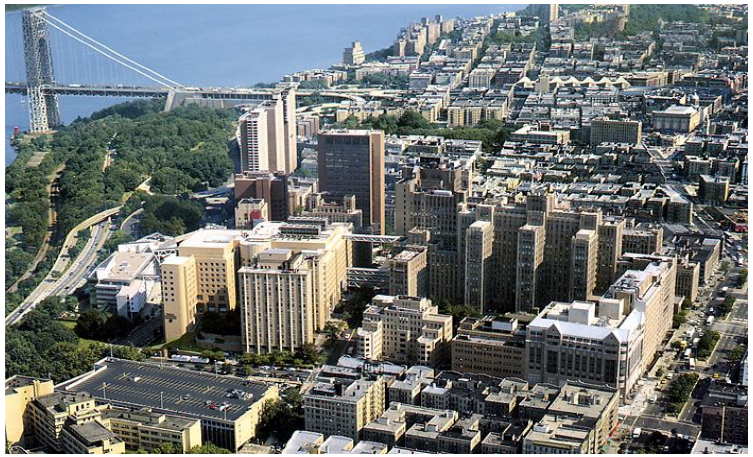


Exciting Developments and Challenges in Diagnosing and Treating Glomerular Diseases

Gerald B. Appel, M.D.

Professor of Medicine

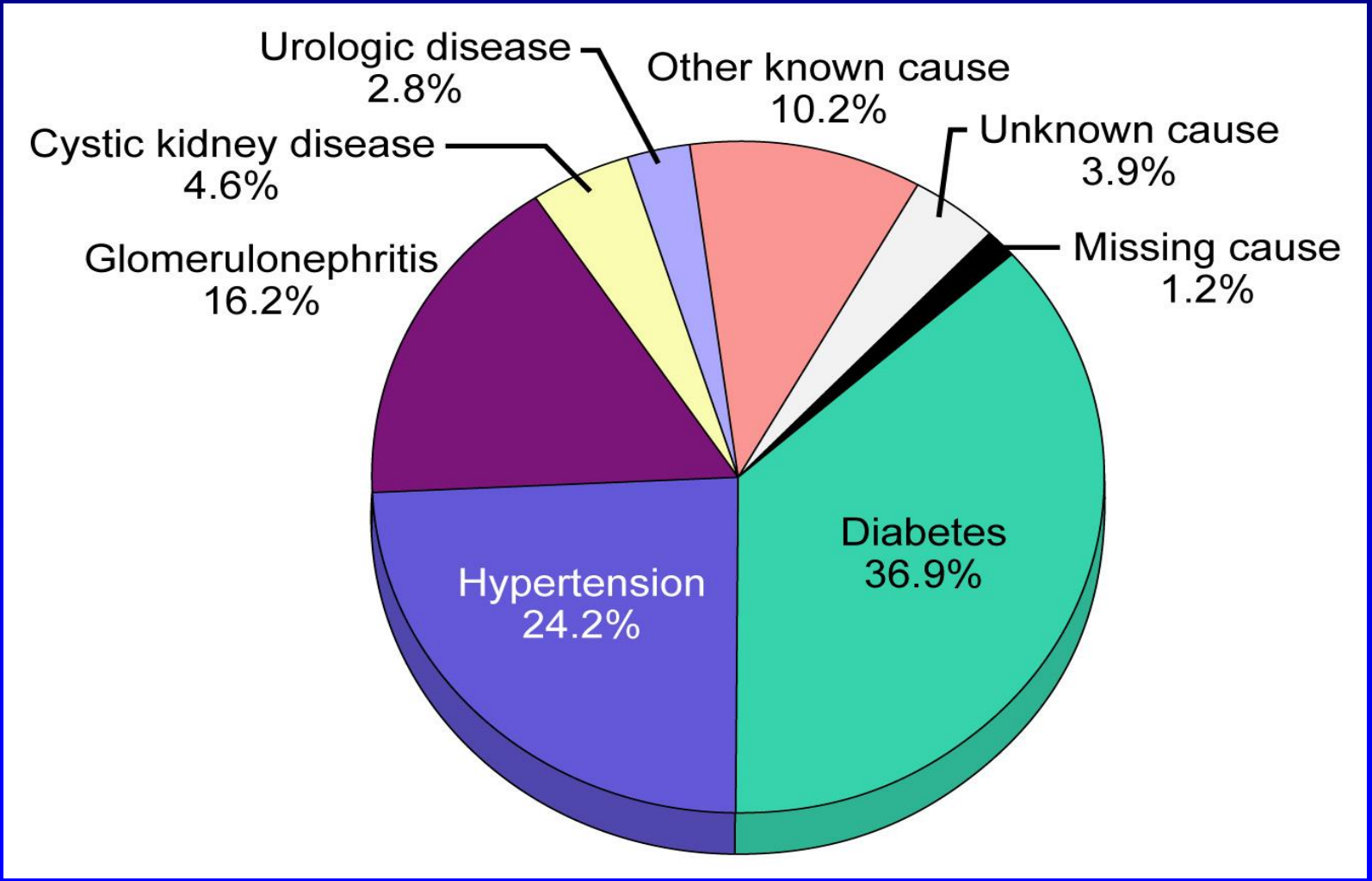
Director - The Center for Glomerular Diseases

Division of Nephrology

Columbia University College of Physicians and Surgeons

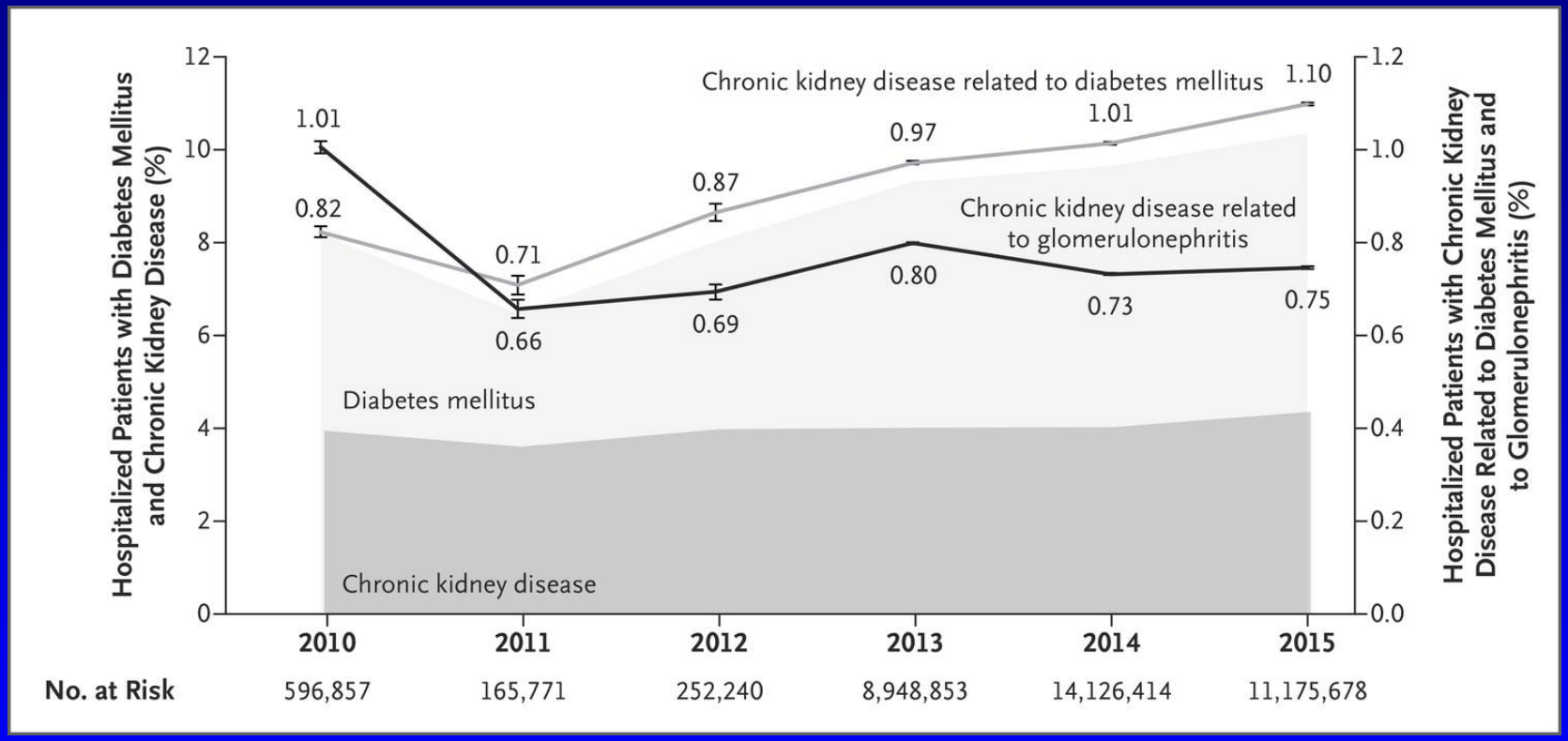
New York May 2019

Etiology of CKD



- **United States Kidney Foundation. www.kidney.org.**

Trends in Chronic Kidney Disease Related to Diabetes and to Glomerulonephritis among Hospitalized Patients in China.



Zhang L et al. N Engl J Med 2016;375:905-906.

Exciting Developments in Diagnosing and Treating Glomerular Diseases

Diagnostic tests –

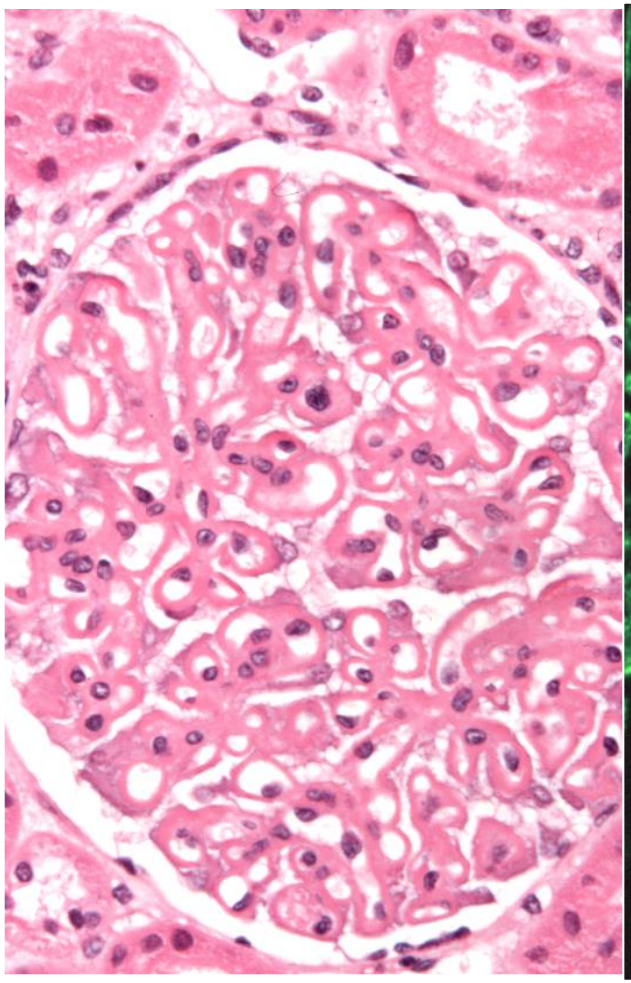
PLA2R in Membranous Nephropathy

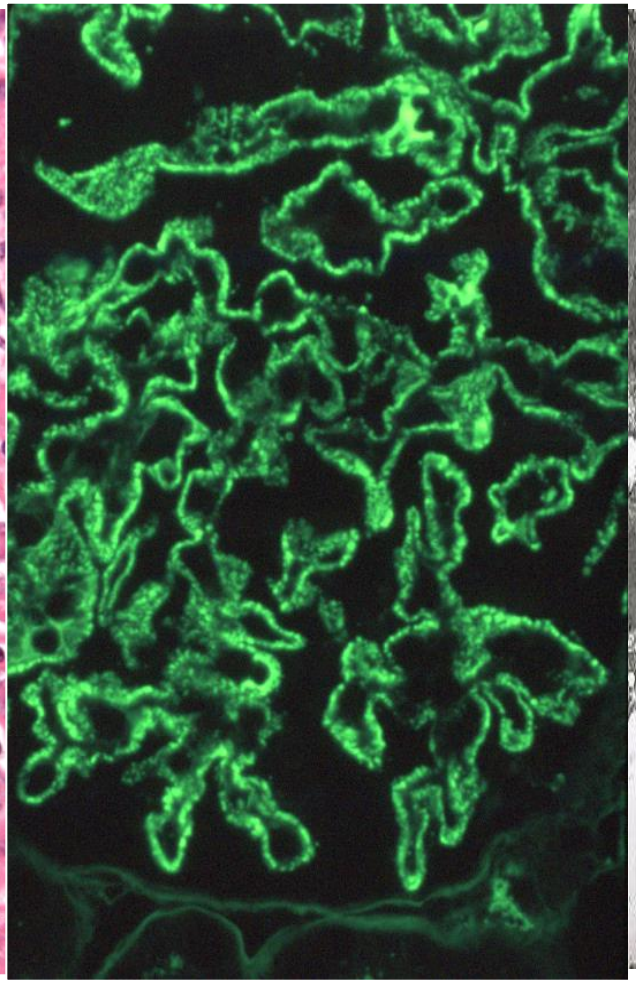
Genetic Screening in Glomerular Disease

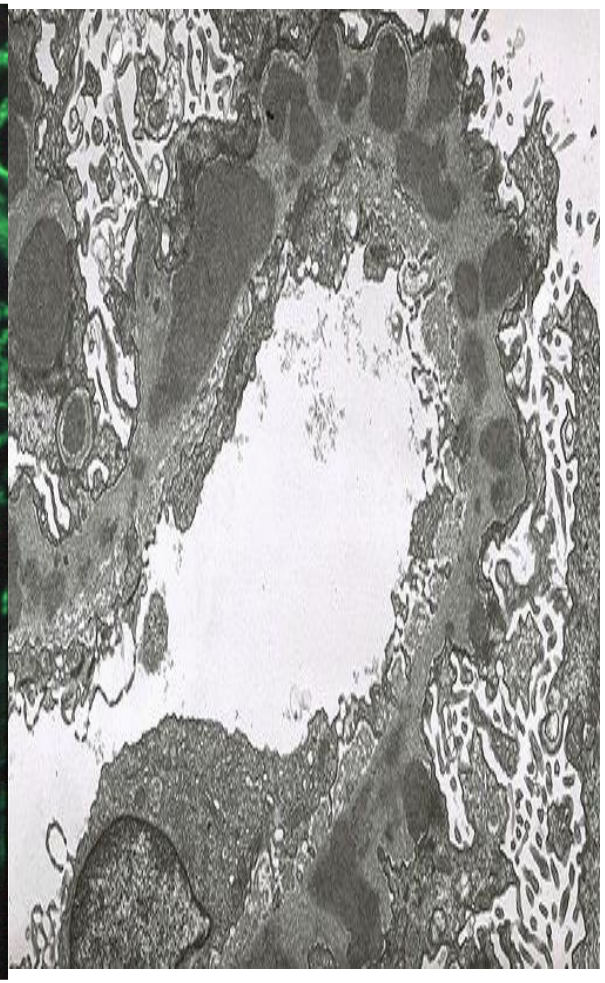
Use of New medications –

Rituximab

Membranous Nephropathy







Most common idiopathic NS in White Adults
Heavy Proteinuria and the Nephrotic Syndrome

