PARASOL

Proteinuria and GFR as Clinical Trial Endpoints in FSGS

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on Behalf of the PARASOL Working Group

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Background

- Focal segmental glomerulosclerosis (FSGS) encompasses a group of rare diseases affecting adults and children, with a high risk of progression to kidney failure. **There are currently no FDA-approved therapies to treat this condition.**
- FDA currently accepts complete remission or near normalization of proteinuria as a surrogate endpoint and basis for traditional approval of investigational drugs in FSGS, but this endpoint may be challenging to achieve given the scarring and heterogeneous nature of the condition and diverse patient population.
- Lesser changes in proteinuria have been proposed as a basis for accelerated or traditional approval, but further investigation of the relationship between short-term changes in key biomarkers of disease activity and progression and long-term clinical outcomes is needed.

Goal

- PARASOL is an international collaborative effort that aims to integrate observational, registry, and clinical trial data to advance the understanding and use of proteinuria and eGFR-based surrogate endpoints for accelerated and traditional approval of new treatments for FSGS, thus facilitating the development of new therapies.

Methods

- Datasets from around the world were identified and are in various stages of regulatory approval for data sharing (Figure 1).
- Datasets that can be integrated at a patient level will be combined for analysis, while those that cannot will serve as independent validation cohorts. Proposed endpoints will be tested in clinical trial data, which is limited in this population (Table 1).
- Required and preferred data elements as well as criteria for cohort selection and design schematic are show in Figure 2.
- A series of three meetings were held between Dec. 2023 and Oct. 2024 to present analytic approach and discuss key findings with key stakeholders.

Data Contributions

Table 1: Contributing datasets by use for analysis.

Patient-level data sharing	Study	Population location	Study design	FSGS definition	Medication Data Available?
Primary Analysis	Neptune	US/Canada	Prospective observational	Biopsy proven FSGS	Yes
Primary Analysis	CureGN	US/Canada/Poland /Italy	Prospective observational	Biopsy proven FSGS	Yes
Primary Analysis	KRN	US	Electronic Health Records	Biopsy proven FSGS or genetic FSGS	Yes
Primary Analysis	UNC	US-North Carolina & SE regional states	Retro- and prospective observational	Biopsy proven FSGS	Yes
Primary Analysis	Gaslini	Italy	Prospective observational	Biopsy proven FSGS	Yes
Primary Analysis	Podonet	Europe, West Asia, North Africa	Retro- and prospective observational	Biopsy proven FSGS or genetic FSGS	Yes
Primary Analysis	Glosen	Spain	Prospective observational	Biopsy proven FSGS	Yes
Primary Analysis	Toronto	Canada-Ontario	Prospective observational	Biopsy proven FSGS	Yes
Primary Analysis	Indiana	US-Indiana	Electronic health record	Biopsy proven FSGS	Very limited
Secondary Analysis	CKID	US	Prospective observational	Biopsy proven FSGS	Very limited
Secondary Analysis	Ottawa Registry	Canada-Ontario	Prospective observational	Biopsy proven FSGS	At biopsy
Trial Comparison	NIH FSGS trial	US	Prospective clinical trial	Biopsy proven FSGS	NA

Validation Datasets (aggregate data)	
Study	Population location
RaDaR	UK
Univ. Hamburg	Germany

Future Registry Datasets Committed to Data Sharing					
Study	Population location	Study	Population location	Study	Population location
C-Probe	US	I-TANGIBLE	India	University of Bari	Italy
GlomCon	US	Kaiser Permanente	US	ACTION trial	Australia
Greek cohort	Greeca	Karolinska Institute	Sweden	DAPA-CKD trial	Global
H3Africa	Africa	Peking Univ. First Hospital	China	DUET trial	US, Europe
Hosp. General de Mexico	Mexico	Uruguay Nat'l Registry	Uruguay	EMPA-kidney trial	Global

Figure 1. PARASOL Global Partnerships

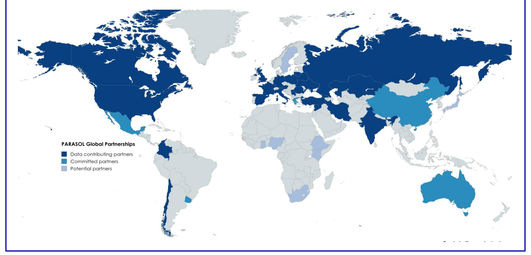


Figure 2a. Required and preferred data elements for registry inclusion.

Required:
At biopsy
- Age, sex
- Labs (UPCR, eGFR)

Longitudinal
- Labs (UPCR, eGFR)
- Kidney failure
- Death
- Length of follow-up

Preferred:
At biopsy
- Serum albumin
- Blood pressure
- Medication exposure
- Kidney pathology
- Kidney genetic results

Longitudinal
- Serum albumin
- Blood pressure
- Medication exposure

Figure 2b. Cohort selection and design for primary analysis.

- **Patients with biopsy-proven or genetic FSGS and UPCR≥1.5 g/g proteinuria and eGFR≥30 ml/min/1.73m^2 at**
  - Any time post-biopsy or genetic diagnosis or up to 3 months prior (**All**)
  - Within 6 months of biopsy/genetic diagnosis (**Incident**)
  - ≥12 months from biopsy/genetic diagnosis (**Prevalent**)

Results

Table 2. Baseline characteristics.

Median (Q1,Q3) or N (%)	All	Pediatric	Adult	eGFR ≥ 60	eGFR < 60	UPCR 1.5-<3.5	UPCR ≥3.5
N	1626	756	870	1141	485	766	860
Age at index	21 (9, 43)	8 (4,13)	42 (30, 56)	15 (7, 34)	42 (19, 59)	23 (10, 44)	19 (9, 43)
% pediatric	756 (46%)	756 (100%)	0 (0%)	640 (56%)	116 (24%)	339 (44%)	417 (48%)
UPCR at index	3.7 (2.3, 7.1)	4.0 (2.2, 8.7)	3.6 (2.3, 6.3)	3.8 (2.3, 7.3)	3.6 (2.2, 6.5)	2.2 (1.8, 2.7)	6.7 (4.7, 10.6)
eGFR at index	82 (56, 110)	98 (74, 128)	68 (47, 94)	98 (79, 113)	44 (36, 52)	80 (54, 108)	84 (56, 112)
Follow-up months post-index	66 (32, 100)	68 (35, 102)	64 (30, 97)	66 (34, 100)	67 (30, 100)	64 (33, 95)	68 (32, 104)
Kidney failure before 84 months	310 (19%)	156 (21%)	154 (18%)	148 (13%)	162 (33%)	114 (15%)	196 (23%)
eGFR 0-24 months post-index	4 (3,7)	4 (2,6)	5 (3,8)	5 (3,8)	4 (3,6)	4 (2, 6)	5 (3, 8)
UPCR 12-24 months post-index	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)

Table 3. Percent response and survival estimates by response thresholds

Response threshold (g/g)	% response*	N events by 84 months in responders	84 month survival (95% CI) - Adjusted	Survival difference at 84 months (95% CI)	Hazard ratio (95% CI)
<0.3	22%	5	0.91 (0.87-0.95)	-0.29 (-0.34 - -0.25)	0.07 (0.03-0.18)
<0.5	28%	8	0.90 (0.86-0.94)	-0.30 (-0.34 - -0.25)	0.09 (0.05-0.19)
<0.7	32%	15	0.87 (0.83-0.92)	-0.27 (-0.32 - -0.22)	0.15 (0.09-0.26)
<1.0	40%	25	0.86 (0.82-0.90)	-0.28 (-0.33 - -0.23)	0.18 (0.12-0.27)
<1.0 g/g^	39%	24	0.86 (0.82-0.90)	-0.28 (-0.33 - -0.22)	0.18 (0.12-0.28
<1.5	50%	39	0.84 (0.80-0.88)	-0.29 (-0.34 - -0.24)	0.20 (0.14-0.28)
<1.5 g/g^	45%	30	0.85 (0.81-0.89)	-0.30 (-0.35 - -0.25)	0.17 (0.12-0.25)

*Among those with at least 24 months follow-up post index (n=1265)
^+ ≥50% decline from index

Figure 5. Who is achieving responder status?

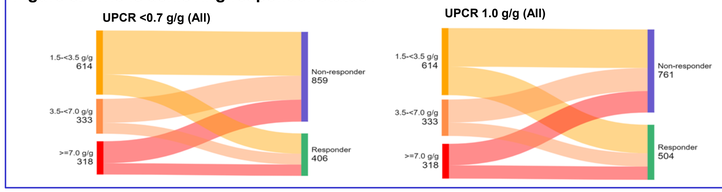


Figure 3. Baseline kidney failure

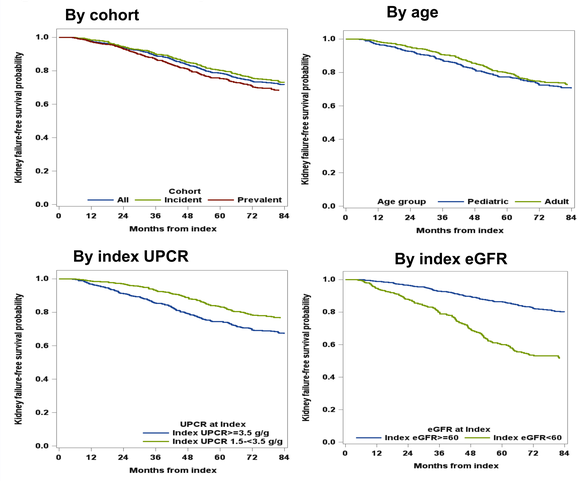
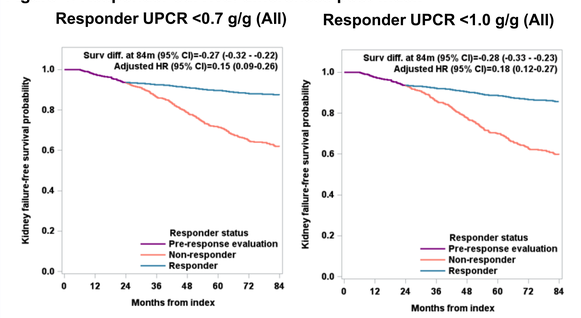


Figure 4. Responder survival differences post-index



Discussion

- 1626 participants have been included in the PARASOL primary analysis from 9 unique cohorts with initial validation performed in 1 cohort.
- eGFR slope is associated with kidney failure but high variability, particularly in an "all comers" population.
- Proteinuria shows similar behavior across thresholds ranging from 0.7 to 1.5 g/g; is biologically plausible and clinically meaningful; robust across subgroups (even sub-nephrotic); results in feasible sample sizes.

Acknowledgements: PARASOL would not have been possible without the generous contribution of all participating datasets and their participants, as well as the support and contributions of the teams at the FDA and EMA. Funding was provided by NephCure, the International Society of Glomerular Disease, and industry partners.

Clinical Trials in FSGS: Where have we been and where are we heading?

Daniel Gale

St Peters Chair of Nephrology, University College London

RaDaR Director

Disclosures

- DPG is chair of the UK Kidney Association Rare Diseases Committee, a Trustee for AlportUK and has received consultancy fees or honoraria from: Alexion, Alnylam, Novartis, Bayer, Britannia, SOBI, Vifor, Judo Bio, Sanofi, Calliditas, Otsuka, Alexion

Rare diseases disproportionately account for kidney failure

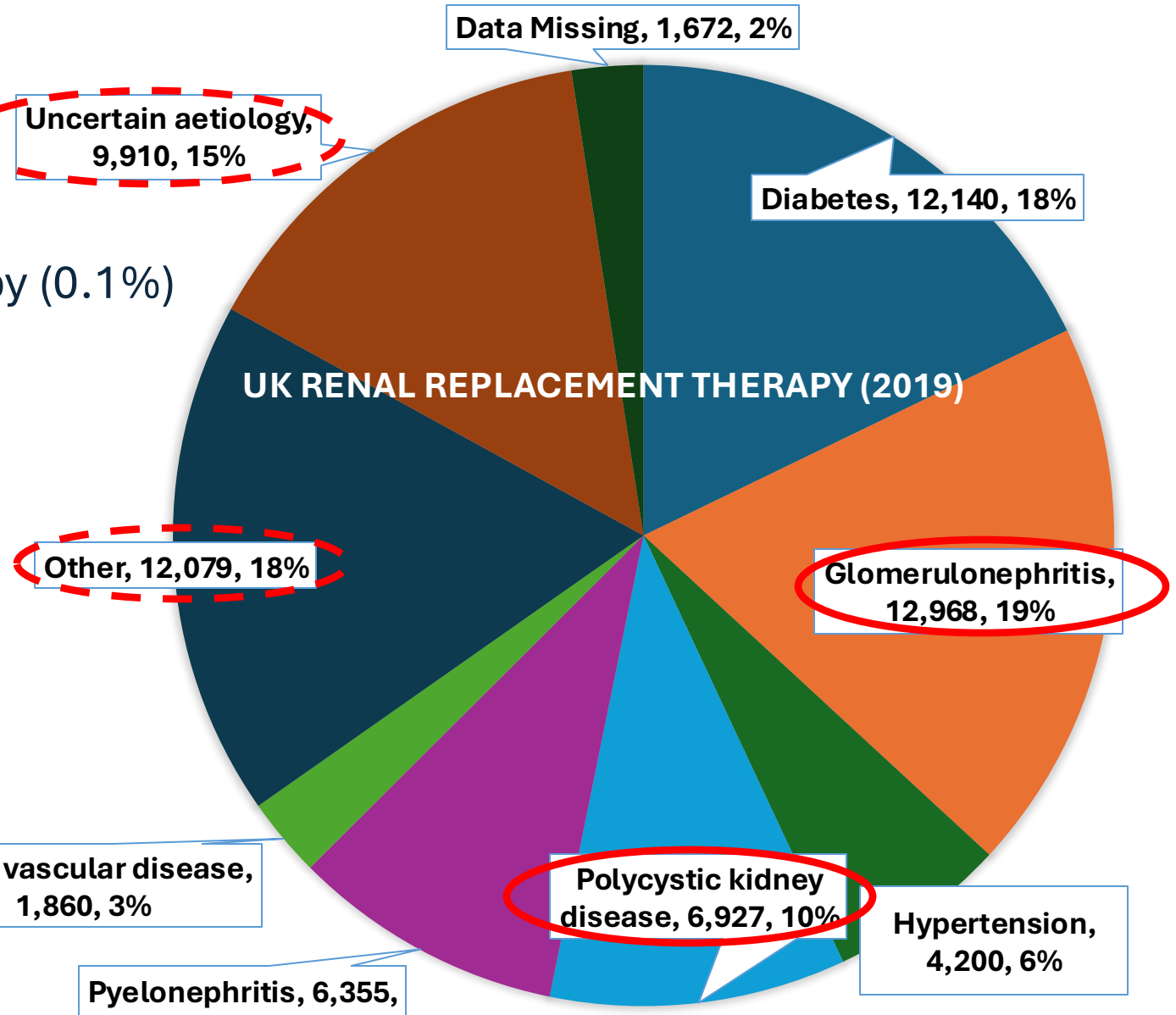
Chronic Kidney Disease

- 2.8 million of UK population (>4%)
- 68,000 receiving renal replacement therapy (0.1%)

Rare Kidney Diseases

- <5% of patients with CKD **but >30% of Kidney Failure (KF)**

RaDaR data showed 28-fold higher 5-year cumulative kidney failure risk in 28,000 with rare kidney diseases compared with 2.8M people with all-cause CKD Wong et al Lancet 2024



UK Renal Registry Annual Report (2021)

Rare renal diseases ≠ CKD

Challenges for rare kidney diseases

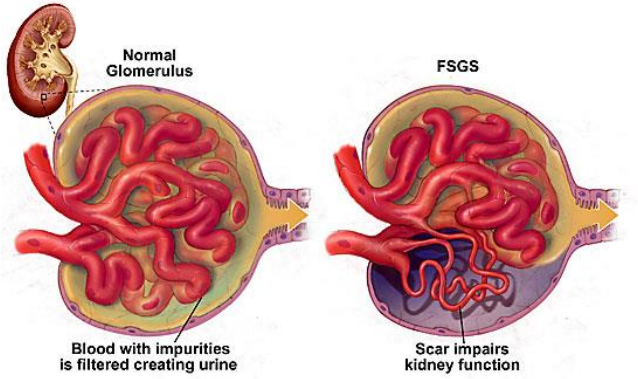
- Rare kidney diseases often affect young people and have a high risk of kidney failure so highly efficacious interventions needed to prevent (rather than just delay) kidney failure
  - Each rare disease is different so many bespoke treatments are needed
- In rare diseases, trials are necessarily small (not enough patients for mega-trials) and duration is short (>2 years not usually feasible)
- Not all rare kidney diseases are homogeneous – some are not even ‘diseases’
- Need to include people with early-stage disease: It is tough to show a treatment effect on scarred kidneys
  - **Unusual to be able to have a kidney failure trial endpoint**

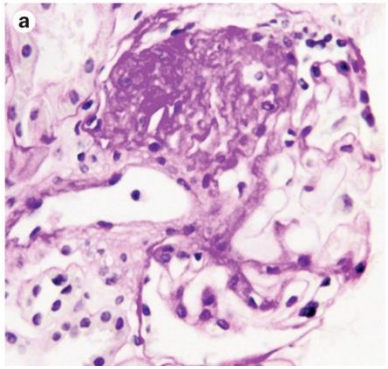
Unmet need for better treatments for FSGS

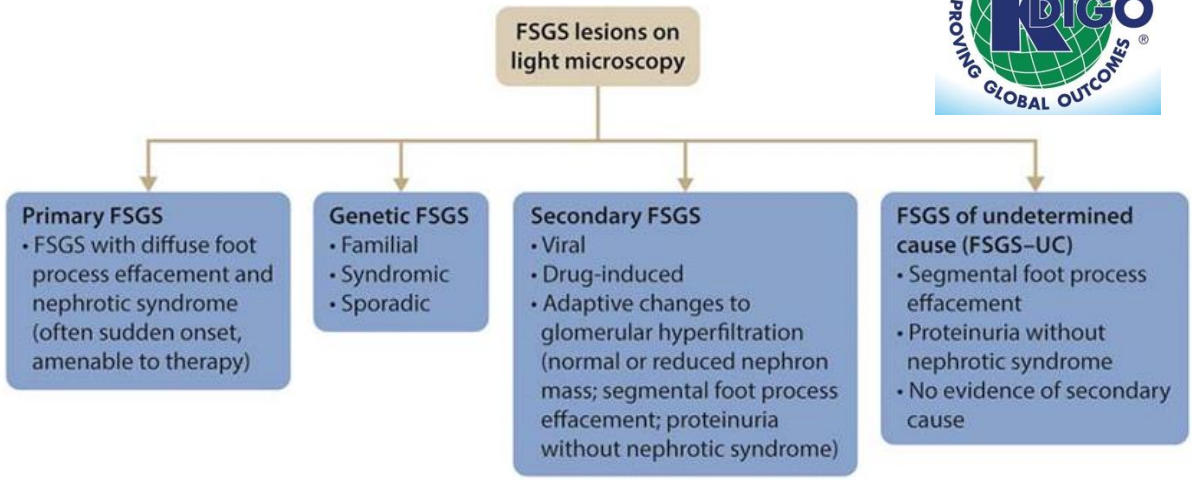
Focal Segmental Glomerulosclerosis (FSGS): a histological lesion, not a disease

