



The Canadian Glomerulonephritis Registry (CGNR) and Translational Research Initiative: Rationale and Clinical Research Protocol

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Abstract

Background: Glomerulonephritis (GN) is a leading cause of kidney failure and accounts for 20% of incident cases of end-stage kidney disease (ESKD) in Canada annually. Reversal of kidney injury and prevention of progression to kidney failure is possible; however, limited knowledge of underlying disease mechanisms and lack of noninvasive biomarkers and therapeutic targets are major barriers to successful therapeutic intervention. Multicenter approaches that link longitudinal clinical and outcomes data with serial biologic specimen collection would help bridge this gap.

Objective: To establish a national, patient-centered, multidimensional web-based clinical database and federated virtual biobank to conduct human-based molecular and clinical research in GN in Canada.

Design: Multicenter, prospective observational registry, starting in 2019.

Setting: Nine participating Canadian tertiary care centers.

Patients: Adult patients with a histopathologic pattern of injury consistent with IgA nephropathy, focal and segmental glomerulosclerosis, minimal change disease, membranous nephropathy, C3 glomerulopathy, and membranoproliferative GN recruited within 24 months of biopsy.

Measurements: Initial visits include detailed clinical, histopathological, and laboratory data collection, blood, urine, and tonsil swab biospecimen collection, and a self-administered quality of life questionnaire. Follow-up clinical and laboratory data collection, biospecimen collection, and questionnaires are obtained every 6 months thereafter.

Methods: Patients receive care as defined by their physician, with study visits scheduled every 6 months. Patients are followed until death, dialysis, transplantation, or withdrawal from the study. Key outcomes include a composite of ESKD or a 40% decline in estimated glomerular filtration rate (eGFR) at 2 years, rate of kidney function decline, and remission of proteinuria. Clinical and molecular phenotypical data will be analyzed by GN subtype to identify disease predictors and discover therapeutic targets.

Limitations: Given the relative rarity of individual glomerular diseases, one of the major challenges is patient recruitment. Initial registry studies may be underpowered to detect small differences in clinically meaningful outcomes such as ESKD or death due to small sample sizes and short duration of follow-up in the initial 2-year phase of the study.

Conclusions: The Canadian Glomerulonephritis Registry (CGNR) supports national collaborative efforts to study glomerular disease patients and their outcomes.

Trial registration: NCT03460054.

Abrégé

Contexte: Les glomérulonéphrites (GN) sont des causes importantes d'insuffisance rénale; elles représentent 20 % des cas incidents d'insuffisance rénale terminale (IRT) au Canada chaque année. Inverser la néphropathie et prévenir la progression vers l'insuffisance rénale est possible, mais deux obstacles majeurs freinent la réussite de l'intervention



thérapeutique: une compréhension limitée des mécanismes sous-jacents de la maladie, de même que l'absence de biomarqueurs non invasifs et de cibles thérapeutiques. Les approches multicentriques reliant les données cliniques longitudinales et les résultats de santé à la collecte d'échantillons biologiques en série permettraient de combler cette lacune.

Objectif: Créer une base de données cliniques nationale en ligne, multidimensionnelle et axée sur le patient, de même qu'une biobanque virtuelle fédérée pour permettre de mener des recherches moléculaires et cliniques humaines sur les GN au Canada.

Type d'étude: Registre d'observation prospectif multicentrique débuté en 2019.

Cadre: Neuf centres de soins tertiaires canadiens.

Sujets: Des patients adultes recrutés dans les 24 mois suivant la biopsie et présentant un profil histopathologique de lésion compatible avec une néphropathie à IgA, une hyalinose segmentaire et focale, une maladie à changement minime, une glomérulonéphrite extra-membraneuse, une glomérulopathie à C3 et une glomérulonéphrite membranoproliférative.

Mesures: La première visite comporte une collecte détaillée des données cliniques, histopathologiques et de laboratoire, la collecte d'échantillons biologiques (sang, urine et écouvillonnage des amygdales), ainsi qu'un questionnaire autoadministré sur la qualité de vie. Pour le suivi, la collecte des données cliniques et de laboratoire, la collecte des échantillons biologiques et les questionnaires s'effectuent tous les six mois.

