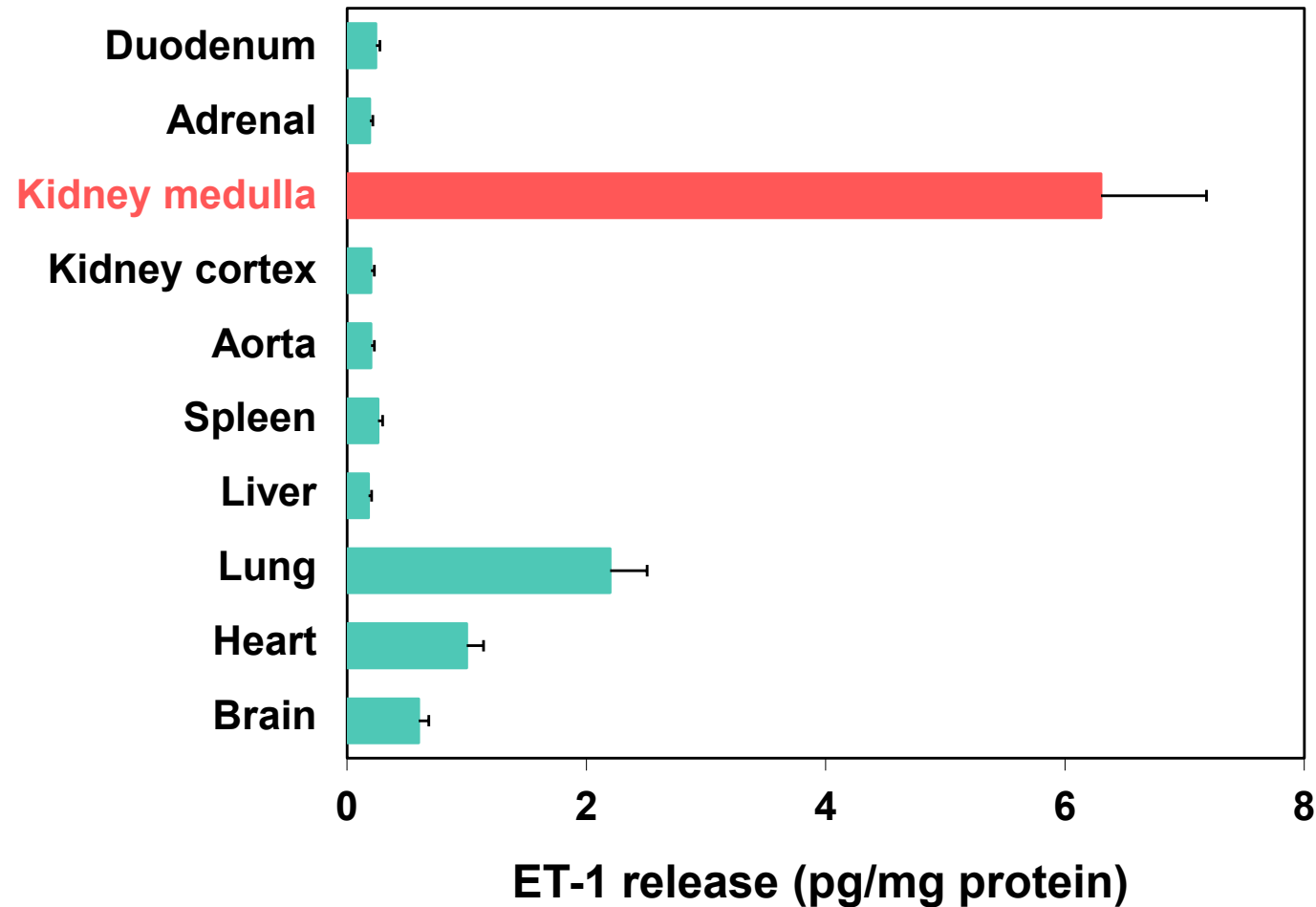


Endothelin-1 (ET-1) Production by the Kidney



Renal ET-1 expression
in kidney disease

Pathophysiology of IgAN

- Proteinuria
- Angiotensin II/AT1

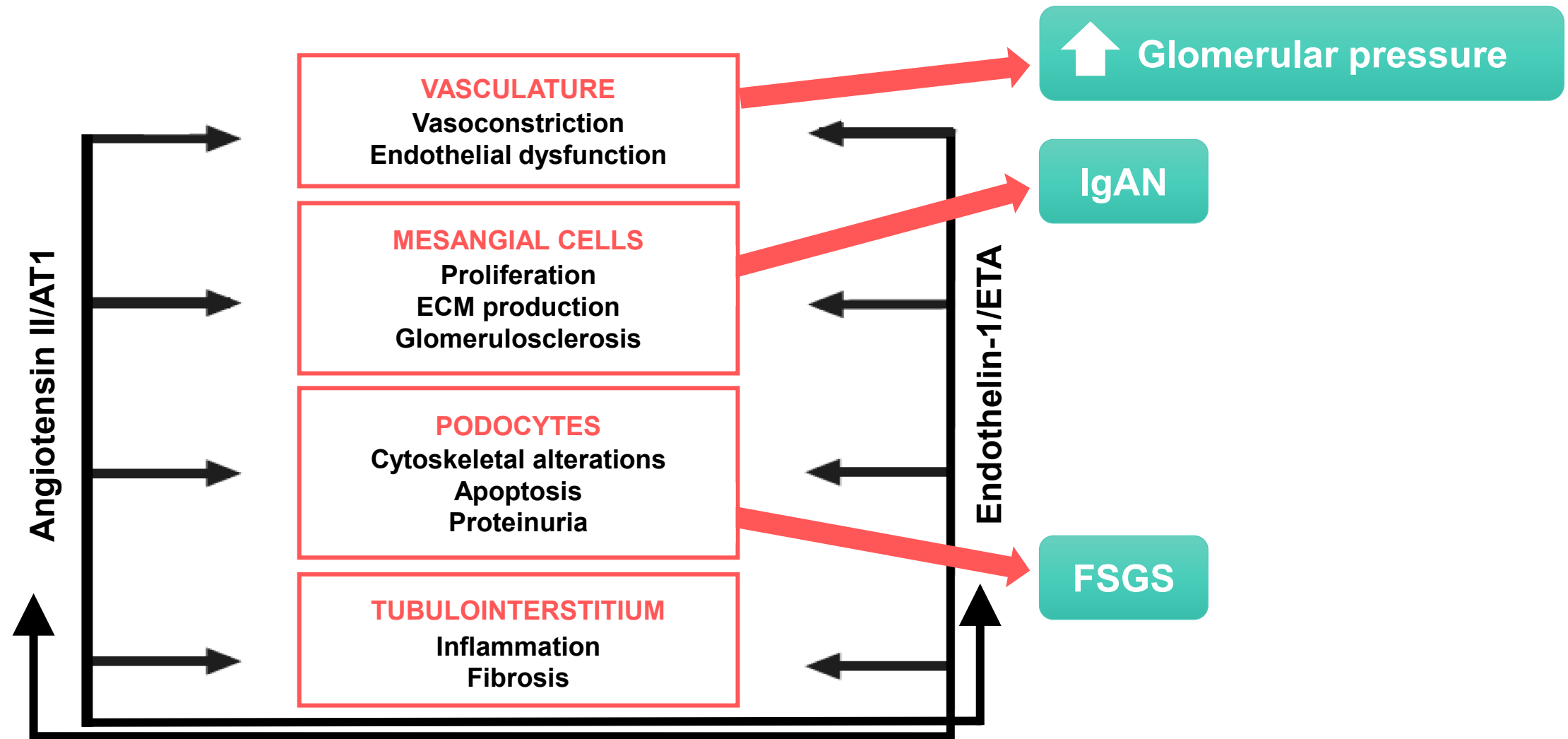


- Cell proliferation
- Apoptosis
- Inflammation
- Fibrosis

Mediated by
Endothelin A
Receptor (ETAR)



Overview of Renal ET-1 & Ang II Actions



Modified from Komers R, Plotkin H. *Am J Physiol Regul Integr Comp Physiol.* 2016;310(10):R877-R884.