- Commoner in young adults, but occurs across the lifespan
- Acute or insidious onset of proteinuria, oedema, hypertension
- Characteristic pattern of injury on biopsy
- Various mechanisms of podocyte damage established/proposed

➢ **Manifestation of 'Podocytopathy'**





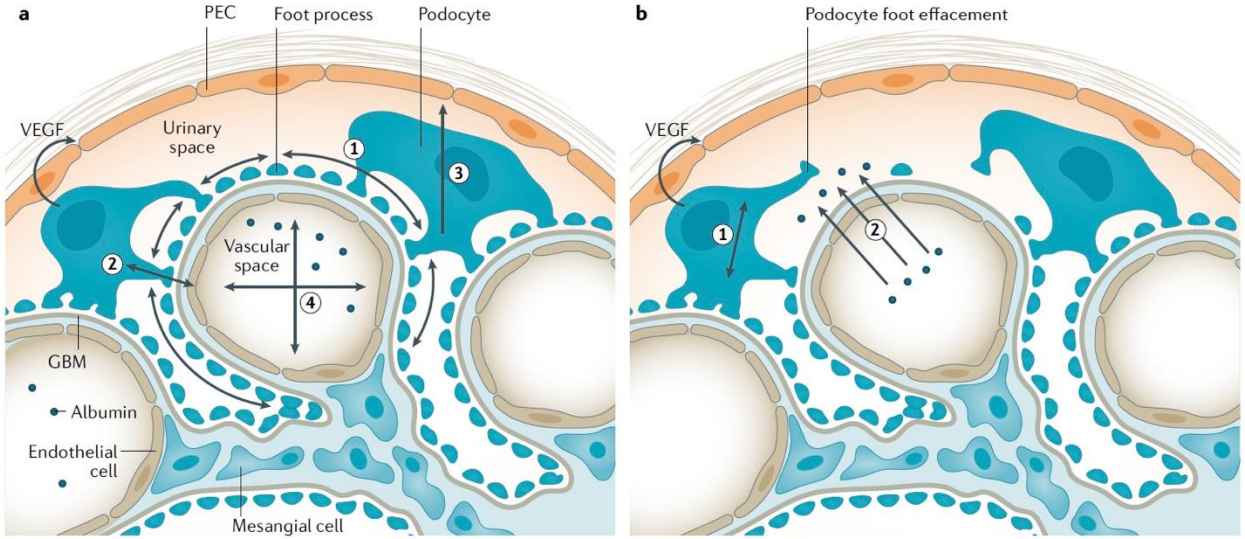


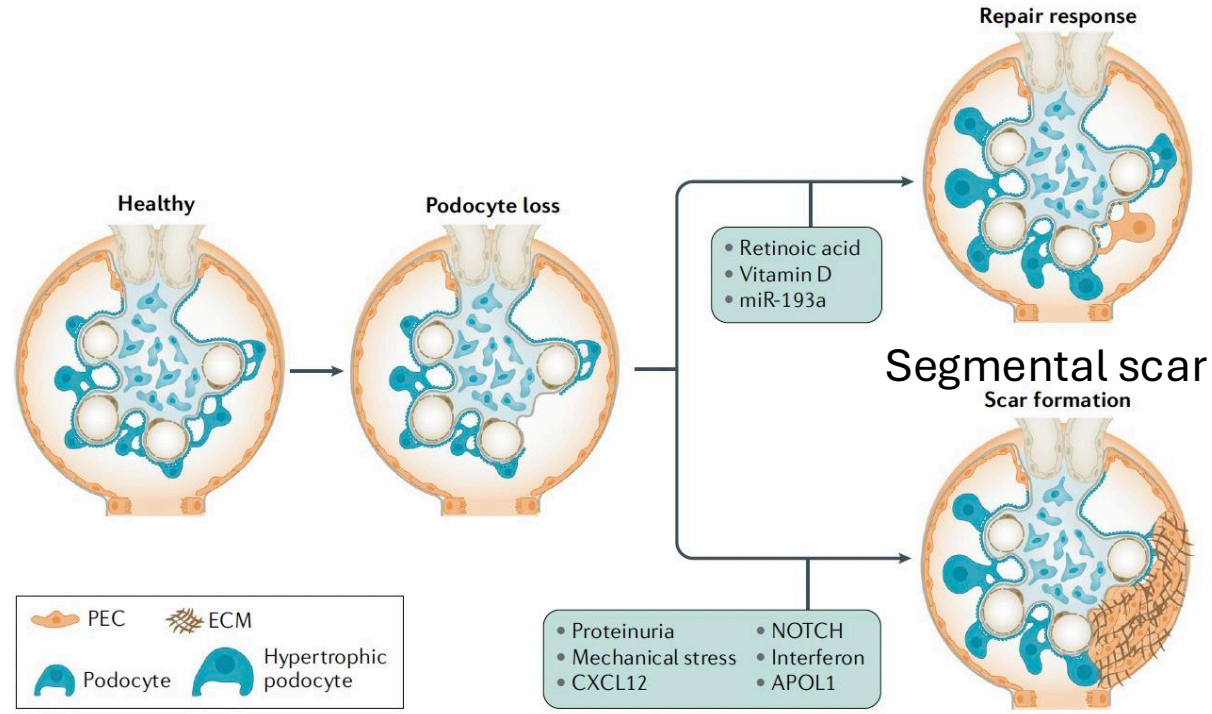
Fogo, A. B. *Nat. Rev. Nephrol.* 2014;
KDIGO Glomerular Disease Guidelines, 2021

Podocytopathy and FSGS

- FSGS can have multiple causes (genetic, immune, toxic etc) but **podocyte injury is a key feature**
- Damage to podocytes manifests histologically as foot process effacement
  - Diffuse FPE is a feature of ‘primary FSGS’
- Ongoing damage can result in dead podocytes
  - Areas of sclerosis/scarring
- Proteinuria can therefore be regarded as the *sine qua non* of (more severe) podocytopathy

Foot process effacement



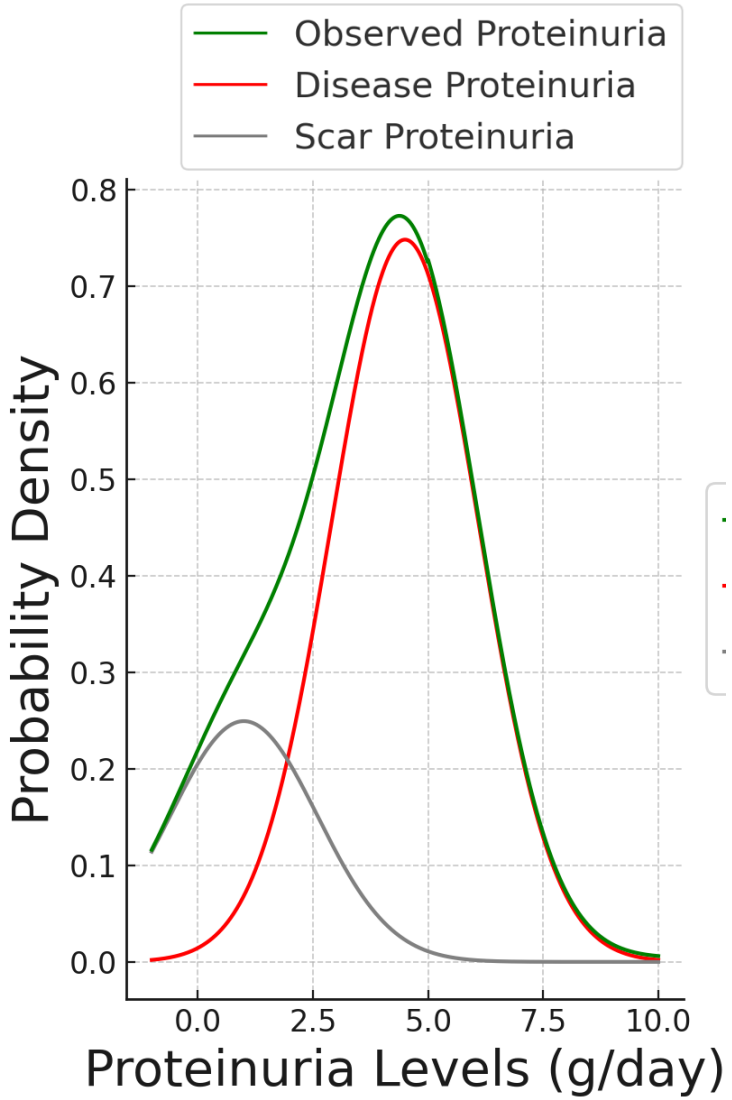


Kopp et al Nat Rev Dis Primers (2020)

Proteinuria as a disease biomarker

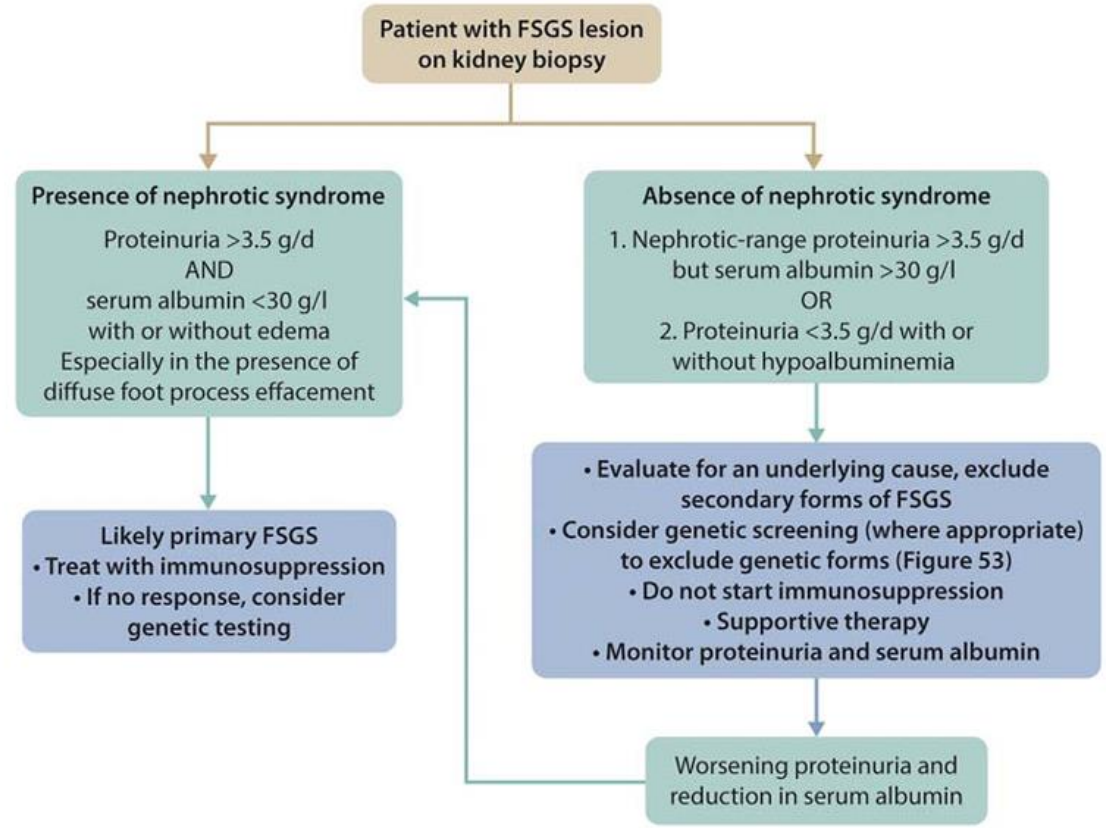
- Proteinuria we can measure is a combination of:
  - Effect of active disease (effaced foot processes of potentially viable podocytes) and
  - Scarring (dead podocytes)
- Interventions effective on reversing foot process effacement may not impact on scar (and vice-versa)

➢**Might be possible to control underlying disease without complete proteinuria remission**



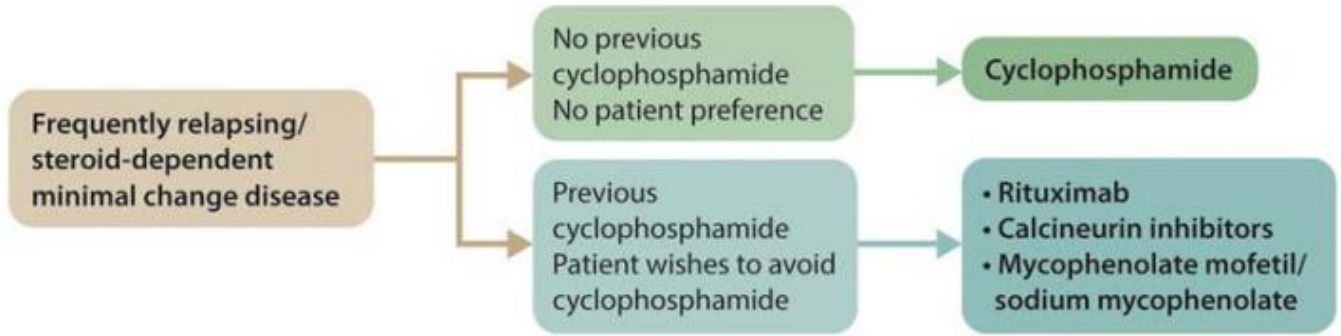
FSGS Treatment

- Therapeutic options are limited and lack tools to match patients to therapies
- Evidence base for existing therapies is weak



Recommendation 6.2.2.1: We recommend that high-dose oral glucocorticoids be used as the first-line immunosuppressive treatment for primary FSGS *(1D)*.

Recommendation 6.3.1.1: For adults with steroid-resistant primary FSGS, we recommend that cyclosporine or tacrolimus be given for ≥6 months rather than continuing with glucocorticoid monotherapy or not treating *(1C)*.

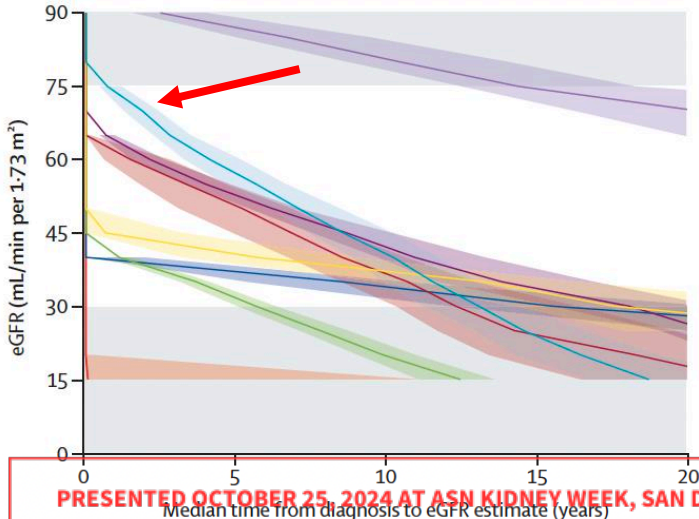


Low	The true effect may be substantially different from the estimate of the effect.
Very low	The estimate of effect is very uncertain, and often, it will be far from the true effect.

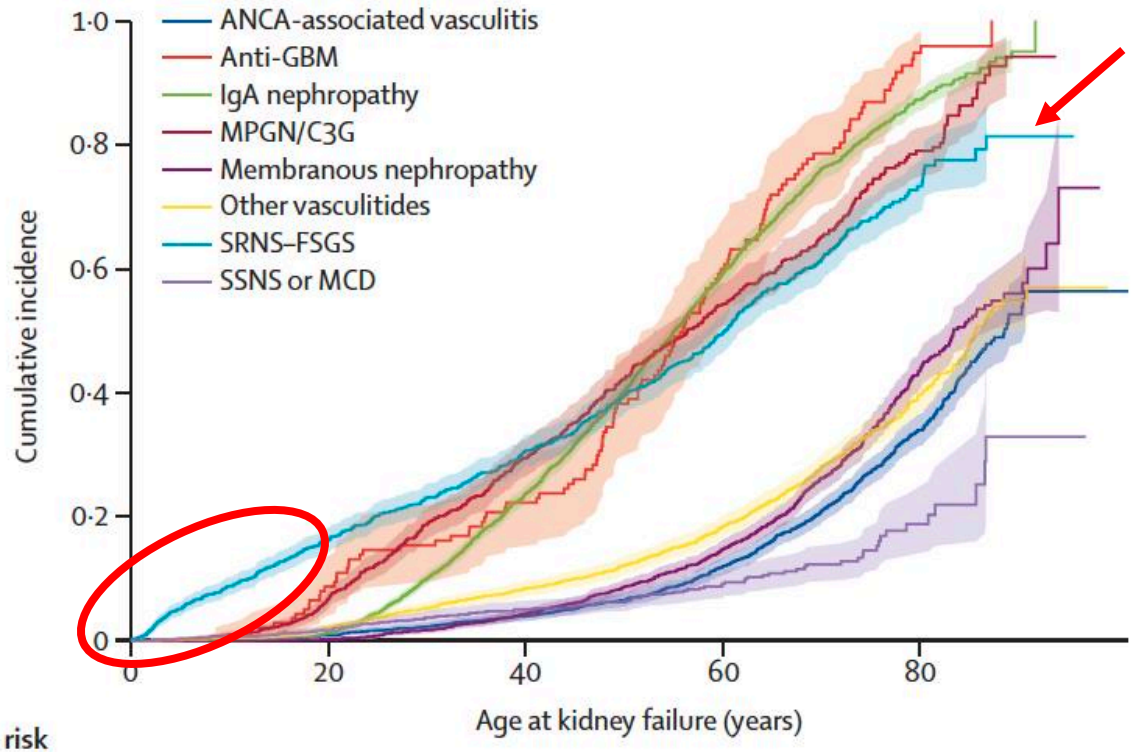
KDIGO Glomerular Disease Guidelines, 2021

Natural History of FSGS

- Very high lifetime risk of kidney failure
  - Particular burden in very young people
  - Median diagnosis age (IQR): 27.7 (7.0-50.6)
  - Median years to KF (IQR): 16.5 (14.1-19.0)
- Patients typically present with well-preserved kidney function but lose it fast



