Advancing Kidney Health
Through Optimal Medication Management

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Clinical Approach and Emerging Therapeutics for Focal Segmental Glomerulosclerosis (FSGS)

Glossary of Terms

- **ACEi** = angiotensin converting enzyme inhibitor
- **APOL1** = apolipoprotein L1
- **ARB** = angiotensin receptor blocker
- **CCR2** = C-C chemokine receptor 2P
- **CLCF-1** = cardiotrophin-like cytokine factor
- **CNI** = calcineurin inhibitor
- **CMV** = cytomegalovirus
- **CR** = complete response
- **CSA** = cyclosporin
- **FSGS** = focal segmental glomerulosclerosis
- **FSGS-UC** = focal segmental glomerulosclerosis of undetermined cause
- **FPE** = Foot Process Effacement
- **GFR** = glomerular filtration rate, either estimated (e) or measured (m)
- **JAK-STAT** = Janus kinase-signal transducer and activator of transcription
- **KDIGO** = kidney disease improving global outcomes

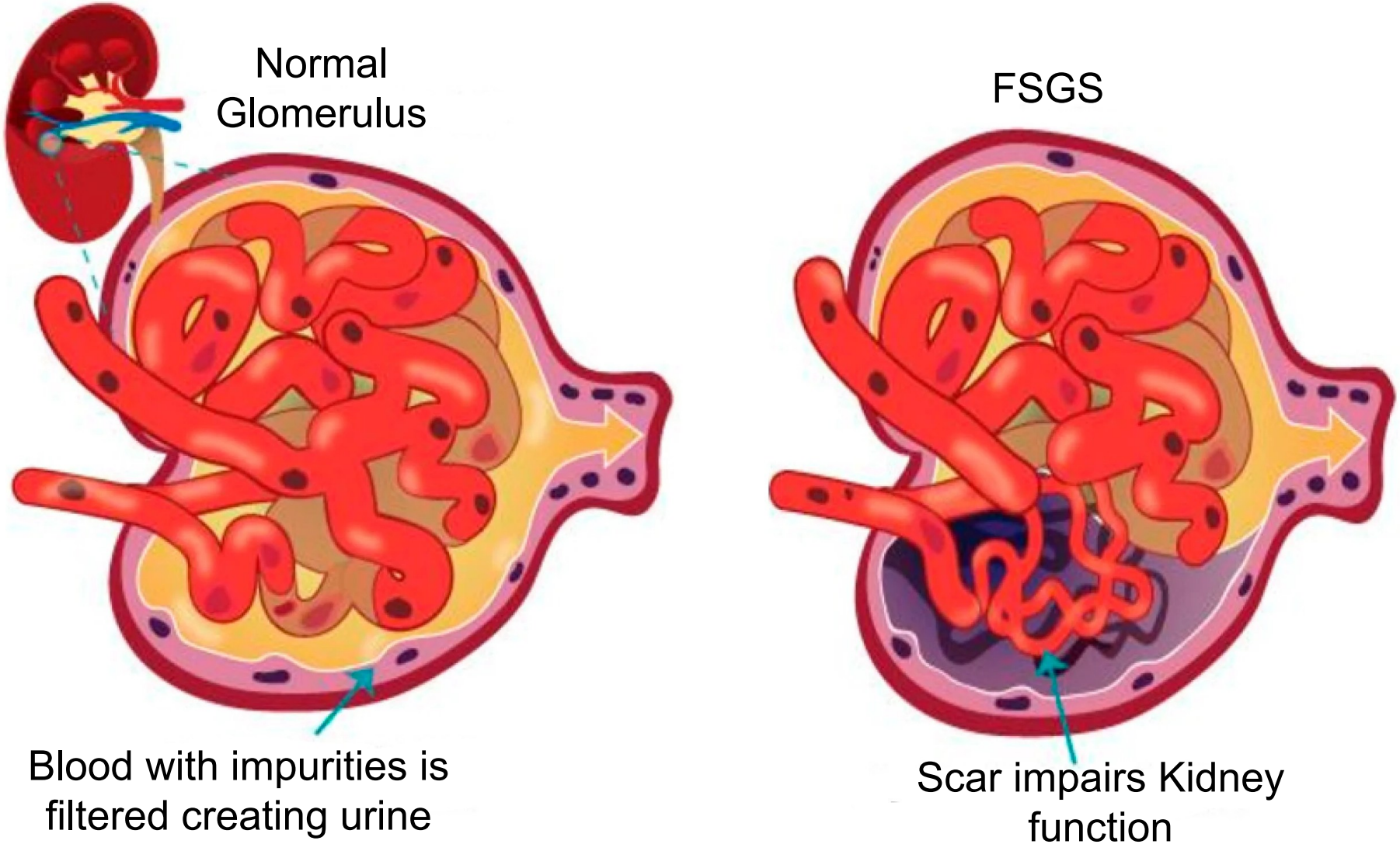
Glossary of Terms

- **KLF15** = Krüppel-like factor 15
- **MCP-1** = monocyte chemoattractant protein-1
- **NFAT** = nuclear factor of activated T-cells
- **PLC** = phospholipase C
- **PR** = partial response
- **RTX** = rituximab
- **MMF** = mycophenolate mofetil
- **sCr** = serum creatinine
- **SGLT-2i** = sodium glucose co-transporter 2 inhibitor
- **suPAR** = soluble urokinase-type plasminogen activator receptor
- **TRPC6** = transient receptor potential canonical 6
- **TNF** = tumor necrosis factor
- **TCR** = T-cell receptor

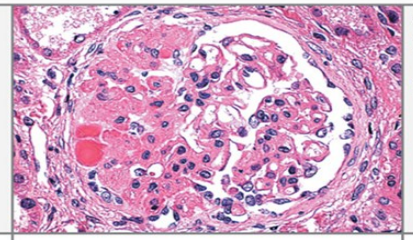
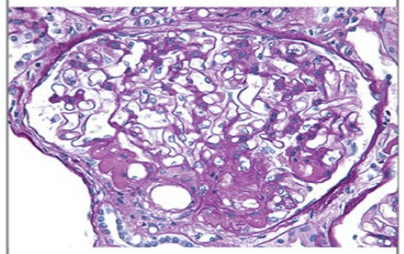
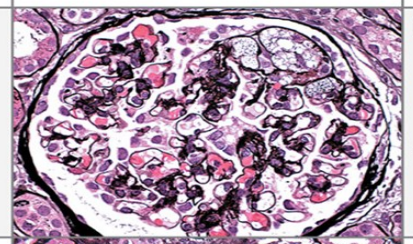
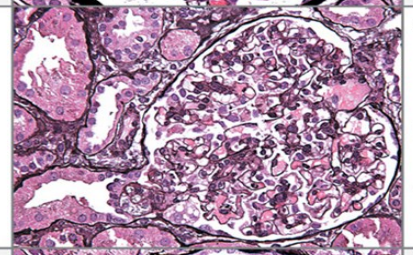
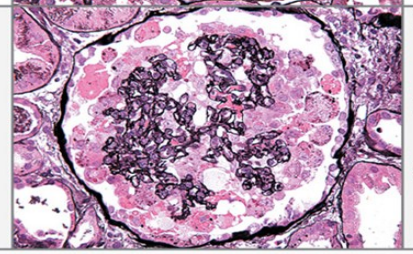
Learning Objectives

- Describe the pathophysiology of FSGS and differentiate between primary, secondary and genetic forms of FSGS.
- Identify key diagnostic findings (UA, kidney biopsy, imaging studies) and the clinical presentation of FSGS (proteinuria, edema, hypertension)
- Identify potential novel therapies based on current understanding of the pathophysiology of FSGS

HISTOPATHOLOGY: Schematic Illustration



HISTOPATHOLOGY: Clinical Subtypes

Histologic Subtype	Glomerular Lesion	Defining Features	Associations	Clinical Features
NOS		The usual generic form of FSGS. FSGS(NOS) does not meet defining criteria for any other variant. Foot-process effacement is variable.	Primary or secondary (including genetic forms and other diverse secondary causes). Cross-sectional studies suggest this is the most common subtype. Other variants can evolve into FSGS (NOS) over time.	May present with the nephrotic syndrome or subnephrotic proteinuria.
Perihilar		Perihilar hyalinosis and sclerosis involving the majority of glomeruli with segmental lesions. Perihilar lesions are located at the glomerular vascular pole. In adaptive FSGS, there is usually glomerular hypertrophy (glomerulomegaly). Foot-process effacement is relatively mild and focal, which probably reflects the heterogeneous adaptive responses of glomeruli.	Common in adaptive FSGS associated with obesity, elevated lean body mass, reflux nephropathy, hypertensive nephrosclerosis, sickle cell anemia, and renal agenesis. Predisposition for vascular pole is probably due to normally increased filtration pressures at the proximal afferent end of glomerular capillary bed, which are heightened under conditions of compensatory demand and vasodilatation of the afferent arteriole.	In adaptive FSGS, patients are more likely to present with subnephrotic proteinuria and normal serum albumin levels.
Cellular		Expansile segmental lesion with endocapillary hypercellularity, often including foam cells and infiltrating leukocytes, with variable glomerular epithelial-cell hyperplasia. There is usually severe foot-process effacement.	Usually primary, but also seen in a variety of secondary forms. This is the least common variant. It is thought to represent an early stage in the evolution of sclerotic lesions.	Usually presents with the nephrotic syndrome.
Tip		Segmental lesion involving the tubular pole, with either adhesion to tubular outlet or confluence of podocytes and tubular epithelial cells. Compared with other variants, it has the least tubular atrophy and interstitial fibrosis. There is usually severe foot-process effacement.	Usually primary. Probably mediated by physical stresses on the paratubular segment owing to the convergence of protein-rich filtrate on the tubular pole, causing shear stress and possible prolapse.	Usually presents with abrupt onset of the nephrotic syndrome. More common in white race. Best prognosis, with highest rate of responsivity to glucocorticoids and lowest risk of progression.
Collapse		Implosive glomerular-tuft collapse with hypertrophy and hyperplasia of the overlying visceral epithelial cells. Hyperplastic glomerular epithelial cells may fill the urinary space, resembling crescents. Severe tubular injury and tubular microcysts are common. There is usually severe foot-process effacement.	Primary or secondary to Viruses: HIV-1, parvovirus B19, SV40, EBV, CMV, hemophagocytic syndrome Drugs: pamidronate and interferon Vaso-occlusive disease: atheroemboli, calcineurin inhibitor nephrotoxicity, and chronic allograft nephropathy	Most aggressive variant of primary FSGS with black racial predominance and severe nephrotic syndrome. Worst prognosis, with poor responsivity to glucocorticoids and rapid course to renal failure.

D'Agati VD, et al. NEJM 2011 PMID 22187987

Clinical Presentation

- Urinalysis and proteinuria, asymptomatic: 100%
  - Dipstick
  - Quantitative testing
  - Hematuria: 30-50%
  - Total protein vs albuminuria
- Edema and nephrotic syndrome: 50-75%
- Hypertension: 40-50%
- CKD: 25-50%

Case Study Example

Patient

A 42-year old male presents with 3+ proteinuria on dipstick testing performed as part of an annual work physical examination. He feels well and denies headaches, vomiting or diarrhea.

PMH

- Hypertension x 5 years
- Social History: African-American ancestry

Medications

Labs/Vitals

Vital	Today	3 mo ago	6 mo ago
BP	146/92 mm Hg		
Weight (lbs)			
Lab	**Today**	**3 mo ago**	**6 mo ago**
serum creatine	1.4 mg/dl		
albumin	3.1 g/dl		
UPCR	5.2		

What additional laboratory testing should be considered?

FSGS: Diagnosis

Kidney

- Digital pathology: computer assisted analysis of tissue

Genetic Testing

- Pediatric patients
- Positive Family history
- Extrarenal findings (eye, ear, brain)

Imaging Studies

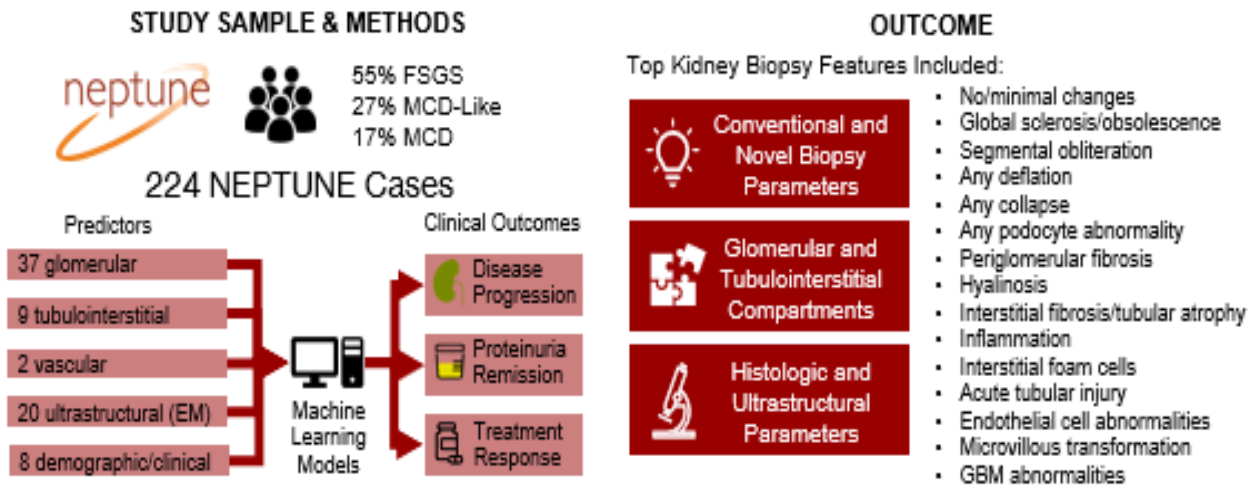
- Ultrasound: kidney size
- MRI: degree of fibrosis

FSGS: Biopsy

Kidney biopsy features most predictive of clinical outcomes in the spectrum of minimal change disease and focal segmental glomerulosclerosis

JASN

JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY



Predictive discrimination of 0.901 for progression, 0.849 for remission, and 0.812 for treatment response. The most predictive descriptors of outcomes included:
Global Sclerosis Or Segmental Sclerosis And IFTA
Adhesion, Interstitial Foam Cells, Deflation, Collapse, Periglomerular Fibrosis, Mononuclear WBCs, Endothelial Cell Abnormalities, Microvillous Transformation, Acute Tubular Injury

NEPTUNE FSGS_MCD Pathology Scoring Report

	Overall Clinical Description (if known)	Answer Choices
A1	Patient age (years)	#
A2	Patient sex	□ Female □ Male
A3	Patient race	[drop down, check all that apply, or free text]
A4	Family history of kidney disease	[free text]
A5	UPCR at current biopsy	# [drop down: mg/mg, mg/g, mg/mmol]
A6	eGFR at current biopsy (mL/min/1.73m^2)	#
A7	Additional notes and comments on clinical description	[free text]
	Overall Pathology Description	
B1	Disease category	□ FSGS □ MCD □ MCD-Like □ Other:
B2	Number of biopsy cores	#
B3	Number of glomeruli	#
	Glomerular Histologic Descriptors	
C1	No or minimal changes*	# or %
C2	Global sclerosis or obsolescence*	# or %
C3	Segmental obliteration*	# or %
C4	Deflation*	# or %
C5	Collapse*	# or %
C6	Podocyte abnormalities*	# or %
C7	Periglomerular fibrosis*	# or %
C8	Glomerular hyalinosis*	# or %
C9	Additional notes and comments on glomeruli	[free text]
	Tubular Histologic Descriptors	
D1	Tubular atrophy*	%
D2	Acute tubular injury*	%
D3	Additional notes and comments on tubules	[free text]
	Interstitial Histologic Descriptors	
E1	Interstitial fibrosis*	%
E2	Interstitial inflammation*	%
E5	Interstitial eosinophils	□ Present □ Absent
E3	Interstitial foam cells*	%
E4	Interstitial edema	□ Present □ Absent
E6	Additional notes and comments on interstitium	[free text]
	Vascular Histologic Descriptors	
F1	Arteriosclerosis	□ None □ 1+/mild □ 2+/moderate □ 3+/severe
F2	Arteriolar hyalinosis	□ None □ 1+/mild □ 2+/moderate □ 3+/severe
F3	Additional notes and comments	[free text]
	Ultrastructural Descriptors	
G1	Number of glomeruli examined ultrastructurally	#
G2	Foot process effacement (%)	□ 0-10 □ 11-25 □ 26-50 □ 51-75 □ >75%
G3	Microvillous transformation*	□ None □ ≤50% (focal) □ >50% (diffuse)
G4	Condensation of the actin-based cytoskeleton	□ None □ ≤50% (focal) □ >50% (diffuse)
G5	Podocyte detachment with newly formed matrix	□ Present □ Absent
G6	Endothelial cell abnormalities*	□ Present □ Absent
G7	Glomerular basement membrane abnormalities*	□ None □ ≤50% (focal) □ >50% (diffuse)
G8	Electron densities or hyaline material	□ Present □ Absent
G9	Additional notes and comments	[free text]

Zee et al . JASN, 2022 PMID 35581011 doi: 10.1681/ASN.