Membranous Nephropathy

3 problems in Dx and Rx MN:

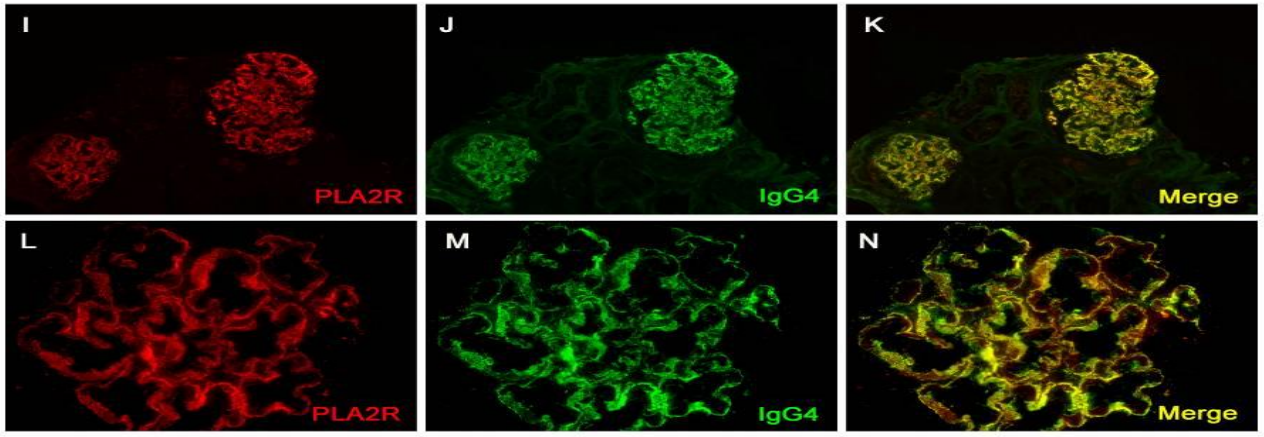
1) 80% Idiopathic but 20% secondary cause - e.g SLE, HBV, > 60 yo Malignancy, etc

2) Only slowly progressive with spontaneous remission rate: 20%-30% - who to treat? Treatment studies are difficult.

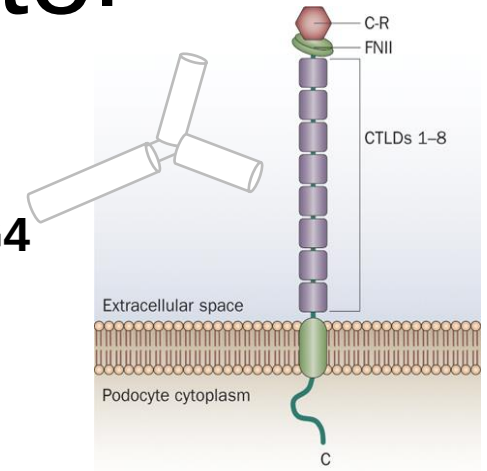
3) No biomarker to follow !!!

Phospholipase A2 Receptor

- 185-kD glycoprotein present on **normal podocytes**
- Found in **immune deposits** of patients with idiopathic MN
- PLA2R and IgG4 **co-localize** on biopsy specimens from pts with idiopathic MN in a typical granular

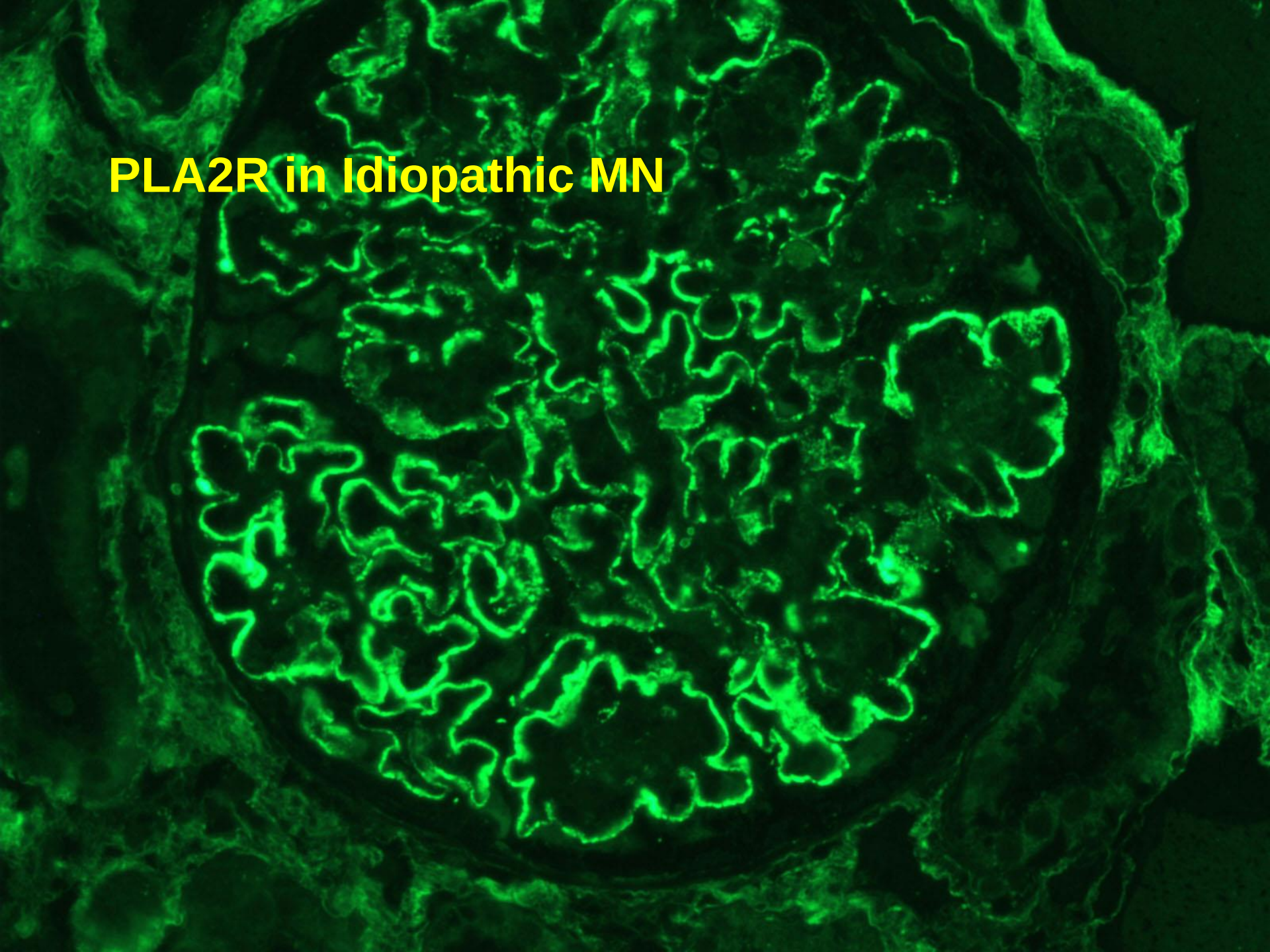


IgG4

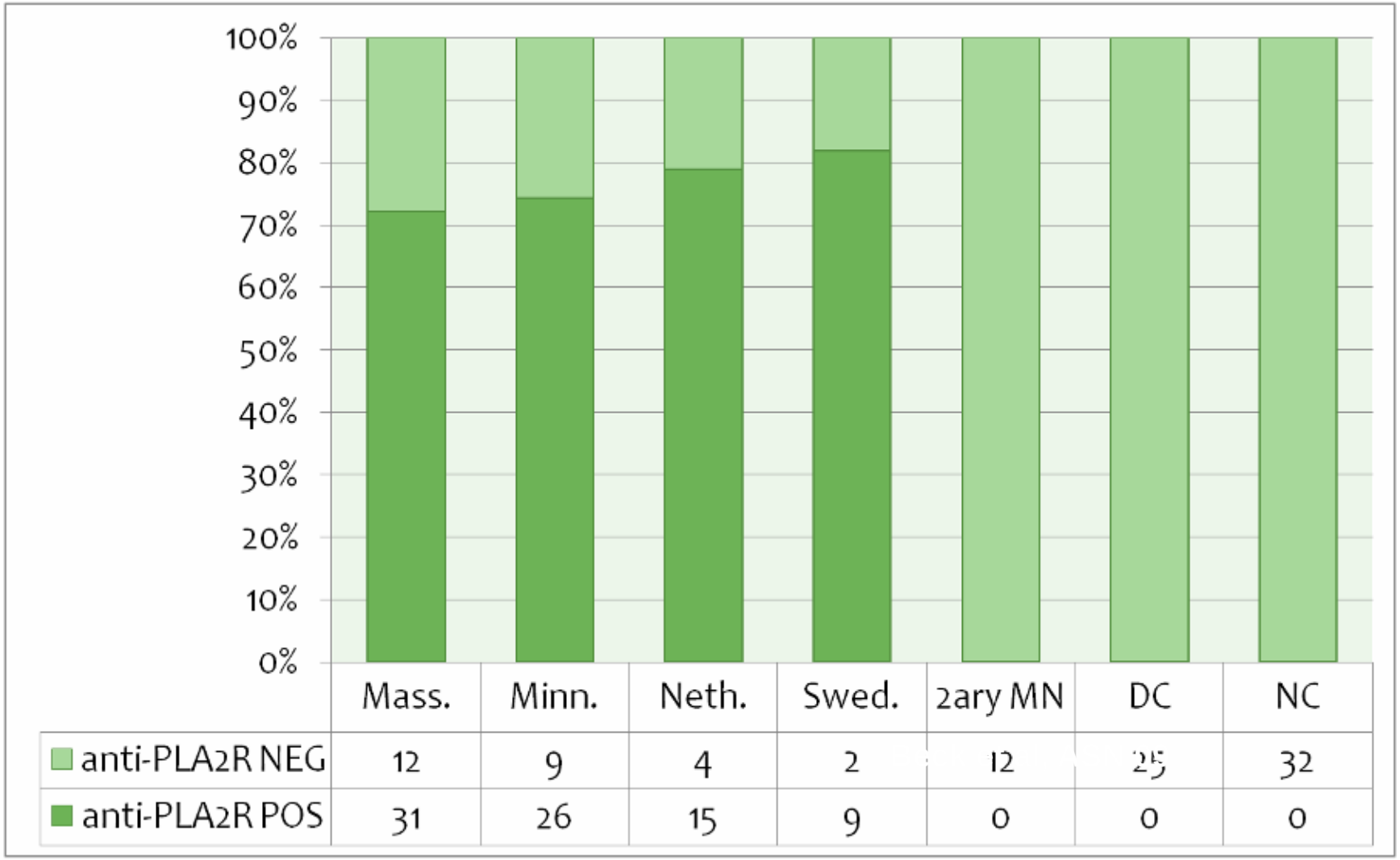


~70-80% of patients with idiopathic, but not secondary, MN have antibodies against PLA_2R

Beck et al., NEJM, July 2, 2009 Rees & Kain, Nature Reviews Nephrology 5, 617-618 , 2009.