Kidney failure

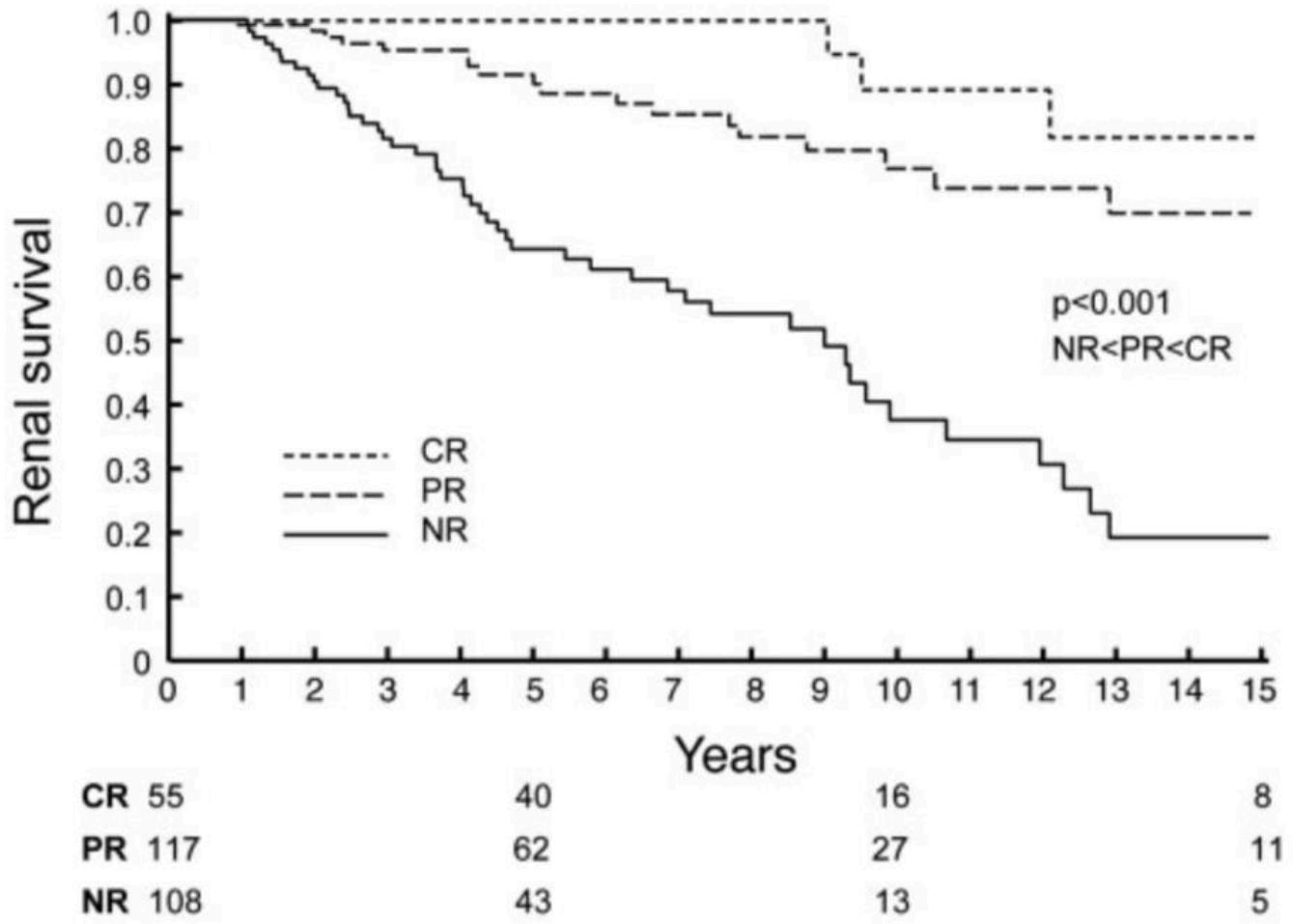


Number at risk (number censored)					
ANCA-associated vasculitis	2375 (0)	2344 (10)	2183 (98)	1697 (413)	425 (1390)
Anti-GBM	137 (0)	125 (0)	102 (5)	51 (7)	4 (13)
IgA nephropathy	4147 (0)	4043 (51)	2741 (481)	959 (1193)	79 (1619)
MPGN–C3G	1089 (0)	933 (85)	585 (228)	293 (332)	36 (481)
Membranous nephropathy	2439 (0)	2425 (8)	2209 (126)	1535 (582)	281 (1514)
Other vasculitides	2331 (0)	2062 (221)	1750 (405)	1286 (694)	319 (1427)
SRNS–FSGS	1536 (0)	1094 (203)	727 (403)	364 (598)	40 (809)
SSNS or MCD	1705 (0)	1092 (588)	715 (933)	373 (1252)	60 (1546)

Wong et al Lancet 2024

Proteinuria and Kidney Failure

- Toronto GN Registry
- 281 initially nephrotic FSGS patients (>3.5g/day)
- Median follow-up 65 months to kidney failure
- CR: UPCR ≤0.3 g/day
- PR: >50% reduction in peak proteinuria and to subnephrotic levels <3.5g/day



Troyanov, et al; JASN, 2005

Proteinuria Outcomes in FSGS trials

Study	Inclusion	Proteinuria endpoints	eGFR endpoints
NANS study, KI 1999; n=49, steroid resistant FSGS CSA + prednisone vs. Placebo + prednisone	≥3.5 g/d	CR ≤0.3 g/d, PR ≤3.5 g/d +50%↘* Relapse >3.5 g/d	Doubling creat, ESKD <12 CG-CrCl Stop points >30%↗creat
Ponticelli, KI 1993 N=45, steroid resistant FSGS CSA vs. Supportive care	≥3.5 g/d	CR ≤0.2 g/d, PR <3.5 g/d Relapse from PR >3.5 g/d	eGFR time 0 vs 6 m: factorial anova ↘50% decline in CG-CrCl
Gipson, KI 2011 N=138, children, young adults CSA vs. MMF/dex	> 1 g/g	CR<0.2g/g, PR 50%↘ + 0.2-2.0 g/g Relapse > 2 g/g.	Change in eGFR over time Kidney failure
Lieberman, JASN 1996 N=25, children CSA vs. Placebo	0.18 g/g	CR ≤ 0.3 g/d, PR ↘supranormal value	Decline in eGFR
Heering, AJKD 2004 N=57, biopsied FSGS Csa vs. Chlorambucil	> 3.5 g/d	PR <3.5 g/d, CR <0.2 g/d	Change in creatinine, ESKD

Slide adapted from S. Troyanov

What can a clinical trial tell us about a drug?

1. Does drug 'work'?
   - i.e. does it have any beneficial effect on disease at all?

   P value < e.g. 0.05
2. What is the magnitude of the drug's effects?
   - Quantify magnitude of benefit in terms of impact on endpoint(s)

   Hazard ratio, absolute or % change or other quantitative estimator of EFFECT SIZE
   - Quantify observed adverse events – but for trials of a novel treatment in a rare disease there is inherent uncertainty (eg uncommon but serious risks not manifesting in short, small trial)

- But patients, clinicians, payers and regulators need to know the extent to which impact on the trial endpoint predicts impact on clinically important patient outcomes in real life
  - Where the endpoint is death or kidney failure this is clear
  - Where it is a surrogate for such hard outcomes more information is needed

Surrogate endpoints: Prentice's tenets

1. The surrogate has to have a strong association with the outcome
   - Relationship can be quantified by longitudinal observational data
2. A treatment effect on the surrogate has to capture the effect of the treatment on the outcome
   - In practice, it is hard to confirm tenet 2 without the long-term trials (that the surrogate is being used to avoid) but evidence from real-world follow-up/observational studies can help over time
   - "Biological plausibility" can provide support: does the mechanism of action of the intervention likely impact on disease in a way that would similarly affect both the surrogate endpoint and the outcome
   - Hence mechanistic data is CRITICALLY IMPORTANT for surrogate endpoint-based trials (more so than trials with hard outcomes as their endpoint)
   - Surrogates on the causal pathway more accessible than surrogates that (might be) off it

Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Statistics in medicine*. 1989;8(4):431-440.

Proteinuria as a clinical trial endpoint

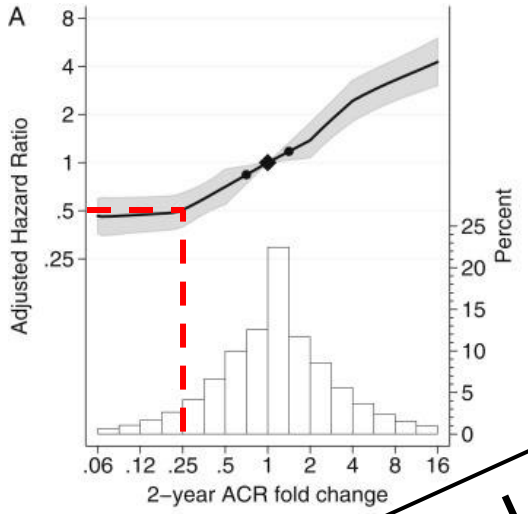
- Proteinuria is a (the?) key clinical manifestation of podocytopathy
  - Biologically plausible indicator of disease activity (depending on drug MOA)
  - Nephrotic syndrome/severe oedema causes problems in some people
- Complete remission (normalization of uPCR) is accepted to be a surrogate for better long-term outcomes
- Various definitions of Partial Remission have been proposed (e.g. halving and below a threshold)
- Quantitative relationship of changes in proteinuria with kidney function/kidney failure less well understood in FSGS
  - What magnitude of reduction in proteinuria would translate to a clinically meaningful reduction in kidney failure risk?

eGFR change as a clinical trial endpoint

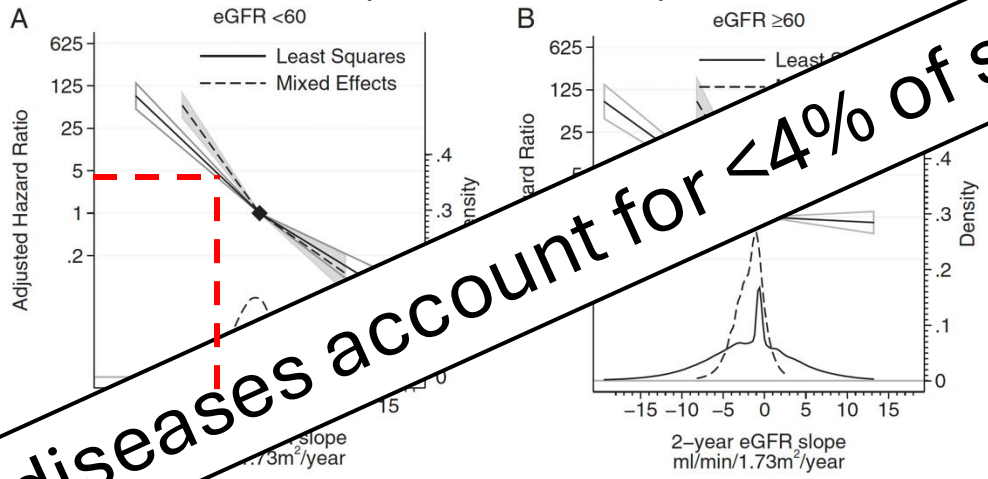
- eGFR loss is a necessary pre-requisite for kidney failure
  - Logical that loss of eGFR early in the disease could predict kidney failure hazard
- Key unresolved questions: given the many factors that contribute to eGFR and the relapsing-remitting nature of some podocytopathies, how STRONGLY does eGFR predict kidney failure risk in patients with FSGS?
  - How noisy is eGFR assessment in FSGS?
- What is more appropriate, change, slope, total slope or chronic slope?
  - Mechanism of action may be important here (effect on glomerular filtration pressure/volume as seen with RAASi, Sparsentan, Tolvaptan)

Proteinuria, eGFR and Kidney Failure in large CKD cohorts

Albuminuria
693,000 participants
(observational)



eGFR
3.9M participants
(observational)



Glomerular diseases account for <4% of subjects

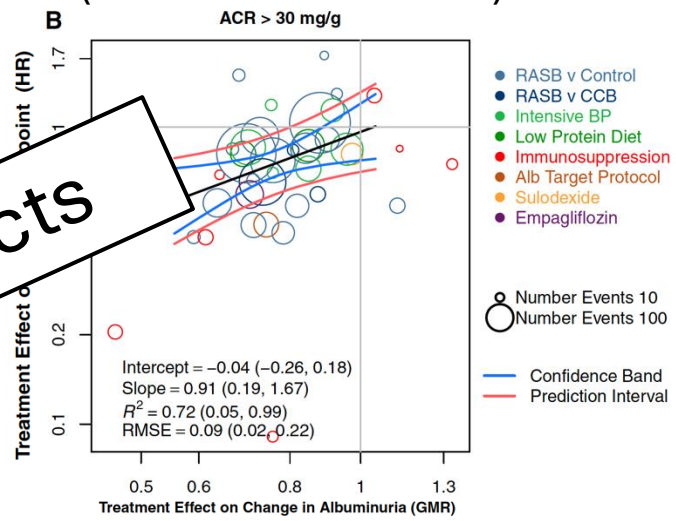
ESKD Risk Associations With Albumi… Baseline Periods: ESKD HR…		…se
		…justed for Regression Dilution (Median Reliability)**
ACR		
1-year	0.82 (0.74-0.91)	0.75 (0.64-0.87)
2-year	0.83 (0.74-0.94)	0.78 (0.66-0.92)
3-year	0.80 (0.71-0.90)	0.76 (0.65-0.87)

C

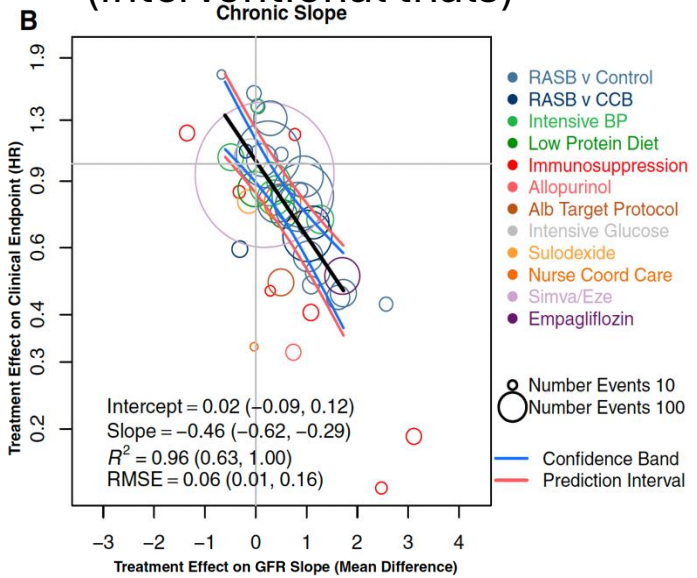
ESKD Risk Associations With eGFR Slope: ESKD HR for 0.75 mL/min/1.73 m²/y Difference		
	Least Square Mean Regression*	Linear Mixed Models Regression**
Baseline eGFR < 60		
1-year	0.88 (0.86, 0.91)	0.79 (0.76, 0.83)
2-year	0.79 (0.77, 0.81)	0.71 (0.69, 0.74)
3-year	0.71 (0.68, 0.73)	0.63 (0.60, 0.67)
Baseline eGFR ≥ 60		
1-year	0.93 (0.92, 0.94)	0.74 (0.69, 0.80)
2-year	0.84 (0.82, 0.87)	0.70 (0.68, 0.72)
3-year	0.77 (0.74, 0.80)	0.66 (0.64, 0.68)

Levey et al AJKD 2018

30,000 participants
(interventional trials)

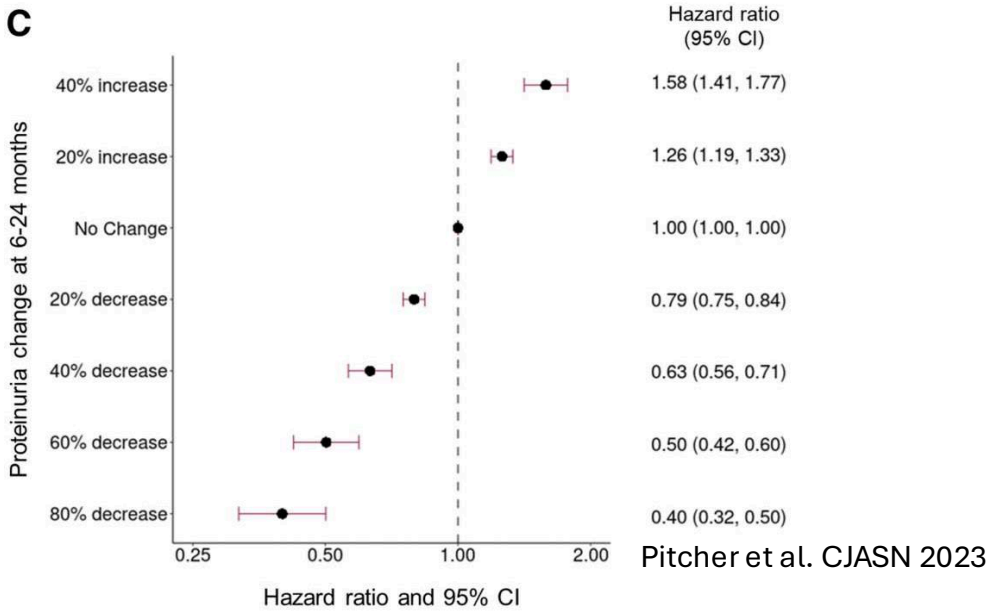


60,000 participants
(interventional trials)



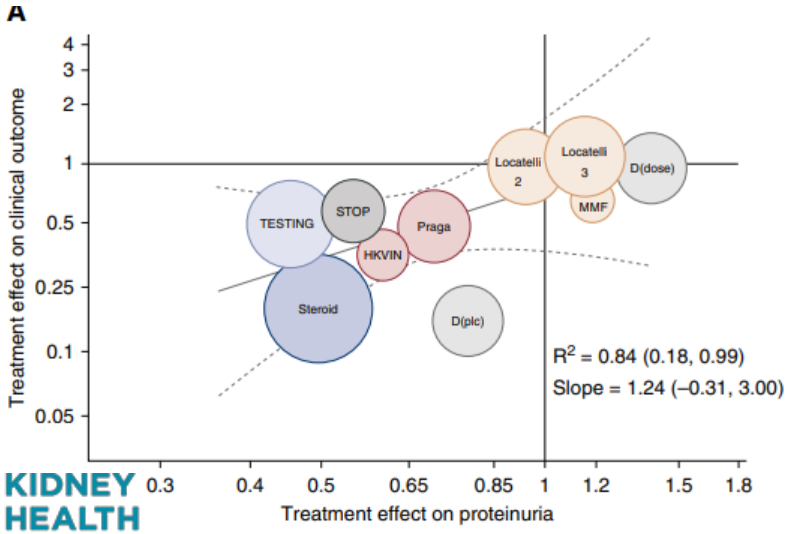
IgA Nephropathy KHI project: Proteinuria as a "reasonably-likely" surrogate endpoint

