Kidney Medicine

The Preserving Kidney Function in Children With CKD (PRESERVE) Study: Rationale, Design, and Methods

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Rationale & Objective: PRESERVE seeks to provide new knowledge to inform shared decision-making regarding blood pressure (BP) management for pediatric chronic kidney disease (CKD). PRESERVE will compare the effectiveness of alternative strategies for monitoring and treating hypertension on preserving kidney function; expand the National Patient-Centered Clinical Research Network (PCORnet) common data model by adding pediatric- and kidney-specific variables and linking electronic health record data to other kidney disease databases; and assess the lived experiences of patients related to BP management.

Study Design: Multicenter retrospective cohort study (clinical outcomes) and cross-sectional study (patient-reported outcomes [PROs]).

Setting & Participants: PRESERVE will include approximately 20,000 children between January 2009-December 2022 with mild-moderate CKD from 15 health care institutions that participate in 6 PCORnet Clinical Research Networks (PEDSnet, STAR, GPC, PaTH, CAPRiCORN, and OneFlorida+). The inclusion criteria were ≥1 nephrologist visit and ≥2 estimated glomerular filtration rate (eGFR) values in the range of 30 to <90 mL/min/1.73 m^2 separated by ≥90 days without an intervening value ≥90 mL/min/1.73 m^2 and no prior dialysis or kidney transplant.

Exposures: BP measurements (clinic-based and 24-hour ambulatory BP); urine protein; and antihypertensive treatment by therapeutic class.

Outcomes: The primary outcome is a composite event of a 50% reduction in eGFR, eGFR of <15 mL/min/1.73 m^2, long-term dialysis or kidney transplant. Secondary outcomes include change in eGFR, adverse events, and PROs.

Analytical Approach: Longitudinal models for dichotomous (proportional hazards or accelerated failure time) and continuous (generalized linear mixed models) clinical outcomes; multivariable linear regression for PROs. We will evaluate heterogeneity of treatment effect by CKD etiology and degree of proteinuria and will examine variation in hypertension management and outcomes based on socio-demographics.

Limitations: Causal inference limited by observational analyses.

Conclusions: PRESERVE will leverage the PCORnet infrastructure to conduct large-scale observational studies that address BP management knowledge gaps for pediatric CKD, focusing on outcomes that are meaningful to patients.

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Pediatric chronic kidney disease (CKD) is rare and has substantial effects on current and future health. Hypertension occurs in 50% of children with CKD,[1,2] and is a major risk factor for decline in kidney function.[2-5] Blood pressure (BP) control is a cornerstone of CKD management. Several clinical practice guidelines provide BP management recommendations for pediatric CKD.[6-9] However, because the evidence base is insufficient, conflicting recommendations and substantial practice variation exist.[10] Available data derive largely from 2 studies: the ESCAPE trial[5] and the Chronic Kidney Disease in Children (CKiD) cohort study.[11,12]

ESCAPE, which concluded 15 years ago, was a European study of 385 children with CKD randomized to intensified or conventional BP control with an angiotensin-converting enzyme inhibitor (ACEi). After 5 years, 30% of the intensified versus 42% of the conventional group met the primary composite end point of a 50% decline in estimated glomerular filtration rate (eGFR), eGFR <10 mL/min/1.73 m^2 or kidney replacement therapy (KRT).[5] ESCAPE's generalizability to routine clinical settings was limited by the use of ambulatory blood pressure monitoring (ABPM) every 6 months, which is not feasible for most children. All participants received a moderately high dose of ramipril and were treated without regard to baseline BP level.

The ongoing CKiD study has enrolled >1,000 children and followed them annually.[11,13] CKiD has identified the important impact of hypertension[14,15] and proteinuria[15-17] on kidney function decline. The effect of elevated BP was greater in participants with glomerular versus non-glomerular CKD etiologies, suggesting the need to study these 2 groups separately. Use of ACEi or angiotensin receptor blockers (ARBs) was associated with a 21%-37%

PLAIN-LANGUAGE SUMMARY

Hypertension is a major modifiable contributor to loss of kidney function in chronic kidney disease (CKD). The purpose of PRESERVE is to provide evidence to inform shared decision-making regarding blood pressure management for children with CKD. PRESERVE is a consortium of 16 health care institutions in PCORnet, the National Patient-Centered Clinical Research Network, and includes electronic health record data for >19,000 children with CKD. PRESERVE will (1) expand the PCORnet infrastructure for research in pediatric CKD by adding kidney-specific variables and linking electronic health record data to other kidney disease databases; (2) compare the effectiveness of alternative strategies for monitoring and treating hypertension on preserving kidney function; and (3) assess the lived experiences of patients and caregivers related to blood pressure management.

reduction in the risk of KRT.[18] The accelerated decline in GFR demonstrated in the 18 months preceding KRT[19] underscores the importance of early intervention, which informed PRESERVE's focus on mild-moderate CKD.