FSGS: Classification

HISTOLOGY

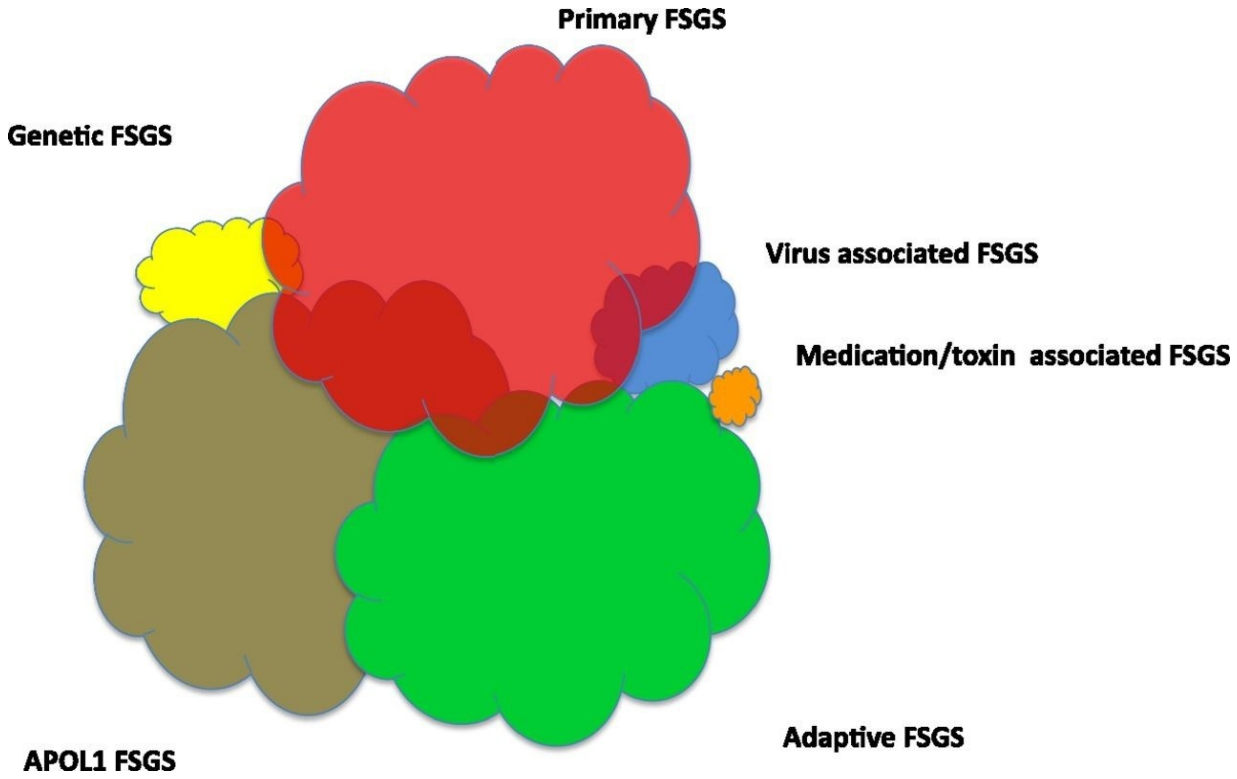
(Illustrations in previous slide)

NOS

Tip

Cellular

Collapsing

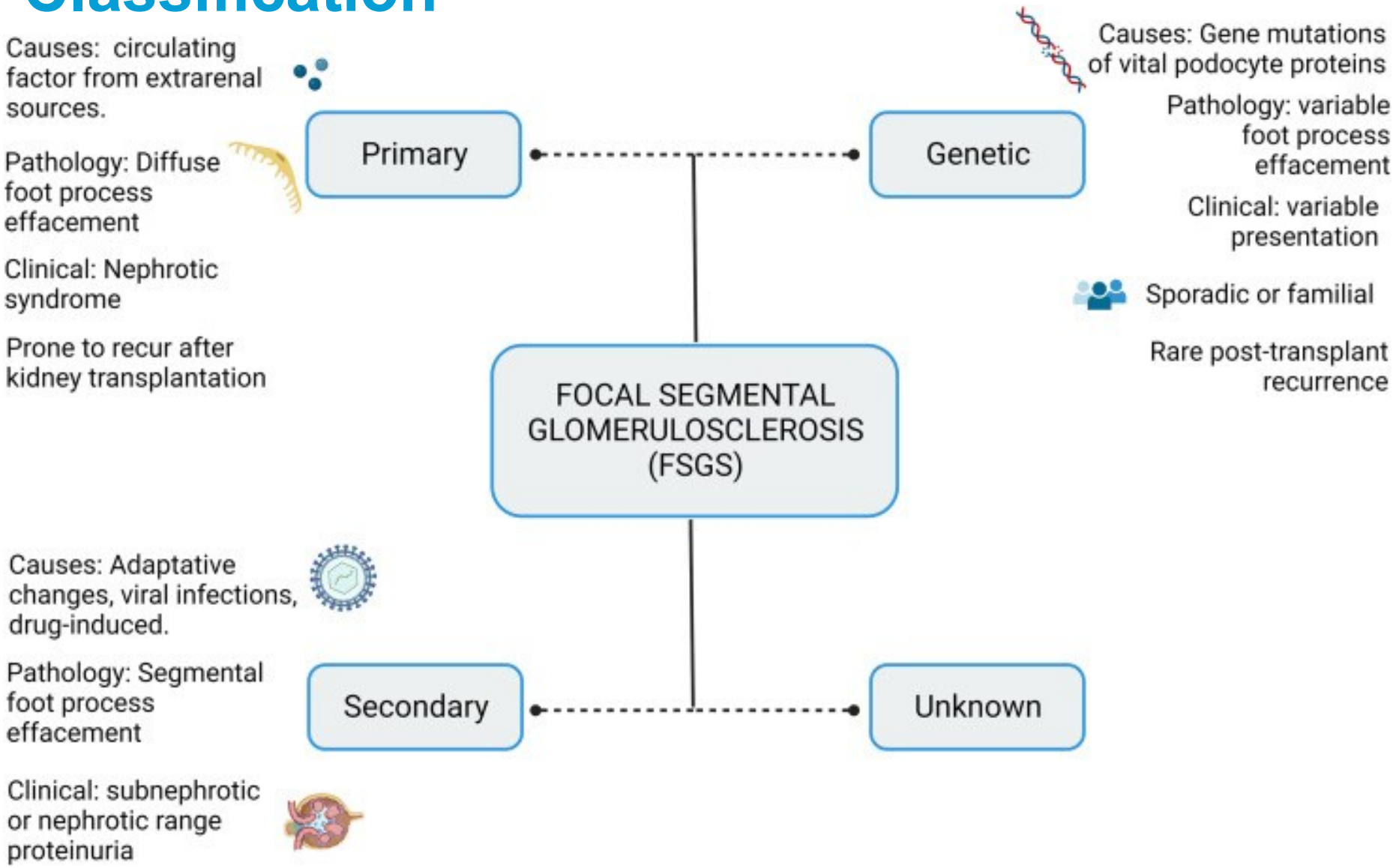


KDIGO Guidelines

- Primary Immune
- Primary Genetic
- Secondary
- Unknown

Rosenberg AZ, et al. CJASN 2017 PMID 28242845

FSGS: Classification



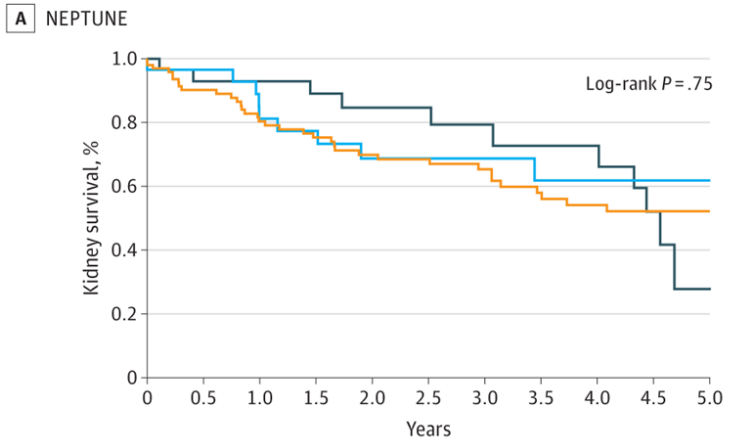
FSGS Prognosis: Age

The guarded prognosis in patients of all ages highlights the need to:

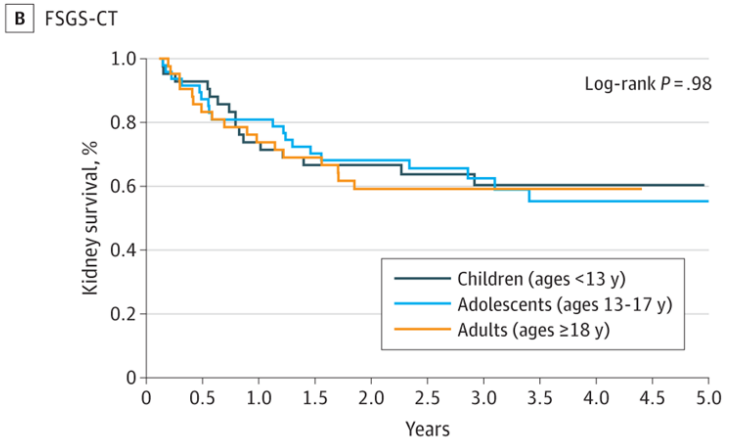
- Develop safe and effective therapies for all patients with FSGS
- Enroll adult AND pediatric patients in future clinical trials

Gipson DS, et al. JAMA Netw Open 2022 PMID 36006643

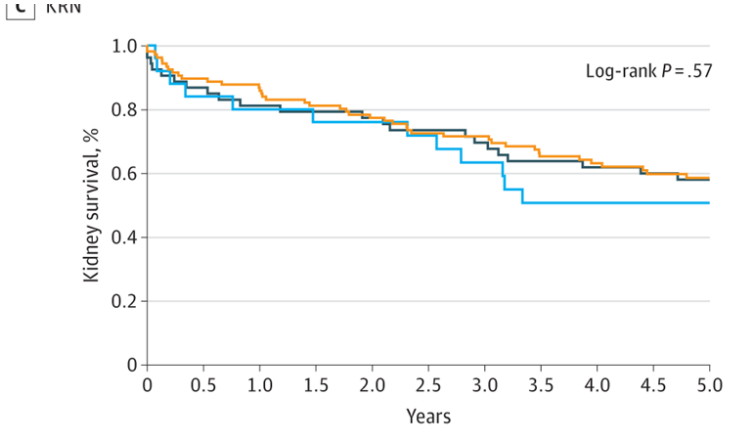
Time to ESKD or 40% Reduction in eGFR by Age



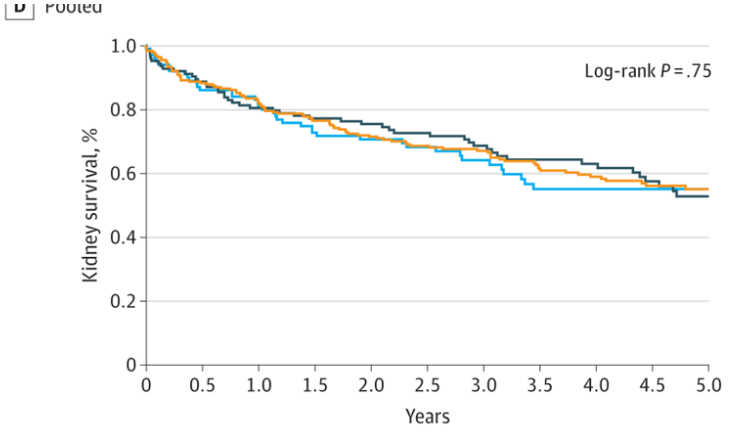
NEPTUNE:
n: 166, 56 events



FSGS-CT:
n: 132, 52 events



Kidney Research Network:
n: 184, 121 events

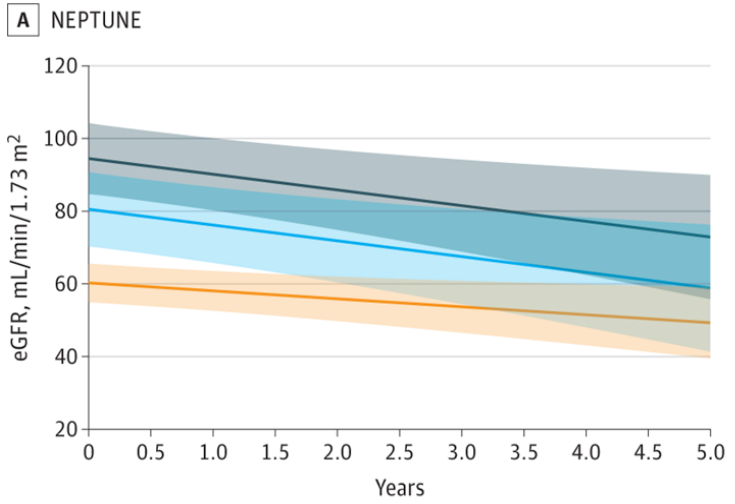


Pooled
n: 482, 229 events

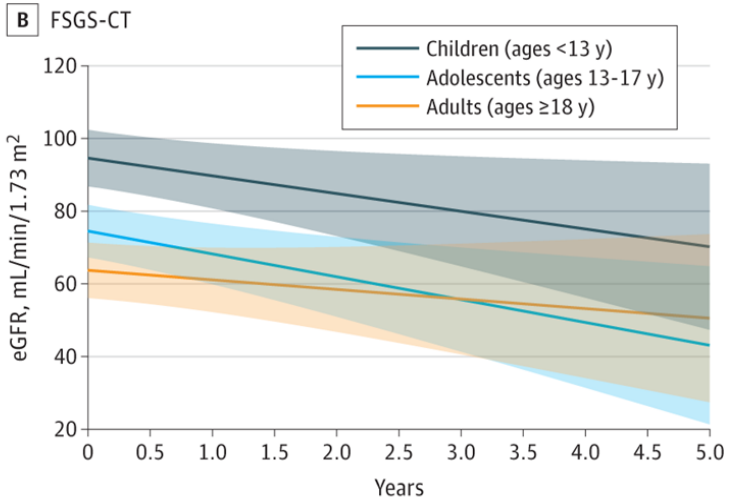
FSGS Prognosis: Age Linear Mixed-Effects Models of eGFR slope

Key Point

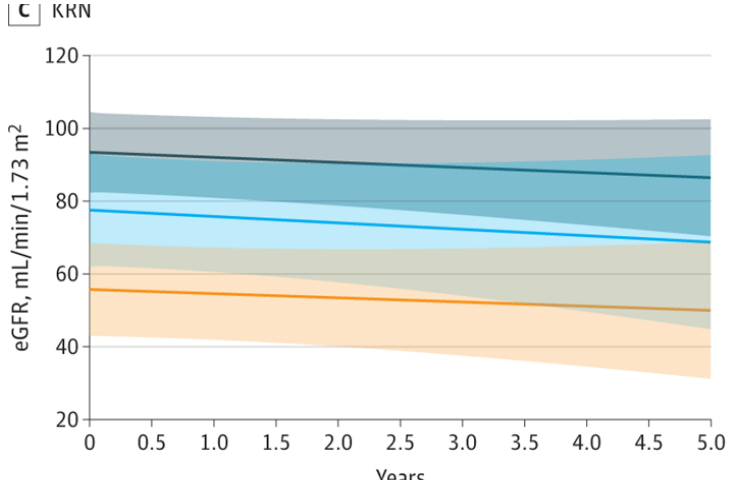
The disease trajectory in patients with FSGS is similar regardless of their age at the time of diagnosis.



