Proteinuria as an End Point in Clinical Trials of Focal Segmental Glomerulosclerosis

Laura H. Mariani, Howard Trachtman,* Aliza Thompson, Barbara S. Gillespie, Michelle Denburg, Ulysses Diva, Duvuru Geetha, Peter J. Greasley, Michelle A. Hladunewich, Robert B. Huizinga, Jula K. Inrig, Radko Komers, Louis-Philippe Laurin, Dustin J. Little, Patrick H. Nachman, Kimberly A. Smith, Liron Walsh, and Keisha L. Gibson*

Focal segmental glomerulosclerosis (FSGS) is a characteristic histopathological lesion that is indicative of underlying glomerular dysfunction. It is not a single disease entity but rather a heterogeneous disorder that is an important cause of nephrotic syndrome and kidney failure in children and adults. The aim of this Kidney Health Initiative project was to evaluate potential end points for clinical trials in FSGS. Our focus is on the data supporting proteinuria as a surrogate end point. Available data support the use of complete remission of proteinuria in patients with heavy proteinuria as a surrogate end point for progression to kidney failure. Substantial treatment effects on proteinuria that are short of a complete remission may also predict the effect of a treatment on progression to kidney failure, but further work is needed to determine how such an end point should be defined. Fortunately, efforts are underway to bring together patient-level data from randomized controlled trials, observational studies, and registries to address this issue.

Complete author and article information provided before references.

Correspondence to L.H. Mariani (lmariani@umich.edu) or H. Trachtman (howardtrachtman21@gmail.com)

**L.H.M. and H.T. contributed equally to this work.*

Am J Kidney Dis. XX(XX):1-8. Published online month xx, xxxx.

doi: 10.1053/j.ajkd.2024.08.011

Background

Focal segmental glomerulosclerosis (FSGS) is a characteristic histopathological lesion that is associated with glomerular barrier dysfunction.[1] When applied clinically, the term FSGS is not a single disease but rather represents a heterogeneous disorder. FSGS has multiple underlying biologic etiologies, which have been classified into 4 clinically based subcategories: primary, genetic, secondary (viral, drug-induced, adaptive), and undetermined cause.[2,3] It affects approximately 200,000 children and adults in the United States, of whom approximately one-fifth have primary disease.[4] The clinical presentation of FSGS is variable, ranging from asymptomatic proteinuria to overt nephrotic syndrome, and the signs and symptoms include edema, pain, and fatigue along with high morbidity from cardiovascular, infectious, and thromboembolic complications. Up to 40%-50% of patients with FSGS progress to kidney failure over 5 to 10 years, a rate that is greater than most other forms of nephrotic syndrome.[5] In reviewing the literature, it is important to recognize that the term FSGS is often used generically in broad strokes without clear definition of the subtype of the disorder being studied.

Other than specific causes of secondary FSGS, there are no medical therapies approved by the US Food and Drug Administration (FDA) for FSGS or any of its subtypes. Although several therapies are used off-label, the data supporting specific management approaches are limited, and many patients respond inadequately. Moreover, the available therapies, often immunosuppressant agents, are associated with significant toxicity.[6-8] As such, there is significant unmet clinical need for new effective and safe treatments.[3]

Ideally, novel FSGS therapies would be targeted at the specific subtype of FSGS and would favorably impact important clinical outcomes such as progression to kidney failure. However, end points such as kidney failure are generally not feasible in clinical trials in FSGS given the time course for progression to kidney failure and the relative rarity of the disease. As such, there is a need to identify other end points that could support the approval of products for FSGS.

The Kidney Health Initiative (KHI), a public-private partnership between the American Society of Nephrology, the FDA, and over 75 companies and organizations in the kidney community, was established in September 2012 "to catalyze innovation and the development of safe and effective patient-centered therapies for people living with kidney diseases."[9,10] The KHI convened a multistakeholder work group to review the available published natural history studies, epidemiologic studies, and clinical trials as well as ongoing work to evaluate potential clinical trial end points for patients with diagnosed FSGS. We will focus on the data supporting proteinuria as a surrogate for clinical outcomes in FSGS.

Many of the studies we will describe are based on data from patients with proteinuria levels over 2-3 g/g, many of whom likely had primary FSGS. However, the disorder is heterogeneous, and some of the patients may have had secondary, genetic, or undetermined causes.[3] As such, the findings are most likely to apply to populations with nephrotic-range proteinuria and primary FSGS. This report is a companion to another that addresses considerations related to the use of changes in kidney function to assess efficacy in clinical trials in FSGS (L.H.M., manuscript in preparation) and a third that will focus on clinical outcome

assessments. These assessments include patient-reported and observer-reported outcome measures for use as end points for FSGS trials.[11]

End Points and Regulatory Pathways for Drug Approval in the United States

Prior to marketing in the United States, a drug must be shown to be safe and effective for its intended use. Approval can be based on substantial evidence of an effect on a clinical outcome (ie, a positive treatment effect on how a patient feels, functions, or survives). Approval can also be based on a surrogate end point. As defined in the *BEST (Biomarkers, EndpointS, and Other Tools)* resource glossary, a surrogate end point does not measure the clinical benefit of primary interest.[12] Instead, it is a substitute for that measure and is expected to predict that clinical benefit based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

Validated surrogate end points can be used to support traditional approval of a drug without the need for additional studies directly demonstrating the anticipated clinical benefit.[12] Such end points are supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate end point predicts a specific clinical benefit. "Reasonably likely" surrogate end points can be used to support accelerated approval, a regulatory pathway intended to expedite patient access to drugs that address an unmet medical need in the treatment of a serious condition. Such end points are supported by evidence that an effect on the surrogate end point predicts a specific clinical benefit, but the evidence supporting a reasonably likely surrogate end point does not have to be as strong as the evidence supporting a validated surrogate end point.