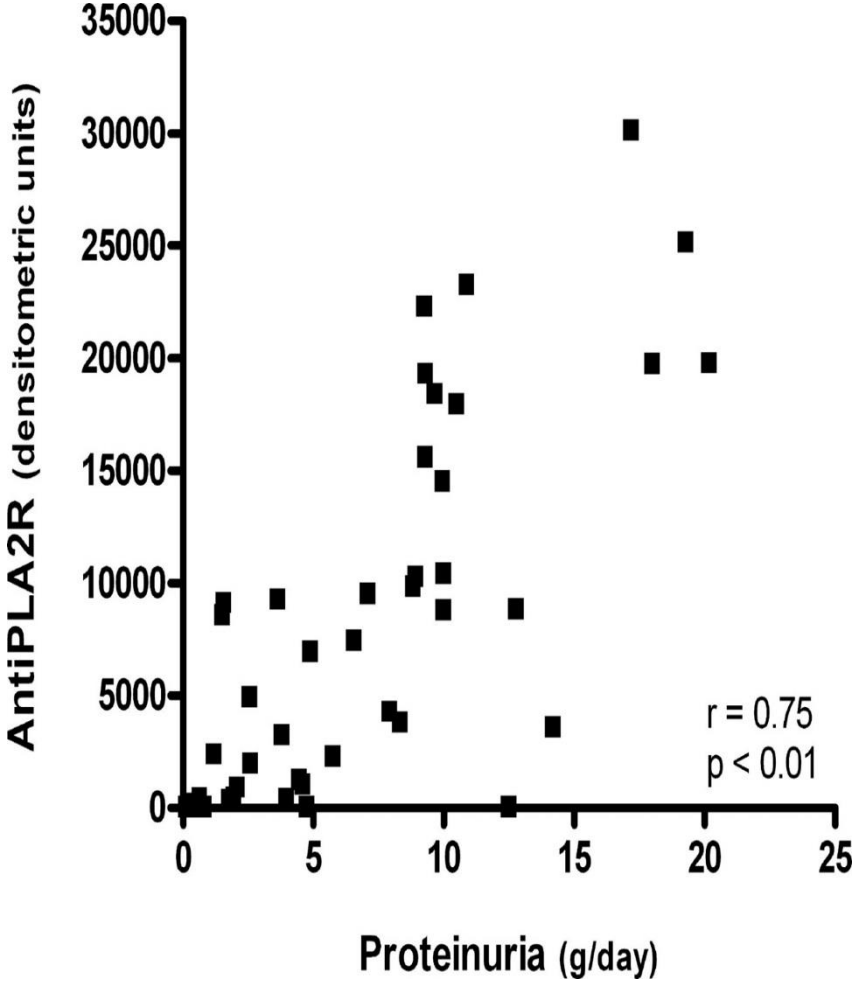

PLA2R in Idiopathic MN

Anti-PLA_2R: sensitivity and specificity

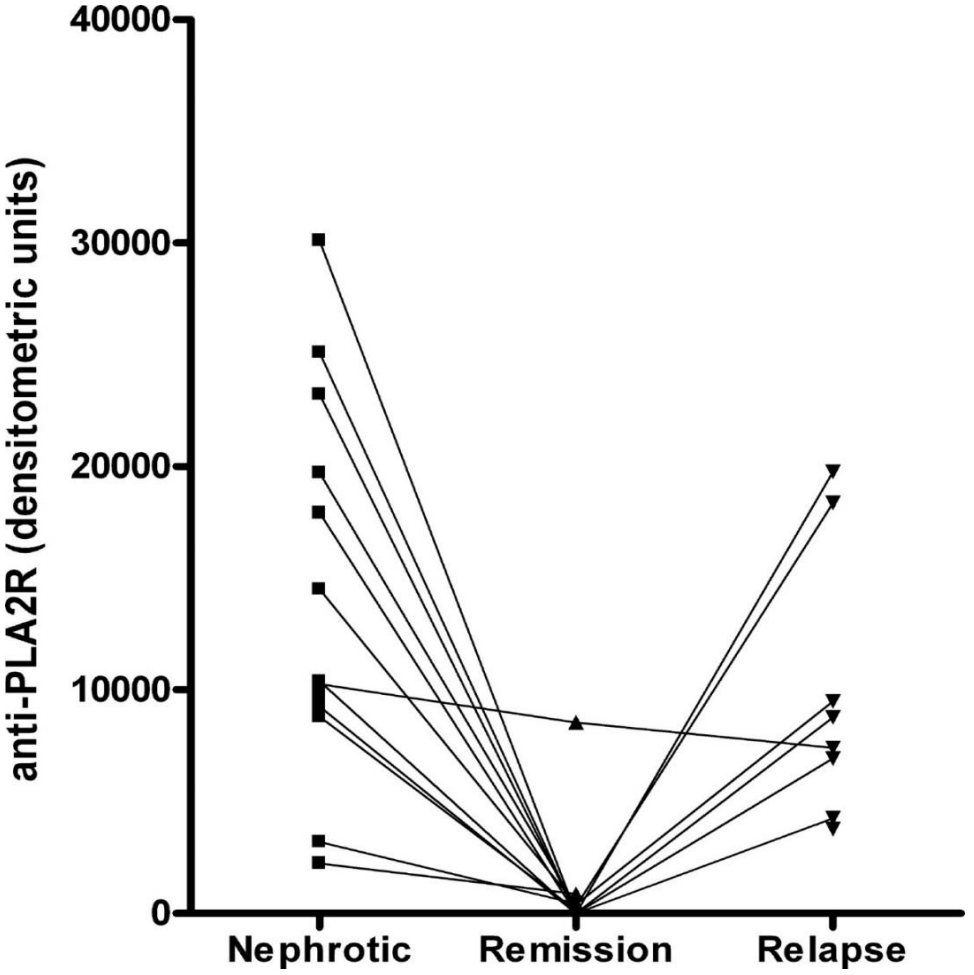


	Mass.	Minn.	Neth.	Swed.	2ary MN	DC	NC
anti-PLA2R NEG	12	9	4	2	12	25	32
anti-PLA2R POS	31	26	15	9	0	0	0

Correlation between the anti-PLA2R antibody level and proteinuria.

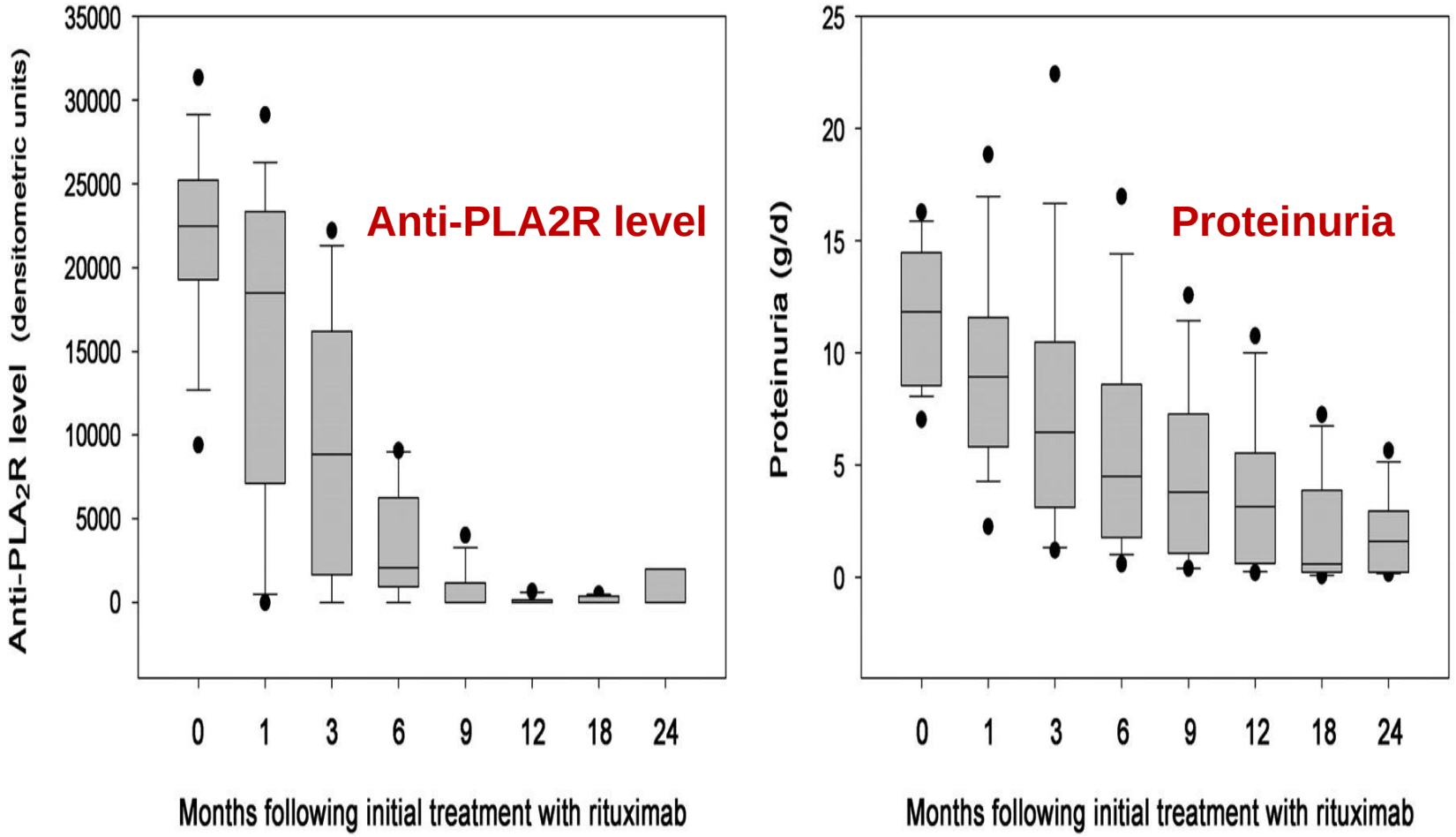


Anti-PLA2R-autoantibody levels during course of 13 anti-PLA2R-positive patients with remission of proteinuria.



Hofstra J M et al. CJASN 2011;6:1286-1291

Disappearance of anti-PLA_2R precedes that of proteinuria.



Beck L H et al. JASN 2011;22:1543-1550

Patients with high-titer aPLA$_2$R are unlikely to undergo spontaneous remission

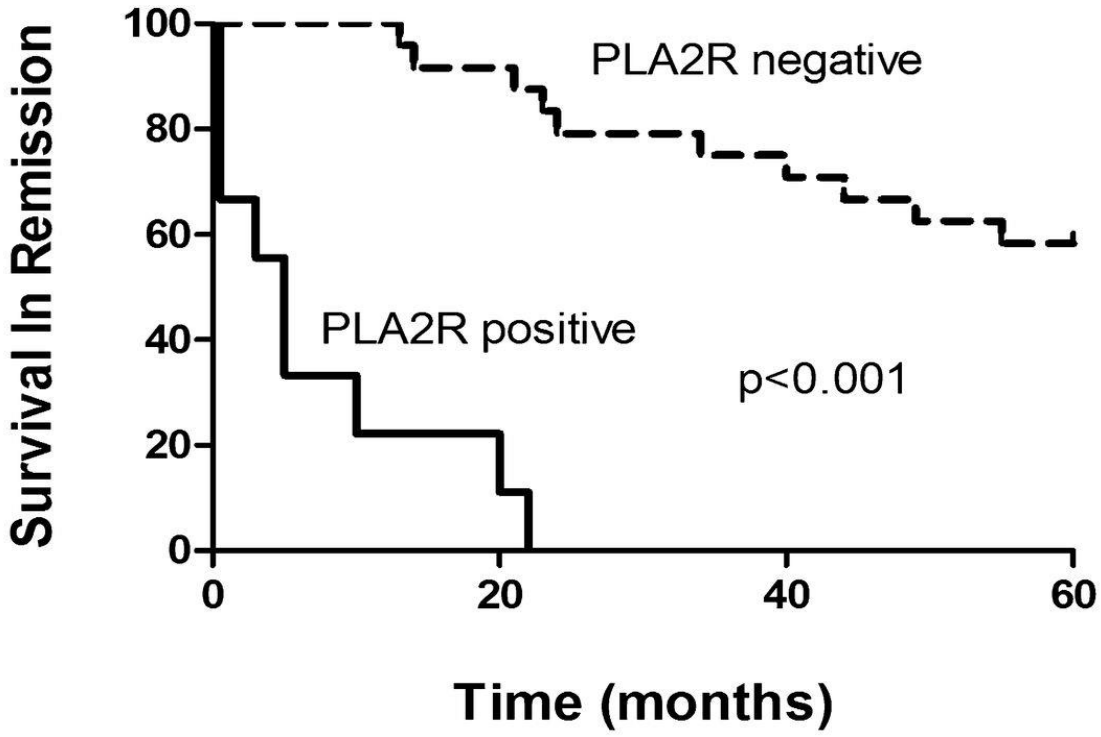
Outcome	aPLA$_2$R titer, by tertile: Low 41–175 U/ml (*n*=26)	Middle 176–610 U/ml (*n*=26)	High >610 U/ml (*n*=27)	*P* Value
Partial remission	11 (42%)	8 (31%)	11 (41%)	NS
Complete remission	7 (27%)	9 (35%)	8 (30%)	NS
Renal failure	1 (4%)	3 (12%)	5 (19%)	NS
Persistent proteinuria	7 (27%)	6 (23%)	3 (11%)	NS
Spont. Remit	10 (38%)	8 (31%)	1 (4%)	<0.01

**No treatment with immunosuppressive agents*

Hofstra JASN 2012

aPLA$_2$R antibody status at end of immunosuppression course predicts survival in remission

None of the patients with +PLA2R antibodies *at the end of therapy* had a persistent remission.