The goal of PRESERVE is to provide new knowledge to inform shared decision-making about BP management in pediatric CKD. PRESERVE will use the National Patient-Centered Clinical Research Network (PCORnet)[20,21] to address the following evidence gaps:

(1) At what level of clinic-assessed BP should antihypertensive treatment be started to best preserve kidney function?
(2) What level of clinic-assessed BP should be targeted over time to best preserve kidney function?
(3) Should antihypertensive treatment initiation thresholds and targets be tailored to the cause of CKD or magnitude of proteinuria?
(4) Given the existing experimental evidence for the renoprotective effects of ACEi/ARB, do electronic health record (EHR) data support their first-line use for BP control in all children with CKD?
(5) What are the trade-offs among BP control, potential harm as evidenced by adverse clinical events, and patients' symptoms, functioning, and quality of life?

METHODS

Aims and Objectives

PRESERVE has 4 aims, each with objectives that guide their scope of work (Box 1).

Study Setting and Organizational Structure

PRESERVE includes 16 institutions in PCORnet, a national network-of-networks that conducts patient-centered outcomes research (Fig 1).[21] PCORnet's infrastructure includes a novel collaboration platform of comprehensive clinical data that is standardized, analysis-ready, and derived from medical institutions and health plans; common network and data governance; streamlined contracting and regulatory agreements; and resources for engaging patients.[22]

PRESERVE is led by PEDSnet (pedsnet.org),[23,24] the only PCORnet network devoted exclusively to children. PEDSnet institutions contributing data include Children's Hospital of Philadelphia, Cincinnati Children's Hospital Medical Center, Children's Hospital Colorado, Lurie Children's Hospital, Nationwide Children's Hospital, Nemours Children's Health, Seattle Children's Hospital, and Stanford Children's Health. An additional 7 institutions (from 4 other PCORnet networks) are participating: University of North Carolina (STAR), Medical College of Wisconsin/Children's Wisconsin and University of Iowa Stead Family Children's Hospital (GPC), University of Michigan/C.S. Mott Children's Hospital and Johns Hopkins Children's Center (PaTH), University of Florida/Shands Children's Hospital, and University of Miami/Holtz Children's Hospital (OneFlorida+). The study protocol was approved by the Children's Hospital of Philadelphia Institutional Review Board (IRB #21-018814), the central institutional review board for all participating sites.

Study Design and Population

Most objectives address clinical outcomes using a retrospective cohort study design. The study period is January 2009 to December 2022. Inclusion criteria are an outpatient, emergency department, or inpatient visit with a medical provider during the study period and 2 or more eGFR values of 30 to <90 mL/min/1.73 m^2 (using the CKiD U25 formula)[25] at least 90 days apart. The cohort entrance date (CED) is defined as the day of the first qualifying eGFR value of 30 to <90 mL/min/1.73 m^2. Exclusion criteria are eGFR ≥ 90 ml/min/1.73 m^2 between the 2 qualifying eGFRs, age <1 or ≥18 years at cohort entrance, no nephrologist visit at any time during the study period, and long-term dialysis or kidney transplant on or before CED. Outcomes are assessed for as long as patients have visits at a participating institution.

Objectives 2.1 and 2.2 use cross-sectional study designs to develop and evaluate BP z scores and operational definitions for hypertension. These analyses will use data from children aged between 3 and <18 years in the PEDSnet population with outpatient visits with valid values for systolic and diastolic BP as well as associated height and weight.

EHR Data Quality

Data quality assessment for PRESERVE applies the systematic framework detailed in Razzaghi et al[26] and the principles outlined in Kahn et al[27] (Fig 2). Phase 1 leverages results from PCORnet's network-wide data curation as well as data quality analyses assessing

Box 1. PRESERVE Aims and Objectives

Aim 1: Enhance the PCORnet CDM for pediatric and rare kidney disease research.

Objectives

1.1 To expand and improve the PCORnet CDM with new pediatric- and kidney-specific variables.
1.2 To perform study-specific data quality assessment and conduct necessary remediation for data quality optimization in response to data quality assessment.
1.3 To perform linkage of EHR data with the CKiD cohort study and USRDS.
1.4 To create an integrated data platform that comprises EHR, ABPM data, and linked data from the CKiD and USRDS for the study cohort as well as reusable tools that are publicly distributed.

Aim 2: Describe and examine the effectiveness of consistent BP and urine protein monitoring for preserving kidney function.