Because there is remaining uncertainty about the relationship between the change in the "reasonably likely" surrogate and the subsequent clinical benefit, the FDA has generally required postmarketing studies to verify and describe the clinical benefit of products approved under the accelerated approval pathway.[13] Because such trials are intended to determine whether the product provides the expected clinical benefit, it is important to have confidence that such studies are adequately powered to detect the clinical benefit. As such, there should be sufficient knowledge of the quantitative relationship between the end point for the surrogate that will be used to support accelerated approval and the end point that will be used to verify the clinical benefit in the postmarketing setting.

Considerations Related to the Assessment of Proteinuria in Clinical Trials

Methods for Assessing Proteinuria in Clinical Trials

Accurate and reliable procedures to measure proteinuria are essential if changes in urinary protein excretion are to be used as a surrogate end point. The methods in current use for assessment of proteinuria are summarized in Table 1. The use of 24-hour urine collection for total protein is considered the gold standard in clinical management and trials of adults with a diagnosis of FSGS. However, 24-hour urine collections are subject to improper collection and subsequent measurement error. Assessment of urinary protein-creatinine ratio (UPCR) in a sample taken from a timed collection, such as a 24-hour urine collection, has been used to mitigate under/overcollection-induced measurement errors.

For individuals in whom collection of a timed urine collection is not feasible without a urinary catheter, such as the very young or incontinent, random or first morning void spot urine samples ease patient burden and make proteinuria assessment possible. Studies suggest, however, only moderate correlation between UPCR in a random spot urine sample and a 24-hour urine collection.[14] This is the rationale for the use of first morning void UPCRs rather than random spot urine UPCRs because first morning void UPCRs correlate more closely with 24-hour urine collections for total protein and exclude orthostatic proteinuria.[14] All measurements of proteinuria that are normalized to urine creatinine concentration to account for urine concentration are susceptible to errors in patients

Table 1. Measurement of Proteinuria in Clinical Trials of FSGS

Method of Measurement	Advantages	Disadvantages
24-h Urine collection for total protein	Gold standard	• Patient burden and inconvenience • Over- or undercollection common • Impractical in young children
24-h Urine collection for UPCR	Impact of over- or undercollection partially mitigated by use of the ratio	
First morning void for UPCR	• Avoids orthostatic changes in proteinuria • Reasonable correlation with 24-h urine collection • Greater feasibility of collecting multiple specimens	• Training required to reduce errors in collection • Reduced accuracy with low muscle mass and with low eGFR
Spot urine sample for UPCR	Easiest to collect	• Susceptible to orthostatic changes • Limited correlation with 24-h urine collection • Reduced accuracy with low muscle mass and with low eGFR

Abbreviations: eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; UPCR, urinary protein-creatinine ratio.

with extremely high or low muscle mass or extremely low creatinine clearance.[15]

The measurement of albuminuria in a 24-hour or spot urine collection is not routine in FSGS unlike diabetic kidney disease, and it is limited by cost and availability. Although there are formulas that enable estimation of albuminuria from measurements of proteinuria, they are not sufficiently accurate, and direct measurement of albuminuria is recommended when clinically indicated.[16]

Table 2 summarizes the commonly used classifications of proteinuria. Nephrotic range proteinuria is defined as >3.5 g/24 hours or UPCR > 3.5 in adults. In pediatric patients, the cutoff for nephrotic proteinuria is >1 g/m^2/24 hours or UPCR > 2. Subnephrotic range proteinuria indicates levels that exceed the upper limit of normal but fall below the nephrotic-range threshold.

When using UPCR, difficulties can arise in patients with low creatinine clearance or diminished muscle mass in which a low urinary creatinine concentration can lead to a falsely elevated UPCR. Thus, uncertainties may remain regarding the thresholds as well as differences between certain patient groups, especially neonates, infants, adolescents, and the elderly.[17] Urine protein laboratory assays and reference standards vary between laboratories. Consequently, a single central laboratory with a static reference is needed for each trial pending the implementation of national urine protein reference standardization.[18] This will help to ensure that the findings are internally valid and provide a meaningful reflection of the antiproteinuric effect of a test therapy.

