

NephCure Accelerating Cures Institute: A Multidisciplinary Consortium to Improve Care for Nephrotic Syndrome



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Introduction: NephCure Accelerating Cures Institute (NACI) is a collaborative organization sponsored by NephCure Kidney International and the University of Michigan. The Institute is composed of 7 cores designed to improve treatment options and outcomes for patients with glomerular disease: Clinical Trials Network, Data Warehouse, Patient-Reported Outcomes (PRO) and Endpoints Consortium, Clinical Trials Consulting Team, Quality Initiatives, Education and Engagement, and Data Coordinating Center.

Methods: The Trials Network includes 22 community- and hospital-based nephrology practices, 14 of which are trial-only sites. Eight sites participate in the NACI Registry, and as of October 2017, 1054 patients are enrolled with diagnoses including but not limited to focal segmental glomerulosclerosis, minimal change disease, membranous nephropathy, IgA nephropathy, and childhood-onset nephrotic syndrome. By using electronic health record data extraction, robust and efficient clinical data are captured while minimizing the burden to site-based network staff.

Results: The Data Warehouse includes her-extracted data from registry patients, PRO development data, and data from completed observational studies and clinical trials. The Clinical Trial Consulting Team provides support for trial design in rare diseases leveraging these data. The PRO and Endpoints Consortium develops shorter-term endpoints while capturing the patient-reported significance of interventions under study. The Quality Initiatives and Education/Engagement cores elevate the level of care for patients. The Data Coordinating Center manages the analysis and operations of the Institute.

Conclusion: By engaging with patients, academia, industry, and patient advocate community representatives, including our Patient Advisory Board, NACI strives for better outcomes and treatments using evidence-based support for clinical trial design.

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KEYWORDS: clinical trials; electronic health record; glomerular disease; nephrotic syndrome; patient advisory; patient-reported outcomes

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In 2009, Kidney Disease: Improving Global Outcomes Glomerulonephritis Guidelines were published and included recommendations for the management of primary proteinuric glomerular diseases, including focal segmental glomerulosclerosis, minimal change

disease, and membranous nephropathy, and steroid-sensitive and steroid-resistant nephrotic syndrome (NS) in children. The evidence grade for these guidelines was quite weak due to a paucity of clinical trials. In addition, commonly used therapies have adverse side effects that adversely influence drug tolerability, dose, and duration. The lack of effective and safe therapeutic options results in adverse short-, intermediate-, and long-term outcomes.

Primary proteinuric kidney diseases (PPKDs), including focal segmental glomerulosclerosis, minimal change disease, and membranous nephropathy, are rare chronic health conditions that negatively affect short-term health and often lead to end-stage kidney disease.¹ The condition of NS with edema, hypoalbuminemia, and large urinary protein losses is associated with an increased risk for acute kidney injury, thromboembolic events, serious infections, and impaired health-related quality of life.²⁻⁵ Nondiabetic glomerular diseases are leading causes of end-stage kidney disease, accounting for 6.3% of incident end-stage kidney disease in adults and 20% of end-stage kidney disease in children,⁶ and 14.3% of prevalent disease in adults and 21.8% in children.^{7,8} Taken together, PPKDs represent a significant patient and public health problem.

In the past decade, advances in biomedical research have occurred that aid in the understanding of the biologic underpinnings of NS.⁹⁻¹² Leveraging these scientific advances into viable treatments and improvement in clinical outcomes depends on our ability to perform high-quality, efficient, and successful clinical trials.^{13,14}

Over the past decade, it has become clear that a novel approach to the care of patients, development of trials, and conduct of trials is necessary to improve outcomes in patients with proteinuric kidney disease. Early and meaningful input from diverse stakeholders, including patients, advocacy groups, industry, clinicians, payers, and researchers, is likely to stimulate progress where traditional individual stakeholder approaches have failed. Recognizing the essential need for innovation, NephCure Kidney International (NKI), a non-for-profit advocacy group, and the University of Michigan partnered with clinicians, patients, and scientists to develop NephCure Accelerating Cures Institute (NACI). NACI was founded in 2015 as a unique collaborative to improve the treatment options and health outcomes of patients with glomerular disease. Barriers to the development and conduct of clinical trials for glomerular diseases and models used to address similar concerns in other health conditions have been identified and used to create the organizational framework of NACI (Figure 1).¹⁵⁻¹⁸ The purpose of this article was to share information about NACI that

may serve as a model for other rare disease therapeutic development initiatives.