Méthodologie: Les patients reçoivent des soins comme établi par leur médecin, et les visites d'étude sont programmées tous les six mois. Les patients sont suivis jusqu'au décès ou jusqu'à la dialyse, à la transplantation ou au retrait de l'étude. Un critère de jugement combiné (IRT, ou diminution de 40 % du débit de filtration glomérulaire estimé après deux ans), ainsi que le taux de déclin de la fonction rénale et la rémission de la protéinurie sont les principaux critères de jugement. Les données phénotypiques cliniques et moléculaires seront analysées par sous-types de GN afin d'identifier les prédicteurs de la maladie et de découvrir de nouvelles cibles thérapeutiques.

Limites: Le recrutement des sujets demeure un des principaux défis puisque les maladies glomérulaires prises individuellement sont relativement rares. La faible taille des échantillons et la courte durée du suivi pendant les deux ans de la phase initiale de l'étude pourraient faire en sorte que les études initiales issues du registre ne soient pas assez puissantes pour détecter de légères différences dans les résultats cliniquement significatifs comme l'IRT ou le décès.

Conclusion: Le *Canadian Glomerulonephritis Registry* (CGNR) appuie les efforts de collaboration nationale visant à étudier les patients atteints de maladies glomérulaires et leur évolution clinique.

Enregistrement de l'essai: NCT03460054

Keywords

glomerulonephritis, protocol, strategy for patient-oriented research, biobank

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Introduction

Glomerulonephritis (GN) is a group of kidney diseases that, although rare (incidence of 0.7-2.8 per 100 000/year depending on specific type of GN), collectively account for 10% of incident cases of end-stage kidney disease (ESKD) in Canada.^{1,2} Patients with GN comprise 21% of the prevalent dialysis and transplant ESKD population, which is nearly the same proportion comprised by patients with diabetes, owing to greater longevity on dialysis and post-transplant.¹ However, unlike kidney disease caused by diabetes or hypertension, reversal of kidney injury and prevention of progression to kidney failure is possible for many types of GN.

Current treatment strategies for GN focus on the use of broad-based immunosuppression, which is often associated with significant toxicity. Furthermore, available demographic, laboratory, and histologic information is often insufficient to identify which patients will benefit most from immunosuppressive therapy. Identification of noninvasive actionable markers of disease progression would allow delivery of more targeted regimens to patients at highest risk of progression.

The Canadians Seeking Solutions and Innovations to Overcome Chronic Kidney Disease (Can-SOLVE CKD) Strategy for Patient-Oriented Research was developed to address chronic kidney disease identification and management. The Canadian GN Registry (CGNR) and Translational Research Initiative is one of the defined and funded projects within the Can-SOLVE CKD network. The objective of this project is to develop a national, patient-centered, multidimensional web-based clinical database and federated virtual biobank to conduct human-based molecular and clinical research in GN. This platform builds on the strengths of successful regional research programs in Canada^{3,4} and leverages experience with international multicenter consortiums that integrate multidimensional molecular and clinical data.^{5,6} The aim is to create a sustainable national platform to study disease natural history, describe the Canadian patient experience with GN, and conduct human-based molecular research in GN. This will transform the current model of translational GN research in Canada and enable identification of actionable biomarkers associated with progressive disease and response to therapy, and develop personalized treatment strategies for patients with GN. Specific core and ancillary studies will address the relationships between quality of life, clinical and noninvasive molecular markers, and disease progression.

Methods

Study Design

The CGNR is a prospective, multicenter, observational registry of patients with biopsy-proven GN recruited within 24

months of initial diagnosis. The registry was launched in 2019 at 9 tertiary care nephrology departments in 8 cities in 6 provinces across Canada (Supplemental Appendix A) and aims to recruit at least 300 patients to be followed for a minimum of 2 years. The CGNR is an observational registry; patients undergo kidney biopsy prior to enrollment as clinically indicated by local treating physicians. Once an eligible GN diagnosis is made, patients receive care as defined by the treating physician and clinical data generated from these encounters are recorded by research staff. The registry also collects results of a self-administered quality of life questionnaire and blood, urine, and tonsil swab biospecimens every 6 months.

