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Corresponding Author: Laura Mariani, MD, MSCE; University of Michigan, MSRB II 4544C, 1150 W. Medical Center Dr., Ann Arbor, MI 48109; lmariani@umich.edu.

*Members of the CureGN Consortium are "Collaborators" shown in Acknowledgements.

Authors' Contributions: Research idea and study design: LHM, ASB, PAC, MFF, MH, MAH, JJH, KK, PHN, CN, MNR, DVR, HT, SEW, CB, PHC, MM, CJP, AR, SV, LB, DC, VD, JCJ, JBK, LPL, KT, RJF, AGG, BWG, DSG, LAG, LBH, MK, BR, WES, LMGW; Statistical analysis: MH, BWG; Supervision and mentorship: RJF, AGG, BWG, DSG, LAG, LBH, MK, BR, WES, LMGW. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriate investigated and resolved.

CureGN Consortium Members: Columbia University (affiliation is Columbia unless otherwise indicated): Wooin Ahn, Gerald B. Appel, Revekka Babayev, Ibrahim Batal, Andrew S. Bomback, Eric Brown, Eric S. Campenot, Pietro Canetta, Brenda Chan, Debanjana Chatterjee, Vivette D. D'Agati, Elisa Delbarba, Hilda Fernandez, Bartosz Foroncewicz (University of Warsaw, Poland), Ali G. Gharavi (Principal Investigator [PI]), Gian Marco Ghiggeri (Gaslini Children's Hospital, Italy), William H. Hines, Namrata G. Jain, Byum Hee Kil, Krzysztof Kiryluk, Wai L. Lau, Fangming Lin, Francesca Lugani (Gaslini Children's Hospital, Italy), Maddalena Marasa, Glen Markowitz, Sumit Mohan, Xueru Mu, Krzysztof Mucha (University of Warsaw, Poland); Thomas L. Nickolas, Stacy Piva, Jai Radhakrishnan, Maya K. Rao, Simone Sanna-Cherchi, Dominick Santoriello, Michael B. Stokes, Natalie Yu, Anthony M. Valeri, Ronald Zviti; Midwest Pediatric Nephrology Consortium (MWPNC): Larry A. Greenbaum (PI; Emory University), William E. Smoyer (PI; Nationwide Children's), Amira Al-Uzri (Oregon Health & Science University), Isa Ashoor (Louisiana State University [LSU] Health Sciences Center), Diego Aviles (LSU Health Sciences Center), Rossana Baracco (Children's Hospital of Michigan), John Barcia (University of Virginia), Sharon Bartosh (University of Wisconsin), Craig Belsha (Saint Louis University/Cardinal Glennon), Corinna Bowers (Nationwide Children's Hospital), Michael C Braun (Baylor College of Medicine/Texas Children's Hospital), Aftab Chishti (University of Kentucky); Donna Claes (Cincinnati Children's Hospital), Carl Cramer (Mayo Clinic); Keefe Davis (Washington University in St. Louis), Elif Erkan (Cincinnat Children's Hospital Medical Center), Daniel Feig (University of Alabama, Birmingham [UAB]), Michael Freundlich (University of Miami/Holtz Children's Hospital), Rasheed Gbadegesin (Duke University Medical Center), Melisha Hanna (Children's Colorado/University of Colorado), Guillermo Hidalgo (East Carolina University), Tracy E. Hunley (Monroe Carell Jr Children's Hospital at Vanderbilt University Medical Center), Amrish Jain (Children's Hospital of Michigan), Mahmoud Kallash (Nationwide Children's Hospital), Myda Khalid (JW Riley Hospital for Children, Indiana University School of Medicine), Jon B. Klein (The University of Louisville School of Medicine), Jerome C. Lane (Feinberg School of Medicine, Northwestern University), John Mahan (Nationwide Children's), Nisha Mathews (University of Oklahoma Health Sciences Center), Carla Nester (University of Iowa Stead Family Children's Hospital), Cynthia Pan (Medical College of Wisconsin), Larry Patterson (Children's National Health System), Hiren Patel (Nationwide Children's Hospital), Adelaide Revell (Nationwide Children's Hospital), Michelle N. Rheault (University of Minnesota Masonic Children's Hospital), Cynthia Silva (Connecticut Children's Medical Center), Rajasree Sreedharan (Medical College of Wisconsin), Tarak Srivastava (Children's Mercy Hospital), Julia Steinke (Helen DeVos Children's Hospital), Katherine Twombley (Medical University of South Carolina), Scott E. Wenderfer (Baylor College of Medicine/Texas Children's Hospital), Tetyana L. Vasylyeva (Texas Tech University Health Sciences Center), Donald J. Weaver (Levine Children's Hospital at Carolinas Medical Center), Craig S. Wong (University of New Mexico Health Sciences Center); The University of North Carolina (UNC; affiliation is UNC unless otherwise indicated): Anand Achanti (Medical University of South Carolina [MUSC]), Salem Almaani (The Ohio State University [OSU]), Isabelle Ayoub (OSU), Milos Budisavljevic (MUSC), Vimal Derebail, Huma Fatima (UAB), Ronald Falk (PI), Agnes Fogo (Vanderbilt), Todd Gehr (Virginia Commonwealth University [VCU]), Keisha Gibson (Vanderbilt), Dorey Glenn (Vanderbilt), Raymond Harris (Vanderbilt), Susan Hogan (UAB), Koyal Jain (UAB), J. Charles Jennette (UAB), Bruce Julian (UAB), Jason Kidd (VCU), Louis-Philippe Laurin (Hôpital Maisonneuve-Rosemont [HMR], Montreal), H. Davis Massey (VCU), Amy Mottl (UNC), Patrick Nachman (UNC), Tibor Nadasdy (MUSC), Jan Novak (UAB), Samir Parikh (OSU), Vincent Pichette (HMR Montreal), Caroline Poulton (UNC), Thomas Brian Powell (Columbia Nephrology Associates), Matthew Renfrow (UAB), Dana Rizk (UNC), Brad Rovin (OSU), Virginie Royal (HMR Montreal), Manish Saha (UNC), Neil Sanghani (Vanderbilt), Sally Self (MUSC); University of Pennsylvania (UPenn; affiliation is UPenn unless otherwise indicated): Sharon Adler (Los Angeles Biomedical Research Institute at Harbor, University of California Los Angeles [UCLA]), Charles Alpers (University of Washington), Raed Bou Matar (Cleveland Clinic), Elizabeth Brown (University of Texas [UT] Southwestern Medical Center), Daniel Cattran (University of Toronto), Michael Choi (Johns Hopkins), Katherine M. Dell (Case Western/Cleveland Clinic), Ram Dukkipati (Los Angeles Biomedical Research Institute at Harbor UCLA), Fernando C. Fervenza (Mayo Clinic), Alessia Fornoni, (University of Miami), Crystal Gadegbeku (Temple University), Patrick Gipson (University of Michigan), Leah Hasely (University of Washington), Sangeeta Hingorani (Seattle Children's Hospital), Michelle Hladunewich (University of Toronto/Sunnybrook), Jonathan Hogan, Lawrence B. Holzman (PI), J. Ashley Jefferson (University of Washington), Kenar Jhaveri (North Shore University Hospital), Duncan B. Johnstone (Temple University), Frederick Kaskel (Montefiore Medical Center), Amy Kogan, (Children's Hospital of Philadelphia [CHOP]), Jeffrey Kopp (NIDDK Intramural Research Program), Richard Lafayette (Stanford), Kevin V. Lemley (Children's Hospital of Los Angeles), Laura Malaga-Dieguez (New York University [NYU]), Kevin Meyers (CHOP), Alicia Neu (Johns Hopkins), Michelle Marie O'Shaughnessy (Stanford), John F. O'Toole (Case Western/ Cleveland Clinic), Rulan Parekh (University Health Network, Hospital for Sick Children), Heather Reich (University Health Network, University of Toronto), Kimberly Reidy (Montefiore Medical Center), Helbert Rondon (University of Pittsburgh Medical Center), Kamalanathan K. Sambandam (UT Southwestern), John R. Sedor (Case Western/Cleveland Clinic), David T. Selewski (University of