Both proteinuria (6-24 months) and eGFR slope (6-30 months) strongly associated with kidney failure hazard over 5 years in IgAN



Pitcher et al. CJASN 2023

- Trial-level analysis of data from 13 controlled trials
- Association between treatment effects on percent reduction of proteinuria and treatment effects on a composite of time to doubling of serum creatinine, ESKD or death
- **Proteinuria Reduction as a Surrogate End Point in Trials of IgA Nephropathy**
- **Multiple new therapies recently approved**



Thompson, A, et al; CJASN 2019

KHI KIDNEY HEALTH INITIATIVE

eGFR & Proteinuria in an FSGS Trial

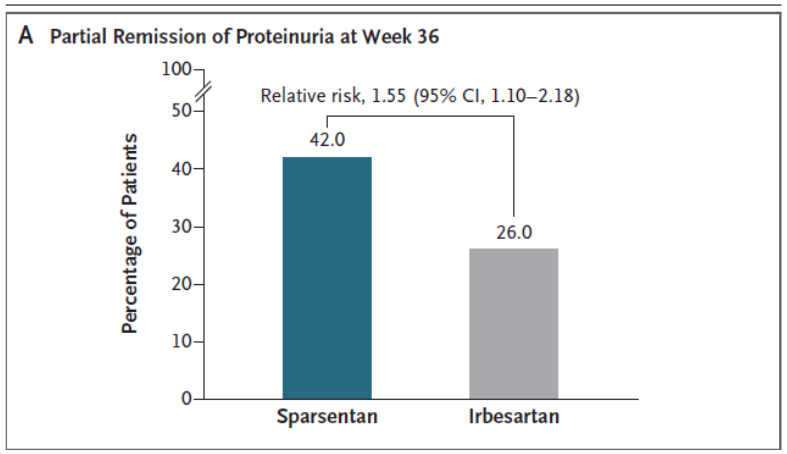
- 371 patients randomized to irbesartan vs. sparsentan
- Age 8-75
- Surrogate: modified PR @36 weeks
- Primary efficacy: eGFR slope from baseline to 4 weeks after end of treatment @ week 112

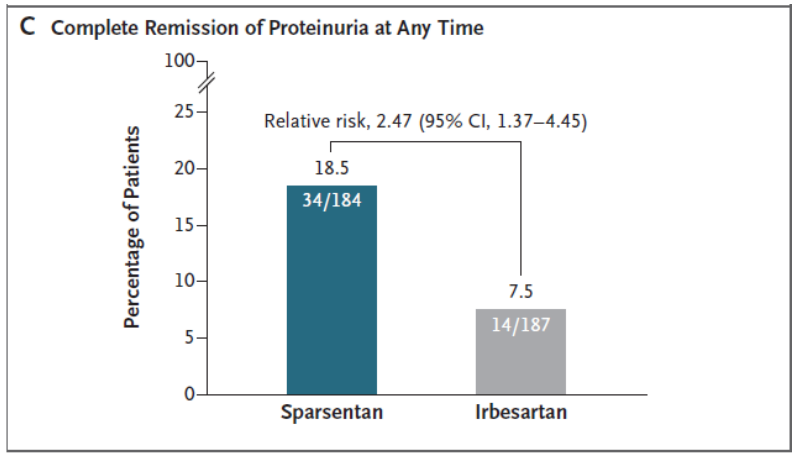
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sparsentan versus Irbesartan in Focal Segmental Glomerulosclerosis

M.N. Rheault, C.E. Alpers, J. Barratt, S. Bieler, P. Canetta, D.-W. Chae, G. Coppock, U. Diva, L. Gesualdo, H.J.L. Heerspink, J.K. Inrig, G.M. Kirsztajn, D. Kohan, R. Komers, L.A. Kooienga, K. Lieberman, A. Mercer, I.L. Noronha, V. Perkovic, J. Radhakrishnan, W. Rote, B. Rovin, V. Tesar, H. Trimarchi, J. Tumlin, M.G. Wong, and H. Trachtman, for the DUPRO Steering Committee and DUPLEX Investigators*





Rheault, M, et al; NEJM Dec 2023

FSGS

Table 2. The eGFR Slope and Change in eGFR.

Variable	Sparsentan (N=184)	Irbesartan (N=187)	Difference	P Value
Least-squares mean eGFR slope (95% CI) — ml/min/1.73 m²/yr				
eGFR total slope*	−5.4 (−6.9 to −3.9)	−5.7 (−7.2 to −4.3)	0.3 (−1.7 to 2.4)	0.75
eGFR chronic slope†	−4.8 (−6.3 to −3.3)	−5.7 (−7.2 to −4.2)	0.9 (−1.3 to 3.0)	0.42
Least-squares mean change in eGFR from baseline to week 112 (95% CI) — ml/min/1.73 m²‡	−10.4 (−12.6 to −8.1)	−12.1 (−14.4 to −9.9)	1.8 (−1.4 to 4.9)	

Rheault, M, et al; NEJM Dec 2023

* The eGFR total slope was the slope from day 1 to week 108.
† The eGFR chronic slope was the slope from week 6 to week 108.
‡ Data are for patients who completed the double-blind treatment period (129 patients in the sparsentan group and 136 patients in the irbesartan group).

IgAN

	Sparsentan group (n=202)	Irbesartan group (n=202)	Between-group difference (95% CI)	p value
Key secondary efficacy endpoints*				
Chronic slope from week 6 to week 110, mL/min per 1·73 m² per year	−2·7 (−3·4 to −2·1)	−3·8 (−4·6 to −3·1)	1·1 (0·1 to 2·1)	0·037
Total slope from day 1 to week 110, mL/min per 1·73 m² per year	−2·9 (−3·6 to −2·2)	−3·9 (−4·6 to −3·1)	1·0 (−0·03 to 1·94)	0·058
Other secondary efficacy endpoint*				
Absolute change from baseline to week 110, mL/min per 1·73 m²	−5·8 (−7·4 to −4·2)	−9·5 (−11·2 to −7·9)	3·7 (1·5 to 6·0)	..
Prespecified exploratory endpoint†				
Absolute change from baseline to week 114, mL/min per 1·73 m²	−6·1 (−7·7 to −4·5)	−9·0 (−10·7 to −7·2)	2·9 (0·5 to 5·3)	..

Data are least-squares mean change (95% CI) in eGFR unless otherwise stated. eGFR=estimated glomerular filtration rate. *Assessed in the full analysis set. †Assessed in patients in the full analysis set who completed the study treatment.

Table 2: Change in eGFR

Rovin, et al; Lancet; Nov 2023

Absence of evidence ≠ evidence of absence of effect:
Need to quantify the noise to assess power

Consequences of uncertainty in FSGS

- Lack of information about relationships with kidney failure of early changes in measurable parameters (proteinuria/eGFR) results in:
  - Uncertainty about how to interpret previous trials
  - Lack of consensus about design of further trials:
    - Power to detect effect on eGFR very different to proteinuria for a study of a given size/duration
- Excessive risk of investing in trials: greater certainty about clinical impact of a specified endpoint would clarify viability (or pathway to translation) of a new intervention for which effect size has been estimated (e.g. from early-phase trials)

KHI Workgroup (2018): Surrogate Endpoints for FSGS

Challenges

- FSGS is a rare and heterogenous glomerular disorder with uncertainty about underlying biology and a lack of sufficient effective treatments
- Mega-trials that can show an effect of a therapy on kidney failure or death are unlikely to be feasible in FSGS
- There is a need to identify earlier surrogate endpoints that could be used to establish efficacy of therapies for patients with FSGS. [*Other than complete proteinuric remission]*

Working Group Charge

- Seek to identify potential short-term and intermediate candidate surrogate outcomes in FSGS by reviewing existing literature & available data

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Working Group Output (Manuscript accepted for publication)

- Extensive landscape review of eGFR, proteinuria and PRO & assessment of available data resources
- **Call to action to assemble sufficient data to answer the question**

PARASOL

Proteinuria and GFR as Clinical Trial Endpoints in Focal Segmental Glomerulosclerosis

A Call to Action: PARASOL project

Proteinuria and GFR as Clinical Trial Endpoints in Focal Segmental Glomerulosclerosis

Specific aims and questions

PARASOL

Proteinuria and GFR as Clinical Trial Endpoints in Focal Segmental Glomerulosclerosis

- Quantify the relationships with kidney failure of early changes in:
  - Proteinuria
  - eGFR
- Use observational data to inform power calculations for future studies using these potential endpoints
  - Allows size/feasibility of trials to be estimated (according to predicted effect size)
- Can relationships established in CKD and IgAN etc be used in FSGS?
  - Is accelerated approval based on proteinuria endpoint followed by full approval based on effect on eGFR slope a viable model for FSGS?
- Is FSGS just too heterogeneous to allow such efforts to succeed with available data sources?

PARASOL

Proteinuria and GFR as Clinical Trial Endpoints in Focal Segmental Glomerulosclerosis

Methodology

- Joint or harmonised (meta- or replication) analyses from large-scale observational cohort studies and registries
  - International collaboration to include as many cohorts as possible – driven by Matthias Kretzler, Laura Mariani and team at University of Michigan
  - Agreed eligibility criteria (clinical parameters and data held)
  - Harmonised analysis plans
  - Exploratory/discovery analyses
  - Replication to confirm key findings and help establish relevance globally
- Stakeholder engagement at all stages
  - Patients, clinicians, academics, industry, regulators

https://www.is-gd.org/parasol

NephCure for Rare Kidney Disease

KHI KIDNEY HEALTH INITIATIVE

FDA U.S. FOOD & DRUG ADMINISTRATION

PARASOL

Proteinuria and GFR as Clinical Trial Endpoints in Focal Segmental Glomerulosclerosis

https://www.is-gd.org/parasol

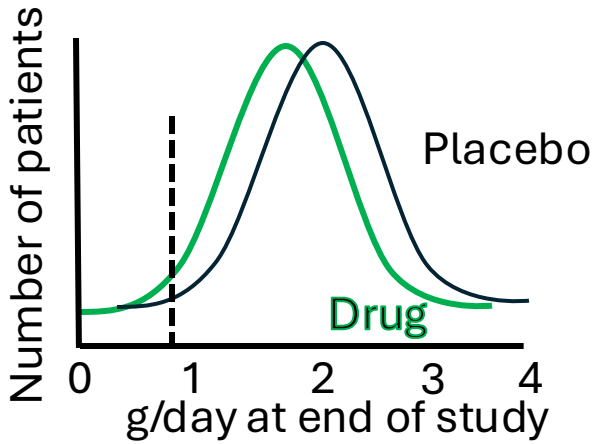
Endpoint model(s) derived from analysis of datasets, to inform feasible trial designs and future regulatory pathways for FSGS

A series of internationally supported cross-stakeholder workshops

- Community discussion and review of the analyses, including FDA, EMA and industry, as well as professional and patient non-profit advocacy organizations
- Kick-off meeting – Washington DC (Dec 9-10, 2023)
- Interim Workshop - Reykjavik (June 8-9, 2024)
- Public Consensus Scientific Workshop - Washington DC (Oct 7-8, 2024)

Dissemination of results

- ASN Kidney Week 2024 session “Advancing the Understanding of Proteinuria and eGFR as FSGS Clinical Trial Endpoints”
- Publications and communications in international peer-reviewed journals



Modeling proteinuria and eGFR slope as surrogate end points for FSGS

Abigail R. Smith, PhD

Northwestern University

KIDNEY WEEK 2024

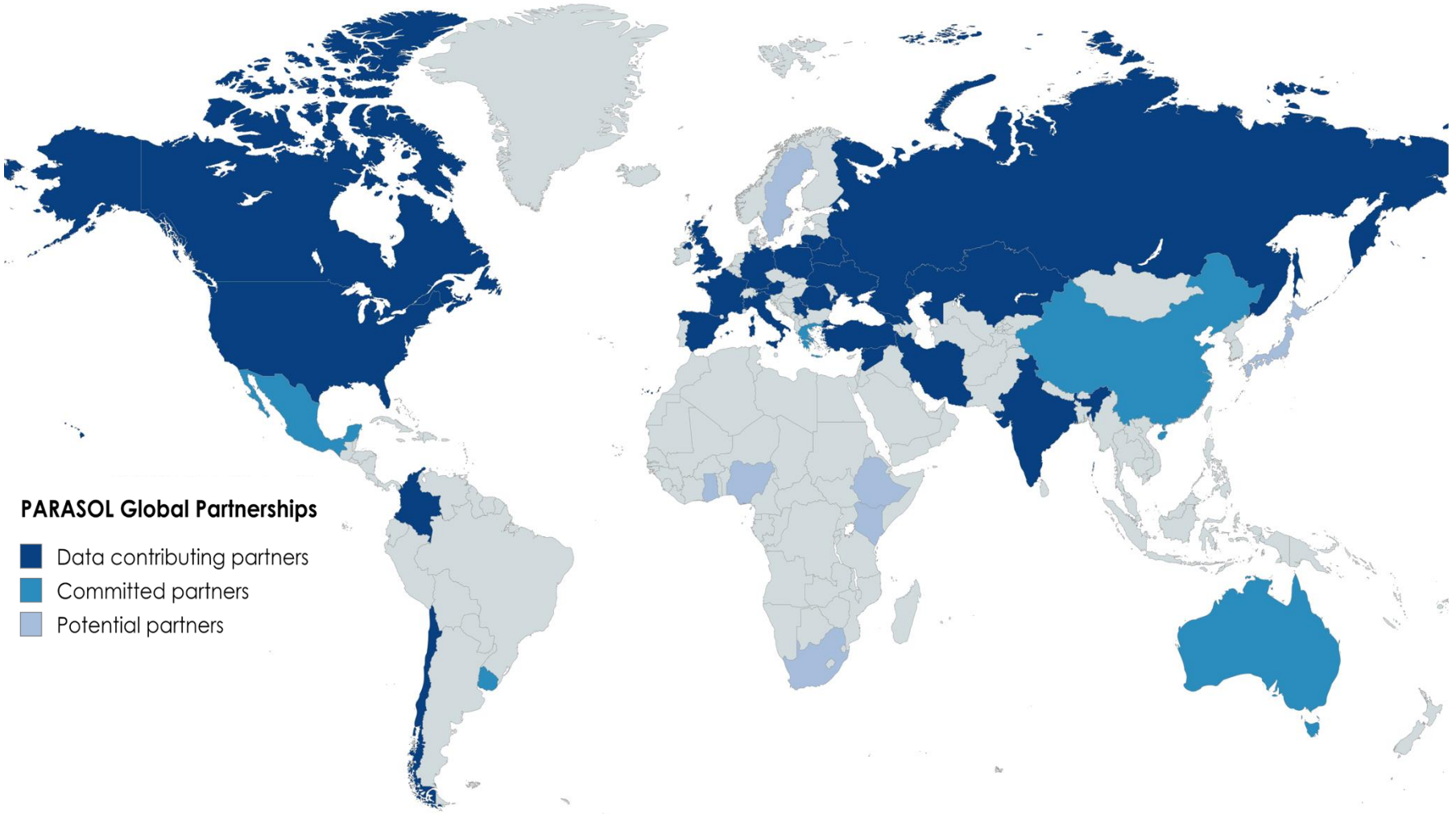
Disclosures

Research funding: HI-Bio (Biogen)

Proteinuria and eGFR as Clinical Trial End Points in FSGS (PARASOL)

- Coalition of nonprofit organizations, academia, registries & trials sharing data and analysis expertise
- Co-sponsors:

Global Partnership



Participating Registries

- NEPTUNE
- CureGN
- KRN
- UNC
- Gaslini
- Podonet
- Glosen
- Toronto GN Registry
- Indiana
- RaDaR (validation)

+ more on the way!

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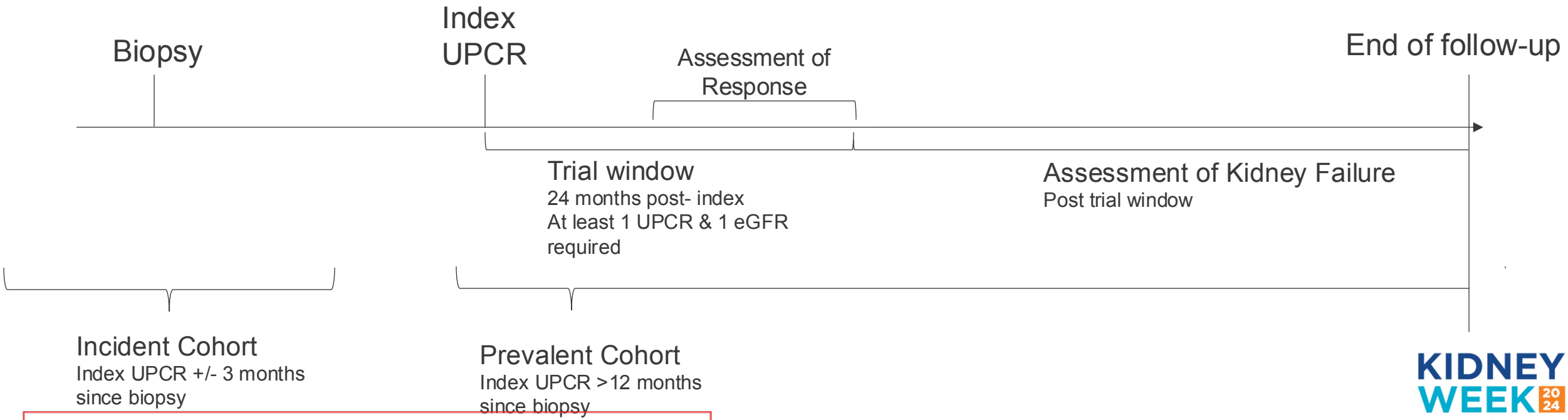
Cohort selection

- **Patients with biopsy-proven or genetic FSGS and UPCR≥1.5 g/g proteinuria and eGFR≥30 ml/min/1.73m^2 at**
  - Any time post-biopsy or genetic diagnosis or up to 3 months prior (**All**)
  - Within 6 months of biopsy/genetic diagnosis (**Incident**)
  - ≥12 months from biopsy/genetic diagnosis (**Prevalent**)