Ethical Considerations

The study was approved by institutional Research Ethics Boards at all participating sites. As the registry protocol does not include an a priori hypothesis or analysis plan for the biological samples, informed consent is written in a manner that allows for future biological research using collected samples. Collection of DNA samples from patients is optional; however, understanding the genetic risks that contribute disease progression is a core element of the study proposal.

Administrative Structure

The CGNR study execution is coordinated by the Applied Health Research Centre (AHRC) of the Li Ka Shing Knowledge Institute of Unity Health (formerly St. Michael's Hospital) in Toronto, Canada. As the Data Management and Coordinating Centre, they are responsible for maintaining regulatory documents, data management and analysis, and providing progress and data reports to participating sites. The CGNR is administered by several committees with representation from all site investigators (Figure 1, Table 1).

The Executive Committee consists of principal investigators and is responsible for successful execution of study objectives, ensuring data quality and security, and enacting recommendations of the Steering Committee. The Steering Committee consists of site investigators, representation from the Executive Committee, and a representative from the Can-SOLVE CKD Patient Advisory Council. The Steering Committee is responsible for review and approval of policies and procedures, recommendations from subcommittees, and publications resulting from core and ancillary studies, as well as resolution of operational disputes and queries. Additional subcommittees include the Recruitment Committee, Biospecimen Committee, and Knowledge Translation Committee. These committees help facilitate patient recruitment, judicious use of biospecimens, and dissemination of findings. Investigators within and external to the CGNR are encouraged to apply for access to clinical data and biospecimens and/or use the CGNR infrastructure for

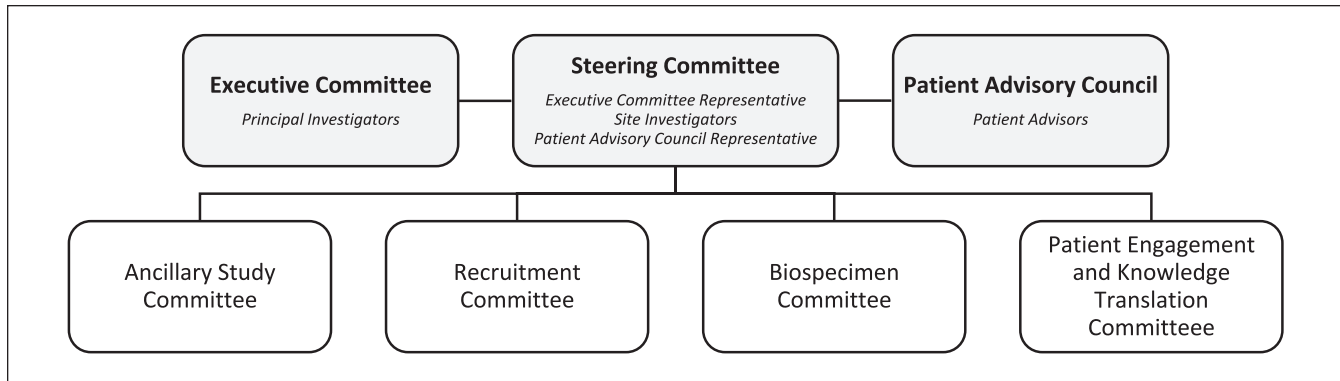


Figure 1. Governance structure.

Table 1. Committee Roles and Responsibilities.

Committee	Key roles and responsibilities
Executive Committee	Successful execution of the programmatic and scientific objectives Liaising with data management and coordinating center to ensure data quality and security
Steering Committee	Enacting recommendations of the Steering Committee Review and approval of policies and procedures Review and approval of recommendations from the subcommittees, including Ancillary Study Committee, Recruitment Committee, Biospecimen Committee, and Patient Engagement and Knowledge Translation Committee Review and approval of publications resulting from core and ancillary studies Resolution of operational disputes and queries
Data Management and Coordinating Centre	Development and programming of electronic case report forms, procedure manuals, and regulatory documents Maintenance of regulatory documents Data management and analysis Providing progress and data reports to the Steering Committee and participating sites
Patient Advisory Council	Identification of research priorities Development of training procedures for patient participation in research Providing input and assistance with patient recruitment Knowledge translation
Ancillary Study Committee	Review and prioritization of studies involving registry data and biospecimens and make recommendations to the Steering Committee Ensuring funding is in place prior to release of samples or data
Recruitment Committee	Patient recruitment
Biospecimen Committee	Ensuring standard operating procedures are in place for sample processing and storage Assessing studies' needs and implementing efficient use of available samples
Knowledge Translation Committee	Dissemination of research findings generated by studies using registry data