CureGN Study Rationale, Design, and Methods: Establishing a Large Prospective Observational Study of Glomerular Disease

Laura H. Mariani, MD, MS[1,2], **Andrew S. Bomback, MD, MPH**[3], **Pietro A. Canetta, MD**[3], **Michael F. Flessner, MD**[4], **Margaret Helmuth, MA**[2], **Michelle A. Hladunewich, MD, FRCP(C), MSc**[5], **Jonathan J. Hogan, MD**[6], **Krzysztof Kiryluk, MD**[3], **Patrick H. Nachman, MD**[7], **Cynthia Nast, MD**[8], **Michelle N. Rheault, MD**[9], **Dana V. Rizk, MD**[10], **Howard Trachtman, MD**[11], **Scott E. Wenderfer, MD, PhD**[12], **Corinna Bowers**[13], **Peg Hill-Callahan, BS, LSW**[2], **Maddalena Marasa, MD**[3], **Caroline J. Poulton, MSW**[7], **Adelaide Revell, BA**[13], **Suzanne Vento, BSN**[11], **Laura Barisoni, MD**[14], **Dan Cattran, MD, FRCPC**[15], **Vivette D'Agati, MD**[16], **J. Charles Jennette, MD**[17], **Jon B. Klein, MD, PhD**[18], **Louis-Philippe Laurin, MD, FRCPC, MSc**[19], **Katherine Twombley, MD**[20], **Ronald J. Falk, MD**[7], **Ali G. Gharavi, MD**[3], **Brenda W. Gillespie, PhD**[21], **Debbie S. Gipson, MD, MS**[22], **Larry A. Greenbaum, MD, PhD**[23], **Lawrence B. Holzman, MD**[6], **Matthias Kretzler, MD**[1], **Bruce Robinson, MD, MS, FACP**[1,2], **William E. Smoyer, MD**[13,24], and **Lisa M. Guay-Woodford, MD**[25] **[CureGN Consortium]**

[1]Division of Nephrology, Department of Medicine, University of Michigan, Ann Arbor, MI

[2]Arbor Research Collaborative for Health, Ann Arbor, MI

[3]Division of Nephrology, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY

[4]NIDDK, NIH, DHHS, Bethesda, MD

[5]Division of Nephrology, Department of Medicine, University of Toronto, Sunnybrook Health Sciences Centre, Toronto, ON

[6]Renal-Electrolyte and Hypertension Division, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

[7]Division of Nephrology and Hypertension, Kidney Center, Department of Medicine, University of North Carolina, Chapel Hill, NC

[8]Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, CA

Michigan), Christine B. Sethna (Cohen Children's Medical Center-North Shore Long Island Jewish Health System), Jeffrey Schelling (Case Western), John C. Sperati (Johns Hopkins), Agnes Swiatecka-Urban (Children's Hospital of Pittsburgh), Howard Trachtman (NYU), Katherine R. Tuttle (Spokane Providence Medical Center), Joseph Weisstuch (NYU), Suzanne Vento (NYU Langone Medical Center), Olga Zhdanova (NYU); Data Coordinating Center: Laura Barisoni (University of Miami), Brenda Gillespie (PI; University of Michigan [UMich]), Debbie S Gipson (PI; UMich), Peg Hill-Callahan (Arbor Research Collaborative for Health), Margaret Helmuth (Arbor Research Collaborative for Health), Emily Herreshoff (UMich), Matthias Kretzler (PI; UMich), Chrysta Lienczewski (UMich), Sarah Mansfield (Arbor Research Collaborative for Health), Laura Mariani (UMich), Cynthia C. Nast (Cedars-Sinai Medical Center), Bruce M. Robinson (PI; Arbor Research Collaborative for Health), Jonathan Troost (UMich), Matthew Wladkowski (Arbor Research Collaborative for Health), Jarcy Zee (Arbor Research Collaborative for Health), Dawn Zinsser (Arbor Research Collaborative for Health); Steering Committee Chair: Lisa M. Guay-Woodford (Children's National Health System).