Objectives

2.1 To generate systolic and diastolic blood pressure z scores in the general pediatric population and contrast them with the normative BP distribution data reported in the 2017 American Academy of Pediatrics Blood Pressure Clinical Practice Guideline.
2.2 To create and evaluate alternative EHR-based operational definitions for measured hypertension based on BP z scores and the clinical definitions of hypertension in the 2017 BP Clinical Practice Guideline.
2.3 To describe current BP and urine protein monitoring practices for children with mild-moderate CKD and to evaluate the effects of monitoring consistency on kidney function decline independent of established clinical risk factors for CKD progression.
2.4 To evaluate heterogeneity of treatment effects for BP and urine protein monitoring.

Aim 3: Compare the effectiveness of BP medication strategies for preserving kidney function.

Objectives

3.1 To evaluate the association of levels of BP and urine protein when treatment was initiated (ie, first prescribed) and kidney function decline.
3.2 To assess the impact of ongoing BP control and absence of urine protein on kidney function decline.
3.3 To examine the associations of antihypertensive treatment strategies with kidney function decline, overall and by CKD etiology and degree of proteinuria.
3.4 To describe and evaluate heterogeneity of treatment effect for BP and urine protein management by sociodemographic and clinical characteristics.

Aim 4: Assess patients' lived experiences related to BP management.

Objectives

4.1 To coproduce a patient-parent survey with leadership provided by parent partners.
4.2 To field a survey that examines patient-centered outcomes by level of BP control and medication management approaches.
4.3 To assess adverse events related to hypertension management using data from the patient survey and EHR.

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CDM, common data model; CKD, chronic kidney disease; CKiD, Chronic Kidney Disease in Children; eGFR, estimated glomerular filtration rate; EHR, electronic health record; USRDS, United States Renal Data System.

eligibility criteria and summary statistics for principal data elements, focusing on ranges and measures of central tendency for quantitative values and tabulation for categorical values across institutions. It consists of 79 checks across 10 domains: anthropometrics, BP, cohort definition, cohort entry, diagnoses, follow-up, laboratory tests, medications, nephrology provider specialty, and procedures. Data quality checks are categorized as testing *completeness* (data attributes are sufficient), *conformance* (data comply to database and PCORnet standards), or *correctness* (data are plausible or have face validity). We examine attrition, outliers, length of follow-up and cohort entry, demographic characterizations, mismapped codes (eg, urine creatinine in source system represented as serum creatinine), missingness of major variables, outlier laboratory test values, duplication errors, and trends over time. Phase 2 applies to patient-level data and comprises 68 additional checks that identify issues related to sequencing of clinical events and temporal trends, missing clinical results and variables, anomalous clinical distributions, and misrepresentation of variables. It includes an additional category for *concordance*, which measures the agreement of clinical data across multiple data elements (eg, correlation between systolic and diastolic BP for all values at an institution). Phase 2 focuses on patient characteristics before and following cohort entry, granularity of geocoded address data, days between height and serum creatinine measurements for eGFR computation, distribution of quantitative laboratory test values and BP measurements, and usage of coding terminologies. In both phases, results are benchmarked across participating institutions to detect potential anomalies, categorized as *counts high*, *counts low*, *values high*, *values low*, *values discordant*, *outlier values*, *missingness*, *atypical code utilization*, or *mapping issues*. All findings identified are communicated to participating institutions via reports, a

