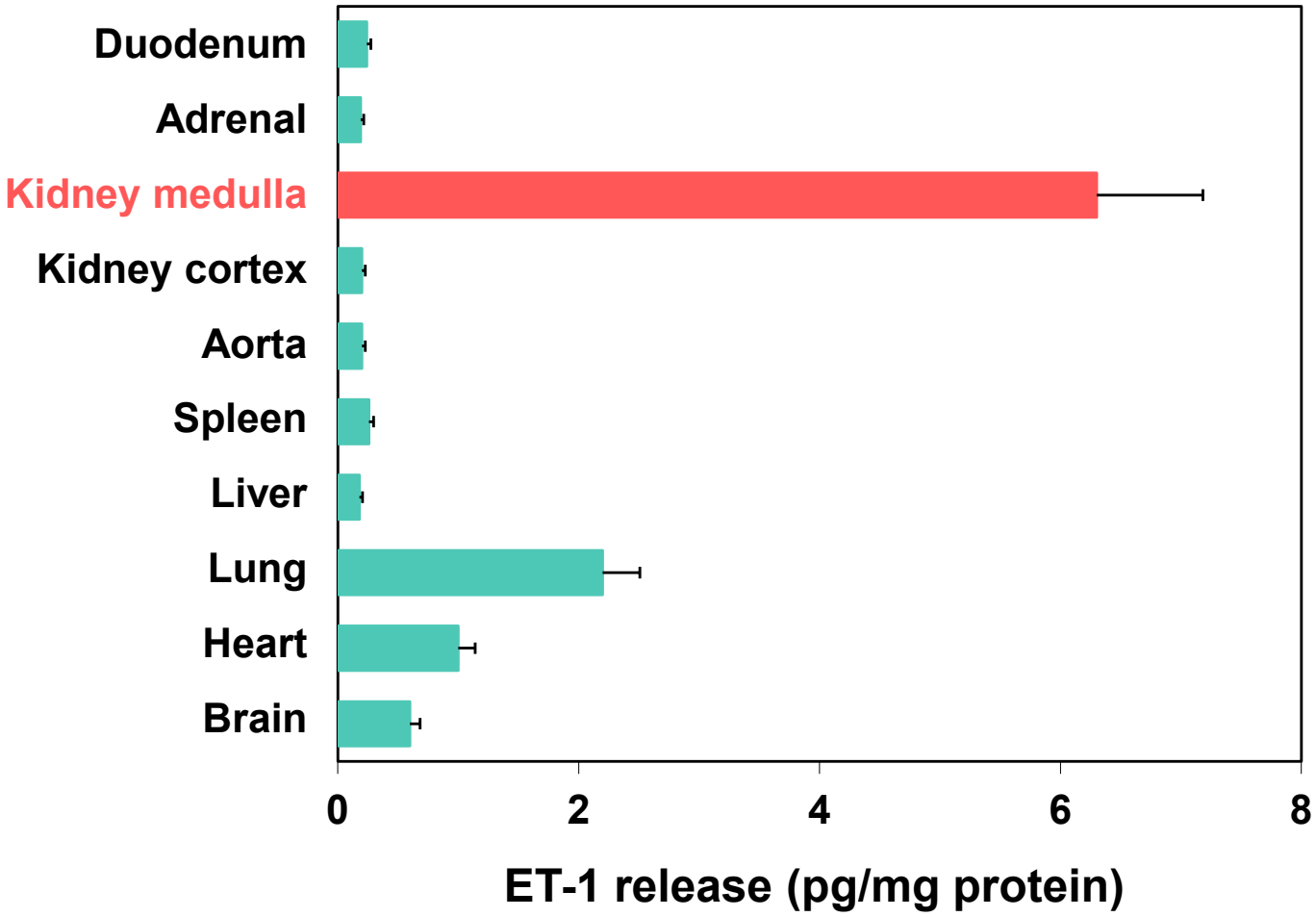
Endothelin-1 (ET-1) Production by the Kidney

