act (MMA) increased the composite rate for reimbursements, augmented those reimbursements with “add-on” payments for pharmaceuticals, and set annual adjustments to the repayment rate to begin in 2006. The MMA also requested from the Secretary of the Department of Health and Human Services (HHS) a report on the feasibility of a “fully bundled dialysis prospective payment system (PPS).” In 2008, based on the recommendations from HHS, the Medicare Improvements for Patients and Providers Act (MIPPA) established a fully bundled PPS (which was implemented in 2011). MIPPA also established a Quality Incentive Program (QIP) that requires ESRD providers to meet specific annual performance metrics.86

However, despite recent payment reforms, Medicare continues to spend nearly $35 billion on ESRD treatments annually,87 which is more than the total yearly budget of the National Institutes of Health (NIH).88 Every year, Medicare pays approximately $87,945 for each hemodialysis patient, $71,630 for each peritoneal dialysis patient, and $32,922 for each kidney transplant patient (see Figure 6 below).89

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86Ibid.
INDUSTRY LANDSCAPE IN THE UNITED STATES

Today, more than 85 percent of hemodialysis and peritoneal dialysis patients in the United States receive services from just two companies: DaVita Healthcare Partners, Inc. and Fresenius Medical Care North America. DaVita is primarily a services company that provides both in-center dialysis care and access to home health care. Fresenius provides dialysis services as well as manufactures hemodialysis and peritoneal dialysis machines, mixing tanks, and monitoring devices. Together, these two companies provide dialysis treatments for 338,000 of the 396,000 patients currently receiving dialysis in the United States.
Table 4. The 10 Largest U.S. Dialysis Providers in 2014

<table>
<thead>
<tr>
<th>DIALYSIS PROVIDER</th>
<th>NUMBER OF PATIENTS</th>
<th>PERCENTAGE OF TOTAL PATIENTS SERVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresenius Medical Care North America</td>
<td>172,006</td>
<td>43.4%</td>
</tr>
<tr>
<td>DaVita Healthcare Partners, Inc.</td>
<td>166,000</td>
<td>42.9%</td>
</tr>
<tr>
<td>U.S. Renal Care</td>
<td>14,387</td>
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<td>14,462</td>
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<td>DSI Renal</td>
<td>6,656</td>
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<td>Satellite Healthcare</td>
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<td>Northwest Kidney Centers</td>
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<td>0.4%</td>
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<td><strong>Total</strong></td>
<td><strong>396,019</strong></td>
<td><strong>100%</strong></td>
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TECHNOLOGY LANDSCAPE

While dialysis technologies have changed little over the past few decades, there have been some advances in recent years, and there are even greater potential advancements on the horizon that will, if successful, redefine what we expect of renal replacement therapies. These potential advancements include:

- Improved portable dialysis systems
- Wearable and implantable artificial kidneys
- Improved biomaterials and synthetic materials

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• Bioengineered kidneys

Each of these advancements has the potential to improve patient quality of life to varying degrees. They are discussed in greater detail below.

**Portable Dialysis Technologies**

Portable and home dialysis systems have become available over the last decade for patients to use at home or while traveling. The definition of “portable” is not standard within the industry; for example, a device that weighs 75 pounds and is much too large for a single person to carry is considered portable. Some companies like DaVita use the terms “portable” and “home dialysis” interchangeably.\(^9^6\) None of the existing portable or home dialysis systems offer true patient mobility, and no data currently exists to support whether such systems improve long-term patient outcomes compared with traditional dialysis treatment systems.\(^9^7\)

Two examples of home hemodialysis machines are described below:

• **NxStage System One**
  - Includes a water purification system (the NxStage Pureflow)
  - Plugs into home electrical outlets (operates on standard electrical current)
  - Portable (weighs 75 pounds and is approximately the size of a large desktop printer, 15x15x18 inches)

• **Fresenius 2008K@home**
  - Usable at home with training (not portable)
  - Allows user customization (date/time, length of treatments)
  - Requires installation of a home water purification system

Other portable and home dialysis systems are currently under development. These systems attempt to take into consideration some of the key barriers to patient mobility and ease of use, including size, weight, and water usage requirements.

Examples of three potential advancements are described below:

• **Neokidney:** A portable system based on peritoneal home dialysis with novel sorbent technology, reducing dialysate need from 40–60 liters to four liters. Currently under

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development by a multinational consortium, the portable kidney would revolutionize patient mobility, as the water needs alone of most dialysis systems make them unsuitable for portability. The target release date for the Neokidney is 2015, with clinical trials targeted for 2017.98

- Medtronic and Apollo Hospitals: A low-cost, portable system being developed by Medtronic, Inc. and Apollo Hospitals Enterprise Ltd.99 This project was launched in October 2013 with a commitment of $25 million in development funding. Since its announcement, however, neither company has released additional information.