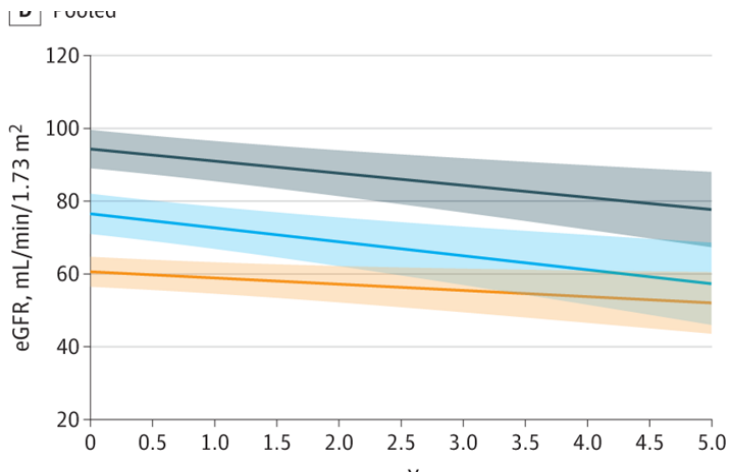
NEPTUNE:
n: 166, 1827 observations



FSGS-CT:
n: 132, 1992 observations



Kidney Research Network:
n: 184, 3082 observations

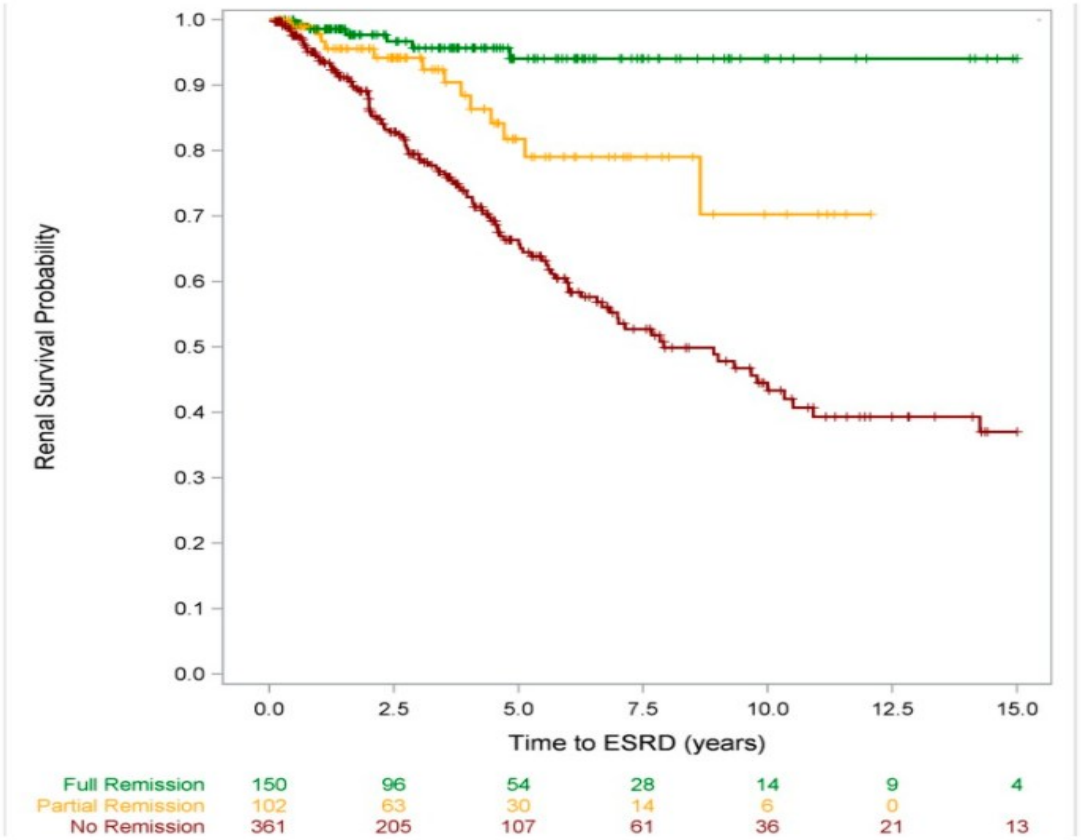


Pooled:
n: 482, 6901 observations

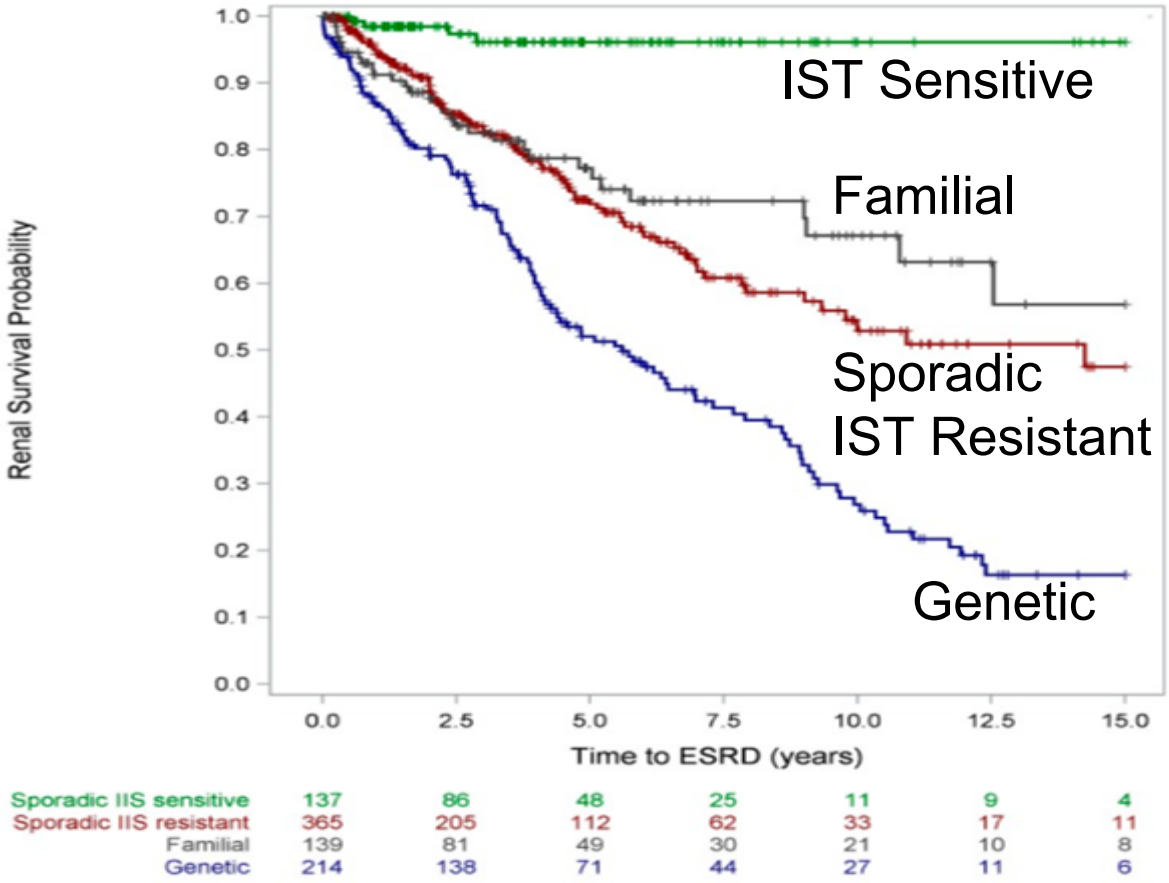
Gipson DS, et al. JAMA Netw Open 2022 PMID 36006643

FSGS Prognosis: Response to Treatment

FSGS Renal Survival by Proteinuria Outcome: CR vs PR vs NR



FSGS Renal Survival by Disease Category: Sporadic IST Sensitive vs Sporadic IST Resistant vs Familial vs Genetic



Population: Age > 3m to < 20 yrs; IPNA

Trautmann A, et al. JASN 2017. PMID 28566477

Clinical Presentation: High Risk Groups

Premature/LBW:

- Congenital compromise in nephron endowment

Reduced Renal Mass:

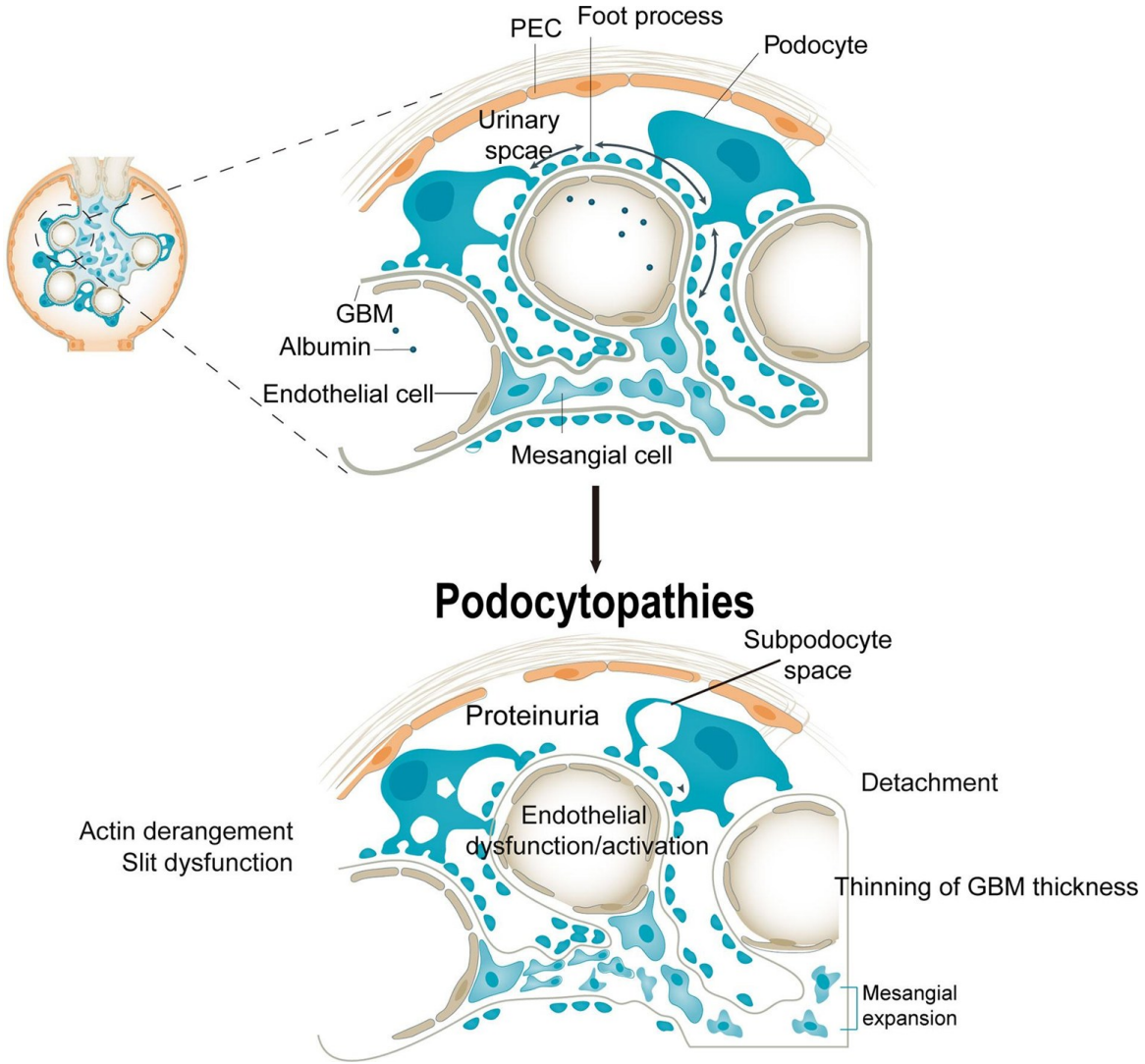
- Treatment of serious diseases

APOL1:

- Disease modifier

Hingorani S, et al. Pediatr Nephrol 2023 PMID 37140708; Abellada AMP. FP Essent 2024 PMID 39163011; Friedman DJ, et al. CJASN 2021 PMID 32616495