METHODS

Data Management and Analysis

Key sources of data are accessible to support trial development, analysis simulation, and quality initiatives. The NACI Data Warehouse manages and stores data from the NACI patient registry, and active and completed trials. This data resource is available for hypothesis generation, hypothesis testing, clinical trial modeling, targeted enrollment, and quality improvement efforts. To support efficient data collection for consenting NACI Registry participants, the participating nephrology practices extract electronic medical records, transform the data into the NACI common data model, and submit data files from the date of electronic health record patient record initiation with monthly updates using secure data transfer methods.

The NACI Data Warehouse includes subject matter areas, including patient demographics, diagnoses, encounters, vital signs and status, clinical laboratory results, medications, procedures, kidney biopsy reports, and end-stage kidney disease and transplant-specific data for patients in the registry. The NACI Data Warehouse also allows for electronic data capture using manual data entry for domains requiring confirmation by the local clinical care team or where local electronic health records have incomplete data domains. Data visualization is provided to all participating sites for local population management and study governance.

Clinical Trials Consulting

A key component to the successful conduct and execution of clinical trials occurs at the trial development phase. During trial development, multiple stakeholders participate in trial design, feasibility, and acceptability to patients' and clinicians' assessment, and consent and recruitment material review. The Clinical Trials Consulting Core represents a feature within NACI that supports clinical trial development and review for investigator and industry-initiated studies. The consultations are tailored to the needs of the requesting investigator with options for participation in a single day workshop with experts in trial design, epidemiology, translational research, clinician and patient engagement, and operational feasibility or remote review of a developed protocol by appropriate experts.

Clinical Trials Network

The Clinical Trials Network is composed of nephrology practices in hospital and community-based settings with clinical trials expertise. The practices have a focus on children, adults, or a combination, thereby ensuring

