Should we always perform a repeat kidney biopsy?

Pros, cons and whys

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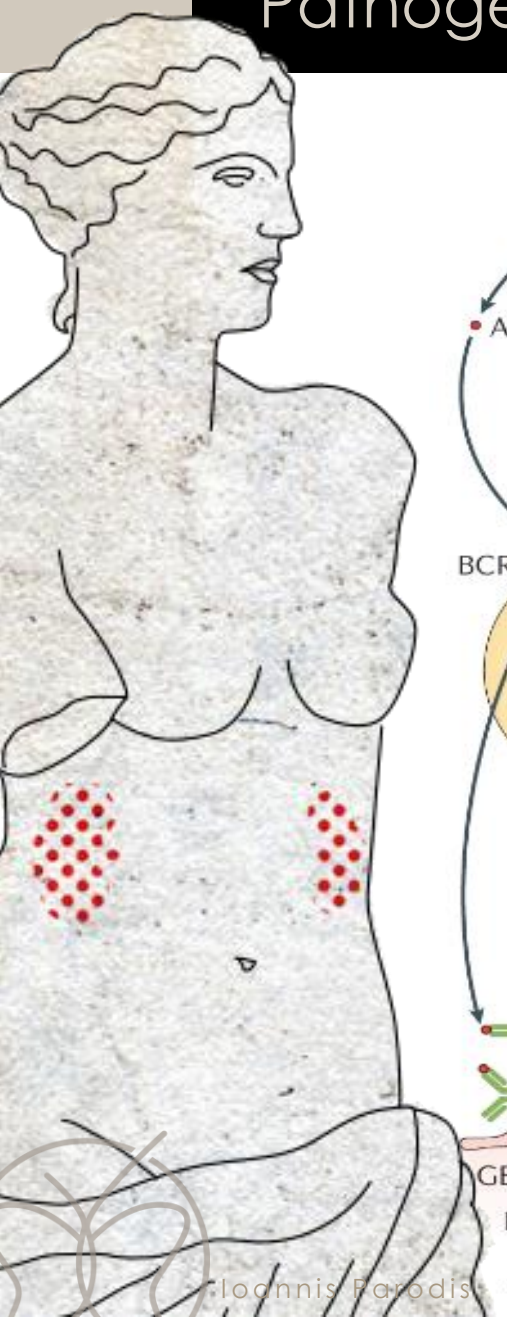
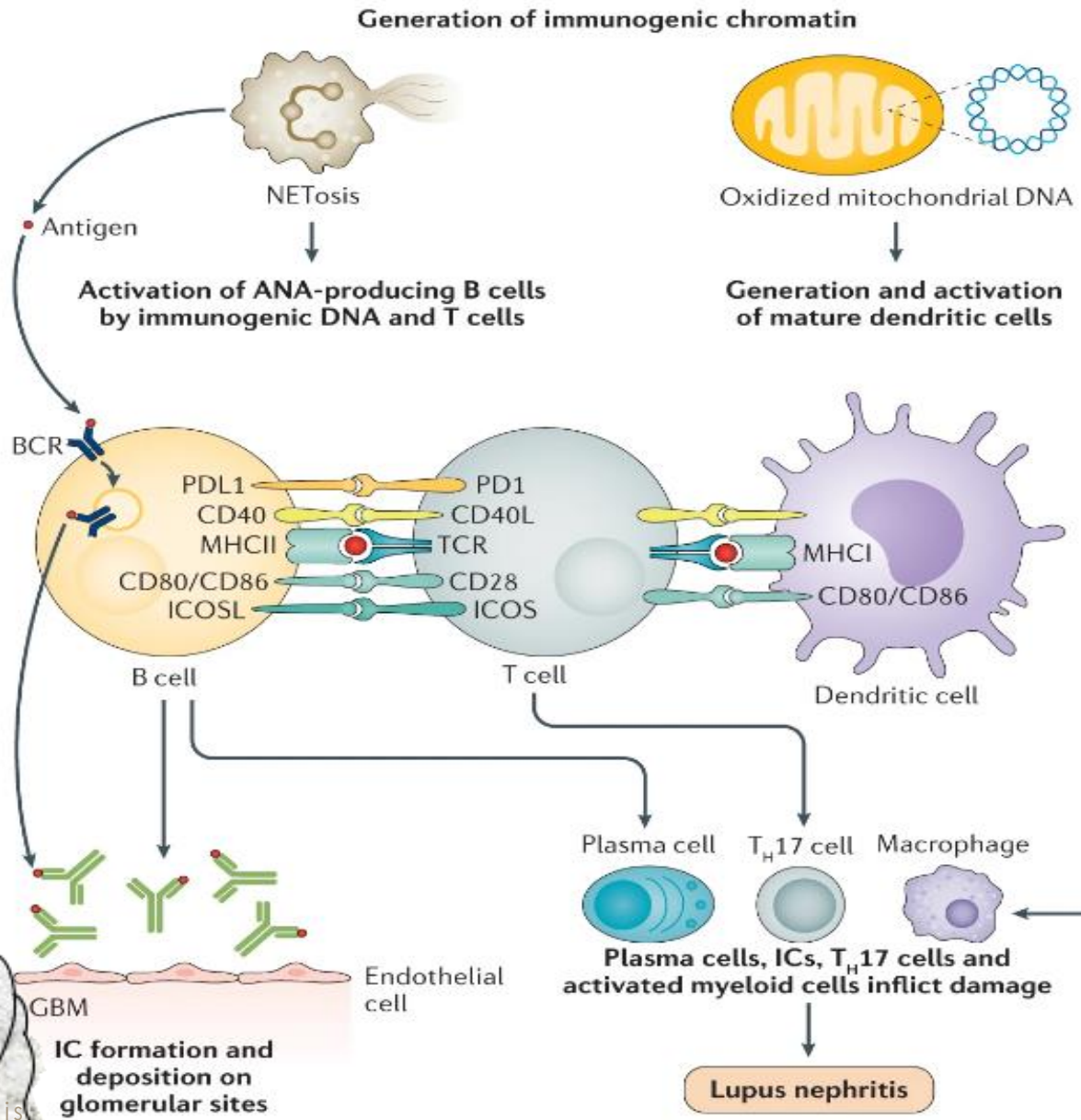
COI Disclosures

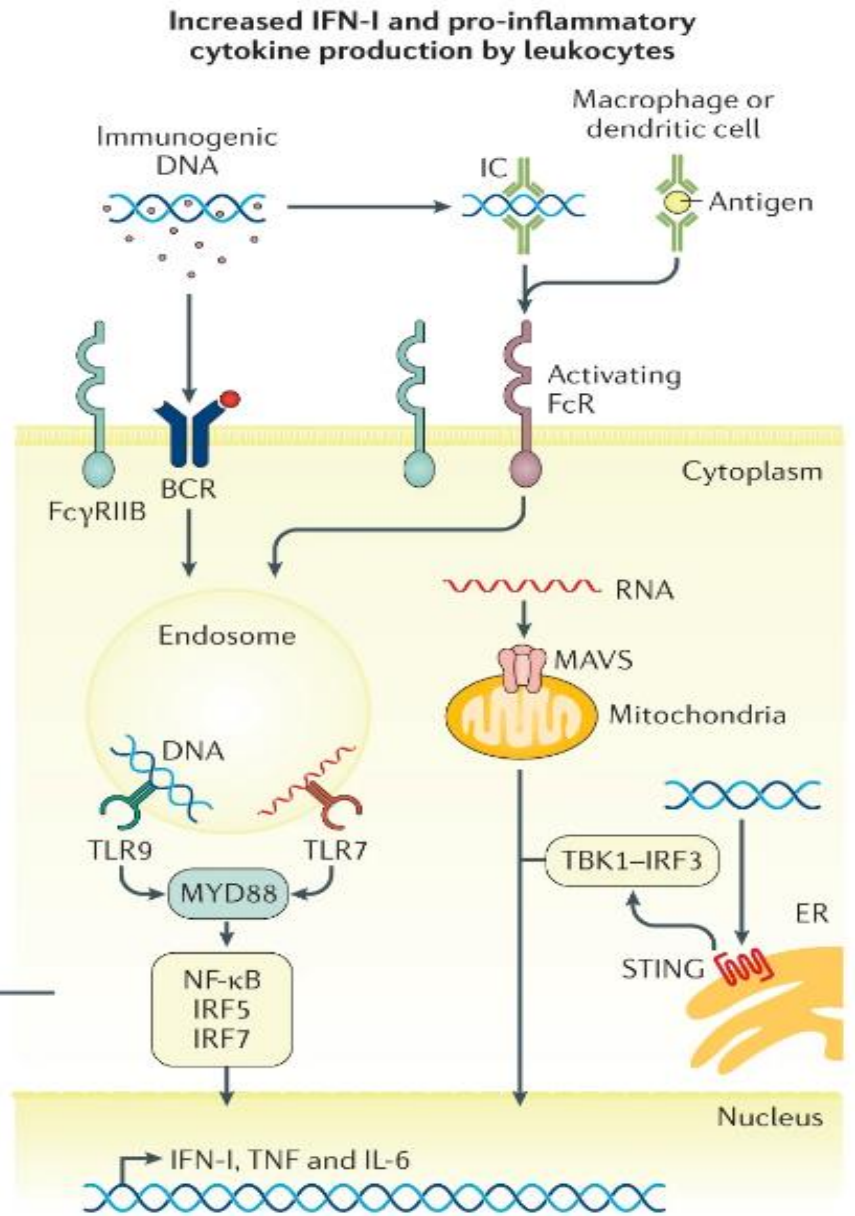
Company name	Honoraria; expenses	Consulting; advisory board	Funded research
Amgen; Aurinia; GSK; Lilly; Roche	x	x	x
AstraZeneca; Gilead; Janssen; Novartis		x	

Anders H-J et al. Nat Rev Dis Primers. 2020

Pathogenetic mechanisms in lupus nephritis





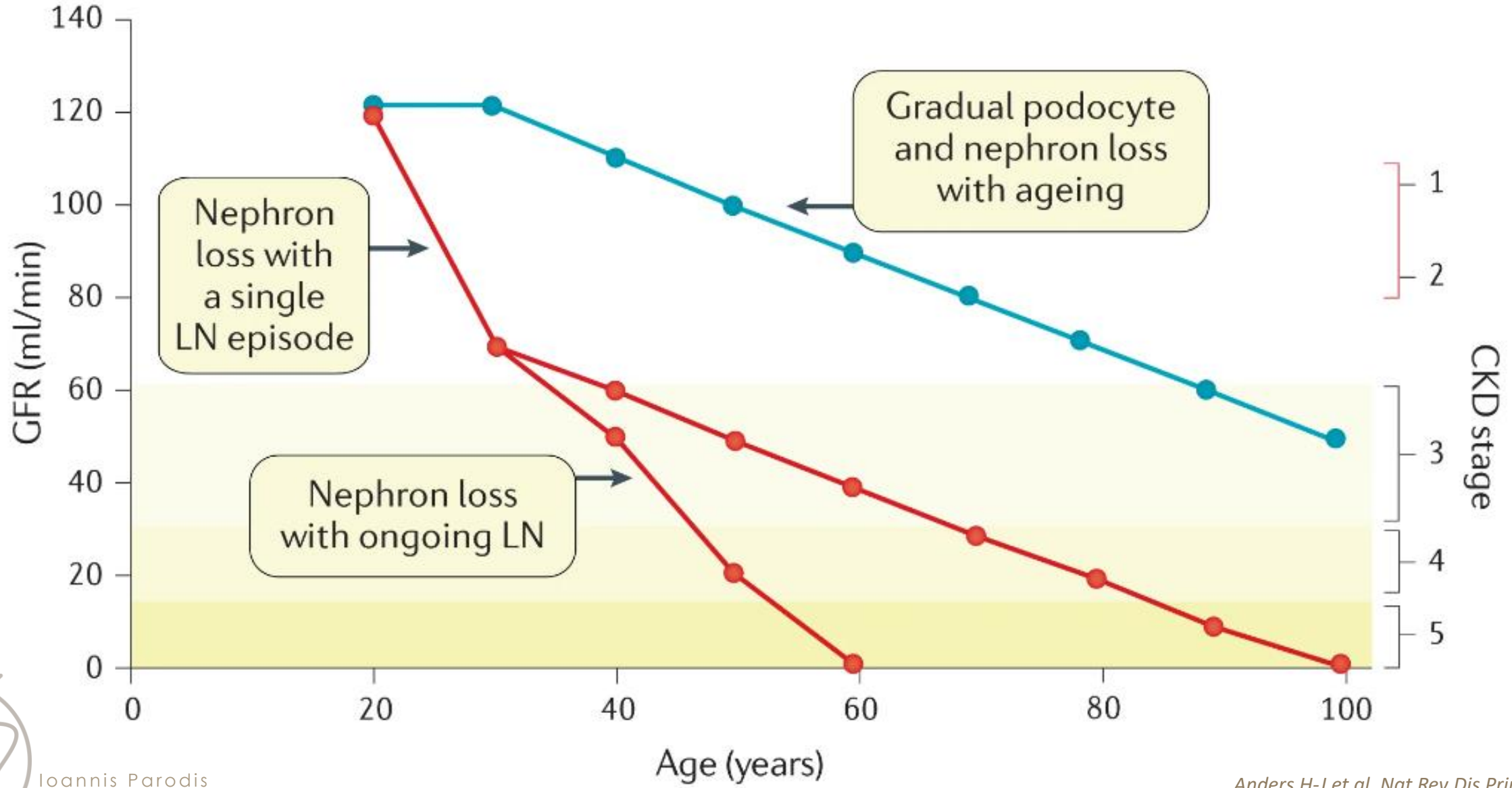


Lupus nephritis

- 35–60% of patients with SLE
- ESKD in 5–20% within 10 years
- Renal function impairment, dependent on
  - Genetic cargo
  - Nephron endowment
  - Disease activity, renal flares
  - Drug-induced toxicity

