The spectrum of lupus nephritis: Therapeutic implications

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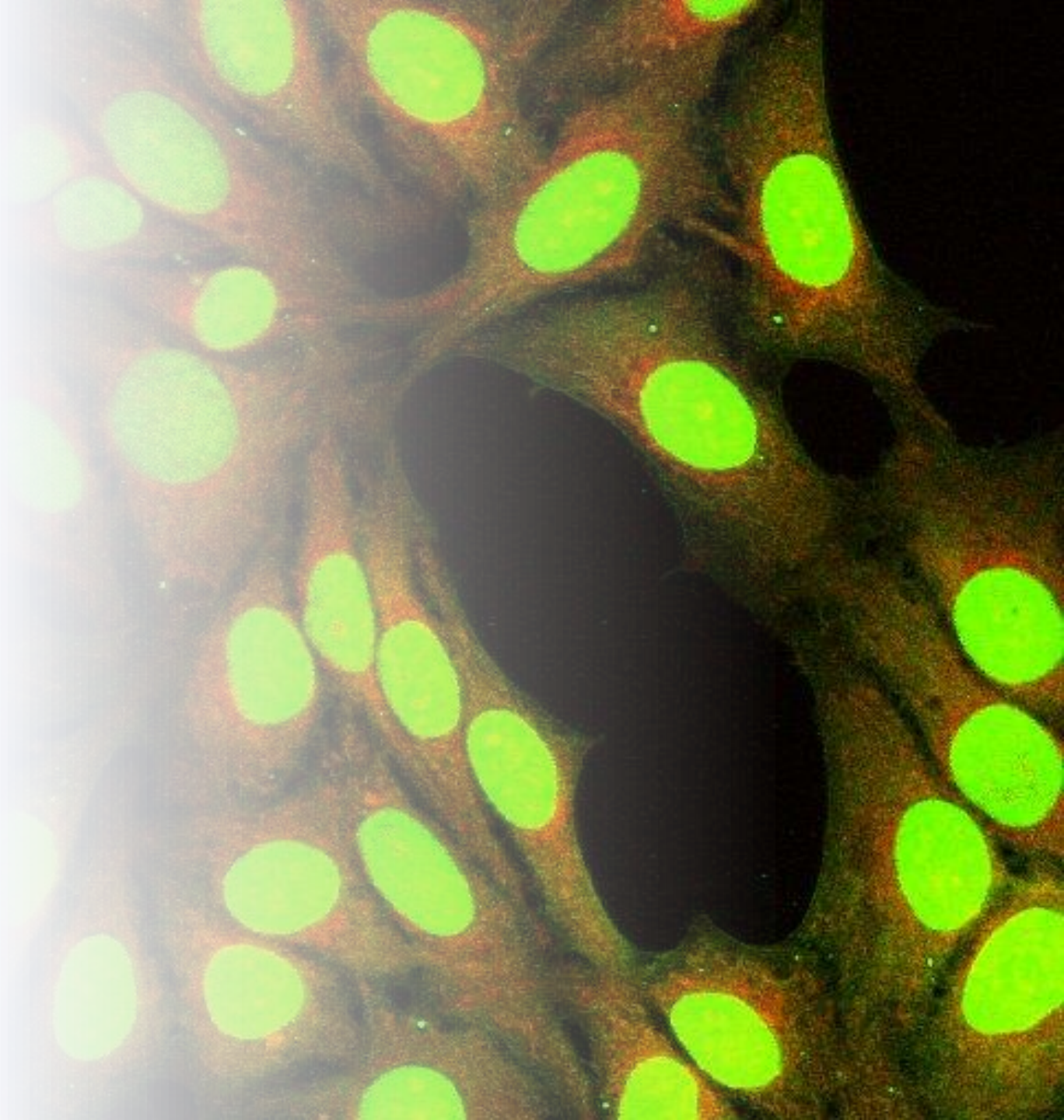
ESPN Webinar
14. May 2021



Disclosures

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Consultancy fees:	GSK, Novartis, Janssen, Kezar

Outline

- Renal involvement in SLE: How you define lupus nephritis?
- LN dissected by histological classes
- LN dissected by histological activity
- LN dissected by specific molecular features
- Therapy responsive versus non-responsive LN
- The „nephritic flare“ of LN
- The „proteinuric flare“ of LN
- LN = CKD and treating „LN“ is only a minor aspect in treating CKD
- Call to action

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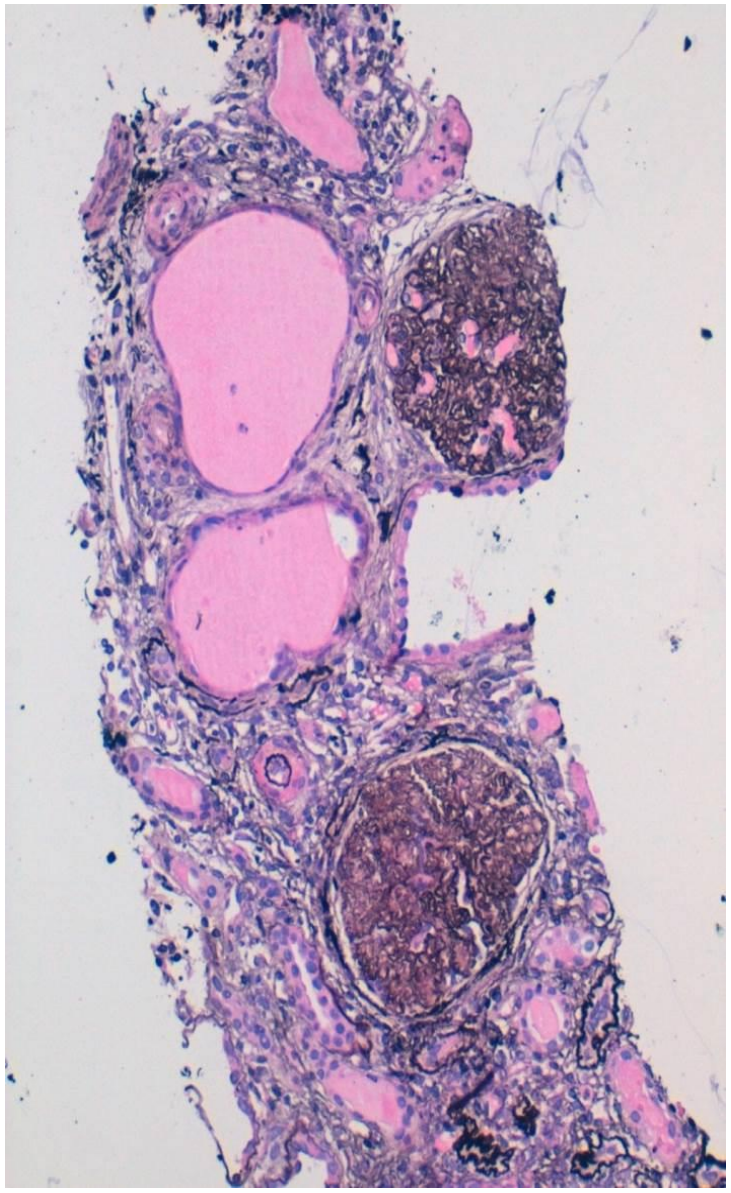
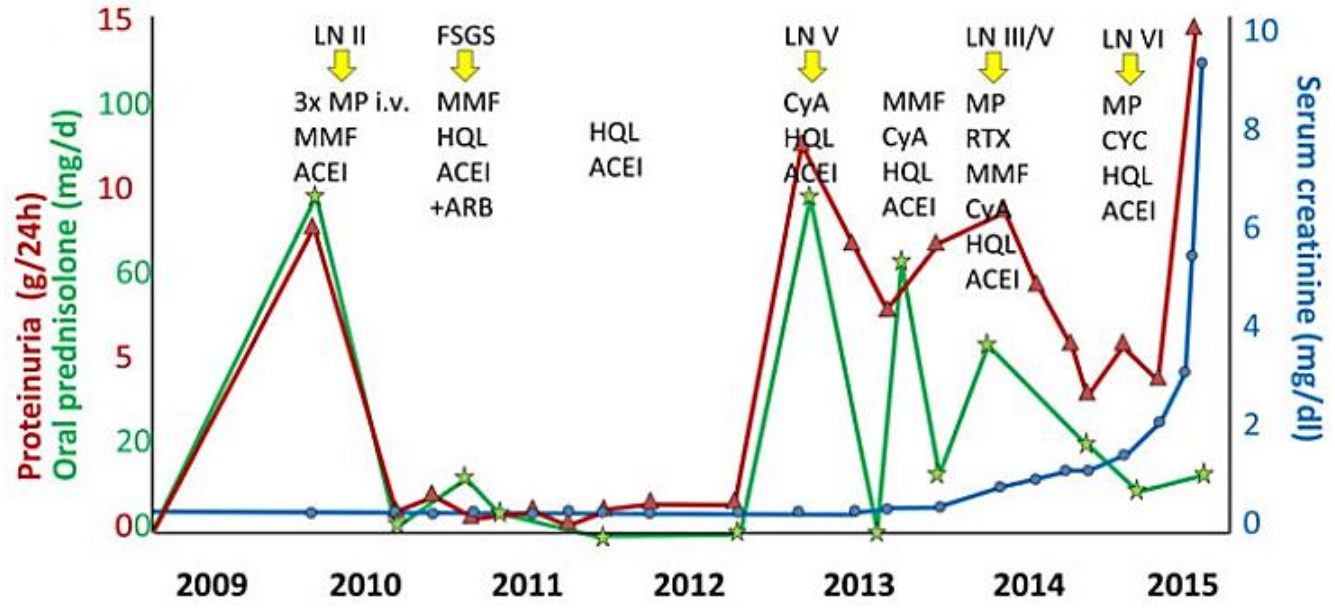
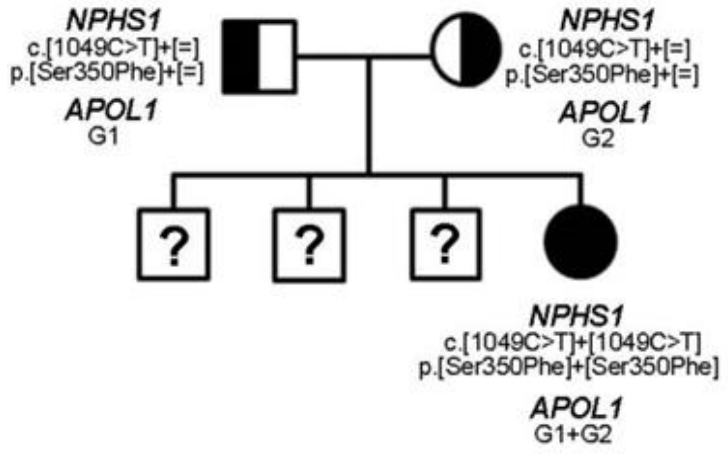
Renal involvement in SLE: How you define LN?