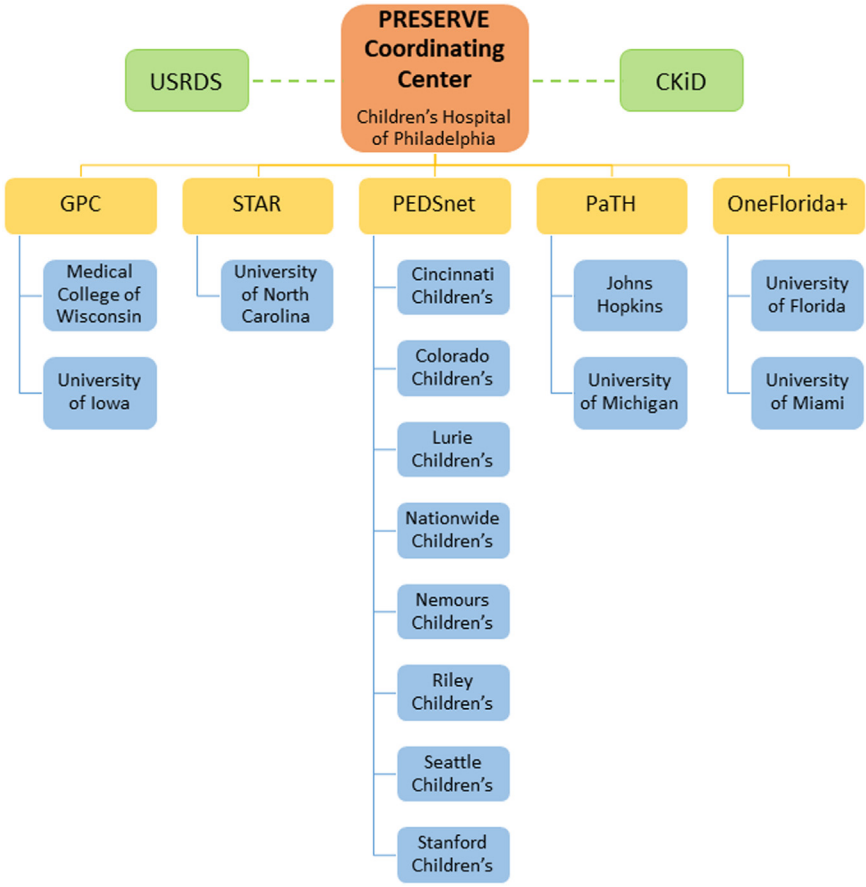

Figure 1. PRESERVE study setting and organizational structure. PRESERVE includes 16 institutions from 5 PCORnet networks: (1) Children's Hospital of Philadelphia (Coordinating Center), Cincinnati Children's Hospital Medical Center, Children's Hospital Colorado, Indiana University/Riley Hospital for Children, Lurie Children's Hospital, Nationwide Children's Hospital, Nemours Children's Health, Seattle Children's Hospital, and Stanford Children's Health (PEDSnet); (2) University of North Carolina (STAR); (3) Medical College of Wisconsin/Children's Wisconsin and University of Iowa Stead Family Children's Hospital (GPC); (4) University of Michigan/C.S. Mott Children's Hospital and Johns Hopkins Children's Center (PaTH); and (5) University of Florida/Shands Children's Hospital and University of Miami/Holtz Children's Hospital (OneFlorida+). PRESERVE also includes linkages with the US Renal Data System (USRDS) and Chronic Kidney Disease in Children (CKiD) study.

tracking system, and a systematic data quality catalog prioritizing issues. Institutional informatics teams provide information about whether the finding is remediable before submission of the finalized dataset. Where findings are not remediable, known limitations can be considered in analysis plans.

Chart Review

We will use random sampling, stratified by CKD stage at CED, to select 1,500 patients (100 per institution) for chart review to evaluate selection criteria, CKD etiology, long-term dialysis, kidney transplant, and hypertension classification. To increase sample size for ABPM data, we will oversample patients most likely to have undergone an ABPM for 75% of the chart review subcohort.

Patient and Parent Engagement

An important goal of PRESERVE is to develop meaningful engagement of parents/caregivers in the research process. The Glomerular Learning Network (GLEAN; glomerularlearningnetwork.org) serves as the leading rare disease partner for PRESERVE. GLEAN includes 9 pediatric health systems (8 of which are in PCORnet). GLEAN improves the health of children with glomerular disease by conducting research and quality improvement. PRESERVE leverages advances in the data quality of kidney-specific variables that resulted from GLEAN and PEDSnet studies.[28-31] Three GLEAN Parent Partners are coinvestigators in PRESERVE and lead the PRESERVE Patient and Parent Workgroup.

Each institution identified parents of patients and youth with CKD to participate in this workgroup. Partners received training through FYREworks (fyreworkstraining.com), a set of interactive, web-based trainings (developed in PEDSnet) that helps parents and patients understand their role in the research process and the importance of their expertise to a research team.[32] Responsibilities of this workgroup include

