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Developing an Edema Clinician-Reported Outcome Measure for Nephrotic Syndrome

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Keywords
Swelling · ClinRO · Focal segmental glomerulosclerosis · Minimal change disease · Membranous nephropathy · Clinical outcomes assessment

Abstract
Introduction: Edema is a common manifestation of proteinuric kidney diseases, but there is no consensus approach for reliably evaluating edema. The objective of this study was to develop an edema clinician-reported outcome measure for use in patients with nephrotic syndrome. ***Methods:*** A literature review was conducted to assess existing clinician-rated measures of edema. Clinical experts were recruited from internal medicine, nephrology, and pediatric nephrology practices to participate in concept elicitation using semi-structured interviews and cognitive debriefing. Qualitative analysis methods were used to collate expert input and inform measurement development. In addition, training and assessment modules were developed using an iterative process that also utilized expert input and cognitive debriefing to ensure interrater reliability. ***Results:*** While several clinician-rated measures of edema have been proposed, our literature review did not identify any studies to support the reliability or validity of these measures. Fourteen clinician experts participated in the concept elicitation interviews, and twelve participated in cognitive debriefing. A clinician-reported outcome measure for edema was developed. The measure assesses edema severity

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in multiple individual body parts. An online training module and assessment tool were generated and refined using additional clinician input and investigative team expertise. ***Conclusion:*** The Edema ClinRO (V1) measure is developed specifically to measure edema in nephrotic syndrome. The tool assesses edema across multiple body parts, and it includes a training module to ensure standardized administration across raters. Future examination of this measure is ongoing to establish its reliability and validity.

Introduction

Edema is a common manifestation of proteinuric kidney diseases such as minimal change disease, membranous nephropathy, and focal segmental glomerulosclerosis. The consequences of edema can be severe including limitation of mobility, dyspnea, pain, limitation of vision associated with periorbital edema, and increased risk of infection if accompanied by skin breakdown. In clinical practice and clinical trials, edema is assessed by history and physical examination. Clinicians utilize various clinical ratings of mild, moderate to severe, or a subjective scale of 0–4+. However, there are no validated, standardized, or objective approaches for the examination and documentation of edema location and severity in patients with proteinuric kidney disease, as confirmed via a literature review.

Previous efforts to develop an assessment tool to quantify edema in other contexts included measurement of the circumference of the lower extremity, longitudinal assessment of water displacement when the foot and ankle are immersed in a container of water, and bioimpedance methods [1–3]. These measures are either not standardized, are not feasible in the clinical setting, or have low inter-examiner reliability (Table 1). In addition, these measures were developed to assess edema in other patient populations, but there are no measures for clinician assessment of edema due to primary proteinuric kidney disease. Therefore, we undertook this study to develop an edema clinician-reported outcome (ClinRO) measure to support the consistent assessment and documentation of edema location and severity for use in children and adults with proteinuric kidney diseases.

Methods

A modified Delphi method that relied on expert input from physicians, nurses, and study coordinators was implemented to ensure the content validity of the new ClinRO measure. This was employed in conjunction with a literature review to identify potentially available clinician edema assessment measures for use in patients with nephrotic syndrome. Using search terms "Edema or Swelling" AND "Clinician or Provider" AND "Nephrotic Syndrome or Focal Segmental Glomerulosclerosis or Minimal Change Disease" from period of January 1, 2000, through the search date of January 1, 2018, the PubMed search engine did not identify any measures.

Following the literature review, an interview guide was developed to elicit concepts related to physical manifestations of edema observed and documented in the routine care and in clinical trials of patients with proteinuric kidney diseases. Expert clinicians familiar with assessing patients with nephrotic syndrome, including internal medicine and pediatric nephrologists and nurses, were recruited to participate in concept elicitation interviews. A demographics and expertise survey was distributed to all interview participants for self-reported data collection.

These concept elicitation interviews were used to inform the development of an initial version of the Edema ClinRO. This was followed by a second round of cognitive debriefing interviews where clinicians reported on their overall level of satisfaction with both the format and the content of the Edema ClinRO measurement tool. Clinicians also provided additional feedback about modifications that were employed and then brought back for additional review as needed. There was full consensus from the clinicians for the final content of the Edema ClinRO measurement tool (specific body parts and format of presentation). Once completed, a training video with post-training assessment was generated and assessed by the clinician authors, and a follow-up interview was conducted with respondents to inform modifications prior to the finalization of the training materials.