Current Definitions of Proteinuria Changes Used in Epidemiologic Studies and Clinical Trials

Proteinuria response to therapy in patients with biopsy-confirmed FSGS and nephrotic-range proteinuria has routinely been divided into 3 subcategories[3] (Table 3). Complete remission (CR) indicates that the individual has achieved normalization of urinary protein excretion; however, few patients with FSGS who are resistant to corticosteroids and other immunosuppressive therapies achieve a durable CR.[19-21] Thus, partial remission (PR) or PR in combination with CR has been used to define at least some response to therapy in patients with primary FSGS and nephrotic range proteinuria. PR has traditionally been defined as ≥50% decline in proteinuria to a level below 3.5 g/24 hours in adults or a UPCR of <2.0 in pediatric patients. No remission (NR) indicates persistent proteinuria or a reduction not meeting criteria for a PR.[3] No studies have been conducted to evaluate the validity of having different PR definitions for adults and pediatric patients. Indeed, when adolescents and adults are included in the same clinical trial, a common PR definition is typically used.[22]

Table 2. Classification of Proteinuria

	24-h Urine Collection (g/24 h)	First Morning Urine Specimen (mg:mg creatinine)
Adult		
Normal	<0.3	0.3
Subnephrotic	0.3-3.5	0.3-3.5
Nephrotic	>3.5	>3.5
Pediatric		
Normal	<100 mg/1.73 m^2 BSA	0.2
Subnephrotic	100-1,000 mg/1.73 m^2 BSA	0.2-2.0
Nephrotic	>1,000 mg/1.73 m^2 BSA	>2.0

Abbreviation: BSA, body surface area.

Table 3. Proteinuria Remission End Points and Their Definitions in Patients With FSGS and Nephrotic Range Proteinuria

End Point	Definition
Complete remission	Proteinuria < 0.3 g/d
Partial remission	≥50% reduction in proteinuria from baseline and between 0.3 and 3.5 g/d
Novel (modified) FSGS partial remission	Proteinuria < 1.5 g/d with a ≥40% reduction from baseline
No response	Failure to achieve either a complete or partial remission as defined above

Abbreviation: FSGS, focal segmental glomerulosclerosis.

Data Supporting Use of Proteinuria as a Surrogate End Point for Clinical Trials in FSGS

Biological Plausibility

Studies have shown that FSGS is a disease of the podocyte, the glomerular visceral epithelial cell, and that dysfunction and structural changes in podocytes alter the glomerular filtration barrier leading to proteinuria.[23] Investigations suggest that podocyte injury over time can result in cell loss, subsequent podocytopenia, tuft adhesion, and segmental glomerulosclerosis.[24-28] Low birth weight and prematurity, which may compromise nephron and podocyte endowment, are associated with a more rapid decline of kidney function in patients with FSGS.[29] In experimental model systems of FSGS, targeted podocyte depletion is associated with both higher levels of proteinuria and progressive glomerular scarring. This suggests that proteinuria is tightly linked to the causative pathway that leads to irreversible injury to the kidney.[30] In patients with biopsy-confirmed FSGS, podocyte depletion has also been shown to correlate with proteinuria and disease progression. Additionally, experimental data suggest that filtered urinary proteins may directly cause tubular injury, leading to inflammation and fibrosis.[31] The exact component of urinary protein, how, and in what settings proteinuria results in progressive tubular damage remain areas of controversy and investigation.[32] Nevertheless, taken together, the existing data support the biological plausibility of proteinuria as a surrogate for effects on disease progression in clinical trials of FSGS.

Epidemiologic Associations Between Proteinuria and Loss of Kidney Function in Adults

Observational studies provide the bulk of the evidence supporting a relationship between proteinuria levels and the loss of kidney function over time. Data from multiple observational studies have shown that patients with nephrotic syndrome have a significantly poorer prognosis than non-nephrotic patients. Specifically, in a review article that aggregated observational data from multiple studies, approximately 50% of patients with nephrotic-range proteinuria progressed to kidney failure over 6-8 years and within 3 years if proteinuria exceeded 10 g/day. By contrast, the 10-year kidney survival exceeded 80% in those with non-nephrotic proteinuria.[33] Similarly, a retrospective study of 250 patients showed that nephrotic syndrome was associated with kidney failure in a multivariable analysis.[34,35] Other studies have reported similar findings: 5-year kidney survival rates of 60%-90% and 10-year kidney survival rates of 40%-60% in patients with nephrotic syndrome, considerably worse than patients with subnephrotic proteinuria.[34-36]

An association between better preservation of kidney function with lower levels of proteinuria has also been observed in longitudinal studies that examine proteinuria over time in response to routine clinical treatment. In these studies, higher levels of proteinuria, often assessed at a single time before and for some time after treatment, have been associated with a greater risk for progressive loss of kidney function in patients with FSGS.[37,38] Data also indicate that pediatric and adult patients who achieve lower levels of proteinuria in response to routine clinical treatment have better preservation of kidney function.[35,39] Achieving CR has consistently been associated with better renal outcomes in primary FSGS.[36,40-42] In the open label extension of the DUET Trial, patients who achieved a CR at any time during the follow-up period had a significantly lower estimated glomerular filtration rate (eGFR) slope and a diminished rate of eGFR loss (−0.5 to −1.0 mL/minute/year) compared with those who never achieved the CR (approximately −7 mL/minute/year). These patients also showed numerically fewer composite kidney failure end points.[43]