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[9]Division of Nephrology, Department of Pediatrics, University of Minnesota Masonic Children's Hospital, Minneapolis MN

[10]Division of Nephrology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL

[11]Division of Nephrology, Department of Pediatrics, New York University Langone Medical Center, New York, NY

[12]Renal Section, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX

[13]Center for Clinical and Translational Research, The Research Institute at Nationwide Children's Hospital, Columbus, OH

[14]Department of Pathology, University of Miami, Miami, FL

[15]Division of Nephrology, University Health Network, University of Toronto, Toronto, ON

[16]Department of Pathology, Columbia University Medical Center

[17]Department of Pathology and Laboratory Medicine, University of North Carolina, Chapel Hill, NC

[18]Nephrology Division, Department of Medicine, The University of Louisville School of Medicine, Louisville, KY

[19]Division of Nephrology, Maisonneuve-Rosemont Hospital, Montreal, QC

[20]Pediatric Nephrology, Medical University of South Carolina, Charleston, SC

[21]Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI

[22]Division of Nephrology, Department of Pediatrics, University of Michigan, Ann Arbor, MI

[23]Emory University and Children's Healthcare of Atlanta, Atlanta, GA

[24]Department of Pediatrics, The Ohio State University, Columbus, OH

[25]Center for Translational Science, Children's National Health System, Washington DC

Abstract

Rationale and Objectives: Glomerular diseases, including minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), and immunoglobulin A nephropathy (IgAN) share clinical presentations, yet result from multiple biological mechanisms. Challenges to identifying underlying mechanisms, biomarkers, and new therapies include the rarity of each diagnosis and slow progression, often requiring decades to measure the effectiveness of interventions to prevent end-stage kidney disease (ESKD) or death.

Study Design: Multicenter prospective cohort study.

Setting and Participants: Cure Glomerulonephropathy (CureGN) will enroll 2,400 children and adults with MCD, FSGS, MN, or IgAN (including IgA Vasculitis) and a first diagnostic kidney biopsy within 5 years. Patients with ESKD and those with secondary causes of glomerular disease are excluded.

Exposures: Clinical data, including medical history, medications, family history, and patient-reported outcomes are obtained, along with a digital archive of kidney biopsy images and blood and urine specimens at study visits aligned with clinical care 1-4 times/year.

Outcomes: Patients are followed for changes in estimated glomerular filtration rate (eGFR), disease activity, ESKD, death, and for non-renal complications of disease and treatment, including infection, malignancy, cardiovascular, and thromboembolic events.

Analytical Approach: The study design supports multiple longitudinal analyses leveraging the diverse data domains of CureGN and its ancillary program. At 2,400 patients and average of 2 years initial follow-up, CureGN has 80% power to detect a hazard ratio of 1.4-1.9 for proteinuria remission and a mean difference of 2.1 to 3.0 mL/min/1.73 m^2 in eGFR per year.

Limitations: Current follow-up can only detect large differences in ESKD and death outcomes.

Conclusions: Study infrastructure will support a broad range of scientific approaches to identify mechanistically-distinct subgroups, identify accurate biomarkers of disease activity and progression, delineate disease-specific treatment targets, and inform future therapeutic trials. CureGN is expected to be among the largest prospective studies of children and adults with glomerular disease, with a broad goal to lessen disease burden and improve outcomes.

Keywords

Glomerular Disease; CureGN; Minimal Change Disease (MCD); Focal Segmental Glomerulosclerosis (FSGS); Membranous Nephropathy (MN); IgA Nephropathy (IgAN); IgA Vasculitis (IgAV); Henoch-Schönlein purpura; Glomerulonephropathy; longitudinal cohort; digital pathology repository; kidney biopsy; patient-reported outcome (PRO); study design; estimated glomerular filtration rate (eGFR); pediatric; adult

INTRODUCTION

Glomerular diseases are the third leading cause of end-stage kidney disease (ESKD) in the United States, accounting for approximately 10,000 incident ESKD cases per year.[1] Immunoglobulin A nephropathy (IgAN), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), and minimal change disease (MCD) constitute the majority of primary glomerular diseases. Recent epidemiological, clinical, and basic research studies have implicated novel genetic and environmental factors in the pathogenesis of these disorders,[2–6] which have begun to reveal underlying molecular pathways that can differentiate etiologically distinct subtypes, identify biomarkers of disease activity, and delineate disease-specific treatment targets.

Despite this progress, there is insufficient translation of basic research into clinical care. There are few and inadequately reliable clinical tools for risk stratification, prediction of remission, treatment selection, and monitoring of drug response. Major challenges to such translational efforts include the rarity of individual glomerular diseases. And, slow disease progression may require years of follow-up to prove the effectiveness of an intervention because alternative endpoints to ESKD have not been definitively validated.

Cure Glomerulonephropathy (CureGN; www.CureGN.org) is a multi-center, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-funded consortium working collaboratively to address these challenges by recruiting a large cohort of participants with MCD, FSGS, MN, and IgAN, and following them prospectively using a common protocol that specifies enrollment criteria, aims, data and sample collection procedures, but not treatment. A key underlying hypothesis is that different disease mechanisms can result in similar pathological and clinical phenotypes, but very different disease courses. Identifying and characterizing these mechanisms will have broad influence on diagnostic classification, accurate prognostication, definition of patient cohorts for clinical trials, and identification of individualized therapies. Most importantly, this study will establish an infrastructure and foster research that enables the nephrology community to answer four questions of central interest to newly-diagnosed patients: What is this disease? Why do I have this disease? What will happen to me? What effective treatments can you offer me?