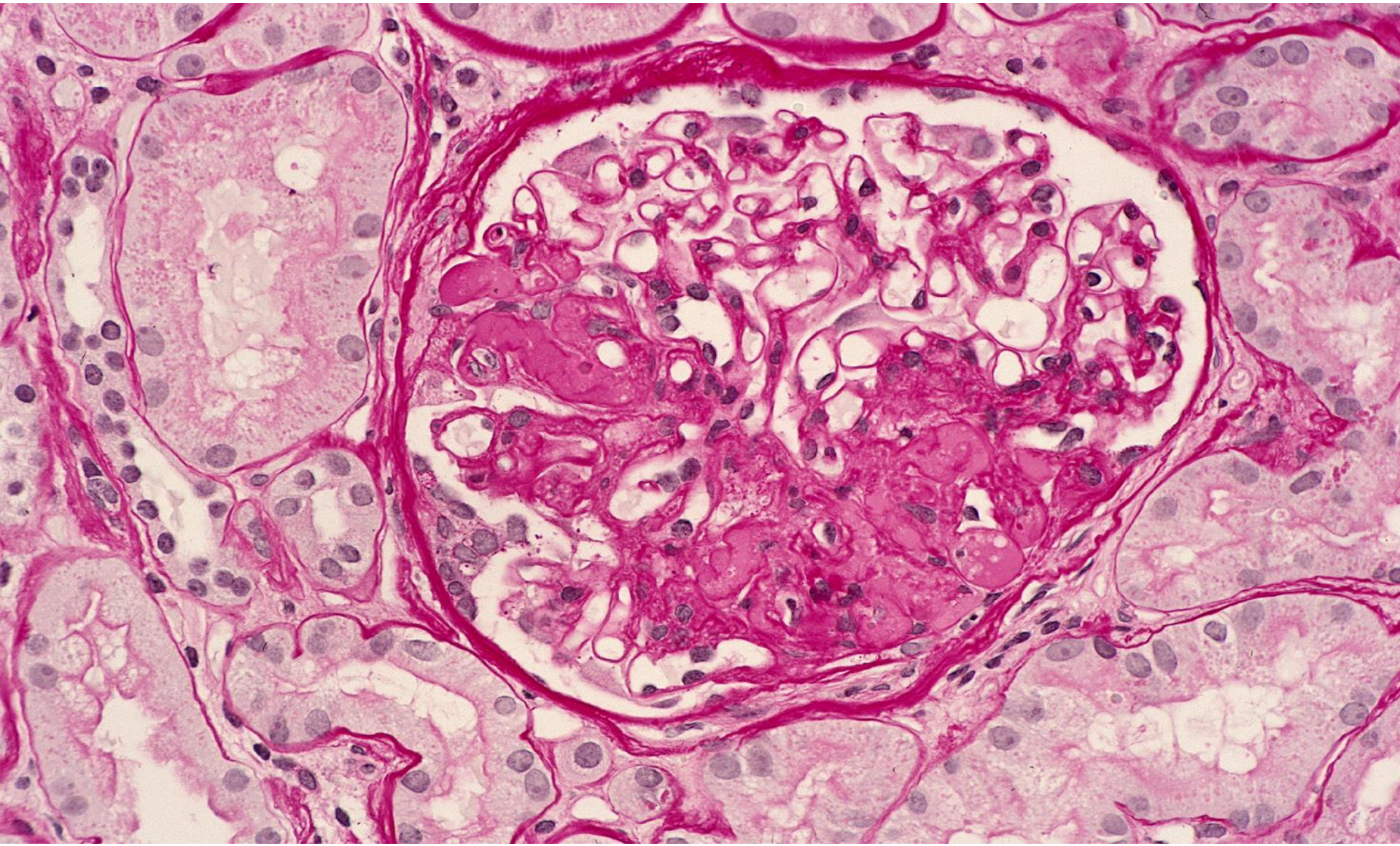
PLA2R positive	9	2	0	0
PLA2R negative	24	22	18	14

Bech A P et al. *CJASN* 2014;9:1386-1392

Anti-PLA2R as a biomarker for Idiopathic MN

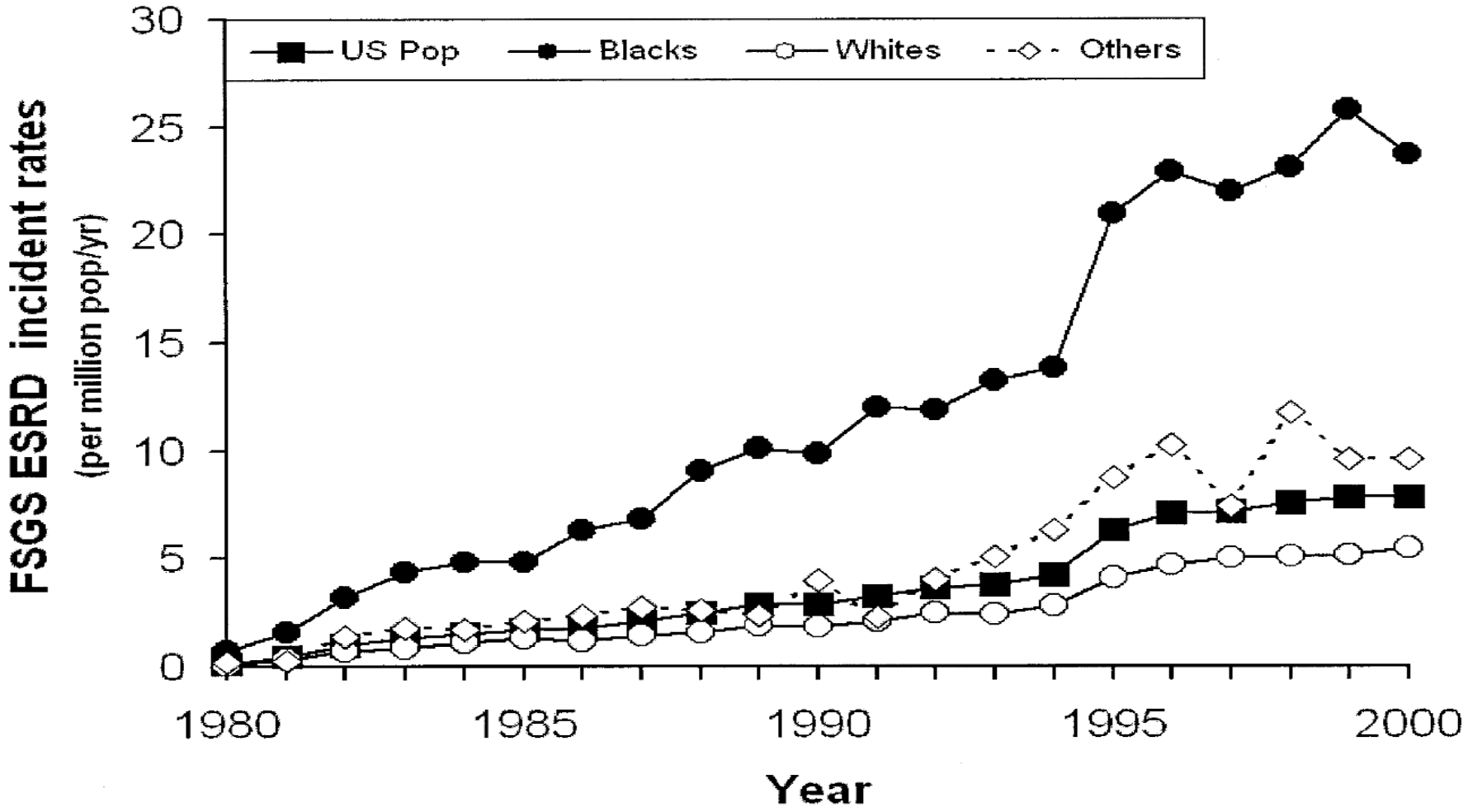
1) Presence of Bx staining for PLA 2R or circulating levels of the antibody are markers for idiopathic disease.
2) Higher titers predict no spontaneous remissions.
3) High titers at end of immunosuppressive medication predict relapse

Focal Segmental Glomerulosclerosis



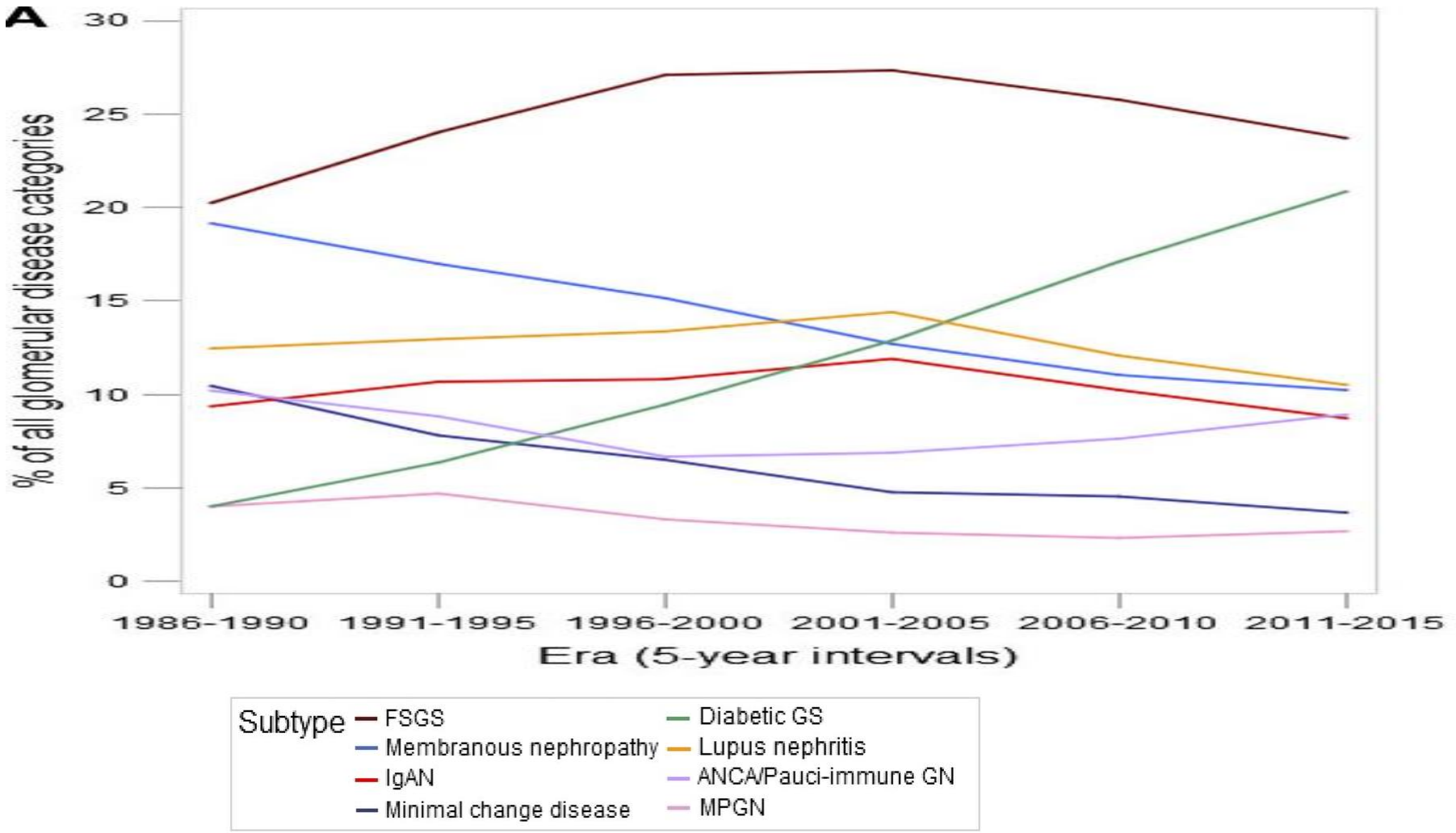
Twenty-one year trend in ESRD due to FSGS in the US

K.Chagriya, P. Eggers, and J B. Kopp. *American Journal of Kidney Diseases* 44.5 (2004): 815-825.

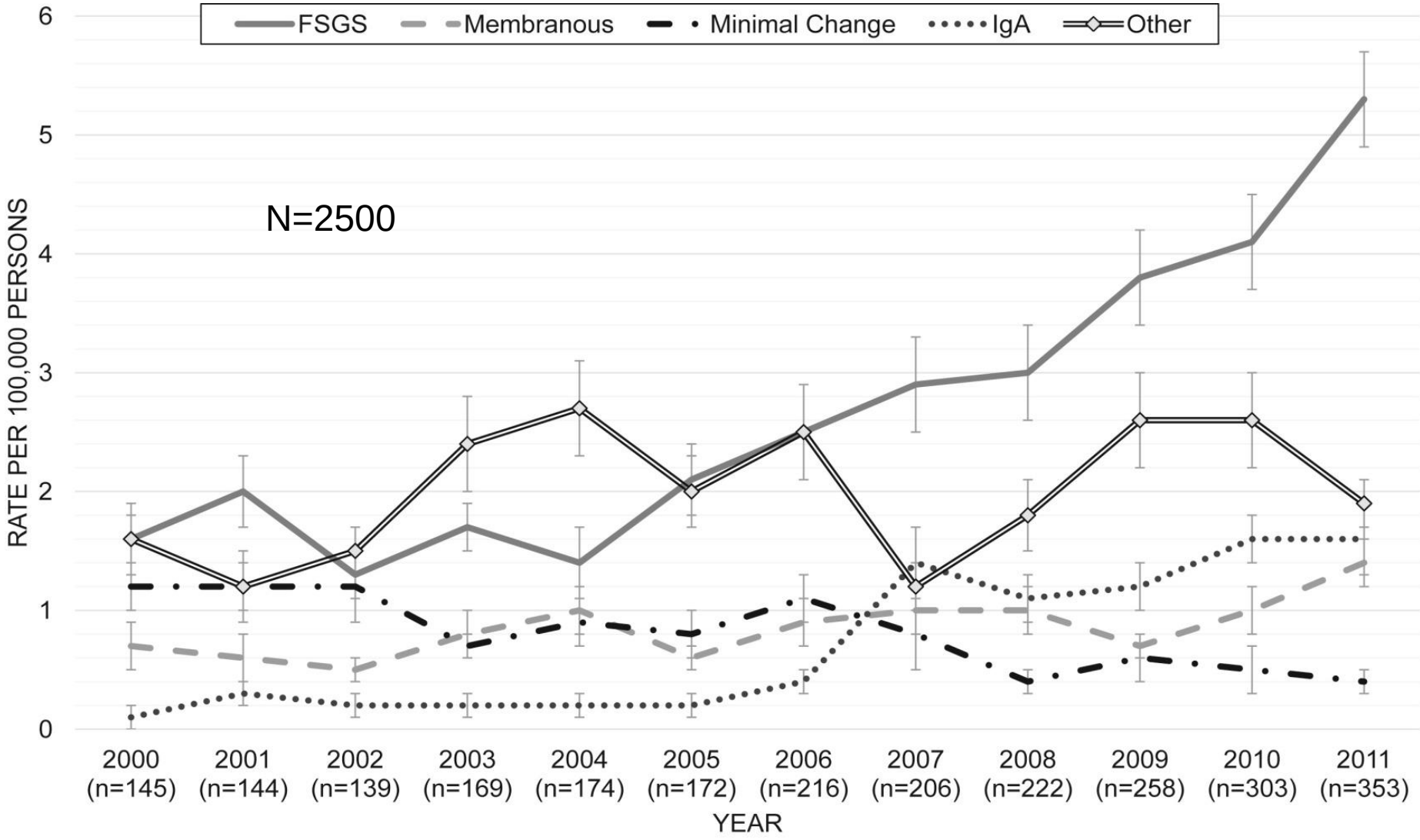


Renal Biopsy frequencies of the most common glomerular disease

M M. O'Shaughnessy et al. CJASN 2017;12:614-623



Biopsy-Proven Primary Glomerulopathies 2000-2011 (Kaiser, S California)