Sample Characteristics

Median (Q1,Q3) or N (%)	All	Pediatric	Adult	eGFR ≥ 60	eGFR < 60	UPCR 1.5-<3.5	UPCR ≥3.5
N	1626	756	870	1141	485	766	860
Age at index	21 (9, 43)	8 (4,13)	42 (30, 56)	15 (7, 34)	42 (19, 59)	23 (10, 44)	19 (9, 43)
% pediatric	756 (46%)	756 (100%)	0 (0%)	640 (56%)	116 (24%)	339 (44%)	417 (48%)
UPCR at index	3.7 (2.3, 7.1)	4.0 (2.2, 8.7)	3.6 (2.3, 6.3)	3.8 (2.3, 7.3)	3.6 (2.2, 6.5)	2.2 (1.8, 2.7)	6.7 (4.7, 10.6)
eGFR at index	82 (56, 110)	98 (74, 128)	68 (47, 94)	98 (79, 113)	44 (36, 52)	80 (54, 108)	84 (56, 112)
Follow-up months post-index	66 (32, 100)	68 (35, 102)	64 (30, 97)	66 (34, 100)	67 (30, 100)	64 (33, 95)	68 (32, 104)
Kidney failure before 84 months	310 (19%)	156 (21%)	154 (18%)	148 (13%)	162 (33%)	114 (15%)	196 (23%)
eGFR 0-24 months post-index	4 (3,7)	4 (2,6)	5 (3,8)	5 (3,8)	4 (3,6)	4 (2, 6)	5 (3, 8)
UPCR 12-24 months post-index	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)

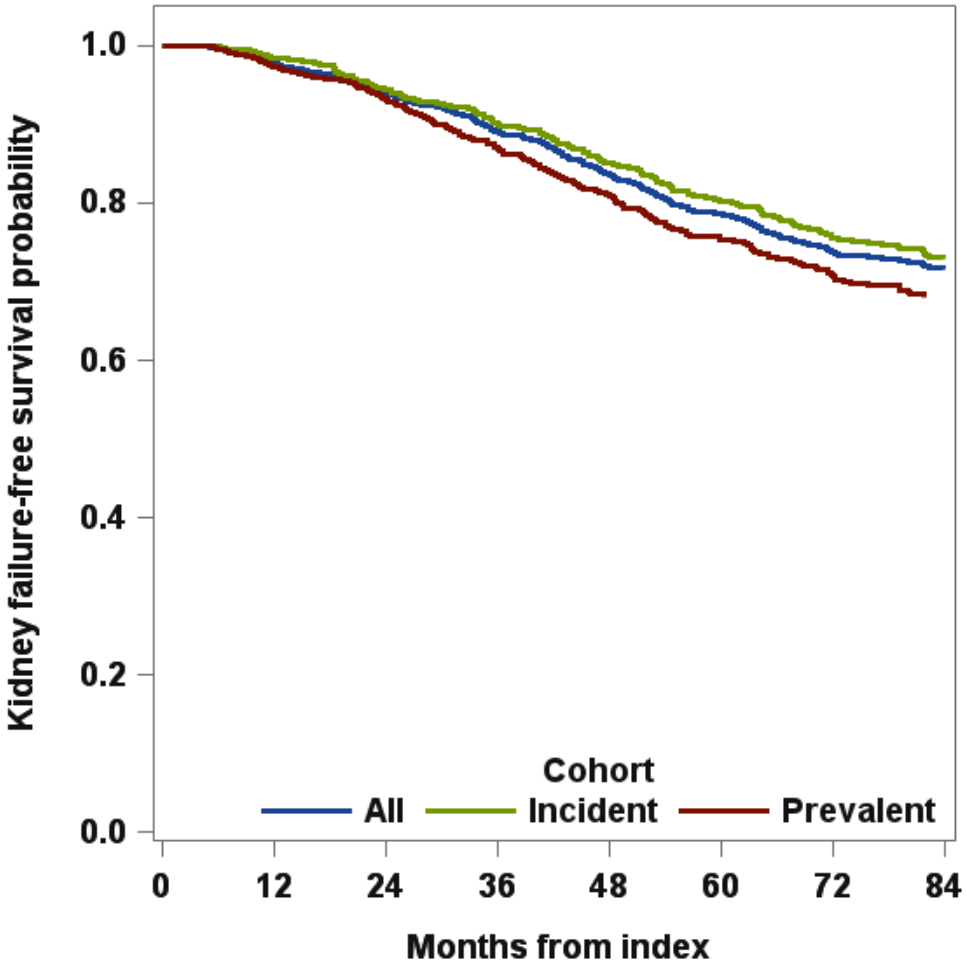
Overview of statistical methods

- **eGFR and UPCR values closest to 3 month "visit" selected**
- **Linear mixed models with random patient intercepts and slopes used to assess eGFR slope over 24 months**
- **UPCR assessed 12-24 months post-index**
  - Last value, time-weighted average
  - Raw value, % reduction from index
- **Cox regression used to assess time to kidney failure after 24 months post-index**
  - Kidney failure=earliest of dialysis, transplant, or persistent eGFR<15 ml/min/1.73m^2
- **All models adjusted for age, sex, index eGFR, index UPCR, data source**
- **Subgroup analysis by age, index eGFR, index UPCR, and prevalent cohort**

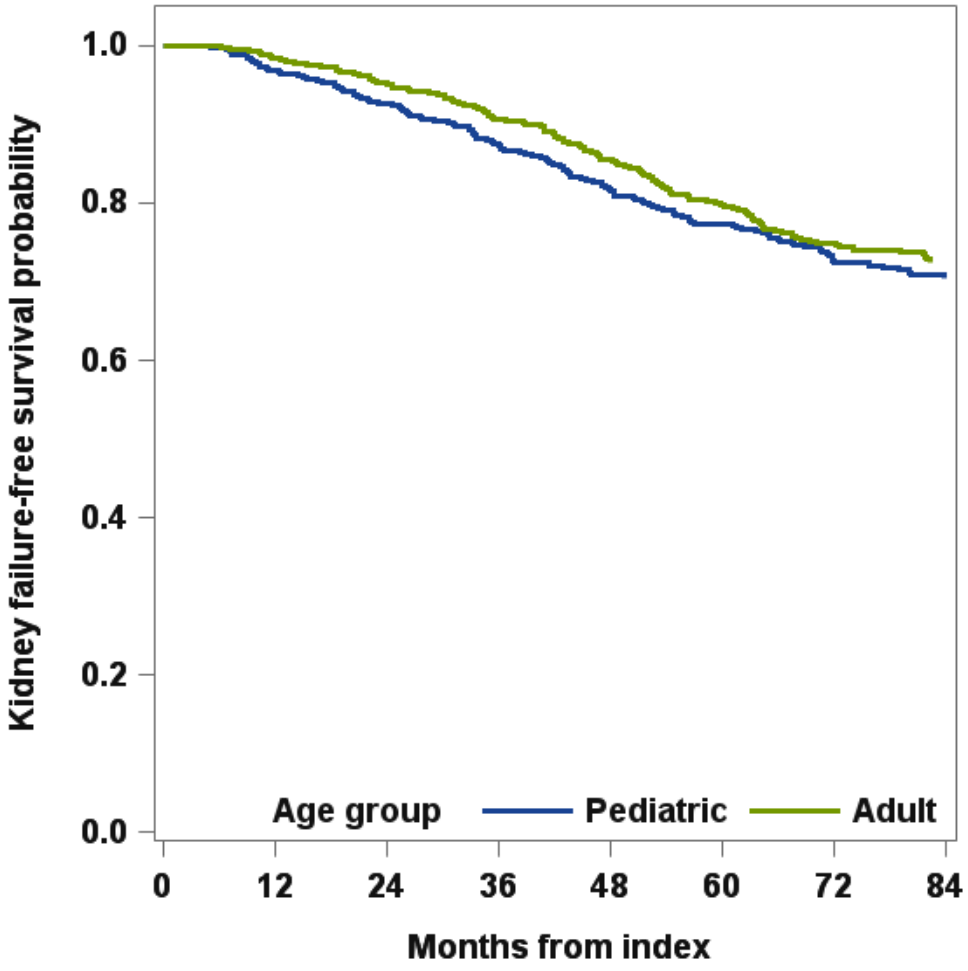
KIDNEY WEEK 2024

Baseline risk of kidney failure

By cohort



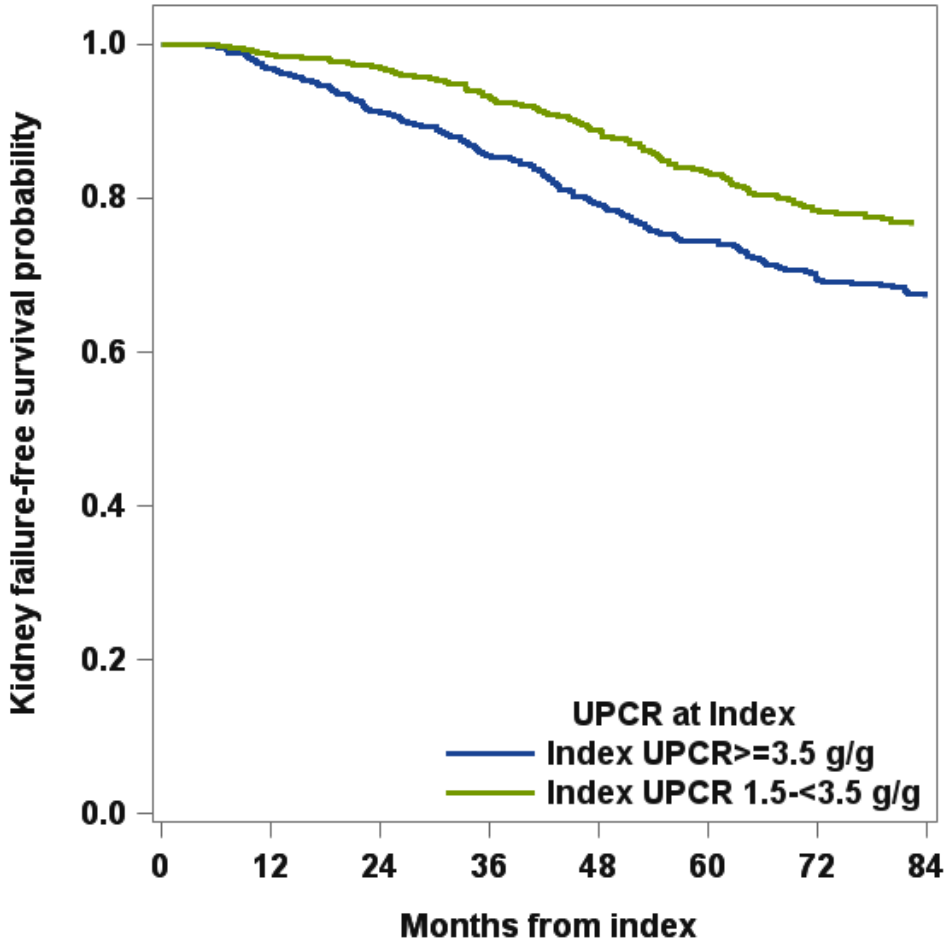
By age



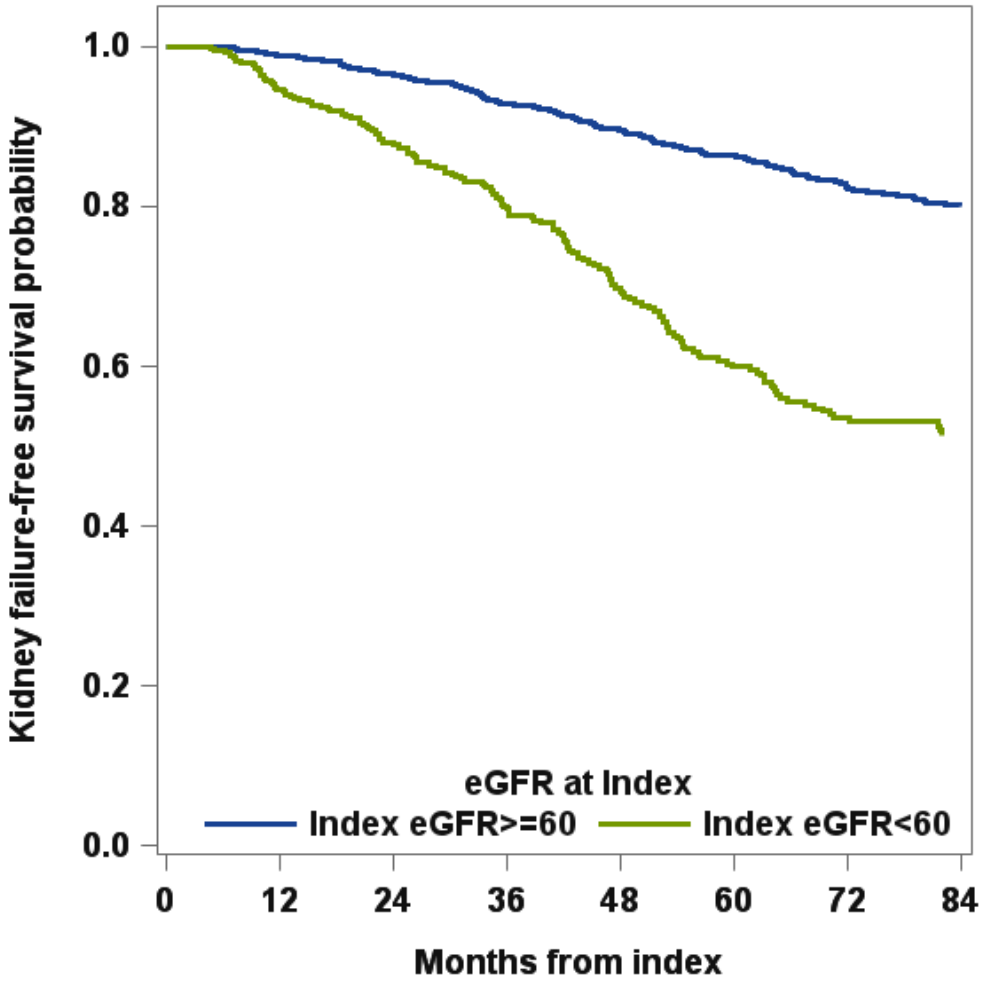
KIDNEY WEEK 2024

Baseline risk of kidney failure

By index UPCR



By index eGFR

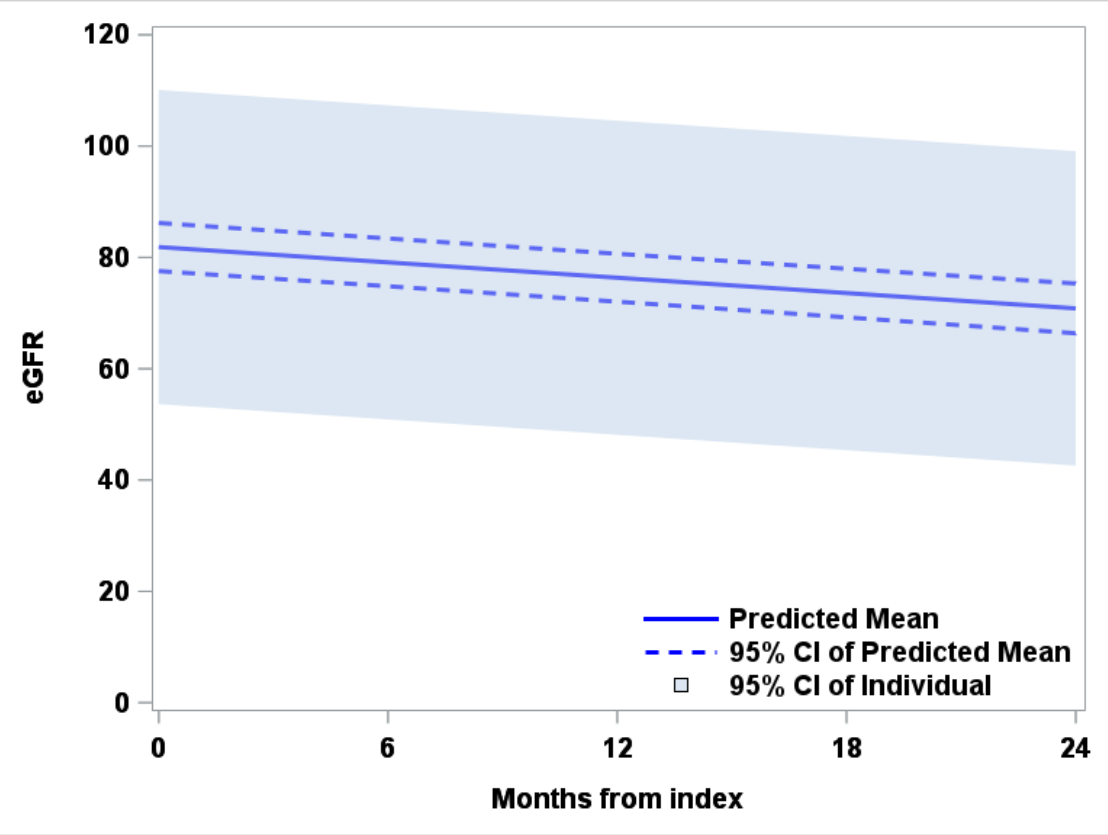


KIDNEY WEEK 2024

Modeling eGFR

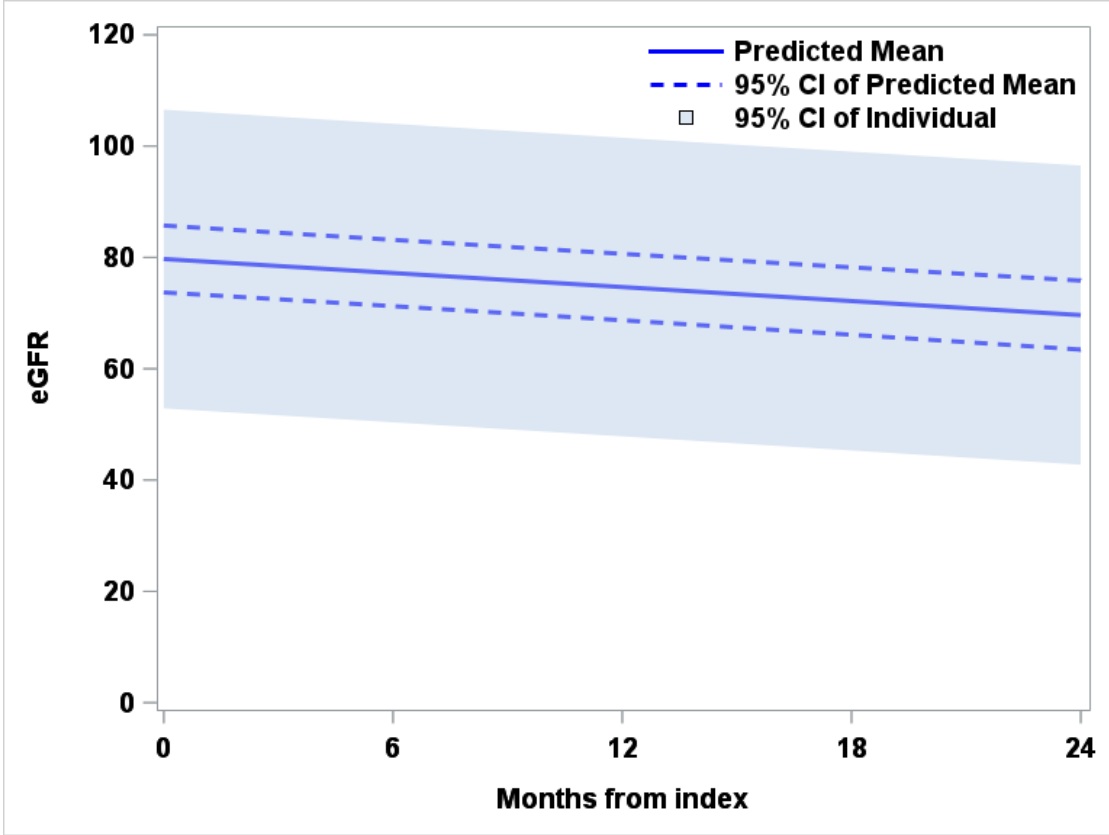
eGFR slope over 24 months

All



Mean (95% CI) change per year=-5.51 (-6.41 to -4.61)