research relevant to the CGNR's scientific goals. Ancillary study applications will be accepted from internal study applicants as well as external investigators and will be reviewed by the Ancillary Study Committee and approved by the Steering Committee.

Exploration of patient research priorities are a primary mandate of the Can-SOLVE CKD network, and patients are engaged in all network projects. The central Can-SOLVE CKD Patient Advisory Council includes more than 30 participants with a spectrum of kidney diseases as well as family

members, caregivers, and kidney donors. Within the CGNR, the Patient Advisory Council has been centrally involved in identification of research priorities and design of study protocols and procedures. In particular, the Patient Advisory Council provided input on the importance of including quality of life data and relating these data to treatment effects and disease outcomes. The Council supports patient recruitment and participation and has provided input for knowledge translation activities. The GRIPP2 reporting checklist was used retrospectively as a quality assurance step in the

Table 2. Inclusion and Exclusion Criteria.

Inclusion criteria	Exclusion criteria
1. Age 18-80 years inclusive 2. Biopsy-proven diagnosis of one of the following GNs within 24 months of enrollment: IgA nephropathy FSGS Minimal change disease Membranous nephropathy Membranoproliferative glomerulonephritis (includes C3 glomerulopathy, dense deposit disease, and immune-complex membranoproliferative glomerulonephritis with monoclonal or polyclonal immunoglobulin deposits) 3. Access to kidney biopsy report 4. eGFR ≥ 30 mL/min/1.73m² 5. Willingness to participate with study requirements and follow-up	1. Evidence of diabetic nephropathy on the kidney biopsy (thickened basement membranes permissible) 2. Serologic evidence of systemic lupus erythematosus (positive ANA or anti-dsDNA) or evidence of lupus nephritis on kidney biopsy 3. History or serologic evidence of connective tissue disease or vasculitis (positive ANCA) 4. Prior solid organ transplant

Note. GNs = glomerulonephritis; FSGS = nephropathy, focal and segmental glomerulosclerosis; eGFR = estimated glomerular filtration rate; ANA = antinuclear antibody; anti-dsDNA = anti-double-stranded antibody; ANCA = antineutrophil cytoplasmic antibody.

documentation of patient and public involvement in this publication (Supplemental Appendix B).⁷

Study Participants

Inclusion and exclusion criteria are outlined in Table 2. To be eligible to participate, patients must be 18 to 80 years of age (inclusive) and have a diagnosis of one of the specified GNs confirmed by a kidney biopsy within 24 months of enrollment. Eligible participants are those individuals with histopathologic pattern of injury consistent with IgA nephropathy, focal and segmental glomerulosclerosis (FSGS), minimal change disease, membranous nephropathy, C3 glomerulopathy, and membranoproliferative glomerulonephritis. To avoid overlap with other existing Canadian and North American databases,^{8,9} patients with underlying systemic lupus and vasculitis are excluded. Patients must have an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73m² using the 4-variable MDRD equation and be willing to adhere to study requirements and follow-up. Patients are excluded if they have concurrent evidence of diabetic nephropathy on the kidney biopsy as this may confound outcomes (thickened basement membranes are permissible), serologic evidence of systemic lupus erythematosus or evidence of lupus nephritis on kidney biopsy, history or serologic evidence of connective tissue disease or vasculitis, or a prior solid organ transplant.