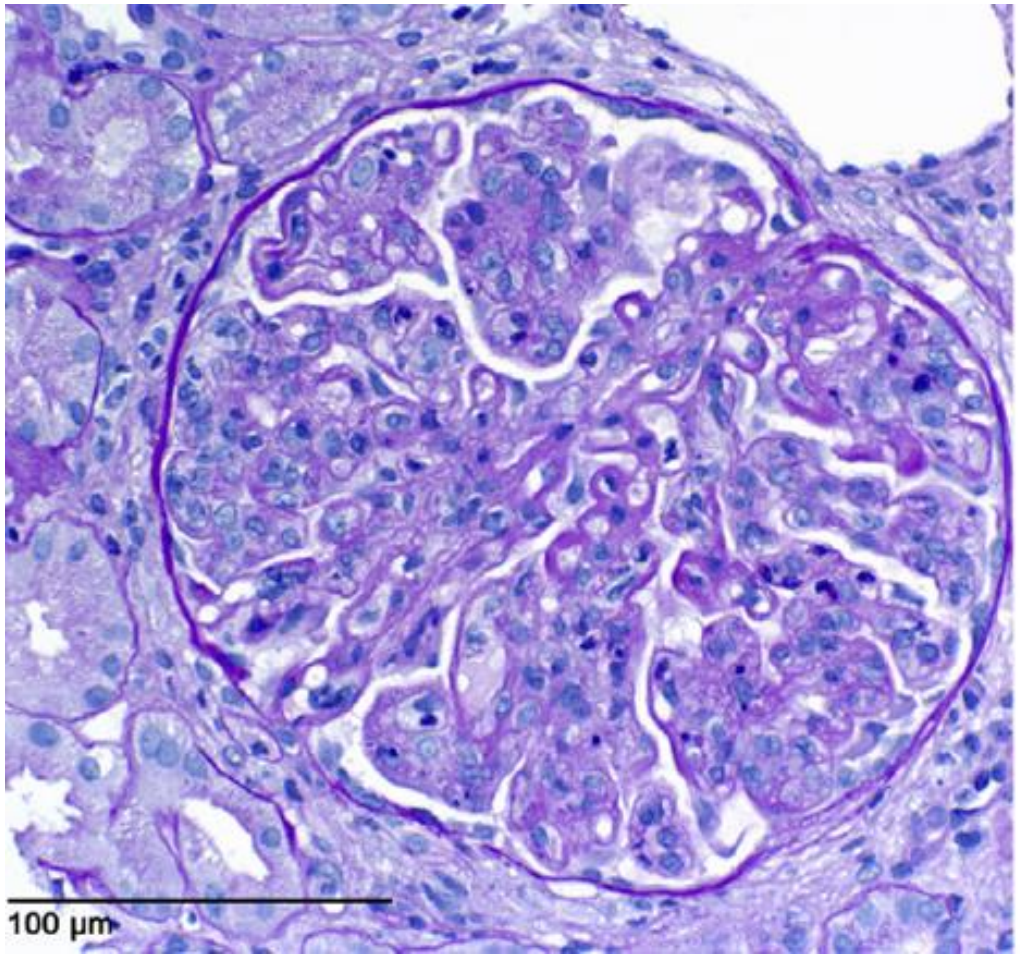


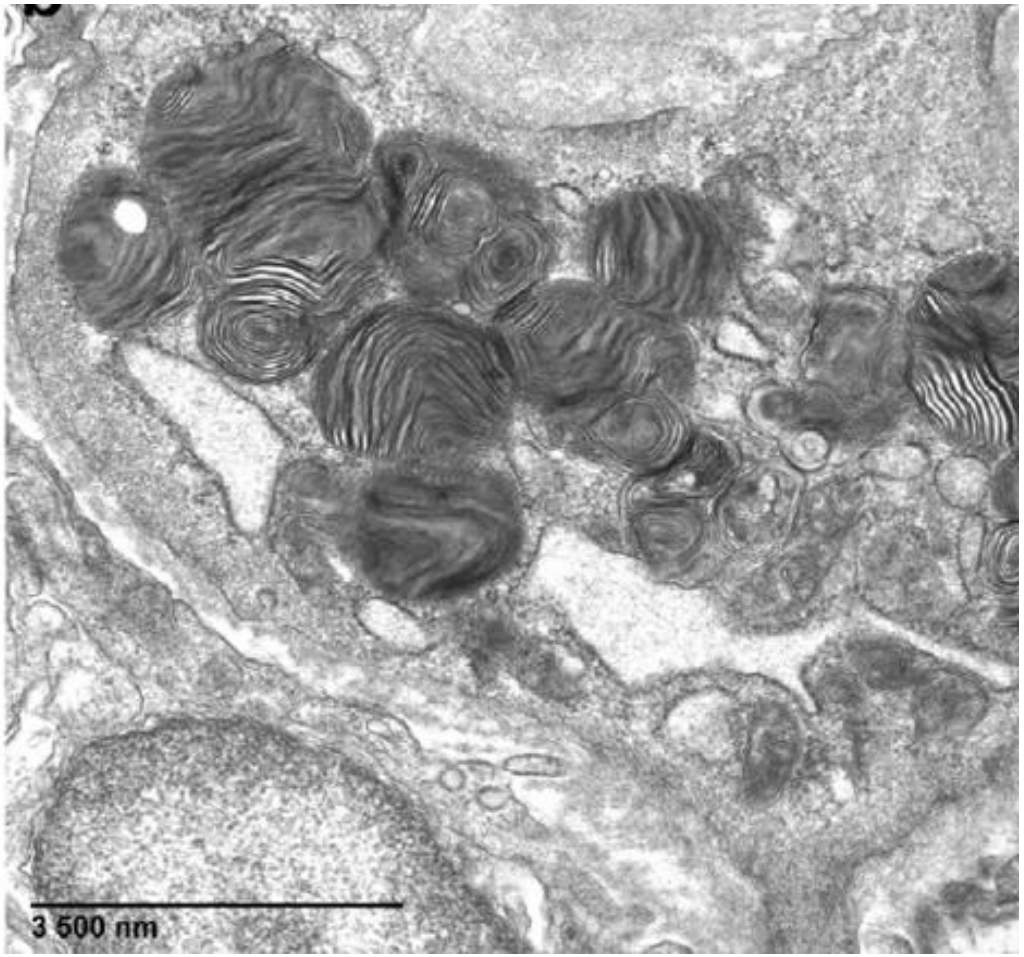


Romagnani, Anders, *et al.* NDT 2016

Renal involvement in SLE: How you define LN?