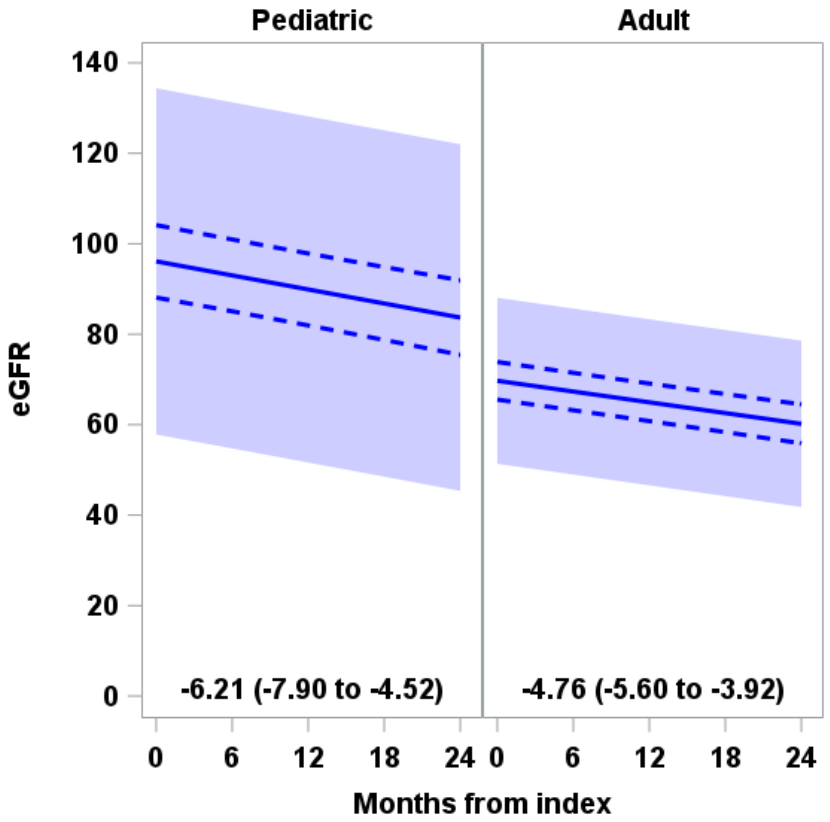
Prevalent



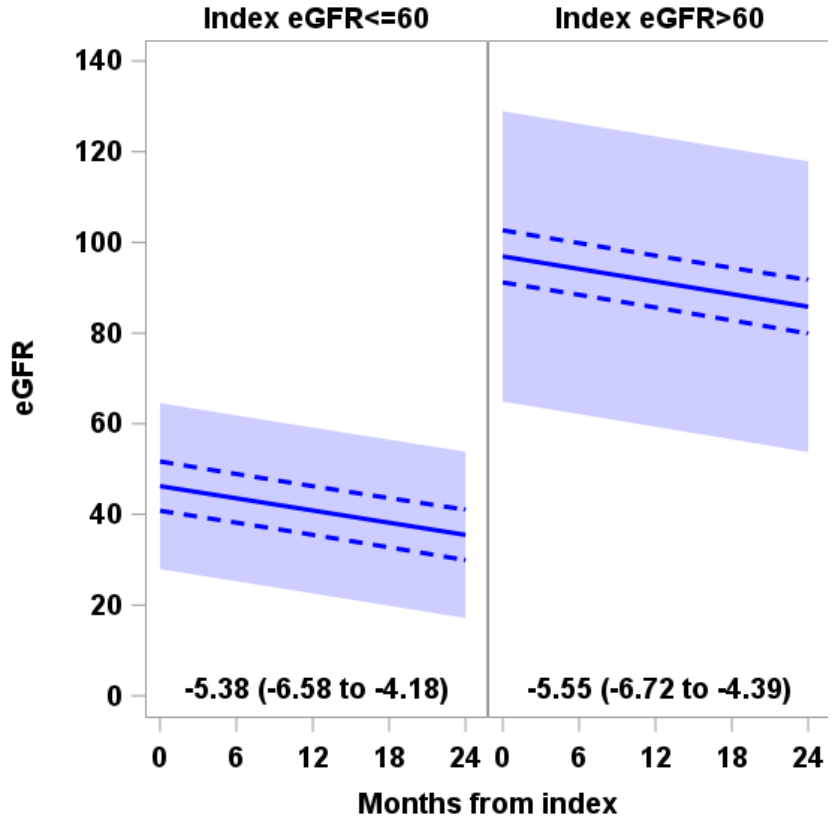
Mean (95% CI) change per year-5.04 (-6.33 to -3.75)

KIDNEY WEEK 2024

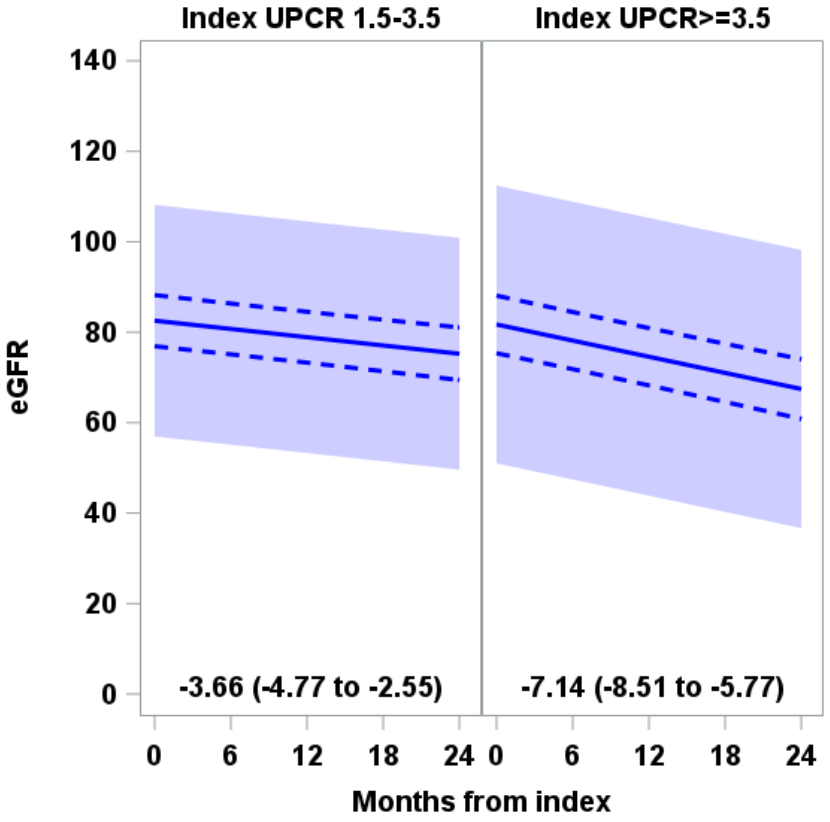
eGFR slope by subgroup (all)



More variability in pediatrics vs. adults



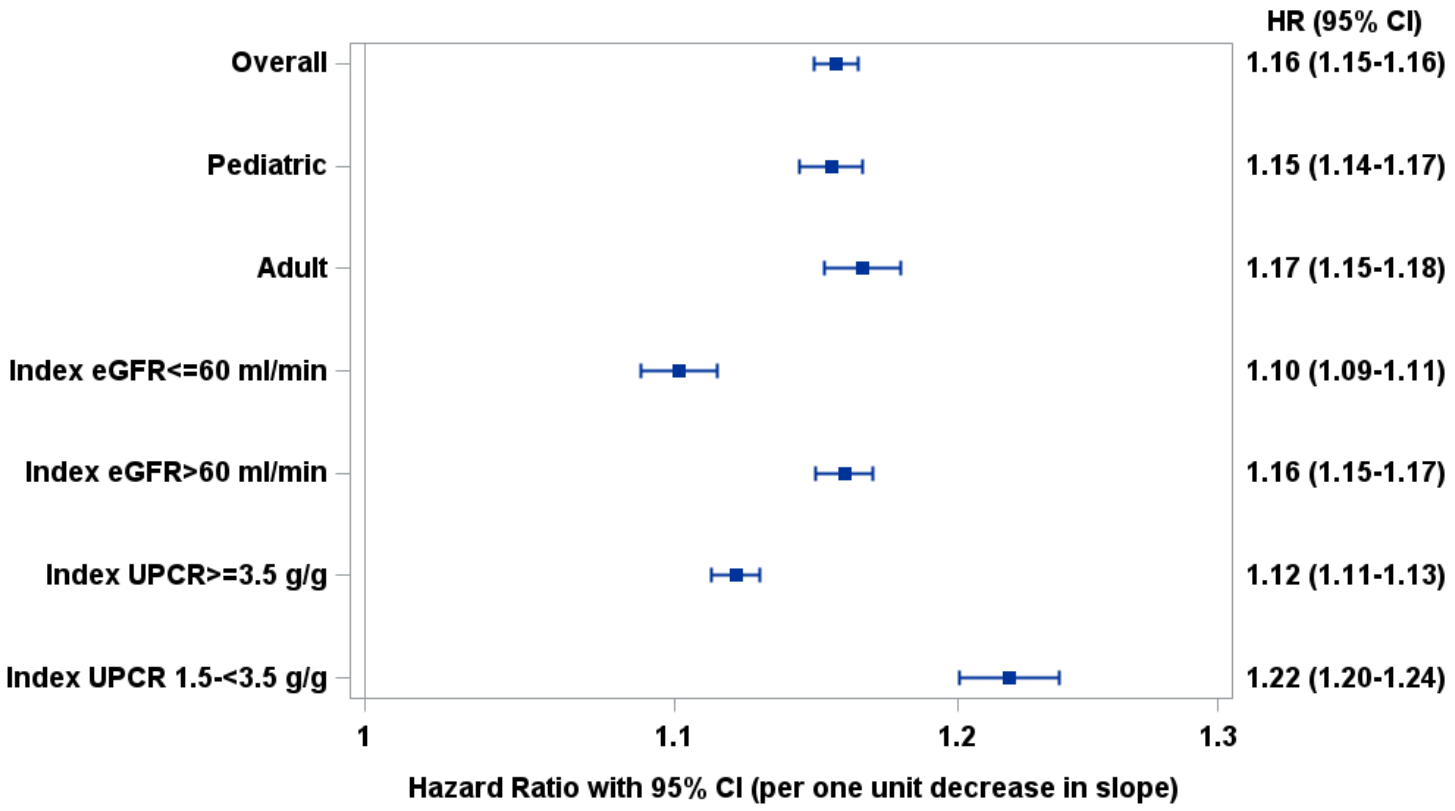
More variability in CKD stage 1-2 vs. Stage 3



Slightly more variability in nephrotic vs. sub-nephrotic

KIDNEY WEEK 2024

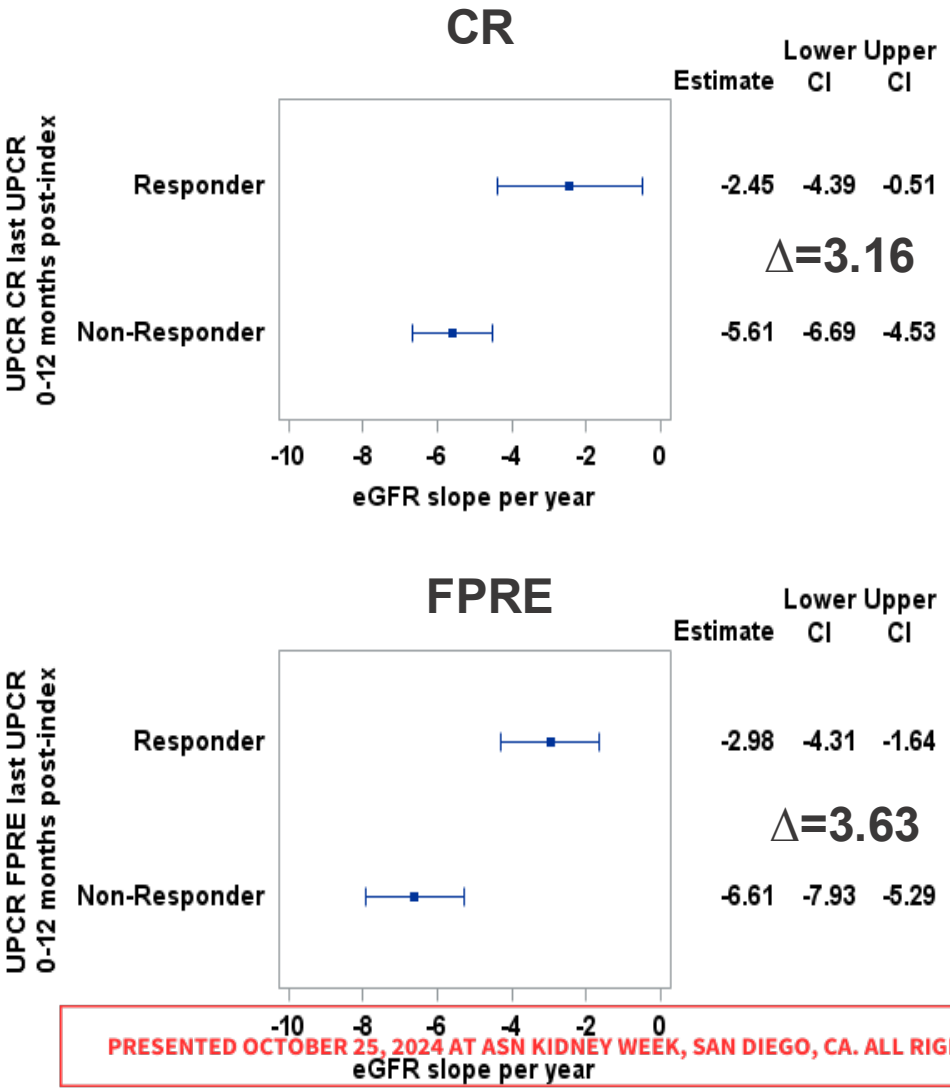
Association between eGFR slope over 24 months and kidney failure (all)



- Each one unit increase in eGFR decline is associated with a 16% increase in hazard of kidney failure
  - Patient with eGFR decline of -4 ml/min/year has 16% higher hazard of KF compared to patient with eGFR decline of -3 ml/min/yr
- Strongest in CKD Stage 3 and nephrotic patients

KIDNEY WEEK 2024

Association between 12-month proteinuria and eGFR slope at 24 months



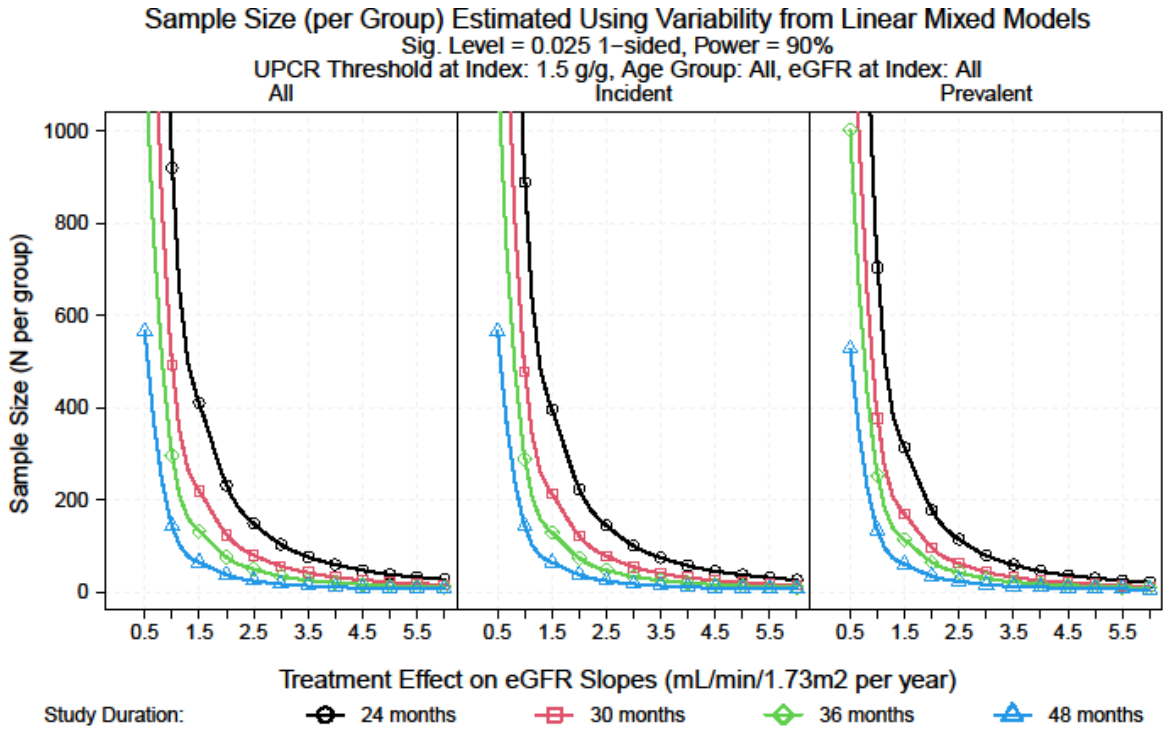
Expected eGFR slope treatment effects

Treatment response %	Control response %		
	10%	15%	20%
25%	0.47	0.32	0.16
30%	0.63	0.47	0.32
35%	0.79	0.63	0.47
40%	0.95	0.79	0.63
45%	1.11	0.95	0.79
50%	1.26	1.11	0.95

30% difference in proteinuria response required to see ~1ml/min/year difference in eGFR slope

Sample size requirements

Treatment Effect (mL/min/1.73 m² per year)	N per Treatment Group		
	All	Prevalent	Prevalent Adults
0.5	3674	2810	2011
1.0	920	704	504
1.5	410	313	225
2.0	231	177	127
2.5	148	114	82
3.0	103	79	57



