UNIKLINIK RWTH AACHEN

LaBooratory of Nephropathology

3rd International Symposium on Functional Renal Imaging, 17th October 2019

Histopathology of AKI

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Pathology & Nephrology
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Funding:

DFG Deutsche Forschungsgemeinschaft

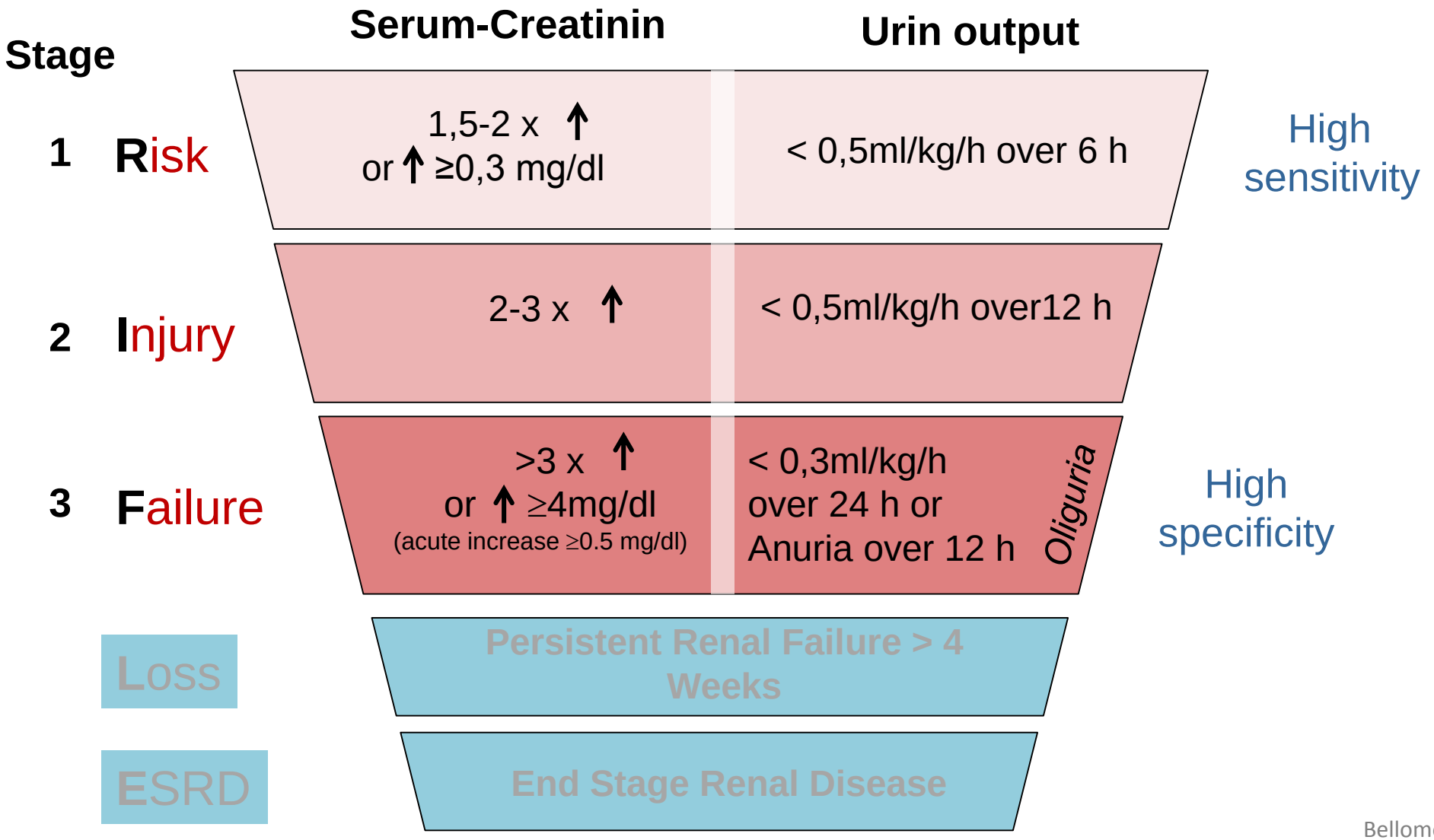
Bundesministerium für Bildung und Forschung

FSGS

Else Kröner Fresenius Stiftung

RWTH AACHEN UNIVERSITY

Classification of acute kidney injury (AKI)

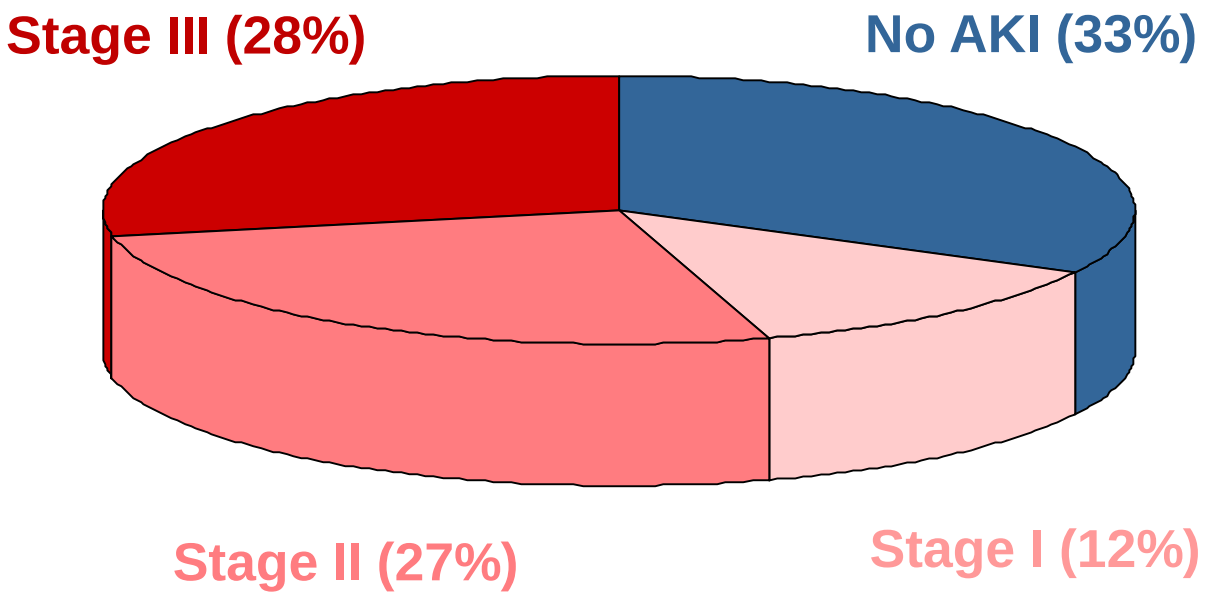


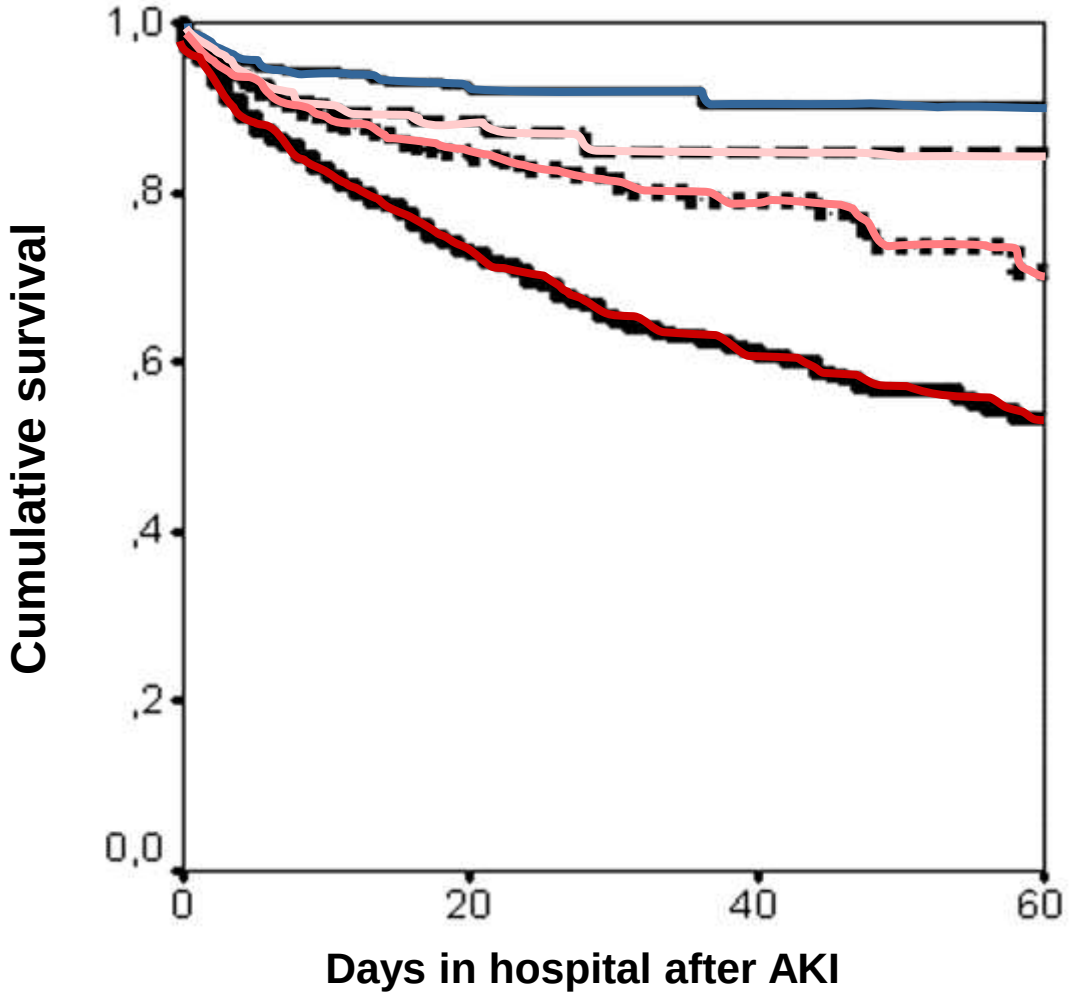
Bellomo et al, Crit Care 2004

AKI is common particularly on intensive wards

retrospective analyses (USA, 7 intensive wards, n=5.383)

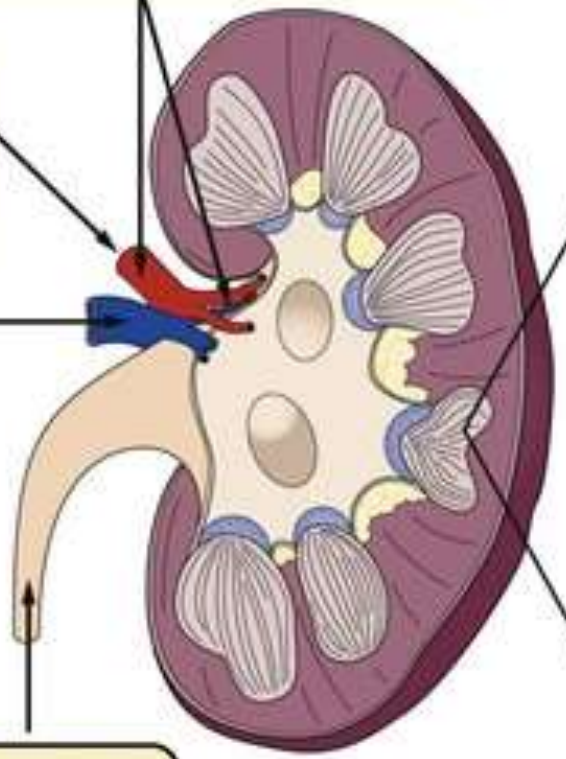
maximal reached RIFLE-stage





Hoste et al, Crit Care 2006

Causes of acute kidney injury (AKI)



1. Pre-renal azotemia
Hypovolemia
Cardiac failure
Hepatorenal syndrome

2. Renal artery
Renal artery occlusion
Large- or medium-vessel vasculitis

3. Small-vessel disease
Thrombotic microangiopathy
Renal atheroembolism
Small-vessel vasculitis

4. Glomerular disease
Anti-GBM disease
Lupus nephritis
Postinfectious glomerulonephritis
Infective endocarditis
Membranoproliferative glomerulonephritis
Cryoglobulinemia
IgA nephropathy/Henoch-Schönlein purpura