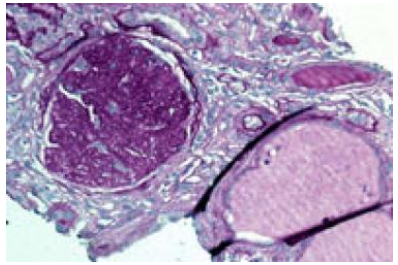
HCQ-induced podocytopathy a renal complication of SLE treatment
M. Fabry as rare comorbidity to SLE/LN

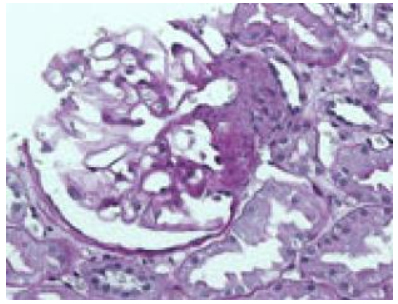


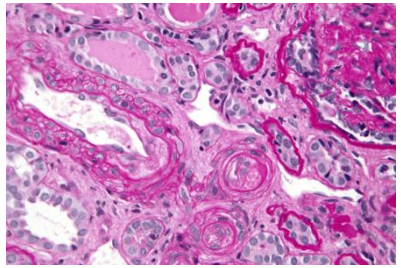


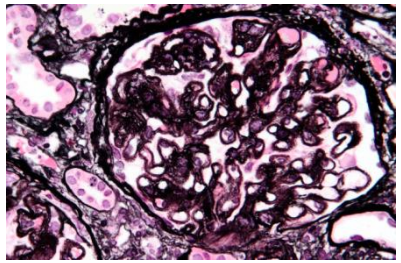
Kidney International (2017) **92,** 271–272

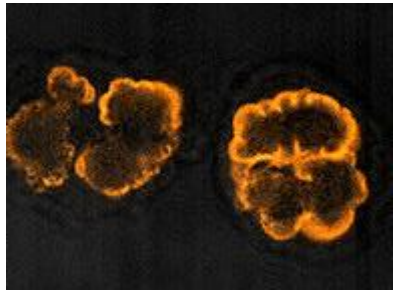
Renal involvement in SLE: How you define LN?





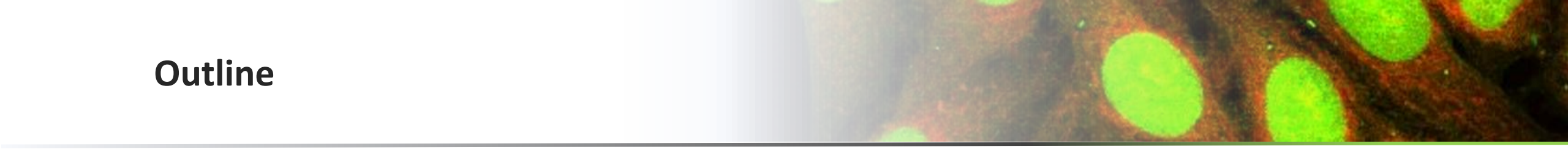






- Homozygous nephrin mutation = unrelated podocytopathy
- APOL1 G1/G2 = APOL1 podocytopathy
- C3 glomerulopathy = genetic or sec. acquired?
- C3 TMA = genetic or sec. acquired?
- incident ANCA vasculitis = sec. acquired?

Outline



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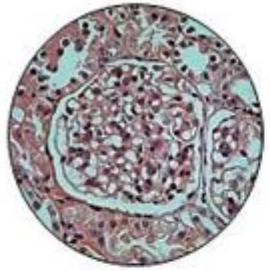
LN dissected by histological classes

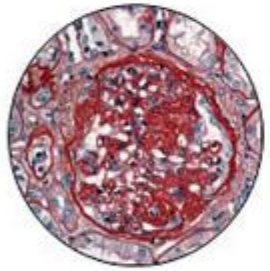
HISTOPATHOLOGICAL CLASSIFICATION OF LUPUS NEPHRITIS



Class I

Minimal Mesangial Lupus Nephritis

- Deposition of imune complexes detectable by immunofluorescence techniques.



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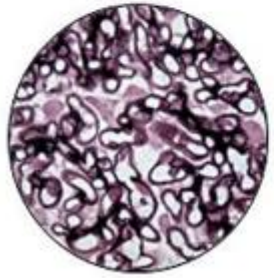
Focal Lupus Nephritis

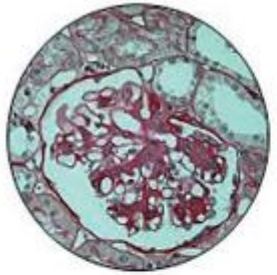
- Active or inactive focal, segmental or global endo/extracapillary glomerulonephritis involving <50% of all glomeruli.



Class V

Membranous Lupus Nephritis

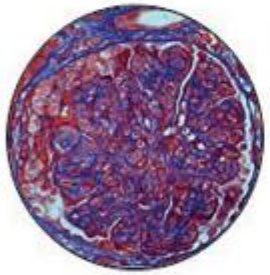
- Global or segmental subepithelial immune deposition or their morphologic sequelae detectable by light, immunofluorescence or electron microscopy, with or without mesangial alterations.
- It can occur in combination with class III or IV and it can manifest advanced sclerosis.



Class II

Mesangial Proliferative Lupus Nephritis

- Mesangial hipercelularity of any degree or mesangial matrix expansion with immune deposits detectable by light microscopy.



Class IV

Diffuse Lupus Nephritis

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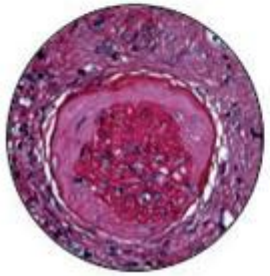


Class VI

Advanced Sclerosis Lupus Nephritis

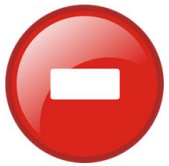
- Lupus Nephritis with terminal prognosis.
- 90% of the glomeruli in global sclerosis.

Origins at WHO, last century

LN dissected by histological classes

Confirms immune complex GN, proliferative vs. membranous GN

Confirms CKD, IFTA indicates amount of lost nephrons (prognosis)



Outdated by concept
No unbiased classification validated by outcome, e.g. Oxford classification for IgAN

Clinically no pendant of clinical RF as in other kidney diseases, e.g. IgAN

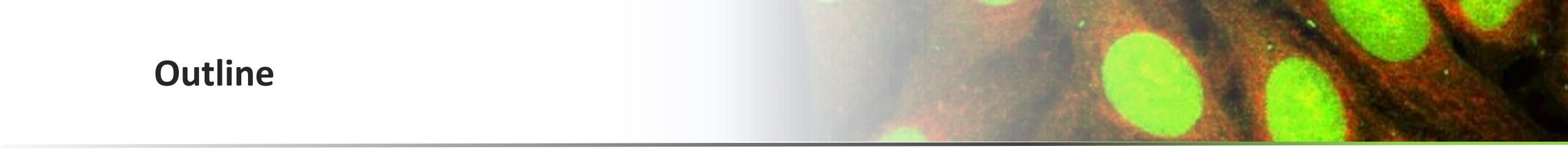
Often confused with stage of LN

Focal versus diffuse proliferative LN?

Lupus podocytopathy, e.g. Class II with nephrotic syndrome

Lesion patterns unrelated to pathophysiology or specific treatment targets

Outline



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LN dissected by histological activity

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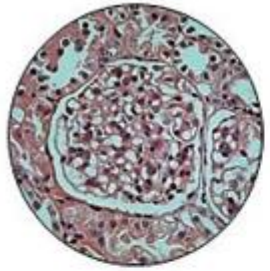

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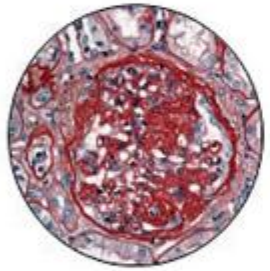

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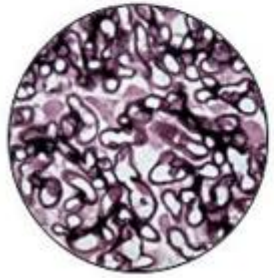
- Manifestations include active lesions (A), chronic inactive lesions (C) or active and chronic lesions (A/C)



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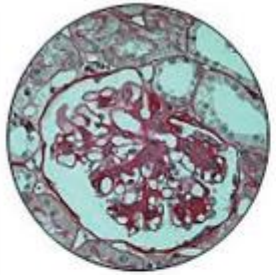

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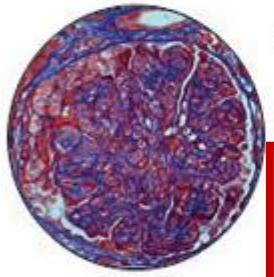

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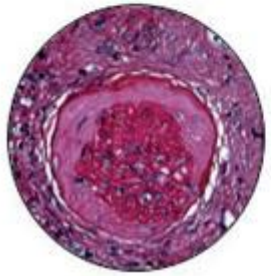
- This class is also divided in: diffuse segmental (IV-S), when ≥ 50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G), when ≥ 50% of the involved glomeruli have global lesions.
- It can also manifest A, C or A/C lesions.