Credit: Ulysses Diva

Summary of challenges with eGFR

- **eGFR slope IS associated with kidney failure**
- **High variability, particularly in an "all comers" population**
  - Lower in adults and those with eGFR<60 ml/min/1.73m^2
- **Sample sizes for accelerated approval with eGFR-based confirmatory endpoint are not likely feasible for FSGS-targeted interventions**
  - May be feasible for large treatment effects and/or targeted populations

Modeling proteinuria

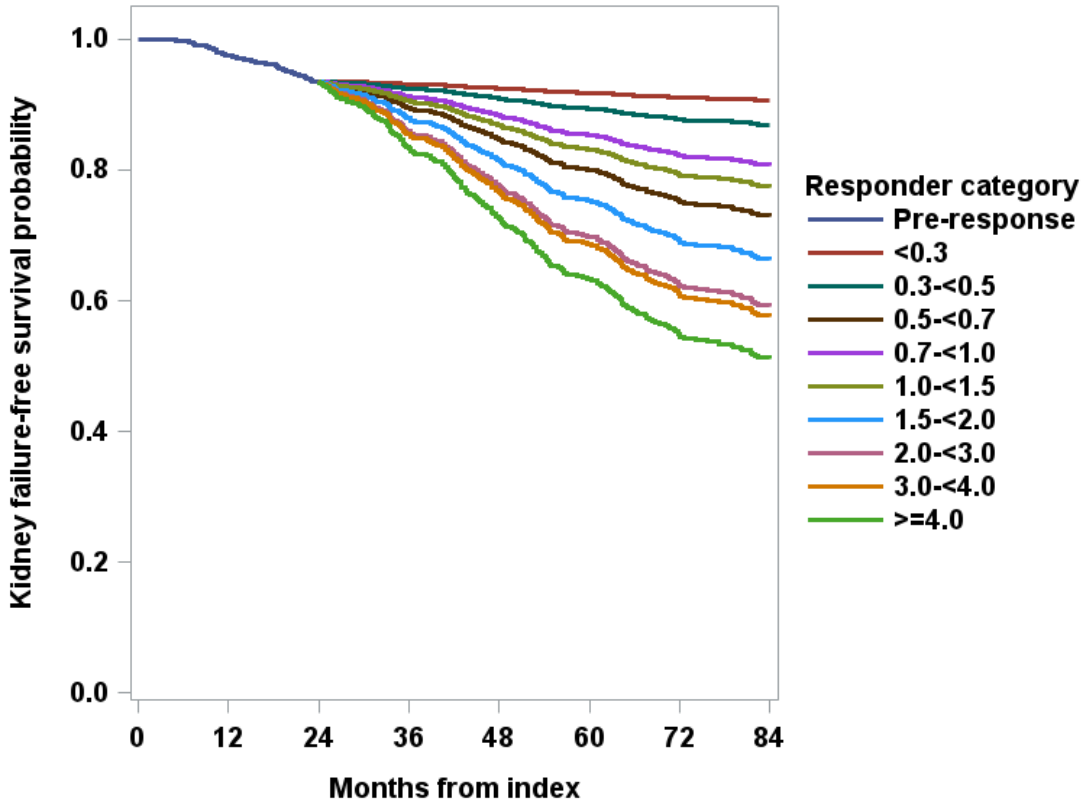
Objectives and Caveats

- **Define minimally acceptable responder endpoint(s) that meet biological plausibility and are clinically meaningful**
  - Continuous outcomes are more statistically efficient but may not represent the same biological processes

- **Assess potential new proteinuria thresholds that are biologically similar to complete remission**
  - Other components of disease progression (e.g., kidney failure, eGFR stability) would likely be incorporated into final endpoint definitions

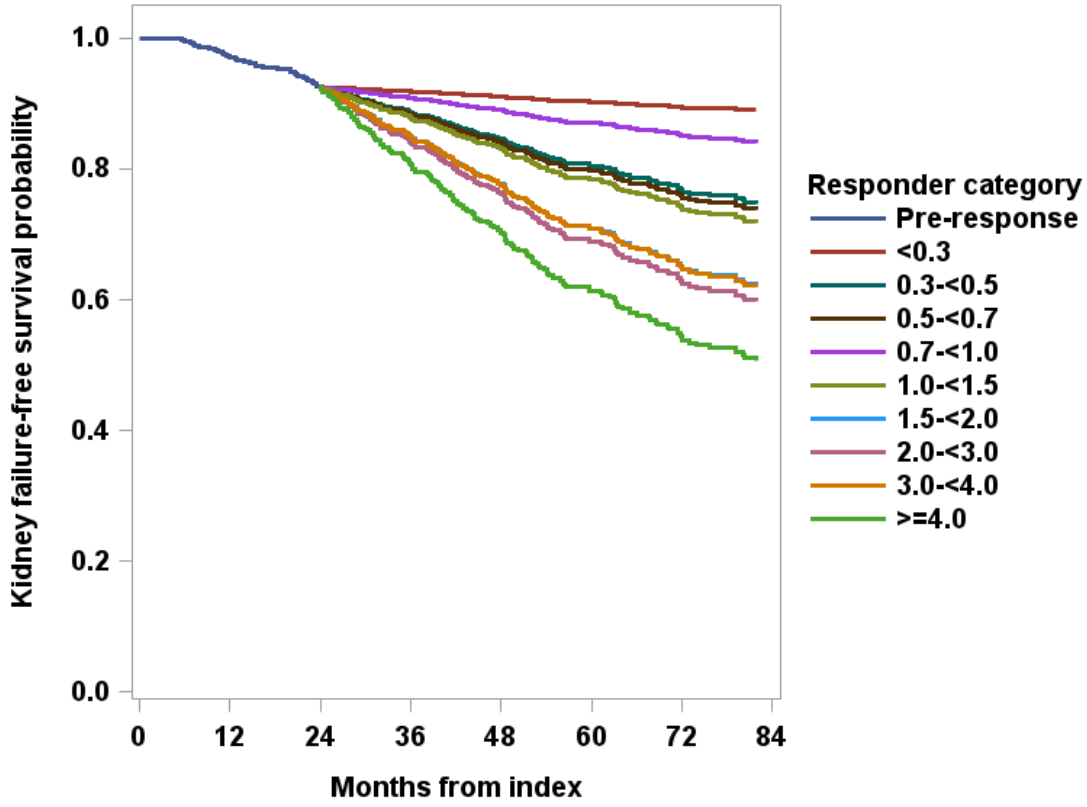
Kidney Failure-free survival by Last UPCR category (assessed at 24 months)

All



24m survival=94%

Prevalent



24m survival=93%

KIDNEY WEEK 2024

Last value thresholds (all)

Response threshold (g/g)	% response*	N events by 84 months in responders*	84 month survival (95% CI) - Adjusted	Survival difference at 84 months (95% CI)	Hazard ratio (95% CI)
<0.3	22%	5	0.91 (0.87-0.95)	0.29 (0.25-0.34)	0.07 (0.03-0.18)
<0.5	28%	8	0.90 (0.86-0.94)	0.30 (0.25-0.34)	0.09 (0.05-0.19)
<0.7	32%	15	0.87 (0.83-0.92)	0.27 (0.22-0.32)	0.15 (0.09-0.26)
<1.0	40%	25	0.86 (0.82-0.90)	0.28 (0.23-0.33)	0.18 (0.12-0.27)
<1.0 g/g^	39%	24	0.86 (0.82-0.90)	0.28 (0.22-0.33)	0.18 (0.12-0.28
<1.5	50%	39	0.84 (0.80-0.88)	0.29 (0.24-0.34)	0.20 (0.14-0.28)
<1.5 g/g^	45%	30	0.85 (0.81-0.89)	0.30 (0.25-0.35)	0.17 (0.12-0.25)

*Among those with at least 24 months follow-up post index (n=1265)
^+ ≥50% decline from index

KIDNEY WEEK 2023

Last value thresholds (prevalent)

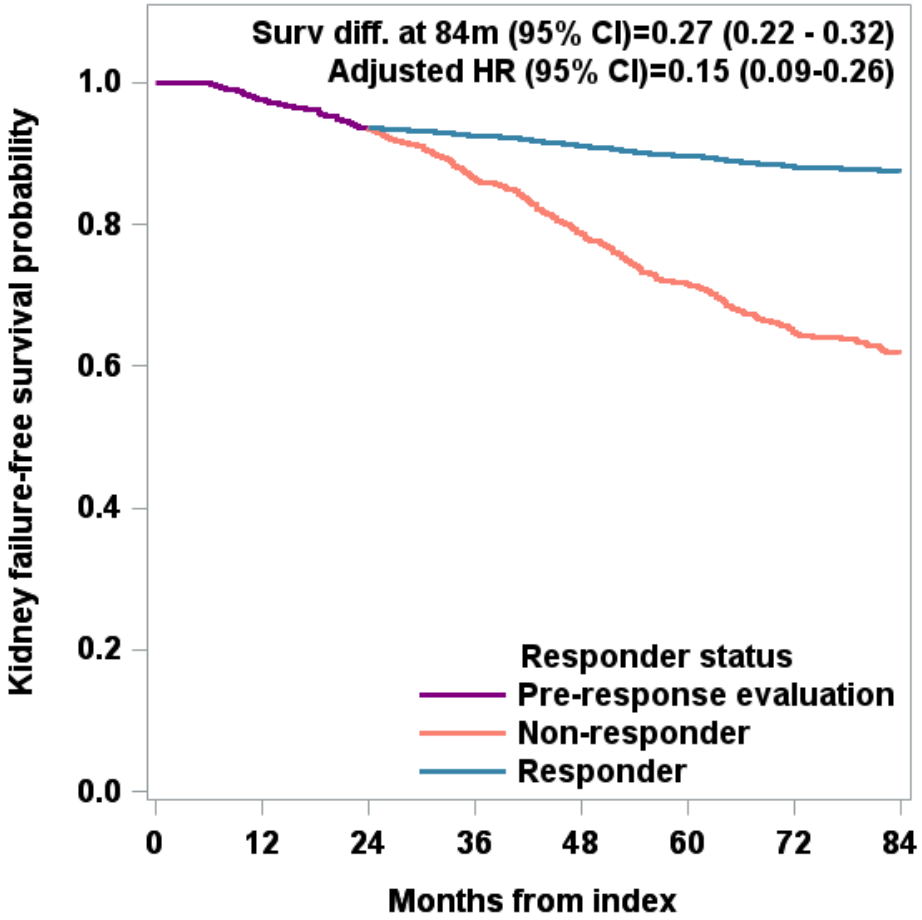
Response threshold (g/g)	% response*	N events by 84 months in responders	84 month survival (95% CI) - Adjusted	Survival difference at 84 months (95% CI)	Hazard ratio (95% CI)
0.3	14%	2	0.89 (0.82-0.94)	0.31 (0.23-0.38)	0.08 (0.02-0.32)
0.5	20%	6	0.84 (0.77-0.93)	0.26 (0.18-0.34)	0.18 (0.08-0.41)
0.7	25%	10	0.82 (0.75-0.90)	0.24 (0.16-0.32)	0.24 (0.13-0.46)
1.0	32%	13	0.82 (0.76-0.90)	0.26 (0.19-0.33)	0.21 (0.12-0.38)
<1.0 g/g^	31%	12	0.83 (0.76-0.90)	0.26 (0.19-0.34)	0.20 (0.11-0.37)
1.5	43%	25	0.79 (0.73-0.86)	0.24 (0.17-0.31)	0.27 (0.18-0.42)
<1.5 g/g^	36%	17	0.81 (0.75-0.88)	0.26 (0.19-0.33)	0.22 (0.13-0.37)

*Among those with at least 24 months follow-up post index (n=751)
^+ ≥50% decline from index

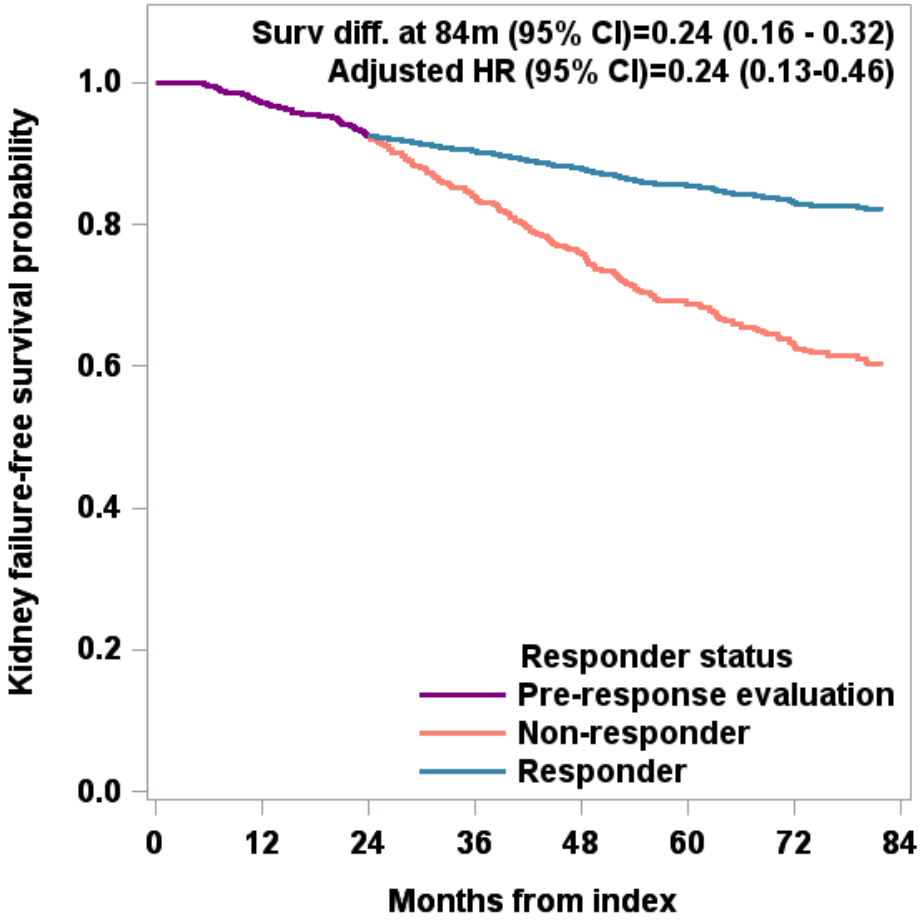
KIDNEY WEEK 2023

Responder: UPCR<0.7 g/g 12-24 months post-index

All

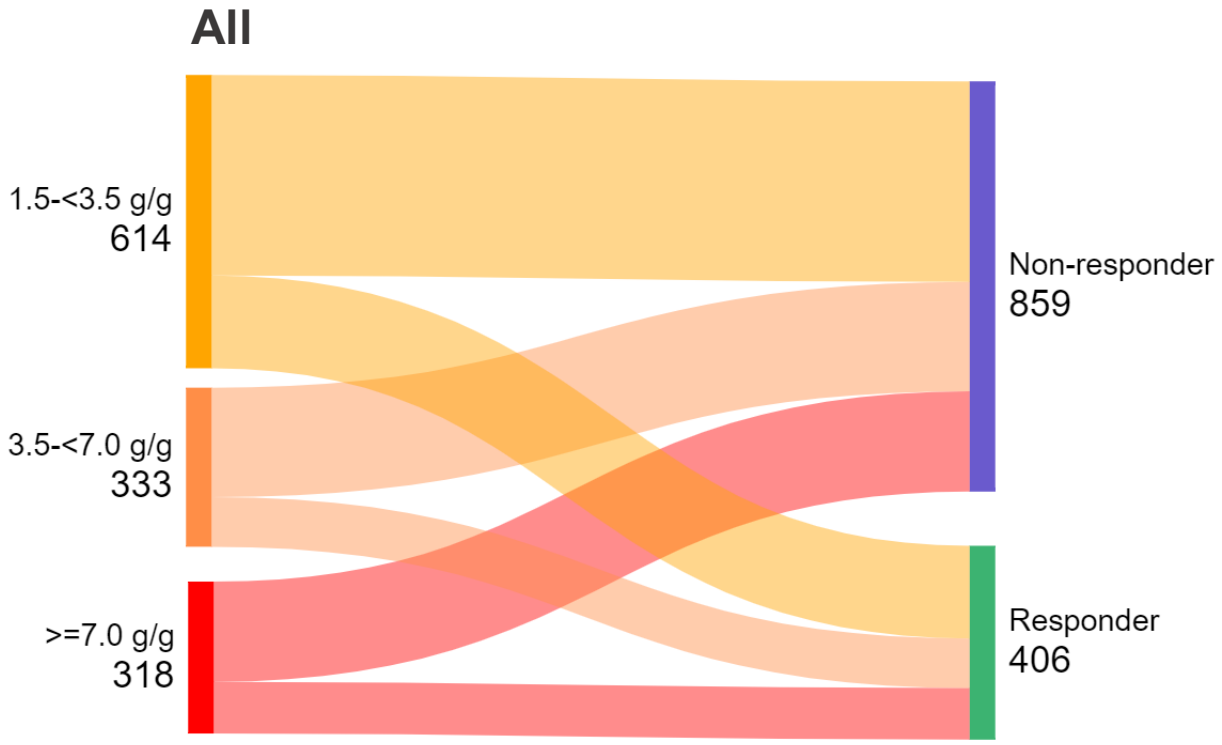


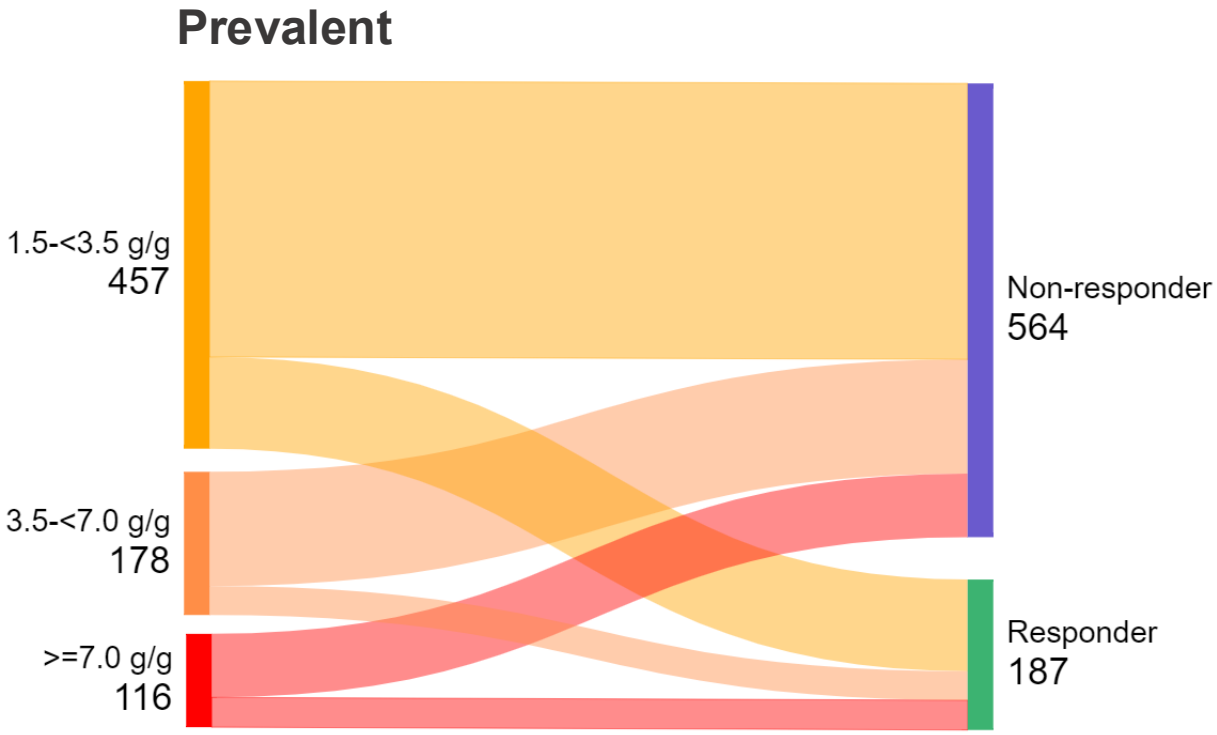
Prevalent



KIDNEY WEEK 2024

Who is achieving responder status (<0.7 g/g)?