Pathophysiology: Central Role of the Podocyte

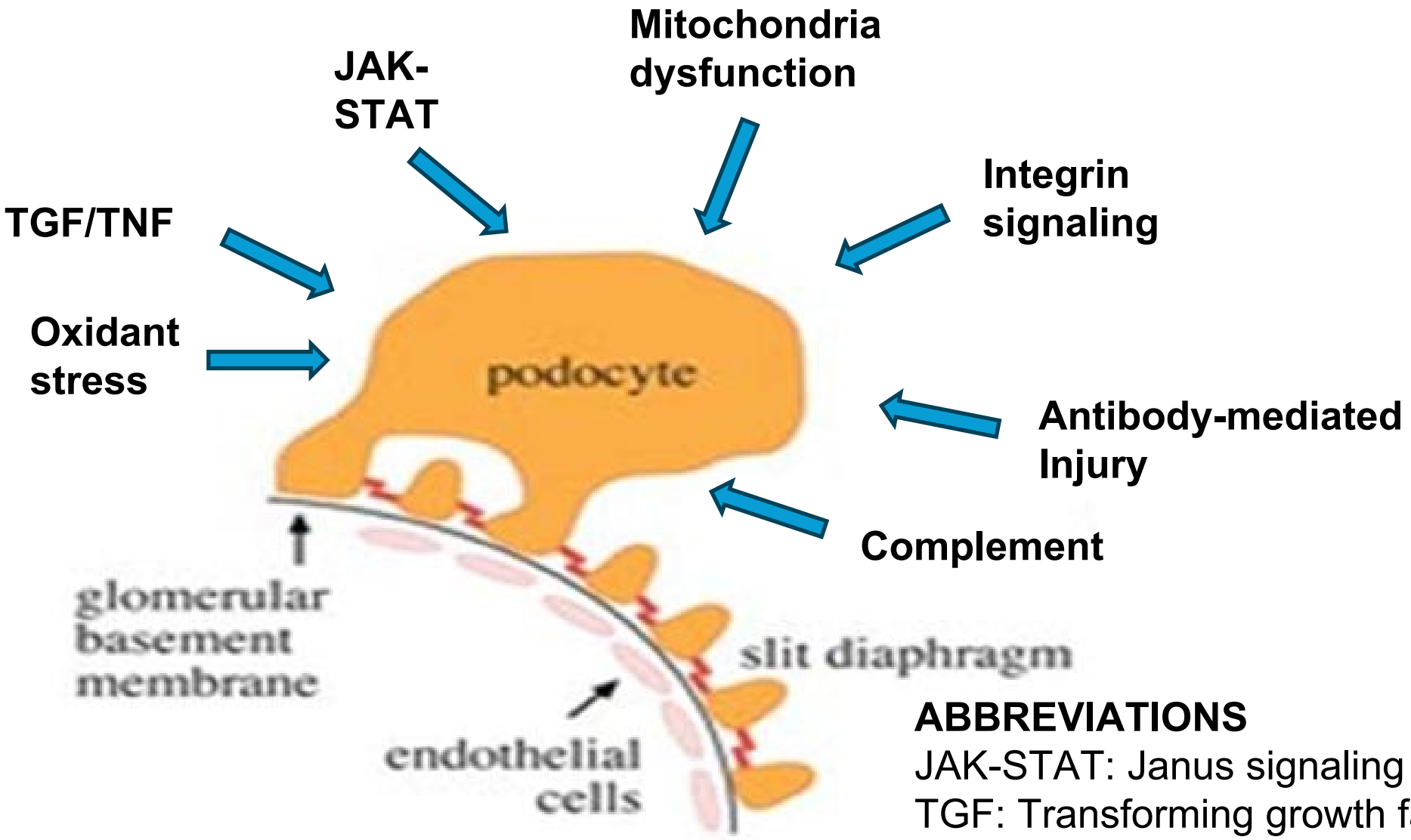


Key Point

- FSGS originates with injury to the podocyte.
- Leads to:
  - Detachment of the glomerular visceral epithelial cell from the glomerular basement membrane
  - Proteinuria, fibrosis, and kidney failure.

Hyperfiltration Glomerular hypertrophy → **CKD Kidney Failure**

Pathophysiology: Mechanisms of Injury



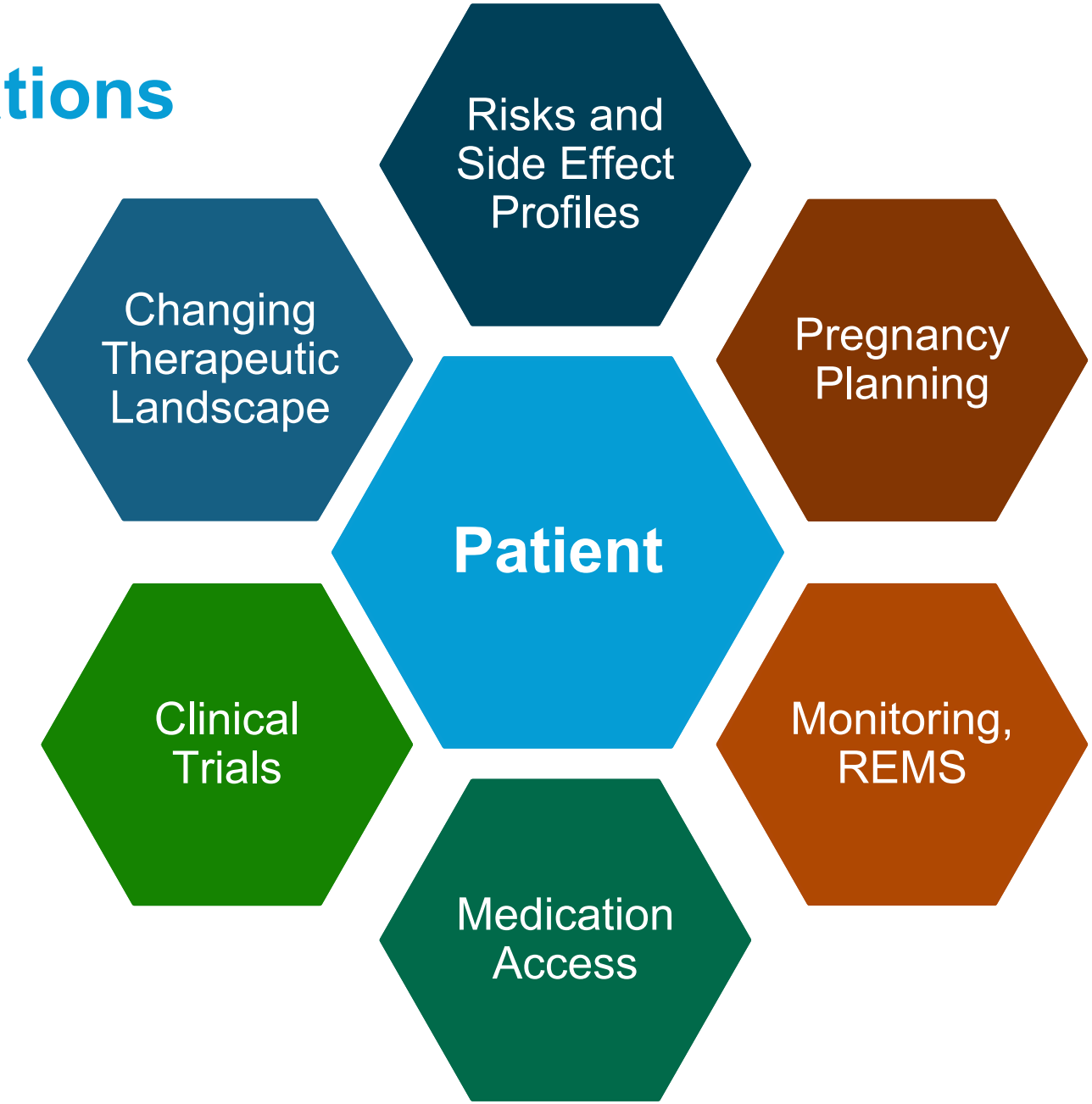
ABBREVIATIONS

JAK-STAT: Janus signaling

TGF: Transforming growth factor

TNF: tumor necrosis factor

Considerations



Embryo/fetal toxicity

- Avoid atrasentan, sparsentan, RASi, and SGLT2i
- Unknown risk with budesonide and iptacopan

REMS

- Sparsentan: LFTs
- Iptacopan: vaccines +/- antibiotic prophylaxis, infection risk

FSGS: Heterogeneous disease entity

1

Clinical Phenotype / Histology
Biobank profile at time of presentation

SSNS | **FSGS/ MCD** | **MGN**

Prospective clinical phenotype

Molecular phenotype

2

Definition of disease subtypes:

- Molecular-Clinical Histological Predictors and Therapeutic targets

FSGS

MCD

1.

2. Cluster

3.

3

Initiation of therapeutic trials in functionally defined patient cohorts

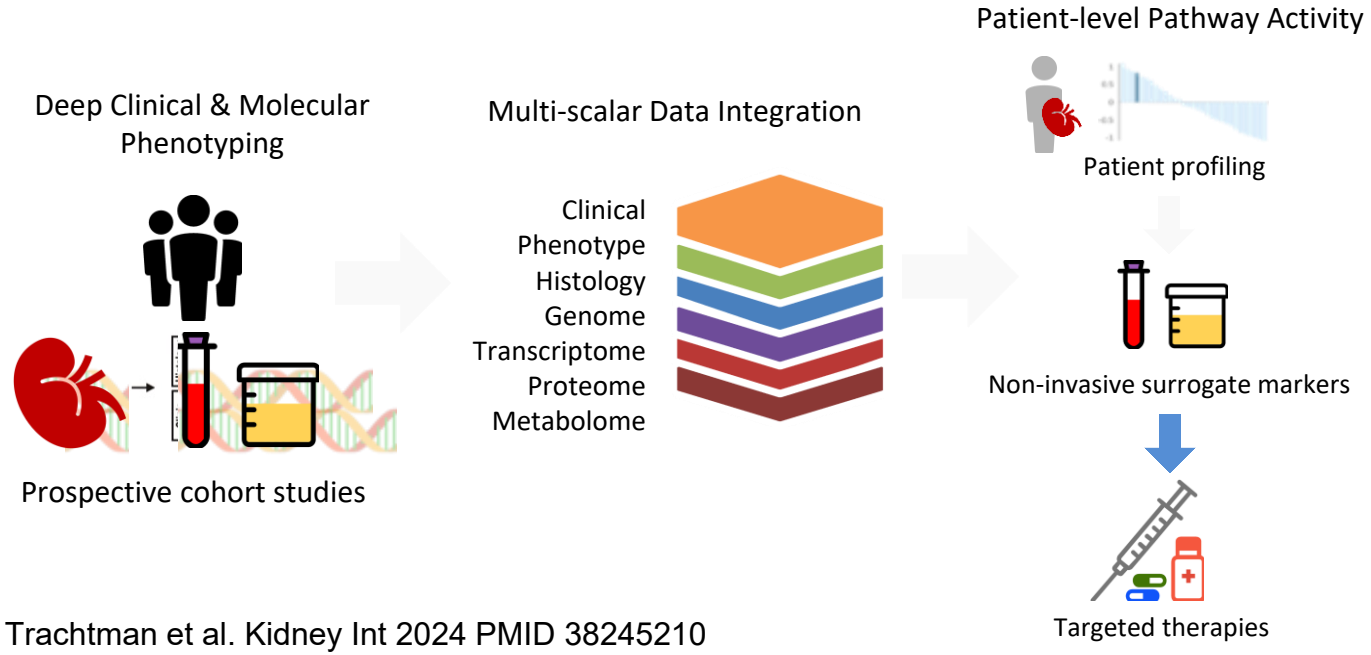
neptune

NEPTUNE Match

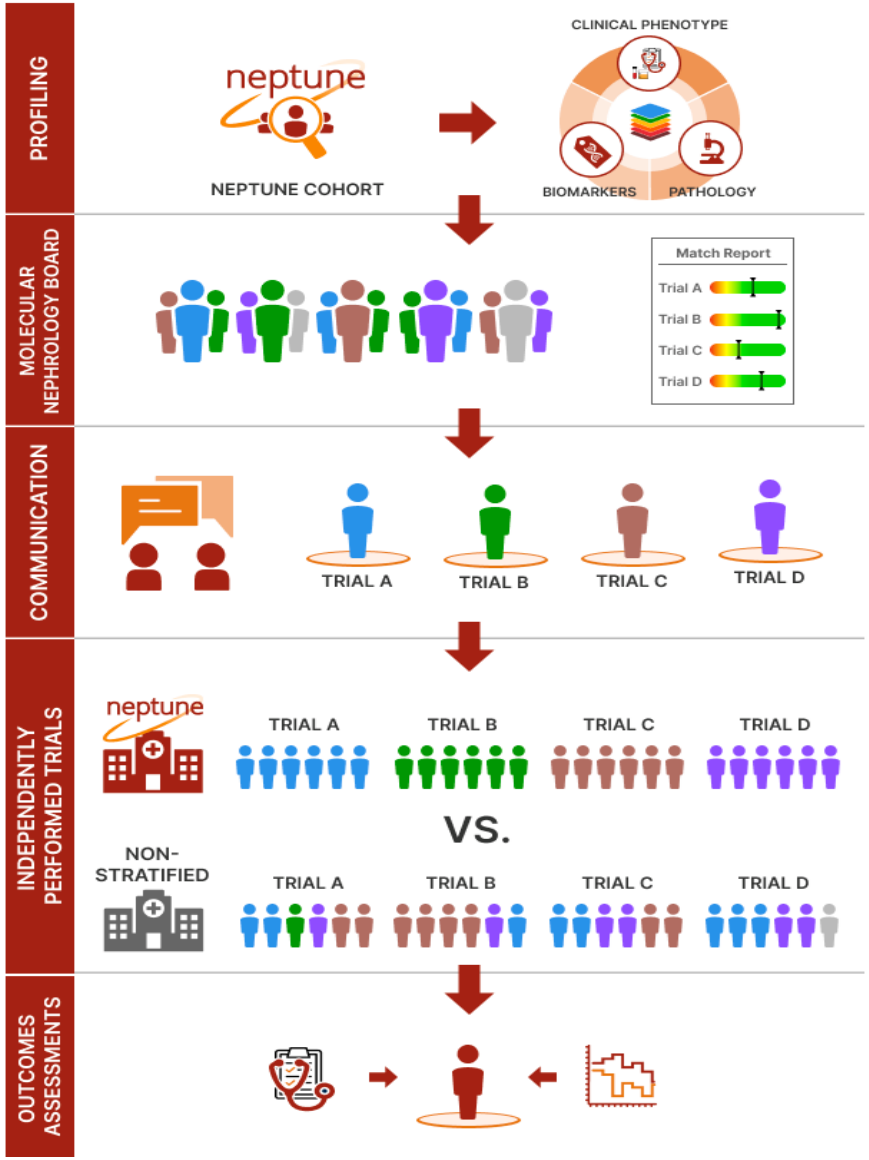
NEPTUNE Match: Mechanisms of injury and heterogeneity

Defining Molecular Subgroups in FSGS to Optimally Match Patient with Candidate Treatment