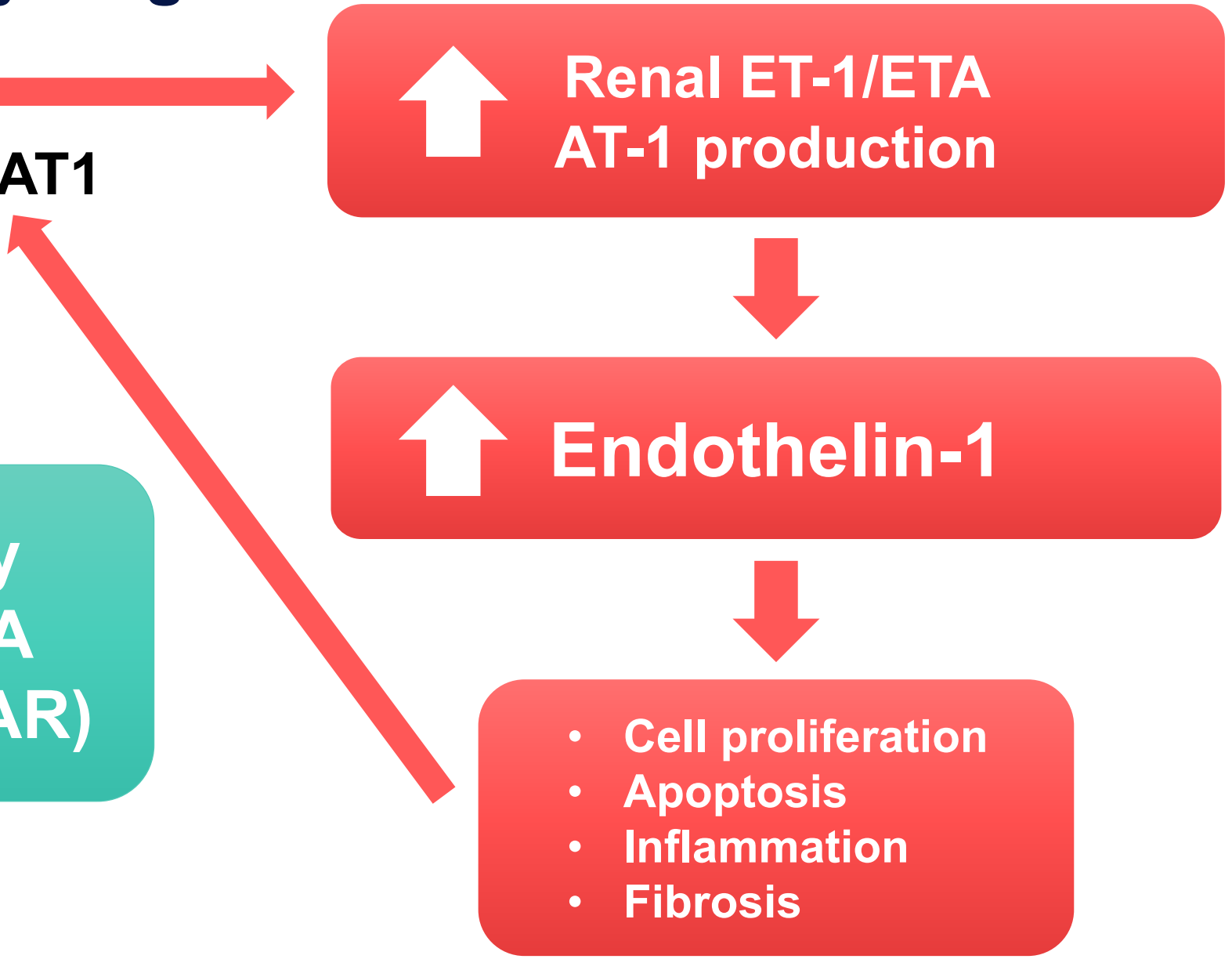


Renal ET-1 expression in kidney disease

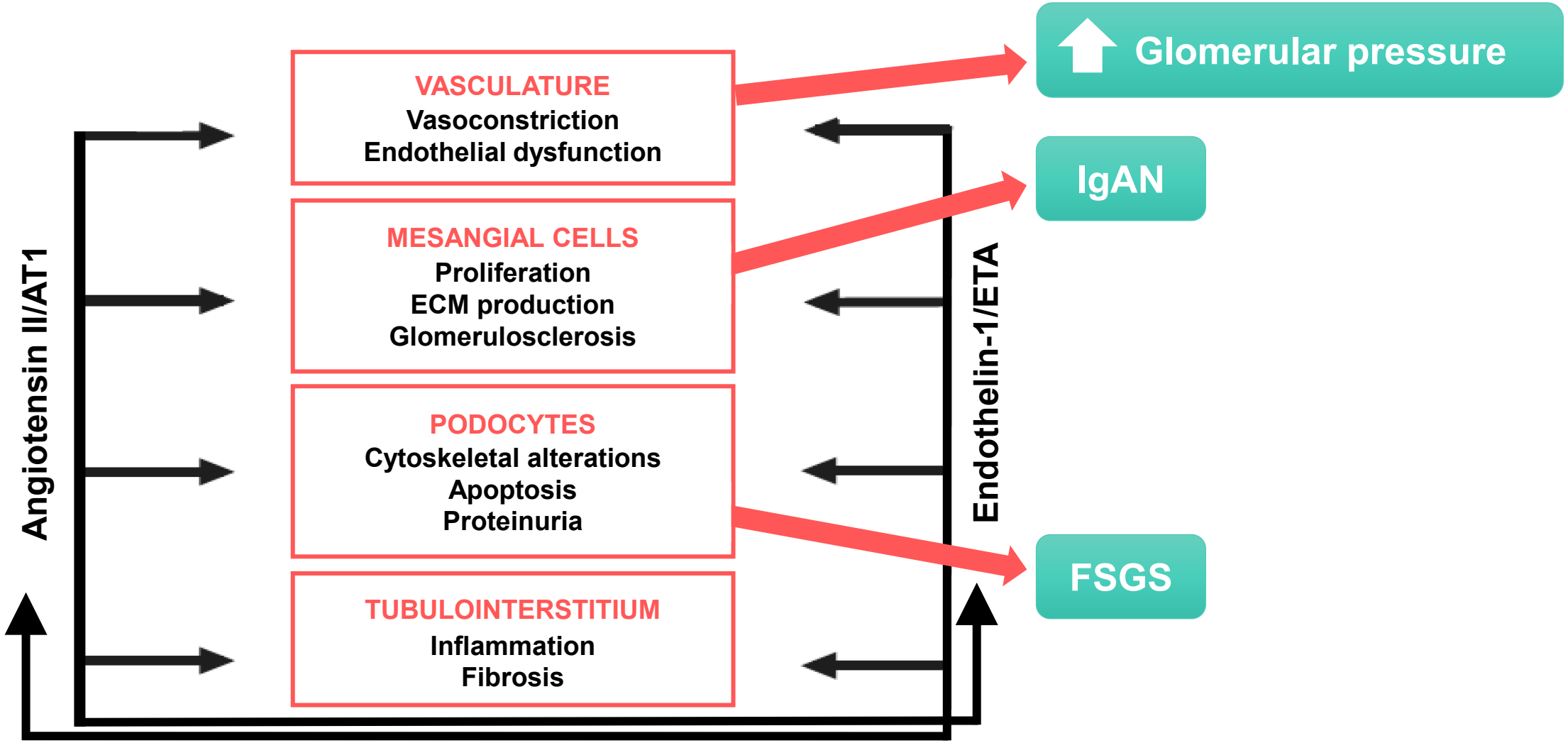
Modified from Kitamura K, et al. *Biochem Biophys Res Commun*. 1989;161(1):348-352. Kohan DE. *Am J Physiol*. 1991;261(2 Pt 2):F221-F226.