METHODS

Organizational Structure Of The Consortium

CureGN participants are recruited concurrently from four Participating Clinical Center (PCC) networks, managed by: Columbia University, Midwest Pediatric Nephrology Consortium, University of North Carolina, and University of Pennsylvania. Each PCC represents multiple clinical sites (currently, 65 US sites, three in Canada, one in Italy, and one in Poland [Box 1] The Data Coordinating Center (DCC) is located at the University of Michigan and Arbor Research Collaborative for Health.

Objectives And Study Desig

Objectives—The scientific aims of the core CureGN study and its future ancillary study program cover four broad areas of research (Box 2).

Study Population—CureGN aims to recruit a racially and ethnically diverse cohort comprising 600 participants for each of the four target diagnoses: MCD, FSGS, MN, and IgAN. At least 30% of the cohort is expected to be pediatric. Study enrollment must occur within 5 years of the patient's first diagnostic kidney biopsy. Inclusion and exclusion criteria are in Box 3. Patients with one of the target diagnoses who have completed the Nephrotic Syndrome Study Network (NEPTUNE)[7] are eligible for enrollment into CureGN for long-term follow-up, regardless of other CureGN exclusion criteria.

For all patients approached for consent, minimal demographic information (e.g., age, sex, race, ethnicity) is recorded to monitor for consent bias and reason for nonparticipation. All patients biopsied at the enrolling site after 1/1/2015 with one of the eligible diagnoses are entered on the screening log to monitor for referral bias by comparing the full cohort to the locally-biopsied subcohort. Institutional Review Board approval was obtained at each enrolling site.

Pathology Review for Study Enrollment—Inclusion and exclusion kidney biopsy criteria, including specimen adequacy, are listed in Table S1. After consent, the pathology report is reviewed by study pathologists to assess eligibility, quality assurance, and diagnosis assignment. If the report is insufficient to determine eligibility or exclusion, pathology materials (slides and images) are reviewed by a study pathologist. If confirmation of eligibility remains uncertain, an additional CureGN pathologist reviews the report and pathology materials for adjudication.

Study Procedures, Data and Sample Collection—After the enrollment visit, study visits occur within contiguous 4-month intervals for the duration of the study to allow alignment with clinical care and to enable sample collection at the time of disease exacerbation or remission (Table 1). Enrollment and subsequent annual visits are required in-person visits. All other visits can be conducted in-person or remotely (phone or email). For in-person visits, a focused physical exam is performed and patient-reported outcome (PRO) measures are assessed (medication adherence, symptoms, and Patient-Reported Outcomes Measurement Information System [PROMIS] items).[8–11]

A fresh, spot urine sample is collected and centrifuged at each visit, and the supernatant and pellet are stored. A 24-hour collection is requested annually for adults and continent children. A first-morning urine sample is requested at non-annual visits. Timed urine and first-morning voids are stored as whole urine. Volumes in pediatric patients are determined by weight (Table S2 & S3). Biospecimens are stored at the NIDDK biorepository, and extracted annually for central measurement of serum creatinine and urine protein-creatinine ratio (UPCR). Estimated glomerular filtration rate (eGFR) will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for adults and the modified Chronic Kidney Disease in Children (CKiD-Schwartz) formula for participants <18 years old.[12,13] For adolescents (defined for the purposes of this study as age 18-26), an average of the two formulas will be used.[14]

For all enrolled participants, outcomes of death (including date and cause) and ESKD (including date, renal replacement modality, and/or transplant donor type) are collected. Participant consent allows linkage to data sources such as Centers for Medicaid and Medicare Services (CMS) and National Death Index to validate ESKD and death events. Other outcomes include non-renal complications of disease and treatment. Patients will be followed until death, study withdrawal, or end of study. Phase one of CureGN will last 5 years; additional phases are anticipated to capture sufficient numbers of ESKD and death events.

Data-Sharing—To maximize use and collaboration around CureGN data sets, a data-sharing and analytic platform was established for use by consortium and ancillary study researchers. TranSMART is an open-source web-based software platform supported by the tranSMART Foundation (transmartfoundation.org) and its open-user community. The password-protected CureGN tranSMART platform is loaded with curated, clinical data at regular intervals. Analytic tools of the platform can be used to identify subcohorts of interest, generate descriptive statistics, and test associations between data elements. As

further data sets are generated (e.g., genomic, proteomics, or metabolomics), these data will be available for analysis, allowing scientists with diverse expertise to collaborate efficiently.

Digital Pathology Repository (DPR)—Kidney biopsy materials from enrolled patients, including glass slides scanned into high-resolution whole slide images (WSIs), digital images of immunofluorescence and electron micrographs, and pathology reports, are collected and uploaded into the CureGN DPR, located at NIH.[15] All submitted cases will undergo scoring by pathologists for defined glomerular, tubulointerstitial, and vascular morphologic features, which will allow assignment into currently-utilized classification systems for the four diseases. The WSIs can be viewed on a computer screen as if viewed under the microscope and allow annotation, morphometric measurements, identification of novel morphologic parameters, and application of machine learning algorithms.

Ancillary Studies Program—The CureGN consortium is committed to collaboration with ancillary investigators to achieve the scientific goals of the study. Investigators within and external to the CureGN sites are encouraged to apply for access to clinical data and biospecimens and/or to use CureGN infrastructure for research relevant to CureGN's over-arching goals. Many ancillary study designs are possible, including observational and interventional studies. Ancillary study applications (available at CureGN.org/Ancillary.aspx) are reviewed by the ancillary studies committee and approved by the Steering Committee.