Anders H-J et al. Nat Rev Dis Primers. 2020
Pons-Estel GJ. Autoimmun Rev 2011

Lupus nephritis



Anders H-J et al. Nat Rev Dis Primers. 2020

Sequential treatment (EULAR/EDTA recommendations)

Induction

- MMF (2–3 g/day)
- EL CYC (seldom NIH)
- MP (0.5–3 g)
- Prednisone 0.3–0.5 mg/kg/day (≤7.5 mg/day by M3–6)

Maintenance

- MMF
- AZA
- (Add-on) CNI (at the lowest dose possible)
- ≥3 years

HCQ; ACEi/ARBs

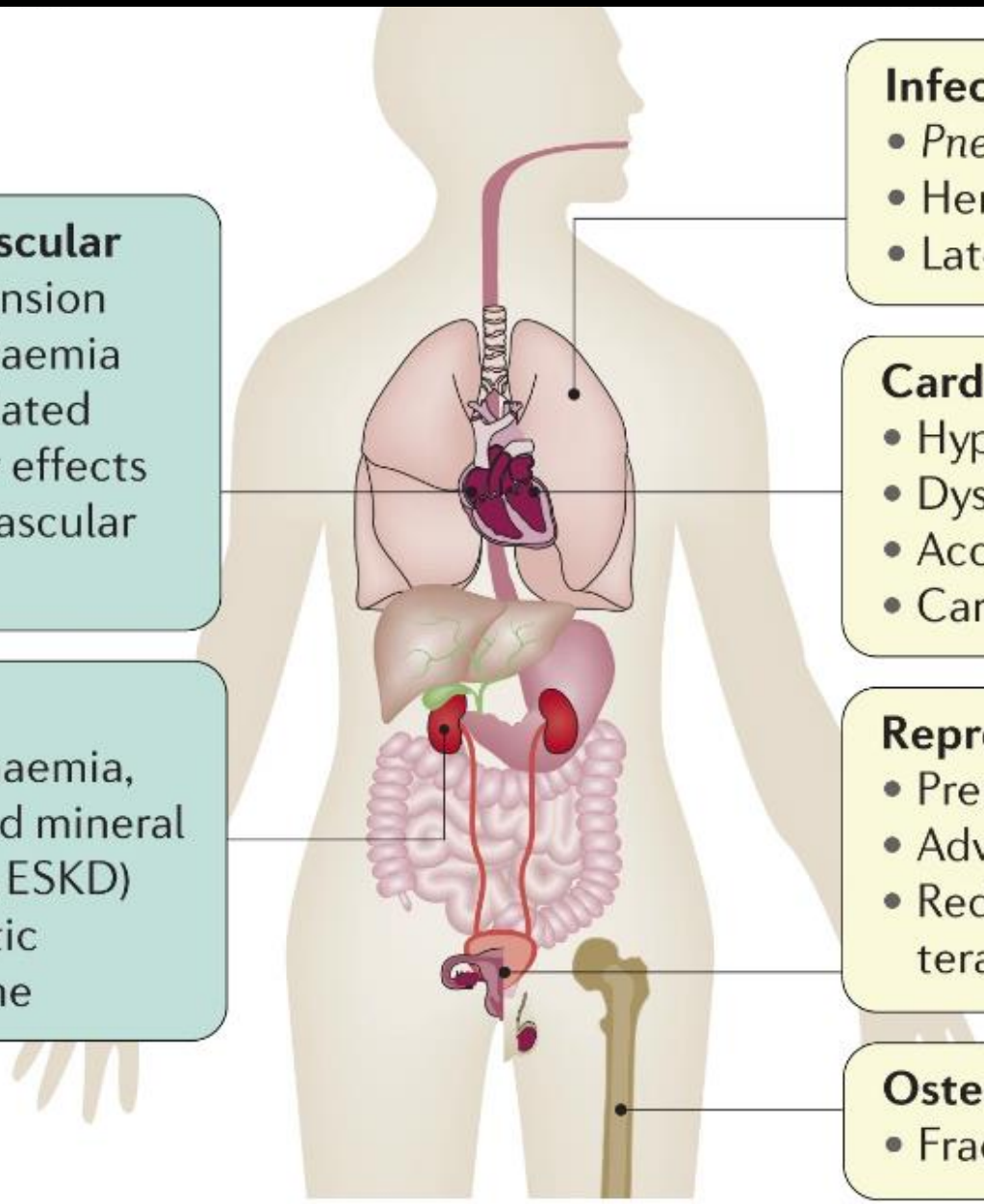
- Proteinuria <0.5–0.7 g/day by 12 months (MAINTAIN; ELNT)
- Proteinuria decrease by ≥50% by 6 months (6–12 if >3 g at BL)
- Control of extra-renal disease

Refractory cases

Switch; CNI; RTX

Fanouriakis A et al. Ann Rheum Dis 2020

Comorbidities and treatment-associated AE



Cardiovascular
- Hypertension
- Dyslipidaemia
- CKD-related vascular effects
- Cardiovascular disease

Renal
- CKD (anaemia, bone and mineral disease, ESKD)
- Nephrotic syndrome

Infections
- *Pneumocystis jirovecii* pneumonia
- Herpes
- Latent tuberculosis

Cardiovascular
- Hypertension
- Dyslipidaemia
- Accelerated atherogenesis
- Cardiovascular disease

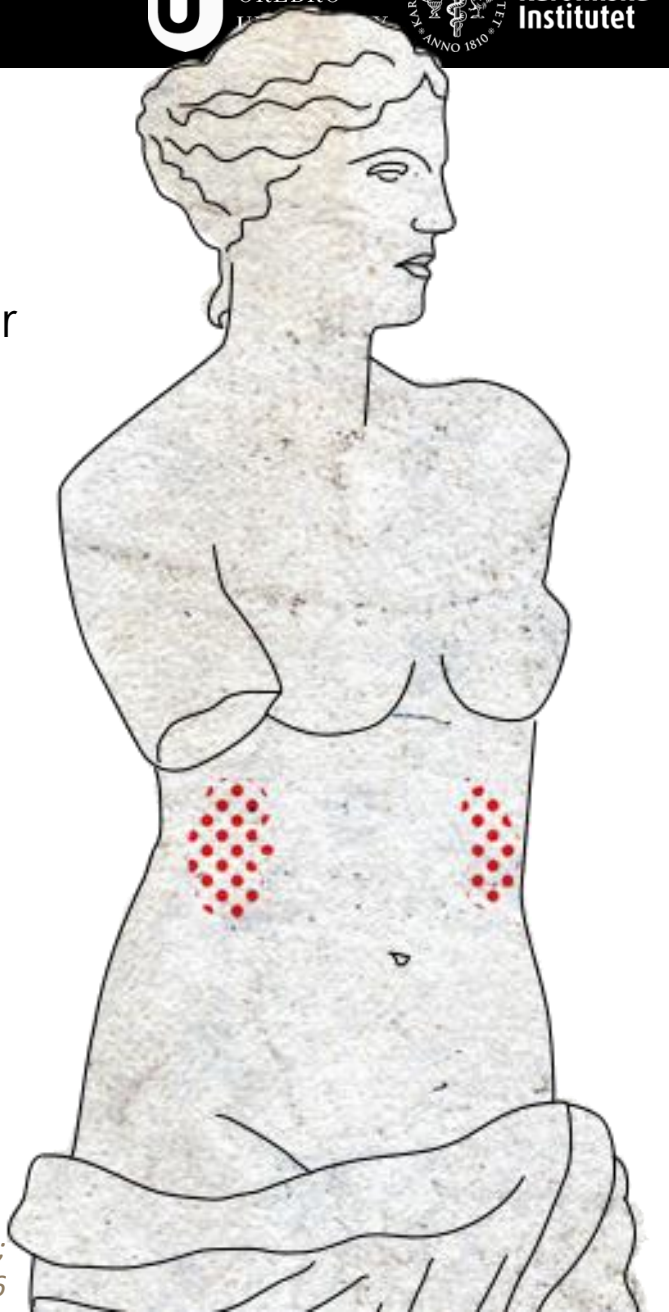
Reproductive
- Premature ovarian failure
- Adverse pregnancy outcomes
- Reduced male fertility and teratogenicity

Osteoporosis
- Fractures

Anders H-J et al. Nat Rev Dis Primers. 2020

Treatment outcome with sequential therapy

- Only 20–30% of patients achieve complete renal response within 1 year
- 20–35% of patients who respond will relapse within 3–5 years
- ≥20% develop CDK
- 5–20% reach ESKD within 10 years

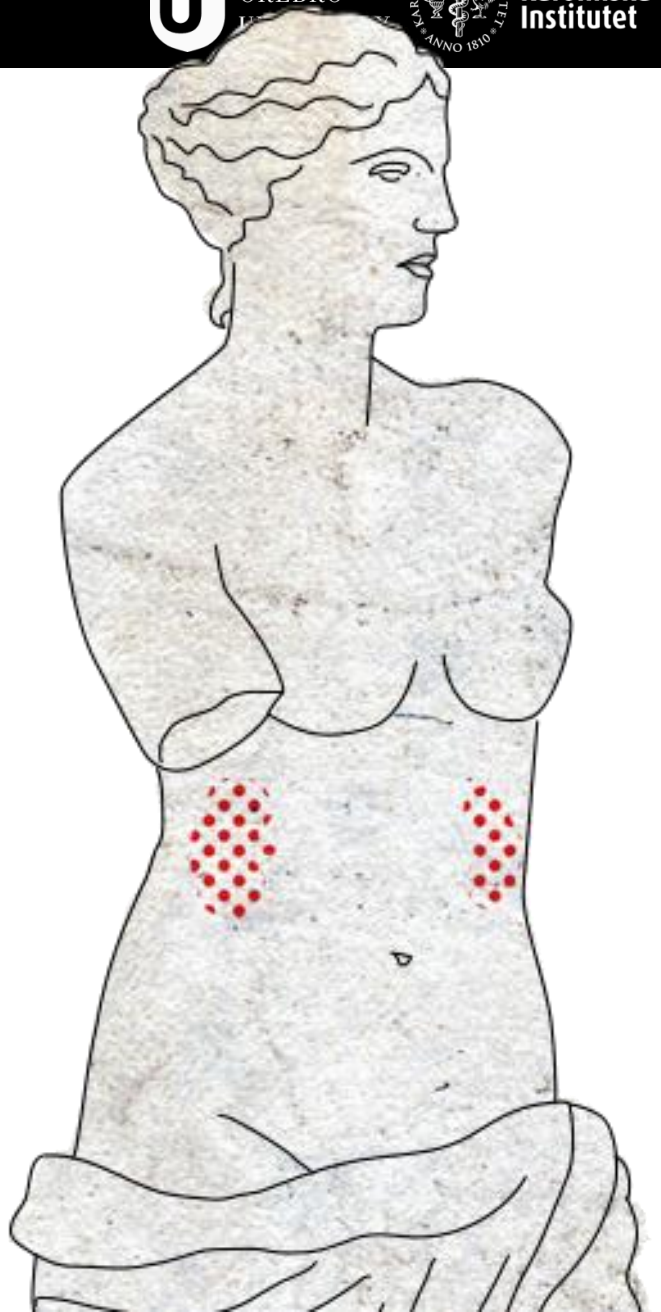


Appel GB et al. J Am Nephro. 2009; Ginzler EM et al. N Engl J Med. 2005;
Anders H-J et al. Nat Rev Dis Primers. 2020; Tektonidou MG et al. Arthritis Rheumatol. 2016