Pathophysiology of IgAN

- **Proteinuria**
- **Angiotensin II/AT1**



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 >1g/day
- Impaired kidney function
- End-organ damage, such as hypertension

Consider a biopsy with proteinuria >0.5g/day

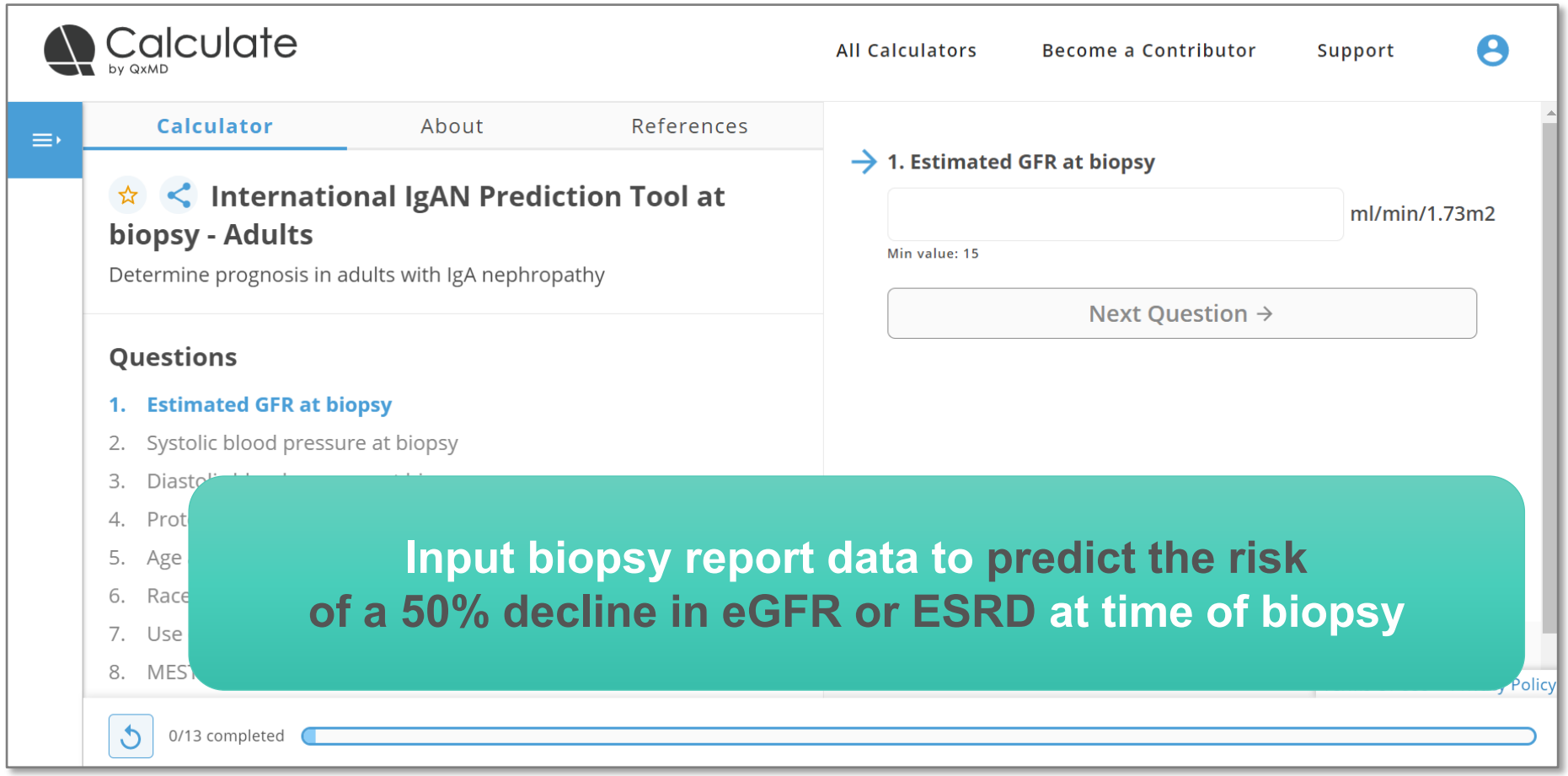
Oxford Classification: MEST-C Score

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

Trimarchi H, et al. *Kidney Int*. 2017;91(5):1014-1021.