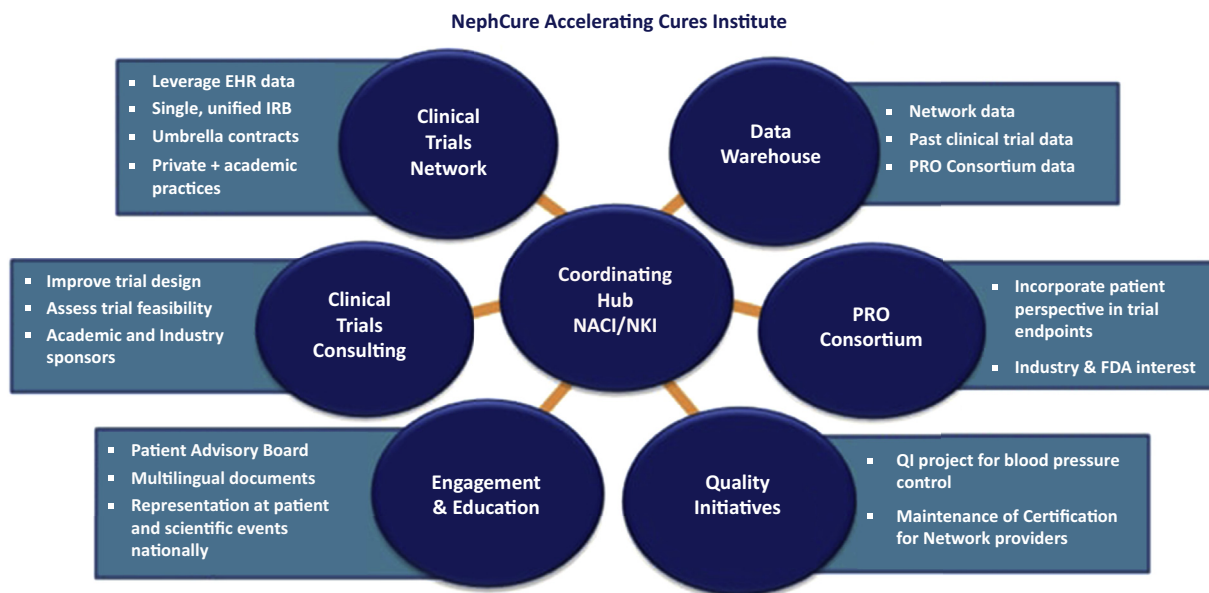


Figure 1. Composition and Core of the NephCure Accelerating Cures Institute (NACI). EHR, electronic health record; FDA, Food and Drug Administration; IRB, institutional review board; NKI, NephCure Kidney International; PRO, patient-reported outcomes; QI, quality improvement.

the network capacity for conducting clinical trials across the pediatric and adult age continuum. The network is governed by representatives from participating institutions, NKI, the coordinating center, and a patient representative. In addition to study participation, patients and nephrology practices participating in the NACI Clinical Trials Network have access to patient educational resources, information about research opportunities, and maintenance of certification and quality improvement programs. The aim of this approach is to build a highly engaged network of patients, providers, and practices.

Network efficiency is a priority in the NACI Network. This network operates under a single institutional review board-of-record for sites within the United States. Sites in other countries follow national regulatory approval processes. A master agreement contract structure is also in place enabling timely contract negotiations across multiple centers for clinical trials and other research projects. These efficiencies are designed to optimize clinical trial initiation.

Patient-Reported Outcome Consortium

Patient-reported outcome (PRO) measures allow clinicians and researchers to capture the patient experience in a quantifiable manner that can be used for clinical care and research purposes.¹⁹ Generic PRO measures have been used in NS and other diseases to describe a patient's health-related quality of life.^{3,4} Although these generic measures enable comparisons between PPKDs and other disease groups, they lack the specificity to fully describe the kidney disease experience in a precise, sensitive, and patient-relevant manner. Specifically, generic measures

do not describe many of salient NS disease characteristics, such as specific symptoms (e.g., edema), overall symptom burden, and the uncertainty related to the relapsing, remitting, and progressive nature of the disease. PRO measures have recently been accepted as viable endpoints for clinical trials and medication labeling.²⁰ The desire to measure and fully incorporate the NS patient experience into clinical decision-making, research, and clinical trials has prompted the development of the PRO Consortium within NACI. The PRO Consortium will seek to develop PRO measures that describe the NS-specific patient experience and NS-specific challenges with health-related quality of life. Following development and validation, these disease-specific PRO tools will be available to incorporate into patient care and clinical trials.

Patient Advisory Board

Incorporating the patient voice into all aspects of the consortium is a key tenant of NACI. The Patient Advisory Board (PAB) was created to achieve this goal and serves the purpose of advising NACI leadership on priorities important to patients with NS. The board was established in January 2016 and is composed of adult patients and family members of children with focal segmental glomerulosclerosis, minimal change disease, membranous nephropathy, and childhood-onset idiopathic NS, not biopsied from NACI site communities. In addition, they represent patients with treatment-responsive and treatment-resistant disease across the spectrum of native kidney, dialysis, and transplant dependence. The members were identified within individual NACI

Network site practices and by the NKI team, introduced to the concept of NACI and the PAB and, when interest was confirmed, recommended to the NACI Steering Committee by letter of recommendation. Each candidate board member was provided written description of NACI and the PAB goals, and invited to participate in an individual conference call to introduce the program, the commitment, and address questions. At the conclusion of these calls, a formal invitation to join the PAB was issued with a request for a minimum participation tenure of 1 year. The PAB meets by conference call 3 times yearly and in person at the NACI Investigator-PAB Annual Meeting. No members of the PAB are employed by a biotechnology company or the pharmaceutical industry. The PAB has reviewed and ratified the PAB charter; reviewed, edited, and approved patient education materials; contributed to research survey design; participated in the development of patient communication strategies; and participated in panel discussions regarding research priorities and future directions of the Institute. The charter does not place limits on the duration of membership. The PAB is a vital component of the NACI as a patient-centered collaborative effort.