Improved prognosis remains a need

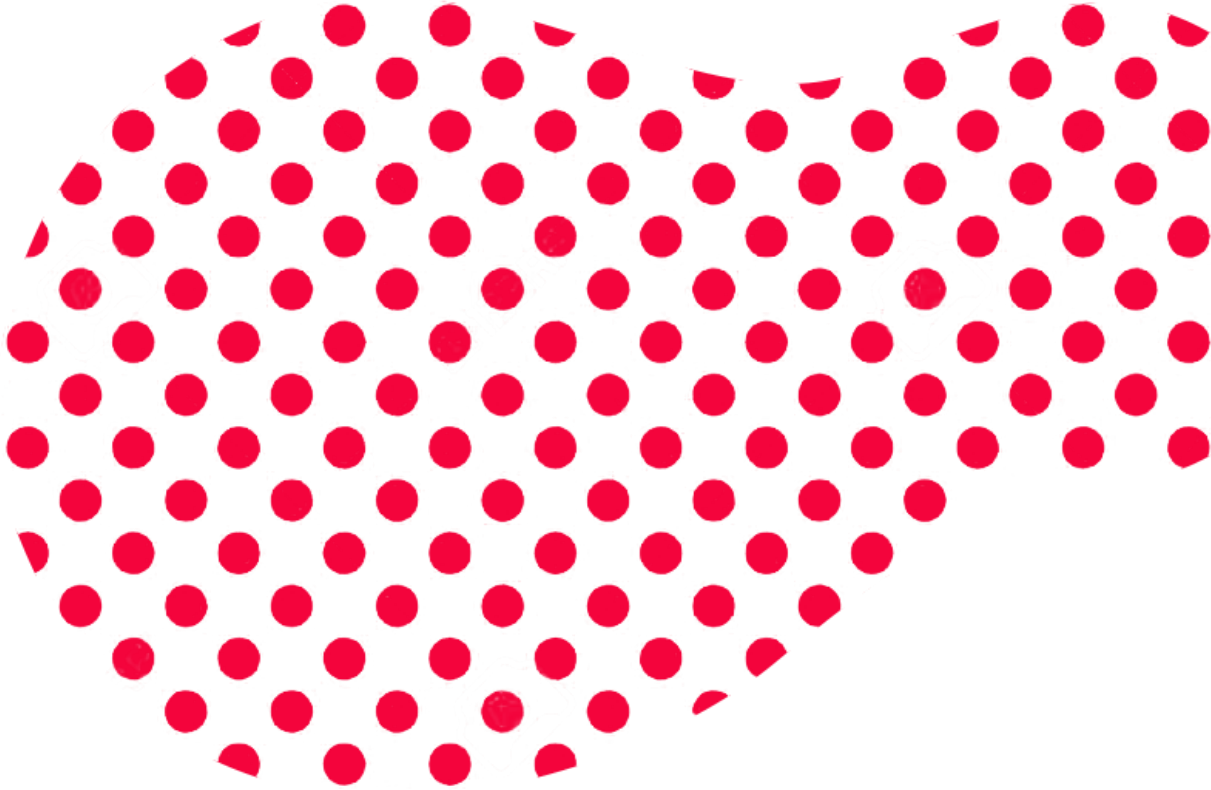
- Treat-to-target approaches

- Combination and personalised therapy



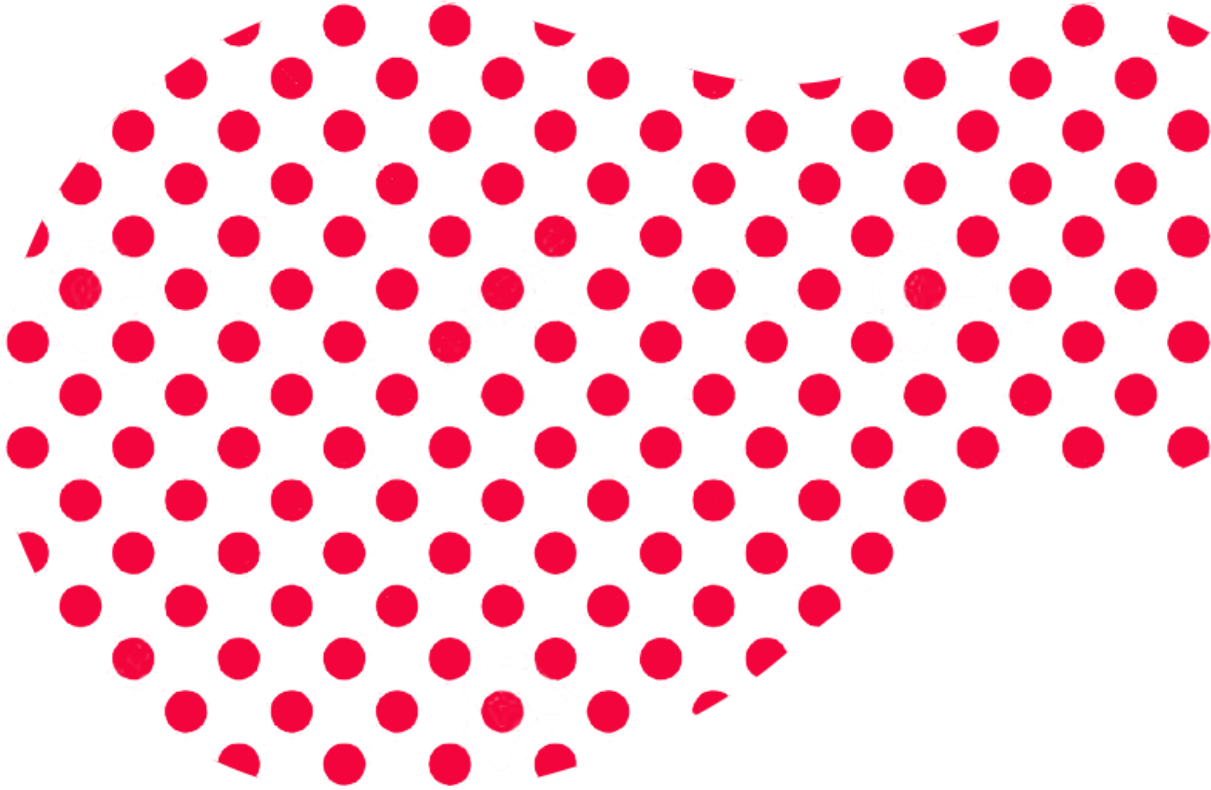
Treat-to-target in lupus nephritis

- Clinical target
- Histopathology-based
- Immunopathological features

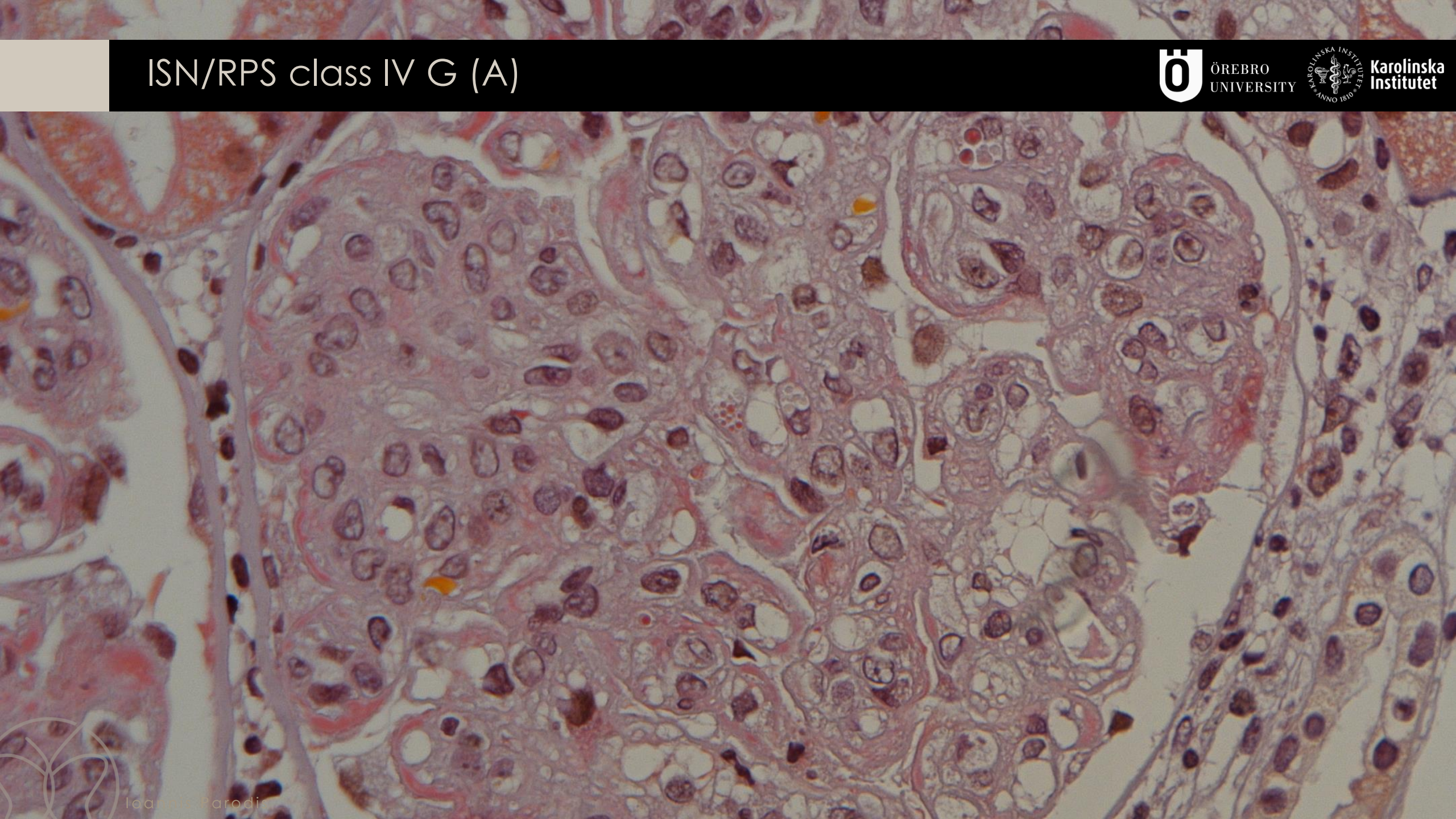


Kidney biopsy

- Indispensable for diagnosis and classification
- No reliable biomarkers reflecting histology



ISN/RPS class IV G (A)