RESULTS

Statistical Analyses

The study design, eligibility criteria, visit schedule, data elements, and sample collection were developed to facilitate the diverse studies within CureGN and its ancillary program. A broad array of statistical approaches will be applied, as appropriate, depending on the scientific question. Methods appropriate for analyses of observational data will be used to minimize the impact of confounding and bias on effect estimates, account for the correlation of repeated measures within individuals, adjust for variable follow-up, and handle missing data using multiple imputation as needed. For factors susceptible to treatment-by-indication bias, we will evaluate whether techniques such as instrumental variables analysis are appropriate or stratification by treatment regimen can be utilized. Because this is a prevalent cohort, survival analyses of time-to-event data, particularly ESKD and death, will require delayed entry into the risk set until time of enrollment (i.e., left-truncation) if time origins such as biopsy date are used. Mixed models of longitudinal trajectories (slopes) in eGFR will be used in preference to two-point time-to-event estimates of 40% or 50% decline in eGFR from baseline. The mixed model has greater statistical power than time-to-event outcomes, and is independent of starting time, which is ideal as participant enrollment occurs at variable times during the 5 years after biopsy. And, common events in glomerular disease, such as acute kidney injury or initiation of a new treatment, offer a unique opportunity to model non-linear trajectories and their association with subsequent trajectory and outcomes.[16]

Analysis methods for proteinuria that make full use of the longitudinal data yield high power to investigate proteinuria trajectories. Examples include modeling integrated UPCRs over

time, rates of proteinuria events (relapse or remission) using Poisson models, time-to-recurrent-events of either relapse or remission, and within-person comparisons of near-term outcomes under different treatments.

For some longitudinal outcomes, such as those based on serum creatinine or urine protein, clinic visit data may be missing not at random due to infrequent clinic visits or clinical endpoints. Observation times are therefore irregular and potentially outcome-dependent. Joint longitudinal and survival models may be useful in these situations. Data from telephone visits will serve to 'fill in' some clinical data and record reasons for missingness, when possible.[17–19]

The large number of potential predictors of outcomes in high-dimensional data (e.g., genomics, proteomics, or metabolomics) generated from biosamples via ancillary funding will require statistical approaches such as machine learning (e.g., penalized regression, support vector machines, and classification trees) to optimally identify predictors, cross-validation to reduce the problem of over-fitting, and adjustment for multiple testing.

Sample Size and Power Calculation

Table 2 shows the statistical power for time-to-event analyses (minimum detectable hazard ratio, MDHR) and analyses of eGFR slopes, repeated assessments of eGFR, and UPCR (minimum detectable difference in slopes, MDDS). For illustration, the estimates are shown for comparisons between two groups of equal size, which could represent any subgroups of interest, (e.g., different diagnoses, adults and children, genetic risk alleles, or treatment exposures). Unequal group sizes would yield less power, and continuous exposures (e.g., biomarker levels) would yield greater power. The outcome event rates were based on published literature and early observed data in the recruited CureGN cohort.[20–24] Analyses using continuous outcomes (e.g., eGFR slope) generally have higher power than time-to-event outcomes due to lost information in replacing repeated values with a single time-to-event that, except for death, is often estimated with error. For example, comparing eGFR slopes between two groups of 1200 subjects each could detect a difference in average eGFR decrease per year of approximately 2.5 mL/min/1.73 m^2 (e.g., an average 1-year drop from 50 to 49 mL/min/1.73 m^2 in one group vs. 50 to 46 mL/min/1.73 m^2 in a second group). This relatively fine distinction available with a continuous repeated-measures outcome can provide optimal power for testing in the overall cohort or in subgroups of interest.

DISCUSSION

CureGN is a large, prospective study of children and adults with glomerular disease, positioned to address the need for more accurate disease phenotyping, risk stratification, and treatment assignment. Although current pathologic classification assists in prediction of progression,[25,26] histopathology alone does not adequately define disease course and response to therapy for all individuals within a given diagnosis. The broadly defined enrollment criteria allow inclusion of the clinically heterogeneous population observed in practice within each diagnosis and the variants not currently well understood (e.g., C1q nephropathy, "secondary" FSGS, IgM deposition). By integrating the multilayered data sets derived from clinical data and biospecimens, CureGN aims to address these knowledge gaps

in diagnosis and disease pathogenesis, identify novel diagnostic and prognostic biomarkers, and discover potential molecular targets for future therapies.[27]

CureGN has unique design elements that differentiate it from, and thus complement, other major kidney disease studies. The large number of CureGN recruitment sites target a racially, ethnically, and geographically diverse population with glomerular disease. Other large nephrology observational studies do not specifically target the glomerular disease population or are limited to more homogeneous patient populations. The Chronic Renal Insufficiency Cohort (CRIC) excluded those actively receiving immunosuppression for glomerulonephritis.[28] The Human Heredity and Health (H3) in Africa Kidney Disease Research Network plans to enroll 400 participants with non-HIV, non-diabetic glomerular disease (along with 3,600 participants with other causes of chronic kidney disease) in an exclusively African population.[29] The CKiD study, in which less than 20% of enrollees were children with glomerular disease, identified differences in risk factors for progression in glomerular versus non-glomerular disease, highlighting the need to examine these populations separately.[30]

NEPTUNE is an ongoing observational, incident cohort of over 500 children and adults.[7] NEPTUNE enrolls patients with suspected MCD, FSGS, or MN (but not IgAN) at the time of their first clinically-indicated kidney biopsy. While a biopsy diagnosis is necessary for CureGN enrollment, collection of biopsy tissue for research purposes is not required. The NEPTUNE protocol, however, incorporates obtaining renal tissue specimens to allow analysis of data from simultaneous tissue, serum, and urine samples with phenotypic data to enable discovery of molecular pathways of glomerular injury.[31–33] While analyses of short-term outcomes have come from the NEPTUNE study,[34] the eligibility of most NEPTUNE subjects to enroll into CureGN at the conclusion of their NEPTUNE follow-up provides a valuable means for obtaining long-term longitudinal information. The harmonized clinical data and biosample collection in the two studies makes CureGN an ideal validation cohort for mechanistic findings arising out of NEPTUNE.