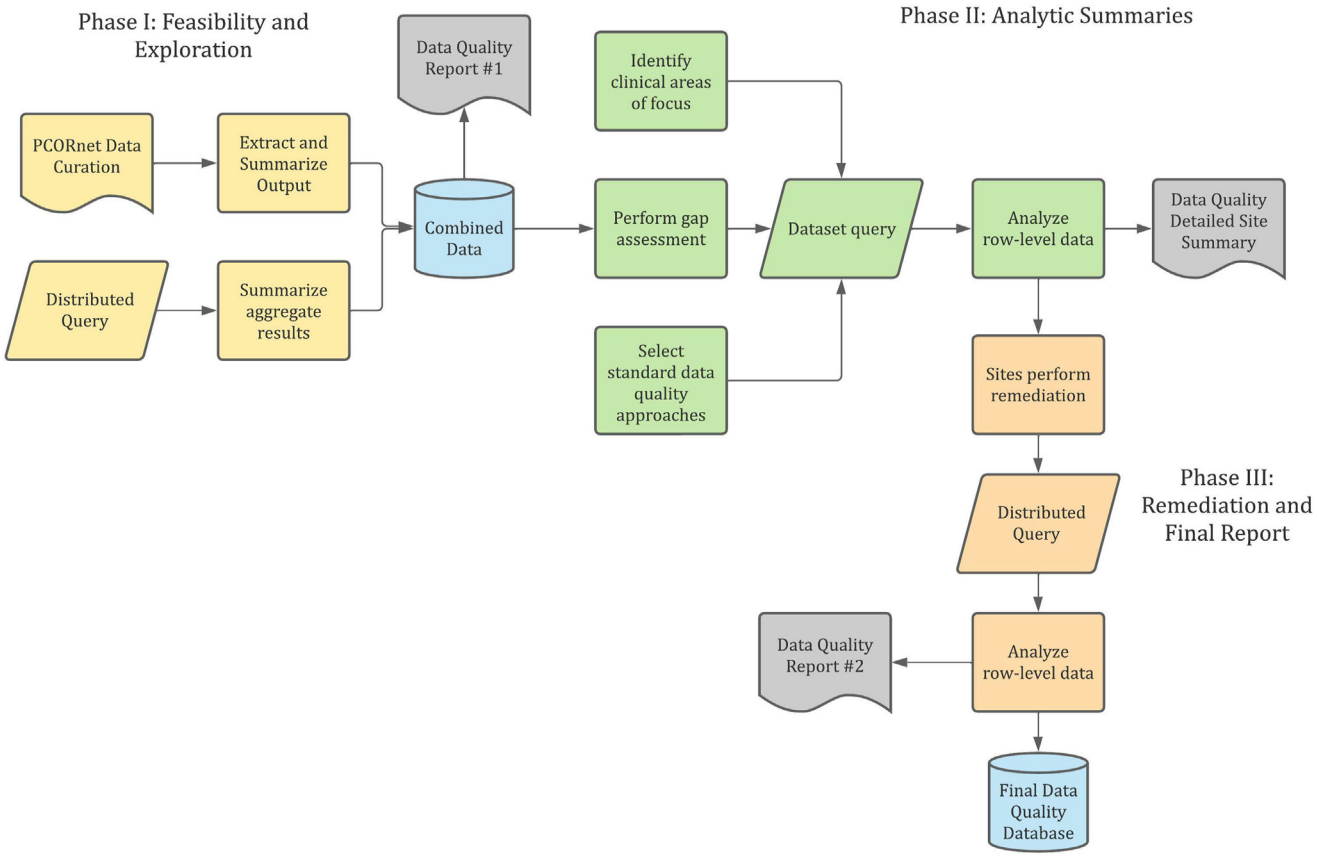

Figure 2. Study-specific data quality assessment for PRESERVE.

development and implementation of approaches for evaluating engagement; coproduction of the protocol for the patient survey, recruitment strategy, and study materials; review and interpretation of results for all aims; and creation of approaches for dissemination of aggregate study results to patient communities.

RESULTS

Outcomes

The primary outcome in PRESERVE will be a 4-part composite of initiation of long-term dialysis, kidney transplant, an eGFR of <15 mL/min/1.73 m^2 or a decrease in eGFR of >50% (Table 1). This variable has been extensively used in pediatric CKD research.[5,14-16,33,34] Kidney function is the most important outcome for patients with pediatric CKD and their families and clinicians reported in the literature[35,36] and described in our Parent Partner Engagement Studio, which occured during study planning.

Although a 50% decline in eGFR has become standard, we will run sensitivity analyses varying the level of decline (eg, 30%-70%)[10] to test the sensitivity of the composite outcome to these thresholds. The secondary outcome will model kidney function using eGFR change over time. Patient-reported outcomes (PROs) will include measures of health status deemed important by parent and youth partners. Exploratory outcomes will be adverse events associated with hypertension management.

Analysis Plan

Aim 1: Enhance the PCORnet Common Data Model for Pediatric and Rare Kidney Disease Research

PRESERVE will improve the PCORnet infrastructure by defining and evaluating the quality of new data elements and variables for kidney-related research: pediatric-specific BP z scores, hypertension (defined by diagnosis terms and recorded BP), eGFR computed for children and young adults, proteinuria, CKD etiologies, antihypertensive medications, long-term dialysis, and kidney transplant. We will develop technical specifications for these variables and create a reusable code for all derived variables as well as data quality analyses.