5. Acute tubular necrosis
Ischemia
Nephrotoxins
Rhabdomyolysis
Radiocontrast agents

6. Acute interstitial nephritis
Drugs
Infection
Systemic disease

7. Intratubular obstruction
Cast nephropathy
Drugs
Crystalluria

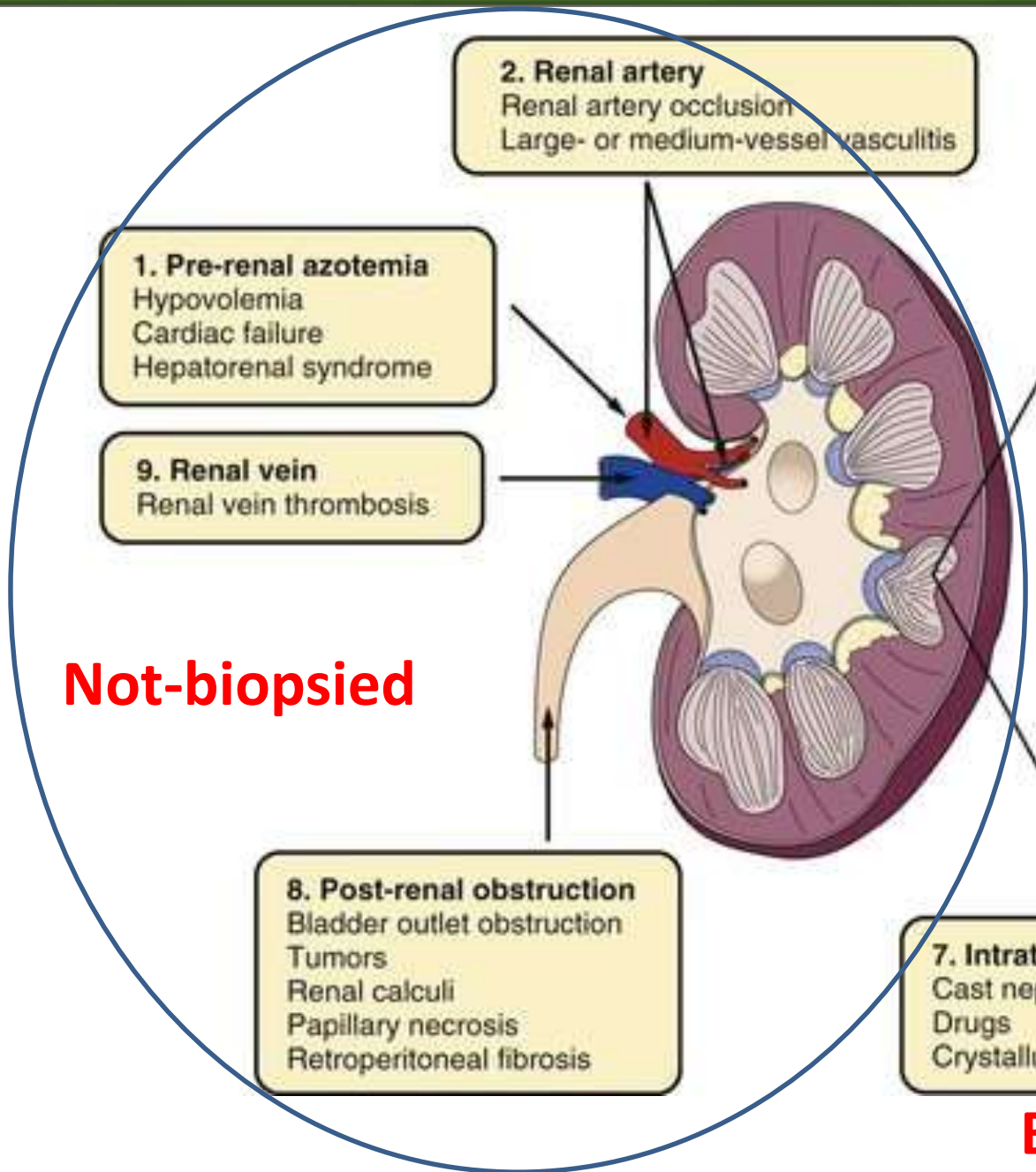
8. Post-renal obstruction
Bladder outlet obstruction
Tumors
Renal calculi
Papillary necrosis
Retroperitoneal fibrosis

9. Renal vein
Renal vein thrombosis

45%

Modified from Floege/Feehally, Comprehensive clinical nephrology

AKI in renal biopsies



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Not-biopsied

Biopsied

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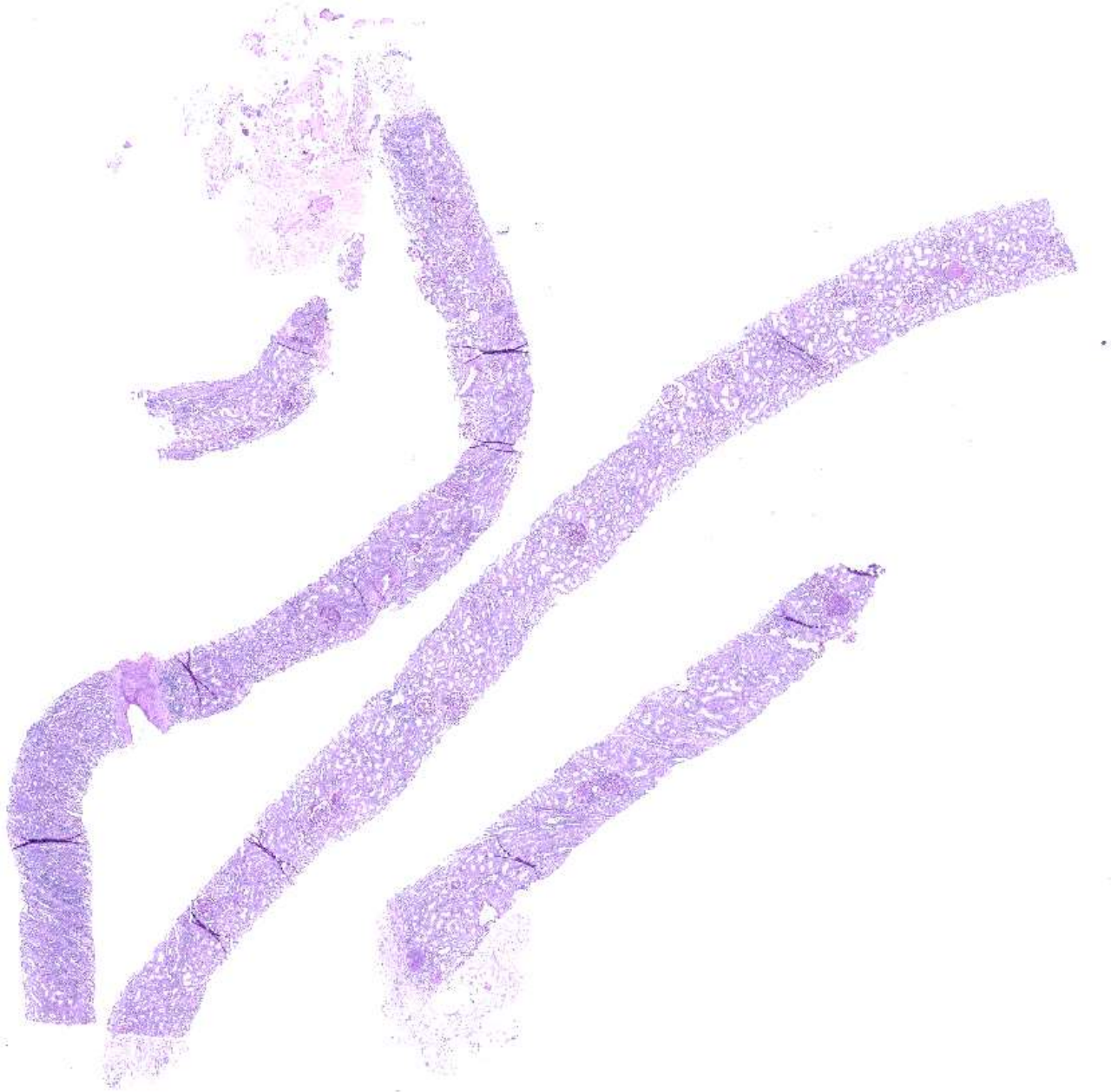
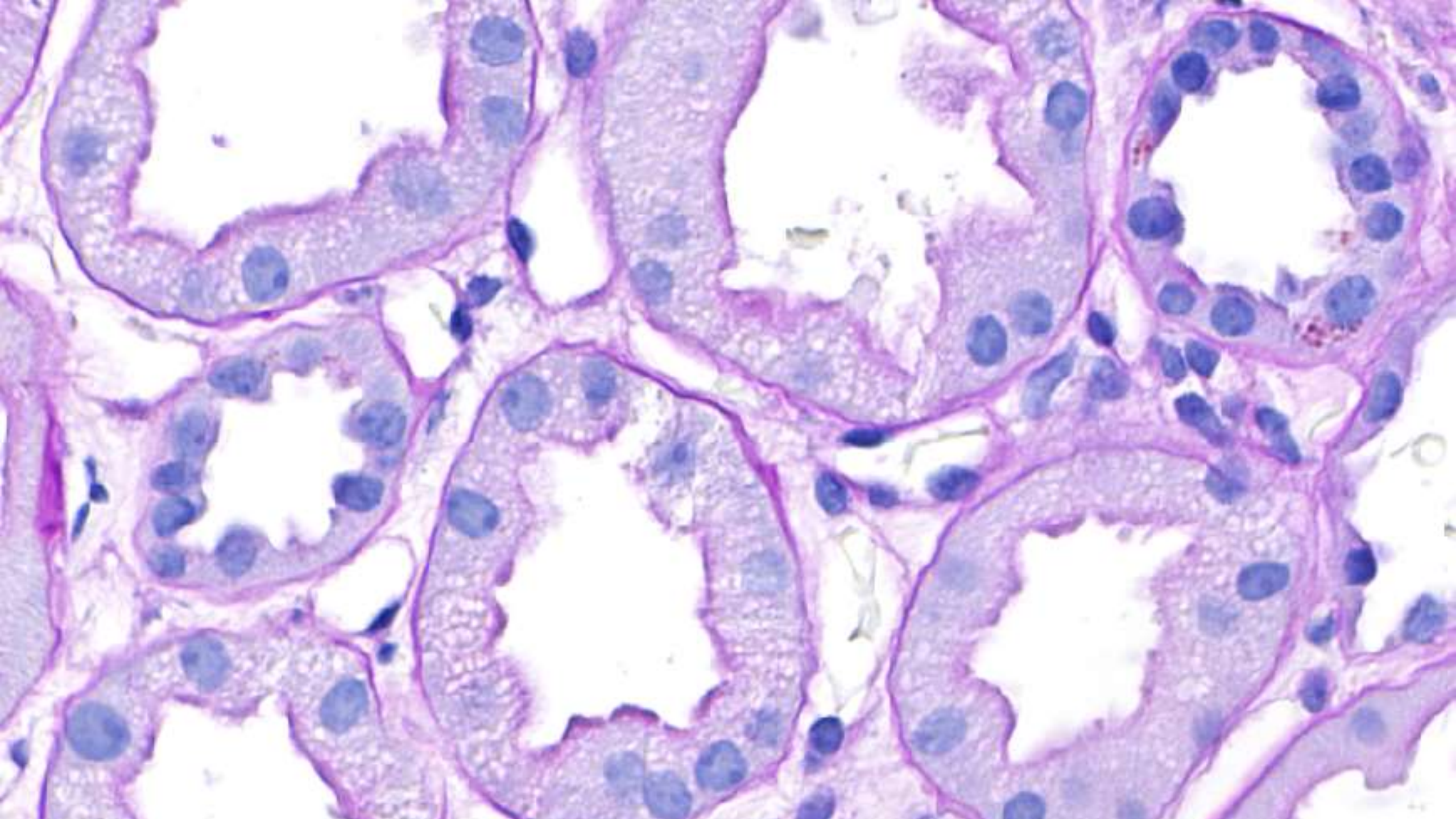
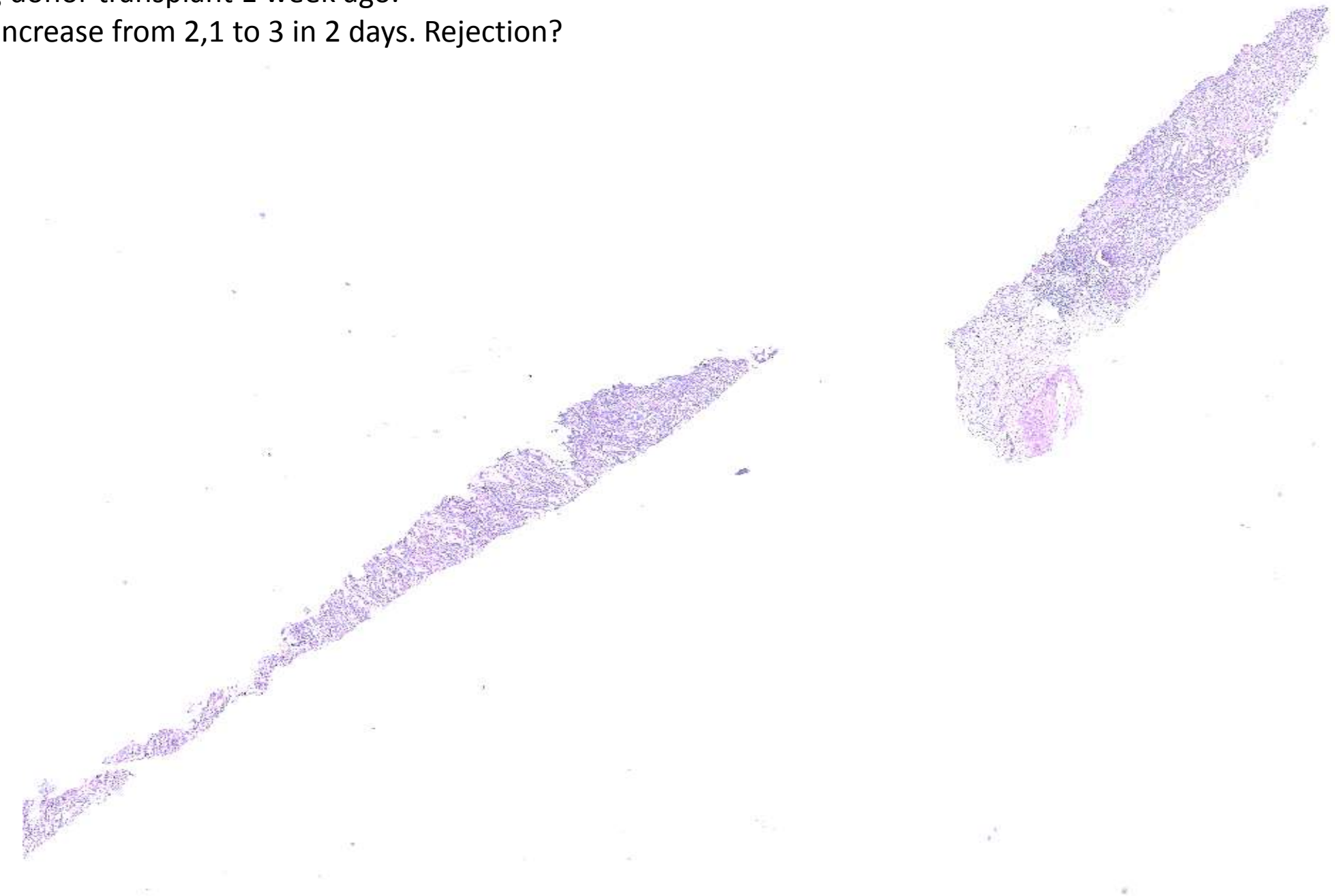
Modified from Floege/Feehally, Comprehensive clinical nephrology