Visit Structure

Physicians at enrolling sites approach potentially eligible patients under their care regarding their willingness to

participate in the registry and, if so, obtain consent for a CGNR research coordinator to contact them. All referred patients are contacted by the study coordinator in person or by telephone for a screening visit (V0). During this encounter, the study coordinator confirms eligibility requirements prior to obtaining informed consent. Signature of the protocol-specific informed consent form by the patient or the patient's authorized representative constitutes the first procedure of the enrollment visit (V1). All patients undergo at least 4 follow-up visits (V2-5) at 6-month intervals (± 1 month) for 24 months. As this interval is in keeping with standard of care,¹⁰ study visits are coordinated with routine clinical care when possible to minimize burden of participation.

Data Collection

All required data are ascertained at study visits using a web-based case report form (eCRF). Clinical data collected at the time of enrollment (V1) include both historical data and visit data generated by routine clinical care (Table 3). Historical data are ascertained from retrospective review of the patient's medical record, with clarification from the patient as required. This includes age, sex, race/ethnicity, date of kidney biopsy, biopsy diagnosis (including an upload of the full pathology report), medical history (including comorbidities, allergies, history of substance use, pregnancy history, and family medical history), history of presenting illness (including clinical symptoms at presentation, history of illness or allergy at presentation, history of immune medication and renin-angiotensin-aldosterone system blockade use), status at presentation and biopsy (including physical parameters

Table 3. Data Collection Protocol.

Parameter	Screening	Enrollment	Follow-up			
Visits	V0	V1	V2	V3	V4	V5
Application of eligibility criteria	X					
Informed consent		X				
Registration						
<i>Date of biopsy, biopsy diagnosis, biopsy report upload</i>		X				
Demographics						
<i>Age, sex, race/ethnicity</i>		X				
Medical history						
<i>Comorbidities, allergies, substance use, family medical history, pregnancy history</i>		X				
History of present illness						
<i>Clinical symptoms at presentation, immune medication history, RAAS blockade history</i>		X				
Secondary work-up						
<i>HIV and hepatitis B/C serology, C3, C4, ANA, anti-dsDNA, ANCA, malignancy screen, functional complement testing and genetic susceptibility testing</i>		X		Update as needed		
Health review						
<i>Clinical symptoms, admissions to hospital</i>						
• Over last 12 months		X				
• Since last visit			X	X	X	X
Physical parameters						
<i>Height and weight, vital signs, physical examination</i>						
• At time of presentation		X				
• At time of biopsy		X				
• At visit		X	X	X	X	X
Laboratory parameters						
<i>CBC and blood chemistry, urinalysis, 24-hour urine protein/creatinine, spot urine ACR/PCR, for MN only: anti-PLA2R, serum immunoglobulins, peripheral flow cytometry</i>						
• At time of presentation		X				
• At time of biopsy		X				
• At visit		X	X	X	X	X
KDQOL questionnaire		X	X	X	X	X
Biospecimen collection						
• DNA		X				
• Blood		X	X	X	X	X
• Urine		X	X	X	X	X
• Tonsil swabs		X	X	X	X	X

Note. RAAS = renin-angiotensin-aldosterone system; C3 = complement 3; C4 = complement 4; ANA = antinuclear antibody; anti-dsDNA = anti-double-stranded antibody; ANCA = antineutrophil cytoplasmic antibody; CBC = complete blood count; ACR = albumin:creatinine ratio; PCR = protein:creatinine ratio; MN = membranous nephropathy; anti-PLA2R = anti-phospholipase A2 receptor; KDQOL = Kidney Disease Quality of Life Instrument.

and routine laboratory measures), and results of the secondary work-up (updated in subsequent visits, V2-5). Additional clinical data collected prospectively at each visit (V1-V5) include a brief health review (including clinical symptoms and hospital admissions over the last 12 months [for V1] and since last visit [for V2-5]), physical parameters, and routine laboratory measures. Physical parameters ascertained at presentation, biopsy, and each visit (V1-5) include height and weight, vital signs, and physical examination. Routine laboratory measures ascertained at presentation, biopsy, and each

visit (V1-5) include complete blood count and blood chemistry, urinalysis, 24-hour urine and creatinine, spot urine albumin:creatinine ratio, and spot urine protein:creatinine ratio. For cases of membranous nephropathy, anti-phospholipase A2 receptor (PLA2R) levels, serum immunoglobulins, and peripheral flow cytometry are also recorded at each visit (V1-5), if available.