Linkage with CKiD will supplement EHR data with adjudicated data related to etiology of kidney disease, measured GFR, and ABPM. The US Renal Data System (USRDS, usrds.org) provides near complete national capture of dialysis and transplantation. Overlapping data elements will be assessed for concordance to estimate error rates in linkage or source data. Where variables conflict, analyses can prespecify which data source should be used (eg, USRDS will take precedence over the EHR for long-term dialysis).

Table 1. PRESERVE Outcomes

	Name of Outcome	Specific Measure	Timepoints	Powered
Primary	Kidney function decline composite	Composite event of 50% reduction in eGFR, kidney replacement therapy, or eGFR < 15 mL/min/1.73 m^2	From CED to end of follow-up	Yes
Secondary	Patient-reported outcome profile	PROMIS Pediatric measures for fatigue, pain, sleep health, anxiety, life satisfaction, and peer relationships Other measures of health status deemed important by parent and youth partners; experience with home BP monitoring	Single time point (date of patient survey)	Yes
Secondary	GFR trajectory	Change in eGFR per unit time	From CED to end of follow-up	Yes
Exploratory	BP treatment adverse events	Diagnosis-based adverse events: hypotension, dizziness, cough, stomatitis, tonsillitis, urinary tract infection, nocturnal enuresis, gastrointestinal symptoms, fatigue, edema, hair loss, respiratory tract infection, pyelonephritis, headache, pericarditis, syncope Laboratory-based adverse events: hyperkalemia, increase in liver enzymes, leukocytopenia, anemia, acidosis Other adverse events: death, ED visit for hypertension, hospitalization for hypertension	From CED to end of follow-up	No

Abbreviations: BP, blood pressure; CED, cohort entrance date; ED, emergency department; eGFR, estimated glomerular filtration rate.

Aim 2: Describe and Examine the Effectiveness of Consistent BP and Urine Protein Monitoring for Preserving Kidney Function

Reference values for age-specific BP were obtained using standardized protocols in research settings and secondary data analyses of these assessments. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents repurposed data from 11 studies to assemble a sample of 63,000 children,[9] including children with overweight and obesity. To develop data unbiased by weight, Rosner et al[37] excluded individuals in the Fourth Report's database who had a body mass index ≥85th percentile and recomputed BP z scores using quantile regression. This approach was used for the normative BP values included in the 2017 American Academy of Pediatrics Clinical Practice Guideline on high BP in children.[6] Using clinic-based assessments from the EHR, we will replicate the methodology used by Rosner et al[37] to compute systolic and diastolic BP z scores by age, sex, and height percentile for children aged 3-17 years without chronic medical conditions, seen for general pediatric care in outpatient settings, and whose body mass index is <85th percentile. We will contrast the results from these analyses with the age-sex-height specific z scores in the American Academy of Pediatrics Clinical Practice Guideline.

We propose to develop and test a set of alternative algorithms for identifying hypertension defined by actual BP values using EHR data from the clinical setting. These algorithms will include BP z score categories and will consider time between measurements and number of measurements. We will evaluate their validity by examining rates of diagnostic coding for hypertension, treatment of hypertension, and characteristics of the patients identified as hypertensive using the alternative definitions.

For the approximately 300 CKiD participants in the PRESERVE database, we will contrast annual CKiD ABPM mean wake BP with a similar measure using all clinic BP assessments within 12 months before the ABPM. We will compute correlations and 95% confidence intervals (95% CIs), accounting for within patient clustering. We will replicate these analyses using ABPM data derived from institutional sources.

We will characterize the frequency and variability, overall and based on patient and institutional characteristics, for BP (clinic-based and ABPM) and urine protein (total protein and microalbumin, adjusted for urine creatinine) monitoring. For each patient, we will compute the proportion of encounters for which a valid BP z score can be estimated. For those individuals with hypertension, we will determine whether they have annual urine protein and ABPM assessments. We will adapt continuity of care indices,[38] such as the usual provider ratio,[39] to create BP and urine protein assessment continuity variables. These predictors will be used to test the hypothesis that consistent evaluation of BP and urine protein during the early phase of CKD can reduce risk of subsequent kidney function decline. We will generate institution-specific reports that show levels of adherence to guidelines for the measures, overall, by calendar time and by patient characteristics (eg, age and eGFR), and identify opportunities for practice improvement. We will describe differences in measured BP,

hypertension, proteinuria, BP monitoring, and urine protein monitoring ecologically by (deidentified) institution and area-level deprivation measures and individually by age, gender, race/ethnicity, CKD etiology, and CKD stage.

Aim 3: Compare the Effectiveness of BP Medication Strategies for Preserving Kidney Function

We will examine rates of the dichotomous composite outcome and the continuous outcome of decline in eGFR over time by level of BP when antihypertensive treatment was initiated. The former will use survival analysis methods, while the latter will employ generalized linear models to assess trajectories. A BP percentile will be assigned based on the maximum of the systolic and diastolic z scores closest to the day of initiation. We will explore categorization of BP by every 5th percentile (e.g., ≥95th, 90-94th, 85-89th,..., <50th), which is enabled by our large sample size.