International IgAN Prediction Tool

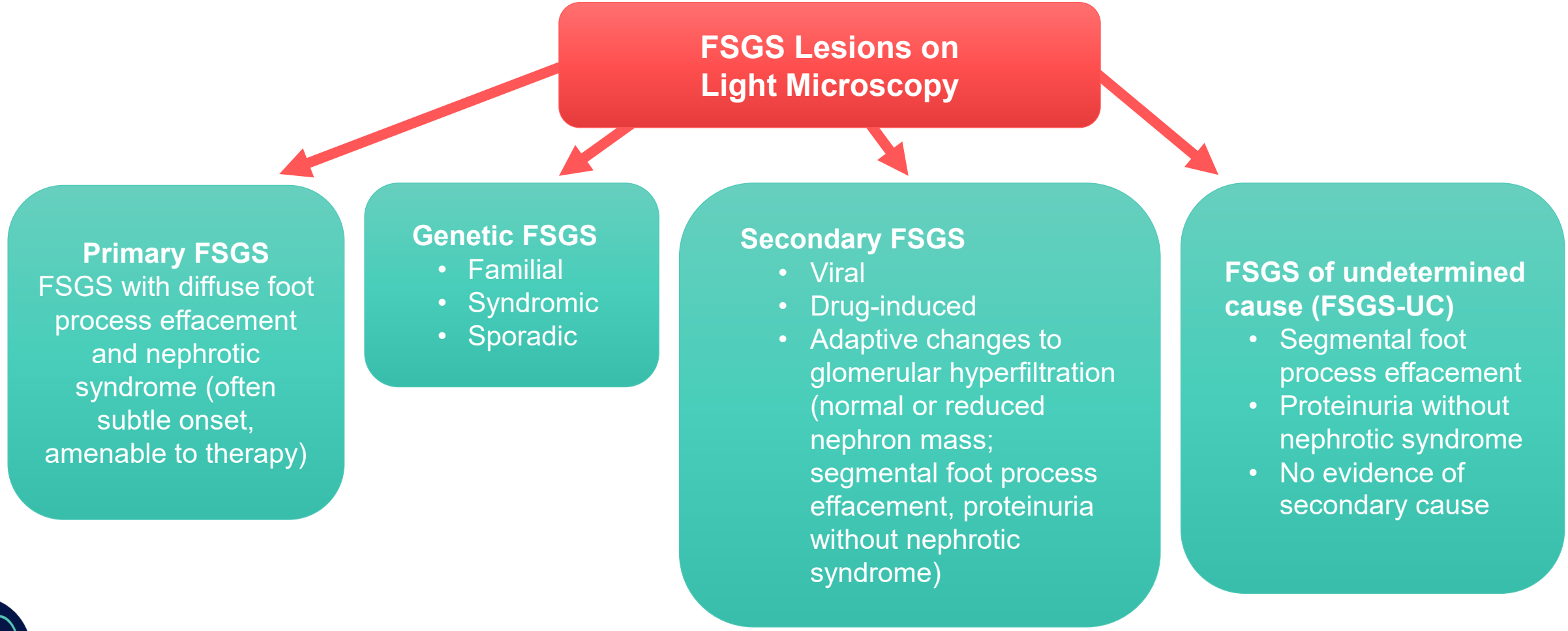
https://qxmd.com/calculate/calculator_499/international-igan-prediction-tool-at-biopsy-adults