Sim JJ..Am J Kidney Dis. 2016 Oct;68(4):533-44

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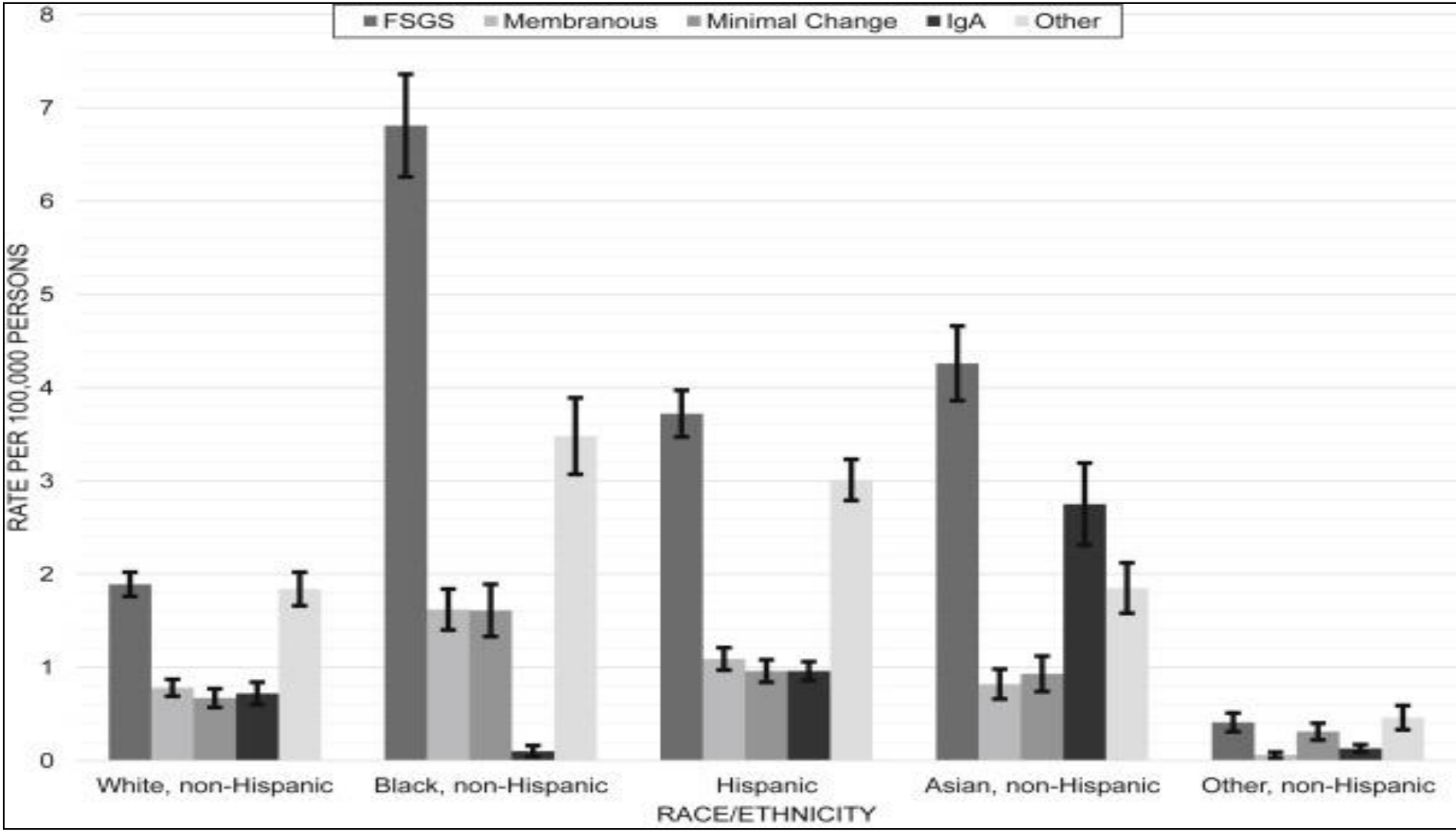
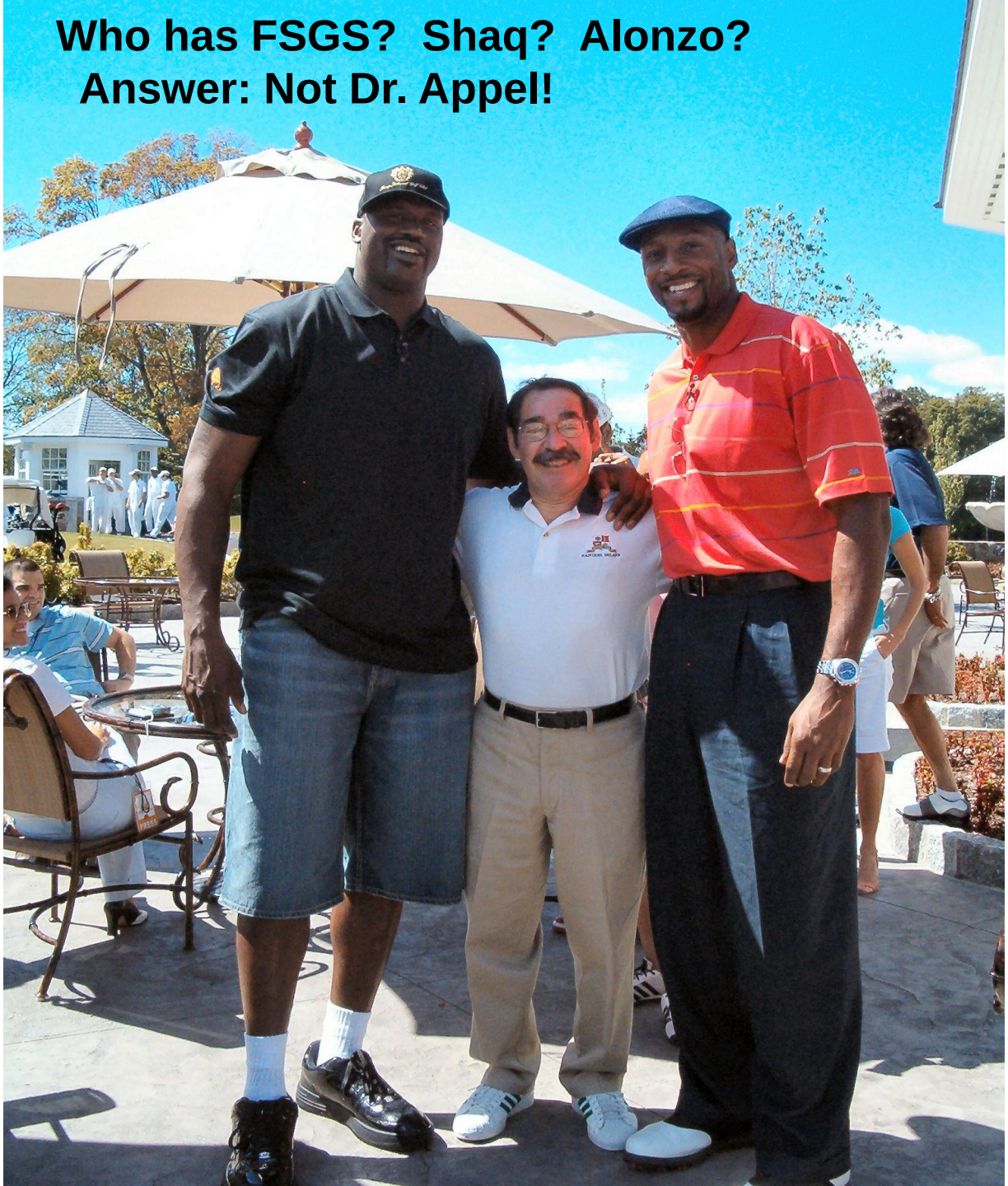


Sim JJ..Am J Kidney Dis. 2016 Oct;68(4):533-44

Who has FSGS? Shaq? Alonzo?
Answer: Not Dr. Appel!

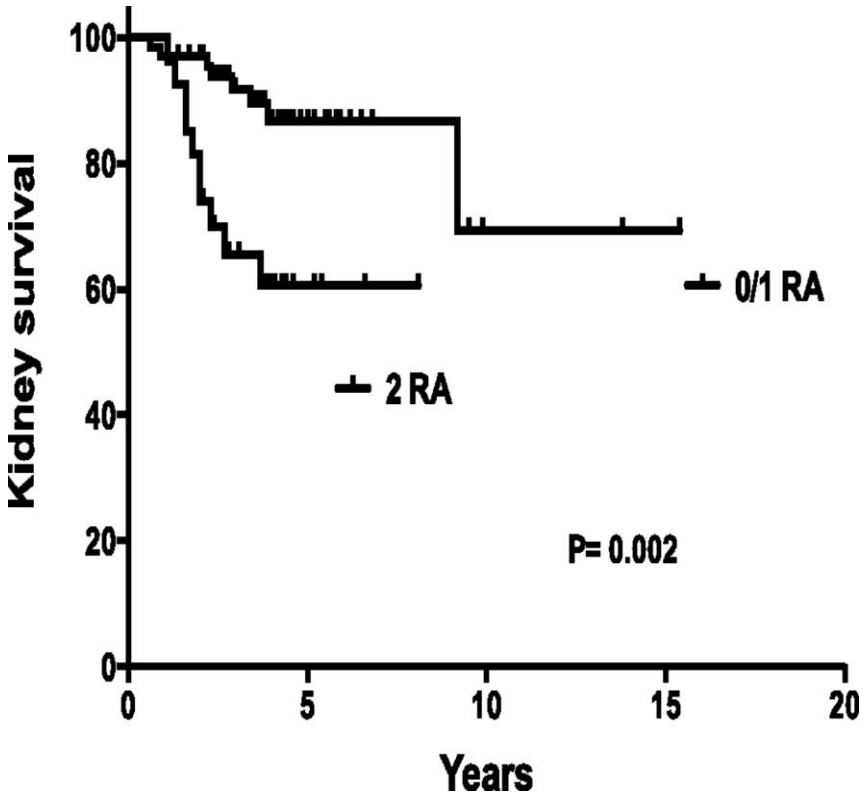


APOL1 and Glomerular Scarring in AA

56 AA and 61 White Americans with FSGS comparing data on single-nucleotide polymorphisms to 1641 E-A and 1800 AA controls.

Strong association of a region on Chromosome 22 containing APOL1.

APOL1 selected for by prevention of Trypanasoma brucei (African Sleeping Sickness)



Shorter Renal survival with 2 APOL1 Risk Alleles

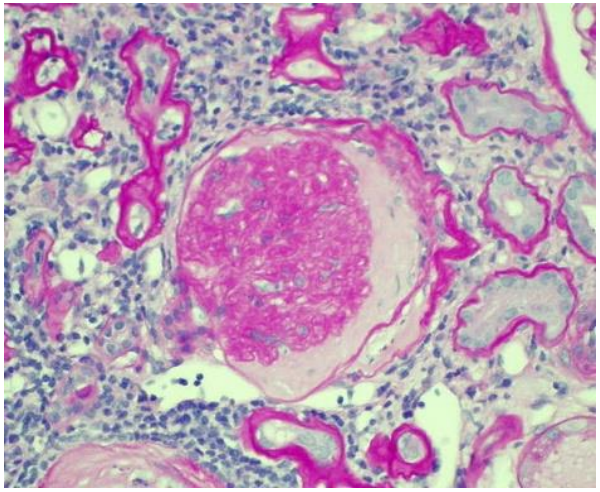
Genovese G, … Appel GB…Pollak MR.
Kidney Int 78:698-704, 2010.