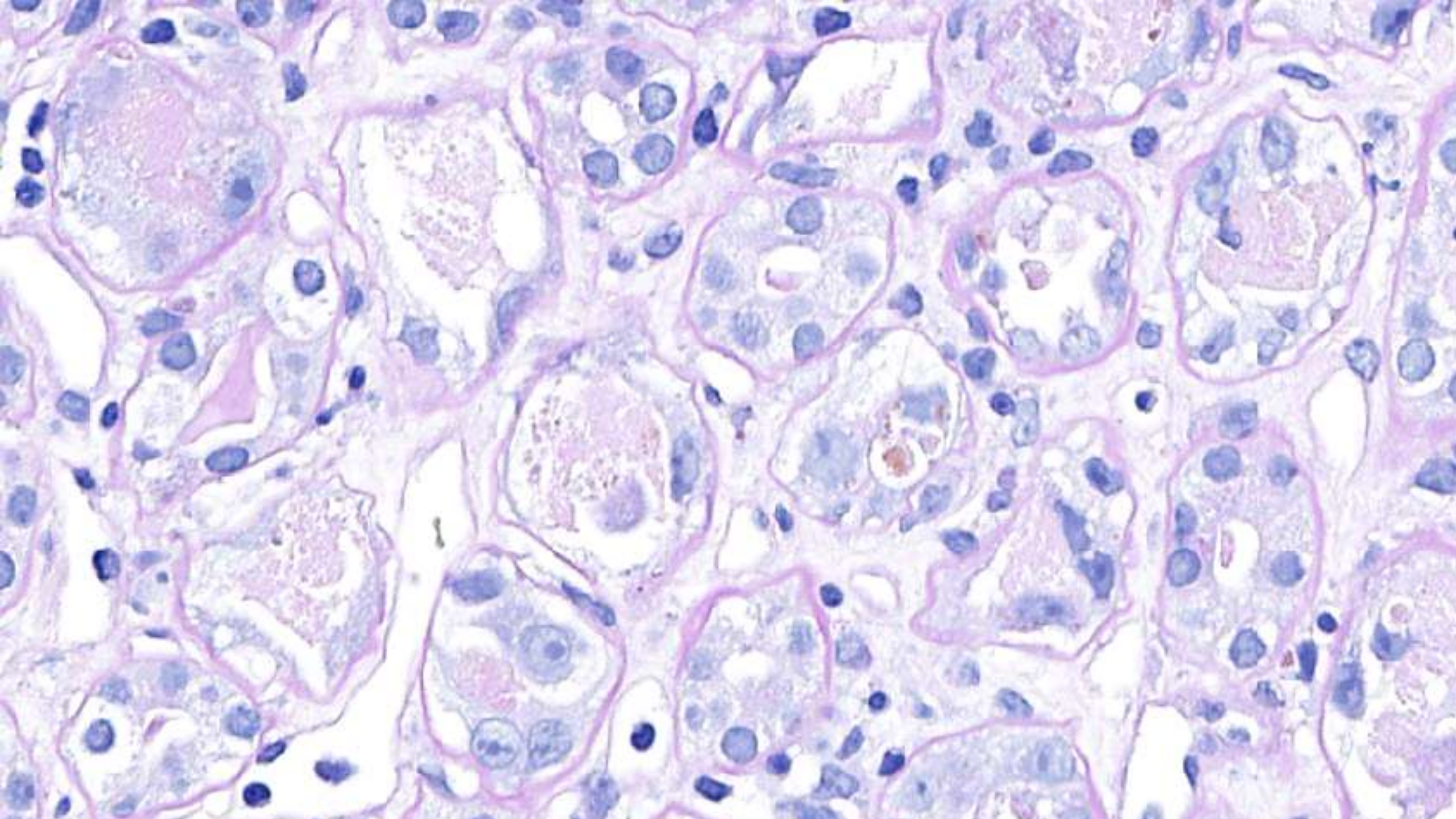
Case 1:
Clinical presentation: unclear AKI, Voltaren medication (NSAID), contact with murine feces

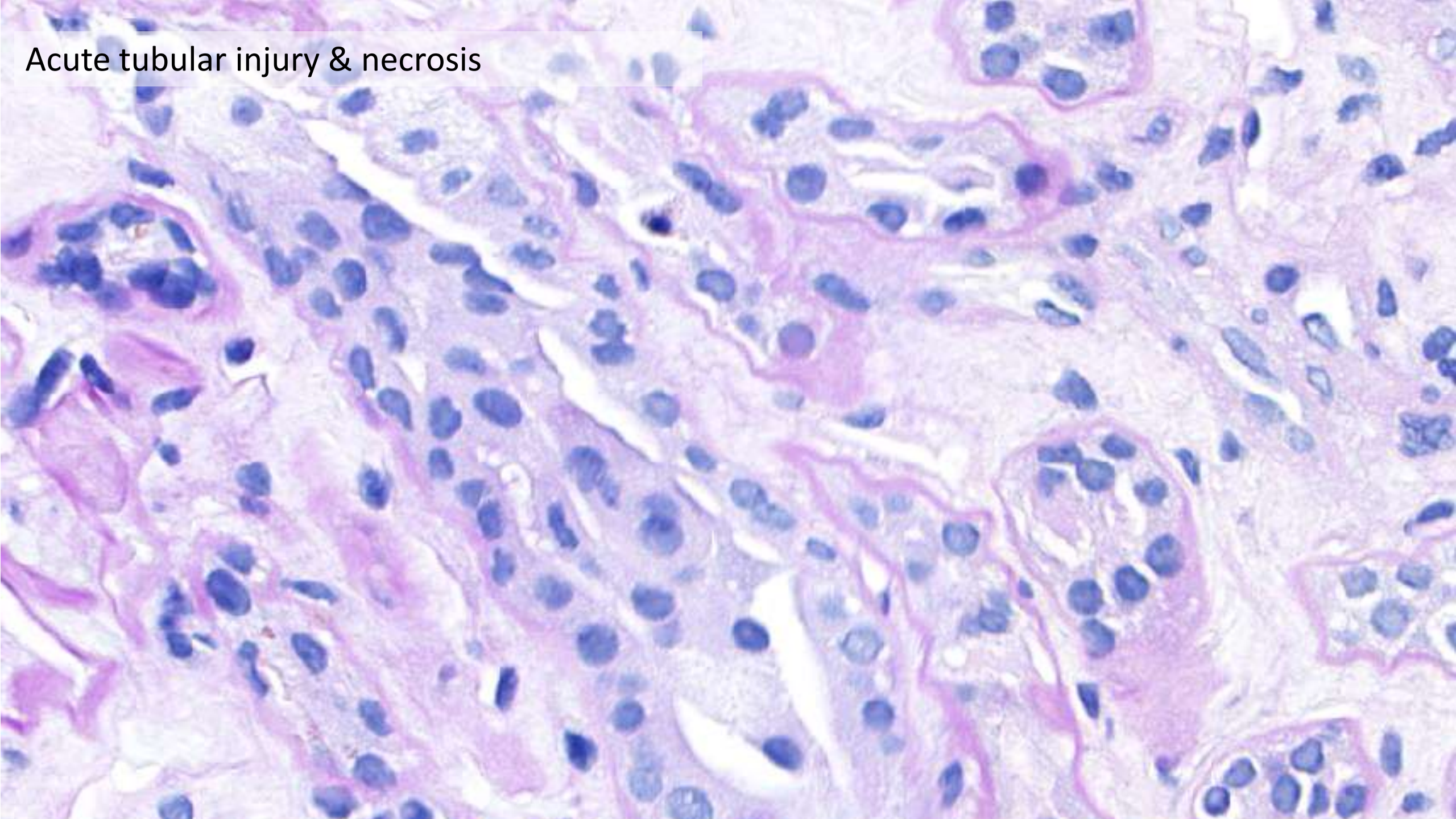




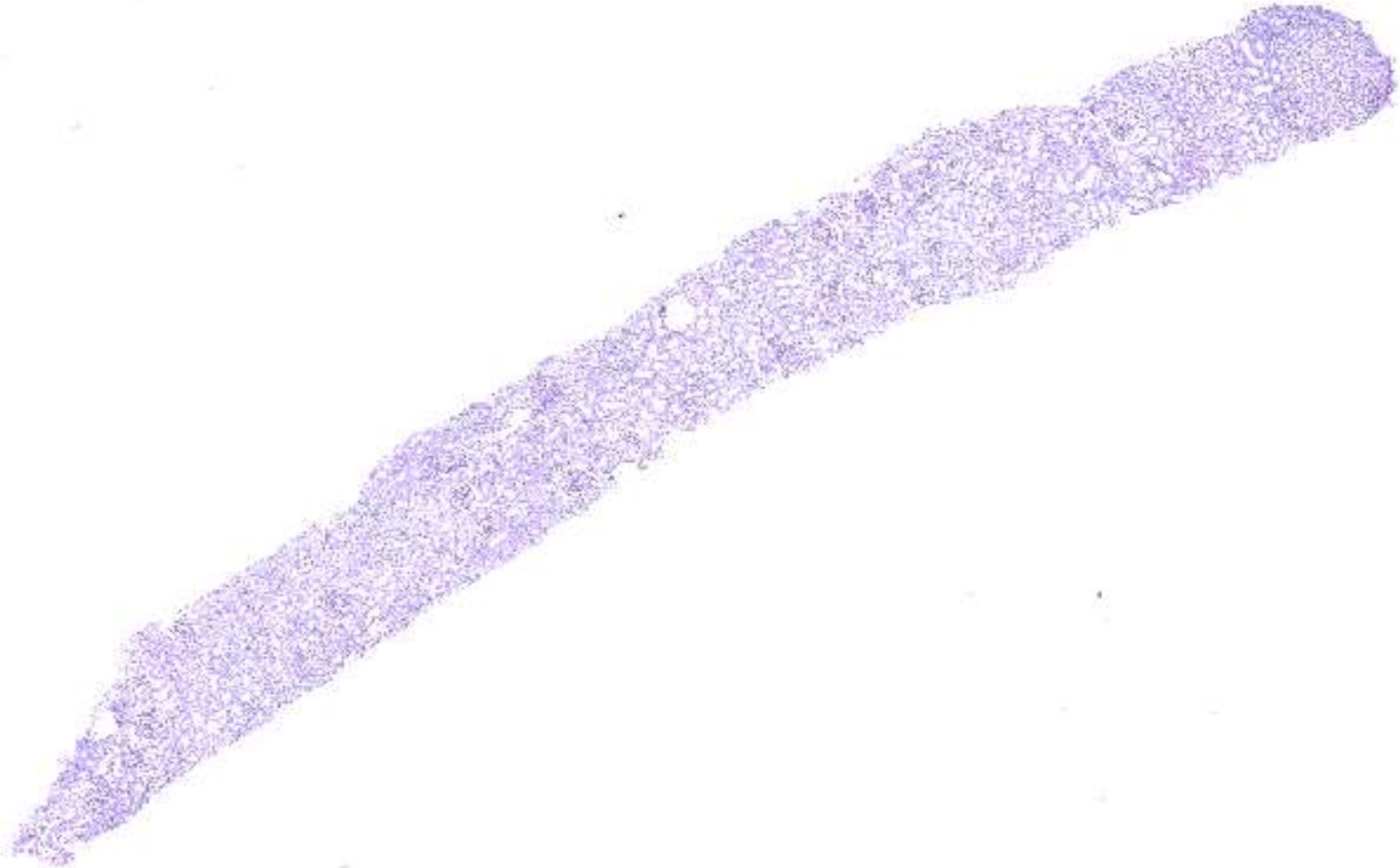
Case 2:
Living donor transplant 1 week ago.
Crea increase from 2,1 to 3 in 2 days. Rejection?