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

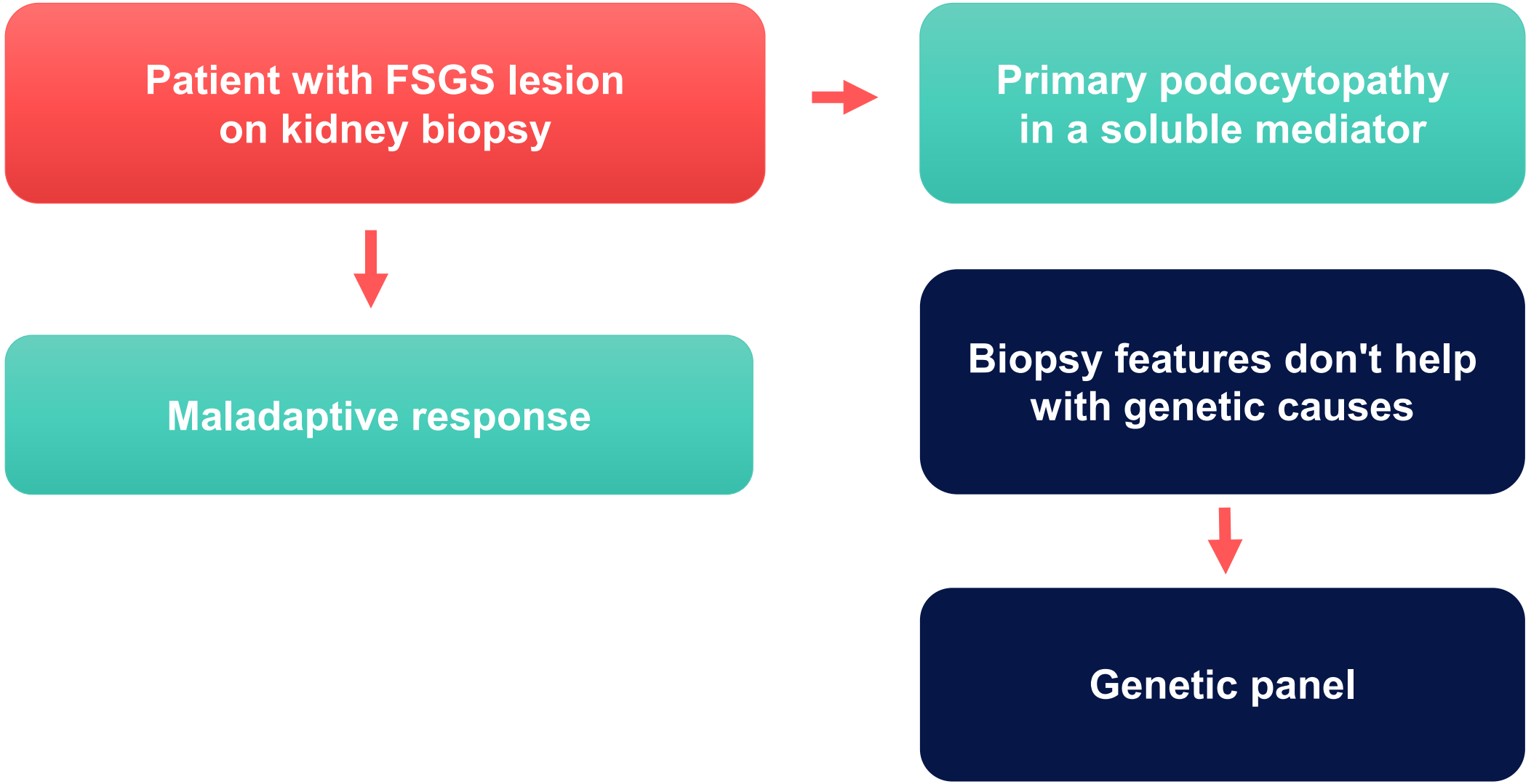
Barbour SJ, et al. *JAMA Intern Med*. 2019;179(7):942-952.