Patient Engagement and Education

NACI providers are committed to ensuring that patients and families have the educational tools and resources needed to gain the necessary knowledge, competence, and confidence to understand and cope with their disease. Shared decision-making tools related to diet modifications, treatment options, and other topics unique to this community are available for patients and clinicians to support treatment decisions. In addition, NKI offers educational webinars for patients and family caregivers. As patients become more empowered and informed, they are better able to share in the decision-making process around their care. This program incorporates well-known chronic disease management tactics of patient and medical team partnerships to improve health outcomes and health care delivery.

Quality Initiatives and Maintenance of Certification

Quality improvement methodology is a part of the current health care environment. The techniques used in improvement science lend themselves to application under real-world conditions of patient care. Unlike the clinical research environment, which is strictly controlled, results from rapid improvement can reach the patient sooner with more immediate impact on outcomes. The systematic utilization of quality improvement methodology has been shown to improve

patient safety and outcomes, decrease waste, and enhance cost savings. To date, application of this science in kidney disease has not been widely studied. NACI will build on the body of knowledge readily available by taking known methodologies and studying the implementation of these improvement science methodologies in PPKD.

NACI's goal is to bring together health care teams, patients, and family caregivers to help design and deliver the care and services that patients need. Together they will develop solutions to gaps in care, and barriers and errors that currently exist in the care of patients with PPKD. Although focus groups and family advisory groups are of great importance and have been the traditional venue to ascertain such needs, our goal is to bring the patient into the health care environment earlier in the process, having the patient partner with us in the initial design and implementation of research and delivery of patient care. With health literacy in the forefront, NACI will reengineer the standards of health care delivery to include shared decision making, patient-oriented agendas, visit co-production, and patient-centered care. The network will shift the focus from information delivery to building skills, for each patient or caretaker regardless of educational, social, or cultural factors to interpret basic health information to make informed decisions with confidence and competence.

Providers have always wanted to do what is best for the patient, but we now recognize that good intentions are not enough to ensure quality care. To guarantee that the right care is given to every patient every time, we must use data and the formal methodology of improvement science. Without these crucial tools, we cannot be sure that we are making and sustaining improvements in patient care. The good news is that training in improvement science methodology gives health care providers a clearly defined framework to achieve better outcomes.

Medical board specialties have established requirements for practice-based quality improvement initiatives to maintain certification. NACI has developed and implemented quality improvement initiatives to improve nephrology health care delivery and PPKD patient outcomes. These initiatives also will serve as a means of meeting the necessary requirements for maintenance of certification for providers within the NACI Network.

Progress to Date

The NACI patient registry has enrolled 1054 patients (75% adults and 25% children). The demographics and patient characteristics of the 1054 patients with complete data are displayed in [Table 1](#). Registry