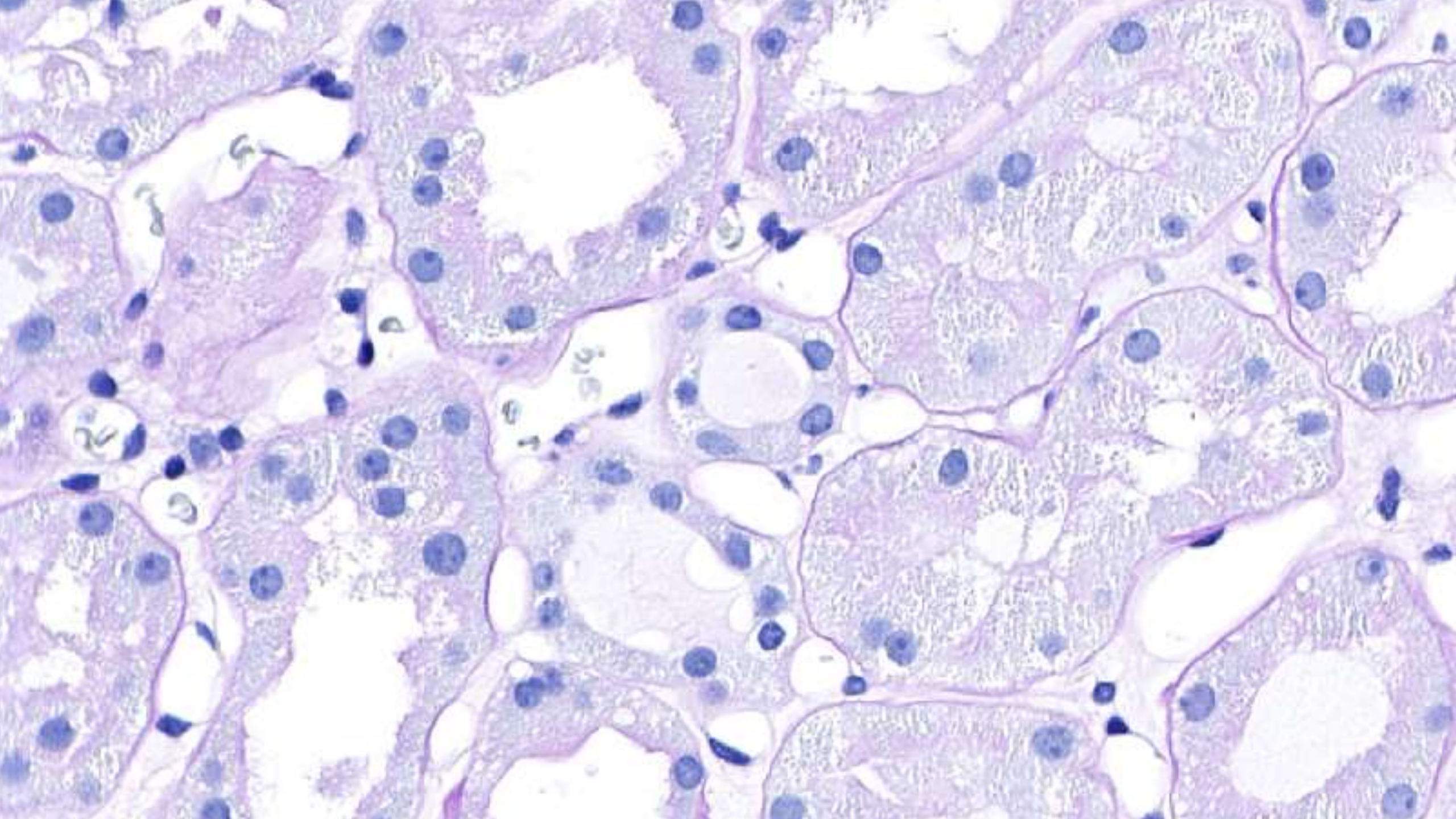




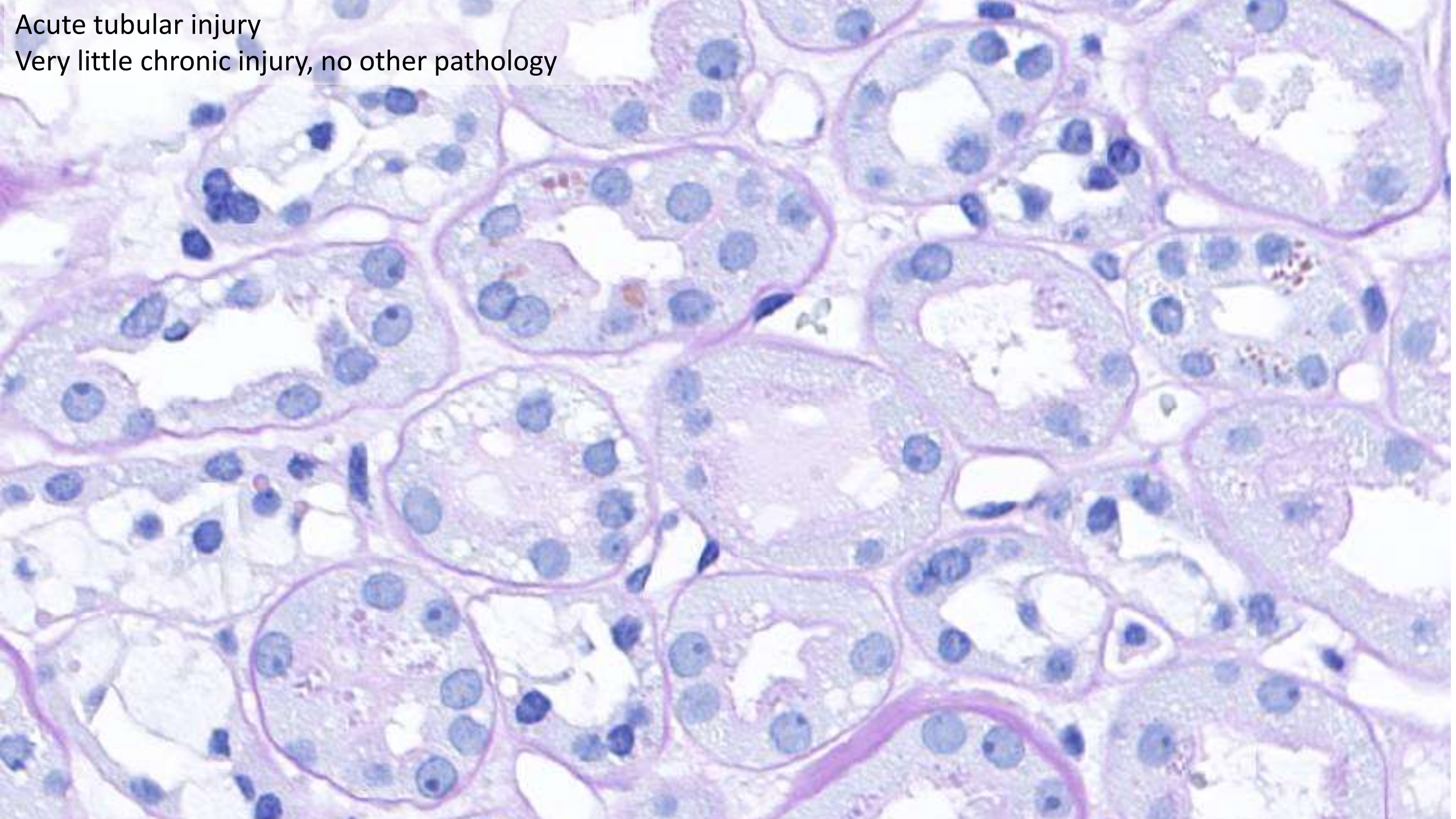

Acute tubular injury & necrosis

Case 3:
Time 0 biopsy, deceased donor

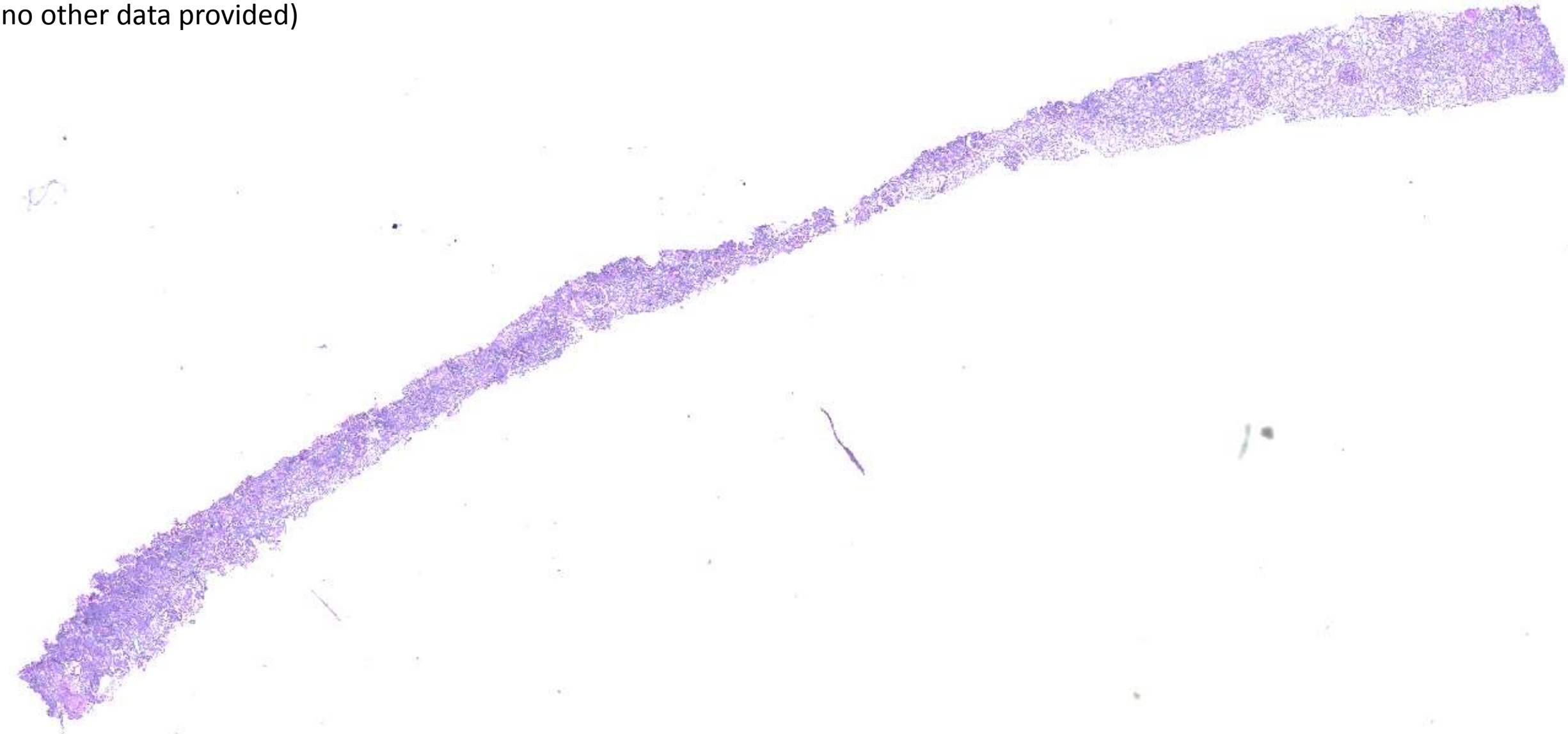


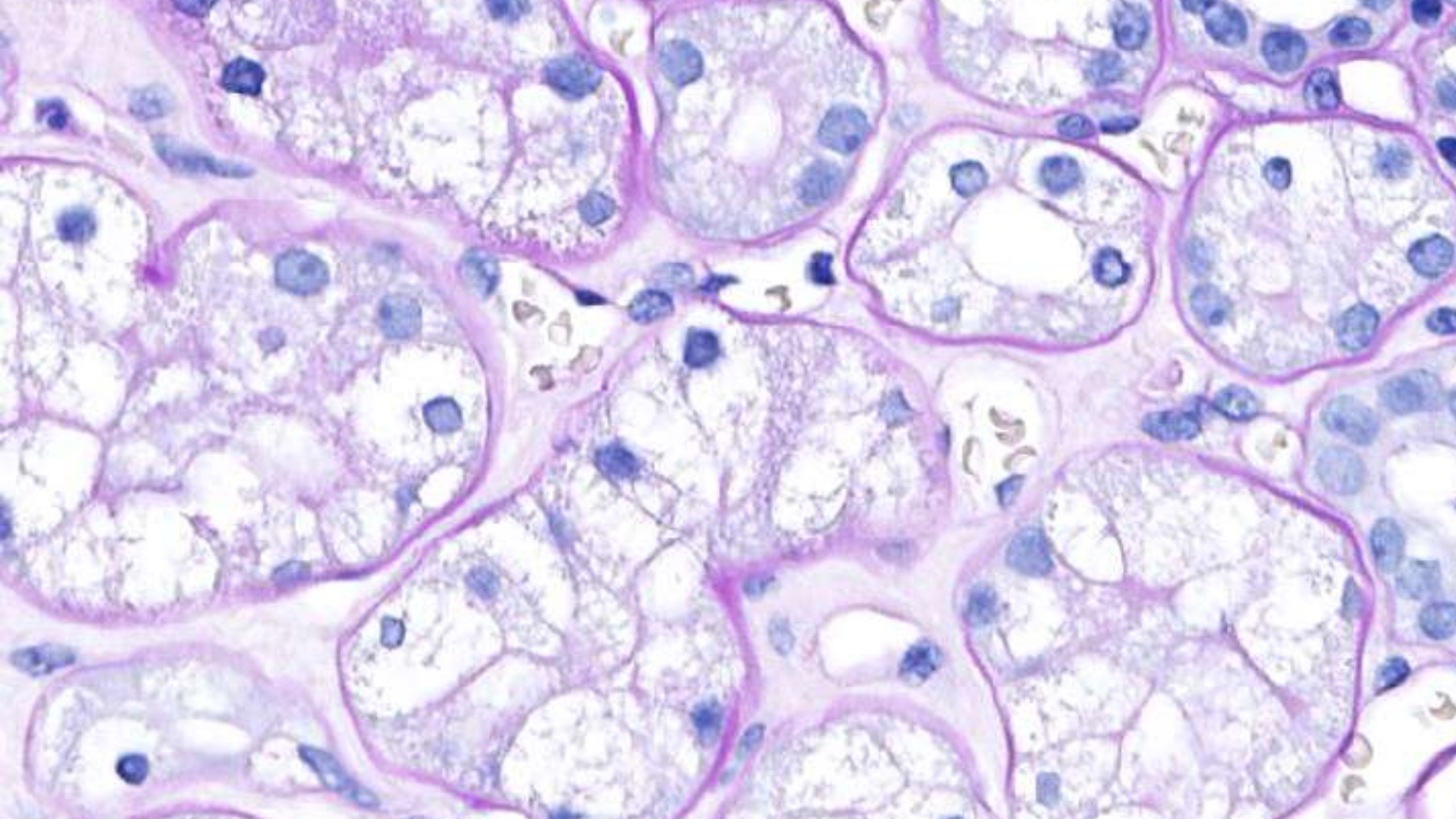