Kopp JB et al.
JASN 2015;26:1443-1448

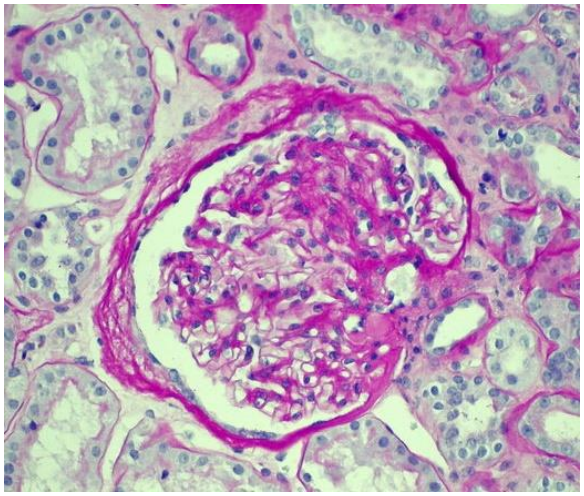
Spectrum of *APOL1*-associated nephropathy

Focal Global Glomerulosclerosis

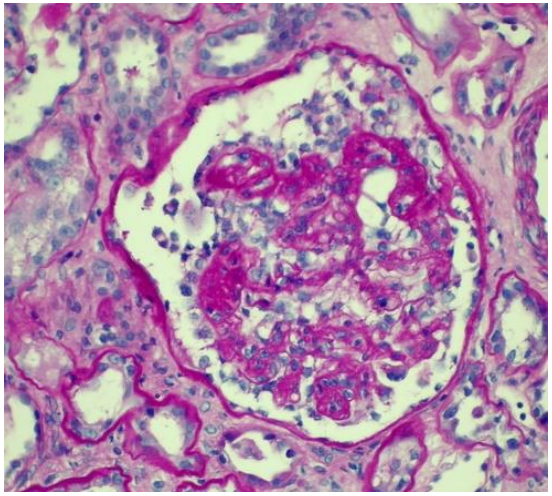
"Hypertension-attributed"



Focal Segmental Glomerulosclerosis



Collapsing FSGS (HIVAN)

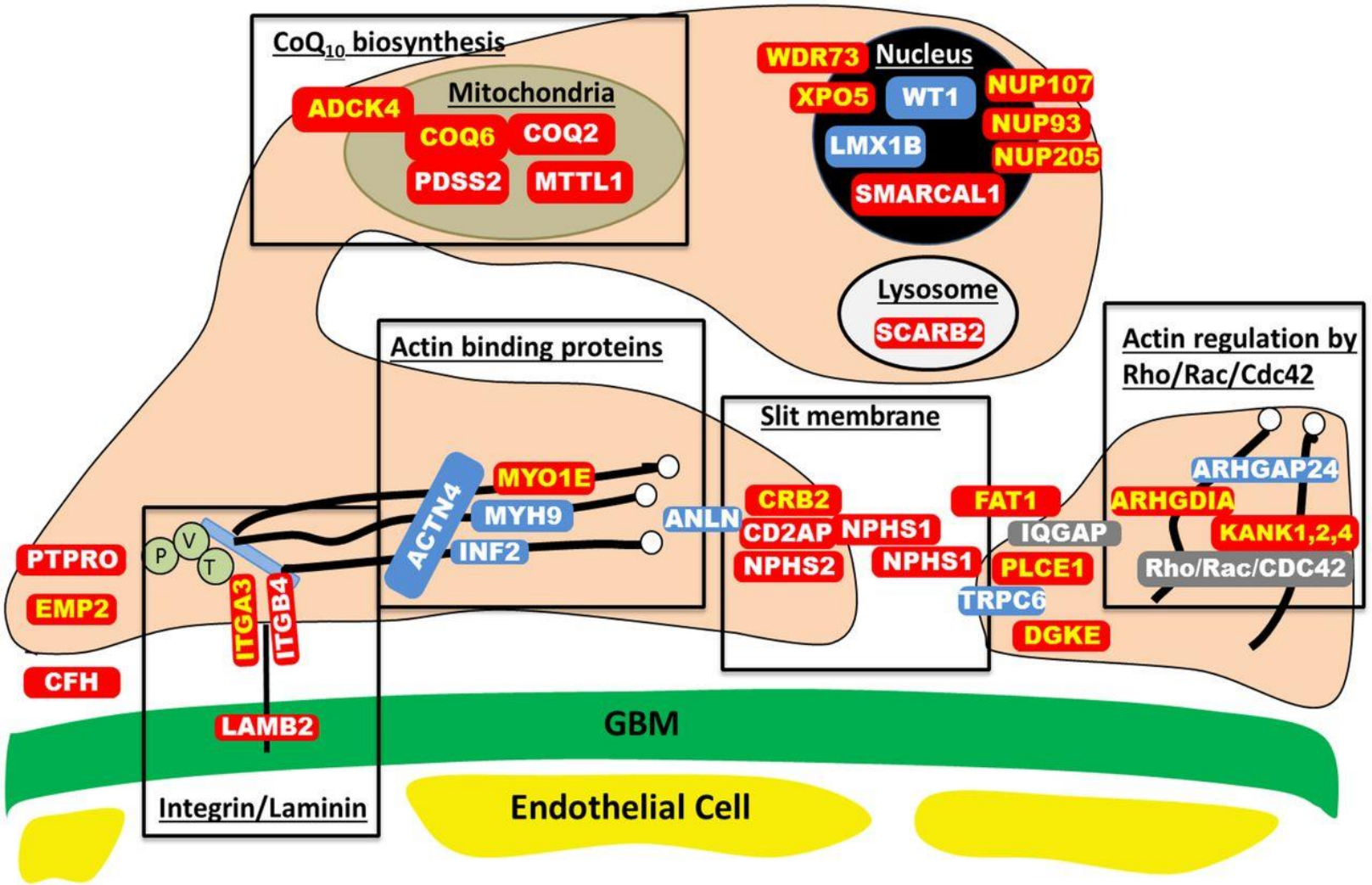


Proteinuria & nephropathy progression rate

Severe lupus nephritis
Sickle cell nephropathy

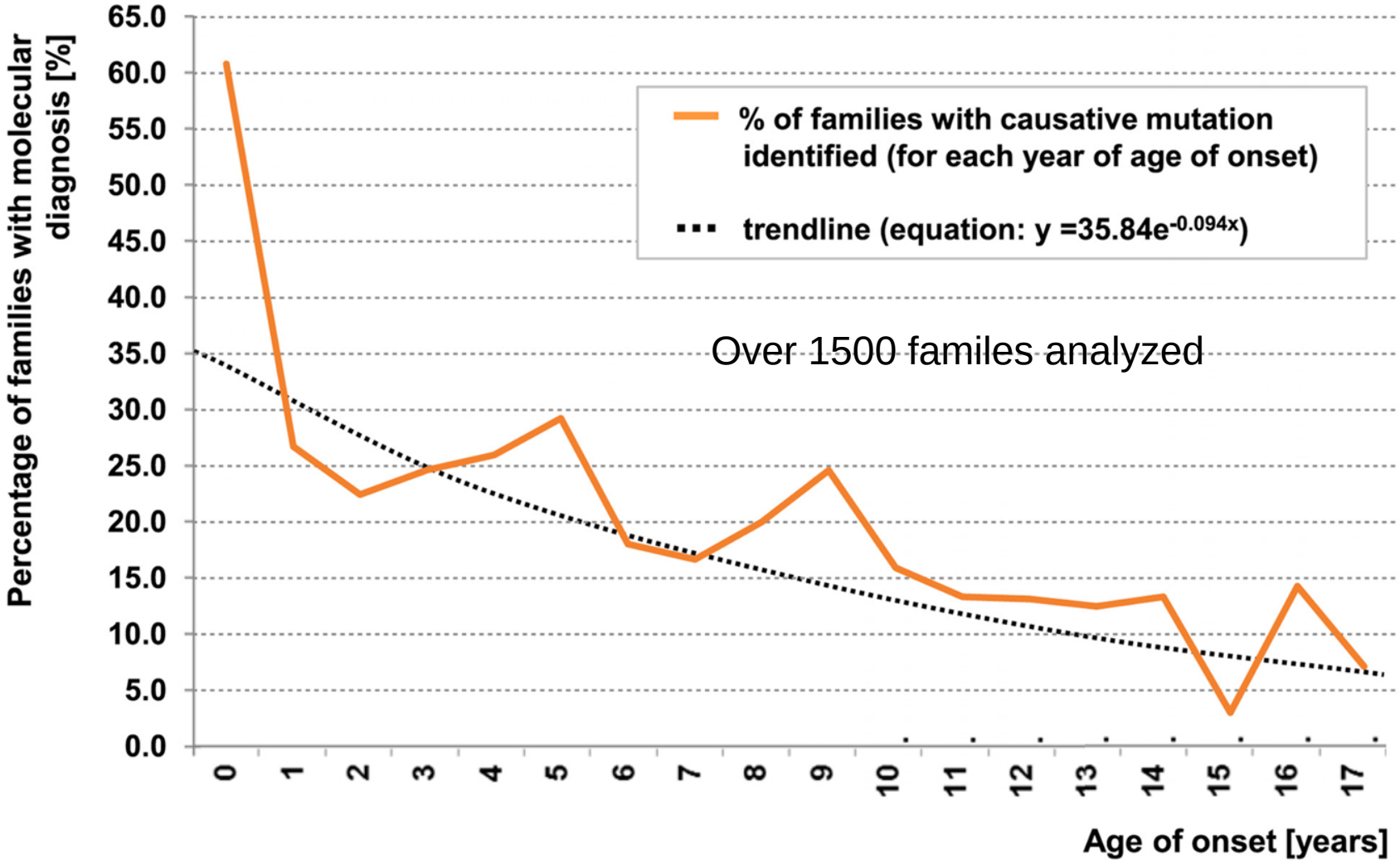
Freedman, Bowden & Rich: Brenner and Rector's The Kidney

Genetic Models of FSGS – 52 genes



Lovric, S., Ashraf, S., Tan, W., & Hildebrandt, F. Genetic testing in steroid-resistant nephrotic syndrome: when and how?.Nephrol Dial Transplant. 2015;11:1802-1813.

A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome (27 genes).



Carolin E. Sadowski et al. JASN 2015;26:1279-1289

The NEW ENGLAND JOURNAL of MEDICINE

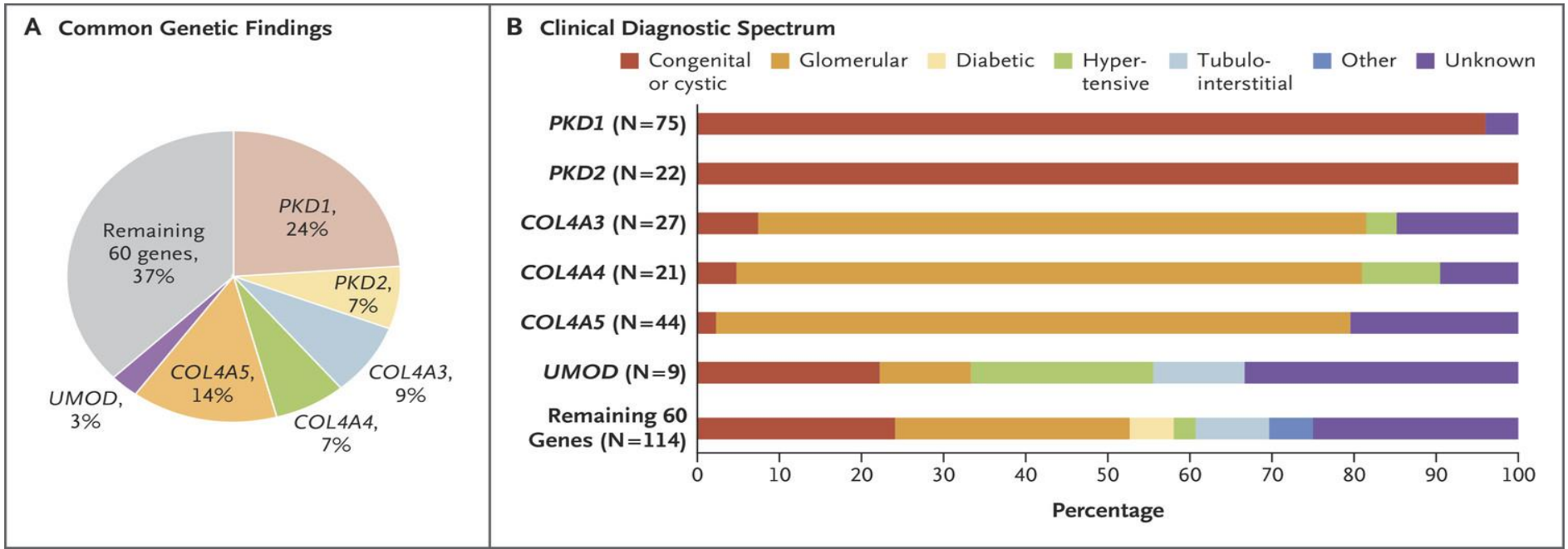
ORIGINAL ARTICLE

Diagnostic Utility of Exome Sequencing for Kidney Disease

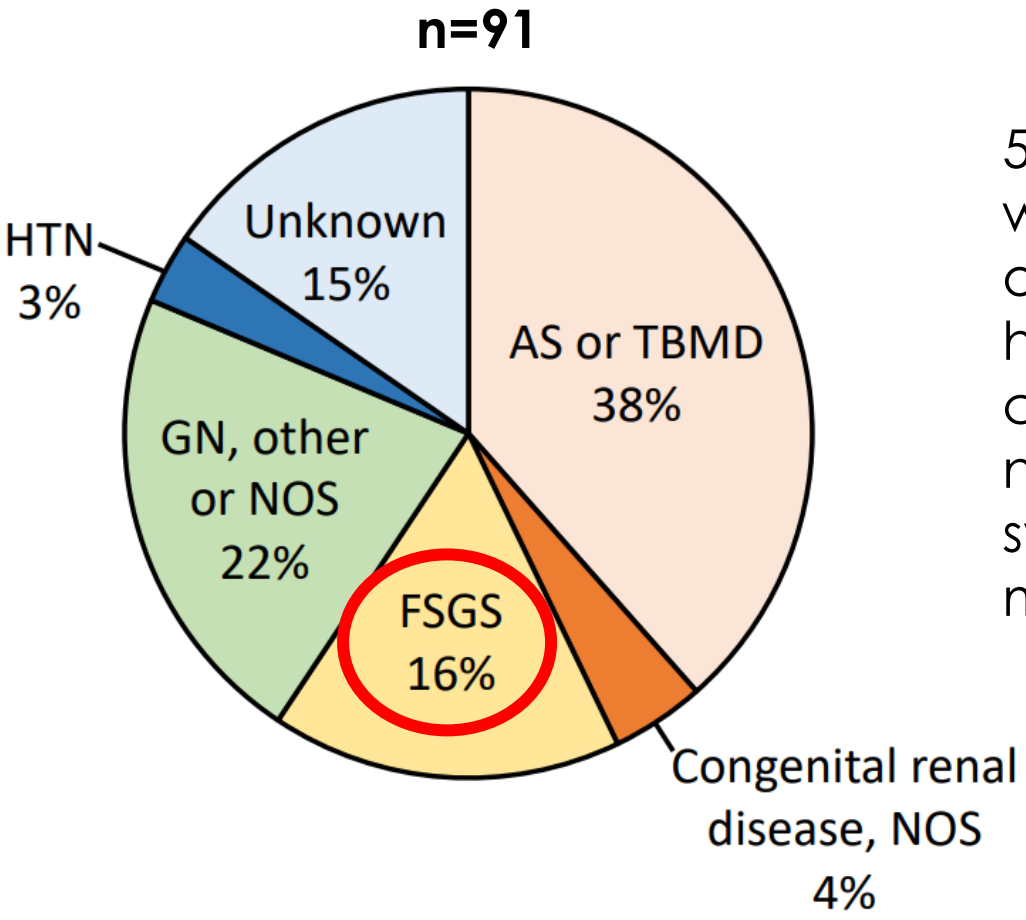
E.E. Groopman, M. Marasa, S. Cameron-Christie, S. Petrovski, V.S. Aggarwal, H. Milo-Rasouly, Y. Li, J. Zhang, J. Nestor, P. Krithivasan, W.Y. Lam, A. Mitrotti, S. Piva, B.H. Kil, D. Chatterjee, R. Reingold, D. Bradbury, M. DiVecchia, H. Snyder, X. Mu, K. Mehl, O. Balderes, D.A. Fasel, C. Weng, J. Radhakrishnan, P. Canetta, G.B. Appel, A.S. Bomback, W. Ahn, N.S. Uy, S. Alam, D.J. Cohen, R.J. Crew, G.K. Dube, M.K. Rao, S. Kamalakaran, B. Copeland, Z. Ren, J. Bridgers, C.D. Malone, C.M. Mebane, N. Dagaonkar, B.C. Fellström, C. Haefliger, S. Mohan, S. Sanna-Cherchi, K. Kiryluk, J. Fleckner, R. March, A. Platt, D.B. Goldstein, and A.G. Gharavi

NEJM.380:142 -151, Jan 2019.