- Purification Technologies: A wearable artificial kidney with reduced power and water consumption needs. Purification Technologies has collaborated with Fresenius to develop the device and has raised a small amount of seed funding from them. Additionally, the U.S. Centers for Medicare and Medicaid Services (CMS) may assist in funding some of the additional $10 million to $15 million required for clinical development.100

Implantable Artificial Kidneys

The development of implantable artificial kidneys would revolutionize RRTs for patients. Such devices would free patients from the tethering of traditional dialysis treatments, as well as provide completely internal, native treatment without the hassle of ongoing treatments, needles, infections at vascular access points, fluid imbalance, and other side effects associated with traditional RRTs. Ideally, implantable artificial kidneys would allow patients to continue working, travel, care for their families, and live much more normal lives than is currently possible with dialysis treatment.

Some advancements in these technologies may be just over the horizon. One potential advancement in this field is an implantable bioartificial kidney currently being developed as a joint project between teams at the University of California, San Francisco and Vanderbilt University.101,102 The bioartificial kidney contains both biological and artificial components, and it may be able to perform filtering, blood pressure maintenance, and pH level regulation, which would provide a significant

100XPRIZE interviews with experts. (2014).
advantage over current treatment modalities. The device has not yet been tested in patients, but the team is currently in preclinical development, with the goal of beginning human clinical trials by 2017.

Another bioartificial kidney project is currently underway at the University of Michigan. The two-part device consists of a blood circuit with a commercial hemofilter and a renal assist device (RAD) that contains living human cells. This project has demonstrated the ability to provide a base level of biological function during filtration (discussed in further detail in the biomaterials section below). The University of Michigan lab is currently in the process of replacing the device’s cellular technology with synthetic membranes that mimic at least some aspects of the biological function that the living cell technology was able to provide.

Innovation in Materials

Advances in biological and synthetic materials for use in dialysis could significantly improve the effectiveness and efficiency of dialysis treatments, leading to improved patient outcomes. By improving filtration and providing additional renal functionality, these materials could bring dialysis closer to replicating real kidney functionality. Some recent advancements in this field show significant promise.

Biomaterials such as those developed using novel cellular therapies can be used to add a limited amount of renal function during the dialysis process, including improved filtration and endocrine molecule production. One example is the renal assist device (RAD) mentioned above. During testing, the RAD exhibited improved ammonia excretion, glutathione metabolism, and vitamin D3 production. However, developmental challenges (such as storage and transportation of living cells) led the development team to shift to synthetic membranes. These membranes are more easily transportable and storable and do provide some improvement in functionality compared with current hemodialysis filtration membranes.

The development of synthetic fibers and membranes that improve uremic solute filtration will improve the standard of dialysis care, despite being simply incremental improvements to dialysis technology. One of the most advanced materials that may be used for this purpose is a nanofiber material fabricated with zeolite-polymer composites that could be designed to filter uremic solutes from the blood. These materials could possibly be used in low-energy and low-water environments to replace more traditional hemodialysis, particularly in developing countries or disaster zones.

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104 Ibid.
Currently, the technology has only been shown to remove creatinine from the blood; however, based on discussions with experts, it should be possible to develop more extensive nanofiber technology that could filter out a much larger range of uremic solutes.\textsuperscript{107}

**Bioengineered Kidneys**

Bioengineered kidneys are often considered the holy grail of organ bioengineering. There are many complexities involved in building a purely bioengineered kidney—from the initial differentiation of the 37 kidney cell types required to the growth of the artificial matrixes and the corresponding functional microarchitecture of a functional organ.\textsuperscript{108} Experts estimate that humanity is 5–20 years away from growing new biological kidneys that have the full functionality of native kidneys.