Research testing includes a self-administered modified Kidney Disease Quality of Life Short Form¹¹ questionnaire completed by patients at each visit (V1-5) and blood, urine,

Table 4. Core Scientific Aims of the CGNR Across 4 Domains.

Domain	Scientific aims
Natural history	To describe the natural history of GN patients in Canada across a spectrum of histologic diagnoses To identify demographic, clinical, and laboratory characteristics associated with remission and progression of GN
Patient experience	To describe the quality of life of patients throughout the course of GN care To relate measures of quality of life to treatment and clinical outcomes
Biomarkers	To describe the relationship between a panel of urinary biomarkers and progression of GN
Genetics	In a subset of subjects, genetic analysis will be performed to define the prevalence pathogenic gene variants. Genotype will be related to clinical outcome and treatment response

Note. CGNR = Canadian Glomerulonephritis Registry; GN = glomerulonephritis.

and tonsil swab biospecimen collection (Table 3). Specimen volumes and tubes required for centralized storage are indicated in Supplemental Appendix B. For those who consent to DNA collection, whole blood will also be collected at baseline (V1) for DNA analysis. Biospecimens will be procured and processed according to a standardized protocol and cataloged using specimen numbers.

Data Management and Security

Upon enrollment, each participant is assigned a unique subject identifier by the Data Management and Coordinating Centre. Only the registering site has access to the corresponding personal identifiers. All clinical data are entered directly by the registering site into Medidata RAVE 5.6.3, a secure encrypted web-based data management system. Biospecimen information is cataloged by registering sites into the Research Electronic Data Capture (REDCap) system. All biospecimens are processed and stored at participating sites, except for DNA samples, which may be shipped to the Data Management and Coordinating Centre for storage and preparation for future DNA extraction. Participating sites always have access to their own data in Medidata RAVE and REDCap.

Follow-Up and Outcomes

All patients are followed until death, dialysis, transplantation, withdrawal from the study, or study end. Outcomes that can be ascertained include those based on (1) threshold changes in eGFR, or ESKD (defined as 2 consecutive measurements of eGFR less than 15 mL/min/1.73m² or dialysis dependence for more than 60 days), (2) rate of eGFR decline (in mL/min/month), and (3) threshold changes in proteinuria or remission status. Complete remission of proteinuria is defined by a 24-hour urine protein excretion ≤ 0.3 g/d proteinuria. Partial remission of proteinuria is defined as 50% reduction in peak 24-hour urine protein and a reduction in 24-hour urine protein excretion to ≤ 3.5 g (but >0.3 g/d) for membranous nephropathy, minimal change disease, FSGS, and membranoproliferative glomerulonephritis and excretion to <1 g/d (but >0.3 g/d) for IgA nephropathy.

Statistical Analysis

The CGNR is designed to generate the necessary clinical, histopathological, and molecular phenotypic data to derive models to identify potential predictors (including clinical parameters and biomarkers) for study outcomes and describe the patient experience with GN. Core scientific aims of the study are provided in Table 4. Study infrastructure supports a broad range of longitudinal scientific approaches to address these aims, as well as those of ancillary studies that are independently funded as the cohort matures.

All study data will be analyzed by a statistician at the Coordinating Centre. Summary statistics will be reported for all available baseline and outcome data and will exclude missing observations. Descriptive tables will report the number of observations available for each variable as well as the number missing. Continuous data will be examined using means and standard deviations as well as medians and interquartile ranges as appropriate. Categorical variables will be summarized using frequencies and percent. Missing data will be handled with multiple imputation as appropriate. In general, logistic regression will be used to evaluate the relationship between predictors (demographic, clinical, and laboratory characteristics, quality of life scores, molecular biomarkers, and genotype, in individual studies) and binary clinical outcomes (threshold changes in eGFR, ESKD, threshold changes in proteinuria, or remission status). Linear regression will be used to evaluate the relationship between these predictors and continuous outcomes (rate of eGFR decline). Additional analyses will test the robustness of these outcomes, evaluate the additional prognostic information afforded by combining molecular biomarker or genotype data with readily available clinical or laboratory characteristics, and evaluate the diagnostic ability of molecular biomarkers. Statistical power calculations will be conducted prior to analyses to ensure at least 80% power to validate a given association with a type 1 error rate of 0.05. As an example, to inform initial recruitment goals, 321 patients were required for 80% power to evaluate the association between urinary biomarker expression and the composite ESKD outcome with a type 1 error rate of 0.05, assuming a conservative event probability of 0.26 (as observed in the