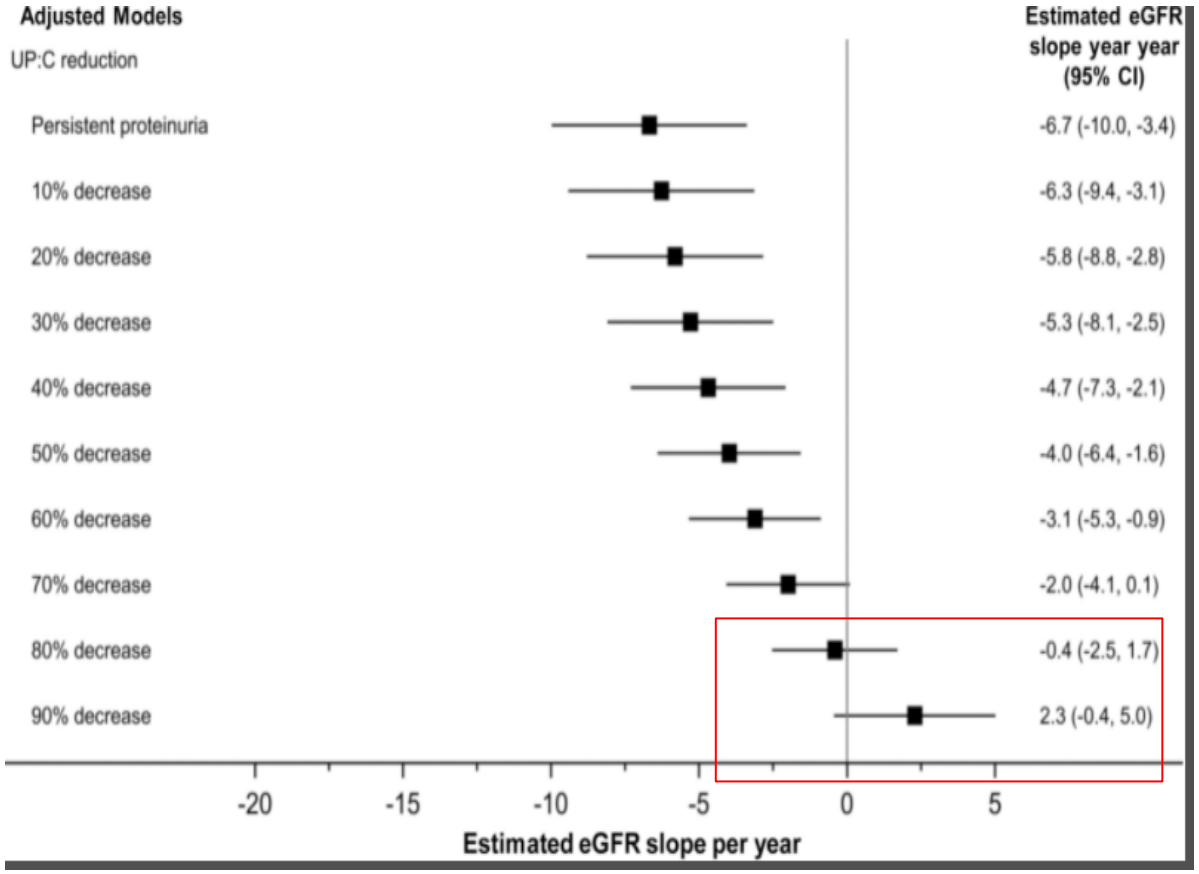
Right Trial for the Right Patient at the Right Time



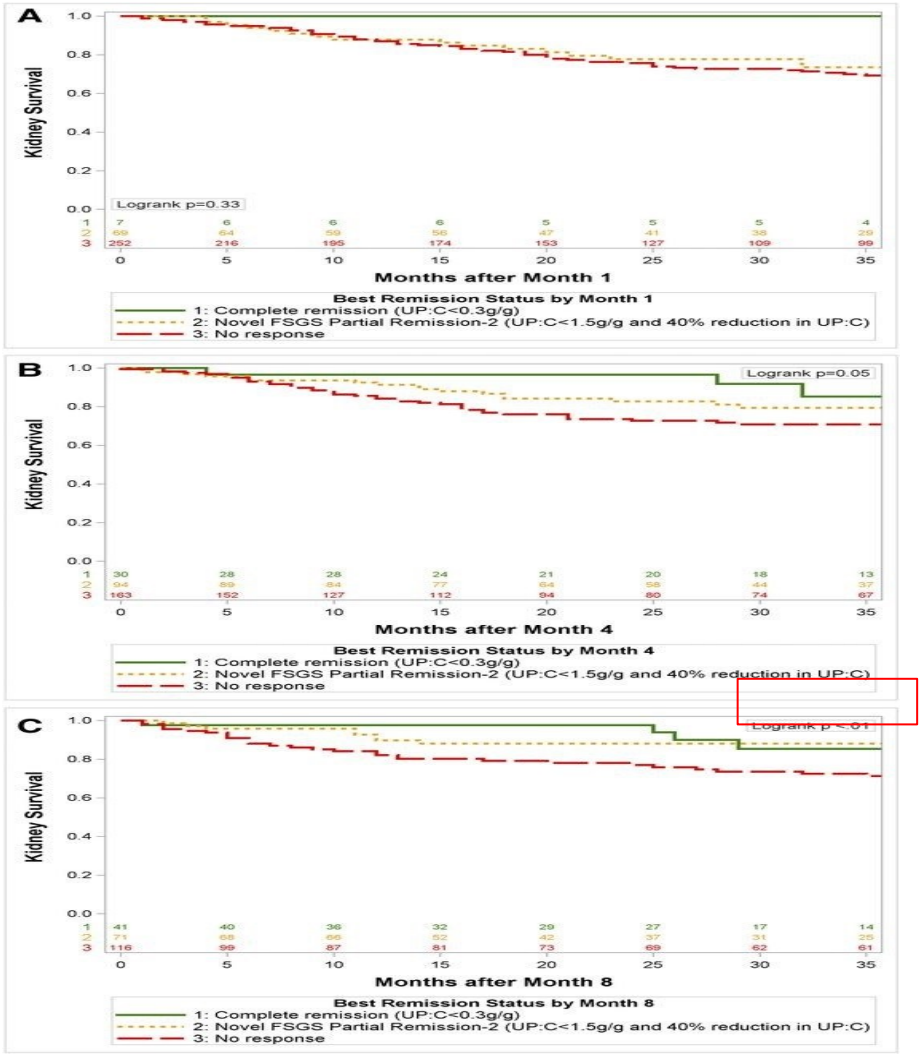
Trachtman et al. Kidney Int 2024 PMID 38245210



Pathophysiology: Impact of Proteinuria Preservation and Kidney Function



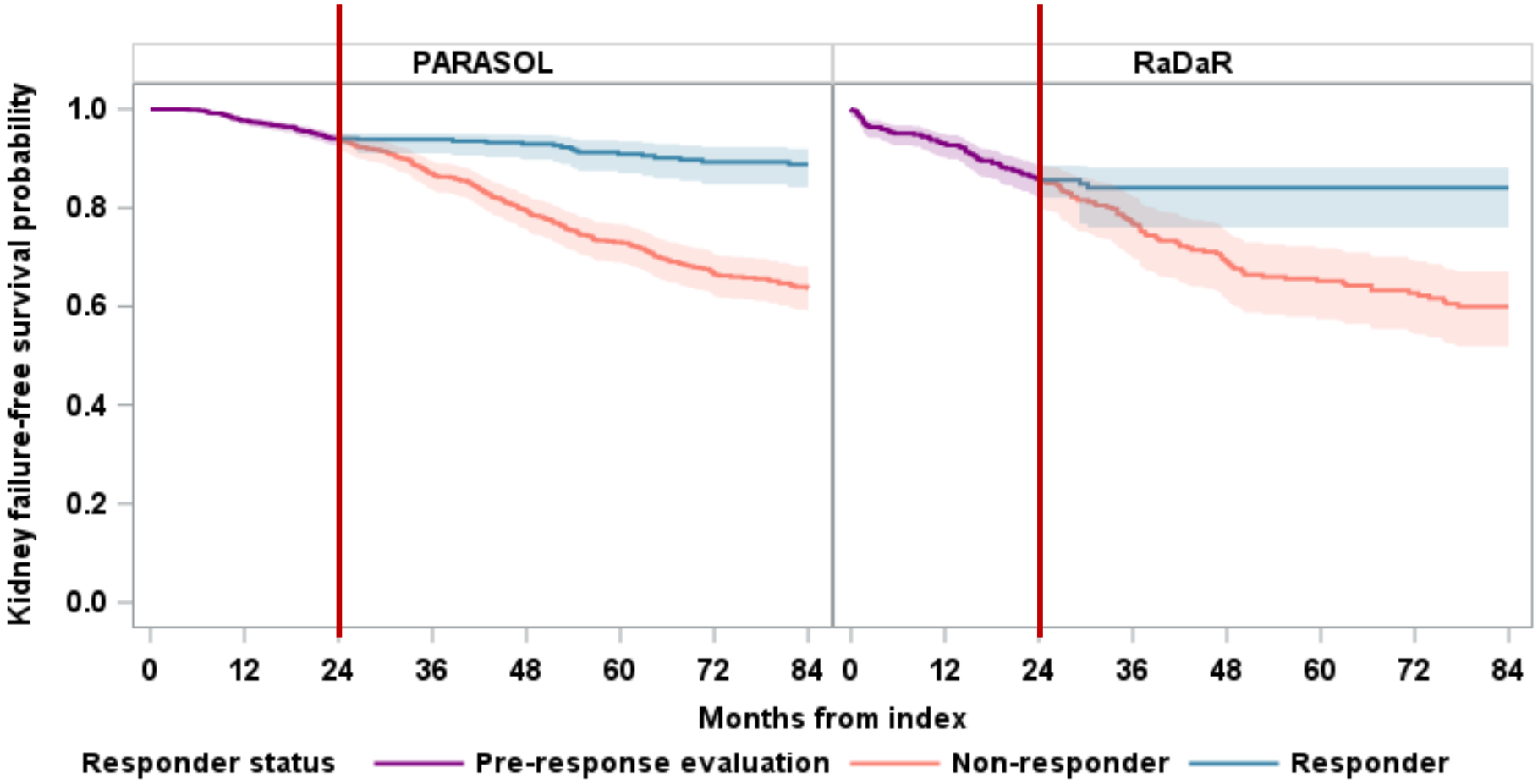
Proteinuria reduction as a continuous variable



Proteinuria reduction as categorical variable

Troost, CJASN, 2018. PMID: 32791086; Troost, AJKD, 2021. PMID: 32791086

FSGS: PARASOL



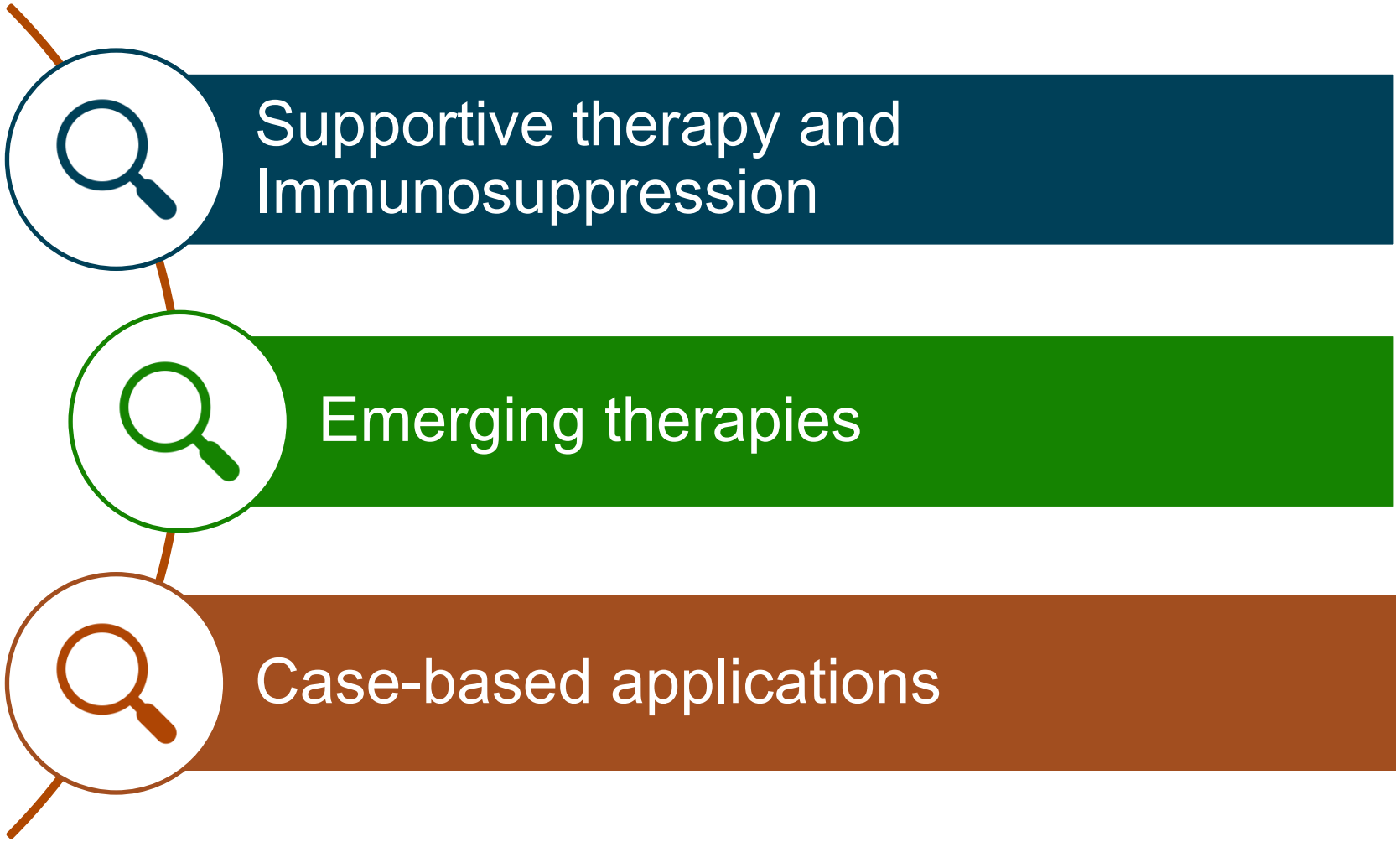
Key Point

This data highlights the impact of proteinuria reduction at 2 years post-diagnosis on the hazard ratio of disease progression (Manuscript in prep)

RESPONDER: UPCR<0.7

Patient Perspective: What FSGS Feels Like

Journey Through Today's Discussion



Why Does it Matter?