Table 1. Description of patients in the NACI Data Warehouse as of October 2017

| Characteristic | All patients, <i>n</i> = 1054 | Adults, <i>n</i> = 793 | Children, <i>n</i> = 261 |
|----------------------------------------------------|----------------------------------|---------------------------|-----------------------------|
| Age, median (IQR) | 37 (18–54) | 46 (31–58) | 11 (8–15) |
| Female, <i>n</i> (%) | 462 (44) | 354 (45) | 108 (41) |
| Race, <i>n</i> (%) | | | |
| White/Caucasian | 584 (55) | 447 (56) | 137 (52) |
| Black/African American | 153 (15) | 117 (15) | 36 (14) |
| Asian | 126 (12) | 88 (11) | 38 (15) |
| Other | 191 (18) | 141 (18) | 50 (19) |
| Hispanic ethnicity, <i>n</i> (%) | 172 (16) | 135 (17) | 37 (14) |
| Diagnosis, <i>n</i> (%) | | | |
| Focal segmental glomerulosclerosis ^a | 273 (26) | 229 (29) | 44 (17) |
| Minimal change disease ^b | 151 (14) | 91 (11) | 60 (23) |
| IgA | 192 (18) | 180 (23) | 12 (5) |
| NS, not biopsied | 125 (12) | 25 (3) | 100 (38) |
| Membranous nephropathy | 107 (10) | 101 (13) | 6 (2) |
| Other | 206 (20) | 167 (21) | 39 (15) |
| Hypertension | | | |
| By use of anti-HTN therapy | 608 (58) | 509 (64) | 99 (38) |
| By persistent elevated blood pressure ^c | 93 (9) | 69 (9) | 24 (9) |
| By record on diagnosis or problem list | 675 (64) | 578 (73) | 97 (37) |
| By any of the above 3 definitions | 826 (78) | 671 (85) | 155 (59) |
| Weight status | | | |
| Underweight | 29 (3) | 20 (3) | 9 (3) |
| Normal | 375 (36) | 223 (28) | 152 (58) |
| Overweight | 281 (27) | 239 (30) | 42 (16) |
| Obese | 310 (29) | 255 (32) | 55 (21) |
| Unknown | 59 (6) | 56 (7) | 3 (1) |
| First serum albumin, median (IQR) | 4.0 (3.6–4.3) | 4.0 (3.6–4.3) | 4.0 (3.3–4.3) |
| First protein: creatinine ratio, median (IQR) | 0.7 (0.1–2.4) | 0.7 (0.2–2.2) | 0.5 (0.1–3.1) |

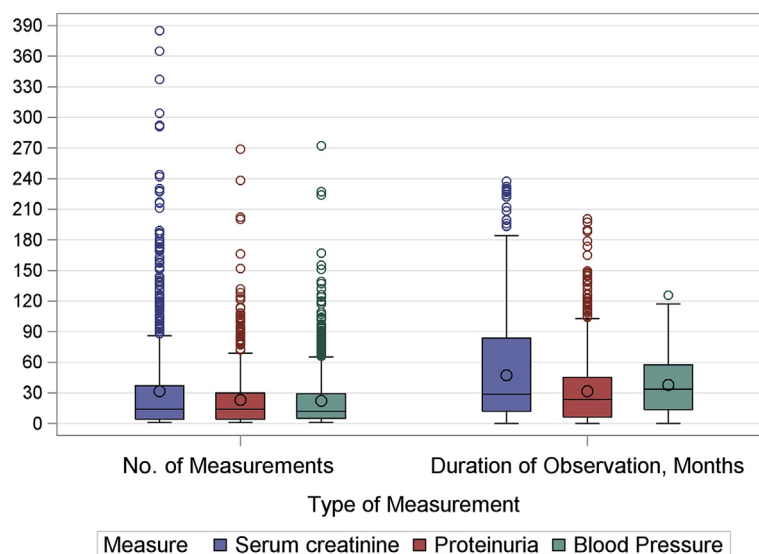
HTN, hypertension; IQR, interquartile range; NACI, NephCure Accelerating Cures Institute; NS, nephrotic syndrome.

^aIncludes 9 C1q nephropathy.

^bIncludes 17 IgM nephropathy and 5 mesangial proliferative glomerulonephritis.

^cTwo of the 3 last blood pressure readings in hypertensive range.

data include a median of 5 (interquartile range [IQR] = 2–9) patient years of data per patient following initial qualifying renal biopsy. The database includes a median of 14 serum creatinine (IQR = 4–37), 14 proteinuria (IQR = 4–30), and 12 blood pressure measurements per patient (IQR = 5–29) (Figure 2). Patient kidney disease is confirmed by the treating nephrologist, and archived kidney biopsy reports are uploaded into the database following redaction of identifiers. The most common kidney diseases in the registry are focal segmental glomerulosclerosis (26%, *n* = 273), minimal change disease (14%, *n* = 151), membranous nephropathy (10%, *n* = 107), and IgA nephropathy (18%, *n* = 192) in addition to pediatric NS, not biopsied (12%, *n* = 125) (see Figure 3). The NACI Analytics Dashboard has been developed to allow site-specific and network-wide visualization of key variables of interest. Example network- and patient-level dashboards and shown in Figures 4 and 5. Most children and adults are chronic kidney disease stages 1 to 3 and represent a large sample of patients early enough in their disease course for clinical trial eligibility. Two clinical trials are launching in 2017. The PRO Consortium has the first disease-specific PRO tool for adults with focal segmental glomerulosclerosis ready for validation and implementation. Shared decision-making educational tools are being tested within network participating sites, and the first maintenance of certification project focusing on hypertension has been initiated. The Trials Network is undergoing expansion and is establishing strategic international network partnerships to support efficient and complete enrollment in clinical trials.