Troyanov et al[39] studied 281 patients older than 16 years of age with pathologic findings of FSGS and nephrotic range proteinuria who were enrolled in the Toronto Glomerulonephritis Registry. Over a median follow-up of 65 months, 55 experienced a CR, 117 had a PR, and 109 had NR. Achieving CR during follow-up was associated with the best outcome with >90% kidney survival. Compared to NR, a PR, as defined previously, was predictive of a slower rate of kidney function decline over time (loss of 0.47 ± 0.65 vs 0.88 ± 1.00 mL/min/month) and a lower risk of end-stage kidney disease (ESKD). Among those who entered PR, the lower the level of proteinuria achieved (<3.5 g, <2 g, vs <1 g) the slower the eGFR decline per year during follow-up.[39] Similarly, in a study of 136 adults with FSGS and proteinuria > 3 g/day treated at 5 centers in the United Kingdom, 5-year kidney survival off dialysis was better in patients who achieved a CR or PR as compared with those with NR (5-year kidney survival of 94% and 53%, respectively).[44]

Epidemiologic Associations Between Proteinuria and Loss of Kidney Function in Pediatric Patients

The relationship between proteinuria and loss of kidney function in children and adolescents appears to be similar to that seen in adults. Thirty-nine pediatric patients with nephrotic syndrome and biopsy-confirmed FSGS treated with steroids at a single Brazilian site were followed for a mean of 7 years. As in adults, persistent nephrotic syndrome during follow-up was associated with progression to kidney failure.[19] Findings in 60 children with diagnosed FSGS and a mean age of 16 years enrolled in the Glomerular Disease Collaborative Network[35] were similar to those reported by Troyanov et al.[39] In this study, 12 children achieved CR, 20 PR, and 28 NR. There was a graded improvement in kidney survival between the categories, with CR associated with a 90% relative reduction in risk of ESKD compared with NR. A similar relationship was seen in data from 1,354 children with steroid resistant nephrotic syndrome enrolled in the PodoNet Registry. In this study, 10-year ESKD-free survival rates were 43%, 72%, and 94% in children who achieved NR, PR, and CR, respectively.[21]

It is important to note that, to date, the studies in children and adults that have explored the association between proteinuria and loss of kidney function have included a heterogenous population of patients with FSGS and it is unclear whether and to what extent the underlying pathogenetic category/cause of disease might alter these relationships.

Novel Definitions of Proteinuria Response and Their Association With Loss of Kidney Function

As previously noted, proteinuria response to therapy in patients with FSGS and nephrotic range proteinuria has routinely been divided into 3 subcategories: CR, PR (traditionally defined as ≥50% decline in proteinuria to a level below 3.5 g/24 hours in adults or a UPCR of <2.0 in pediatric patients), and NR. To determine whether an alternative definition of PR could be developed that more strongly associates with kidney outcomes than the conventional definition, Troost et al[45] analyzed data from 466 patients with biopsy-confirmed FSGS and an eGFR > 30/min/1.73 m^2 and proteinuria > 1 g/g who had a median follow-up of 27 (IQR, 13-43) months. The analyses included 5 independent cohorts (1 derivation and 4 validation cohorts); the median UPCR at entry into these cohorts ranged from 2.4 to 4.2 g/g. Using receiver operator curve methods, a novel definition of PR, termed the FSGS partial remission end point (FPRE) (40% proteinuria reduction and proteinuria < 1.5 g/g) was defined in the

derivation cohort. Each patient in the validation cohort was then classified as reaching the FPRE by months 1, 4, and 8 after baseline. When measured at months 4 and 8—that is, at early times that could be used in a clinical trial to assess for an interim response to an intervention—achieving the FPRE was associated with long-term kidney outcomes (ie, time to the composite of 50% decline in eGFR from baseline and ESKD), a relationship that appeared to be stronger than the conventional definition of PR.

Troost et al[37] also evaluated the association between the percentage change in UPCR and the annual rate of decline in eGFR using data from 138 patients with steroid-resistant FSGS enrolled in the US National Institutes of Health randomized control FSGS trial with 78 weeks of follow-up. This trial compared cyclosporine with mycophenolate mofetil plus dexamethasone. Defining the proteinuria end point as a continuous variable, as opposed to as a categorical variable (ie, CR, PR, or NR), would provide more statistical power for the same sample size. In addition, evaluating the end point as a percentage change could enable enrollment over a broader range of baseline proteinuria levels such as those included in this trial. In the Troost study, a 1-unit reduction in log-transformed UPCR over 26 weeks was associated with a 3.9 mL/min/1.73 m^2 per year (95% CI, 2.0-5.8 mL/min/1.73 m^2 per year) slower rate of decline in eGFR, a difference that remained significant after adjusting for CR. Lowering proteinuria by 40%-50% was associated with a 30%-40% reduction in the annual rate of decline in eGFR; however, the impact on the final level of proteinuria—nephrotic or subnephrotic—was not assessed. There was also a relationship between time-varying proteinuria and time to the composite outcome of ESKD or 40% decline in eGFR, with a hazard ratio per 1-unit reduction in log-transformed UPCR over 26 weeks of 0.2 (95% CI, 0.1-0.4).