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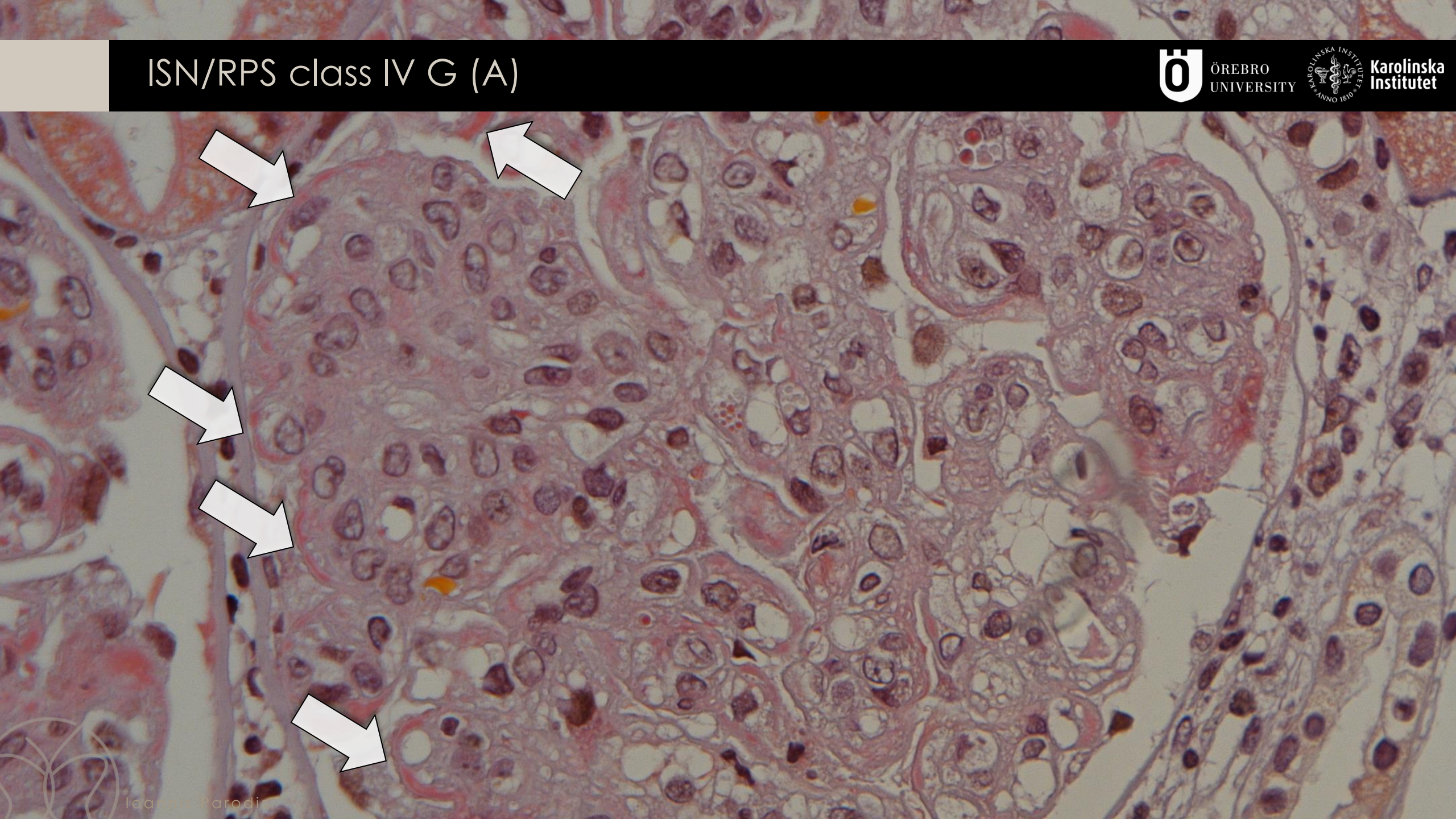
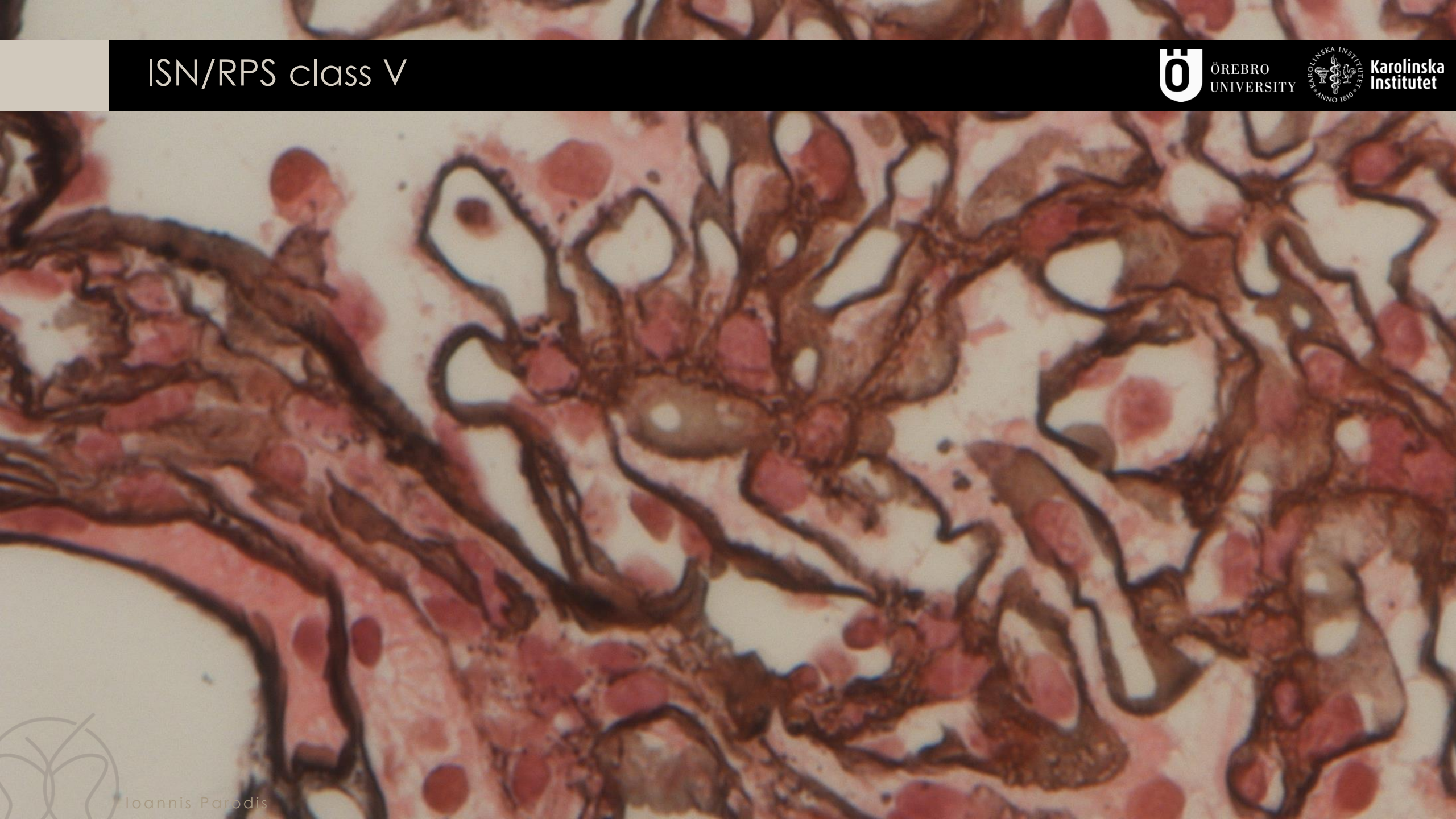
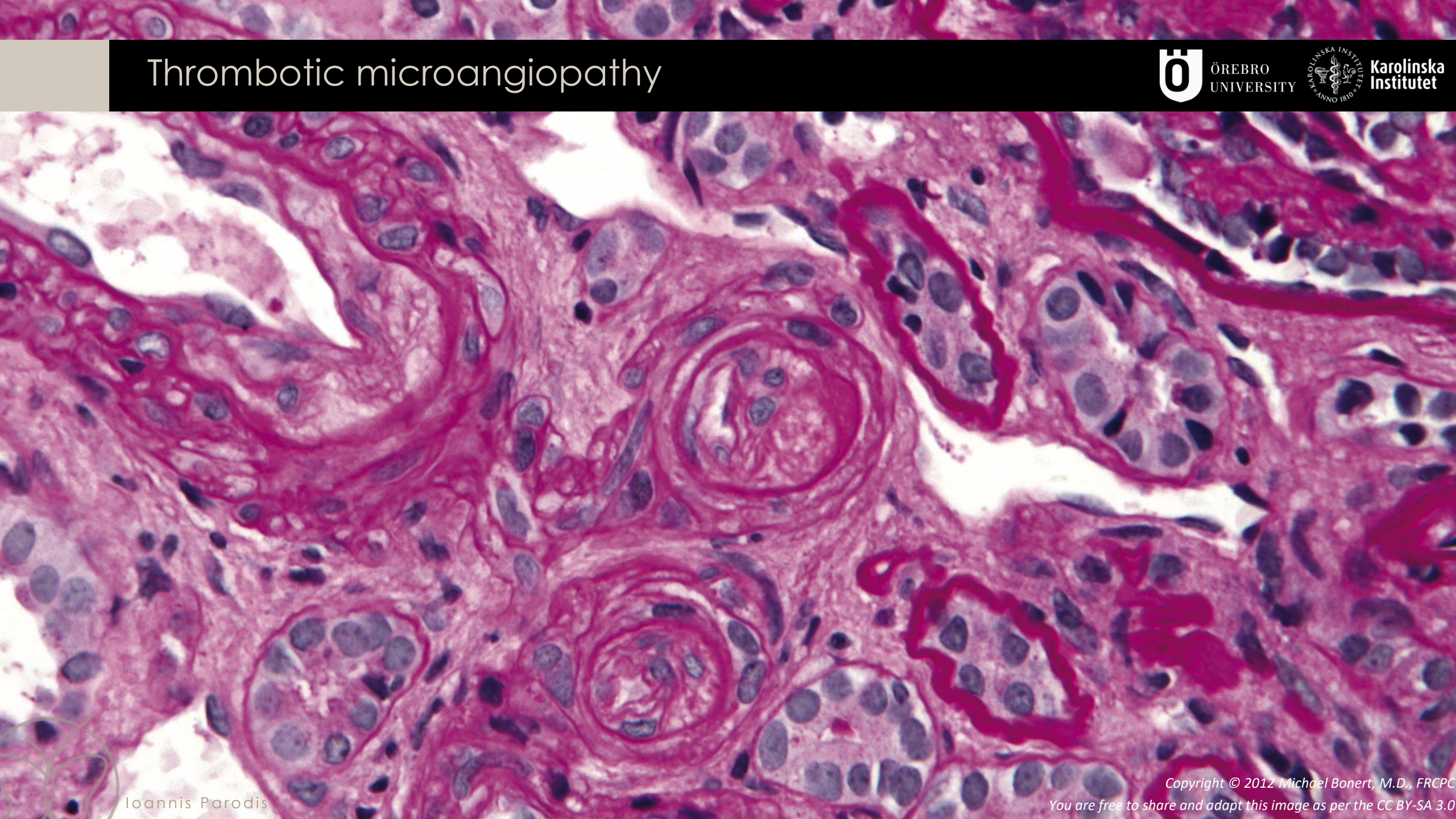


ISN/RPS class V



Thrombotic microangiopathy



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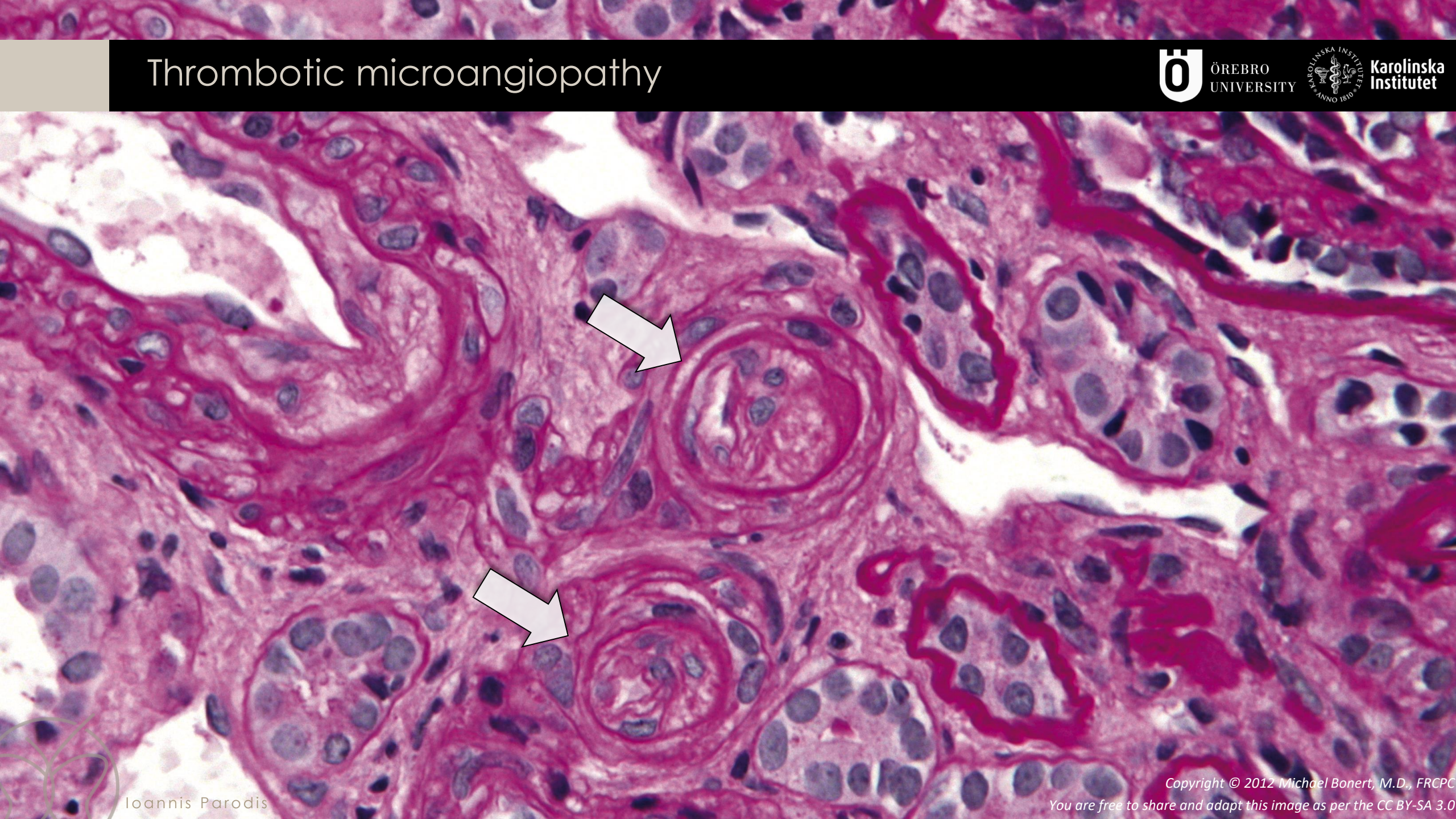