307 of 3315 pts (9.3%)



Clinical diagnostic spectrum of patients with diagnostic variants in COL4A3-5



56 of the 91 patients **(62%)** with *COL4A3*, *COL4A4*, or *COL4A5* mutations **did not** have clinical diagnoses of the classically associated nephropathies (Alport syndrome or thin basement membrane disease)

Groopman EE … Gharavi AG Diagnostic Utility of Exome Sequencing for Kidney Disease" NEJM.380: 142 -151, 2019.

Treatment of Membranous Nephropathy and FSGS

Steroids – Prednisone

CNIs - Cyclosporine and Tacrolimus

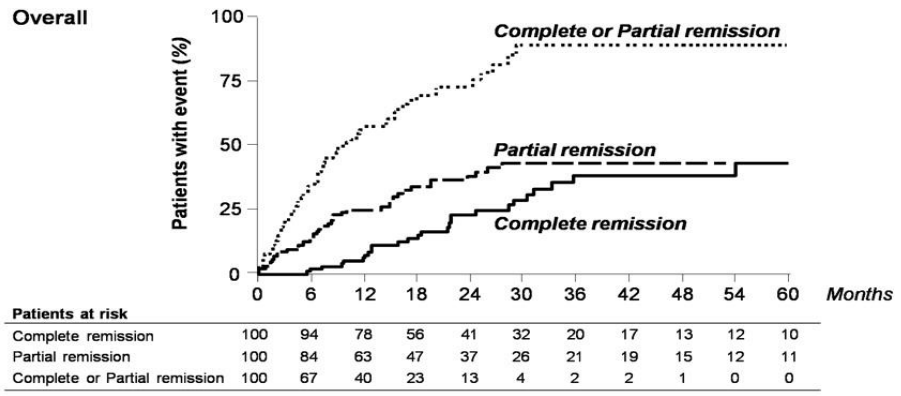
Cyclophosphamide

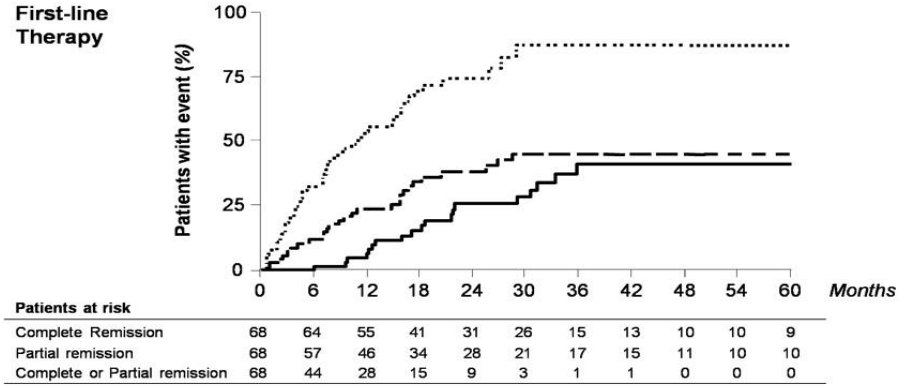
Mycophenolate Mofetil

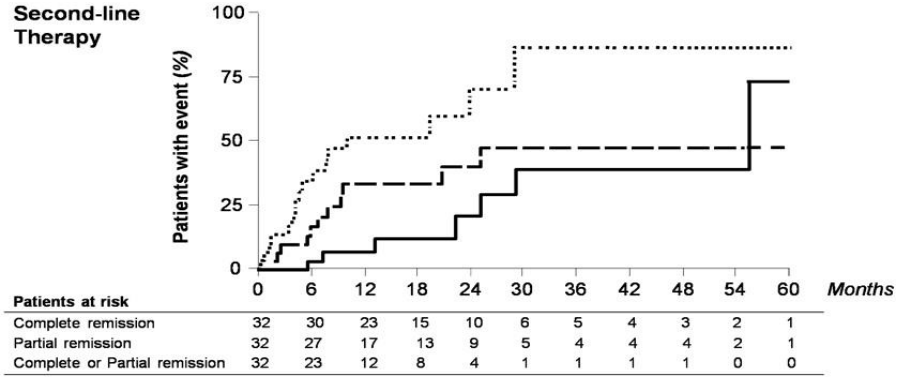
? Role of Rituximab

Rituximab: uncontrolled case series

- N=100
- Partial+Complete remissions = 65/100
- Complete remissions = 27/100
- Median time to remission 7.1 months (IQR 3.2-12.0 months)
- Median total followup 29 months
- 18/65 relapsed
- 11/18 went back in remission (PR+CR) after more rituximab