Treatment Effects on Proteinuria and Loss of Kidney Function in Randomized Controlled Trials

To date, few randomized controlled trials have been conducted in patients with FSGS. In one trial, 49 adults with steroid-resistant FSGS and proteinuria > 3.5 g were placed on low-dose prednisone and then were randomized to placebo (n = 23) versus cyclosporine (n = 26).[46] After 26 weeks, 3 patients (12%) receiving cyclosporine had achieved CR, and 15 (57%) had achieved PR, whereas only 1 of the patients (4%) in the placebo arm had achieved PR. No CRs were reported in the placebo arm. Of the 19 patients who were evaluated through week 200, 2 out of 7 (29%) in the cyclosporine arm reached a 50% decline in creatinine clearance compared with 6 out of 12 (50%) in the placebo arm.

In another trial, 25 children with FSGS were randomized to receive cyclosporine or placebo for 6 months. At 6 months, a reduction in proteinuria was observed in the cyclosporine arm (from 152 ± 162 mg/kg per 24 hours at baseline to 37 ± 42 mg/kg) whereas no significant change in proteinuria was reported in the placebo arm (from 167 ± 137 mg/kg per 24 hours at baseline to 195 ± 174). Among patients with "technically acceptable" clearance studies, there was a similar fractional decline in measured GFR (values obtained before the initiation and after the discontinuation of study drug) in the 2 groups (from 103 ± 37 to 83 ± 19 mL/min/1.73 m^2 in the cyclosporine group and from 86 ± 31 to 75 ± 31 mL/min/1.73 m^2 in the placebo group) over the 6-month period.[47] Data on long-term kidney outcomes in patients who participated in the trial were not systematically captured.

The DUPLEX Study, investigating sparsentan versus irbesartan in 371 patients with FSGS without known secondary causes and a UPCR of 1.5 g/g or greater, is the first randomized controlled trial that incorporated the FPRE (ie, achieving a 40% reduction in proteinuria and proteinuria < 1.5 g/g) as an end point in a planned interim analysis for accelerated approval.[44] The clinical trial was not submitted for accelerated approval on the interim analysis of the FPRE, in part based on the magnitude of treatment effect between sparsentan versus the active control irbesartan (FPRE of 42% vs 26% at 36 weeks) and FDA's request for 2-year eGFR data.[48] Analysis of the 2-year data after completion of the double-blind period demonstrated a sustained antiproteinuric effect of sparsentan versus irbesartan as measured by change in UPCR from baseline and the proportion of patients achieving FPRE. However, the effect on FPRE did not translate into a statistically significant difference in eGFR slope between the study arms at 108 weeks.[49]

Although these findings suggest that the treatment effects on FPRE may not predict relevant clinical outcomes, further exploration of data from patients with FSGS is needed to understand this issue and the potential utility of FPRE as a reasonably like surrogate end point in clinical trials of FSGS.

Conclusion

FSGS is not a single disease entity but rather a heterogeneous disorder that is an important cause of nephrotic syndrome and kidney failure in children and adults. It is a serious condition for which there is an urgent unmet need for effective treatments. To facilitate drug development for this condition, the KHI convened a multistakeholder work group to evaluate potential surrogate end points that could be used in clinical trials to support the approval of products for FSGS. We have focused on the data supporting proteinuria as a surrogate end point.

Biologic plausibility coupled with compelling epidemiologic data support the use of a sustained CR as a surrogate end point in patients with primary FSGS with nephrotic range proteinuria. In both children and adults with primary FSGS with nephrotic range proteinuria, achieving a CR is associated with highly favorable long-term kidney survival. Moreover, given the role of the podocyte in FSGS and the link between injury to the podocyte and proteinuria, achieving CR plausibly reflects

"remission" of the active underlying disease process in patients with this condition. As such, this work group believes the available data support the use of CR as a validated surrogate end point and basis for traditional approval of drugs intended to treat primary FSGS with nephrotic range proteinuria. Although the available data suggest that substantial reductions in proteinuria short of a CR could also predict the effect of new treatments on the loss of kidney function, further work is needed to support the use of such end points as a basis for traditional or accelerated approval.

The conventional definition of PR is quite broad and spans a large range of quantitative reductions in proteinuria. PR definitions also vary between adults and children. As such, recent and future efforts focused on refining the definition of PR, as well as evaluating the relationship between proteinuria, assessed as a continuous variable, and loss of kidney function are critical. Future efforts are needed to understand whether and to what extent the subcategory or underlying cause of FSGS alters these relationships.

We believe many of the gaps in our understanding of proteinuria as a surrogate end point can be addressed through the sharing and analysis of patient-level data from clinical trials, observational studies, and registries.[45-50] In IgA nephropathy, data sharing led to the development of models describing the quantitative relationship between treatment effects on proteinuria assessed relatively early after initiation of therapy and (1) kidney outcomes and (2) eGFR slope.[50] The availability of such models, which have been used by sponsors to design development programs to support accelerated approval and to power the required postmarketing confirmatory trials, has transformed the drug development landscape for IgA nephropathy. We believe such data sharing efforts could also transform the drug development landscape for FSGS. Progress in identifying effective therapies for patients with FSGS is more likely when adequately validated proteinuria-based surrogate end points are used in clinical trials in which enrollment is based on mechanistic subtype and not lesion category. Efforts spearheaded by the NephCure Foundation in partnership with the International Society of Glomerular Disease, the KHI, and National Kidney Foundation are underway to bring together and analyze the available data from observational studies, interventional trials, and registries to develop such models (https://www.is-gd.org/parasol).