**Figure 2.** Availability of key data elements per patient in the NephCure Accelerating Cures Institute Data Warehouse.

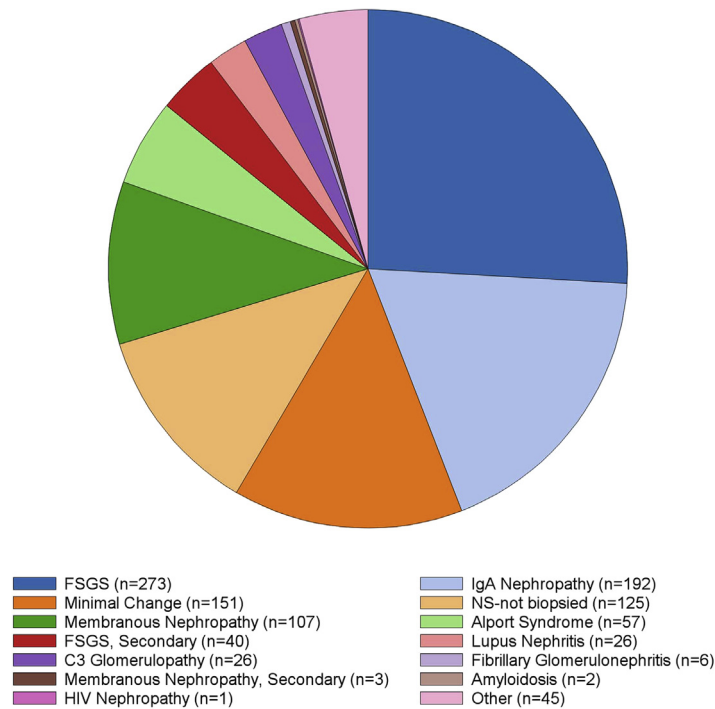


Figure 3. Primary diagnoses in NephCure Accelerating Cures Institute. FSGS, focal segmental glomerulosclerosis.

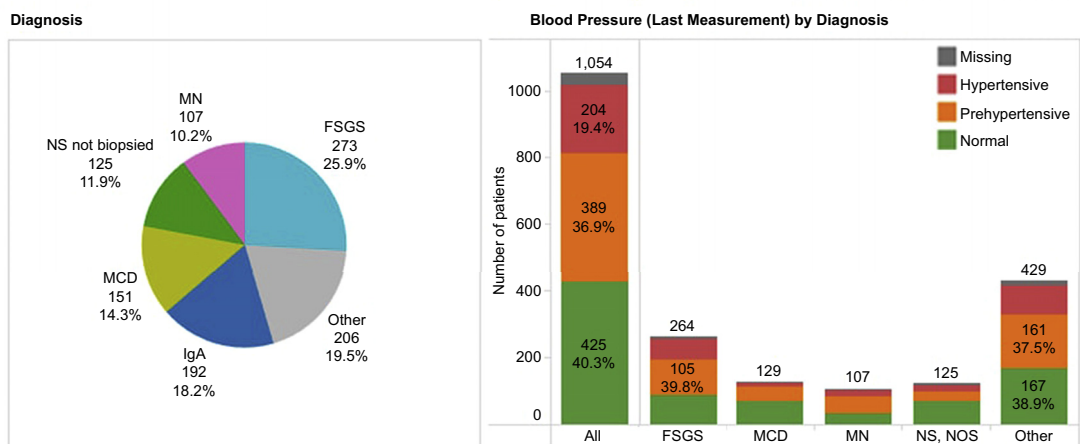
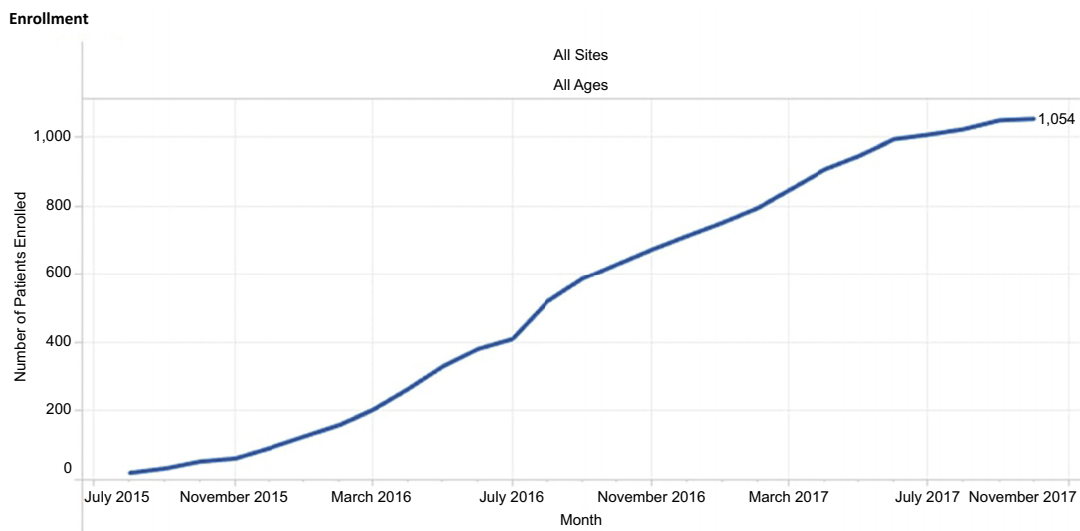