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- 90% of the glomeruli in global sclerosis.

Weening, *et al.* JASN 2003

LN dissected by histological activity

First biopsy: Activity is the target of immunosuppressive therapy

Repeat biopsy: Potential to define immunological remission

Membranous LN?

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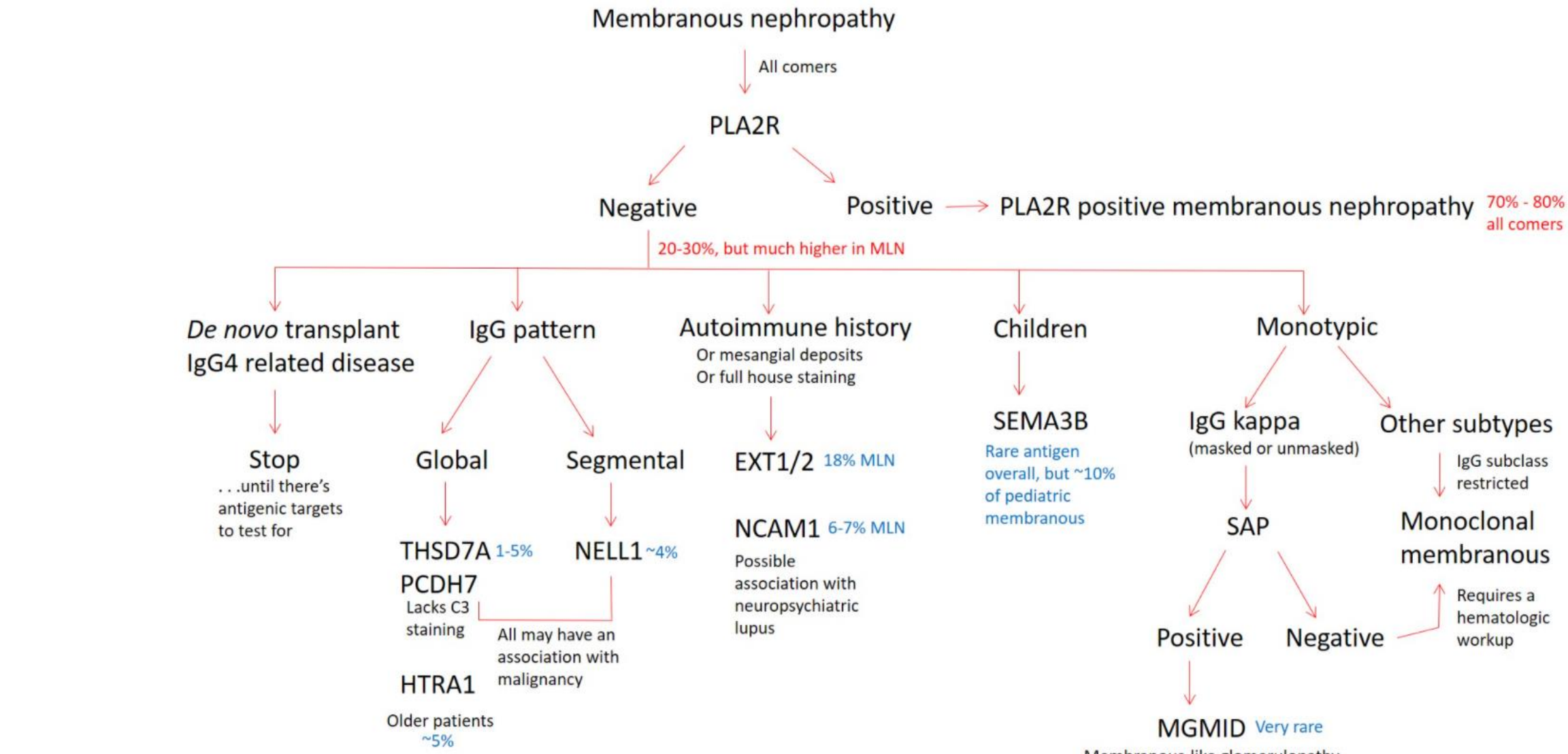
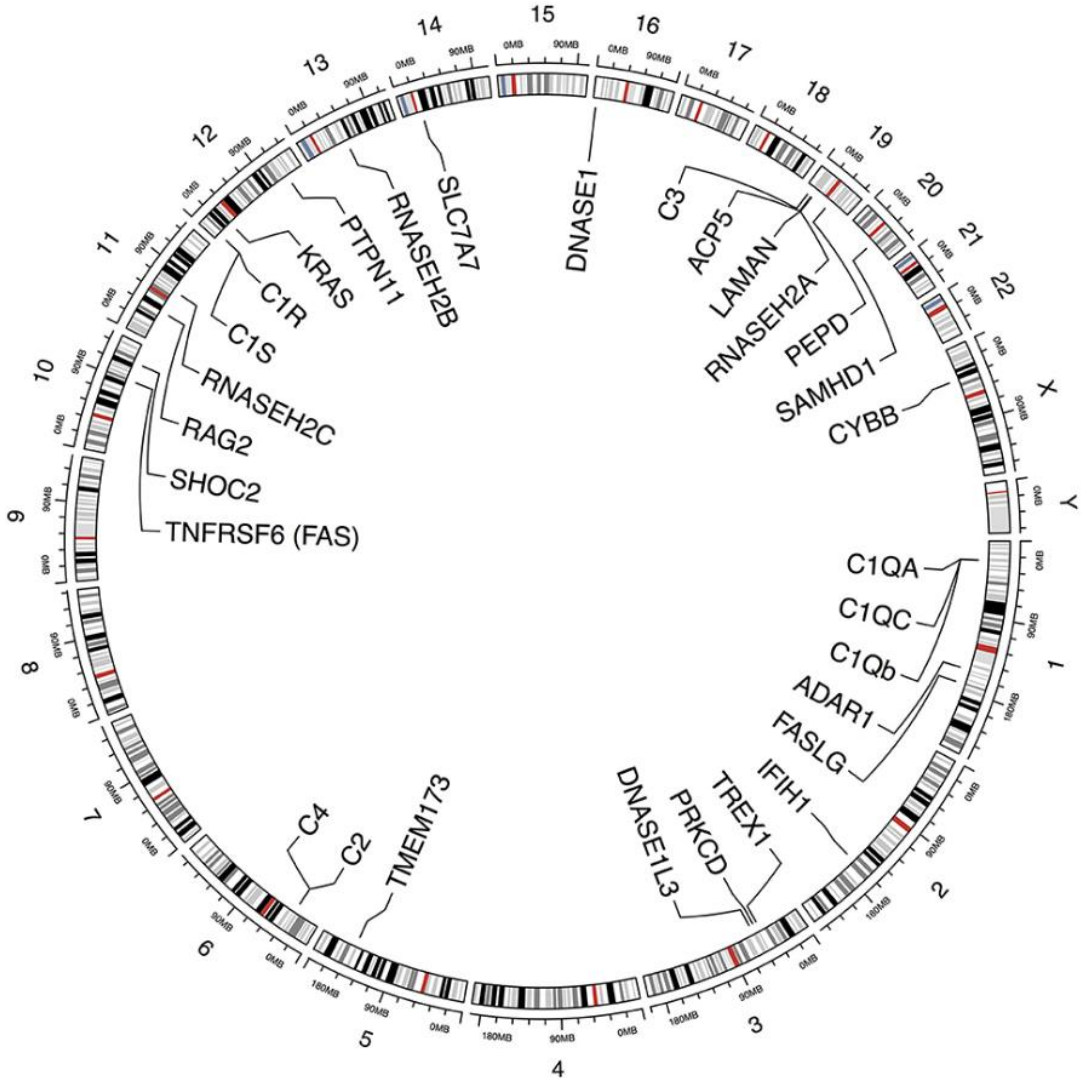
LN dissected by specific molecular features