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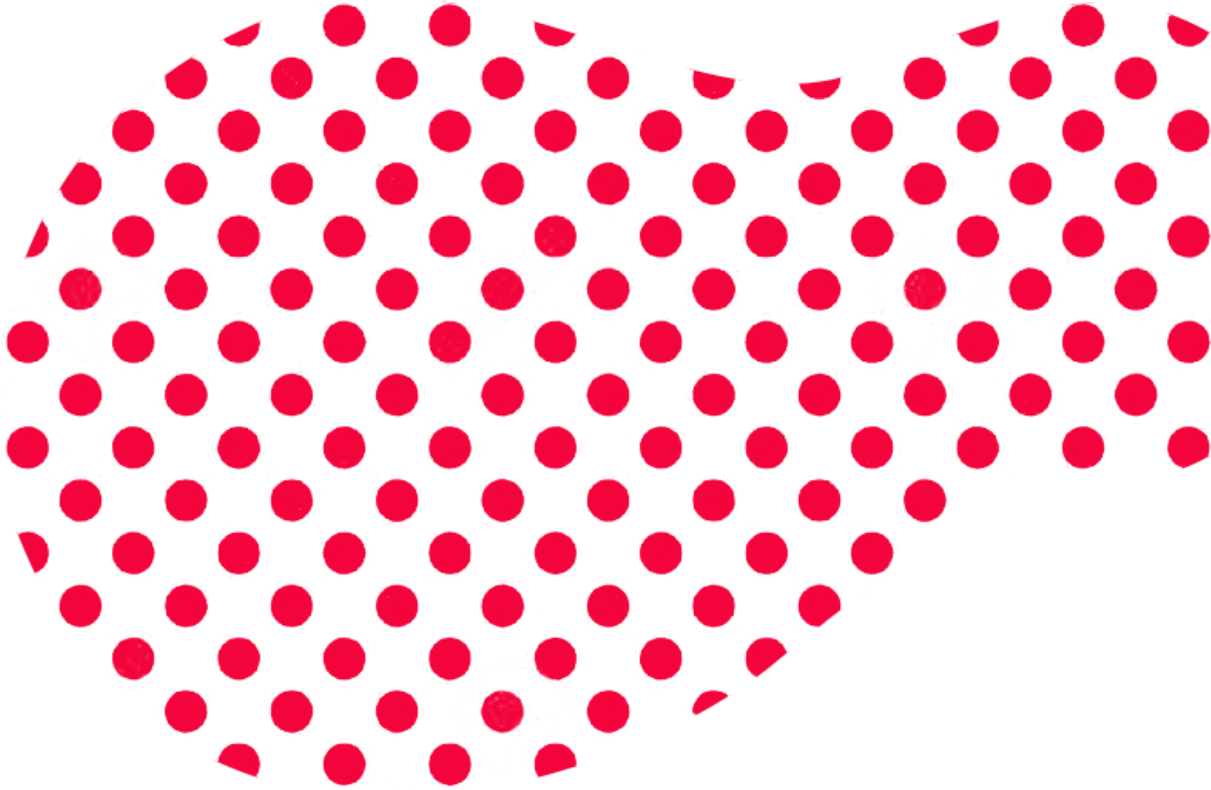
Repeat kidney biopsy

- What does it actually mean?
- When should we perform it?
- Is it safe?



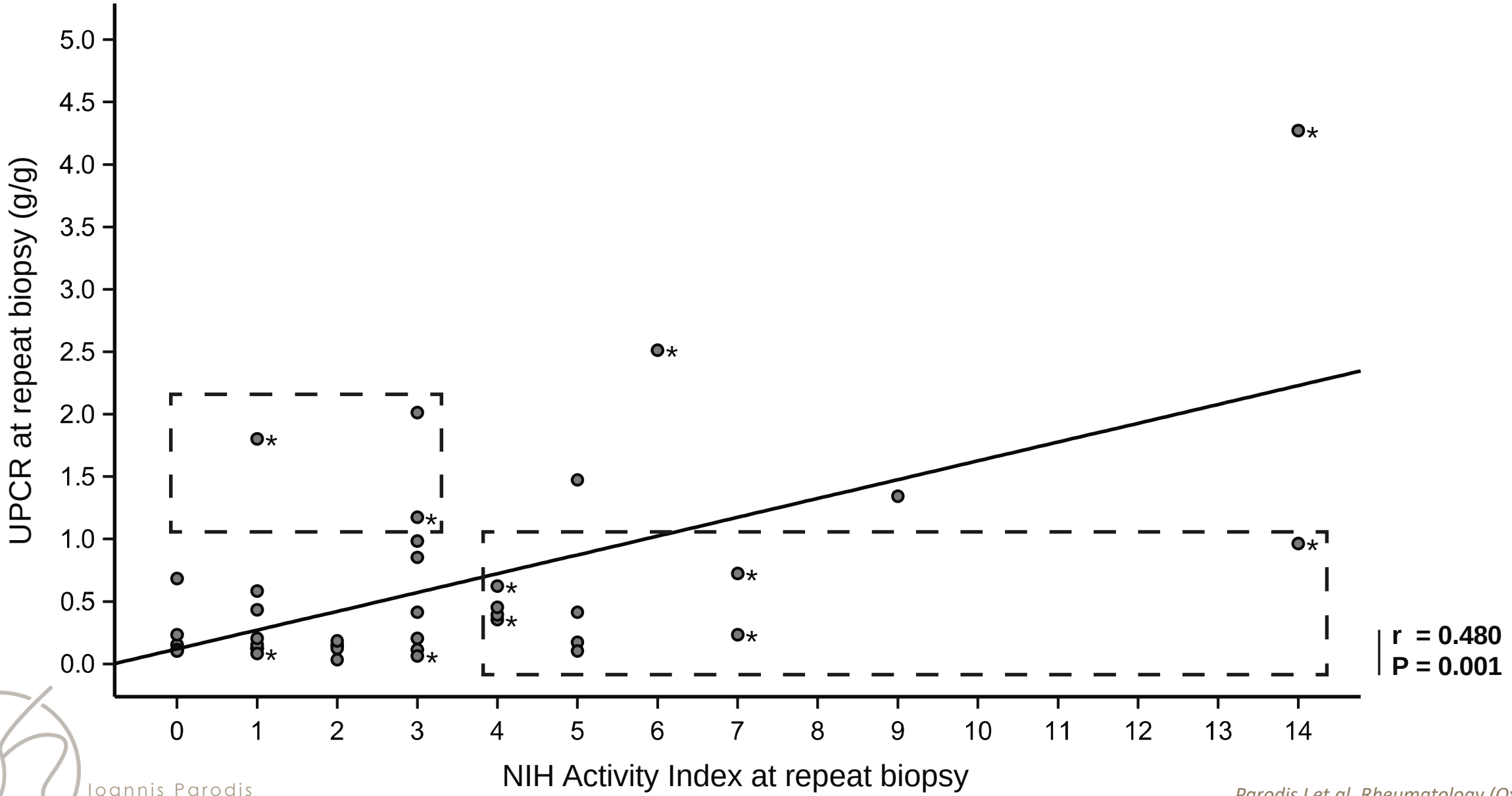
Anders H-J. Ann Transl Med. 2018; Hogan JJ et al. Clin J Am Soc Nephrol. 2016; Parodis I et al. Lupus Sci Med. 2015

Discordance between clinical and histological outcome

ISN/RPS class III or IV	Histological responders	Histological non-responders
Complete clinical responders	71%	29%
Partial clinical responders	47%	53%

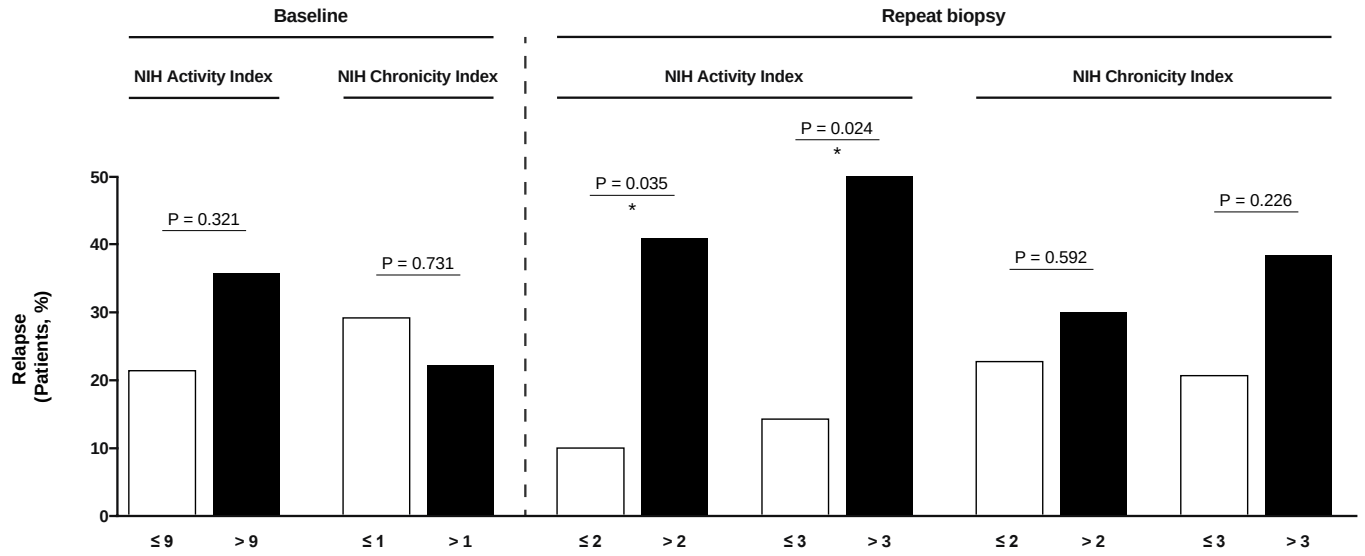
Zickert A et al. Lupus Sci Med. 2014

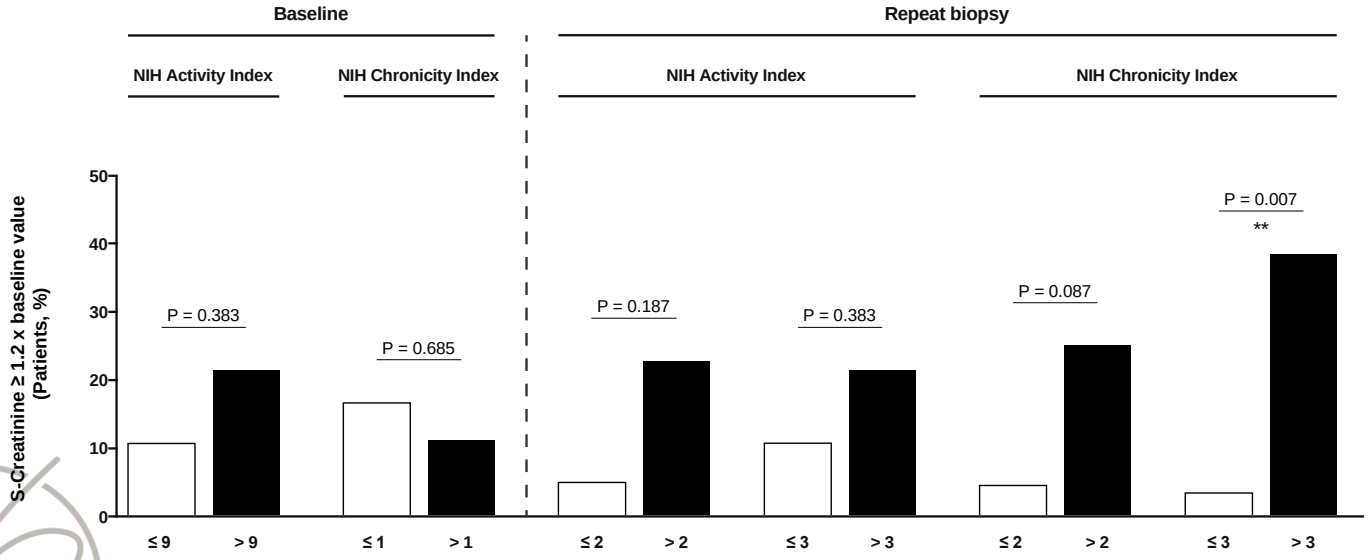
Discordance between clinical and histological outcome