Figure 4. Example NephCure Accelerating Cures Institute network dashboard. FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; MN, membranous nephropathy; NOS, not otherwise specified; NS, nephrotic syndrome.



Figure 5. Example NephCure Accelerating Cures Institute patient dashboard. BMI, body mass index; Dec., December; eGFR, estimated glomerular filtration rate; Jan., January; Jun., June; UP:C, urine protein: creatinine ratio.

Hypertension Quality Indicators

Analysis of the data from participating patients has demonstrated that hypertension is present by diagnosis (64%), by antihypertensive therapy, excluding renin-angiotensin system blockade (58%), and by persistently elevated blood pressures (9%). A diagnosis of hypertension on the problem list or the visit encounter is associated with higher rates of antihypertensive therapy (75% vs. 27%, $P < 0.001$). Furthermore, antihypertensive therapy is initiated a median of 61 days (IQR 1–296) from the time of 2 or more consecutive qualifying elevated blood pressures, which is much faster than results published from primary care practice settings.²¹

Funding Sources and Sustainability Plans

The NACI program began with a partnership between the nonprofit entities NKI and the University of

Michigan. This partnership provided key organizational infrastructure as in-kind and monetary contributions and leveraged complementary skills and resources for the initial development and pilot phase. In the second year of the program, unrestricted donations were provided to NKI from 2 pharmaceutical companies, Retrophin and Pfizer, to support NACI development and thereby offset some of the fund-raising burden of NKI. The sustainability plan is based on the premise that the research of the organization is fundable through governmental, nongovernmental, and private entities, and that the cost of program maintenance would be less than program development. In the second and third years of the program, project-specific grant proposals were submitted, and sponsored research initiatives have been launched. The transition from a financially dependent program in the initial operating years to one

in which most of the program is supported through extramural research funding is ongoing at this time. For others seeking to replicate this program, program development and sustainability models are best developed with the initial partners, tailored to the expected duration and magnitude of the funding and partnership and buttressed by mitigation plans that anticipate and manage the inevitable ebb and flow of sponsored research programs.

In conclusion, PPKD represents rare diseases that for decades have been relatively stagnant in the development of new treatments and health outcomes. In this article, we described the development of a unique consortium that involves a diverse group of stakeholders that supports the identification and testing of new therapies through clinical trials and improves patient health outcomes. This program may serve as a viable model to improve the outcomes in patients with other rare diseases.

DISCLOSURE

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