- FSGS is a heterogeneous disease (primary, secondary, genetic, undetermined origin)
- It has a variable response to therapy with high relapse rates.
- There are limited RCT data that help guide therapy.
- Available therapies have significant clinical toxicity

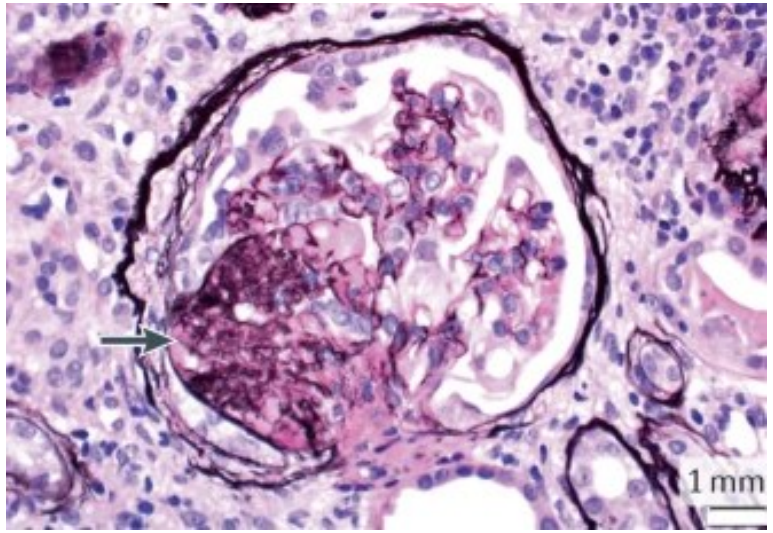
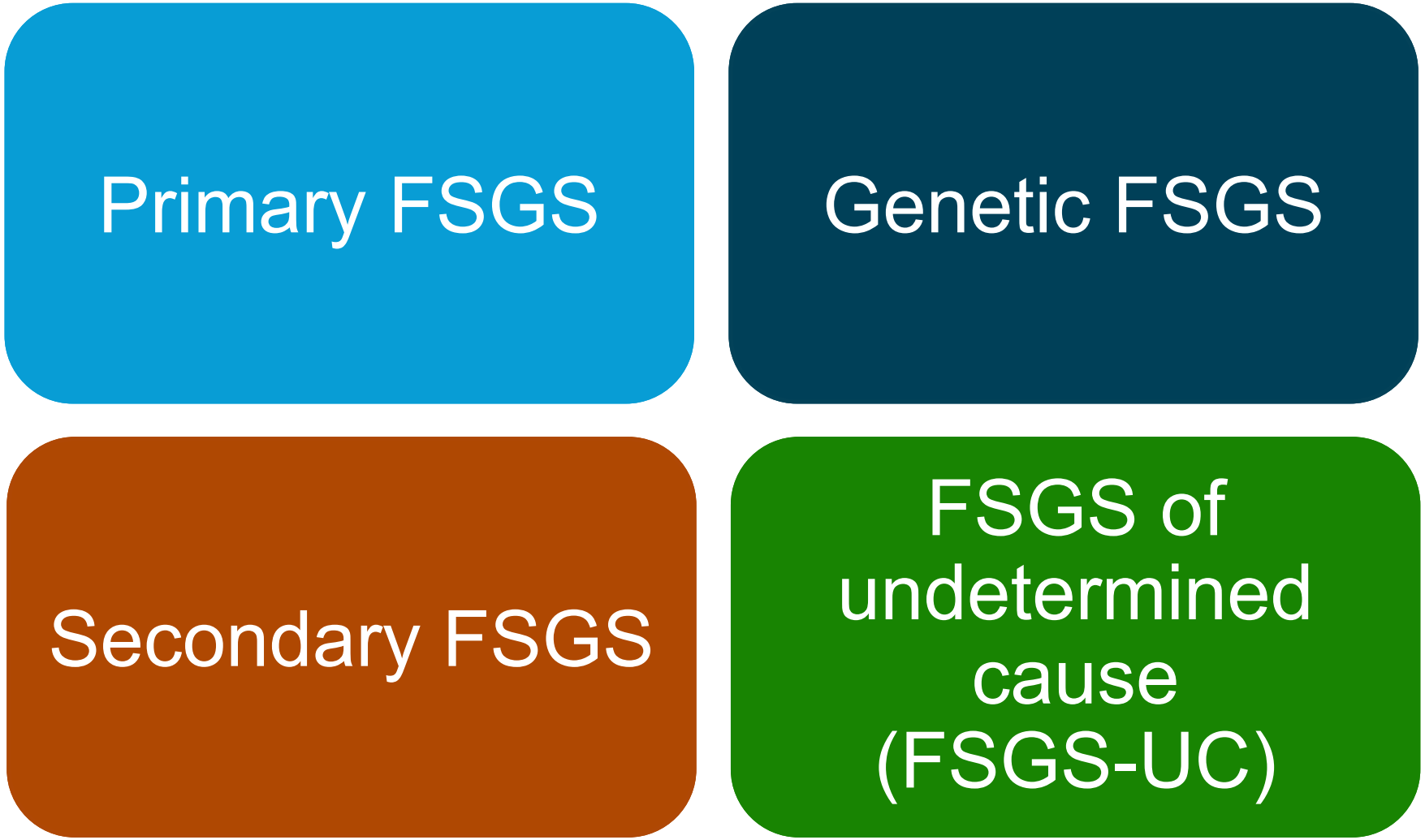


Image shows perihilar segmental glomerulosclerosis under light microscopy

Proteinuria	10 year survival
Nephrotic range	57%
Non-nephrotic range	92%

Image sourced from De Vriese AS, et al. Nature Reviews Nephrology 2021;17:619-630; Rydell JJ et al. Am J Kid Dis 1995;25:534-542

Types of FSGS



Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. Kidney Int 2021;100(4S):S1-S276.

Types of FSGS: Primary FSGS

- Also known as “idiopathic”
- Most responsive to immunosuppressants
- Characterized by an abrupt onset of nephrotic syndrome and diffuse foot process effacement
- Likely due to circulating permeability factor

Primary FSGS

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. Kidney Int 2021;100(4S):S1-S276.

Types of FSGS: Genetic FSGS

Genetic FSGS

- Phenotyping is essential in the initial workup of patients with FSGS
- Steroid-resistant FSGS (11-24% harbor disease-causing variants in type IV collagen or podocyte genes)

Age of Disease Onset	Mutation Identification
First year of life	60 – 100%
Young children	40 – 60%
Older children	25 – 40%
Adolescents	10 – 25%
Adults	9 – 14%

Forms of Genetic FSGS

- Familial
- Sporadic
- Syndromic

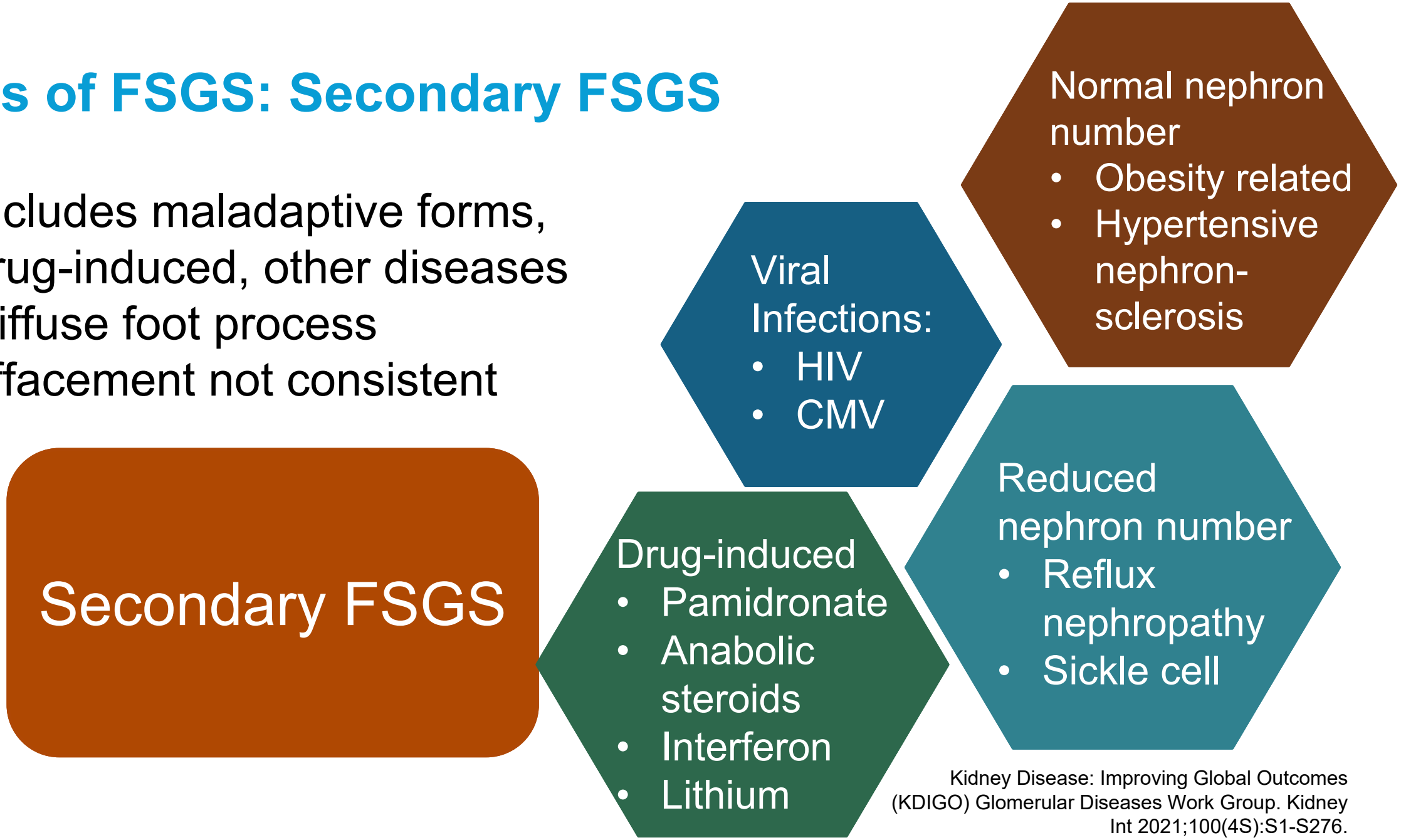
Examples of Key Genes

- Nephrin (NPHS1)
- Podocin (NPHS2)
- Podocin variant (R229Q)
- Cytoskeletal (ACTN4)
- Cytoskeletal (INF2)
- Cation channel protein (TRPC6)
- APOL1 (G1 and G2)

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. Kidney Int 2021;100(4S):S1-S276.; De Vriese AS, et al. J Am Soc Nephrol 2018;29:759-774; Beck LH, et al. Am J Kid Dis 2023;82(2):P121-175.

Types of FSGS: Secondary FSGS

- Includes maladaptive forms, drug-induced, other diseases
- Diffuse foot process effacement not consistent



Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. Kidney Int 2021;100(4S):S1-S276.

Types of FSGS: FSGS of Undetermined Cause (FSGS-UC)

FSGS of undetermined cause (FSGS-UC)

Absent of:

- Genetic cause
- Identifiable secondary cause
- Foot process effacement

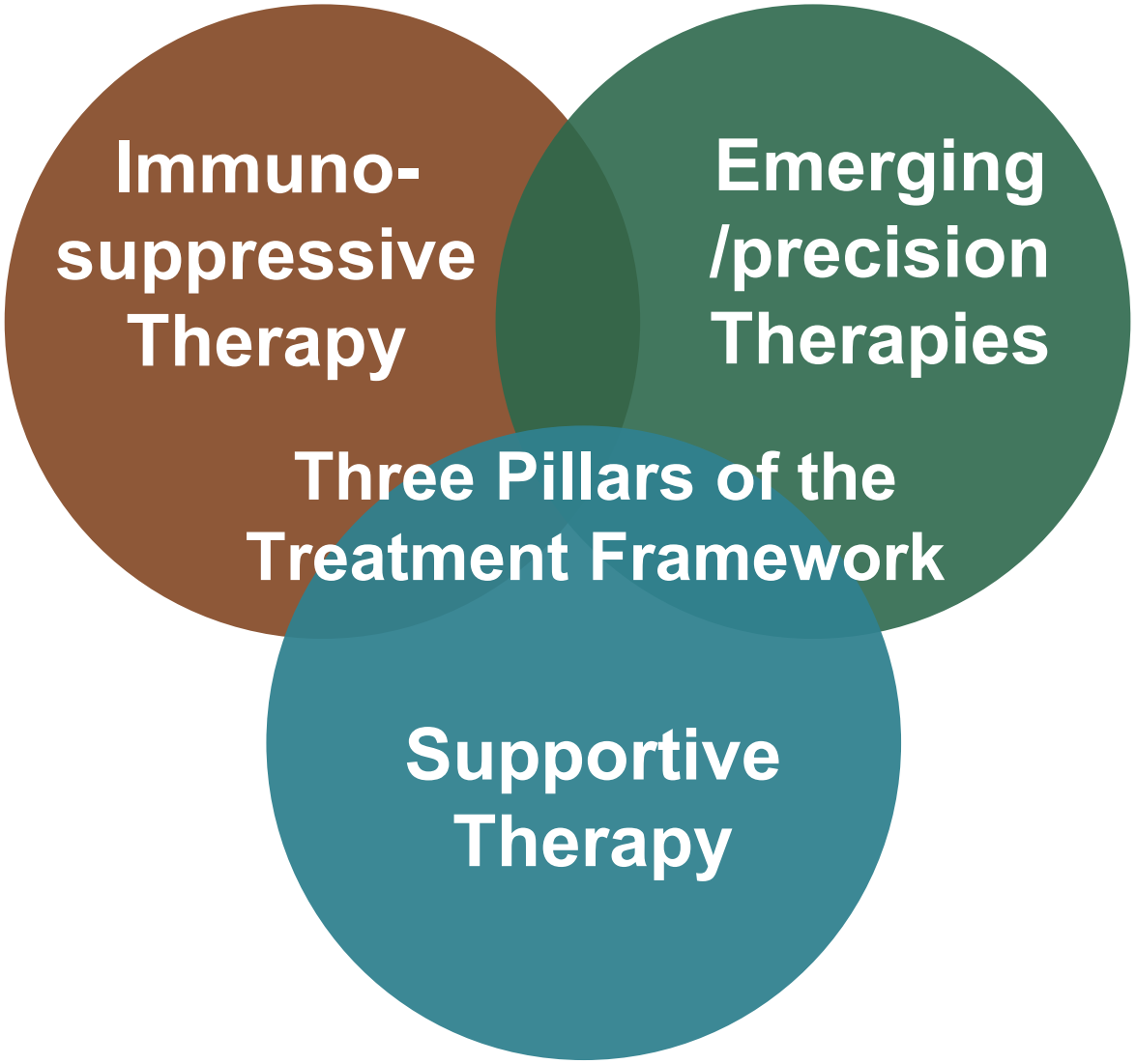
Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. Kidney Int 2021;100(4S):S1-S276.

Definitions – Suggested KDIGO Harmonization

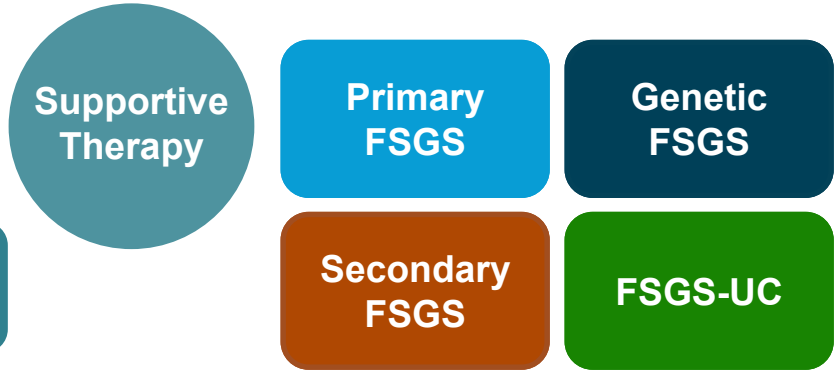
Term	Definition
Complete remission (CR)	Reduction of proteinuria to < 0.3 g/d or UPCR < 300 mg/g; stable serum creatinine and serum albumin > 3.5 g/dL
Partial remission (PR)	Reduction of proteinuria to 0.3 – 3.5 g/d or UPCR 300 – 3500 mg/g and a decrease of 50% from baseline
Relapse	Proteinuria > 3.5 g/d or UPCR > 3.5 g/g after CR has been achieved or an increase in proteinuria by > 50% during partial remission
Steroid-resistant FSGS	Presence of proteinuria of > 3.5 g/d or UPCR > 3.5 g/g with < 50% reduction from baseline despite prednisone 1 mg/kg/d or 2 mg/kg every other day for at least 16 weeks
Steroid-dependent FSGS	Relapse occurring during or within 2 weeks of completing glucocorticoid therapy
CNI-resistant FSGS	Persistence of proteinuria > 3.5 g/d or UPCR > 3.5 g/g with < 50% reduction from baseline despite appropriate trough levels of CNIs for 4-6 months
CNI-dependent FSGS	Relapse occurring during or within 2 weeks of completing CNI therapy > 12 months

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. Kidney Int 2021;100(4S):S1-S276.