Despite the long timeline, significant advancements are being made in this field, including stem cell-based therapies that will be capable of regenerating damaged tissues and organs; three-dimensional organoids that exhibit some kidney-like activities; partially functional bioengineered rat kidneys that have been capable of producing a urine-like substance before succumbing to coagulation; and the development of porcine (pig) kidneys that are transplantable.\textsuperscript{109,110,111}

At the Ott Laboratory for Organ Engineering and Regeneration at Harvard University, researchers have decellularized rat, porcine, and human kidneys and “seeded” the resulting scaffolds (the structural architecture of the organ) with kidney cells. The cells grew over the scaffold, and the bioengineered organ produced rudimentary urine within one week.\textsuperscript{112}

Attempts have also been made to three-dimensionally print a kidney, but experts estimate that such kidneys would lack any functionality.\textsuperscript{113}

## REGULATORY LANDSCAPE

A wearable or implantable RRT fits the definition of a medical device and would therefore be heavily regulated. In the United States, a medical device is defined by the Food and Drug Administration

\textsuperscript{107}XPRIZE interviews with experts. (2014).
\textsuperscript{110}Harari-Steinberg, O., Pleniceanu, O., & Dekel, B. (2011). Selecting the optimal cell for kidney regeneration: Fetal, adult, or reprogrammed stem cells. *Organogenesis, 7*(2), 123–134.
\textsuperscript{112}Ott Laboratory for Organ Engineering and Regeneration. (n.d.). Kidney regeneration. Retrieved from http://ottlab.mgh.harvard.edu/?page_id=143
\textsuperscript{113}XPRIZE interviews with experts. (2014).
(FDA) as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

Anything that is labeled, promoted, or used in a manner as defined above is regulated by the FDA and must meet specific regulatory requirements. Medical devices are divided into three distinct classes based on the risks associated with each device:

- **Class I**
  - Low risk and subject to the least regulation
  - Examples: dental floss, examination gloves, and bandages

- **Class II**
  - Medium risk and subject to additional regulation
  - Examples: powered wheelchairs, acupuncture needles, and infusion pumps

- **Class III**
  - Highest risk and subject to the greatest level of regulation
  - Devices that support or sustain human life
  - Generally subject to premarket approvals
  - Examples: replacement heart valves, pulse generators, implantable pacemakers

Novel devices are reviewed on a case-by-case basis to determine their class. Classification procedures are described in the Code of Federal Regulations, Title 21, Part 860, usually referred to as 21 CFR 860.

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115 Ibid.
116 Ibid.
The FDA allows for two regulatory pathways for the marketing of medical devices:

1. The 510(k) process is used for a medical device that can be demonstrated to be substantially equivalent to an existing approved technology. Ninety-nine percent of medical devices enter the marketplace via this process. This pathway rarely requires clinical trials.  

2. The premarket approval process is for novel technologies and typically requires clinical trials. Therefore, new medical device innovation accounts for a fraction of new devices entering the marketplace.

The two main regulatory markets for medical devices are the United States and Europe. The European Medicines Agency (EMA) is the equivalent of the U.S. FDA in Europe. Some experts argue that because the FDA has set up regulatory barriers that exceed those of the EMA, many medical device companies have opted to go through the EMA for approvals and enter the European marketplace rather than seek FDA approval in the United States. These experts estimate that FDA approval for novel medical devices can take up to four years longer than EMA approvals, creating an innovation lag in the United States. This regulatory issue could present a big challenge for American medical device innovators looking to develop novel approaches to ESRD care, and it has been flagged as a major hurdle by many of the medical device experts interviewed by XPRIZE.

Based on the classification criteria outlined by the FDA and expert feedback that XPRIZE received during its research, it is likely that a wearable RRT would fall under the premarket approval pathway to Class III device classification. For example, the FDA has required that current innovations in wearable hemodialysis technologies follow this pathway, which includes human clinical trials.

No FDA-approved implantable artificial kidneys currently exist. Any implantable artificial kidney device would be life-supporting and would present significant potential risk to a patient. Therefore, the FDA would almost certainly classify such technology as a Class III device requiring premarket approval. This pathway would require both preclinical animal testing and human testing prior to receiving marketing authorization from the FDA.

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120 Ibid.
121 XPRIZE interviews with experts. (2014).
ROOT CAUSE ANALYSIS AND MARKET FAILURES

A significant number of challenges and market failures contribute to the growing problem of kidney disease. These challenges have been synthesized into the three major categories listed in Table 5 below.

| **High Social Burden** | • Direct public and private costs  
|                        | • Indirect costs to economy and society  
|                        | • Poor public health  
|                        | • Lack of education and awareness  
| **Few Incentives to Innovate** | • Public policy and regulations  
|                        | • Lack of funding  
|                        | • Slow pace of innovation  
| **Poor Patient Outcomes** | • High morbidity  
|                        | • High mortality  
|                        | • Side effects of treatments: malaise, immobility, health complications, etc.  