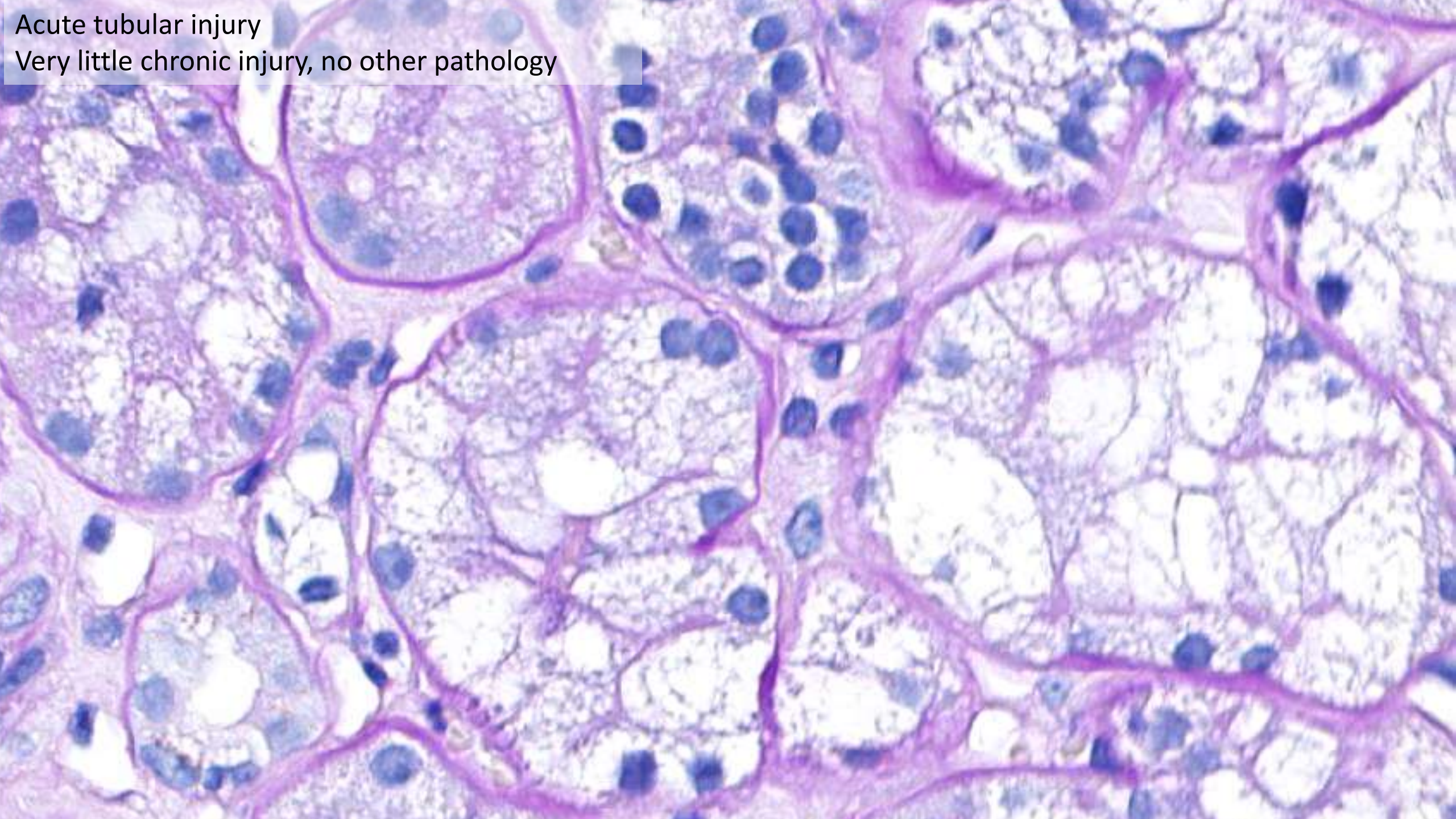
Acute tubular injury
Very little chronic injury, no other pathology



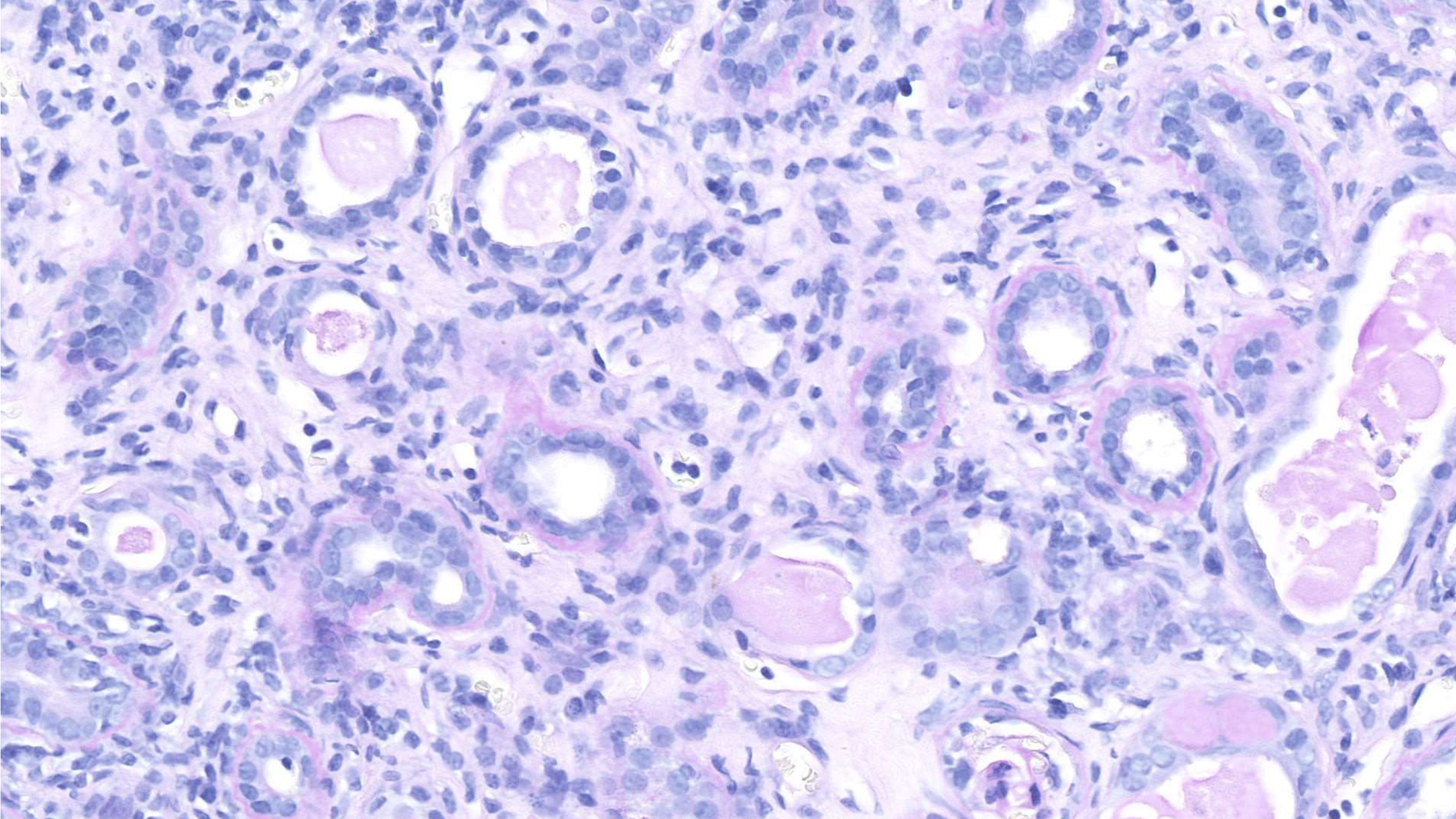
Case 4:
Transplant biopsy after reperfusion
(no other data provided)