This study was reviewed and approved by the Institutional Review Board of the University of Michigan (HUM00148440). Prior to participation, interview respondents were notified of the purpose of their participation and of the study sponsor. Continuation in the study was considered implied consent by the Institutional Review Board, and formal written consent was not required.

Results

Participants

Descriptive data for the clinician sample are provided in Table 2. Fourteen clinical experts took part in the semi-structured interviews. Considerations for the spectrum of edema severity, location of edema, and commonly used approaches to document nephrotic syndrome-associated edema were elicited from respondents in the first interview. Participants indicated that certain body parts were more important in the assessment of edema in certain patient subgroups. For example, many participants noted that examining the sacral area for edema in the inpatient setting is important, whereas it is less informative in the outpatient setting. It was largely agreed that examining the genitals in male pediatric patients is important because scrotal swelling is

Table 1. Currently available peripheral edema assessment measures for diabetes and dialysis populations

Measure	Population	Sample size	Advantages	Disadvantages
Clinician assessment of edema pit and recovery[2]	>21 years old, type 2 diabetes mellitus	20	• Clinically feasible and efficient	• Low reliability (ICC* 0.05–0.53)
Patient questionnaire[2]	>21 years old, type 2 diabetes mellitus	20	• Clinically feasible • General agreement with clinician assessment	• Patient-reported, not clinician-reported, outcome
Foot and ankle water displacement volumetry[2]	>21 years old, type 2 diabetes mellitus	20	• High reliability (ICC 0.93–0.96)	• Poor clinical feasibility • Isolated to the foot and ankle only
Ankle circumference[2]	>21 years old, type 2 diabetes mellitus	20	• High reliability (ICC 0.97)	• Isolated to the ankle only
Figure-of-eight measurement[2]	>21 years old, type 2 diabetes mellitus	12	• Clinically feasible and efficient	• Challenging for clinicians • Mixed reliability (ICC 0.64–0.86)
Edema and modified edema tester[2]	>21 years old, type 2 diabetes mellitus	9	• Not assessed due to small sample size	• Low reliability (ICC 0.12–0.75) and variable reliability by pressure
Bioimpedance technology[5]	Adult dialysis patients	–	• Operator-independent	• Complex technology • Ignores body composition (subcutaneous fat, skin resistance) • Lack of validation studies

*ICC, interclass correlation coefficient (at least 0.75 considered favorable).

Table 2. Clinician expert respondent characteristics summary

Role	Practice duration, years, mean ± SD	Number of participants round 1, *N* = 14	Number of participants round 2, *N* = 12
Nephrologist, internal medicine	15.9±9.12	6	3
Nephrologist, pediatrics	29.0±7.45	3	4
Nephrologist, internal medicine/pediatrics	18.0	1	1
Research nurses	13.5±2.06	4	4

common in this population. Internal medicine nephrologists largely agreed that assessing the abdomen in obese patients is difficult.

Survey of Practices to Assess Edema

Respondents variably reported evaluation of both ankles and feet or only one of these locations. Periorbital edema was more commonly evaluated by pediatric nephrologists compared to internal medicine nephrologists. Clinicians were inconsistent in their approach to documenting edema when edema is asymmetrical, but it was widely agreed that this was a rare condition. Recording the most severely affected side was considered most helpful by some physicians, while others expressed concern that asymmetrical edema may reflect the presence of a coexisting medical condition. A minority of experts recommended that both sides could be assessed and then averaged.

Examination for pitting edema was consistently recommended. There was general consensus among experts that the clinician should press for 5 seconds. However, there was little consensus on how deep a clinician would have to press for edema to be considered severe. Answers ranged from two to 6 mm, and some experts said they were not sure because they do not measure the depth of the indentation in their practice. Consensus was also lacking on how much force to apply when assessing pitting edema.