Kidney disease places a high cost on society, as well as on individuals. In the United States alone, Medicare spends nearly $35 billion on ESRD treatments annually,\(^\text{124}\) which is more than the total yearly budget of the National Institutes of Health (NIH).\(^\text{125}\) Medicare has found it difficult to enforce a high standard of care while ensuring universal access for patients. Federal records show that dialysis centers are not inspected as frequently as they should be and that mortality and hospitalization rates are not improving.\(^\text{126}\) Patients with ESRD often experience extreme financial hardship during their treatments, as the burden of dialysis (poor health and being tethered to dialysis machines multiple times a week) causes many to lose their jobs.\(^\text{127}\) As kidney disease disproportionately impacts minority groups, the elderly, and the impoverished, individuals and families with limited resources bear an inordinate amount of the burden.\(^\text{128,129,130}\)

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\(^{127}\) XPRIZE interviews with experts. (2014).


Government policies that determine reimbursement for ESRD treatments, regulatory requirements, and research funding combine to create a web of perverse incentives that hinder innovation in the kidney space.

In addition to the previously mentioned lack of funding from the NIH, the development and approvals process for therapeutic devices further hinders innovation. Any Class III device requiring premarket approval will require both preclinical animal testing and human testing prior to receiving marketing authorization from the FDA. These costs can be exorbitant. A 2010 Stanford University report found that it costs, on average, $94 million to develop a Class III device and successfully gain FDA premarket approval. Of that total, more than $75 million (nearly 80 percent) is spent on “FDA-linked” stages required for bringing a high-risk Class III device to market.

Innovators rely heavily on government grants and venture capital to fund the development of innovative medical devices, and these time- and resource-intensive approval processes often prevent potential funders from investing in novel technologies. Finding sufficient funding has grown even more challenging recently; 2014 venture capital funding is estimated at $2.5 billion—a drop to 2005 levels—hitting those working in higher risk development (e.g., Class III development) particularly hard.

[I am] “forced to turn down investing in too many promising medical innovations—technologies that you and I would want access to in order to help our loved ones if they needed them—because it is difficult to predict how long and how much capital it will take to get a particular innovation approved by the FDA and into patient care.”

—Ross Jaffe, MD Venture Capitalist, Versant Ventures

Testimony before the U.S. House Energy and Commerce Subcommittee on Health, February 2012

134 Ibid.
Finally, despite the high annual cost of care, patients on dialysis experience poor quality of life and health outcomes. They often suffer from malaise and weariness. They are immobilized by being tethered to dialysis machines. Many experience a deep sense of dependency, often resulting in depression, which in turn leads to worse health outcomes.  

Dialysis does not cure kidney disease; it simply prolongs lives. Dialysis does not provide all the functionality of a kidney (mineral, fluid, and hormone management) and provides only 5–10 percent of filtering functionality. Patients suffer from high mortality and multiple comorbidities while on dialysis. In fact, the side effects of dialysis are so significant that patients are frequently admitted to emergency rooms with cardiovascular difficulties and sepsis (an inflammatory response to bacterial infection). The death rate among dialysis patients in the United States is 25 percent—much higher than that in Japan and other industrialized nations. (The rate in Japan has remained stable at 10 percent over the last three decades.) Short treatment times, minimally trained dialysis staff, and isolation during treatment are all factors that have been found to correlate with increased mortality among U.S. patients.  

The challenges of high social burden, lack of traditional investment from funders, and poor patient outcomes can seem overwhelming. However, an incentive prize that leverages investments, brings innovators and researchers together, promotes a patient-centric solution, and educates the public on the severity of the problem can address—and overcome—these challenges.  

**CONCLUSION**

XPRIZE believes the kidney space is ripe for disruption. A prize competition could address the lack of effective, patient-centric treatments for end-stage renal disease (ESRD) and revolutionize the space by incentivizing innovation in a stagnant field that has only seen incremental innovation in the past three decades, resulting in new technologies for treating ESRD that lead to improved patient outcomes and a reduced social burden.
APPENDICES

APPENDIX A: INTERVIEWEES AND VISIONEERING PARTICIPANTS
APPENDIX B: STAGES OF CHRONIC KIDNEY DISEASE
APPENDIX A: INTERVIEWEES AND VISIONEERING PARTICIPANTS

The following is a list of interviewees and Visioneering participants who graciously provided guidance and input regarding the contents of this prize design. Please note that the conclusions and content within the report are those of XPRIZE and do not necessarily reflect the opinions of the individuals listed.