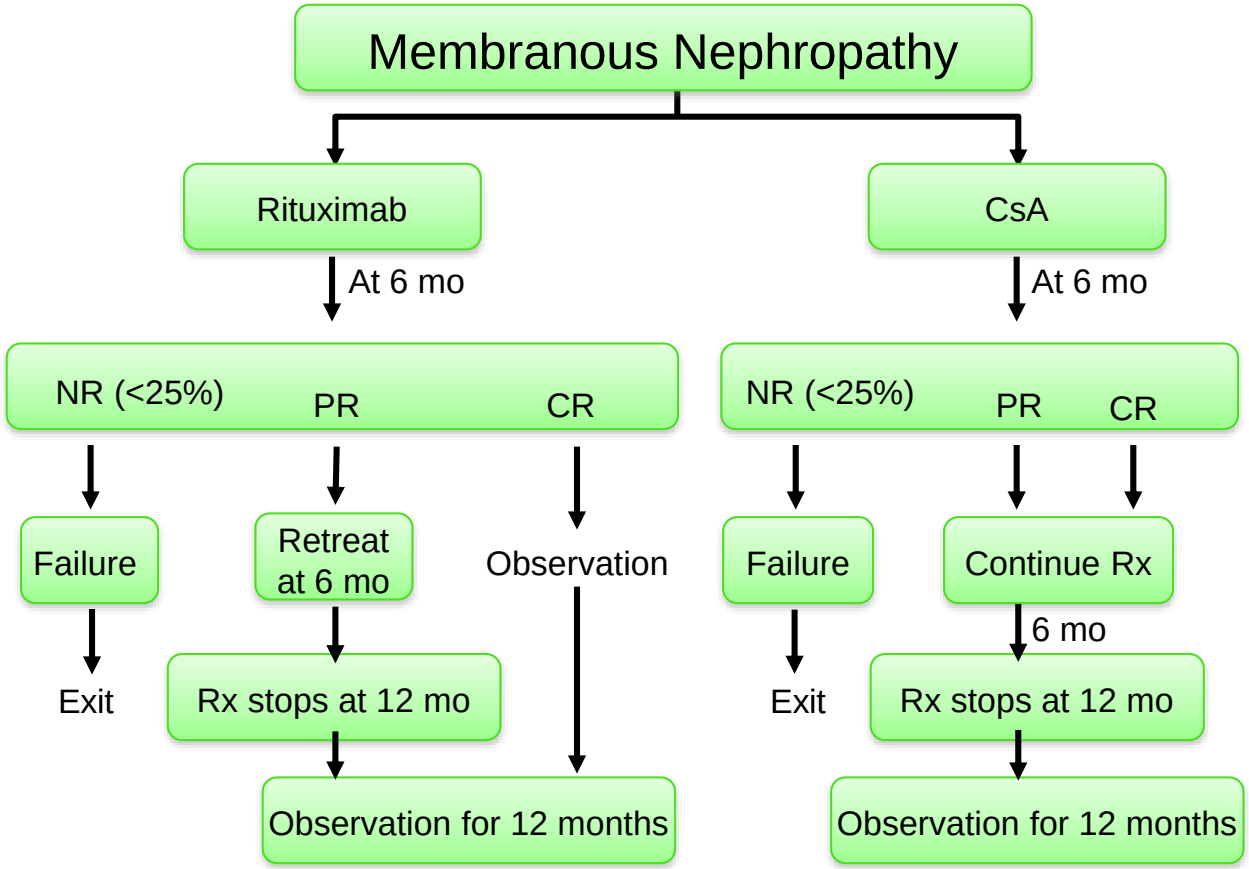






Ruggenenti P et al. JASN 2012;23:1416-1425

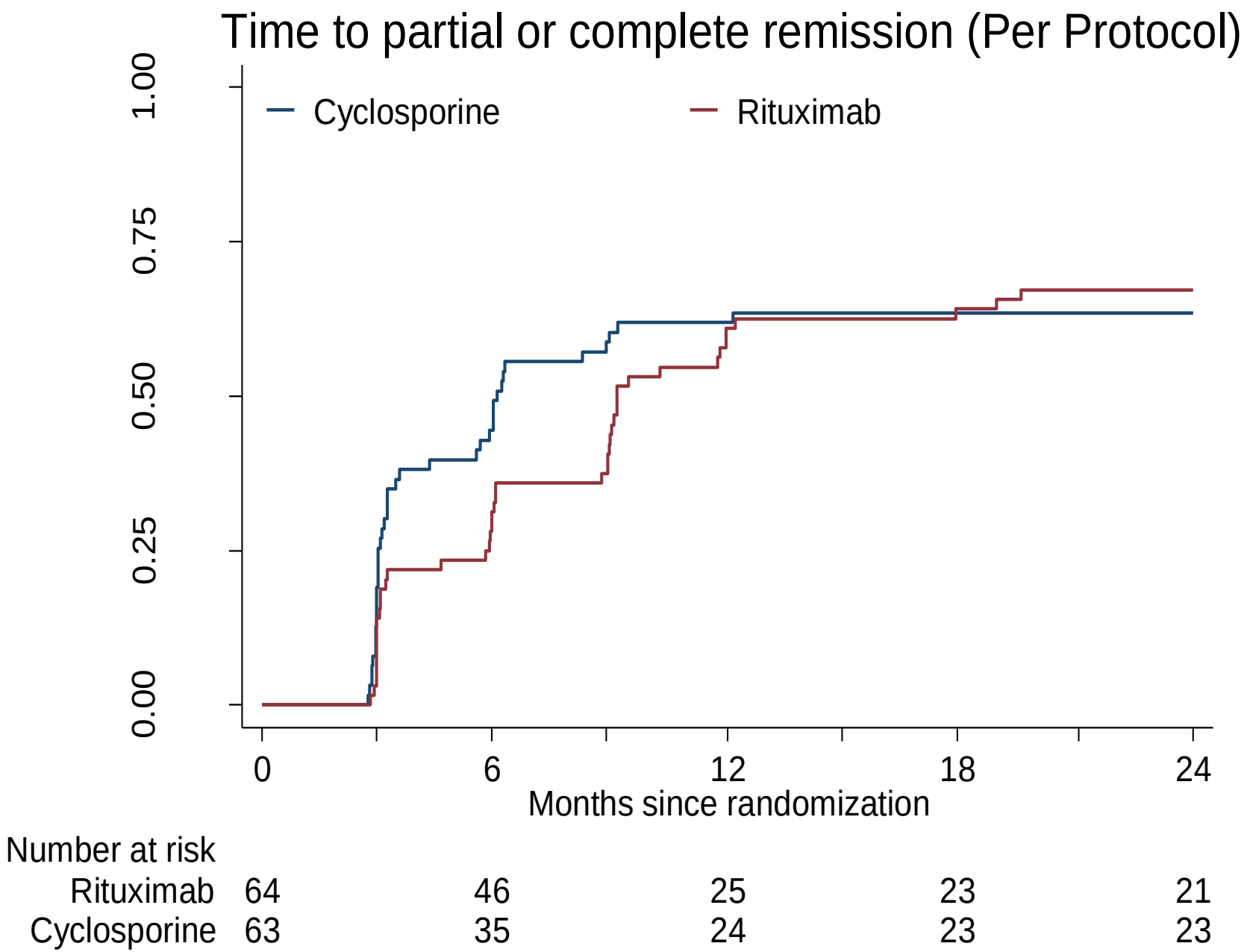
Rituximab: MENTOR TRIAL

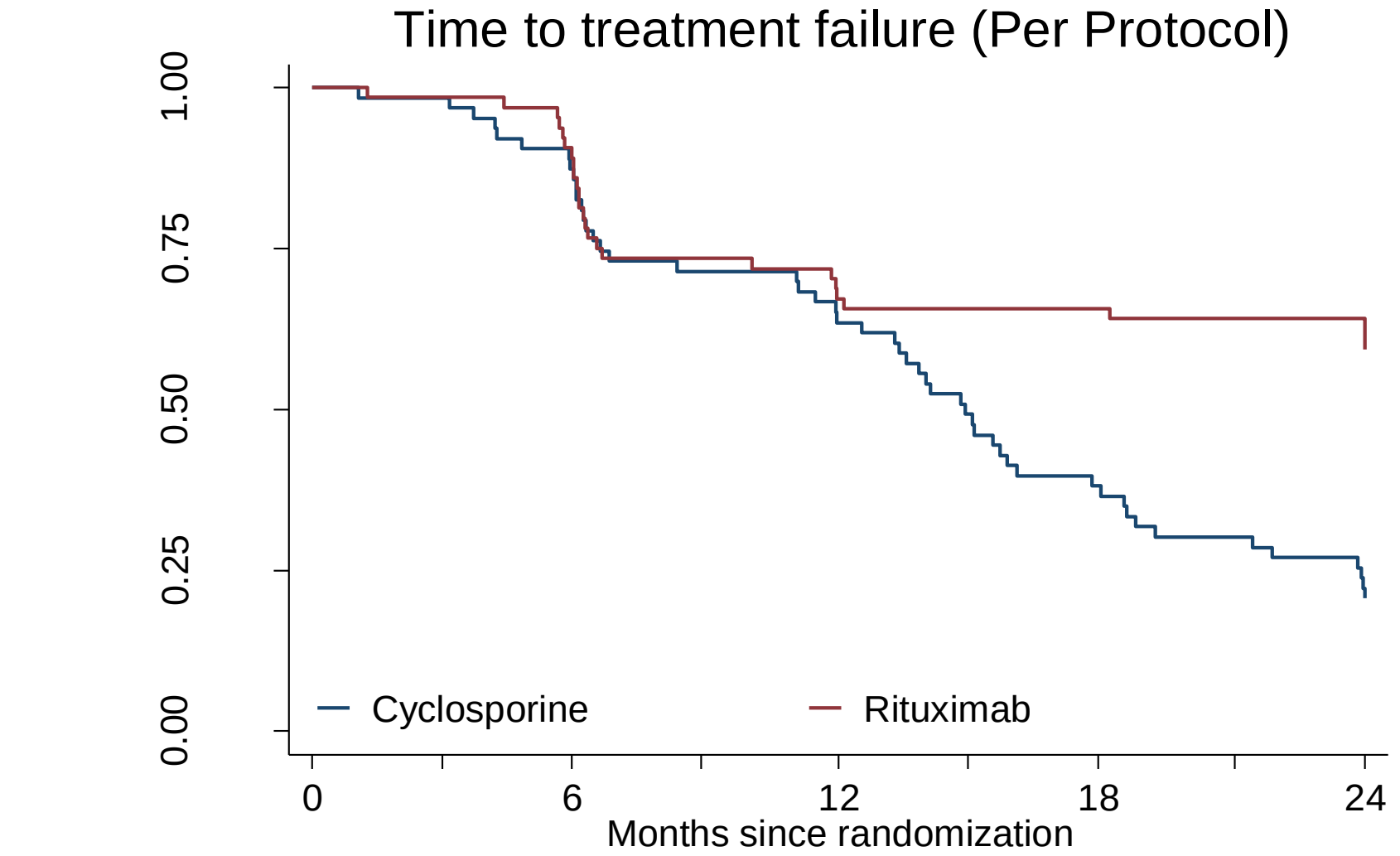


ASN abstract 2018

MENTOR Baseline Characteristics

Physical Parameters	CSA				RTX			
	Mean	**SD**	**Min/Max**	**Median**	**Mean**	**SD**	**Min/Max**	**Median**
Age	53 (n=63)	12	26/76	53	52 (n=62)	13	26/76	54
Sex	52 M (82.5%)		11 F (17.5%)		45 M (72.6%)		17 F (27.4%)	
BP - Systolic (mm Hg)	123 (n=63)	14	95/165	122	127 (n=62)	14	92/176	128
BP - Diastolic (mm Hg)	76 (n=63)	10	59/100	76	75 (n=62)	10	52/96	76
Weight (kg)	91 (n=63)	20	52/156	88	96 (n=62)	23	55/159	92
Proteinuria (mg/24h)	**10329 (n=63)**	**4457**	**5069/ 20670**	**8873**	**10470 (n=62)**	**5075**	**5100/ 27525**	**8876**
Serum Albumin (g/dL)	**2.6 (n=63)**	**0.6**	**1.6/4.1**	**2.6**	**2.7 (n=62)**	**0.6**	**1.6/3.7**	**2.7**
Serum Creatinine (mg/dL)	**1.3 (n=63)**	**0.4**	**0.6/2.5**	**1.3**	**1.2 (n=62)**	**0.4**	**0.5/2.5**	**1.2**
Estimated GFR - MDRD mL/min/1.73m^2	65 (n=63)	24	28/159	58	66 (n=62)	25	29/133	61

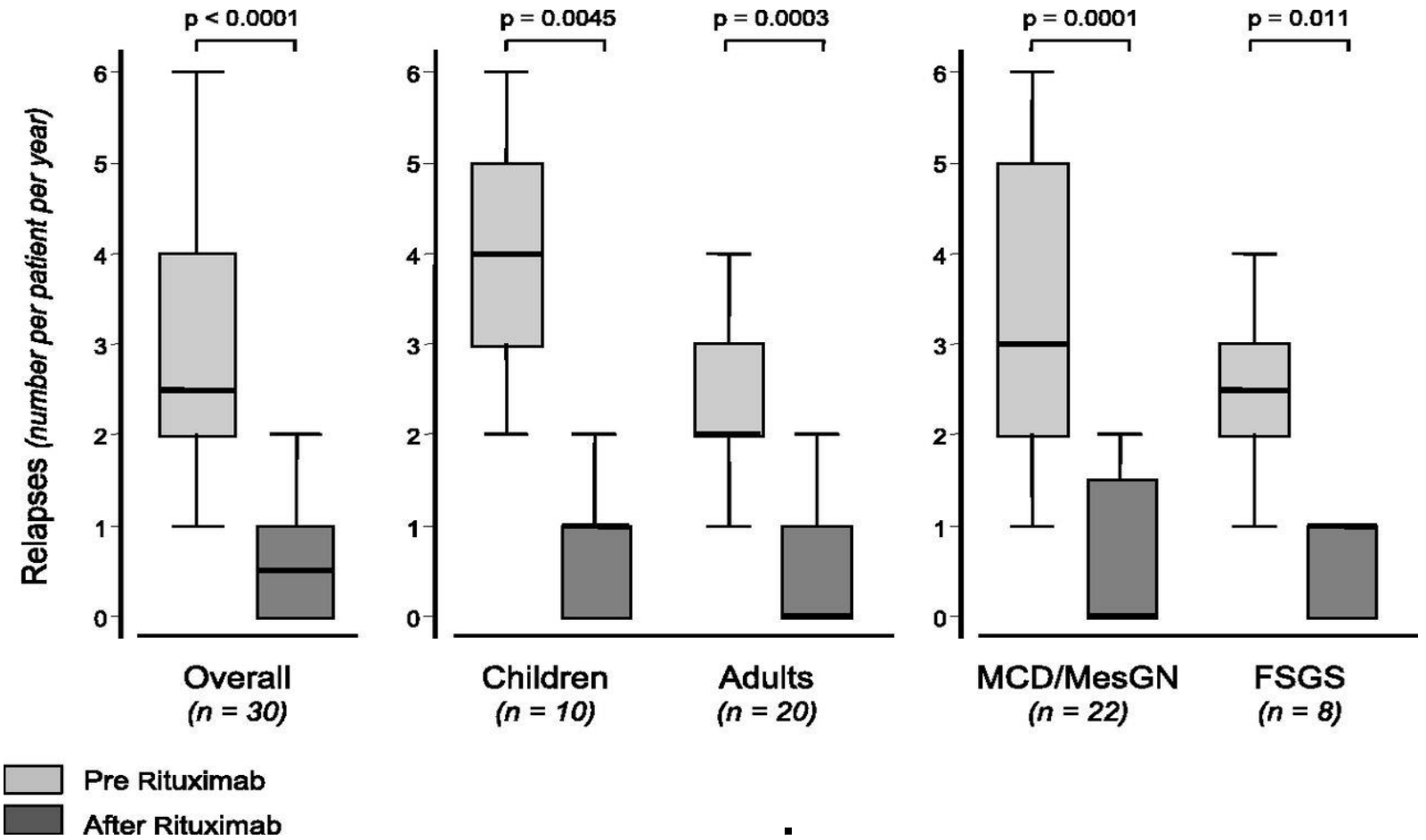

Time to partial or complete remission (Per Protocol)
Cyclosporine
Rituximab
1.00
0.75
0.50
0.25
0.00
0
6
12
18
24
Months since randomization
Number at risk
Rituximab 64 46 25 23 21
Cyclosporine 63 35 24 23 23



Number at risk					
Rituximab	64	58	43	42	41
Cyclosporine	63	55	40	24	14

Rituximab in Steroid Dependent or Frequently Relapsing Idiopathic Nephrotic Syndrome Ruggenenti P et al.

20 adults & 10 children 5/20 adults = frequently relapsing NS
Rituximab 375mg/m2 > another dose if >5 B-cell/mm3 after 1 wk



JASN 2014;25:850-863

Rituximab Treatment of MCD and FSGS in Adults – CUMC Experience

- 82 Adults with MCD/FSGS seen at CUMC from 2014-2019 treated with Rituximab
- 43 MCD, 32 FSGS, 7 podocytopathy
- 41 FR/SD, 7 Infrequent R, 9 SR, 25 MDR
- Mean follow up 28 months

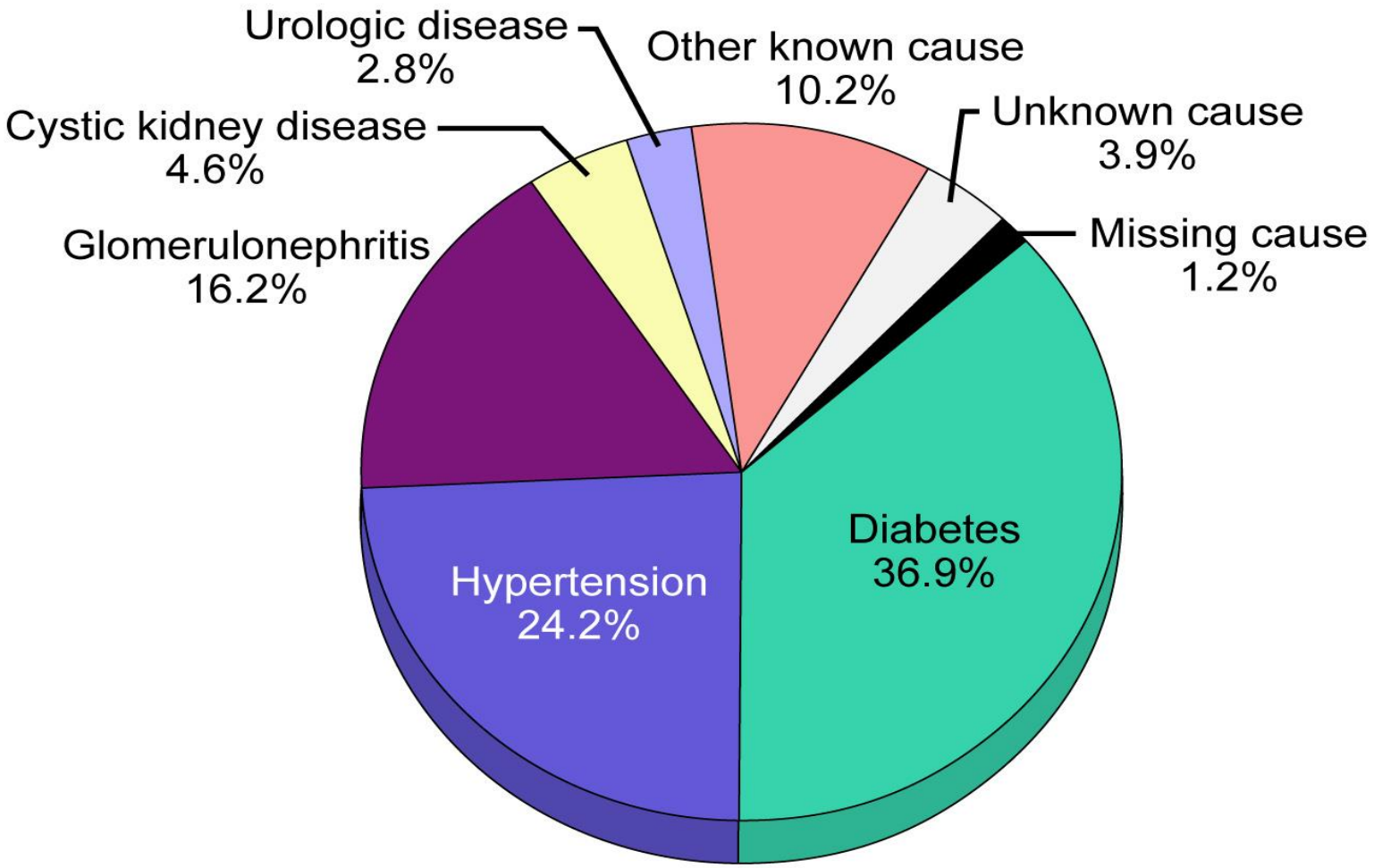
- **At follow-up:**
  - **65% (53/82) in CR or PR**
  - **22/53 (42%) in CR/PR –stopped all other immunosuppression**
  - **Of 25 Multi-Drug R, 11 achieved CR/PR**
  - **10/82 (23%) progressed to ESRD**

Regunathan R, Jeyabalan A, Ahn W, Bomback A, Canetta P, Appel GB (preliminary data) ASN Abstract on 58 pts 2017

Needs in Glomerular Disease

- New Biomarkers for Dx and Prognosis
- More and Better Access to Inexpensive Genetic Testing
- More controlled testing of Newer Medications (many FDA available for other diseases already).
- Cooperation between Academics , Industry, and Patients

Etiology of CKD - ESRD



www.kidney.org