

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 |
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| <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

- **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

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

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

- **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

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

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

- **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

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

- ***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

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

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

- **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

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

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

- ***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.