Participant Interviews

Content from the first round of interviews was used by the study team to generate the initial version of the Edema ClinRO (alpha). Cognitive debriefing interviews were then conducted with twelve clinicians, including eight physicians and four study coordinators and nurses. Modifications to the ClinRO (alpha) were made based on participant input, and the Edema ClinRO V1 was finalized (shown in Fig. 1). The following areas are included in

Nephrotic Syndrome Edema Rating Scale

INSTRUCTIONS: This scale is designed to assess edema that is specific to nephrotic syndrome. Ratings should be based on the clinician's impression using all available information, including the clinical exam and information provided by the patient when available. Circle the numerical value associated with your rating for each area of the body.

Peri orbital	0	Absent	No obvious swelling
		Mild/Moderate	Area around eyes is visibly swollen (without impairment of vision or blinking)
	2	Severe	Swelling is very obvious and interferes with blinking or with opening of eyes
Arms	0	Absent	No obvious swelling
		Mild/Moderate	Mild swelling is visible
	2	Severe	Endorse if any of the following: pitting; arms seem grossly swollen or distorted
Hands	0	Absent	No obvious swelling
		Mild/Moderate	Mild swelling is visible
	2	Severe	Pitting on dorsal part of hand or swelling that impairs flexion in fingers
Sacral	0	Absent	No indent made by pressing
		Mild/Moderate	Slight indent OR moderate indent (pitting is present and S4mm deep)
	2	Severe	Large indent (pitting is severe and >4mm deep)
Abdomen	0	Absent	No obvious swelling
		Mild/Moderate	Fluid wave is present but not tense
	2	Severe	Tense ascites or pitting edema present
	99	Unable to assess	Circle a reason: Obesity other: _____
Genitals *Only examine if endorsed by patient*	0	Absent	No patient-endorsement
		Mild/Moderate	Swelling is visible, but no obvious difficulty with mobility
	2	Severe	Swelling visibly impedes mobility

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(Figure continued on next page.)

the ClinRO: periorbital, arms, hands, sacral, abdomen, genitals, thigh, lower leg, and ankle or foot. Thighs and genitals are only to be assessed if patients endorse swelling in these areas.

A training video was developed to provide online training to promote consistent, reliable assessment of edema by clinicians and clinician-investigators using the Edema ClinRO (V1) measure (shown in Fig. 2a–d). The 8-min video includes training on how to rate edema severity for each body part and questions to ask the patient to guide the clinician's edema assessment. A post-training quiz assessed understanding of the material covered in the video and the ability of the trainee to