CureGN also complements important work from large registry studies. PodoNet,[35,36] the Toronto Glomerulonephritis Registry,[37–39] the University of North Carolina Glomerular Disease Collaborative Network,[39–41] Midwest Pediatric Nephrology Consortium,[42–44] British Columbia Glomerulonephritis Registry,[45] Canadian Childhood Nephrotic Syndrome Project,[46] the UK National Registry of Rare Kidney Disease (RaDaR),[47] and the North American Pediatric Renal Trials and Collaborative Studies Group[48] have published data on risk factors for disease progression. Comparisons of CureGN data can be made to registry data with respect to relevant patient risk factors and outcome rates. Many of these registries incorporate biosamples and genetic testing, and comparing data across populations would increase power for novel biomarker discovery and provide independent cohorts for validation.[49,50]

CureGN has several important study design features that support the overall study goals. The inclusion of children makes the cohort generalizable to all patients affected by these diseases. While the natural history and disease pathogenesis may be unique in the pediatric population, the inclusion of both children and adults allows these differences to be analyzed.

It also facilitates studies of the genetic causes of disease, progression rates across the age spectrum, and the interaction of growth and puberty on disease activity and response to therapy. Children with biopsy-proven MCD are especially valuable for inclusion, as they often have a severe disease phenotype with high morbidity from longterm immunosuppression.

Another unique design element is the inclusion of patients up to 5 years from biopsy. These diseases are often lifelong, requiring monitoring and therapy over many years, and putting patients at risk for both renal and non-renal complications (e.g., malignancy, diabetes, cardiovascular events) many years after the initial biopsy. In pediatric patients, in particular, the time of biopsy is dependent on local clinical practice and thus variable relative to disease onset. By recruiting prevalent participants at various disease stages, CureGN includes those who are newly diagnosed as well as those resistant to or dependent on immunosuppressive therapy, those who have relapsed, and those in remission. This diversity allows investigation of patient characteristics, genetic risk factors, and longitudinal biomarkers which may, for example, predict relapse after tapering immunosuppression, response to second-line agents, development of diabetes or malignancy, or likelihood of long-term preservation of eGFR. A 5-year post-biopsy window was selected to balance scientific value against increasing burden and decreasing quality of longer retrospective data collection. Importantly, most centers were using electronic health records at least 5 years prior to start of recruitment, which aids in the data extraction for this study.[51]

The contiguous windows of the study visit schedule allows in-person study visits to align with clinical visits and maximize biosample collection at times of disease activity flares and therapy changes. Recent advances in glomerular disease biomarkers include the discovery of the M-type phospholipase A_2 receptor (PLA_2R) as the target antigen in most patients with MN, studies of galactose-deficient IgA1 and anti-glycan response in IgAN, and associating mutations in Apolipoprotein A1 to the development of kidney disease in patients of African ancestry.[52–54] The number of genetic mutations identified in glomerular disease patients has expanded greatly in the last decade, yet their causative role in disease is less certain.[55] The CureGN biosamples provide a platform for the identification, testing, and validation of novel biomarkers, and help to address the large gaps that remain in understanding how to integrate these biomarkers and genetic data into clinical management.[55–57]

The CureGN patient-reported outcome (PRO) measures were selected to capture information of health-related quality of life (HRQoL), symptoms and medication adherence, and provide a generic PRO background upon which disease-specific PRO tools could be developed or validated within CureGN. PROMIS instruments were developed using general populations and validated in general and disease-specific populations. CureGN PROMIS domains are those shown to be responsive to disease status in pediatric nephrotic syndrome patients and equivalent domains for adults.[9,11,44] The selected symptom concepts were identified in an FSGS PRO development study.[10] Adherence assessment is included due to the well-described concern for poor medication adherence in chronic diseases, which has not been previously well studied in glomerular disease as a potentially disease-modifying variable.

The comprehensive DPR, containing the digitized biopsy materials, is another unique CureGN resource. The repository will be used to collect morphologic parameters currently used in the classification of the four disease categories, as a reference to assess associations with clinical outcome.[58–60] But, the DPR has several additional advantages. It is remotely accessible to multiple pathologists simultaneously and thus allows for discovery and validation of novel morphologic analysis protocols, testing protocol reproducibility, image annotation for training and standardization,[61] and application of computer-aided image analysis (e.g., Convolutional Neural Networks).[62,63,58,64] In the NEPTUNE study, a smaller DPR has been used to identify structural features associated with disease progression not currently employed in traditional classification systems.[60,64–66] Digital pathology is becoming the new standard practice in clinical research, and DPR protocols have been implemented in multiple other renal consortia, assembling a virtual pathology archive across multiple continents and populations.[67,68] And, whole slide imaging was recently approved by the US Food & Drug Administration (FDA) for primary pathologic diagnosis and is likely to become the primary method for pathologic interpretation of specimens.[69,70] The permanent DPR will allow studies by investigators within and outside CureGN to establish computational pathology models currently developing in non-renal disease, which allow integration of structural information with other “omics” data sets to improve clinical outcome prediction.[67,68,71]