Article Information

Authors' Full Names and Academic Degrees: Laura H. Mariani, MD, MS, Howard Trachtman, MD, Aliza Thompson, MD, MS, Barbara S. Gillespie, MD, Michelle Denburg, MD, Ulysses Diva, PhD, Duvuru Geetha, MD, Peter J. Greasley, PhD, Michelle A. Hladunewich, MD, MS, Robert B. Huizinga, PhD, RN, Jula K. Inrig, MD, MS, Radko Komers, MD, PhD, Louis-Philippe Laurin, MD, MSc, Dustin J. Little, MD, Patrick H. Nachman, MD, Kimberly A. Smith, MD, MS, Liron Walsh, MD, and Keisha L. Gibson, MD, MPH.

Authors' Affiliations: Renal Division (LHM) and Department of Pediatrics/Nephrology (HT), University of Michigan, Ann Arbor, Michigan; Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring (AT, KAS), Clinical Development, Late Cardiovascular, Renal and Metabolism, AstraZeneca, Gaithersburg (DJL), and School of Medicine, Johns Hopkins University, Baltimore (DG), Maryland; Fortrea, Durham (BSG), and Kidney Center, University of North Carolina, Chapel Hill (BSG, KLG), North Carolina; Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania (MD); University of Minnesota, Minneapolis, Minnesota (PHN); Goldfinch Bio, Boston, Massachusetts (LW); Travere Therapeutics, San Diego, California (UD, JKI, RK); Research and Early Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden (PJG); University of Toronto, Toronto, Ontario (MAH); Aurinia Pharmaceuticals, Victoria, British Columbia (RBH), and Division of Nephrology, Maisonneuve-Rosemont Hospital, Montreal, Quebec (L-PL), Canada.

Address for Correspondence: Laura H. Mariani, MD, MS, University of Michigan, Renal Division, 1150 W Medical Center Dr, SPC 5676, MSRBII 1560, Ann Arbor, MI 48109. Email: lmariani@umich.edu or Howard Trachtman, Department of Pediatrics, University of Michigan, 1150 W Medical Center Dr, Med Sci 1/ARF 251, Ann Arbor, MI 48109-0168. Email: howardtrachtman21@gmail.com

Support: This work was supported by the Kidney Health Initiative (KHI), a public-private partnership between the American Society of Nephrology, the US Food and Drug Administration, and over 75 member organizations and companies to enhance patient safety and foster innovation in kidney disease. KHI funds were used to defray costs incurred during the conduct of the project, including project management support, which was expertly provided by Melissa West at the American Society of Nephrology. The funders did not have a role in defining the content of the manuscript.

Financial Disclosure: The funders make every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the members of the work group. More information on KHI, the work group, and the conflict of interest policy can be found at www.kidneyhealthinitiative.org.

Acknowledgements: The authors want to express their appreciation to Debbie S. Gipson, MD, MS, and thank her for her important contribution to this project during her tenure at the University of Michigan. During the preparation of this article, Dr Diva was an employee of Travere Therapeutics, and Dr Walsh was an employee of Goldfinch Bio.

Disclaimer: The views and opinions expressed in this publication are those of the authors and do not necessarily reflect the official policies of any KHI member organization or the US Department of Health and Human Services, nor does any mention of trade names, commercial practices, or organizations imply endorsement by the US Government.

Peer Review: Received May 29, 2024, in response to an invitation from the journal. Evaluated by 2 external peer reviewers, with direct editorial input from an Associate Editor and a Deputy Editor. Accepted in revised form August 11, 2024.

References

1. Gipson DS, Troost JP, Spino C, et al. Comparing kidney health outcomes in children, adolescents, and adults with focal segmental glomerulosclerosis. *JAMA Netw Open*. 2022;5(8):e2228701. doi:10.1001/jamanetworkopen.2022.28701
2. Rosenberg AZ, Kopp JB. Focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol*. 2017;12(3):502-517. doi:10.2215/CJN.05960616
3. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice

guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(4S):S1-S276. doi:10.1016/j.kint.2021.05.021