Parodis I et al. Rheumatology (Oxford). 2020

Repeat biopsy portends relapse and long-term outcome





Variables	Coefficient	P value
NIH Activity Index at baseline	- 0.03	0.736
NIH Activity Index > 9 at baseline	0.40	0.474
NIH Chronicity Index at baseline	- 0.20	0.477
NIH Chronicity Index > 1 at baseline	- 0.20	0.835
NIH Activity Index at rebiopsy	0.20	0.007 **
NIH Activity Index > 2 at rebiopsy	1.50	0.053
NIH Activity Index > 3 at rebiopsy	1.60	0.014 *
NIH Chronicity Index at rebiopsy	0.10	0.438
NIH Chronicity Index > 2 at rebiopsy	0.40	0.514
NIH Chronicity Index > 3 at rebiopsy	0.80	0.206
Acute glomerular lesions at baseline	0.02	0.838
Acute TI lesions at baseline	- 0.39	0.528
Chronic glomerular lesions at baseline	- 0.10	0.866
Chronic TI lesions at baseline	- 0.16	0.650
Acute glomerular lesions at rebiopsy	0.18	0.010 *
Acute TI lesions at rebiopsy	0.41	0.419
Chronic glomerular lesions at rebiopsy	0.72	0.044 *
Chronic TI lesions at rebiopsy	- 0.02	0.944

HR (95% CI): 0.125 0.25 0.5 1 2 4 8 16

Variables	Coefficient	P value
NIH Activity Index at baseline	0.10	0.381
NIH Activity Index > 9 at baseline	0.70	0.364
NIH Chronicity Index at baseline	- 0.30	0.415
NIH Chronicity Index > 1 at baseline	- 0.40	0.624
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NIH Chronicity Index at rebiopsy	0.60	0.016 *
NIH Chronicity Index > 2 at rebiopsy	1.70	0.110
NIH Chronicity Index > 3 at rebiopsy	2.50	0.022 *
Acute glomerular lesions at baseline	0.15	0.344
Acute TI lesions at baseline	0.35	0.673
Chronic glomerular lesions at baseline	-0.64	0.526
Chronic TI lesions at baseline	0.00	0.999
Acute glomerular lesions at rebiopsy	0.02	0.863
Acute TI lesions at rebiopsy	2.19	0.009 **
Chronic glomerular lesions at rebiopsy	0.51	0.252
Chronic TI lesions at rebiopsy	0.73	0.038 *

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Parodis I et al. Rheumatology (Oxford). 2020

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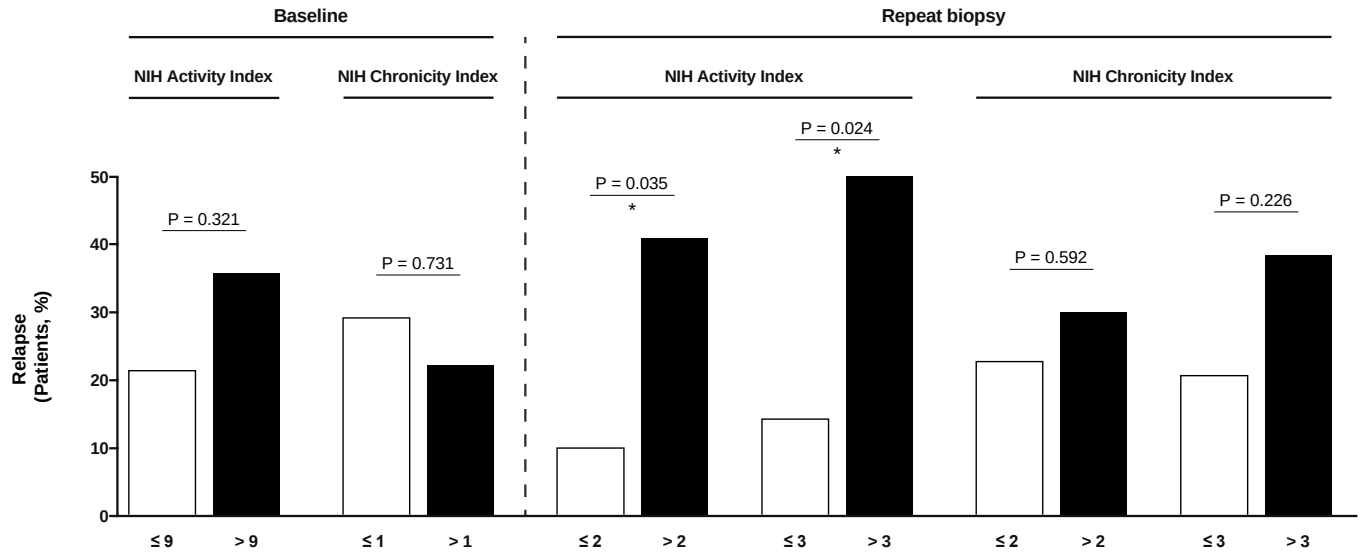

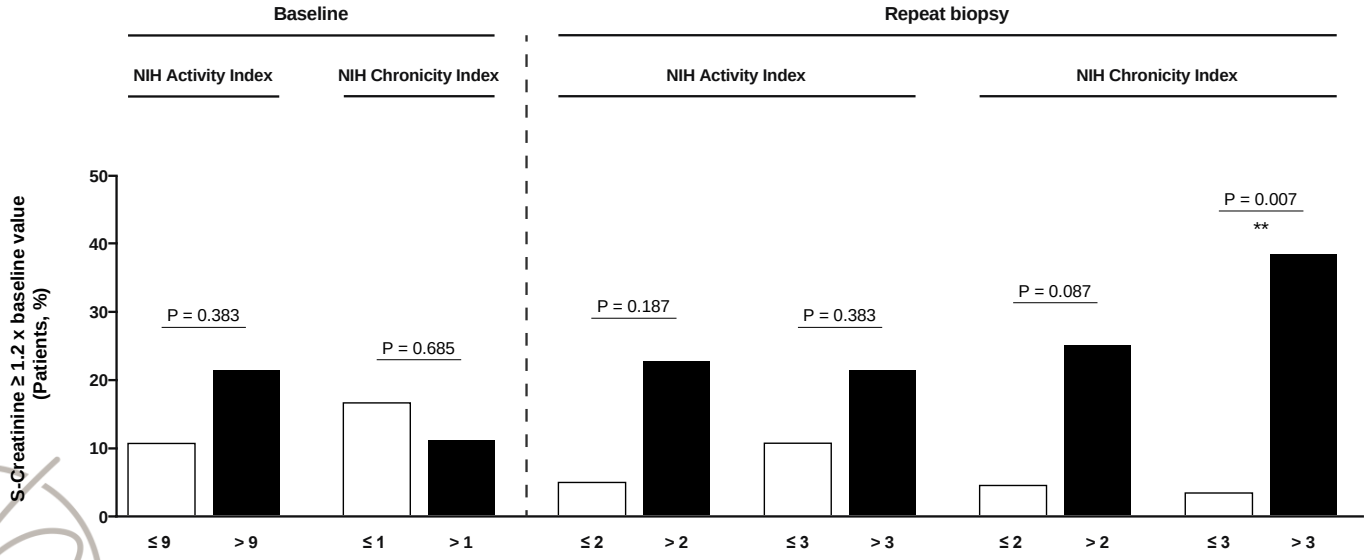

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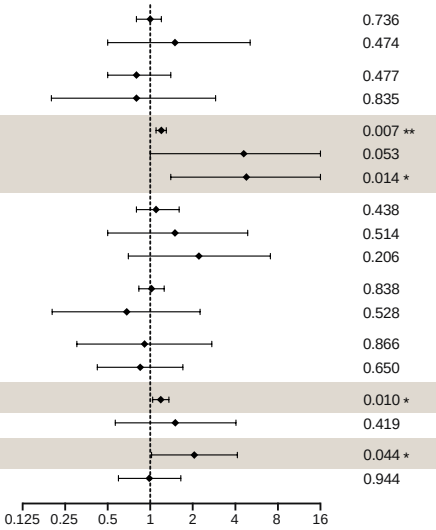

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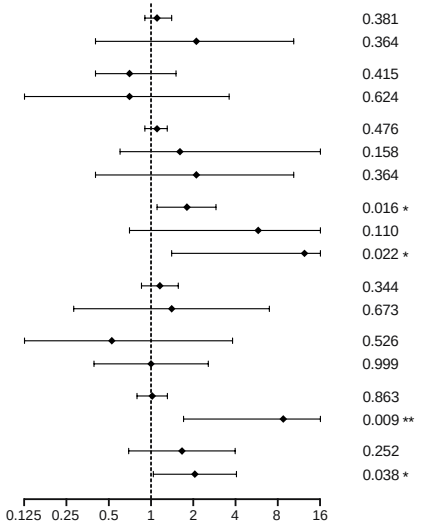

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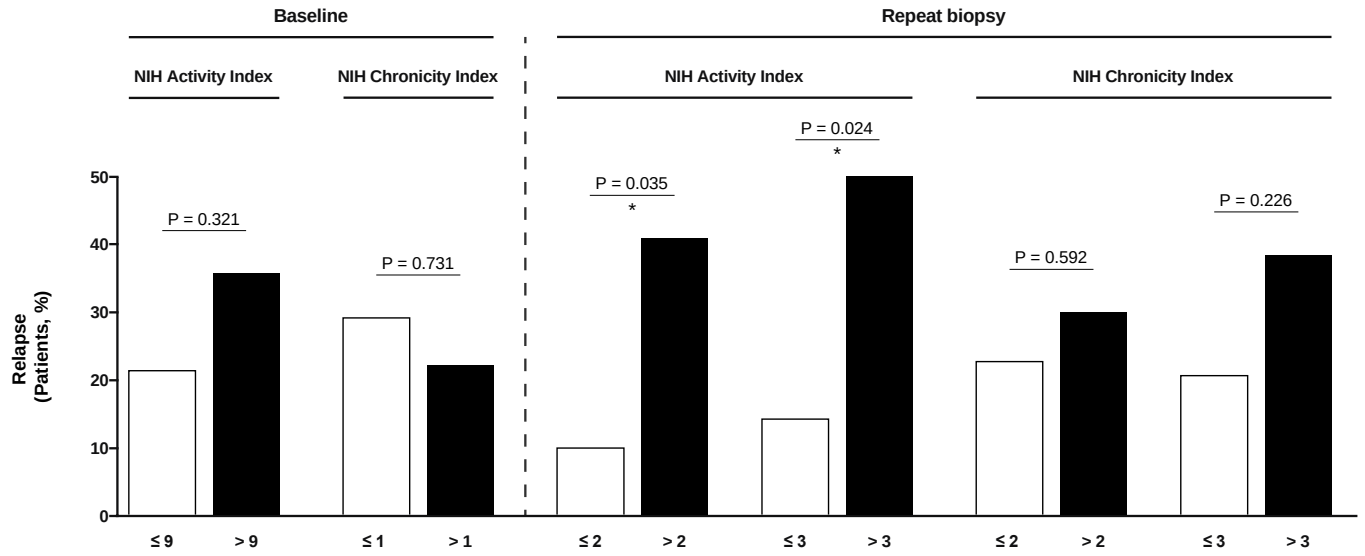