NEPTUNE cohort, which included pediatric patients with low risk of events) and a hazard ratio of 2.0. Additional analyses may be conducted later depending on the completeness and availability of data.

Discussion

The current approach for GN relies on often nonspecific clinical parameters and histopathology for diagnosis without an understanding of its molecular basis, which in turn limits clinical decision making, therapeutic options, and favorable patient outcomes. The purpose of the CGNR is to address these limitations by facilitating a wide range of human-based studies that encompass bench to bedside. These include mechanistic investigations and studies to identify disease-specific biomarkers for diagnosis and monitoring, while also identifying patients for clinical studies including randomized control trials.

Current therapeutic choices are limited to broad-based immunosuppressive agents for patients with clinical evidence of progressive disease. These agents can be associated with significant toxicity and clinicians lack tools to reliably identify who would benefit most from exposure to these agents. Not surprisingly, nonspecific clinical parameters and histopathologic features do not fully account for the variability in presentation, disease progression, and responses to treatment. Lack of molecularly informed diagnoses has also severely limited therapeutic development, casting nephrology far behind other fields.^{12,13} Drug development is further hampered by the lack of sensitive, mechanistically relevant biomarkers to monitor clinical response and drug efficacy. Many GNs are rare and slow to progress; reaching hard endpoints such as kidney failure may take several years. Understanding the core molecular processes driving disease and progression of GN will aid in prognostication and in selecting patients most likely to respond to therapies. A major barrier, however, to these translational efforts has been the rarity of glomerular disease variants. Multicenter approaches integrating detailed longitudinal clinical data with biospecimen collection for genetic, transcriptomic, and proteomic analyses are required.

The CGNR is a national, patient-centered, multidimensional web-based clinical database and federated virtual biobank designed to address these knowledge gaps through human-based molecular and clinical research GN. This unique data source, which collects detailed longitudinal clinical and outcomes information and serial biologic specimens from patients with the most common glomerular diseases worldwide,² will be the foundation on which to characterize disease natural history, clinical practice patterns, and patient experience, as well as apply precision medicine methodology to identify molecular causes, biomarkers, and novel therapeutic targets.¹⁴⁻¹⁷ Patient-reported outcome measures will also enrich our understanding of the status of patients with glomerular disease beyond traditional clinical and

laboratory-based assessments.¹⁷ Taken together, this work will advance our ability to individualize treatment to modify disease trajectory and reduce burden of illness and unnecessary medication toxicity.

The CGNR builds on the strengths of other regional registries and biobanks in Canada and the United States, including the Toronto Glomerulonephritis Registry,¹⁸ an established translational research and clinical trials hub, the British Columbia Glomerulonephritis Registry,⁴ the Biobank for the Molecular Classification of Kidney Disease,¹⁹ Cure Glomerulonephropathy (CureGN),⁵ and the Nephrotic Syndrome Study Network (NEPTUNE)⁶ to ensure high-quality data collection. Harmonization with international standards for specimen procurement will facilitate international collaboration, which will enable increased power for gene discovery, novel biomarker discovery, and provide independent cohorts for validation. In contrast to other multicenter studies, the CGNR engages patients at all phases of research. This ensures research questions and methods align with patient priorities, facilitates patient recruitment and retention, and ensures meaningful knowledge translation. The CGNR also empowers participating centers to build capacity for translational research. By design, participating centers have control over their own clinical data and biospecimens. Investigators can probe the database at any time to allow identification of consented patients, available biospecimens, and interested collaborators to rapidly design and execute clinical and translational research in GN.