Diagnose Patients Earlier

- Kidney biopsy required to diagnose IgAN or FSGS
- Rethink threshold for biopsy
- Make diagnosis as soon as possible
- Provide therapy at beginning of disease



Diagnosing IgAN & FSGS

- Raise awareness
- Educate colleagues
 - Abnormal urine analysis
 - Abnormal serum creatinine
 - Elevation in blood pressure

Underlying kidney disease



Traditional Criteria for Kidney Biopsy

- Proteinuria $>1\text{g/day}$
- Impaired kidney function
- End-organ damage, such as hypertension

**Consider a biopsy with
proteinuria $>0.5\text{g/day}$**



Oxford Classification: MEST-C Score

Mesangial proliferation	M
Endocapillary hypercellularity	E
Segmental glomerulosclerosis	S
Tubular interstitial inflammation and fibrosis	T
Presence of crescents	C



International IgAN Prediction Tool

https://qxmd.com/calculate/calculator_499/international-igan-prediction-tool-at-biopsy-adults

Calculate by QxMD

All Calculators Become a Contributor Support

Calculator About References

International IgAN Prediction Tool at biopsy - Adults

Determine prognosis in adults with IgA nephropathy

Questions

1. Estimated GFR at biopsy
2. Systolic blood pressure at biopsy
3. Diastolic blood pressure at biopsy
4. Proteinuria at biopsy
5. Age at biopsy
6. Race at biopsy
7. Use of immunosuppressants at biopsy
8. MEST score at biopsy

1. Estimated GFR at biopsy

ml/min/1.73m2

Min value: 15

Next Question →

0/13 completed

Input biopsy report data to predict the risk of a 50% decline in eGFR or ESRD at time of biopsy



KDIGO: Classification of FSGS

FSGS Lesions on Light Microscopy

Primary FSGS

FSGS with diffuse foot process effacement and nephrotic syndrome (often subtle onset, amenable to therapy)

Genetic FSGS

- Familial
- Syndromic
- Sporadic

Secondary FSGS

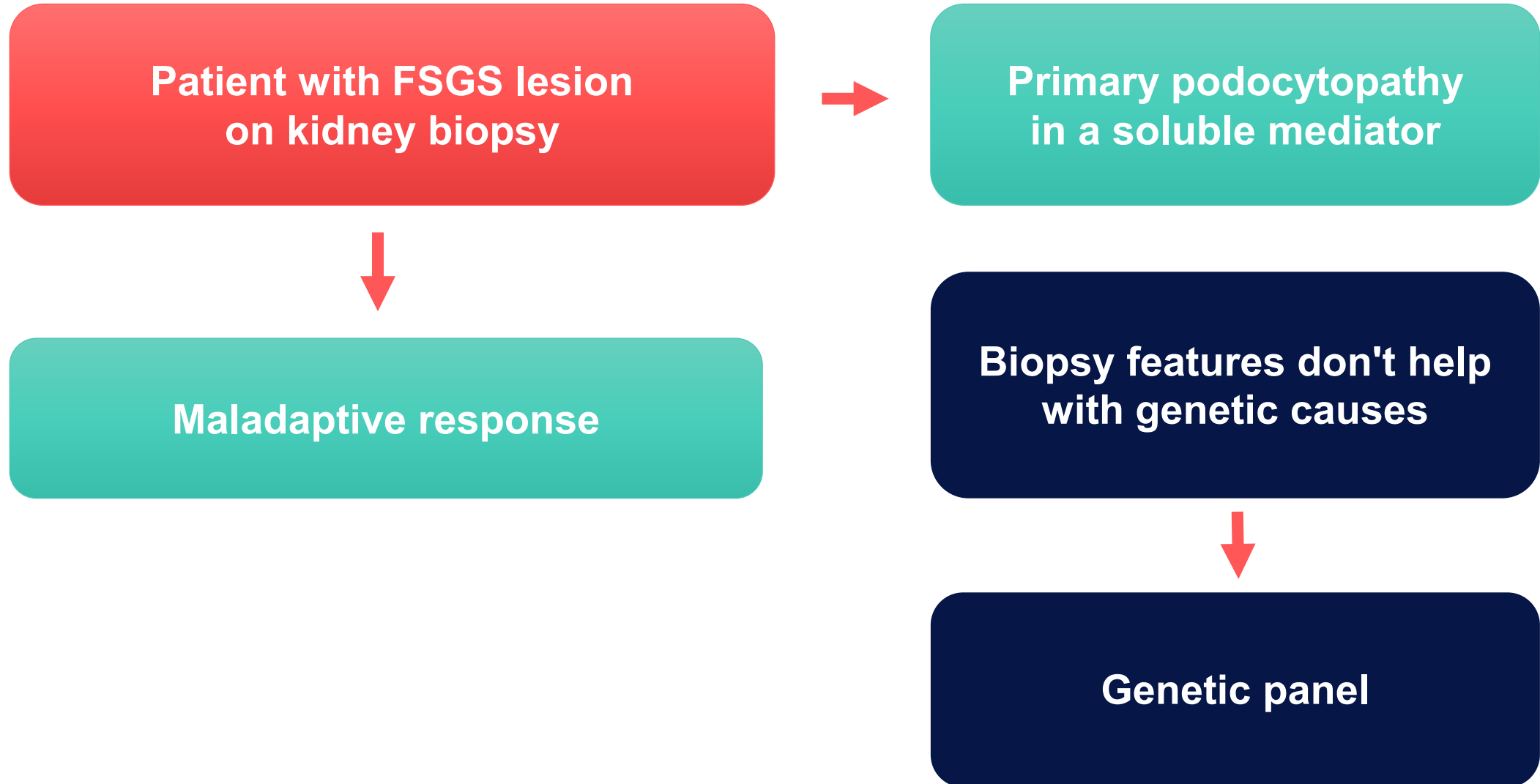
- Viral
- Drug-induced
- Adaptive changes to glomerular hyperfiltration (normal or reduced nephron mass; segmental foot process effacement, proteinuria without nephrotic syndrome)