Treatment Framework



Supportive Therapy: Foundation of Care



RAAS blockade (ACEi/ARB)

- Limited RCTs
- Meta-analysis demonstrates 50% reduction in UPCR

Blood pressure optimization

- Target < 120/70 mmHg
- Blood pressure may be difficult to achieve in patients with NS

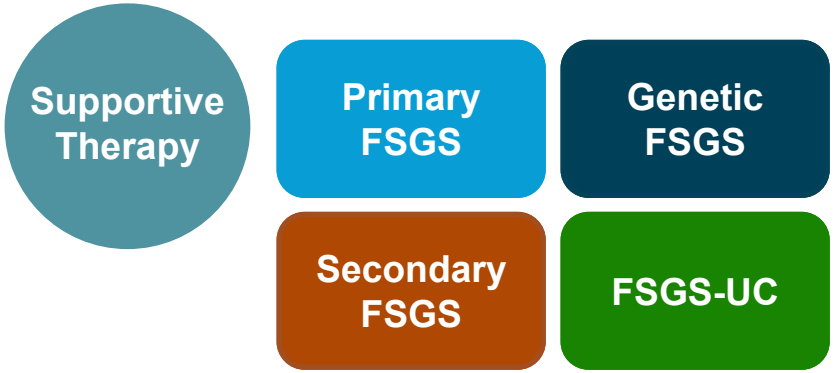
Sodium restriction

- < 2 grams/day

Cardiovascular risk reduction

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group; Kidney Int 2021;100(4S):S1-S276; Campbell KN, et al. Kidney Med 2022;4(5):100457; Orth SR, et al. N Engl J Med 1998;338:1202-1211

SGLT2 Inhibitors in FSGS



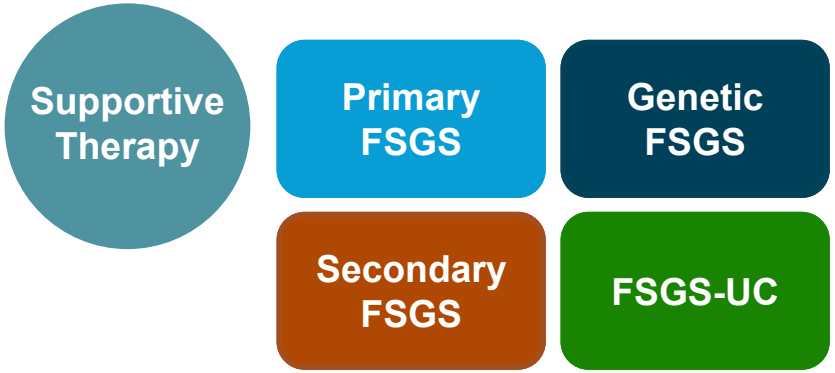
- Not disease-specific
- Limited enrollment of patients with FSGS
  - Immunosuppression an exclusion criteria (CREDENCE; DAPA-CKD; EMPA-KIDNEY)
- Use supported by DAPA-CKD subgroup
- Add-on to supportive therapy

Group	Primary endpoint[a]	eGFR decline[b] (mL/min/1.73m^2/year)	UACR reduction
Dapagliflozin	4 (8.9%)	-1.9	-26.1%
Placebo	7 (11.9%)	-4.0	-9.9%

[a] composite of sustained ≥50% eGFR decline, ESKD, or kidney/CV death; [b]chronic slope

Wheeler DC, et al. Nephrol Dial Transplant 2022;37: 1647-1656; The EMPA-KIDNEY Collaborative Group. N Engl J Med. 2023;388:117-27; Perkovic V, et al. N Engl J Med 2019;380:2295-2306.

Supportive Care for Nephrotic Syndrome



Diuretics

- Edema control
- Refractory edema: loop and thiazide combination

Statins

- Lipid abnormalities
- Dosing of “statins” may be impacted by NS

Anticoagulation

- Select patients
- Albumin threshold < 2.0 – 2.5 g/dL

Immunosuppression

Immuno-suppressive Therapy

Use immunosuppression

- Primary FSGS

Do NOT use immunosuppression

- Genetic FSGS
- Secondary FSGS
- FSGS-UC

Glucocorticoids (First-Line)

Immuno-suppressive Therapy

Primary FSGS

Prednisone	• 1 mg/kg/day (max 80 mg) • 2 mg/kg every other day (max 120 mg)
Duration	• Up to 16 weeks • Continue ≥ 6 months if response
Steroid Response	• Complete remission: 28-74% • Adults less responsive than children
Mechanism	• Systemic immunosuppression • Upregulation of Krüppel-like factor 15 (KLF15) ○ May mediate cytoprotective effect

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. Kidney Int 2021;100(4S):S1-S276; Guo Y, et al. J Am Soc Nephrol 2024;35(12):1671-85.

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Immuno-suppressive Therapy

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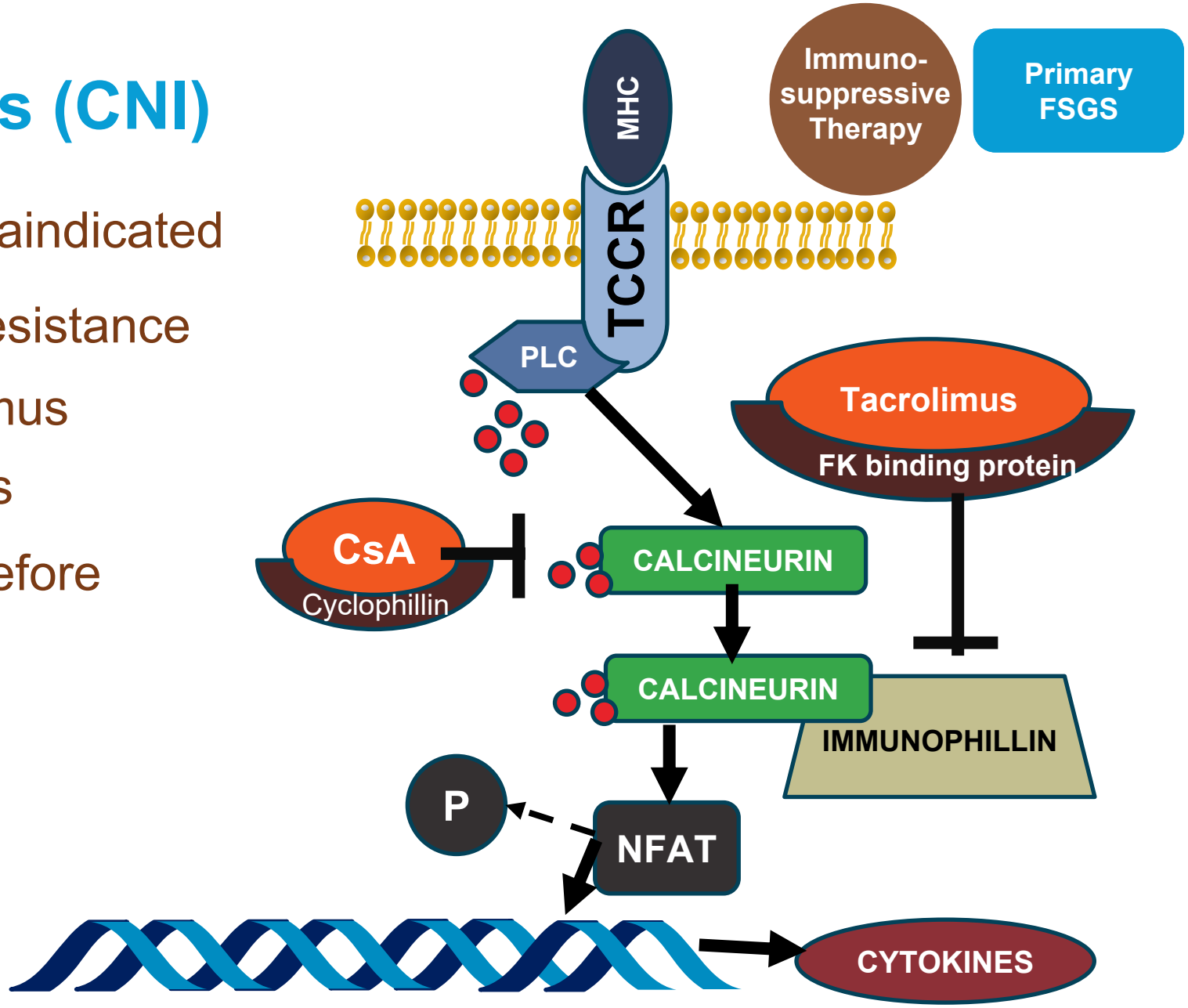
Steroid Response	• Complete remission: 28-74% • Adults less responsive than children
Mechanism	• Systemic immunosuppression • Upregulation of Krüppel-like factor 15 (KLF15) ○ May mediate cytoprotective effect

- Glucocorticoid response should be seen within 4-8 weeks
- No RCTs of prednisone compared to placebo or no treatment.
- Doses and durations extrapolated from studies of children with NS.
- Optimal dose and duration have not been defined.

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. Kidney Int 2021;100(4S):S1-S276.

Calcineurin Inhibitors (CNI)

- First-line if steroid contraindicated
- First choice in steroid resistance
- Cyclosporine or tacrolimus
- 60–70% remission rates
- Must treat ≥6 months before failure
- Maintain ≥12 months if responsive



Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. Kidney Int 2021;100(4S):S1-S276.

Calcineurin Inhibitors (CNI)

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Primary FSGS

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- 60–70% remission rates
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- Maintain ≥12 months if responsive

- Mechanism beyond immunosuppression reported
- Stabilization of actin cytoskeleton
- Opportunity for precision with multi-omic (RNA-seq) intrarenal profiling identified gene networks linked to CNI response
- Recent findings of associated noninvasive biomarkers (KIM-1, MMP-7, TNFR-2) improving prediction of complete remission (AUC 0.85 vs 0.77)
- Findings support biomarker-driven personalization of CNI therapy to improve outcomes and reduce unnecessary long-term toxicity;
- External validation needed

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. Kidney Int 2021;100(4S):S1-S276. Laurin L-P, et al. Can J Kidney Health Dis 2017;4:2054358117692559. Eddy S, et al. J Am Soc Nephrol 2024;35(10)(Suppl):10.1681/ASN.2024t4wfszbh

Calcineurin Inhibitors (CNI): Dosing and monitoring

Immuno-suppressive Therapy

Primary FSGS

Cyclosporine Dosing	• 3 – 5 mg/kg split every 12 hours • Target trough 100 – 175 ng/mL
Tacrolimus Dosing	• 0.05 – 0.1 mg/kg split every 12 hours (unless extended release) • Target trough 5 – 10 ng/m
Monitoring	• Creatinine ↑ >30% → reduce dose • BP, glucose, electrolytes • Drug interactions (CYP3A4/P-gp)

Consider CYP3A5 genotyping to guide initial dosing if available

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. Kidney Int 2021;100(4S):S1-S276.

Calcineurin Inhibitors (CNI): Dosing and monitoring

Immuno-suppressive Therapy

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Monitoring	• Creatinine ↑ >30% → reduce dose • BP, glucose, electrolytes • Drug interactions (CYP3A4/P-gp)

Voclosporin trial (NCT03598036) terminated early by company due to recruitment challenges

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. Kidney Int 2021;100(4S):S1-S276.

Rituximab (anti-CD20 antibody)

Immuno-suppressive Therapy

Primary FSGS

- Best for:
  - Steroid-dependent
  - Frequently relapsing disease
- Not first-line standard
- 70-87% remission
- Relapse ↓ dramatically
  - Median of 4 relapses to 0 after treatment
  - Median relapse-free duration extended (16-50 months)
- Steroid-sparing
- 375 mg/m^2 x 4 weekly doses
  - Prescreening; premedication; monitoring

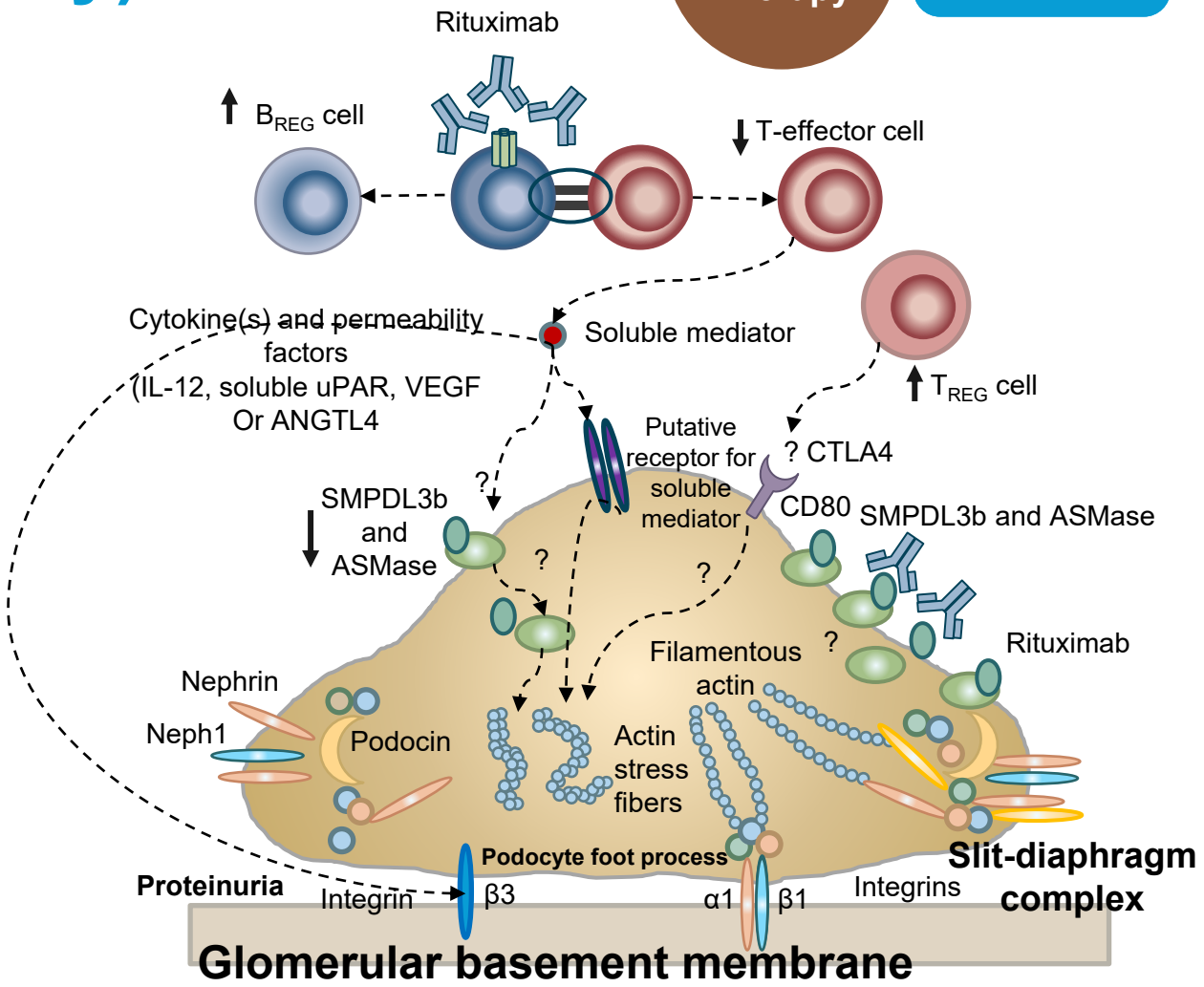


Figure adapted from Sinha A, et al. Nature Reviews Nephrology 2013;9:154-169

Mycophenolate (MMF)

Immuno-suppressive Therapy

Primary FSGS

- Limited efficacy
- Steroid-sparing option
- Not first-line
- May be considered in patients with SR-FSGS after remission induced by CNI
- Typical dose 1-2 grams per day
- Risk for teratogenicity (boxed warning)

Cattran D. et al. *Clinical Nephrology*. 2004; **62** (6): 405-411.