Using clinic BP assessments, BP control will be allowed to vary with each visit, and the mean of the systolic and diastolic z-scores[6] will be selected as the measure of a visit's BP level and categorized into a BP quantile. Although larger quantile bands of BP control have been used in prior studies,[14] the size of our sample allows us to refine our analytic approach by separating into smaller categories. We will estimate the cumulative survival for each BP category using the counting process formulation.[40] Participants enter the risk set at a visit when BP is assessed and exit when they change BP category at a subsequent visit, are lost to follow-up, or experience the composite event. Regarding Kaplan-Meier plots, patients will be allowed to remain in or change their risk set between encounters. Because the comparator is time-dependent, it is likely that the assumptions of the proportional hazards model will not be met, in which case we will explore the extended cox model which allows for inclusion of time-dependent covariates.[41] We will also explore use of accelerated failure time models. In a prior CKiD study, the accelerated failure time model was selected as the preferred model for evaluating kidney function decline because of accelerated decline among patients whose kidney function was nearing kidney failure.[16]

We will contrast the effects of ACEi and ARBs with those of other antihypertensive medications used as first-line treatments and with each other on kidney function decline. Models will control for factors related to first-line therapy decision-making, such as age and gender, serum potassium, asthma, cardiac disease, and eGFR. We will compare different dynamic treatment strategies for minimizing kidney function decline through 2 approaches. The first will use latent class analysis to determine if there is a parsimonious set of pathways for antihypertensive treatment. If so, we will contrast rates of kidney function decline by treatment pathway. In the second approach, we will fit marginal structural models, which accommodate observational study designs that require adjustment for time-varying covariates and outcomes that dynamically interact with one another, which is the case for BP level and antihypertensive treatment.[42,43] We will evaluate heterogeneity of treatment effect by CKD stage, CKD

Table 2. Characteristics of the Study Cohort

Characteristic	N (%)
Sex	
Female	10,100 (51.1%)
Male	9,646 (48.9%)
Race and ethnicity	
Asian or Pacific Islander/Other/ Unknown	2,111 (10.7%)
Black or African-American	4,188 (21.2%)
Hispanic	2,854 (14.5%)
White	10,593 (53.6%)
Age at cohort entry (y)	
Mean (SD)	9.4 (5.3)
Median [Q1, Q3]	10.0 [4.4, 14.3]
Calendar year of cohort entry	
2009-2012	6,974 (35.3%)
2013-2015	4,959 (25.1%)
2016-2018	4,943 (25.0%)
2019-2021	2,870 (14.5%)
Qualifying serum creatinine measurement (mg/dL) at CED	
Mean (SD)	0.74 (0.33)
Median [Q1, Q3]	0.70 [0.50, 0.90]
Qualifying eGFR measurement (mL/min/ 1.73 m^2) at CED (using U25)	
Mean (SD)	71.4 (15.3)
Median [Q1, Q3]	76.0 [63.3, 83.4]
eGFR measurements per person-year (between CED to last in-person visit)	
Mean (SD)	5.8 (19.9)
Median [Q1, Q3]	1.7 [0.8, 4.3]
At least 1 glomerular disease diagnosis	
N	16,656 (84.4%)
Y	3,090 (15.6%)
At least 1 hypertension diagnosis	
N	10,455 (52.9%)
Y	9,291 (47.1%)
At least 1 elevated blood pressure (4th report blood pressure z scores)	
N	5,950 (30.1%)
Y	13,796 (69.9%)
Height z score at CED (CDC z scores – age ≥2 y)	
Mean (SD)	−0.4 (1.4)
Median [Q1, Q3]	−0.3 [−1.3, 0.5]
Missing	2514 (12.7%)
Years from CED to last in-person visit	
Mean (SD)	6.6 (3.6)
Median [Q1, Q3]	6.1 [3.6, 9.3]
Nephrology visits per person-year (between CED to last in-person visit)	
Mean (SD)	4.3 (8.3)
Median [Q1, Q3]	1.8 [0.5, 4.8]

Note: Preliminary data from 19,746 patients meeting cohort inclusion criteria from January 2009 to December 2021 across 15 institutions contributing data to PRESERVE. Data extracted for cohort through December 2022.

etiology, and proteinuria. We will evaluate disparities by sociodemographic characteristics. Table 2 shows the characteristics of the study sample.