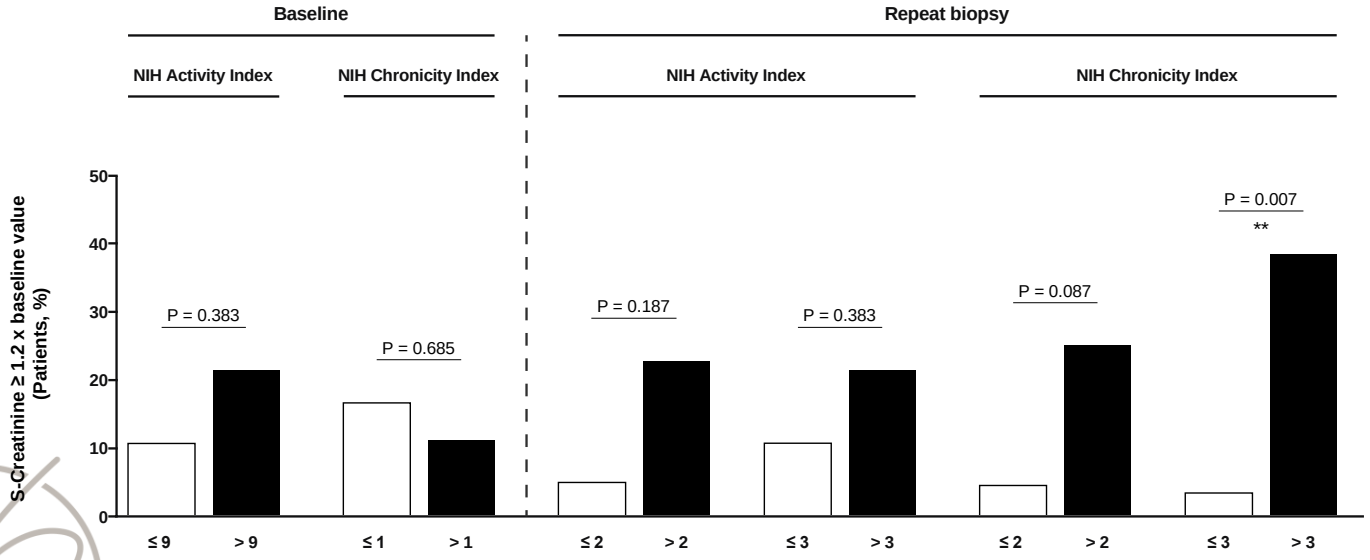

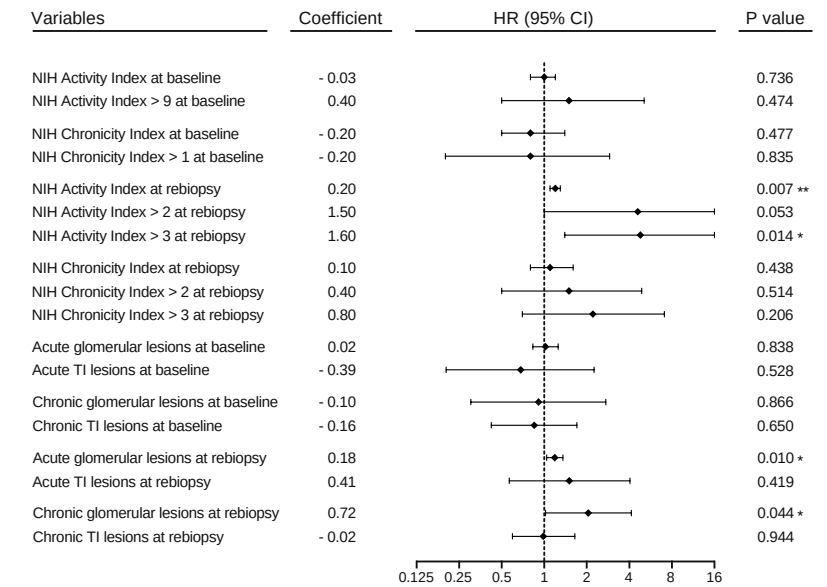

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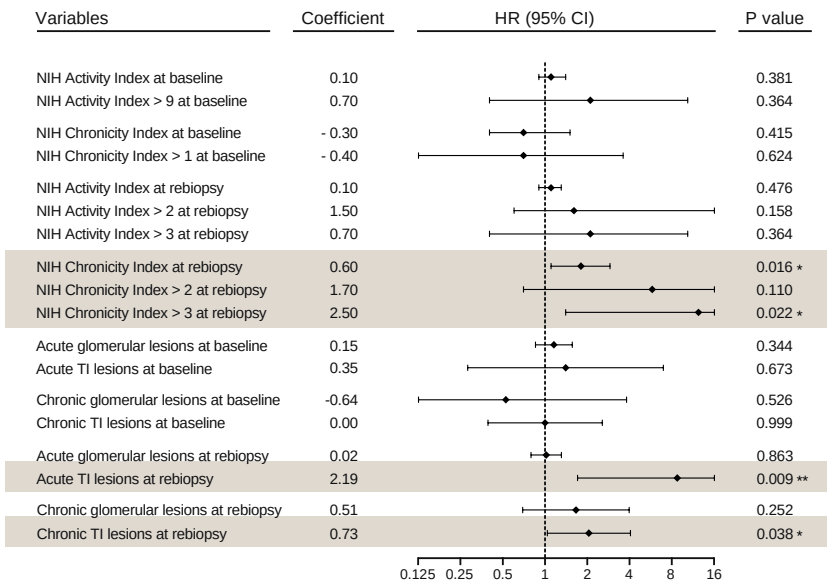

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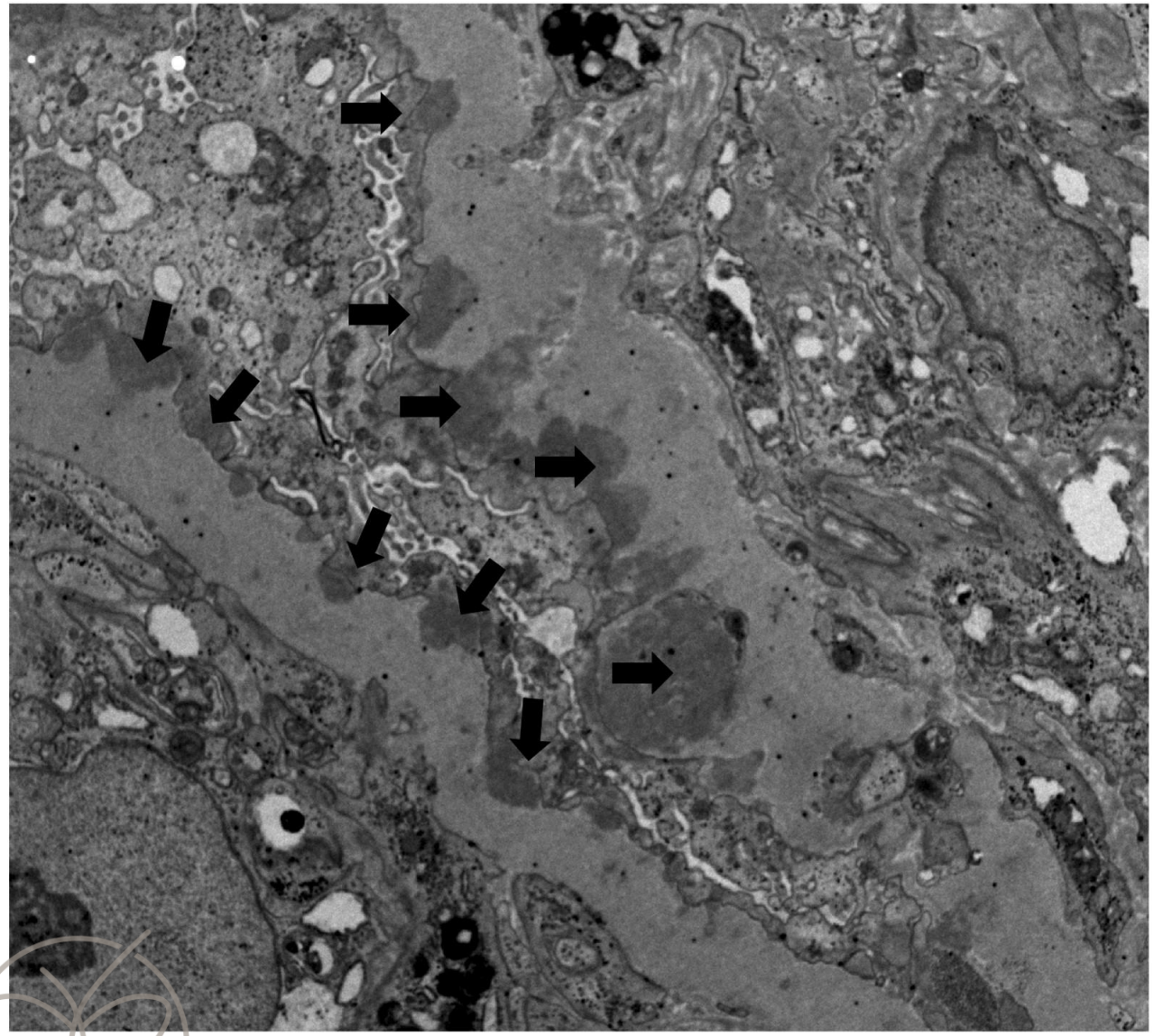
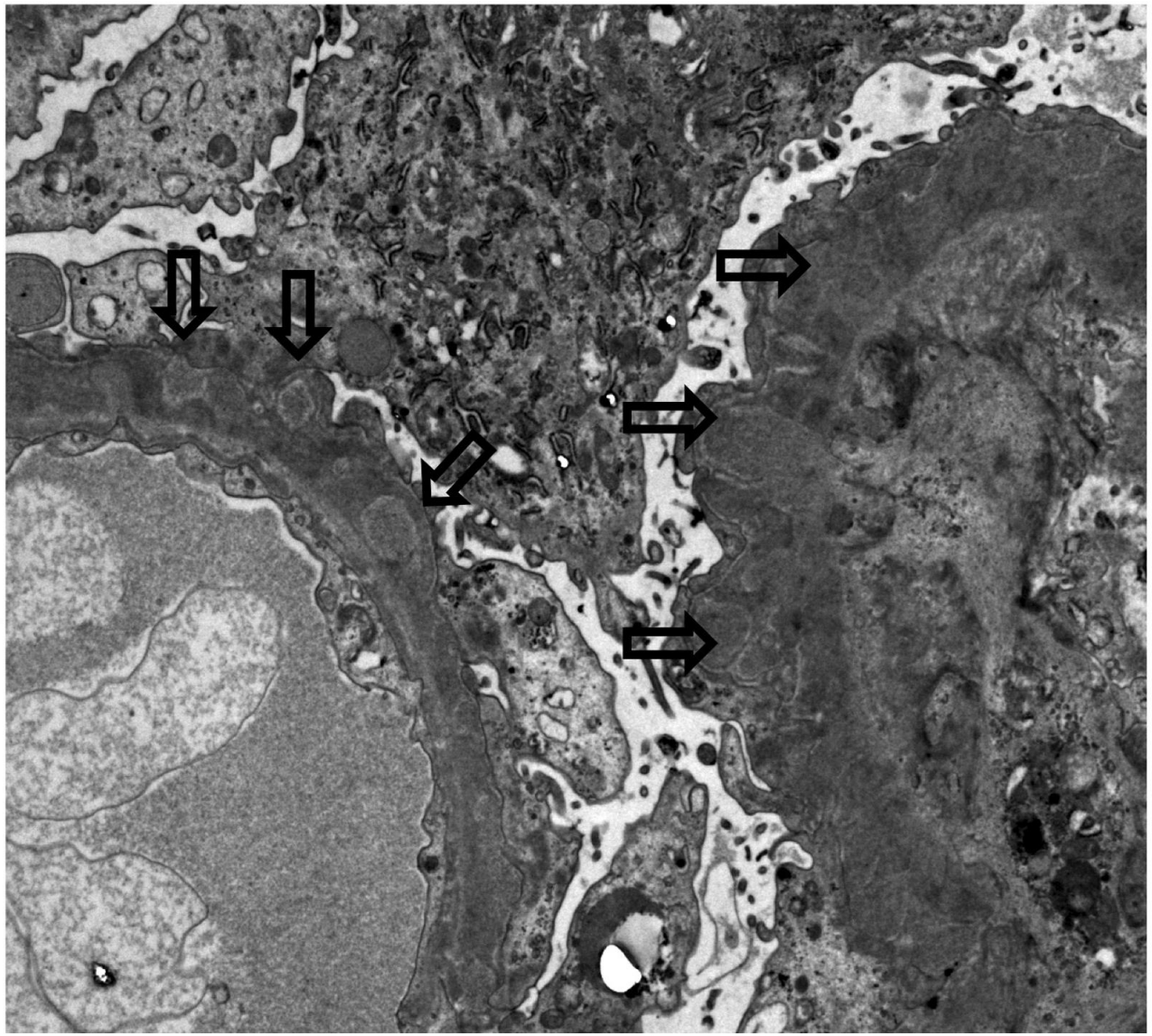
Parodis I et al. Rheumatology (Oxford). 2020