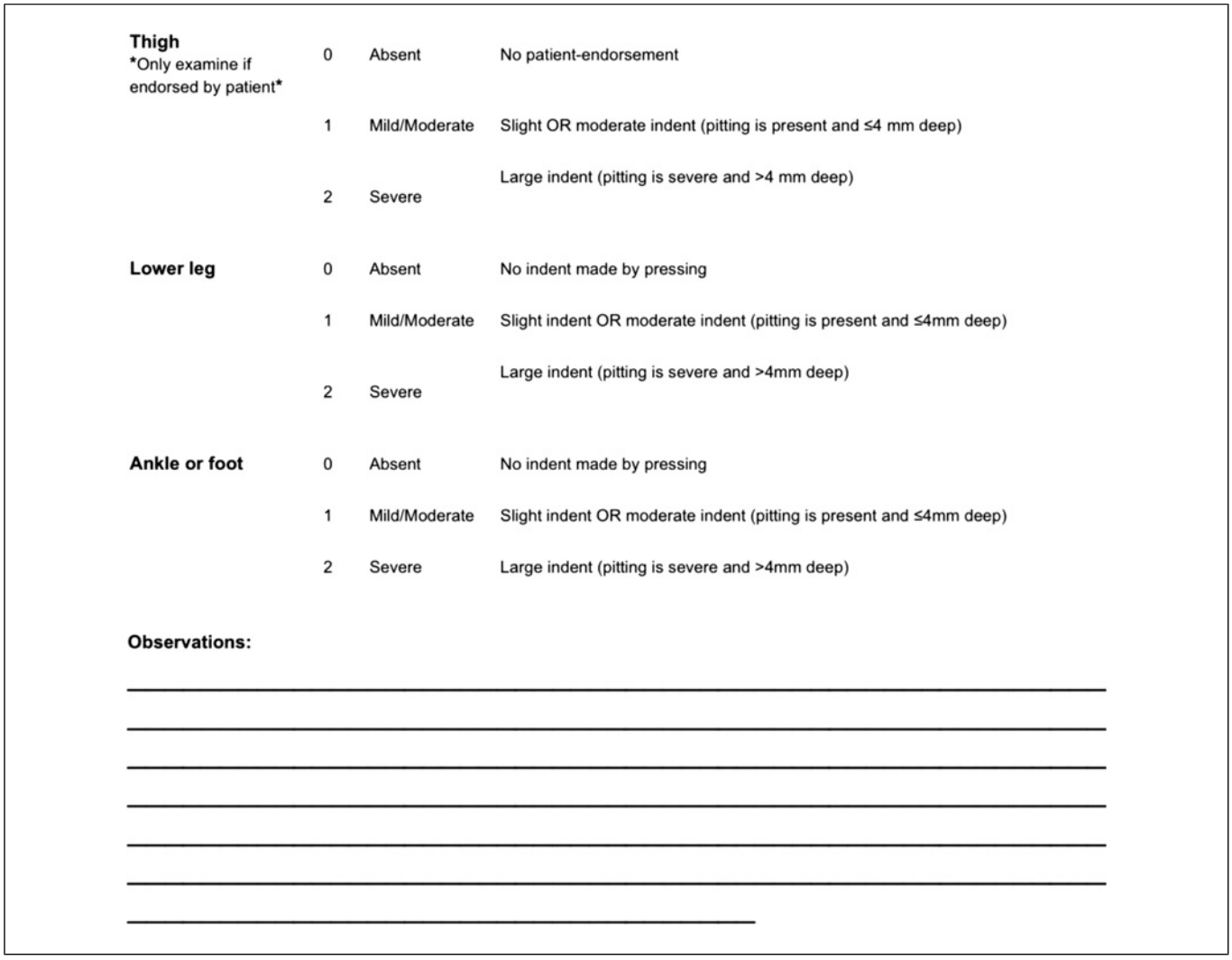

Fig. 1. Edema ClinRO measure developed for use in patients with nephrotic syndrome.

accurately score edema using the Edema ClinRO (V1). Clinicians must score at least 90% to pass the training, and a certificate is generated to document successful completion of the online training program.

Discussion

We conducted this study to generate a ClinRO measure that could be used by clinicians and clinician-investigators to assess and document the presence, location, and severity of edema in patients with proteinuric kidney disease, both in clinical practice and for patients enrolled in clinical trials. With expert input from physicians, nurses, and study coordinators, the Edema ClinRO (V1) measure and training tools were developed.

A literature review confirmed a scarcity of edema assessment measures. Assessment of changes in body weight has been proposed in the assessment of edema in patients with heart failure [4]. However, changes in body weight from causes unrelated to edema introduce errors that diminish the precision of this approach. Water displacement measures to assess pedal edema have been examined in diabetic nephropathy populations but have not been widely implemented and are time-consuming [2]. Bioimpedance methods have been used to assess total body water and volume control in dialysis patients [5]. These approaches have not been tested in patients with nephrotic syndrome. A recent bioimpedance simulation study was published and concluded that future research is warranted to determine the feasibility of the method [3]. Another study tested the