*Percentages in blue are of the PLA2R negative cases

LN dissected by specific molecular features



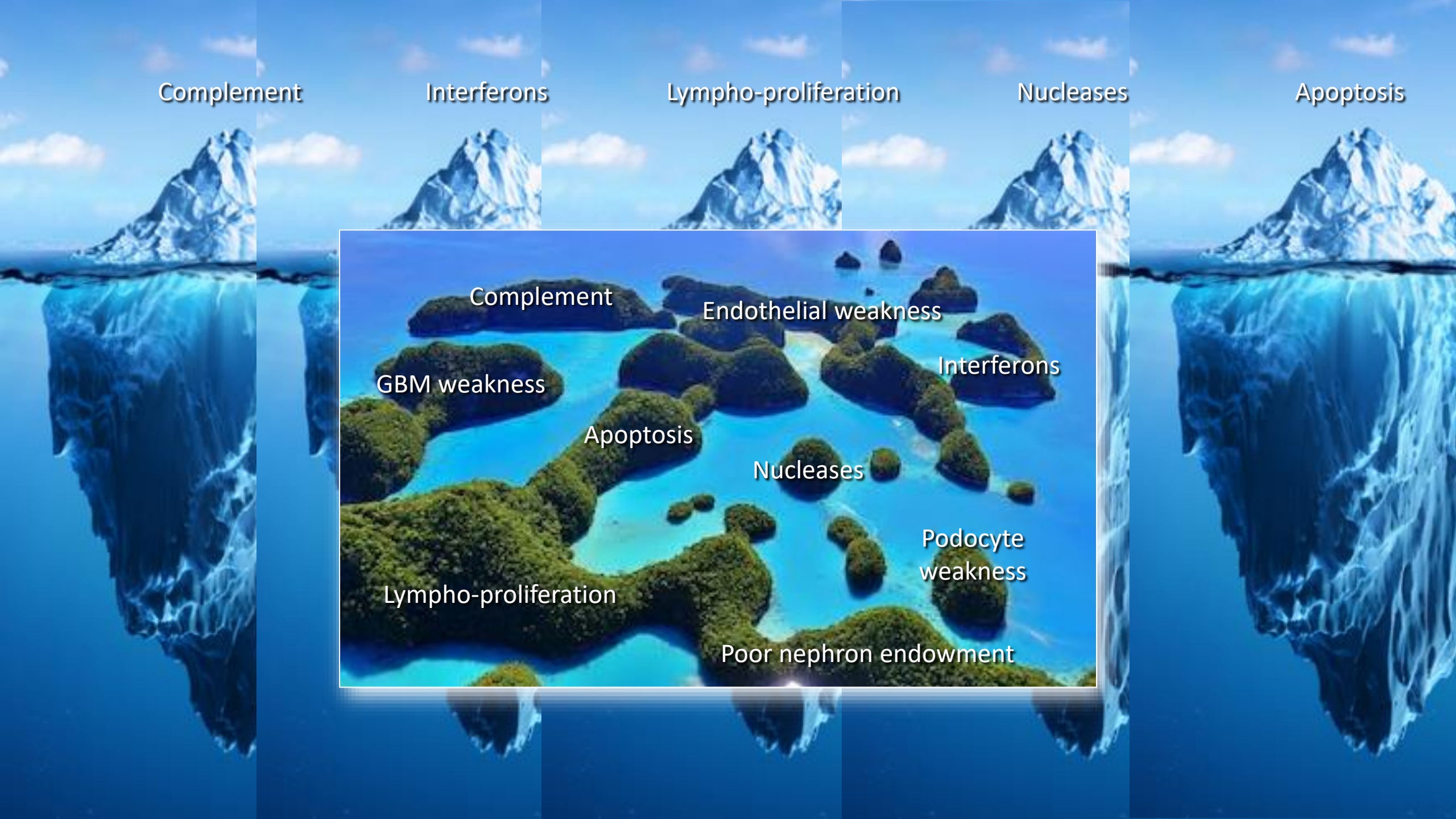
IFNopathies

Complementopathies

DNAse/RNAse-deficiencies

Autoimmune LymphoProliferative Syndrome (ALPS), …

Alperin, *et al.* Frontiers Immunol 2018


Complement
Interferons
Lympho-proliferation
Nucleases
Apoptosis
Complement
Endothelial weakness
Interferons
GBM weakness
Apoptosis
Nucleases
Podocyte weakness
Lympho-proliferation
Poor nephron endowment

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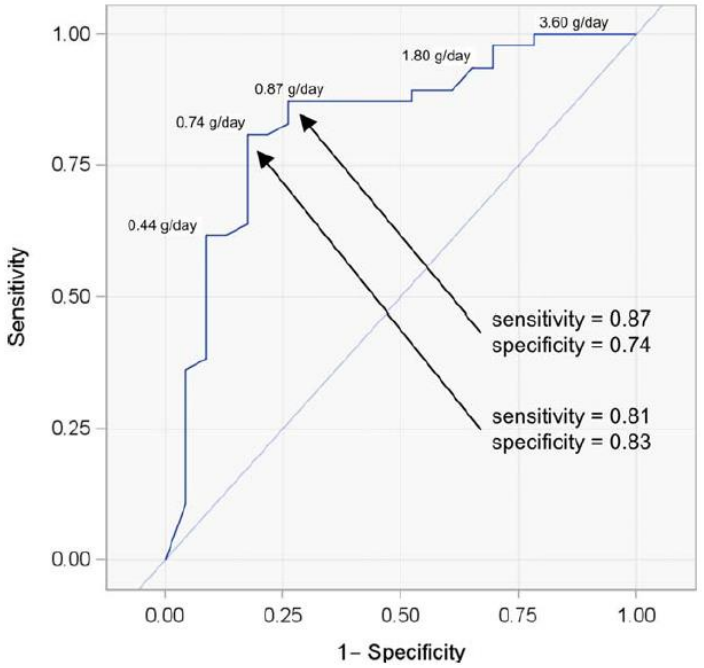
Therapy-responsive versus non-responsive LN

- Response to first-line treatment is generally a good marker of outcome
- How to define response to treatment ?
- Proteinuria is a marker for many things
  - Activity
  - Glomerular hyperfiltration
  - Persistent damage
- Sediment is difficult
- What matters is immunological response -> Repeat biopsy