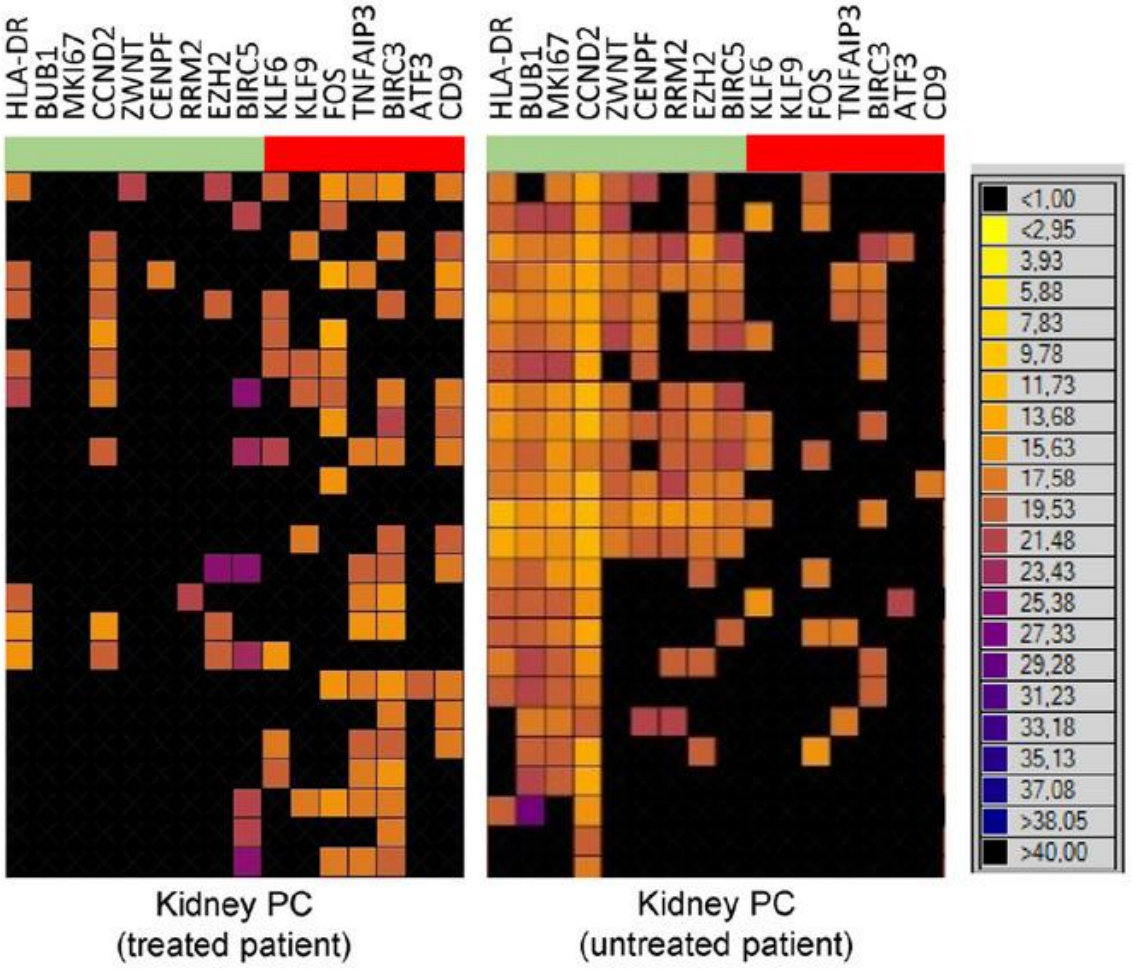
Immune deposit resorption post-rituximab in class V

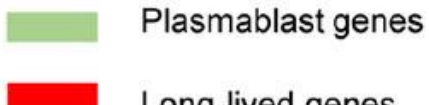


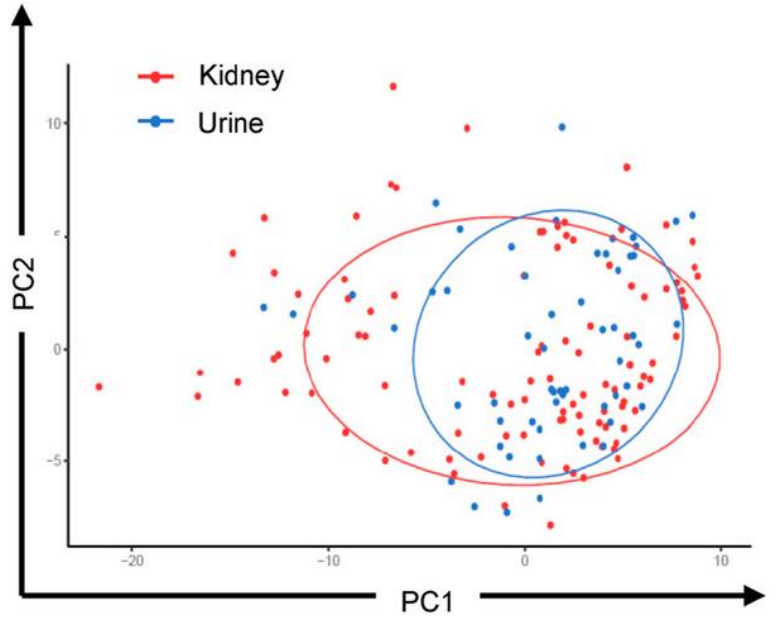


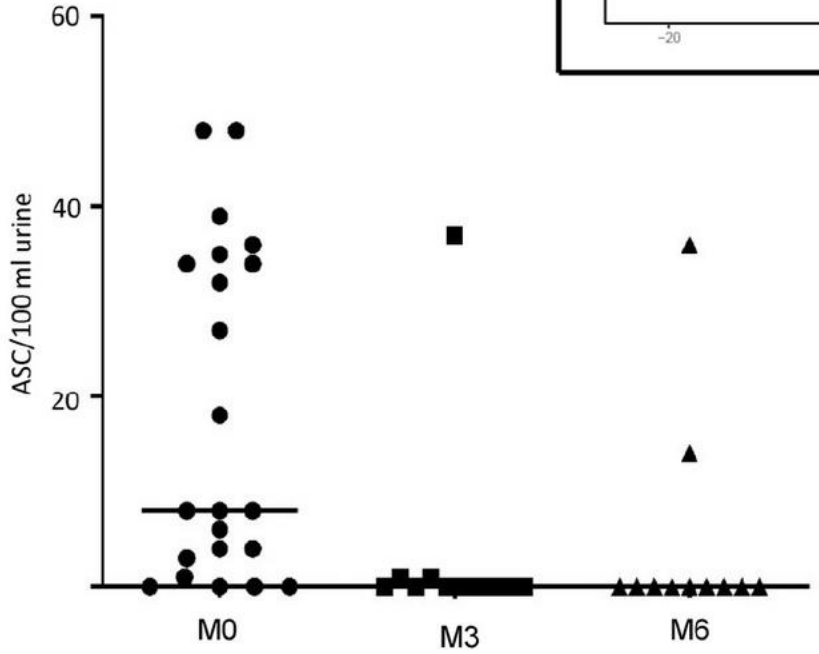
Zickert A et al. Rheumatology (Oxford). 2021

Similar ASC transcription profiles in kidney and urine









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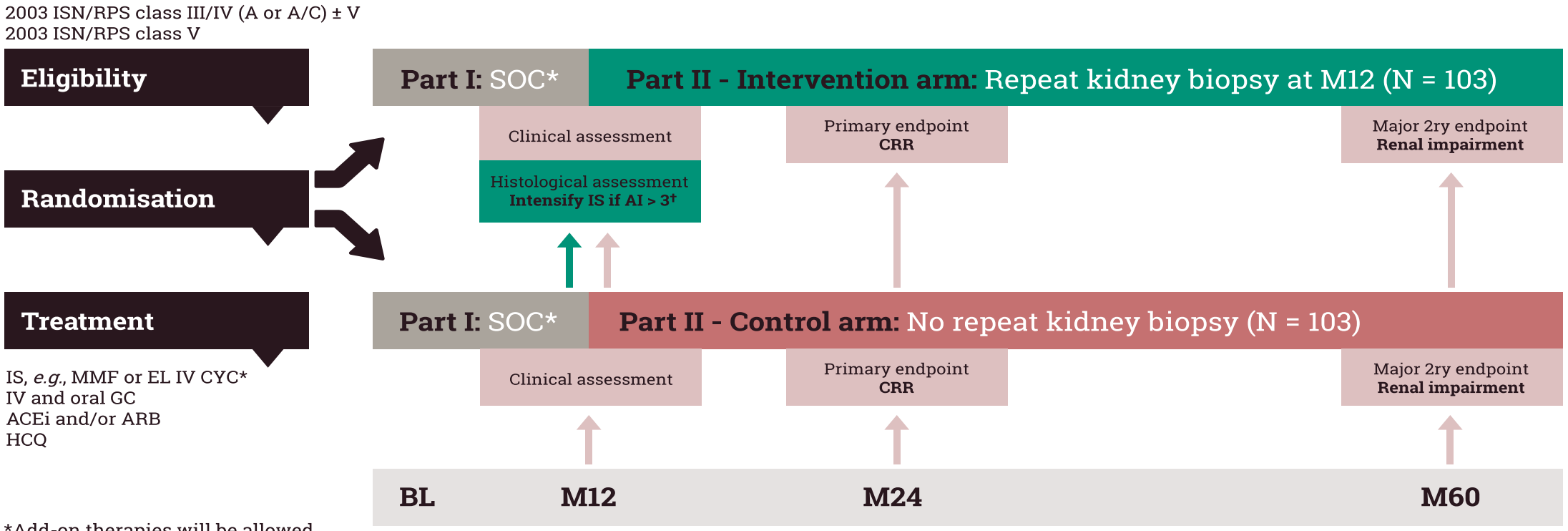
Crickx E et al. Arthritis Rheumatol. 2021

ReBioLup

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



*Add-on therapies will be allowed, including drugs within the frame of 12-month lasting clinical trials.

†Applies for 2003 ISN/RPS class III/IV (± V) LN at baseline. For pure membranous (2003 ISN/RPS class V) LN at baseline, individual assessment of the repeat biopsy at the site should steer the decision of treatment.

Part I (BL–M12): Observational

Part II (M12–M60): Interventional

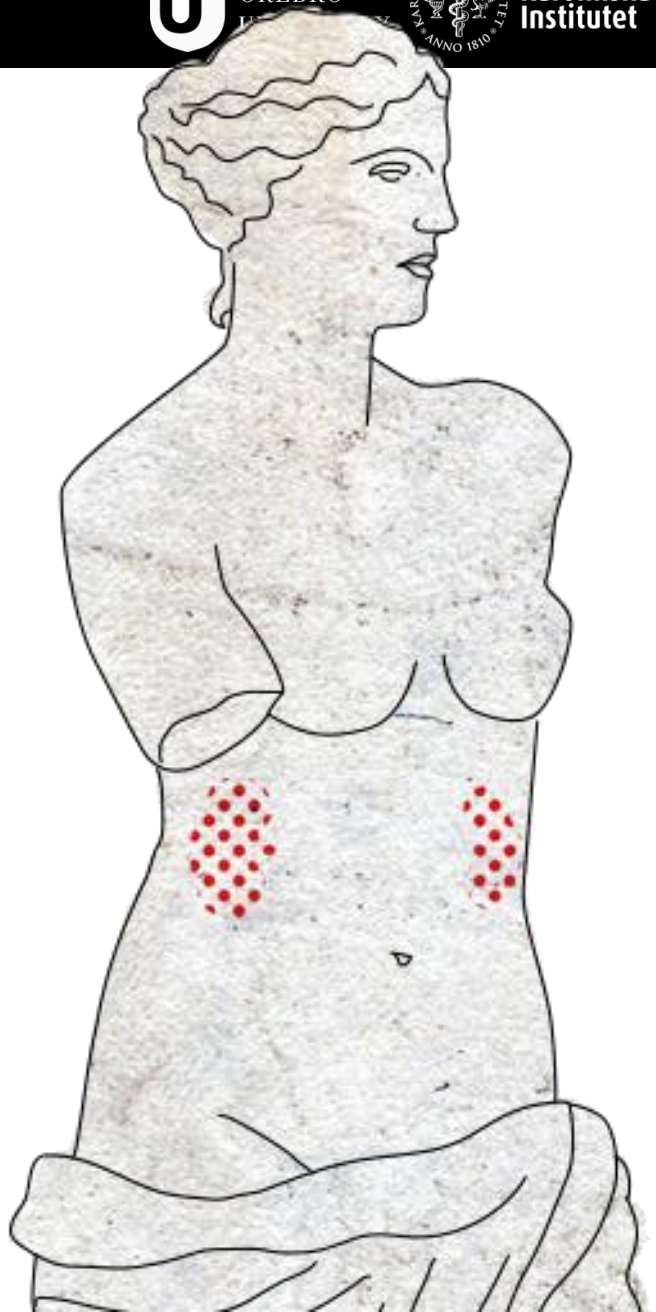
Abbreviations:
LN: lupus nephritis; ISN: International Society of Nephrology; RPS: Renal Pathology Society; MMF: mycophenolate mofetil; EL: Euro-Lupus; CYC: cyclophosphamide; GC: glucocorticoids; ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blocker; HQC: hydroxychloroquine; UPCR: urine protein/creatinine ratio; CRR: complete renal response; IS: immunosuppression; AI: activity index; SOC: standard of care; BL: baseline; M: month

- http://rebiolup.com
- http://rebiolup.com/collaborators

- https://www.clinicaltrials.gov/ct2/show/NCT04449991

Summary

- Current SoC does not meet the expectations
- T2T approach against nephron loss
- Repeat biopsy as an essential part of T2T strategies
  - Until reliable biomarkers are available
- Person-centred approaches are necessitated



Q & A

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School of Medical Sciences, Örebro University