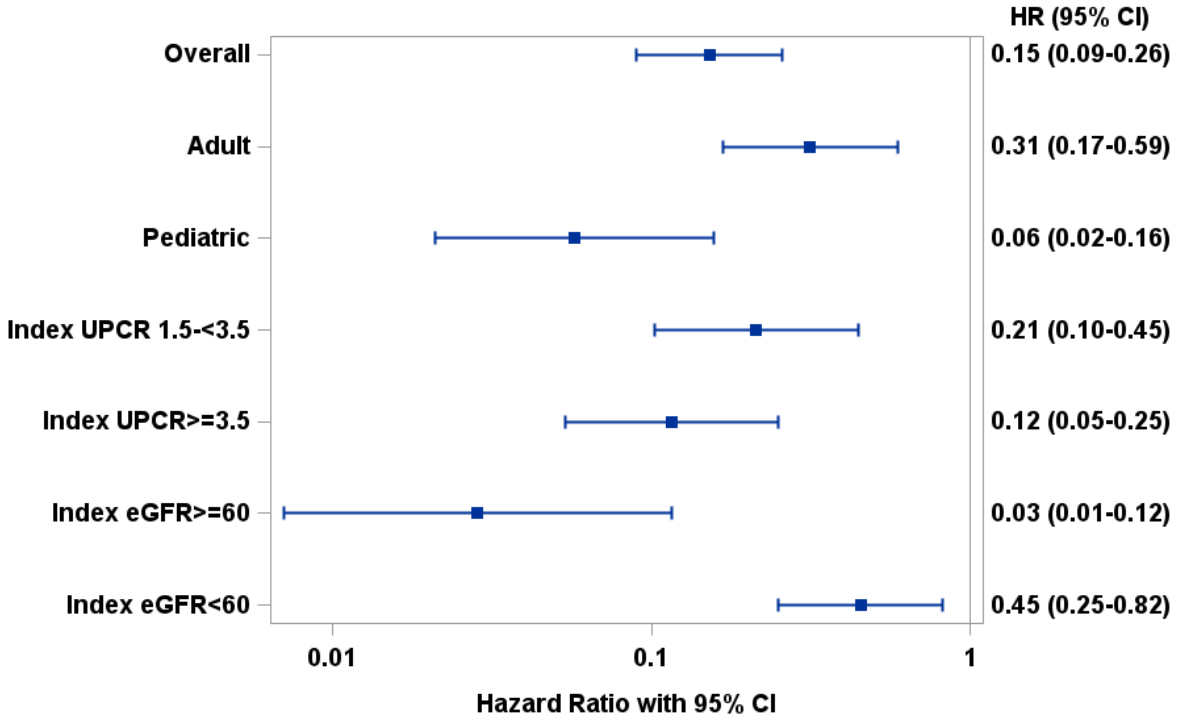


Index UPCR	N (%) Responders (All)	N (%) Responders (Prevalent)
1.5-<3.5 g/g	194/614 (32%)	114/457 (25%)
3.5-<7 g/g	104/333 (31%)	36/178 (20%)
≥7 g/g	108/318 (34%)	37/116 (32%)

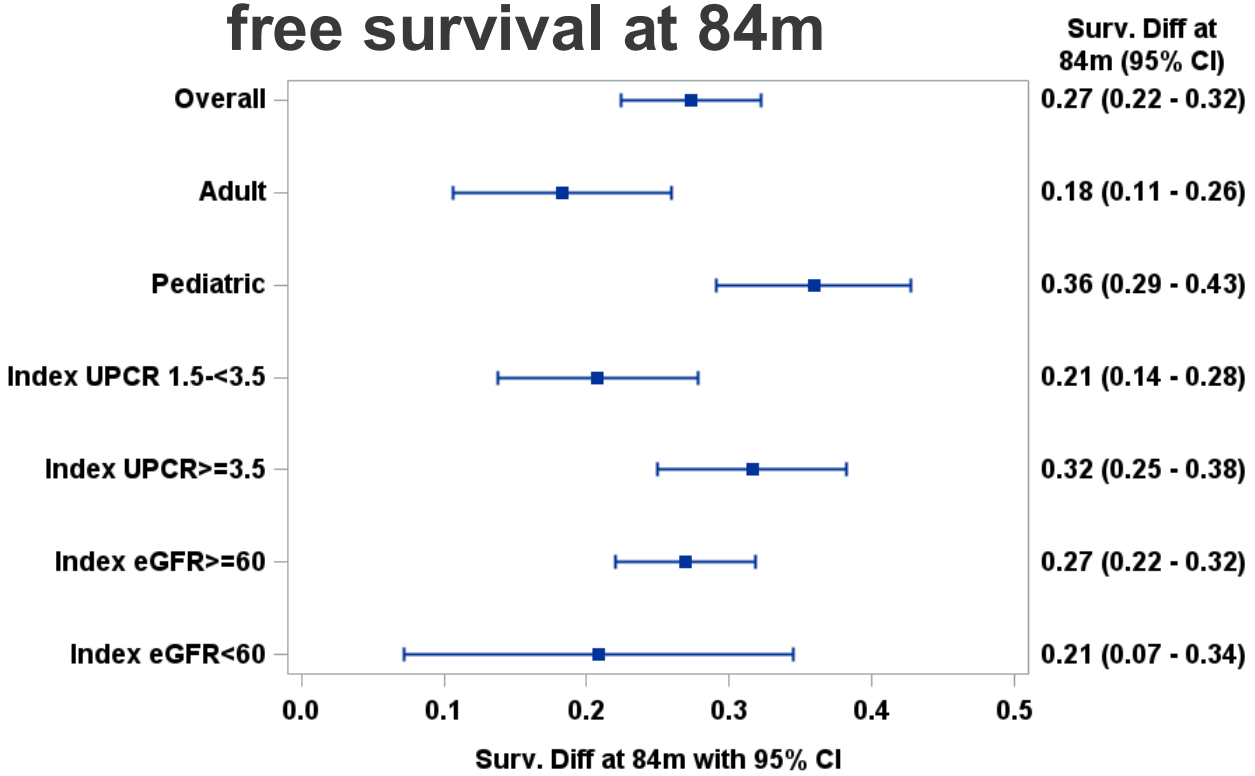
KIDNEY WEEK 2023

Performance across subgroups (<0.7 g/g, all)

Hazard ratios (log scale)



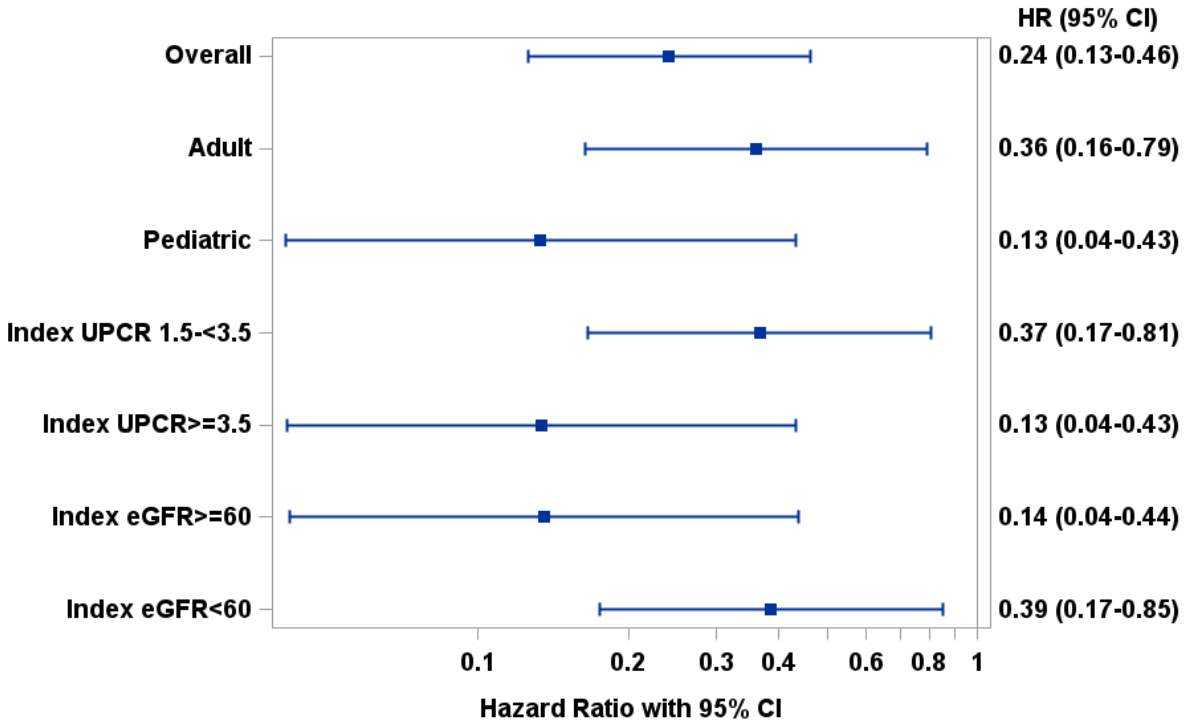
Difference in kidney failure-free survival at 84m



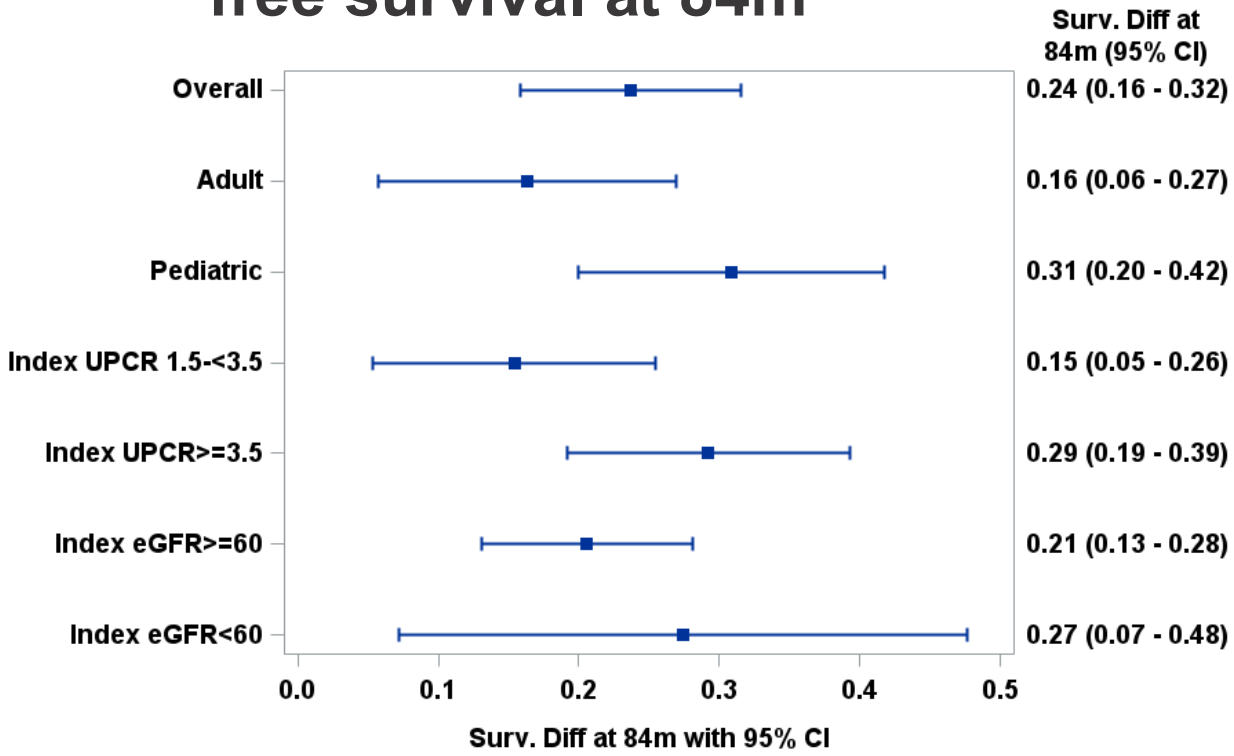
KIDNEY WEEK 2024

Performance across subgroups (<0.7 g/g, prevalent)

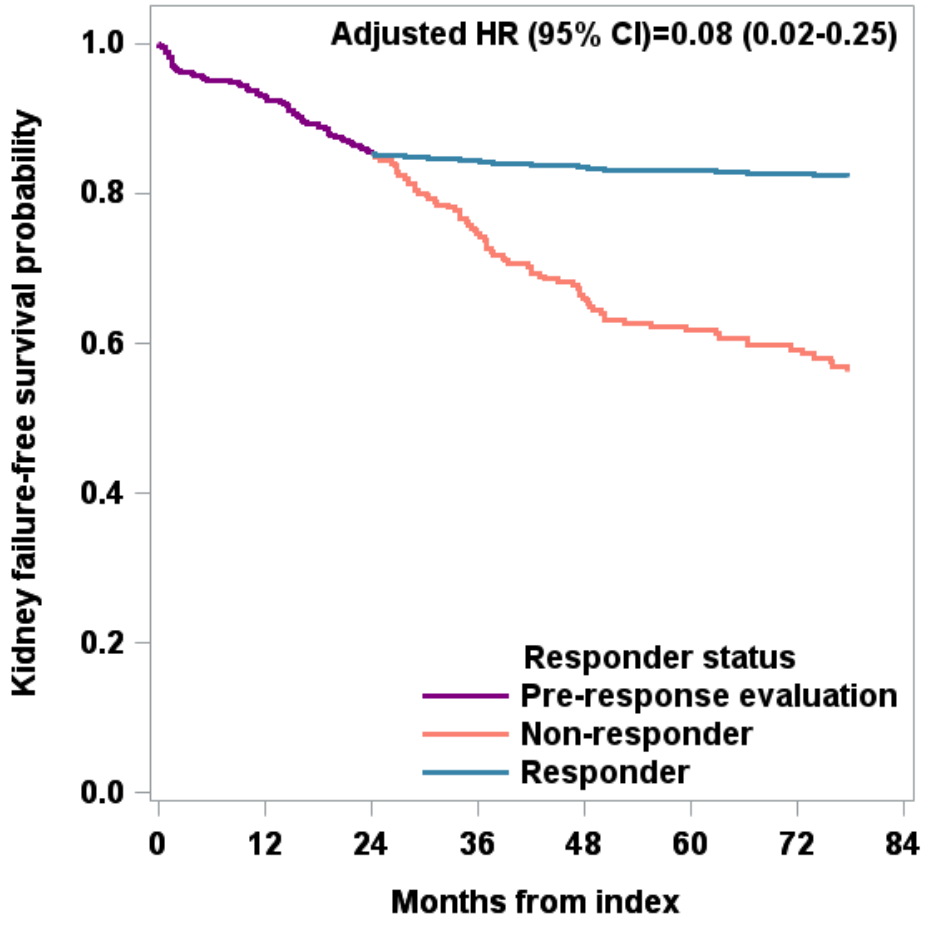
Hazard ratios (log scale)



Difference in kidney failure-free survival at 84m



Independent validation in RaDaR (<0.7 g/g)



Months from index	PARASOL		RaDaR	
	N KF (n=406, 32%)	84m Survival (95% CI) – Adjusted	N KF n=(143, 39%)	84m Survival (95% CI) – Adjusted
36	1 (0%)	0.93 (0.91-0.94)	2 (1%)	0.84 (0.80-0.88)
48	4 (1%)	0.91 (0.89-0.94)	3 (2%)	0.83 (0.79-0.88)
60	10 (2%)	0.90 (0.87-0.93)	3 (2%)	0.83 (0.78-0.88)
72	14 (3%)	0.88 (0.84-0.92)	3 (2%)	0.83 (0.77-0.88)
84	15 (4%)	0.87 (0.83-0.92)	3 (2%)	0.82 (0.76-0.88)

Credit: David Pitcher

Sample size considerations

- **Missing/unknown proteinuria response are considered non-responders**
- **Kidney failures within 24 months post-index are considered non-responders regardless of UPCR**

% response control arm	% response treatment arm	Risk difference	N per group
0.21 (prevalent)	0.36	0.15	190
	0.41	0.20	110
	0.51	0.30	50
0.27 (all)	0.42	0.15	210
	0.47	0.20	120
	0.57	0.30	55

500-1000 per group needed to detect 1ml/min/yr difference in eGFR slope

- Proteinuria risk difference range 0.25-0.30 based on eGFR slopes from CR and FPRE

KIDNEY WEEK 2024

Conclusions

- **Similar behavior across thresholds ranging from 0.7 to 1.5 g/g**
- **Biologically plausible and clinically meaningful**
  - Consider role of 50% decline when index UPCR≥1.5 g/g (built into 0.7 g/g threshold)
  - Response threshold below 0.7 are plausibly similar to complete remission
  - Higher thresholds may also represent substantial biological improvement that slows disease progression for those at highest risk of progression
- **Robust across subgroups**
  - Even sub-nephrotic group
- **Feasible sample sizes**

Acknowledgements

- Margaret Helmuth
- David Pitcher
- Ulysses Diva
- Laura Mariani
- Alex Mercer
- Hailey Desmond
- Contributing registries
- PARASOL co-sponsors
- And many others!