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<tr>
<th>NAME</th>
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<tr>
<td>Kevin Abbott *</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>Brian Anthony*</td>
<td>Massachusetts Institute of Technology</td>
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<tr>
<td>Tony Atala</td>
<td>Wake Forest School of Medicine</td>
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<td>Aaron Baker</td>
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<td>Vito Campese</td>
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<td>Deidre Crews</td>
<td>Johns Hopkins University</td>
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<td>Jeremy Deffield*</td>
<td>Biogen Idec</td>
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<td>Sanjoy Dutta</td>
<td>Juvenile Diabetes Research Foundation</td>
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<td>Mitsuhiro Ebara</td>
<td>National Institute for Material Science</td>
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<tr>
<td>Ron Falk</td>
<td>University of North Carolina</td>
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<td>William Fissell*</td>
<td>Silicon Kidney</td>
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<tr>
<td>Chris Folk</td>
<td>Amgen</td>
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<tr>
<td>Gregory Germino*</td>
<td>National Institutes of Health</td>
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<tr>
<td>Matt Goodman</td>
<td>3Scan</td>
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<tr>
<td>Anthony Gucciardo</td>
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<td>Thomas Gustafson</td>
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<td>Garth Graham</td>
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<td>Melissa Grunlan</td>
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<td>Ray Hakim</td>
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<td>Kyle Harris*</td>
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<td>Tod Ibrahim*</td>
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<td>Yordan Kostov*</td>
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<td>Laura Lightbody*</td>
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<td>Murray Loew*</td>
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<tr>
<td>Mark Lukaszewski*</td>
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<td>Tammi Marcoullie</td>
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<td>Raj Mehrotra</td>
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<td>Mallika Mendu</td>
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<td>Rachel Meyer*</td>
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<tr>
<td>Steven Minger</td>
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<tr>
<td>Sharon Moe*</td>
<td>Indiana University Division of Nephrology</td>
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<td>Bruce Molitoris</td>
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<tr>
<td>Carolyn Neuland</td>
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<td>Grant Olan*</td>
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<td>Harald Ott*</td>
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<tr>
<td>Sandeep Patel*</td>
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<td>Uptal Patel*</td>
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<td>Govind Rao*</td>
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<td>Martine Rothblat</td>
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<td>Shuvo Roy*</td>
<td>University of California San Francisco</td>
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<td>Minnie Sarwal</td>
<td>University of California San Francisco</td>
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<tr>
<td>John Sedor*</td>
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<td>Murray Sheldon</td>
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<td>Abhi Vase*</td>
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<td>Dan Weiner</td>
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<tr>
<td>Jason Wertheim*</td>
<td>Northwestern University</td>
</tr>
<tr>
<td>Otto Wilson*</td>
<td>Catholic University</td>
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</tbody>
</table>

* Denotes a Visioneering participant
APPENDIX B: STAGES OF CHRONIC KIDNEY DISEASE

CKD progression is charted along five stages, with stage 1 representing a minor loss of kidney function and stage 5 representing complete kidney failure. Stage 5 results in ESRD.

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<th>Kidney Function</th>
<th>Patient Symptoms</th>
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</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>• Normal to very mild loss of kidney function</td>
<td>• Often no symptoms</td>
</tr>
<tr>
<td></td>
<td>• Glomerular filtration rate (GFR) &gt; 90 mL/min</td>
<td></td>
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<tr>
<td>Stage 2</td>
<td>• Mild to moderate loss of kidney function</td>
<td>• High blood pressure</td>
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<td></td>
<td>• GFR = 60–89 mL/min</td>
<td>• Protein in urine</td>
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<tr>
<td>Stage 3</td>
<td>• Moderate to severe loss of kidney function</td>
<td>• Anemia</td>
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<tr>
<td></td>
<td>• GFR = 30–59 mL/min</td>
<td>• Early bone disease</td>
</tr>
<tr>
<td>Stage 4</td>
<td>• Severe loss of kidney function</td>
<td>• Fatigue</td>
</tr>
<tr>
<td></td>
<td>• GFR = 15–29 mL/min</td>
<td>• Swelling</td>
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<tr>
<td></td>
<td></td>
<td>• Nausea</td>
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<tr>
<td></td>
<td></td>
<td>• Vomiting</td>
</tr>
<tr>
<td>Stage 5</td>
<td>• End-stage renal disease (kidney failure)</td>
<td>• Fatigue</td>
</tr>
<tr>
<td></td>
<td>• GFR &lt;15 mL/min</td>
<td>• Swelling</td>
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<td>• Nausea</td>
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<td></td>
<td>• Vomiting</td>
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<td></td>
<td></td>
<td>• Bone pain</td>
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<tr>
<td></td>
<td></td>
<td>• Unexplained weight loss</td>
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<td>• Loss of appetite</td>
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<td>• Inability to urinate</td>
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<tr>
<td></td>
<td></td>
<td>• Confusion</td>
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<tr>
<td></td>
<td></td>
<td>• Difficulty concentrating</td>
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