Emerging Therapies Overview

Emerging /precision Therapies

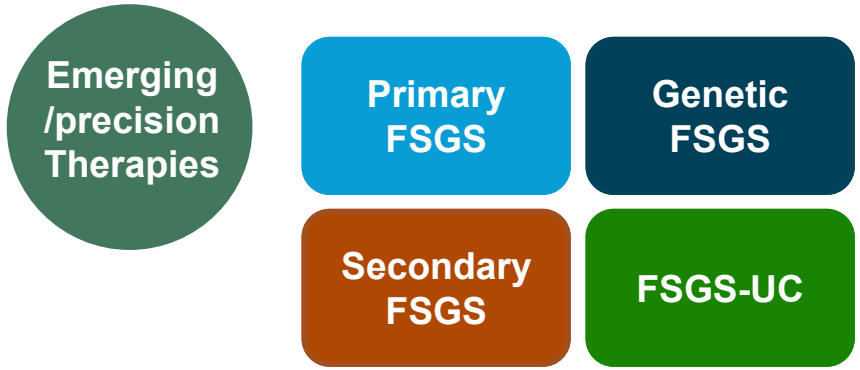
Targeted

- Podocyte-focused

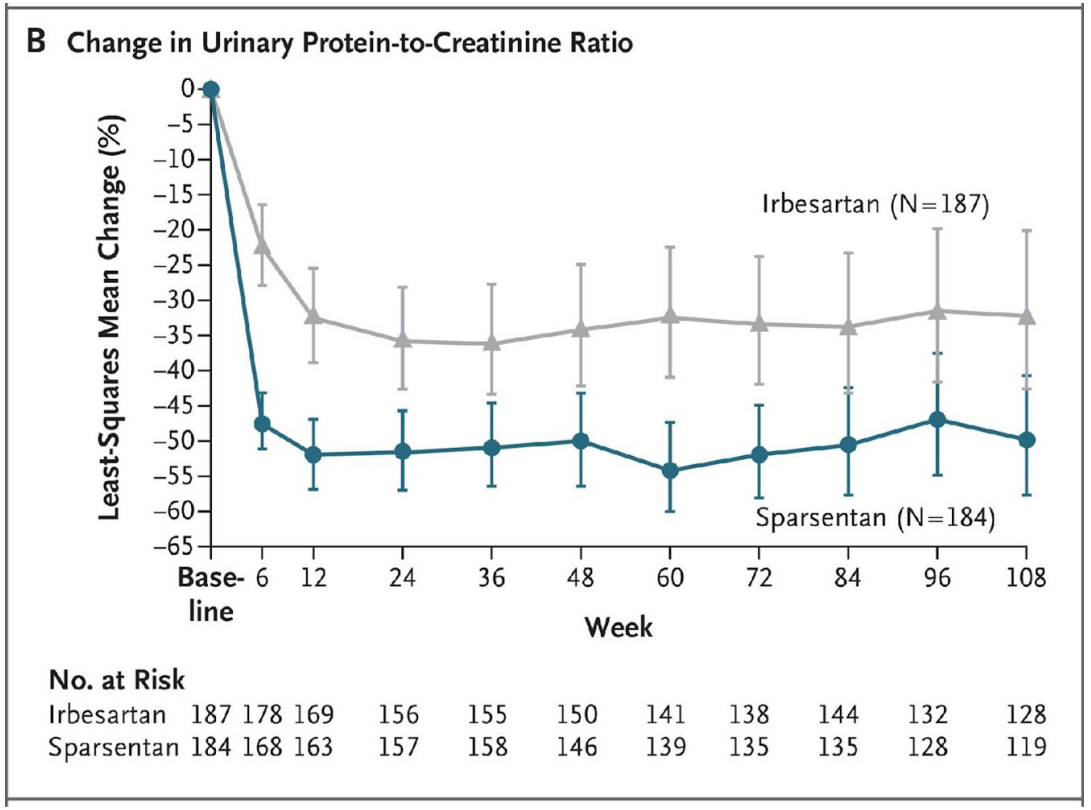
Precision Medicine

Moving Beyond Immunosuppression

Sparsentan (Dual Endothelin Antagonist/ARB)



- FDA-approved for FSGS and IgA nephropathy
- DUPLEX study (n = 371)
  - 42% of sparsentan arm achieved PR
  - 26% of irbesartan arm achieved PR
  - No eGFR benefit at 108 weeks.
  - Similar safety profile
- Dose 400 mg daily
- Available through REMS
  - Hepatoxicity; Embryo-fetal toxicity



Rheault MN, et al. N Engl J Med 2023;389:2436-45

Agents on the horizon

Primary FSGS | Genetic FSGS | Secondary FSGS | FSGS-UC

Mechanism	Agent(s)	Use	Results (if applicable)	Status
APOL1 inhibitors	Inaxaplin	Genetic (APOL1) FSGS	47.6% reduction in UPCR at 13 weeks	Phase 2 trials
TRPC6 inhibitors	BI 764198 (Apecotrep)	Primary FSGS Genetic FSGS	40% reduction in UPCR at 12 weeks	Phase 3 trial (Apecotrep)
CTLA4-Ig fusion proteins	Abatacept	Primary FSGS	Induced PR or CR in 5 patients	RCT terminated due to poor enrollment
Anti-suPAR antibody	WAL0921	FSGS		Phase 2
CCR/MCP antagonism	Ilacirnon DMX-200	FSGS		Phase 2
JAK-STAT inhibitors	Baricitinib	Genetic (APOL1) FSGS		Phase 2
AMP Kinase activators	Metformin	FSGS		Phase 2
sGC stimulator	Praliciguat	FSGS		Phase 2
CD19 inhibitors	VB119	FSGS		Phase 2 terminated (sponsor change)

Trachtman H, et al. Am J Kid Dis 2026;87(4):573-81;Granata S, et al. J Transl Med 2026;24(1):346

TRPC6 Inhibition: (Apecotrep (BI 764198))

Emerging /precision Therapies

Primary FSGS

Genetic FSGS

Podocyte-targeted Therapy

2026 Phase 2 Trial (n = 62)

- Patients with Primary FSGS and Genetic FSGS were recruited
- 35% of active treatment arm achieved ≥25% proteinuria reduction
- 7% of placebo arm ≥25% proteinuria reduction

Early But Promising

The drug was well-tolerated with stable blood pressure and eGFR, suggesting a cytoprotective effect on podocytes rather than hemodynamic changes

Trachtman H, et al. Lancet 2026; 407; 587-98.

APOL1 Inhibition (Inaxaplin)

Emerging /precision Therapies

Genetic FSGS

- Precision therapy – Selective inhibitor of APOL1 channel function
- Phase 2a clinical study (n = 13)
  - Biopsy proven FSGS with 2 APOL1 variants
  - 47.6% proteinuria reduction
- Well tolerated
  - No treatment discontinuations
  - No serious adverse effects

13% of African-Americans carry two APOL1 risk alleles (~6 million individuals)

Egbuna O, et al. N Engl J Med 2023;388:969-79.
Srinivasan V, et al. Kidney Med 2025;7(9):101062.

Treatment Algorithm

Start:

- RAAS + supportive care

Primary + Nephrotic:

- Steroids

Steroid Resistant:

- CNI

Relapse:

- Rituximab

Genetic:

- Consider targeted therapy

Emerging /precision Therapies

Case Study: Patient #1

Patient

33-year-old Caucasian woman, 75 kg

Allergies: NKDA, NKFA
Presented with sudden onset edema one week ago. Urine was collected for 24 hours and today is a follow-up to discuss results.
Plan:

1. Kidney biopsy scheduled
2. Initiate losartan 25 mg daily
3. Initiate atorvastatin 10 mg daily
4. Sodium restriction

Medications

Furosemide 40 mg daily

PMH

None

Labs/Vitals

Vital	Today	One week ago
Blood pressure	118/68	120/70
Pulse	80	78
Lab	**Today**	**One week ago**
SCr (mg/dL)	0.75	0.68
eGFR (mL/min/1.3m^2)	108	118
sAlb (g/dL	2.6	2.5
24hr Uprot (g/d)	7.6	-
LDL (mg/dL)	-	190
Autoimmune panel	-	wnl

Case Study: Patient #1

Patient

33-year-old Caucasian woman, 75 kg

Allergies: NKDA, NKFA
Patient returns to clinic after 8 weeks on prednisone and losartan. Losartan was recently discontinued due to several hypotensive episodes. Proteinuria has decreased but still elevated. Patient is starting to demonstrate Cushingoid features

Medications

Furosemide 40 mg daily

Prednisone 75 mg daily

PMH

CKD secondary to primary FSGS

Labs/Vitals

Vital	Today	Baseline
Blood pressure	120/70	120/70
Pulse	84	78
Lab	**Today**	**Baseline**
SCr (mg/dL)	0.75	0.68
eGFR ($mL/min/1.3m^2$)	108	118
sAlb (g/dL	2.8	2.5
24hr Uprot (g/d)	3.9	7.6
LDL (mg/dL)	162	190
Autoimmune panel	-	wnl

Defining Success

Complete remission:
- <0.3 g/day proteinuria
- Serum albumin > 3.5 g/dL

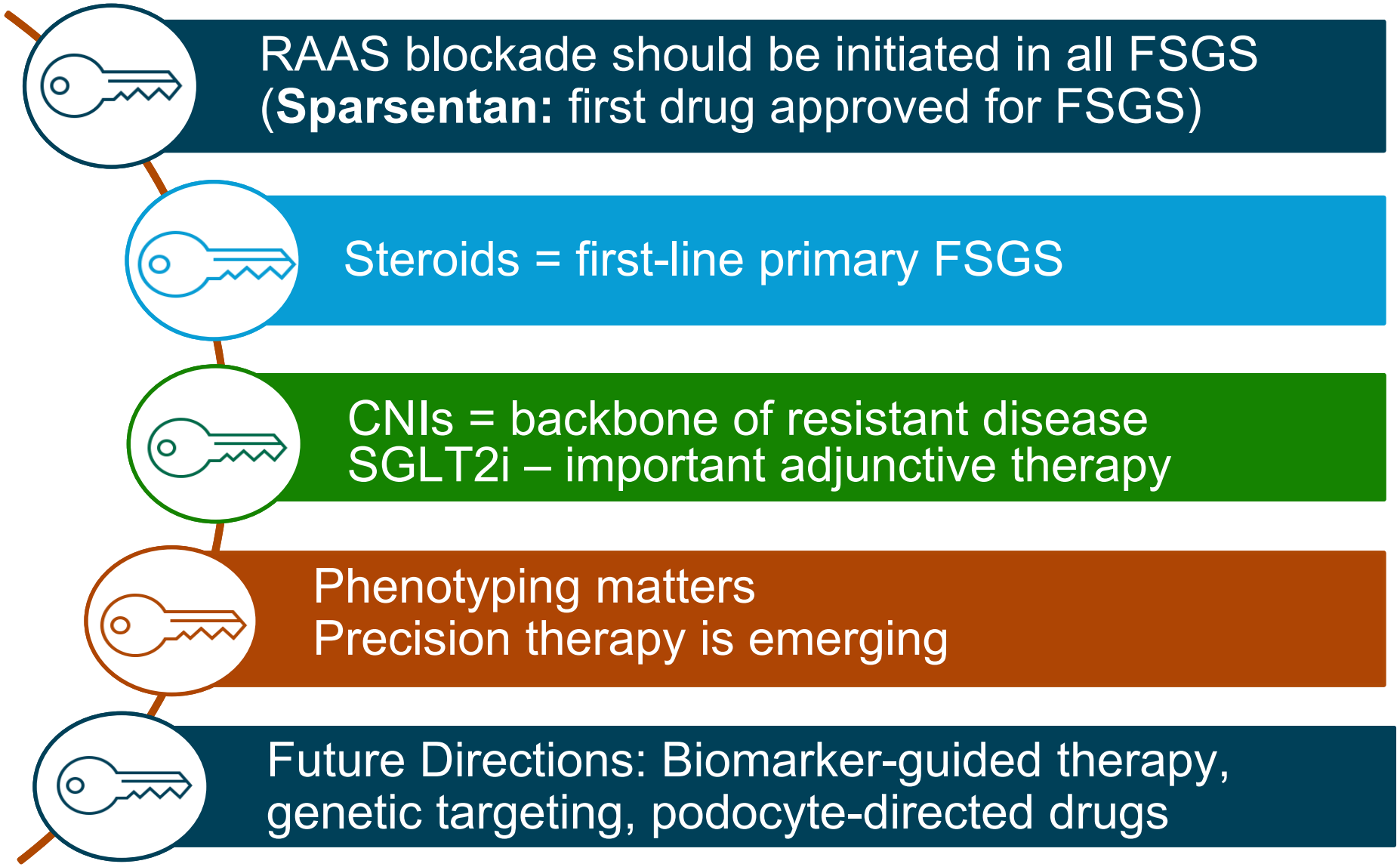
Partial remission:
- UPCR 300-3500 mg/g
- ≥50% reduction

Novel endpoint
- < 1.5 g/day + ≥40% reduction

Monitoring therapy

- Proteinuria trends (assess every 1-3 months)
    - Monthly: early in therapy and after dose changes; every 3 months if stable
- eGFR slope (assess every 1-3 months
    - More frequent if on CNIs
        - Every 1-2 weeks during initiation and dose titration x 1-2 months
        - >30% rise in SCr from baseline is key threshold – requires dose reduction
        - If no decline after dose reduction – requires discontinuation
- Drug toxicity
    - Glucocorticoids (hyperglycemia; hypertension; hyperlipidemia, bone loss; infection; adrenal suppression)
    - CNI (kidney injury; hypertension; new-onset diabetes; electrolyte disorders, dyslipidemia, hyperuricemia)
    - Sparsentan (hepatoxicity, teratogenicity; hypotension; kidney injury; hyperkalemia, fluid retention)

Key Takeaways



Additional Resources

- NephCure (https://nephcure.org/about)
  - Offers:
    - Patient navigation tools
    - Clinical trial awareness
    - Community support networks
  - Particularly strong for rare disease engagement
- National Kidney Foundation (Kidney.org)
  - Excellent patient-friendly explanation of:
    - Disease basics
    - Symptoms
    - Diagnosis and treatment
  - Ideal for clinic handouts or patient portals

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Advancing Kidney Health

Through Optimal Medication Management

Thank you!