A number of limitations of the CureGN study are acknowledged. The current 5-year phase of the study is under-powered to detect small differences in clinically-meaningful, but rare, outcomes such as ESKD or death. Although extended follow-up in future phases of the study will address this issue, the current phase of CureGN will optimize statistical power by using mixed models based on eGFR slope and repeated disease activity events to test risk factors for accelerated rates of progression. The exclusion of patients with diabetes at the time of biopsy will limit extrapolation of findings to this important subgroup of patients. However, patients developing diabetes after biopsy are retained. CureGN has locally, not centrally, processed kidney biopsies, with resulting image variability due to processing methods. Pediatric participants will require dedicated efforts to maintain long-term follow-up as they transition to adult care settings. Treatment strategies are not protocolized, so analyses will have to account for medication exposure heterogeneity. Associations of treatment with outcome and interaction with biomarkers may need to be validated in independent studies with standardized therapeutic regimens. Finally, CureGN is not designed as a population-based sample, and thus epidemiological inference requires caution. Whereas most pediatric patients receive initial care at academic centers (yielding a representative CureGN sample), adult patients often receive initial care from local physicians, with more severe cases referred to academic centers. A subset of CureGN participants who had their initial biopsy at the enrolling center are more representative of the underlying source population and can be analyzed for population-based inference.

In conclusion, we describe the objectives, organizational structure, and clinical protocol for CureGN, a multi-center, NIDDK-funded consortium that is recruiting a large, diverse cohort of pediatric and adult patients with MCD, FSGS, MN, and IgAN. We anticipate that CureGN will foster collaborative research activity that will identify common and distinct disease mechanisms for the four diagnoses, which may have similar presenting histological

and clinical phenotypes, but very different disease courses. It has established an infrastructure to promote translational research and apply these findings to improve clinical outcomes in glomerular disease patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1.

PCCs and clinical sites

Columbia University PCC

PI: Ali G. Gharavi

Columbia University

Giannina Gaslini Children's Hospital, Italy

Medical University of Warsaw, Poland

Midwest Pediatric Nephrology Consortium PCC

Co-PIs: William E. Smoyer & Larry A. Greenbaum

Children's Hospital of Michigan

Children's Hospital of New Orleans/LSU Health Sciences Center

Children's Mercy Hospital

Children's National Medical Center

Cincinnati Children's Hospital

Connecticut Children's Medical Center Duke University Medical Center (Pediatrics)

East Carolina University Brody School of Medicine

Emory University

Helen DeVos Children's Hospital

Levine Children's Hospital/Carolinas Medical Center

Lurie Children's Hospital

Mayo Clinic (Pediatrics)

Medical College of Wisconsin

Medical University of South Carolina, Children's Hospital

Nationwide Children's Hospital

Oregon Health and Science University

Riley Children's Hospital

St. Louis University/Cardinal Glennon Children's Medical Center

Texas Children's Hospital/Baylor College of Medicine

Texas Tech Health Sciences Center

University of Alabama, Birmingham, Children's of Alabama

University of Colorado-Children's Colorado

University of Iowa Children's Hospital University of Kentucky

University of Miami (Pediatrics)/Holtz Medical Center

University of Minnesota Children's Hospital

University of New Mexico Health Sciences Center

University of Oklahoma Health Sciences Center

University of Virginia, Pediatric Nephrology

University of Wisconsin, Madison

Vanderbilt Pediatric Nephrology

Washington University in St. Louis

University of Pennsylvania PCC

PI: Lawrence B. Holzman

Case Western University/University Hospitals

Medical Case Medical Center

Children's Hospital of Los Angeles

Children's Hospital of Philadelphia

Cleveland Clinic

Cohen Children's Medical Center/North Shore

Hospital Long Island Jewish Medical Center

Hospital for Sick Children, Canada

Johns Hopkins University

Los Angeles Biomedical Research Institute at

Harbor-UCLA

Mayo Clinic (Adults)

Montefiore Medical Center NIDDK

New York University

Stanford University

Sunnybrook Health Sciences Centre

University Health Network University of Miami (Adults)

University of Michigan

University of Pittsburgh/Children's Hospital of Pittsburgh

University of Pittsburgh School of Medicine

University of Pennsylvania

University of Texas Southwestern

University of Washington

Seattle Children's Hospital

Spokane Providence Medical Center

Temple University

University of North Carolina PCC

PI: Ronald Falk

Columbia Nephrology Associates

Hôpital Maisonneuve-Rosemont, University of Montreal, Canada

Medical University of South Carolina

The Ohio State University

University of Alabama at Birmingham

University of North Carolina Kidney Center

Vanderbilt University (Adults)

Virginia Commonwealth University

All sites are US sites, unless indicated.

Abbreviations: PCC, participating clinical center; PI, principal investigator; NIDDK, _____; UCLA, _____.

Box 2.

Scientific aims of CureGN, to be addressed by core and ancillary studies

Epidemiology

- To describe the disease trajectory under current clinical care
- To estimate event rates for clinically meaningful outcomes
- To identify patient characteristics (demographic, clinical, laboratory, environmental) associated with glomerular disease and non-renal complications of disease
- To identify clinical predictors of short- and long-term outcomes, including therapeutic responses
- To evaluate intermediate outcomes, such as proteinuria, as potential surrogates for longer-term outcomes

Biomarkers

- To identify and characterize clinical, histological, molecular, and genetic biomarkers that are linked to glomerular disease pathogenesis, disease outcomes, or that might be used to improve disease classification
- To identify biomarkers that may be employed in clinical practice or clinical trials to predict disease trajectory, disease activity, or response to therapy

Genetics

- To understand the genetic architecture of the four glomerulopathies, including studies of germline sequence variation, somatic mutations, epigenetic changes, and transcriptomic profile, and their impact on disease presentation and clinical outcome
- To study gene-gene and gene-environment interactions that contribute to the development of the four glomerulopathies and/or their response to therapy
- To devise systems genetics approaches to clarify pathogenesis

PROs

- To identify PROs (e.g., symptom burden, physical function, and quality of life) associated with primary glomerular diseases
- To validate disease-specific instrument(s) that assess the impact of disease and its therapy on patients
- To test the associations of PROs with disease progression

Abbreviations: PRO, patient-reported outcome; CureGN, _____.