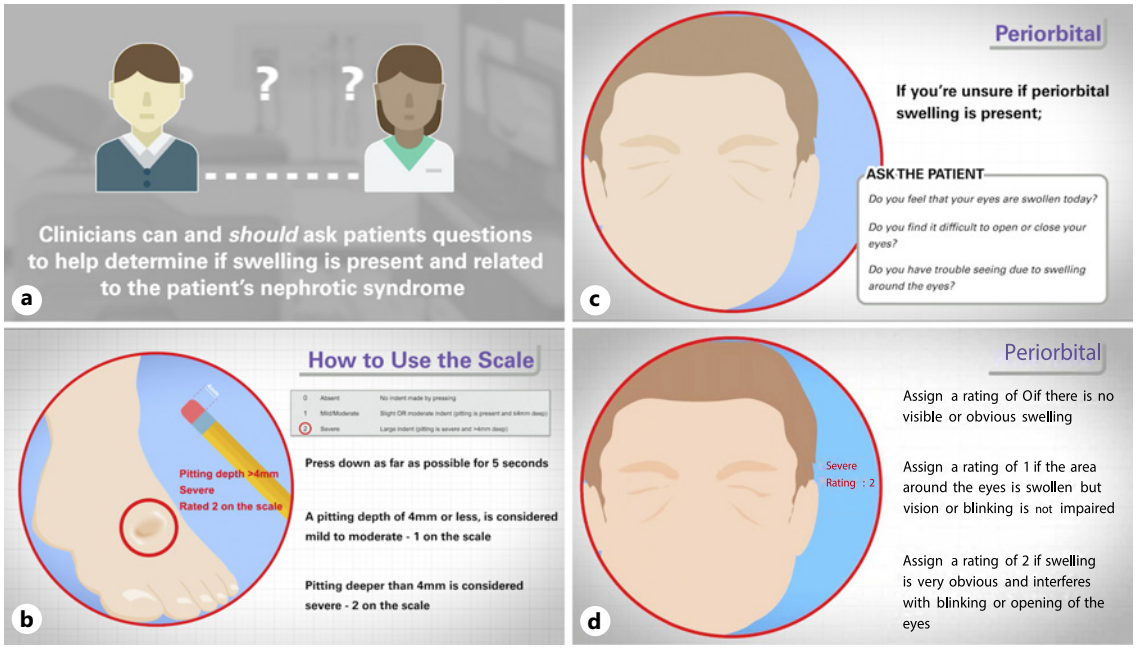

Fig. 2. Example content from the Edema ClinRO training module. **a** Training the clinician to include patient answers to edema-related questions in the assessment. **b** The depth of the pitting edema used in the edema rating. **c** Example questions that a clinician may ask the patient to assess for the presence of periorbital edema. **d** The periorbital edema rating definitions and severe periorbital edema are shown.

relationship between surface imprint and circumferential measurements as a potential evaluation method for edema but found there to be no significant relationship [6]. Measuring the circumference of the leg at a single point by using a device such as the Leg-O-Meter has been shown to be reproducible but is only helpful for estimating the volume of the lower limb at the location where the circumference was measured. The circumference data cannot be extrapolated to estimate the volume of the entire leg [1]. Ultrasonography has been proposed for edema assessment with use of a gel pad reportedly improving reliability. However, when ultrasound is used alone, varying interpretation by ultrasound technicians raises questions about reliability and reproducibility [7]. The figure-of-eight method for assessing trauma-related swelling was shown to be reliable in healthy participants and participants with an ankle injury. However, in a follow-up study, the reliability between the right and left ankles was inconsistent, and the data suggested that this method was more reliable on the left versus the right ankle [2]. A wearable device has been developed to monitor edema continuously and in real-time. While the device is reliable, the prototype is still in its early stages, and more work on the device's hardware and algorithms is needed [8].

ClinRO tools are important as they may serve as clinical trial endpoints and can standardize the assessment of particular aspects of patient health status. In the context of proteinuric kidney diseases, the study team endeavored to develop an edema-specific ClinRO for clinical trial use. The developed ClinRO assessment tool was produced following two rounds of interviews that included a total of fifteen clinical experts. Unlike many other edema assessment methods, this ClinRO focuses on the evaluation of edema in multiple body parts and specifically in patients with nephrotic syndrome. Furthermore, the ClinRO and training video were designed with the intent of promoting a standardized and reliable approach to assess edema in clinical practice and research studies.

This tool provides investigators with standard objective measures by which to assess edema at each body area, as opposed to the subjective 0–4+ scale traditionally utilized by clinicians, which has limited inter-examiner reliability [2]. In interviews, clinical experts identified difficulty with reliably assessing small differences in severity, especially between mild and moderate edema. Furthermore, the clinical significance of mild versus moderate edema was questioned. Because of this, mild and moderate edema were grouped into a single category,

allowing for a simplified scoring algorithm and less subjectivity. We hypothesize that the scale of the new ClinRO assessment tool will allow investigators to meaningfully determine the severity of a patient's edema with increased precision.