Clinical response



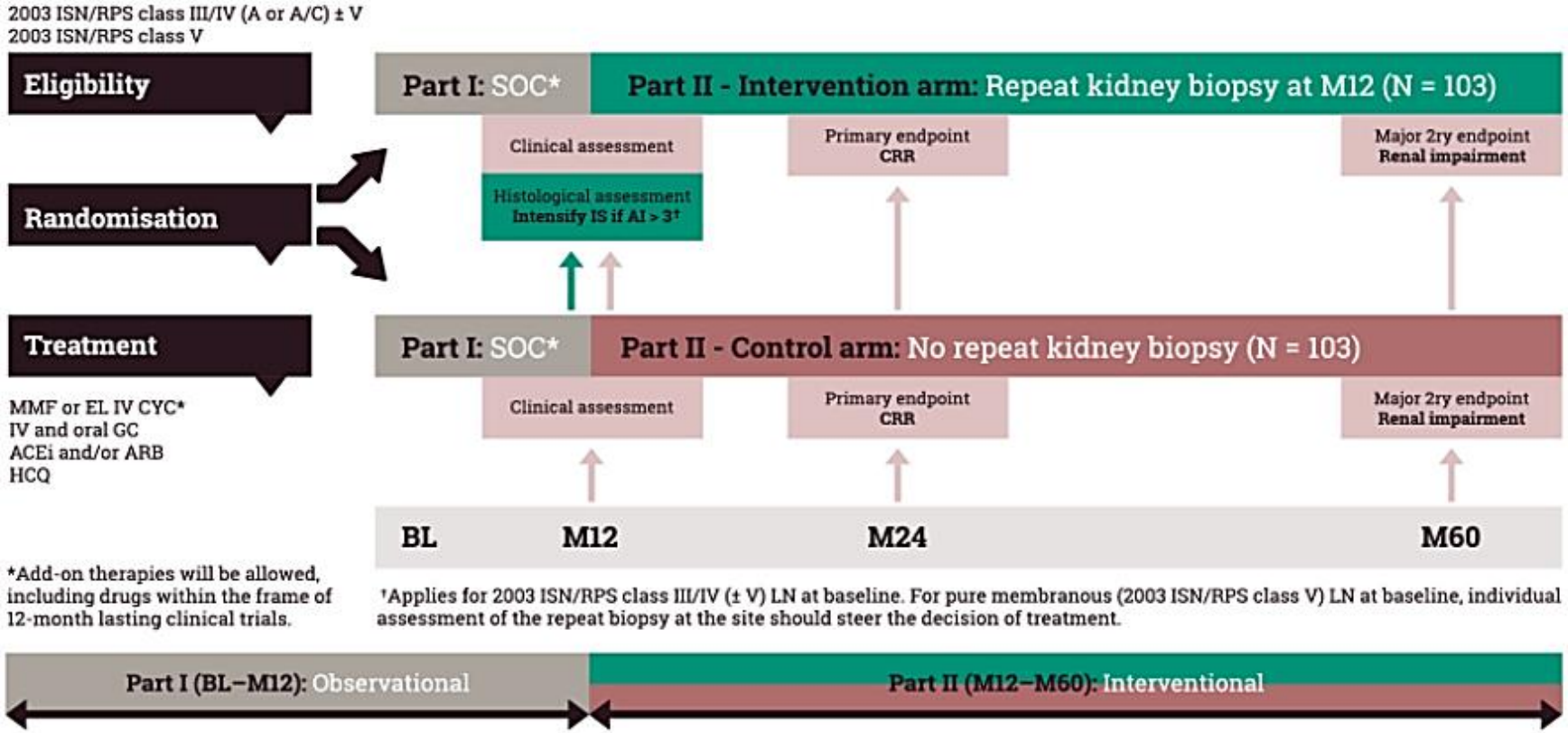
Dall`Era, et al. Arthritis&Rheum 2015

Therapy-responsive versus non-responsive LN

Lupus Nephritis Trials Network
www.lupusnephritis.org

ReBioLup

Per-protocol repeat kidney biopsy in incident cases of lupus nephritis



http://rebiolup.com/

Therapy-responsive versus non-responsive LN

The mighty „Refractory LN“

- If its LN, it should respond to immunosuppression

- If it doesn`t:
  - Drug non-adherence
  - Drug dose?
  - Second round of diagnostics (extended labs, podocytopathy repeat biopsy, genetics/APOL1)
  - Causes of hyperfiltration, BMI?, ACEi?, sodium-free diet?

Not sure, if „refractory LN“ really exists

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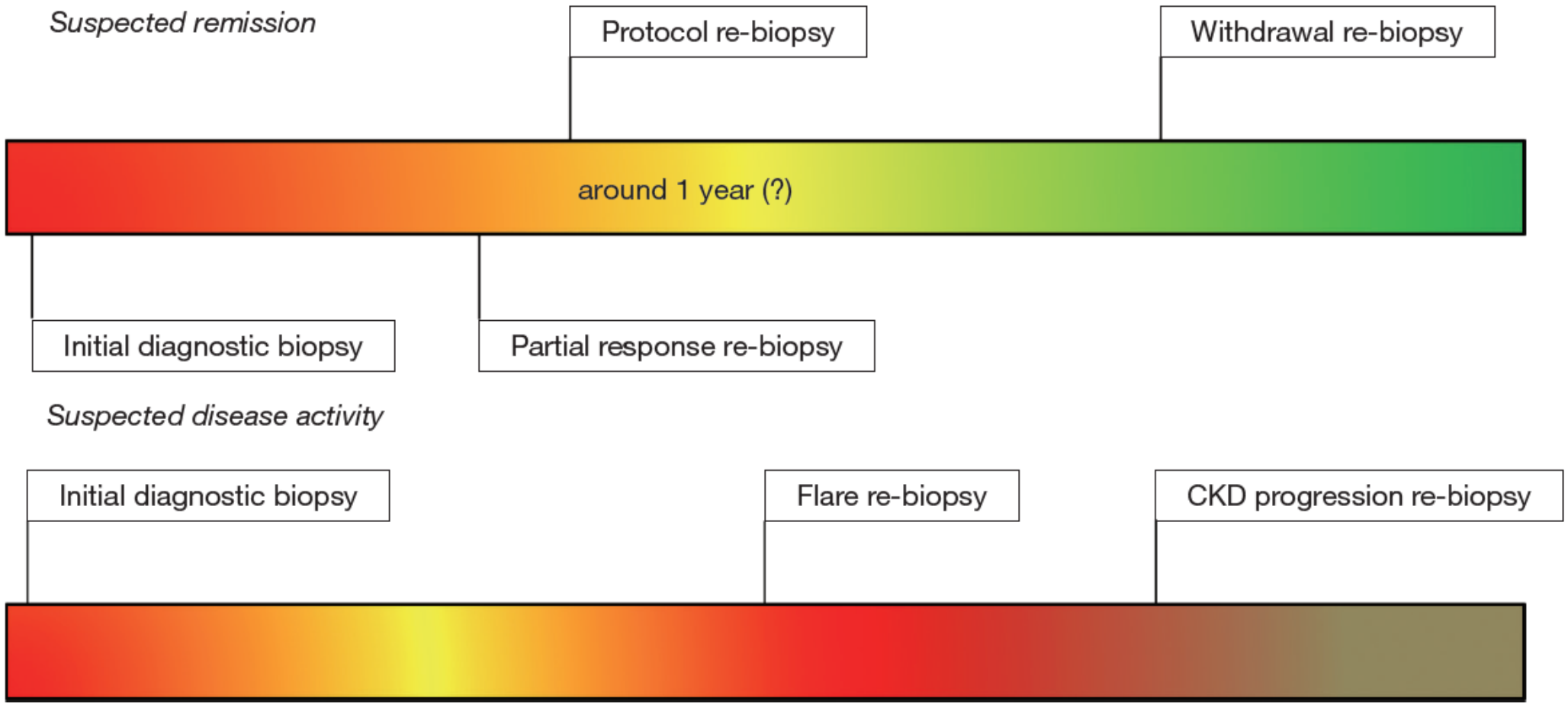
The „nephritic flare“ of LN



Anders HJ. Ann Transl Med. 2018

The „nephritic flare“ of LN

Distribution of the ISN/RPS classes at the first and repeat renal biopsies in 686 well-documented published cases of patients with repeat biopsy performed only on clinical indications.

	Reference biopsy					
Repeat biopsy	**I**	**II**	**III**	**IV**	**V**	**VI**
I	2	3	0	1	0	0
II	1	15	8	40	2	0
III	0	13	26	25	4	0
IV	0	29	34	158	13	0
V	1	11	9	37	62	1
VI	0	1	1	15	1	2
Mixed II+V	0	0	0	2	1	0
Mixed III+V	0	6	7	21	19	0
Mixed IV+V	0	3	2	11	9	1