Box 3.

Inclusion and exclusion criteria

Inclusion Criteria

- Diagnosis of MCD, FSGS, MN, or IgAN on first diagnostic kidney biopsy
  - IgM nephropathy, C1q nephropathy, and IgA vasculitis (Henoch-Schonlein purpura nephritis) are included
- First diagnostic kidney biopsy within 5 years of study enrollment
- Access to first kidney biopsy report and/or slides
- All ages
- Willingness to comply with study requirements
- Informed consent/assent

Exclusion Criteria

- ESKD (long-term dialysis or kidney transplant) at time of screening
- Institutionalized patient
- Solid organ or bone marrow transplant recipient at the time of first kidney biopsy
- Diagnosis of any of the following at the time of first diagnostic kidney biopsy:
  - Diabetes mellitus
  - Systemic lupus erythematosus
  - HIV infection
  - Active malignancy, except for non-melanoma skin cancer
  - Active Hepatitis B or C virus infection (positive viral load)

MCD, _____; FSGS, _____ ; MN, _____ ; IgAN, _____ ; HIV, _____.

Table 1.

Overview of data elements and biosamples

Visit	Eligibility	Enrollment	In-Person Follow-Up	Remote Follow-Up
Screening Log Data				
Demographics	X			
Biopsy diagnosis	X			
Exclusion criteria	X			
Consent/assent	X	(X)[a]		
Medical Data				
Comorbidities		X	X	X
Family history		X	X	
Birth history		X	X[b]	
Pregnancy history		X	X	
Prior disease course		X		
Interim disease course			X	X
Subsequent renal biopsy			X	X
Clinical trial participation		X	X	X
Medications[c]		X	X	X
Hospitalizations		X	X	X
ESKD status			X	X
Vital status			X	X
Physical exam		X	X	
Vital signs		X	X	
PRO Data				
Symptoms		X	X	X
PRO questionnaires		X	X	
Local Laboratory Tests*				
Blood chemistries, Hematology studies, Coagulation studies, Rheumatologic and Infectious serologies, Urine studies		X	X	X
Central Laboratory Tests**				
Serum creatinine		X	X	
24-hour, morning void, or spot urine (protein, creatinine)[d]		X	X	
Biospecimens				
Blood sample, including DNA and RNA		X	X	
Immortalized cell lines[e]		X		
24-hour, morning void, or spot urine[d]		X	X	

* if measured, based on abstraction from clinic record

** measured by CureGN laboratory

(a) If not previously performed

(b) If not previously collected

(c) Immunosuppressive medication since disease onset is collected at enrollment and updated at all visits. All other concurrent medications, vaccines, and supplements are collected at all visits using a searchable database of RxNorm.

(d) Attempts should be made to collect a 24-hour urine sample on an annual basis. For all other visits, a morning void collection in a designated, pre-labeled container should be obtained. Additionally, a spot collection should be done during the visit, noting the time of collection.

(e) Pediatric patients only

Abbreviations: ESKD, end-stage kidney disease; PRO, patient-reported outcome.

Table 2.

MDHR for time-to-event outcomes and MDDS for comparisons within disease type (n=600) and overall (n=2400)

Outcome	**Event rates per person year**	**MDHR* for n=600 (300/group)**	**MDHR* for 1=2400 (1200/group)**
Time to ESKD or death *	0.03-0.08	1.7 to 2.6	1.5 to 1.9
Time to loss of 50% eGFR from baseline *	0.04-0.15	2.1 to 7.3	1.8 to 3.6
Time to complete remission of proteinuria (<0.3 g/d) *^	0.20-0.70	1.6 to 2.3	1.4 to 1.9
Outcome	**SD of subgroup**	**MDDS+ for n=600 (300/ group)**	**MDDS+ for n=2400 (1200/group)**
eGFR slope+ (mL/min/1.73 m2 per year)	18.4-26.4	4.2-6.1	2.1-3.0
eGFR (mL/min/1.73 m2) repeated measures++	13.5-22.6	2.8-4.6	1.4-2.3
UPCR (mg/mg) repeated measures++	2.4-4.5	0.4-0.8	0.2-0.4

*MDHR (minimum detectable hazard ratio) is based on the following assumptions: Patient follow-up time of 2 years for more common events (loss of 50% eGFR from baseline and complete remission of proteinuria). Patient follow-up time of 10 years for more rare events (ESKD or death); a loss to follow-up rate at an average rate of 0.1 per year, 80% power, alpha=0.05, an intra-cluster correlation of 0.05, and the between-site normalized standard deviation of site sample sizes of 0.15. Event rates per person year represent ranges over the four disease types.

+MDDS (minimum detectable difference in slopes) based on differences between groups in mean person-specific slopes of eGFR values. Slopes are interpreted as eGFR change per year; SD of disease-specific eGFR slopes: MCD 20.5, FSGS 26.4, MN 24.2, and IgAN 18.4.

++MDDS for eGFR and UPCR repeated continuous outcomes are based on differences between groups in mean slopes of eGFR and UCPR values. Slopes are interpreted as eGFR or UPCR change per year; SD of disease-specific eGFR: MCD 22.6, FSGS 15.6, MN 13.5, and IgAN 15.8. SD of disease-specific UPCR: MCD 4.5, FSGS 3.0, MN 3.6, and IgAN 2.4.

^Group sizes for time-to-complete remission of proteinuria excluded 1/3 of the group who were in remission at enrollment.

Abbreviations: eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin A nephropathy; MCD, minimal change disease; MN, membranous nephropathy; SD, standard deviation.