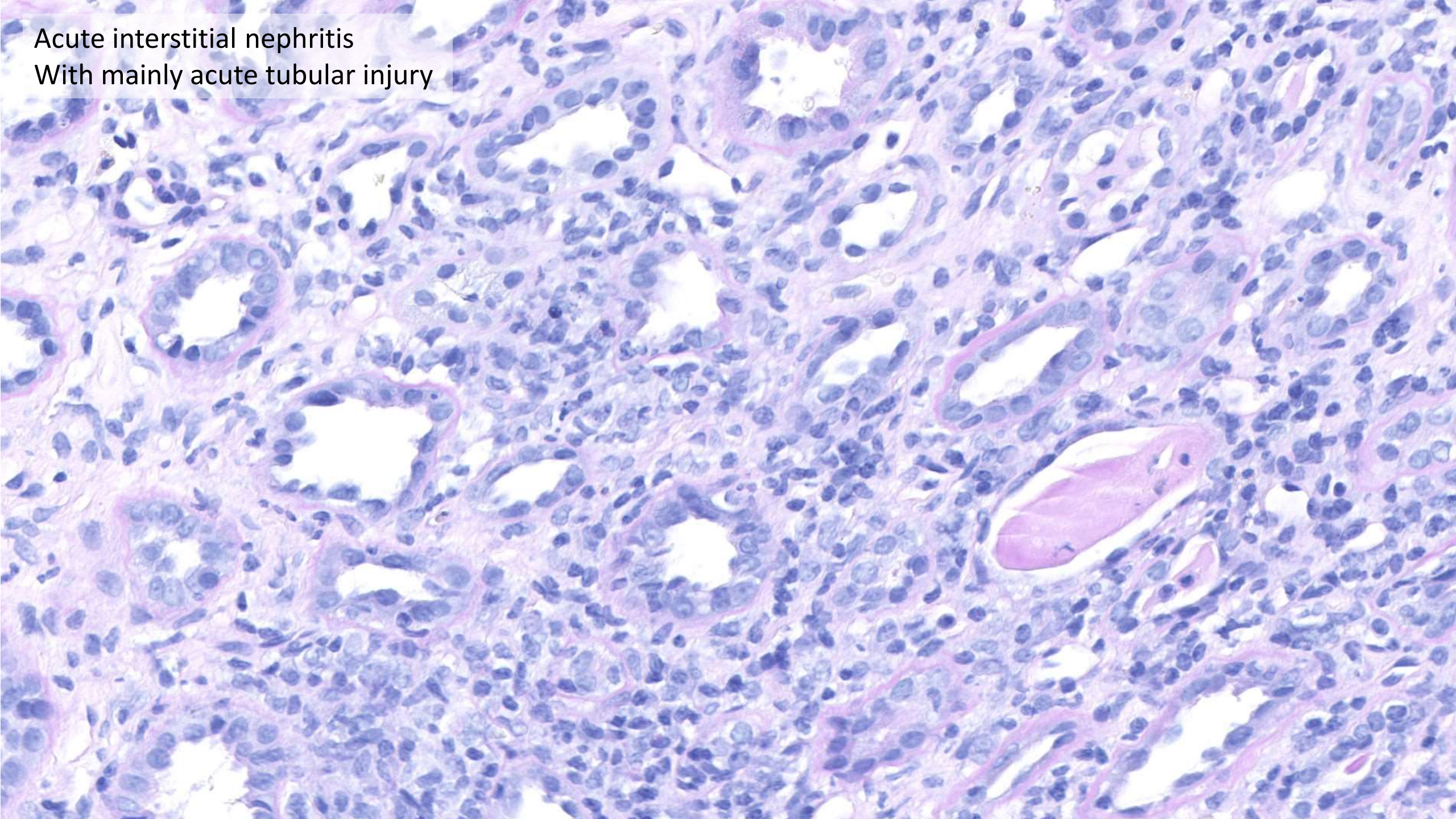




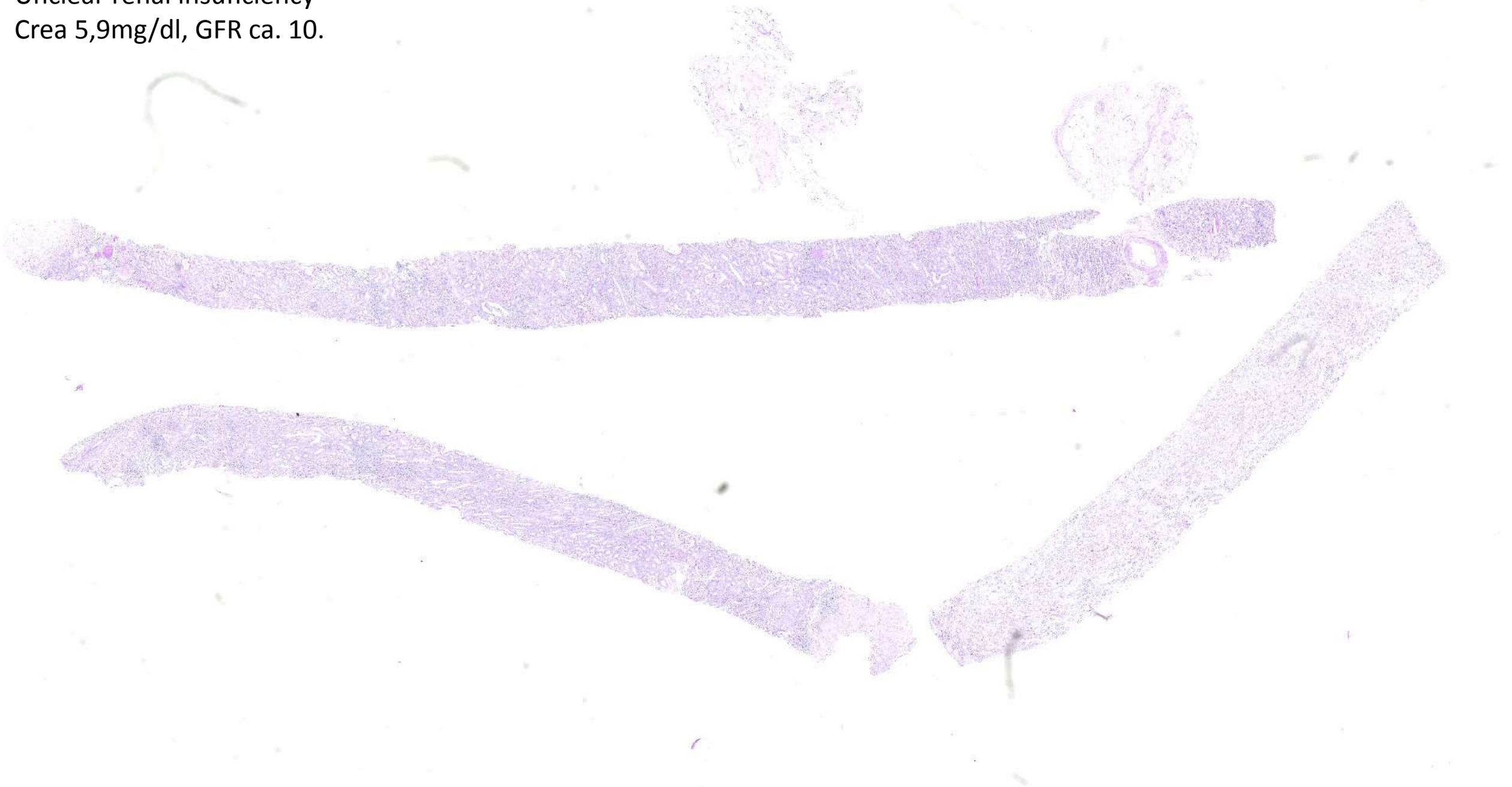

Acute tubular injury
Very little chronic injury, no other pathology

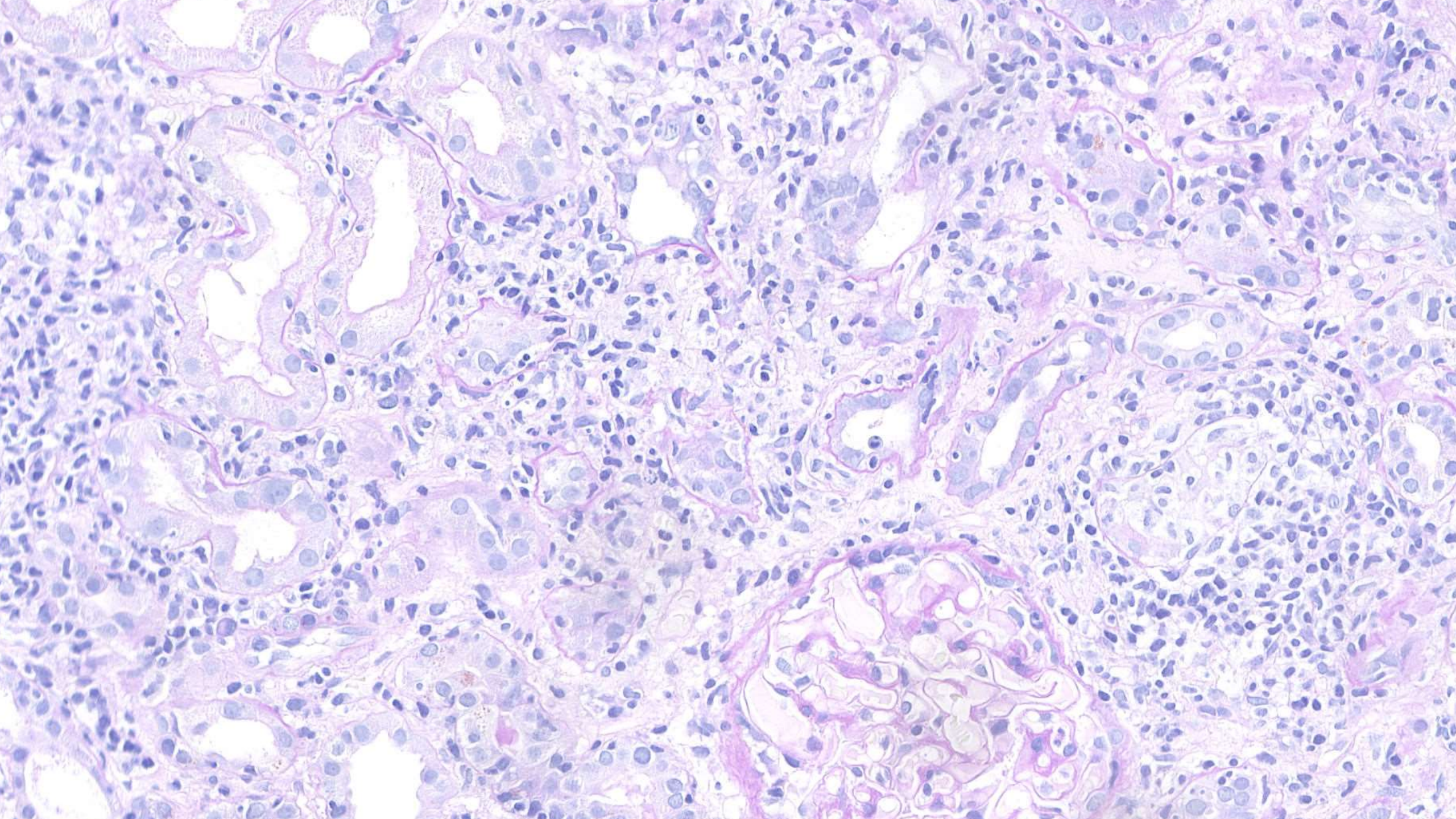
Case 5:
Unclear renal insufficiency
No medication



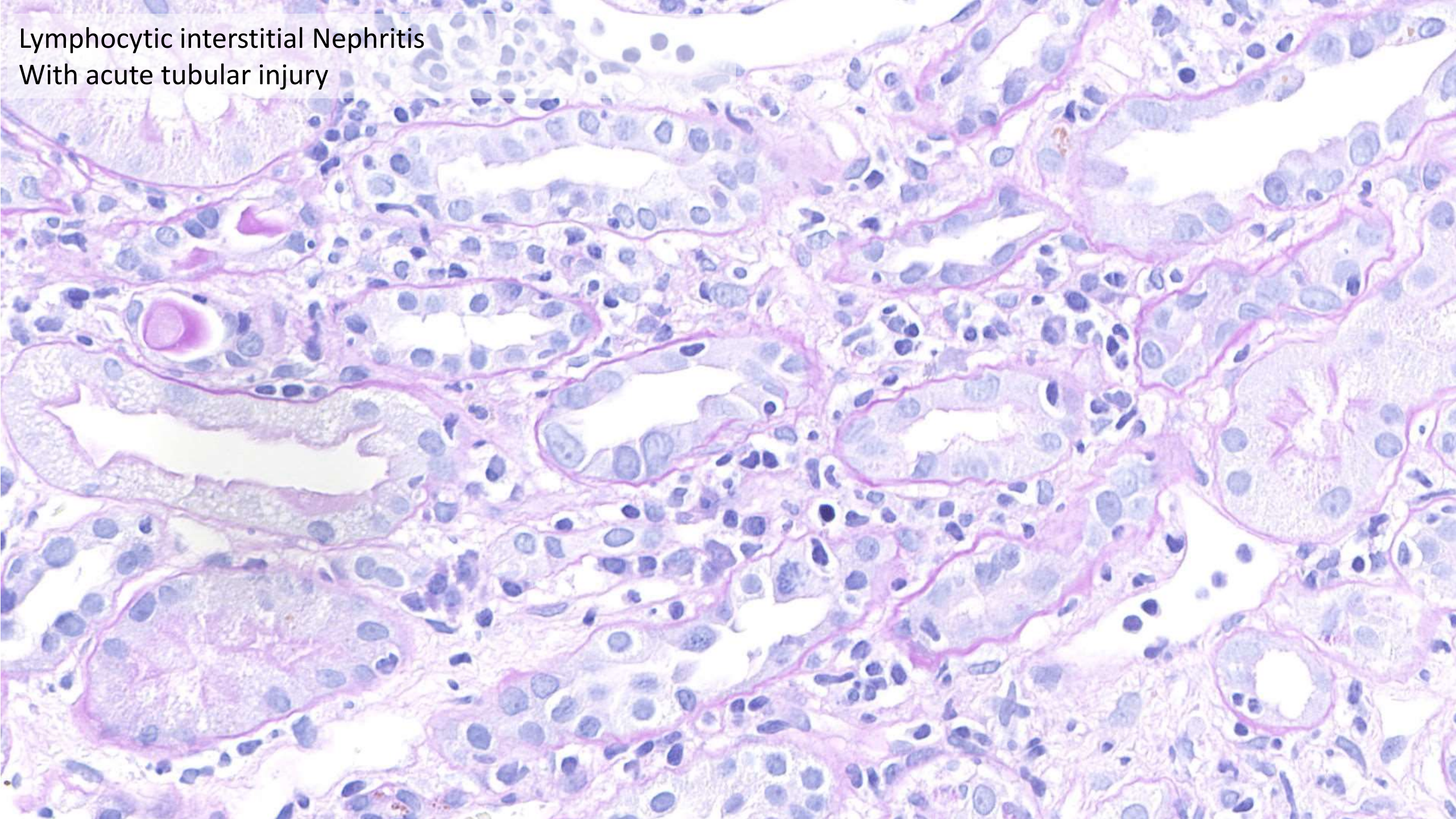

Acute interstitial nephritis
With mainly acute tubular injury

Case 6:
Unclear renal insuficiency
Crea 5,9mg/dl, GFR ca. 10.