4. Munis M, Chen Q, Hill TM, et al. Incidence rates of primary focal segmental glomerulosclerosis (FSGS) within a diverse adult Southern California population, 2010-2021. *J Am Soc Nephrol*. 2023;34(11S):270. doi:10.1681/ASN.20233411S1270a
5. Johansen KL, Chertow GM, Gilbertson DT, et al. US Renal Data System 2021 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2022;79(4)(suppl 1):A8-A12. doi:10.1053/j.ajkd.2022.02.001
6. Meyrier A. Treatment of focal segmental glomerulosclerosis. *Expert Opin Pharmacother*. 2005;6(9):1539-1549. doi:10.1517/14656566.6.9.1539
7. Glenn DA, Henderson CD, O'Shaughnessy M, et al. Infection-related acute care events among patients with glomerular disease. *Clin J Am Soc Nephrol*. 2020;15(12):1749-1761. doi:10.2215/CJN.05900420
8. Oh GJ, Waldo A, Paez-Cruz F, et al. Steroid-associated side effects in patients with primary proteinuric kidney disease. *Kidney Int Rep*. 2019;4(11):1608-1616. doi:10.1016/j.ekir.2019.08.019
9. Archdeacon P, Shaffer RN, Winkelmayer WC, et al. Fostering innovation, advancing patient safety: the kidney health initiative. *Clin J Am Soc Nephrol*. 2013;8(9):1609-1617. doi:10.2215/CJN.01140113
10. American Society of Nephrology/US Food and Drug Administration. Kidney Health Initiative. Updated February 13, 2024. Accessed October 21, 2024. https://khi.asn-online.org/
11. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). *Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. Food and Drug Administration, US Department of Health and Human Services; December 2009. https://www.fda.gov/media/77832/download
12. FDA-NIH Biomarker Working Group. Validated surrogate endpoint. In: *BEST (Biomarkers, EndpointS, and Other Tools)*. US Food and Drug Administration, National Institutes of Health; Updated November 13, 2020. https://www.ncbi.nlm.nih.gov/books/NBK453484/
13. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). *Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics*. OMB Control No. 0910-0765. US Food and Drug Administration, US Department of Health and Human Services; May 2014. https://www.fda.gov/media/86377/download
14. Hogan MC, Reich HN, Nelson PJ, et al. The relatively poor correlation between random and 24-hour urine protein excretion in patients with biopsy-proven glomerular diseases. *Kidney Int*. 2016;90(5):1080-1089. doi:10.1016/j.kint.2016.06.020
15. Heerspink HJL, Brantsman AH, Zeeuw D, et al. Albuminuria assessed from first-morning-void urine samples versus 24-hour urine collections as a predictor of cardiovascular morbidity and mortality. *Am J Epidemiol*. 2008;168(8):897-905. doi:10.1093/aje/kwn209
16. Sumida K, Nadkarni GN, Grams ME, et al. Conversion of urine protein-creatinine ratio or urine dipstick protein to urine albumin-creatinine ratio for use in chronic kidney disease screening and prognosis: an individual participant-based meta-analysis. *Ann Intern Med*. 2020;173(6):426-435. doi:10.7326/M20-0529
17. Martin H. Laboratory measurement of urine albumin and urine total protein in screening for proteinuria in chronic kidney disease. *Clin Biochem Rev*. 2011;32(2):97-102. https://pmc.ncbi.nlm.nih.gov/articles/PMC3100287/
18. Lieske JC, Bondar O, Miller WG, et al. A reference system for urinary albumin: current status. *Clin Chem Lab Med*. 2013;51(5):981-989. doi:10.1515/cclm-2012-0768
19. Martinelli R, Okumura AS, Pereira LJ, Rocha H. Primary focal segmental glomerulosclerosis in children: prognostic factors. *Pediatr Nephrol*. 2001;16(8):658-661. doi:10.1007/s004670100639
20. Gipson DS, Troost JP, Lafayette RA, et al. Complete remission in the Nephrotic Syndrome Study Network. *Clin J Am Soc Nephrol*. 2016;11(1):81-89. doi:10.2215/CJN.02560315
21. Trautmann A, Schaidt S, Lipska-Ziętkiewicz BS, et al. Long-term outcome of steroid-resistant nephrotic syndrome in children. *J Am Soc Nephrol*. 2017;28(10):3055-3065. doi:10.1681/ASN.2016101121
22. Gipson DS, Trachtman H, Kaskel FJ, et al. Clinical trial of focal segmental glomerulosclerosis in children and young adults. *Kidney Int*. 2011;80(8):868-878. doi:10.1038/ki.2011.195
23. Ahn W, Bomback AS. Approach to diagnosis and management of primary glomerular diseases due to podocytopathies in adults: core curriculum 2020. *Am J Kidney Dis*. 2020;75(6):955-964. doi:10.1053/j.ajkd.2019.12.019
24. De Vriese AS, Sethi S, Nath KA, et al. Differentiating primary, genetic, and secondary FSGS in adults: a clinicopathologic approach. *J Am Soc Nephrol*. 2018;29(3):759-774. doi:10.1681/ASN.2017090958
25. Jefferson JA, Shankland SJ. The pathogenesis of focal segmental glomerulosclerosis. *Adv Chronic Kidney Dis*. 2014;21(5):408-416. doi:10.1053/j.ackd.2014.05.009
26. Kohan DE, Barton M. Endothelin and endothelin antagonists in chronic kidney disease. *Kidney Int*. 2014;86(5):896-904. doi:10.1038/ki.2014.143
27. Siragy HM, Carey RM. Role of the intrarenal renin-angiotensin-aldosterone system in chronic kidney disease. *Am J Nephrol*. 2010;31(6):541-550. doi:10.1159/000313363
28. Wickman L, Afshinnia F, Wang SQ, et al. Urine podocyte mRNAs, proteinuria, and progression in human glomerular diseases. *J Am Soc Nephrol*. 2013;24(12):2081-2095. doi:10.1681/ASN.2013020173
29. Hingorani S, Gibson KL, Xie Y, et al. The association of low birthweight and prematurity on outcomes in children and adults with nephrotic syndrome—a NEPTUNE cohort study. *Pediatr Nephrol*. 2023;38(10):3297-3308. doi:10.1007/s00467-023-05876-3
30. Wharram BL, Goyal M, Wiggins JE, et al. Podocyte depletion causes glomerulosclerosis: diphtheria toxin-induced podocyte depletion in rats expressing human diphtheria toxin receptor transgene. *J Am Soc Nephrol*. 2005;16(10):2941-2952. doi:10.1681/ASN.2005010055
31. Lidberg KA, Muthusamy S, Adil M, et al. Serum protein exposure activates a core regulatory program driving human proximal tubule injury. *J Am Soc Nephrol*. 2022;33(5):949-965. doi:10.1681/ASN.2021060751
32. Baines RJ, Brunskill NJ. Tubular toxicity of proteinuria. *Nat Rev Nephrol*. 2011;7(3):177-180. doi:10.1038/nrneph.2010.174
33. Korbet SM. Clinical picture and outcome of primary focal segmental glomerulosclerosis. *Nephrol Dial Transplant*. 1999;14(suppl 3):68-73. doi:10.1093/ndt/14.suppl_3.68
34. Wehrmann M, Bohle A, Held H, Schumm G, Kendziorra H, Pressler H. Long-term prognosis of focal sclerosing glomerulonephritis. An analysis of 250 cases with particular regard to tubulointerstitial changes. *Clin Nephrol*. 1990;33(3):115-122.