9,2%

11,4%

79,0%

Narvaez, et al. Medicine 2017

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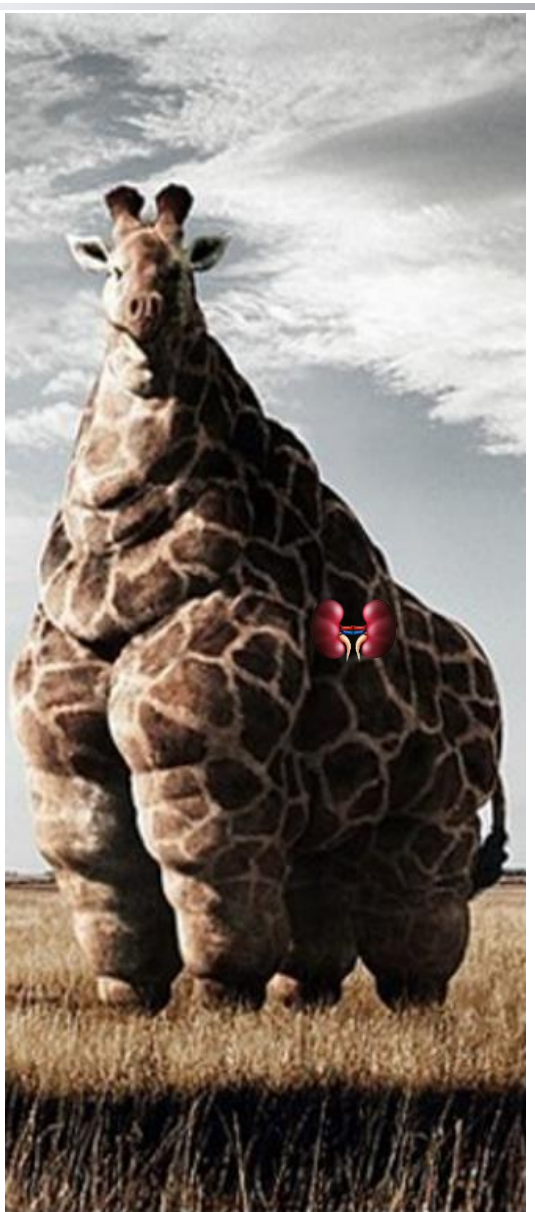
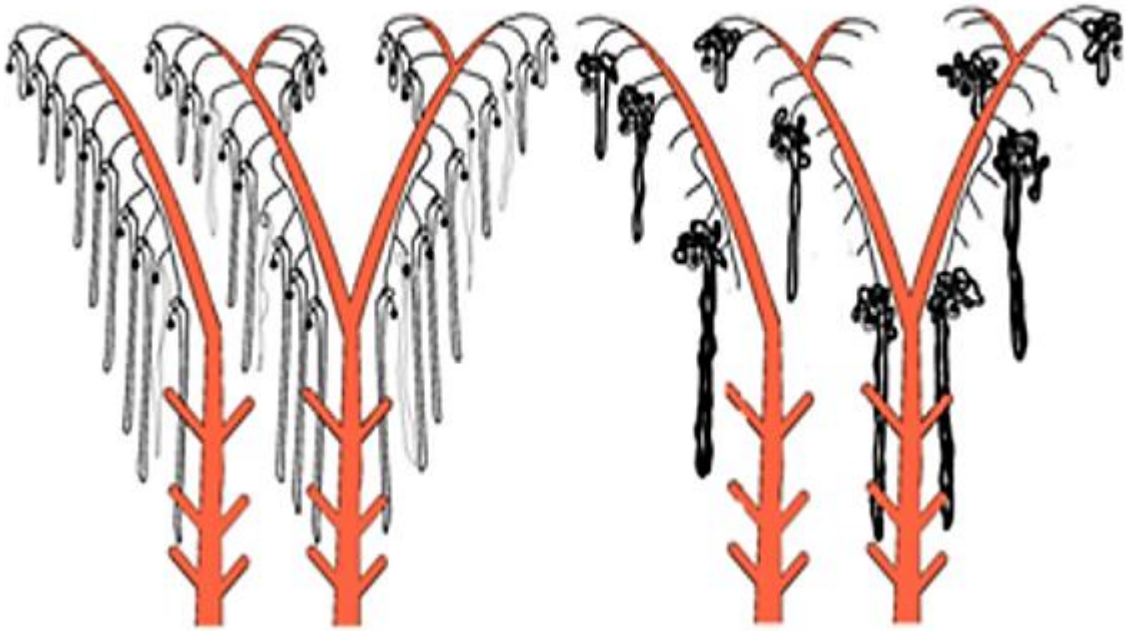
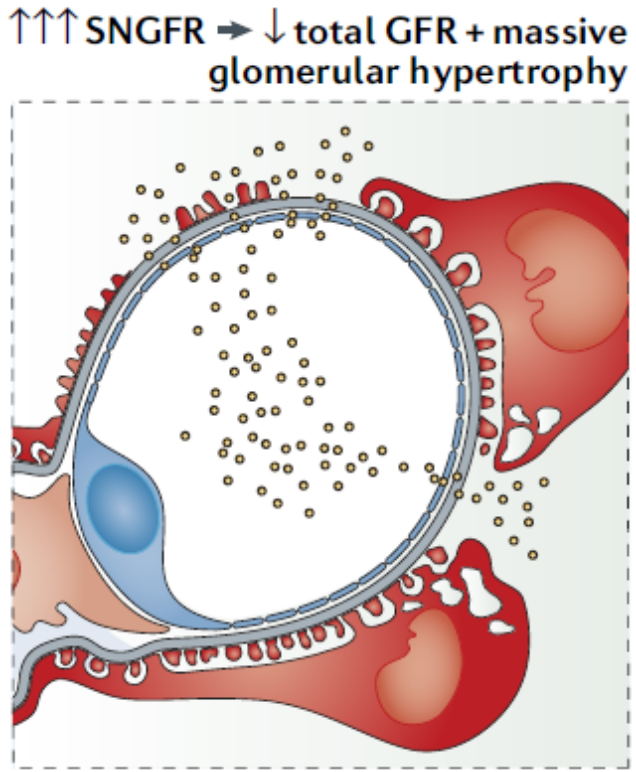


Obesity and/or diabetes affect the kidney like a permanent pregnancy!

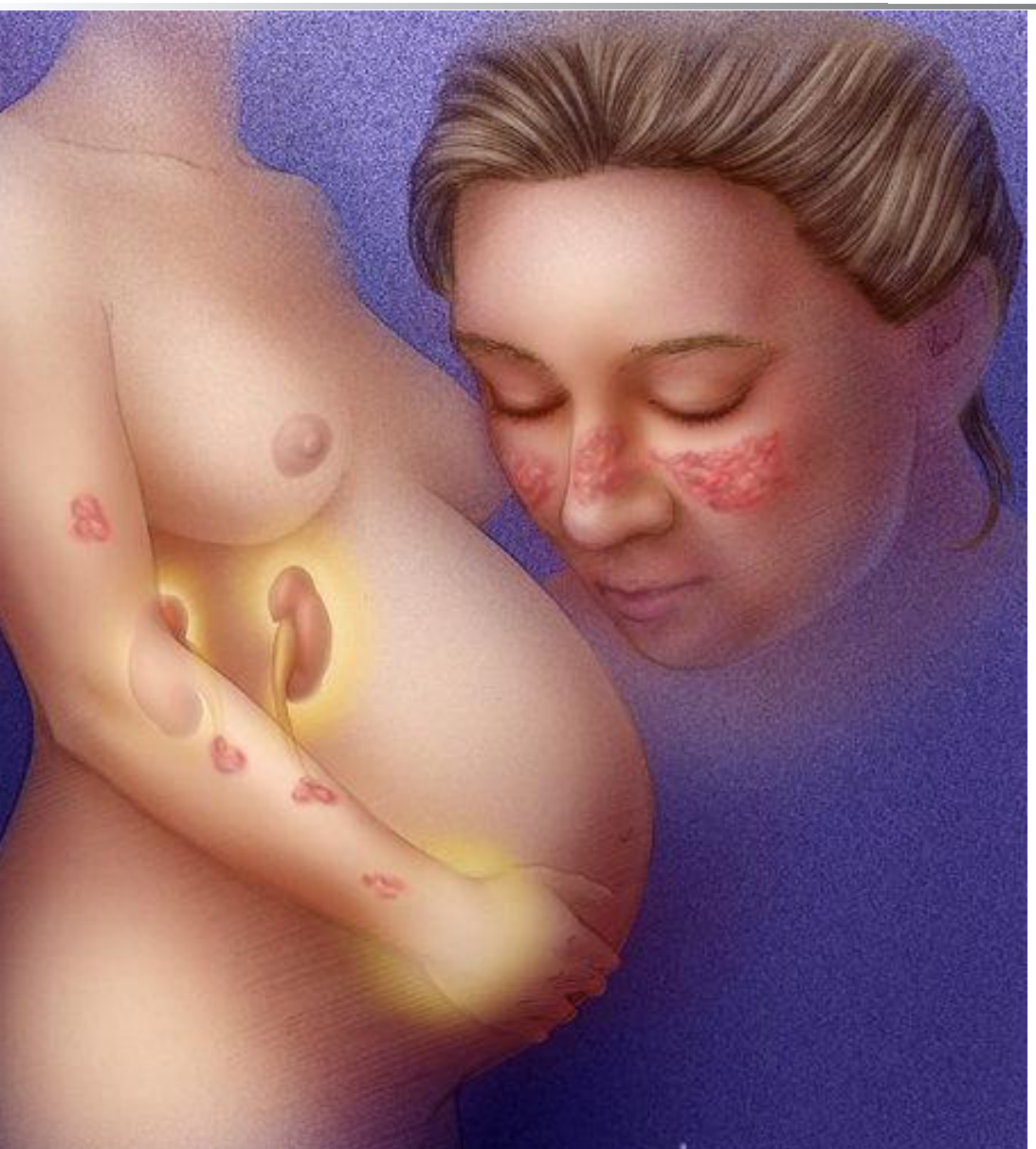
= persistent hemodynamic overload to the remnant nephrons of a LN kidney
= single nephron hyperfiltration = podocyte stress and loss
= proteinuria, sec. FSGS, CKD progression