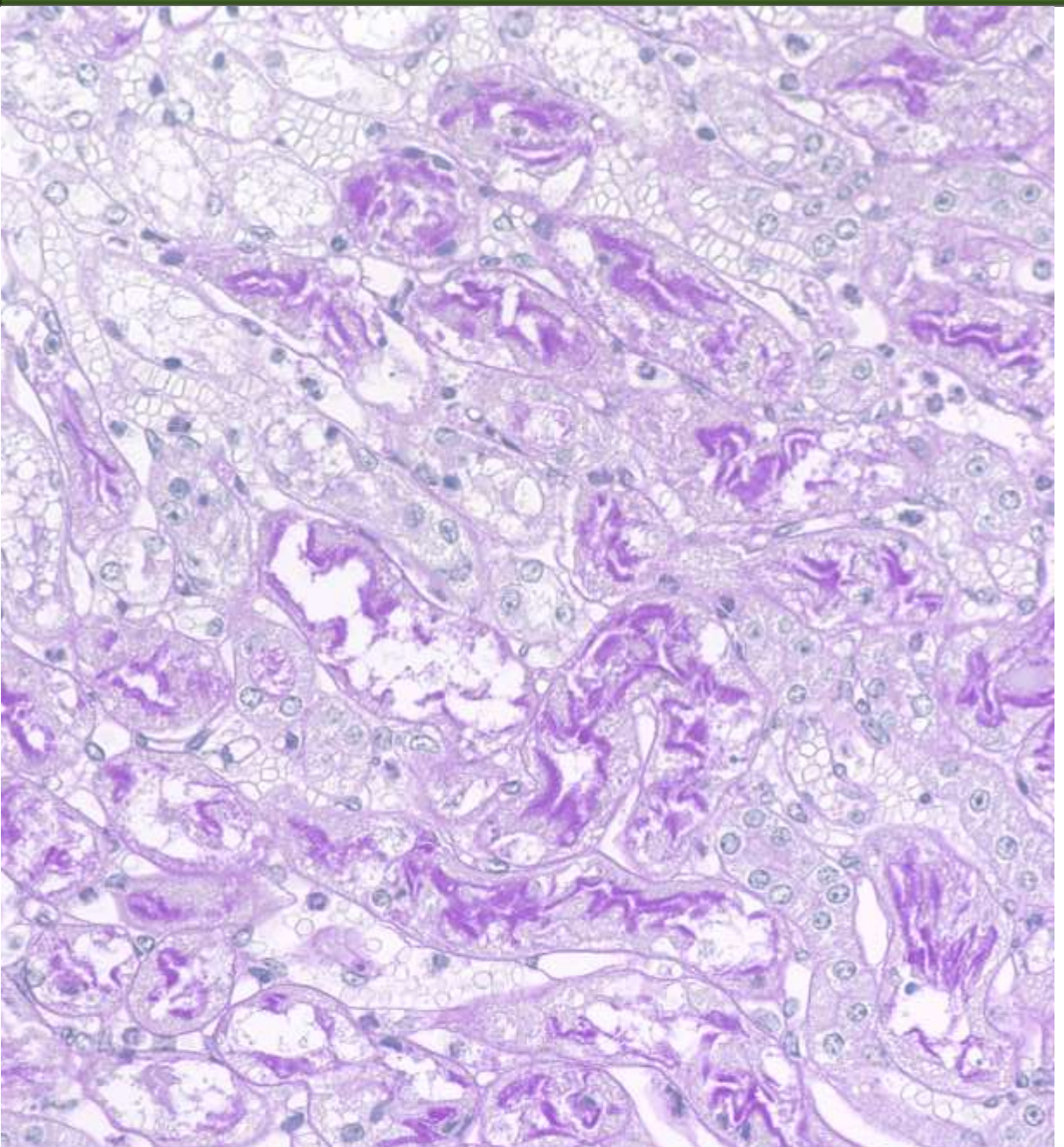


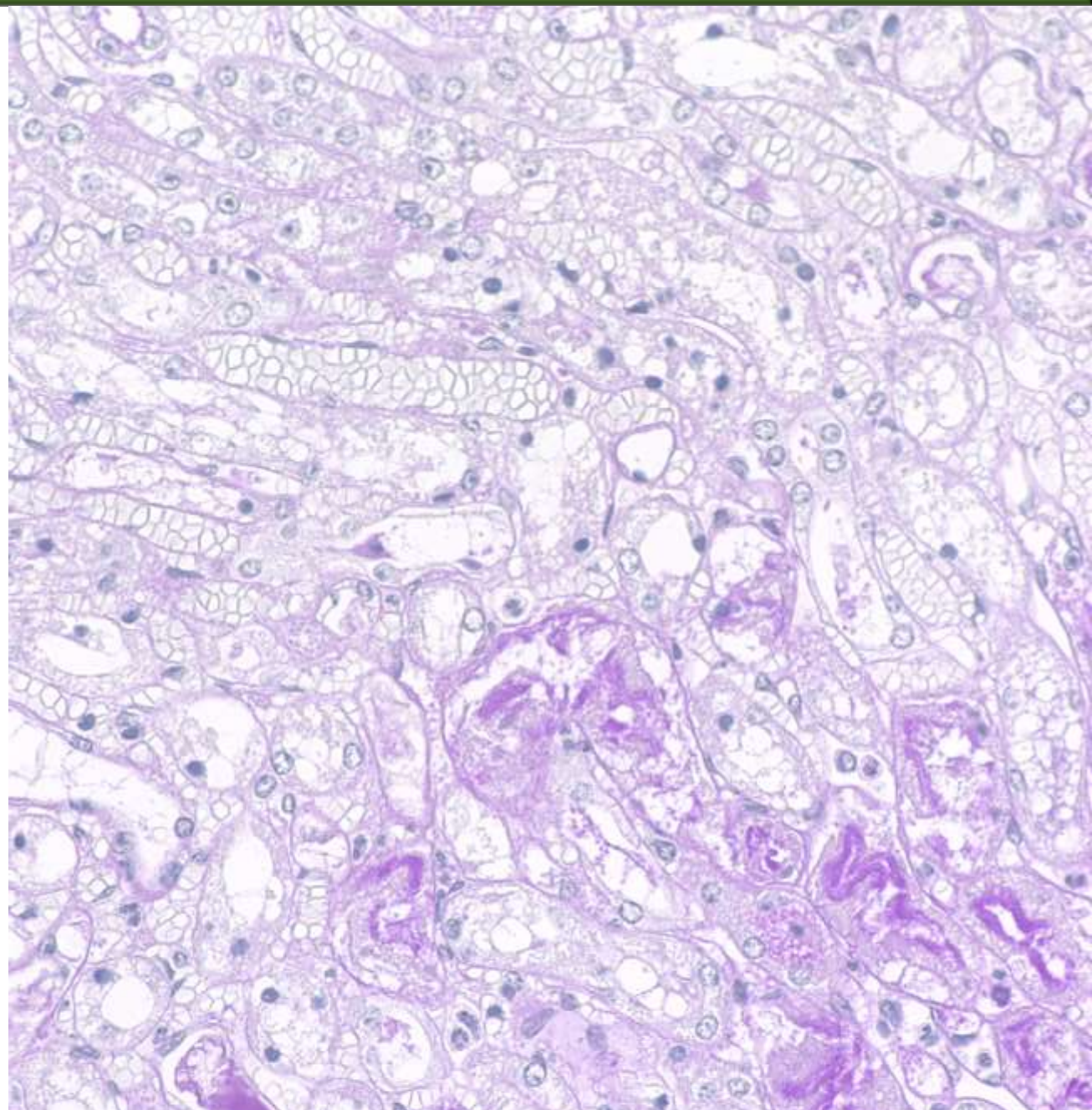


Lymphocytic interstitial Nephritis
With acute tubular injury

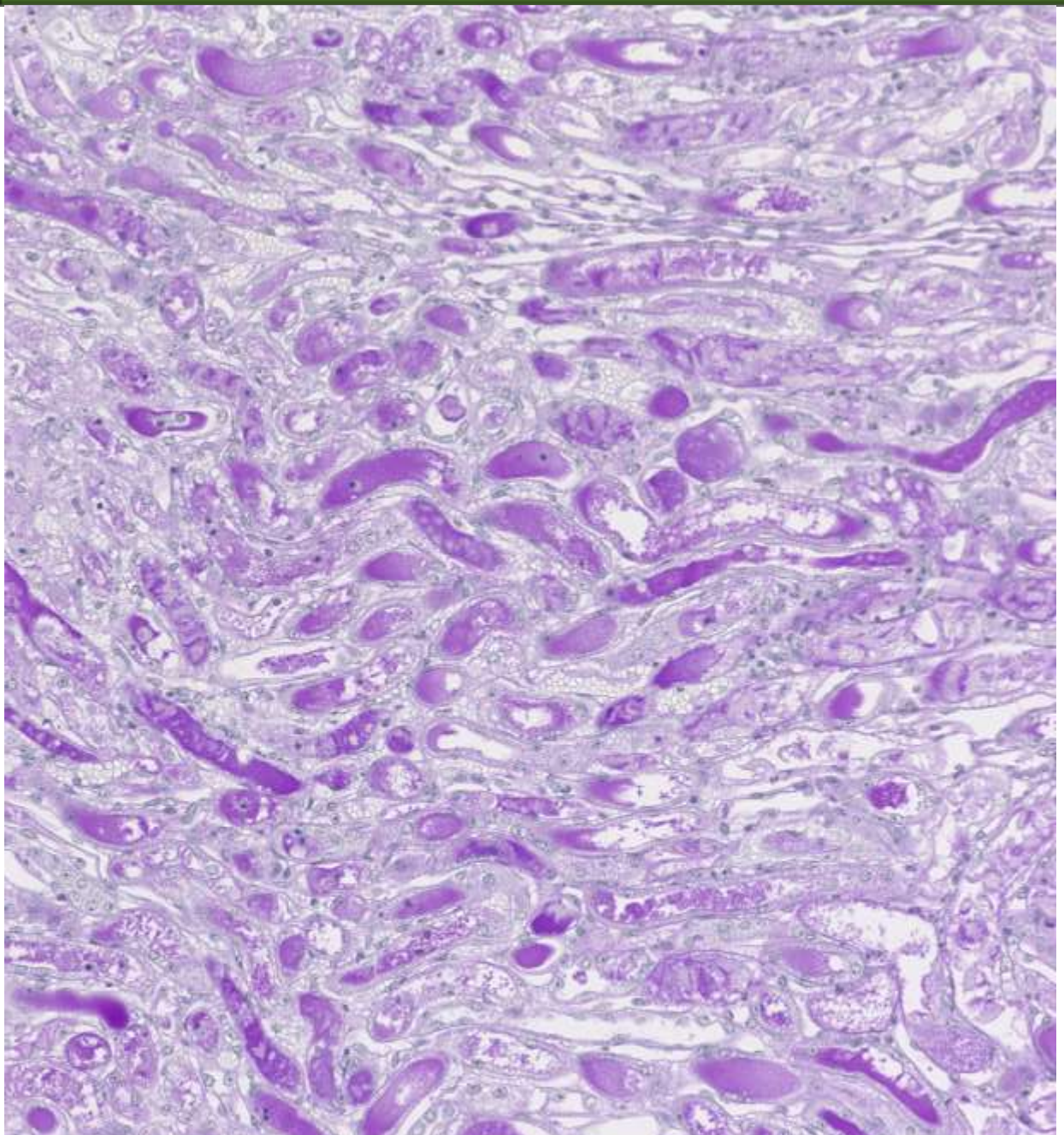


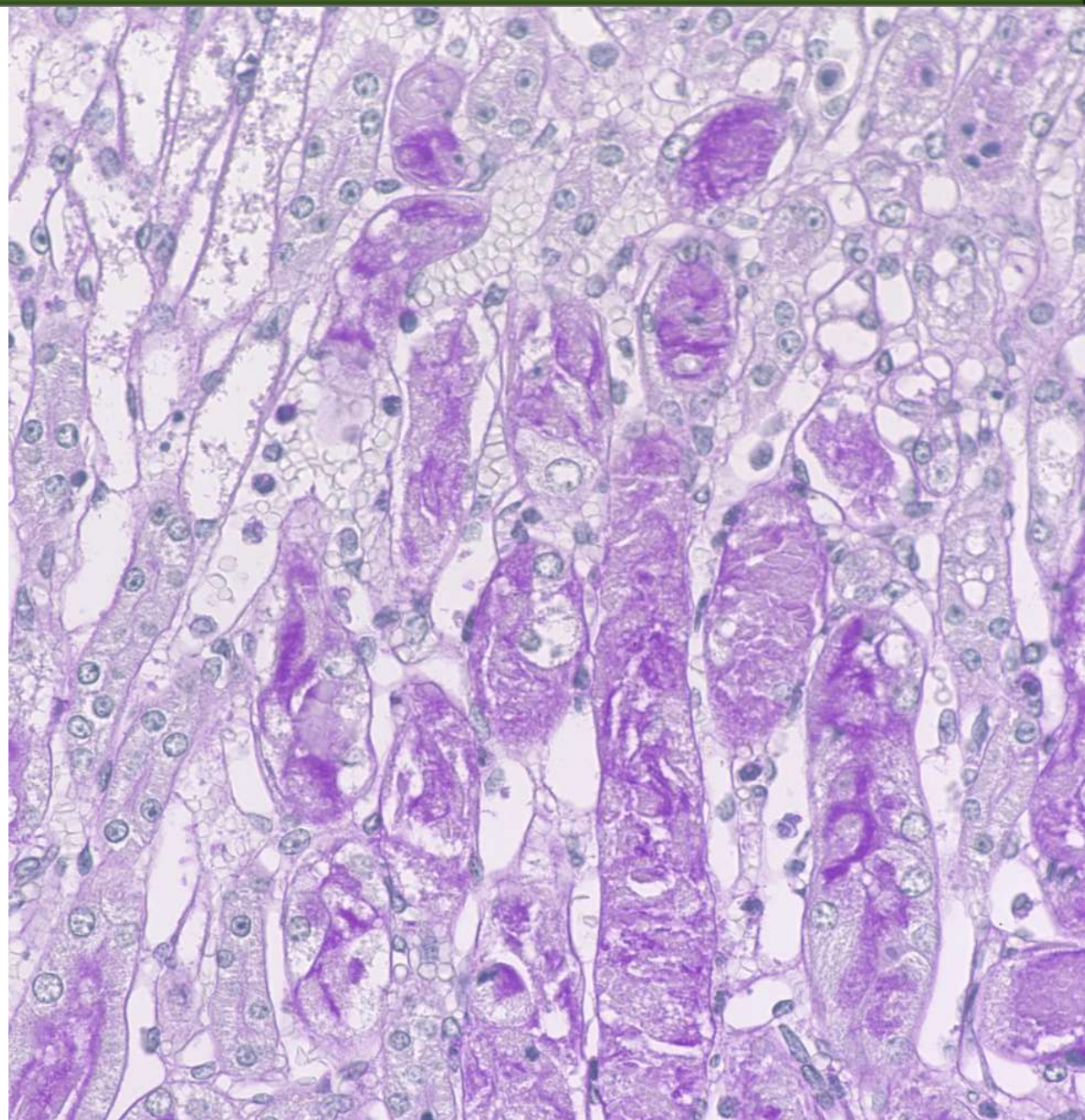
Ischemia-reperfusion injury in mice (warm, 35 min, females, time-point 6 hrs)