35. Gipson DS, Chin H, Presler TP, et al. Differential risk of remission and ESRD in childhood FSGS. *Pediatr Nephrol*. 2006;21(3):344-349. doi:10.1007/s00467-005-2097-0
36. Rydel JJ, Korbet SM, Borok RZ, Schwartz MM. Focal segmental glomerular sclerosis in adults: presentation, course, and response to treatment. *Am J Kidney Dis*. 1995;25(4):534-542. doi:10.1016/0272-6386(95)90120-5
37. Troost JP, Trachtman H, Spino C, et al. Proteinuria reduction and kidney survival in focal segmental glomerulosclerosis. *Am J Kidney Dis*. 2021;77(2):216-225. doi:10.1053/j.ajkd.2020.04.014
38. Forster BM, Nee R, Little DJ, et al. Focal segmental glomerulosclerosis, risk factors for end stage kidney disease, and response to immunosuppression. *Kidney360*. 2020;2(1):105-113. doi:10.34067/KID.0006172020
39. Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC. Toronto Glomerulonephritis Registry Group. Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. *J Am Soc Nephrol*. 2005;16(4):1061-1068. doi:10.1681/ASN.2004070593
40. Korbet SM, Schwartz MM, Lewis EJ. Primary focal segmental glomerulosclerosis: clinical course and response to therapy. *Am J Kidney Dis*. 1994;23(6):773-783. doi:10.1016/s0272-6386(12)80128-4
41. Schwartz MM, Korbet SM, Rydell J, Borok R, Genchi R. Primary focal segmental glomerular sclerosis in adults: prognostic value of histologic variants. *Am J Kidney Dis*. 1995;25(6):845-852. doi:10.1016/0272-6386(95)90566-9
42. Pei Y, Cattran D, Delmore T, Katz A, Lang A, Rance P. Evidence suggesting under-treatment in adults with idiopathic focal segmental glomerulosclerosis. Regional Glomerulonephritis Registry Study. *Am J Med*. 1987;82(5):938-944. doi:10.1016/0002-9343(87)90155-0
43. Trachtman H, Diva U, Murphy E, Wang K, Inrig J, Komer R. Implications of complete proteinuria remission at any time in focal segmental glomerulosclerosis: sparsentan DUET Trial. *Kidney Int Rep*. 2023;8(10):2017-2028. doi:10.1016/j.ekir.2023.07.022
44. Stirling CM, Mathieson P, Boulton-Jones JM, et al. Treatment and outcome of adult patients with primary focal segmental glomerulosclerosis in five UK renal units. *QJM*. 2005;98(6):443-449. doi:10.1093/qjmed/hci072
45. Troost JP, Trachtman H, Nachman PH, et al. An outcomes-based definition of proteinuria remission in focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol*. 2018;13(3):414-421. doi:10.2215/CJN.04780517
46. Cattran DC, Appel GB, Hebert LA, et al. A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. North America Nephrotic Syndrome Study Group. *Kidney Int*. 1999;56(6):2220-2226. doi:10.1046/j.1523-1755.1999.00778.x
47. Lieberman KV, Tejani A. A randomized double-blind placebo-controlled trial of cyclosporine in steroid-resistant idiopathic focal segmental glomerulosclerosis in children. *J Am Soc Nephrol*. 1996;7(1):56-63. doi:10.1681/ASN.V7156
48. Travere Therapeutics. Travere Therapeutics provides regulatory updates on its development programs. Press release, August 3, 2022. https://ir.travere.com/news-releases/news-release-details/travere-therapeutics-provides-regulatory-updates-its-development
49. Rheault MN, Alpers CE, Barratt J, et al. Sparsentan versus Irbesartan in focal segmental glomerulosclerosis. *N Engl J Med*. 2023;389(26):2436-2445. doi:10.1056/NEJMoa2308550
50. Thompson A, Carroll K, Inker LA, et al. Proteinuria reduction as a surrogate end point in trials of IgA nephropathy. *Clin J Am Soc Nephrol*. 2019;14(3):469-481. doi:10.2215/CJN.08600718