Aim 4: Assess Patients' Lived Experiences Related to BP Management

A Delphi survey of patients, caregivers and healthcare professionals in 48 countries found top priorities to include kidney function, mortality, life satisfaction, and BP;[36] each of these outcomes will be assessed in PRESERVE. We will build on prior work that demonstrated content validity of the Patient-Reported Outcomes Measurement Information System (PROMIS) measures in prospective studies of children with chronic disease, including 212 children with CKD.[44]

PRO measures in the PRESERVE survey will be selected based on input from the Patient and Parent Workgroup and expert clinicians. The survey will be completed by youth with CKD aged 8-21 years and parents of youth aged 8-17 years with CKD (target enrollment of 750 patients). The survey data will enable us to examine patient experiences with ABPM and PROs by level of BP control and medication management approaches. The coordinating center will identify a subset of the PRESERVE cohort at each site meeting inclusion criteria for the survey (≥1 hypertension diagnosis code and ≥1 exposure to an antihypertensive medication). Methods of recruitment will include emails, telephone calls, in-person conversations, letters, EHR portal messages, and text messages.

DISCUSSION

PRESERVE will provide key information on kidney function preservation and evaluation of clinical BP measures using an unprecedented large EHR cohort for pediatric CKD and with comprehensive stakeholder engagement. This study builds on the epidemiologic data from CKiD and leverages a large volume of point-of-care measures to model kidney function trajectory and time to kidney failure. There are limited longitudinal data on outcomes in children with CKD after transitioning to adult care. Linkage of PCORnet data with USRDS will enable ascertainment of this primary outcome for the study population beyond their pediatric care at participating centers. Moreover, PRESERVE will contrast management practice benefits (preservation of kidney function) with potential harms (adverse events and PROs).

Although 24-hour ABPM is considered the gold standard for assessing BP control, it is challenging to use repeatedly in children outside of the research setting. A recent study demonstrated that protocolized clinic systolic BPs were not inferior to ABPM systolic BPs for risk discrimination of outcomes, including left ventricular hypertrophy and kidney failure.[45] The volume of longitudinal clinic BP measurements available in this study represents a unique opportunity to define optimal BP thresholds and targets for treatment initiation and longitudinal control. The incorporation of ABPM data in our study enables classification and predictive accuracy assessments of clinic measurements, which will facilitate new guidelines based on real-world patterns of care.

The ongoing engagement of patient/parent and clinician partners and dissemination of findings both within participating centers and to the broader pediatric nephrology community will accelerate their incorporation into clinical practice and new evidence-based guidelines.

In contrast to prospective cohort studies and clinical trials, our study includes an unselected sample focusing on children with mild-moderate CKD, when BP management practices may have the largest impact. The sample is also large enough for subgroup analyses to describe the heterogeneity of treatment effect based on kidney disease etiology, baseline proteinuria and eGFR, and other clinical factors.

Observational methods require causal inference methodology because unobserved covariates may affect assignment to the comparator groups and outcome.[46] Although we have selected covariates based on clinical input, we will mention this limitation in all manuscripts and provide sufficient detail (following STROBE criteria) for others to judge validity. For objectives evaluating BP and urine protein monitoring, confounding by indication may be a challenge. BP and urine protein are likely to be monitored more frequently because of greater CKD severity and risk of CKD progression. We will consider use of propensity scores to address this issue.

PRESERVE includes source EHR data across 16 institutions, each with different clinical workflows and changes to their EHR over the study period, which introduce heterogeneity and possible measurement error into the data. PCORnet has tried to mitigate this by implementing a common data model (CDM) and robust data characterization program. Although these processes produce analysis-ready data, they do not change fundamental differences in clinical workflows across institutions.

The study sample is drawn from 16 regional children's hospitals and may not be representative of all children with this rare condition in the US. These referral centers may serve children with greater levels of comorbid or other health conditions that complicate their care. However, 73% of the US pediatric nephrology workforce is linked to academic medical centers.[47] We will evaluate representativeness by contrasting the distribution of BP in the general pediatric population in PEDSnet with normative data from the National High BP Education Program[6]; comparing demographic and clinical characteristics of the PRESERVE population at initiation of KRT with USRDS; contrasting patient populations and rates of outcomes across institutions, as cross-institutional convergence strengthens external validity; performing a PCORnet-wide query and contrasting patients in our sample with those not in our sample.

In summary, PRESERVE will leverage the PCORnet infrastructure to conduct observational studies that address BP management knowledge gaps in an unprecedented large, national cohort of children with CKD, focusing on outcomes that are meaningful to patients. Enhancements to the PCORnet CDM will produce a sustainable infrastructure for future research in pediatric CKD and other rare pediatric conditions for which BP and kidney function are important measures.

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