KDIGO: Classification of FSGS



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

FSGS: Kidney Biopsy for Underlying Cause



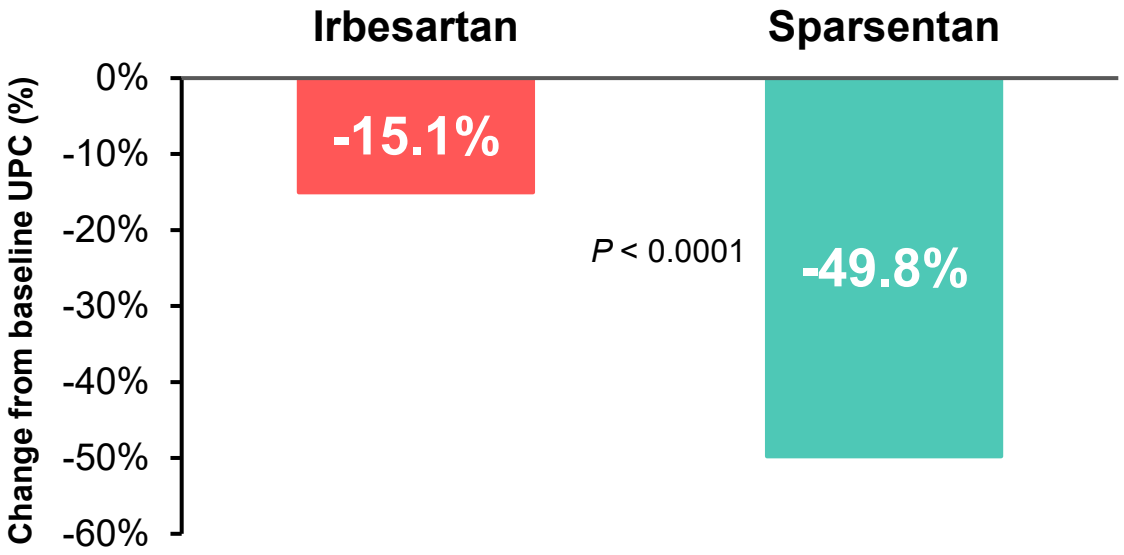
KDIGO: Treatment of a Patient with IgAN

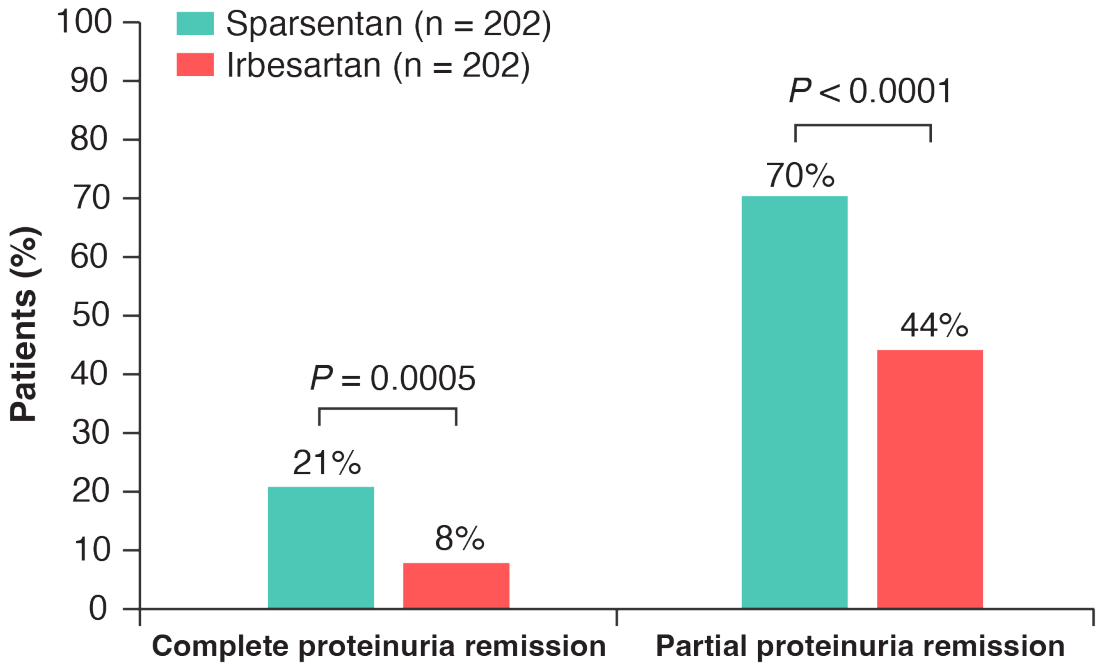
Blood pressure control (125/75 mm Hg)
Healthy weight
Dietary sodium restriction
Exercise regularly
Maximal tolerated dose of RAS inhibitor, whether or not hypertensive
Reduce proteinuria
Address any cardiovascular risk factors

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

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%

Syed YY. *Drugs*. 2023;83(6):563-568. Sparsentan. Prescribing information. Travere Therapeutics, Inc.; 2023.

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