To improve the feasibility of this assessment's use in both clinical and research settings, we did not place limitations on aspects such as positioning of the patient during assessment. Without a set position that the patient must be in during the exam, this tool can be used in both outpatient and inpatient settings. We hypothesize that the assessment of different body areas for edema allows for a similar score, whether supine or upright. As dependent edema shifts from one area to another with positional change, there will be corresponding changes in identifiable edema. In this way, the measure can be valuable even through shifts in position.

As a clinician-reported outcome measure, the Edema ClinRO (V1) does not contain certain elements including pain and limitation of mobility that are better suited in a patient-reported outcome such as the Patient-Reported Outcomes Measurement Information System, which has been found to reliably identify health-related quality of life profiles in children and adults with nephrotic syndrome [9]. We also elected to omit rare consequences of edema, such as skin breakdown, following our interviews with clinical experts.

The Edema ClinRO (V1) measure developed in this study represents a tool that is easy to implement and that can be used to quantify the serial evaluations of edema. It is accessible for free to clinicians and researchers through the Kidney Research Network at https://www.kidneyresearchnetwork.org/outcome-and-endpoints. Before its widespread use can be recommended, the ClinRO (V1) tool requires further testing in diverse cohorts of adults and children with nephrotic syndrome to determine its reliability, reproducibility, and practical utility for clinical trials, prospective observational studies, and clinical care. Other questions for future studies include whether this tool can be used as a reliable assessment of edema improvement and resolution and what parameters would define each of these.

Statement of Ethics

This study was reviewed and approved by the Institutional Review Board of the University of Michigan (HUM00148440). Prior to participation, interview respondents were notified of the purpose of their participation and of the study sponsor. Continuation in the study was considered implied consent by the Institutional Review Board, and formal written consent was not required.

Conflict of Interest Statement

Joshua Thurman receives royalties from Alexion Pharmaceuticals, Inc. He is a consultant for, will receive royalty income from, and holds stock in Q32 Bio Inc. He is also on the data review team for Goldfinch Bio. Michelle O'Shaughnessy is a consultant for Chinook Pharmaceuticals. Noelle Carlozzi, through the University of Michigan, received research funding for the design and conduct of this study. Laura Mariani, through the University of Michigan, has received research funding from the NIH, DOD, Nephcure Kidney International, and Boehringer Ingelheim unrelated to this work. She also receives personal consulting fees from Reata Pharmaceuticals, Callidtas Therapeutics, and Travere Therapeutics. Howard Trachtman is a consultant to Travere, Goldfinch Bio, Roche, and Walden and receives research funding from the NIH, DOD, and Natera. He is also Chair of DMC for pediatric studies conducted by Otsuka and is on the editorial board of Scientific Reports, Glomerular Diseases, Pediatric Nephrology, and Kidney360. Debbie Gipson, through the University of Michigan, received research funding for the design and conduct of this study from Goldfinch Bio and, through the University of Michigan, receives funding for research or consulting from Goldfinch Bio, Genentech, Roche, Boehringer Ingelheim, Travere, AstraZeneca, Novartis, Pfizer, Vertex, Reata, NIH, CDC, and FDA. Youssef Farag is a past employee of Goldfinch Bio. Liron Walsh is a past employee of Goldfinch Bio. All other authors report no conflicts of interest.

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Author Contributions

Debbie S. Gipson designed the study, conducted the analysis, and wrote, reviewed, and approved the manuscript. Maisha Pal transcribed interviews, wrote, reviewed, and approved the manuscript. Hailey Desmond contributed to the study design, implementation, and data collection as well as editing the final manuscript. Charles Anderson participated in the scoping literature review, data analysis, and manuscript drafting and editing. Liron Walsh and Youssef Farag participated in the study design, data analysis review, and manuscript editing. Christine Simon transcribed interviews and edited the manuscript. Noelle Carlozzi conducted data collection and analysis, drafted the manuscript, and reviewed and approved the manuscript. Howard Trachtman, Susan Massengill, Patrick Gipson, Panduranga Rao, Joshua Thurman, Jeffrey Kopp, Elaine Kamil, Jennifer Lamothe, Laura H. Mariani, Paula LaFleur, Suzanne Vento, and Michelle O'Shaughnessy participated in concept elicitation interviews and edited the manuscript.

Data Availability Statement

All data are included in this article. Data are available by contacting kidneyresearchnet@med.umich.edu. Further inquiries can be directed to the corresponding author.

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