FSGS of undetermined cause (FSGS-UC)

- Segmental foot process effacement
- Proteinuria without nephrotic syndrome
- No evidence of secondary cause



FSGS: Kidney Biopsy for Underlying Cause



KDIGO: Treatment of a Patient with IgAN

Blood pressure control (125/75 mm Hg)

Healthy weight

Dietary sodium restriction

Exercise regularly

**Maximal tolerated dose of RAS inhibitor,
whether or not hypertensive**

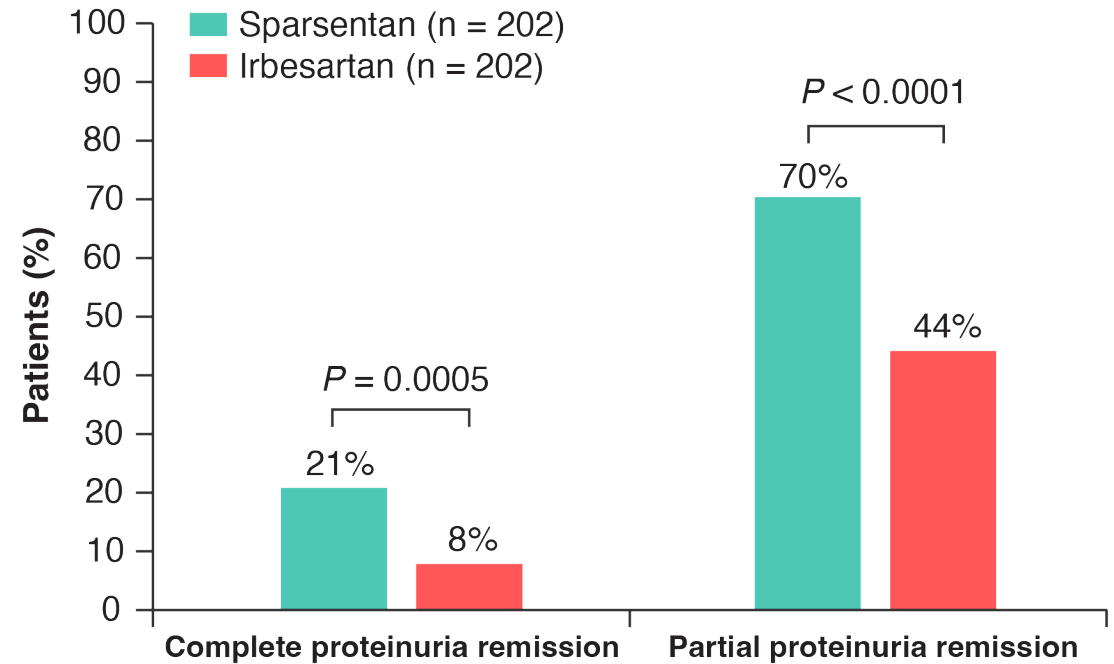
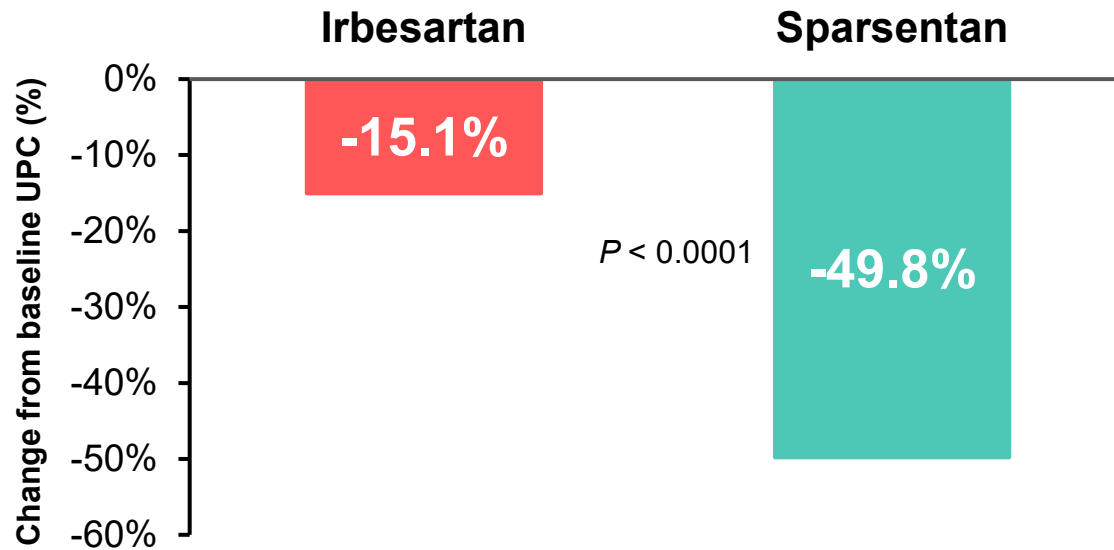
Reduce proteinuria

Address any cardiovascular risk factors



PROTECT IgAN Study: Interim Analysis

- Adults with IgAN and persistent proteinuria (>1 g/day)



UPC, urine protein-creatinine ratio.
Heerspink HJL, et al. *Lancet*. 2023;401(10388):1584-1594.



FDA Gives Sparsentan Accelerated Approval

“to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a UPCR ≥ 1.5 g/g”

	Sparsentan (N = 202)	Irbesartan (N = 202)
Peripheral edema	14%	9%
Anemia	5%	2%
ALT or AST >3X ULN	2.5%	2%