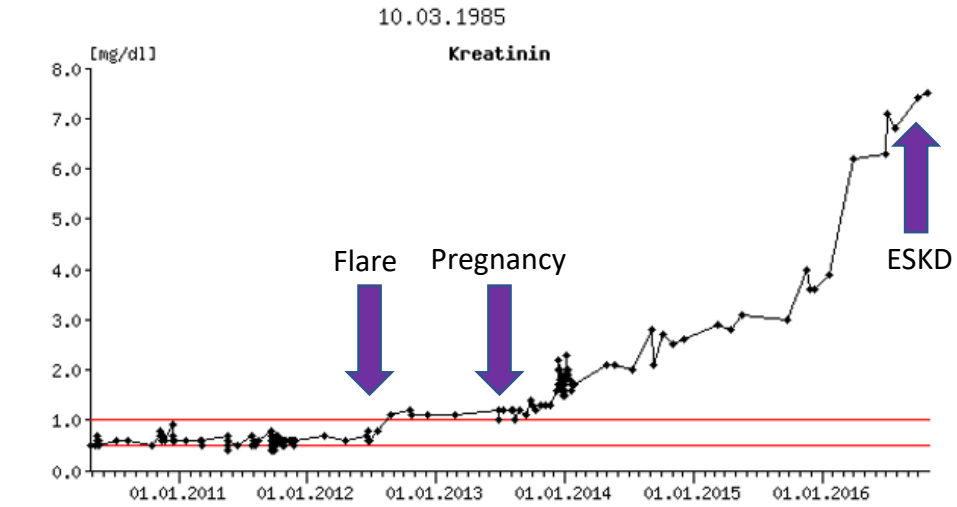


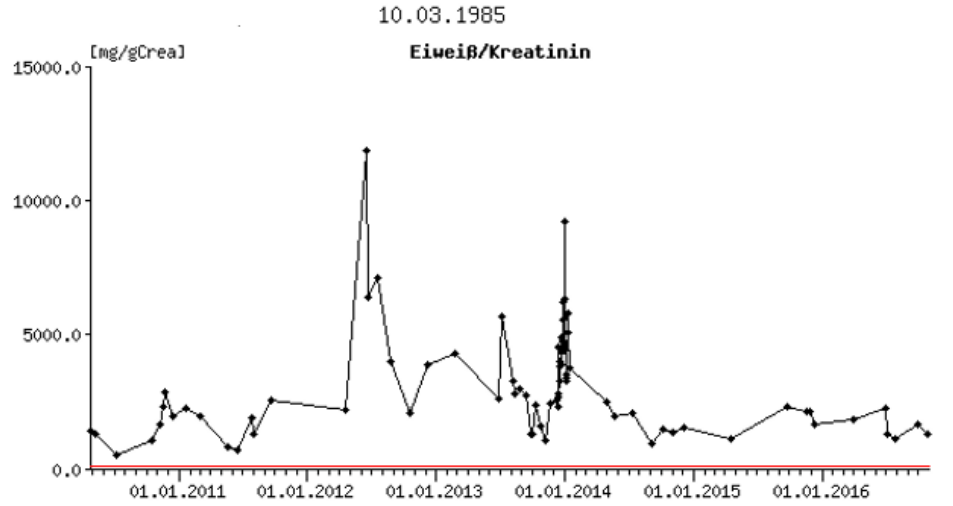


Anders HJ, et al. Nat Rev Nephrol 2018

The „proteinuric flare“ of LN







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Call to action

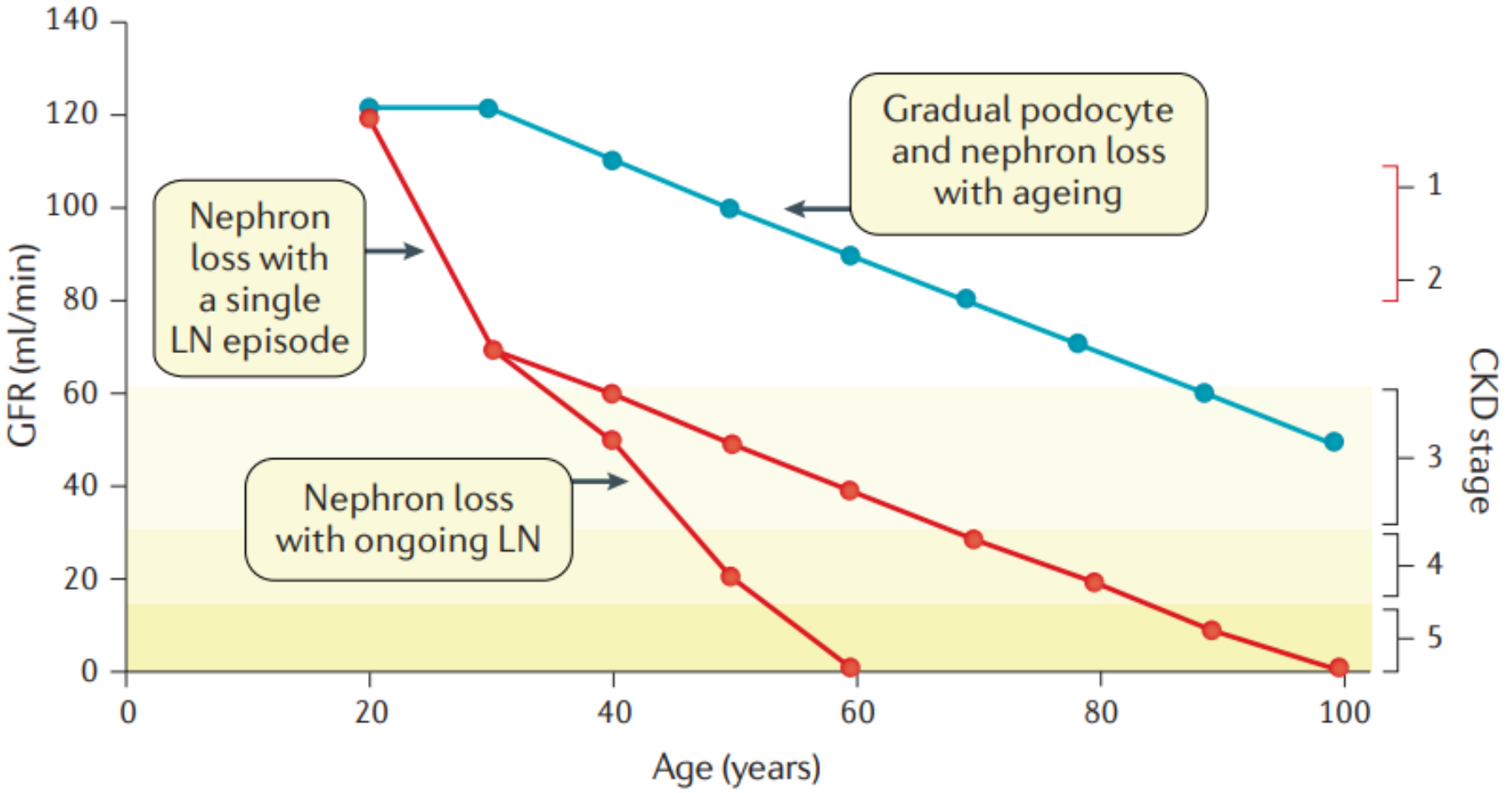
LN = CKD

Criteria for CKD (either of the following present for >3 months)	
Markers of kidney damage (one or more)	Albuminuria (AER ⩾30 mg/24 h; ACR ⩾30 mg/g (⩾3 mg/mmol)) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min per 1.73 m^2 (GFR categories G3a-G5)

Abbreviations: ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease; GFR, glomerular filtration rate.

KDIGO CKD Classification 2012

LN = CKD



Anders, et al. Lupus nephritis. Nat Rev Dis Primers 2020

LN = CKD

- First priority: CV mortality (BP, lipids, diabetes, smoking)
  Infection mortality (minimize steroids, vaccinate, hygiene)

- Minimize hemodynamic and metabolic overload of the remnant nephrons
  - Keep or reach BMI <25
  - Low-salt diet
  - Avoid dihydropyridine calcium channel blockers
  - With maximal RAS inhibition (effect +)
  - Plus SGLT2 inhibitor (no studies, effect likely +++)
  - Be careful with pregnancies, they can destroy CKD kidneys

- Avoid all nephrotoxins, namely smoking, NSAIDs and cyclosporin A, (PPIs)

- Avoid blood sampling in from potential shunt veins

- Avoid blood transfusions (HLA sensitization)

LN = CKD

If your patients have (West-) African anchestors:

Determine APOL1 genotype (prevalence up to 30%)

1 or 2 APOL1 risk alleles represent a dose-dependent weakness of the kidney to HTN and any kidney disease

Patients with LN and 1 or 2 APOL1 risk alles are rapid CKD progressors unresponsive to IS treatment

Maximize the control of glomerular hyperfiltration to prolong kidney lifespan!

Outline

Renal involvement in SLE: How you define lupus nephritis?

LN dissected by histological classes

LN dissected by histological activity

LN dissected by specific molecular features

Therapy responsive versus non-responsive LN

The „nephritic flare“ of LN

The „proteinuric flare“ of LN

LN = CKD and treating „LN“ is only a minor aspect in treating CKD

Call to action

A call to action

- IC-GN is only one of many forms of kidney disease in SLE
- Unbiased classification for LN is needed
- Treatment targets activity!!! Classification by activity?
- Pathophysiology is heterogeneous and classes I-VI do not indicate that
- There is no „refractory LN“: Adherence?, repeat diagnostics
- „Nephritic flare“: Mostly undertreatment, no biopsy needed
- „Proteinuric flare“: Mind causes of glomerular hyperfiltration, SGLT2 inhibitors (?)
- LN = CKD and must be treated as CKD, SGLT2 inhibitors (?)