There are already many excellent examples of successful integrative biology approaches in glomerular disease.¹⁴ One notable example is the use of mass spectrometry proteomics to identify the M-type PLA2R as an autoantigen in idiopathic membranous nephropathy.²⁰ Since its discovery in 2009, commercial immunoassays for anti-PLA2R and immunostaining of kidney biopsy specimens for PLA2R have become increasingly available and widely adopted for diagnosis, monitoring disease activity, and predicting disease recovery. Ongoing research will help clarify the role of anti-PLA2R in selecting patients for therapeutic trials and predicting recurrence after kidney transplantation, while defining target epitopes which may help predict disease severity and prognosis.²¹

The CGNR provides a platform for similar work in identification, testing, and validation of novel biomarkers. One of the pilot studies we have proposed builds on prior research with the NEPTUNE cohort.⁶ In this study, we identified a set of noninvasive urinary biomarkers that correlate with tissue fibrosis and functional loss in patients with GN. We now propose to use the CGNR platform to evaluate if this noninvasive urinary signature is associated with the composite outcome of ESKD or a 40% decline in eGFR at 2 years, rate of renal function decline, and remission of proteinuria in a Canadian population of patients with primary GN. As novel pharmacologic agents are now available that directly target the urinary proteins identified, this work may support

exploration of use of these agents for treatment of glomerular disease.

Another pilot study proposed aims to define genetic variants associated with FSGS in adults and correlate these with clinical outcomes. Genetic studies in FSGS have contributed substantially to our understanding of its biology, highlighting a central role of podocyte injury in its pathogenesis.²² There are now more than 40 genes implicated in hereditary forms of FSGS,²³ but what is missing from these studies are detailed clinical data to derive robust genotype-phenotype correlations that can guide practice. The CGNR will address these limitations by establishing a multiethnic Canadian adult cohort of patients with FSGS and detailed longitudinal clinical outcomes who have available archived DNA to facilitate gene discovery, determine genetic epidemiology, and describe phenotypic correlations. This is a critical first step in identifying therapeutic targets and there are several examples demonstrating this as a successful approach, including PCSK9 inhibitors for the management of hypercholesterolemia²⁴ and CFTR corrector/potentiators in cystic fibrosis.^{25,26}

One of the major challenges to this type of study is patient recruitment and retention. Active involvement of participating centers in the design and execution of studies, incorporation of financial support for recruitment and follow-up in the budget structure, and infrequent compulsory visits will ensure success. With an initial 24-month follow-up goal, initial studies may be underpowered to detect small differences in clinically meaningful outcomes, such as ESKD or death. Extended follow-up in future phases of this study will address this issue. An additional challenge is the laborious data collection involved, which could impact long-term sustainability of the project. Long-term success will depend on ongoing engagement of participating centers, which is enhanced by allowing investigators to maintain local control of their data and biospecimens. The number and diversity of participating centers at study launch is reflective of the timeliness of this endeavor and the support for a democratic collaborative research platform. In the future, formalized collaboration with pediatric GN cohorts and harmonization with shared pediatric protocols would also be a valuable addition to the current registry platform.

Conclusion

As a leading cause of ESKD, more effective, targeted, and personalized therapies for patients with GN are urgently required. The CGNR is a national, patient-centered, multidimensional web-based clinical database and federated virtual biobank, which supports national collaborative efforts to study disease natural history and practice patterns, characterize patient-reported outcomes, identify actionable biomarkers, and develop personalized treatment strategies for patients with GN. With patient engagement and national collaboration at the core of registry design and execution, the CGNR

transforms the current model of translational GN research in Canada.

Ethics Approval and Consent to Participate

All participants provided informed consent to participate prior to enrollment. The study was approved by institutional Research Ethics Boards at all participating sites. The coordinating site approval is REB 16-6110 at University Health Network. The study is registered at [clinicaltrials.gov](https://clinicaltrials.gov/NCT03460054) NCT03460054.

Consent for Publication

All authors have reviewed the manuscript and consent to its publication.

Availability of Data and Materials

The CGNR is pleased to review requests to access data and biosamples for ancillary studies.

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Supplemental Material

Supplemental material for this article is available online.

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