DUPLEX FSGS Study

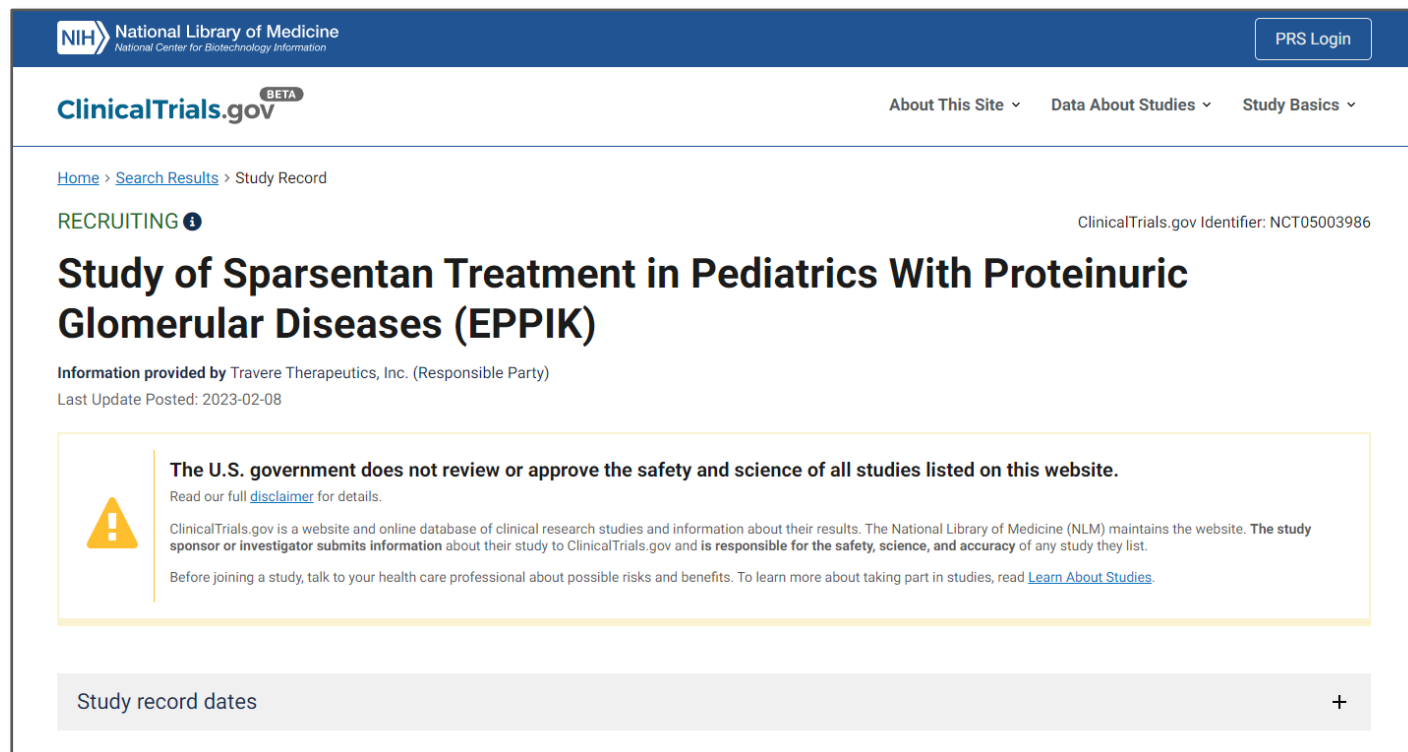
- Proteinuria was reduced by 50% with sparsentan compared with 32% for irbesartan
- More patients achieved partial and complete proteinuria remission on sparsentan
- Final analysis is pending

No impact on PROTECT phase 3 data



Clinical Trials & Pediatric Patients

- EPPIK Study (NCT05003986)
 - Evaluating sparsentan
 - Pediatric patients with IgAN, FSGS, Alport syndrome



The screenshot displays the ClinicalTrials.gov website interface. At the top, the NIH National Library of Medicine logo is visible on the left, and a 'PRS Login' button is on the right. Below the header, the 'ClinicalTrials.gov' logo is accompanied by a 'BETA' badge. Navigation links for 'About This Site', 'Data About Studies', and 'Study Basics' are present. The main content area shows the breadcrumb 'Home > Search Results > Study Record'. The study status is 'RECRUITING' with an information icon, and the ClinicalTrials.gov Identifier is 'NCT05003986'. The study title is 'Study of Sparsentan Treatment in Pediatrics With Proteinuric Glomerular Diseases (EPPIK)'. Below the title, it states 'Information provided by Traverre Therapeutics, Inc. (Responsible Party)' and 'Last Update Posted: 2023-02-08'. A prominent yellow warning box contains the text: 'The U.S. government does not review or approve the safety and science of all studies listed on this website.' It includes a link to the full disclaimer and a note that the sponsor or investigator is responsible for safety, science, and accuracy. At the bottom, there is a section for 'Study record dates' with a plus sign to expand it.