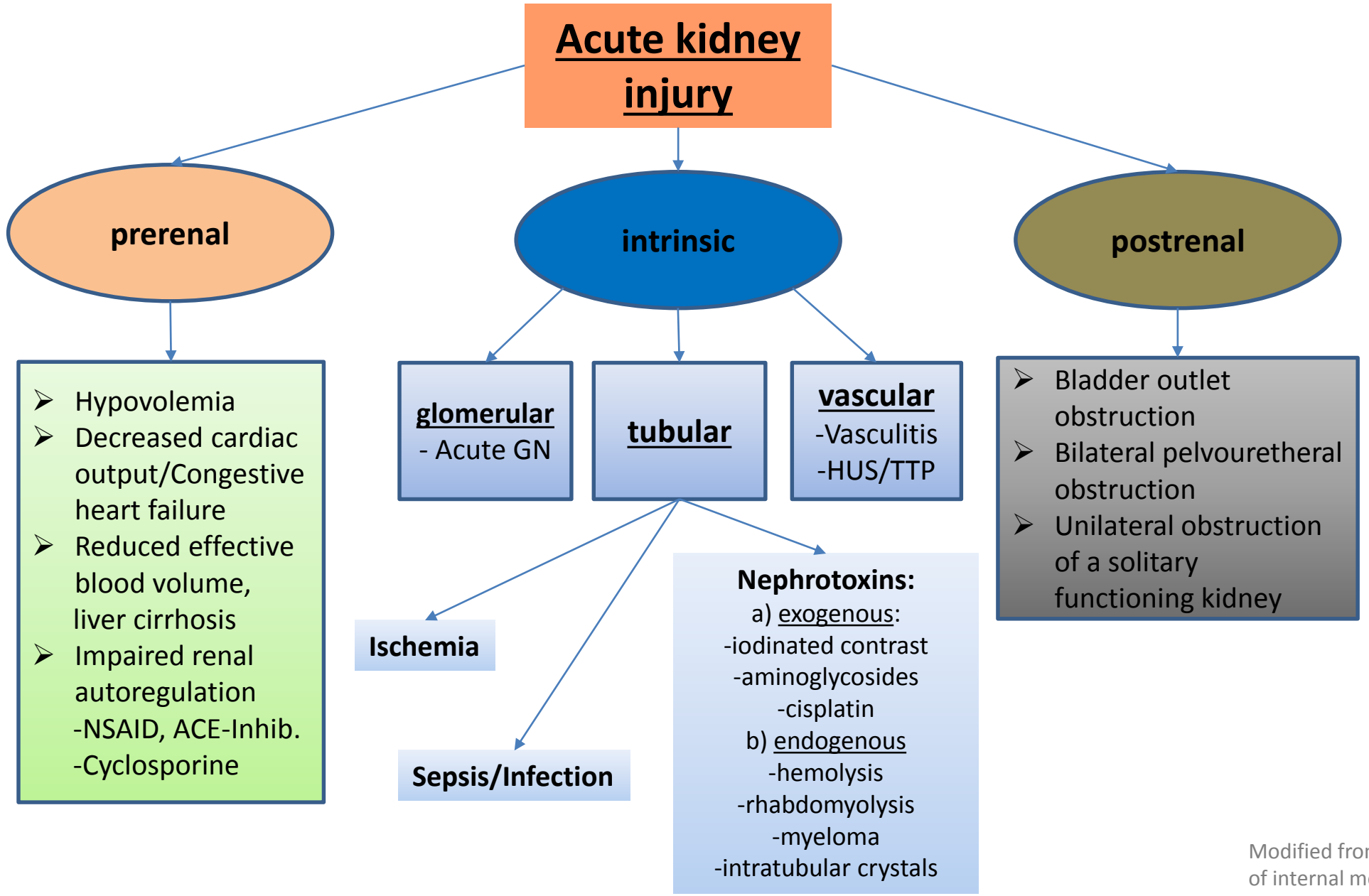


Ischemia-reperfusion injury in mice (warm, 35 min, females, time-point 24 hrs)



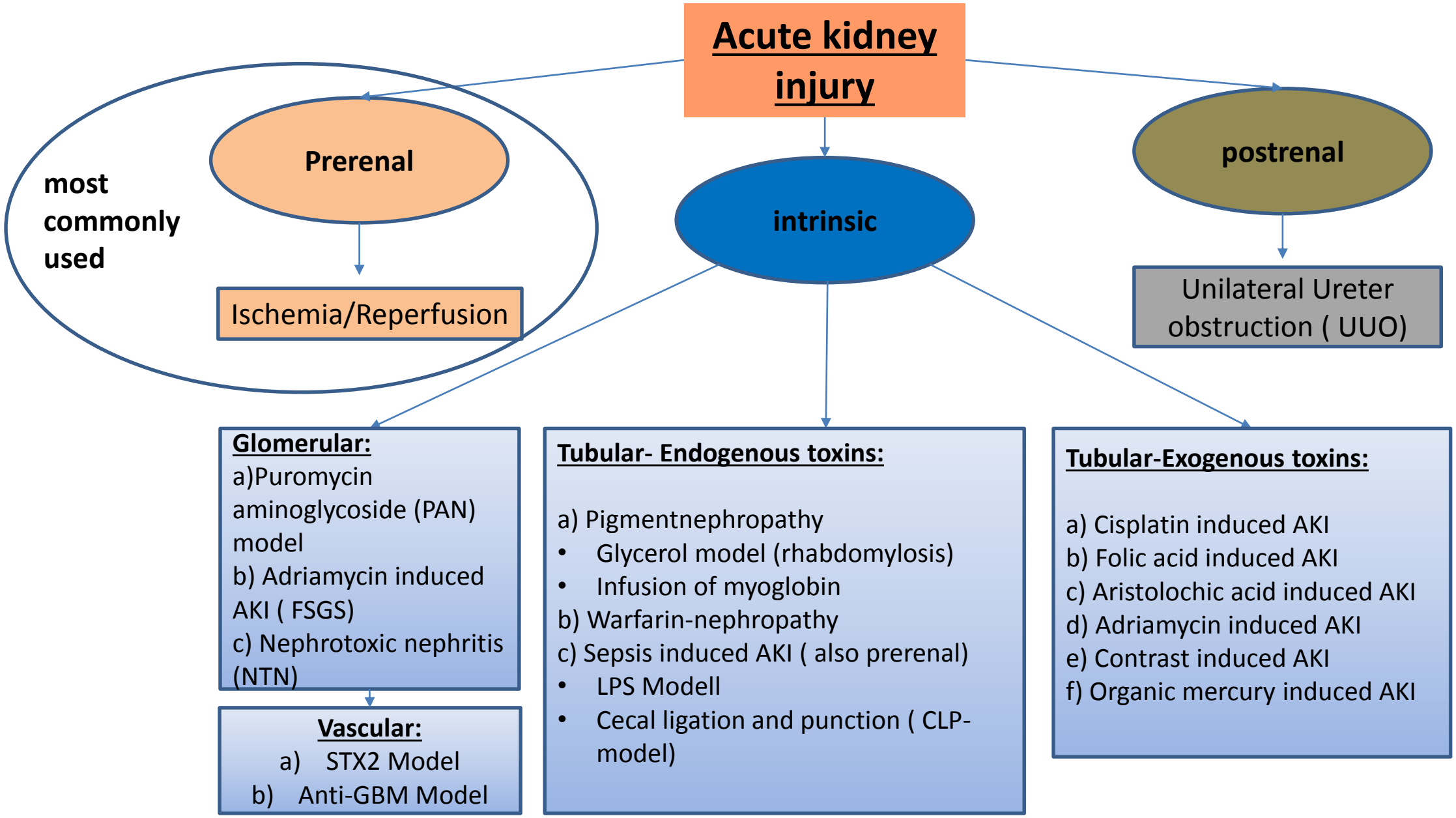


Etiology of acute kidney injury (AKI)

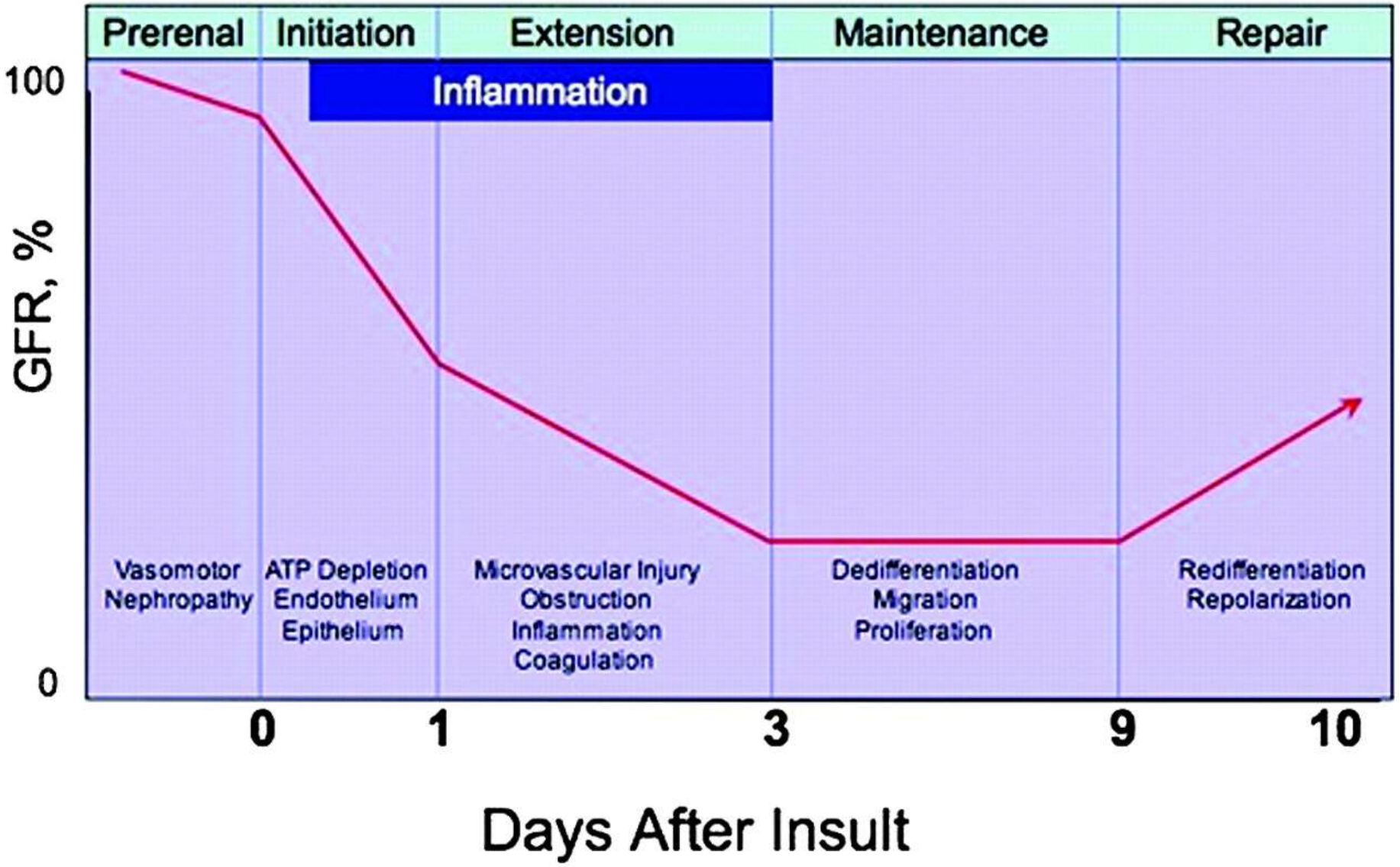


Modified from Harrison's Principles of internal medecine, 20th edition

Conventional animal models for AKI

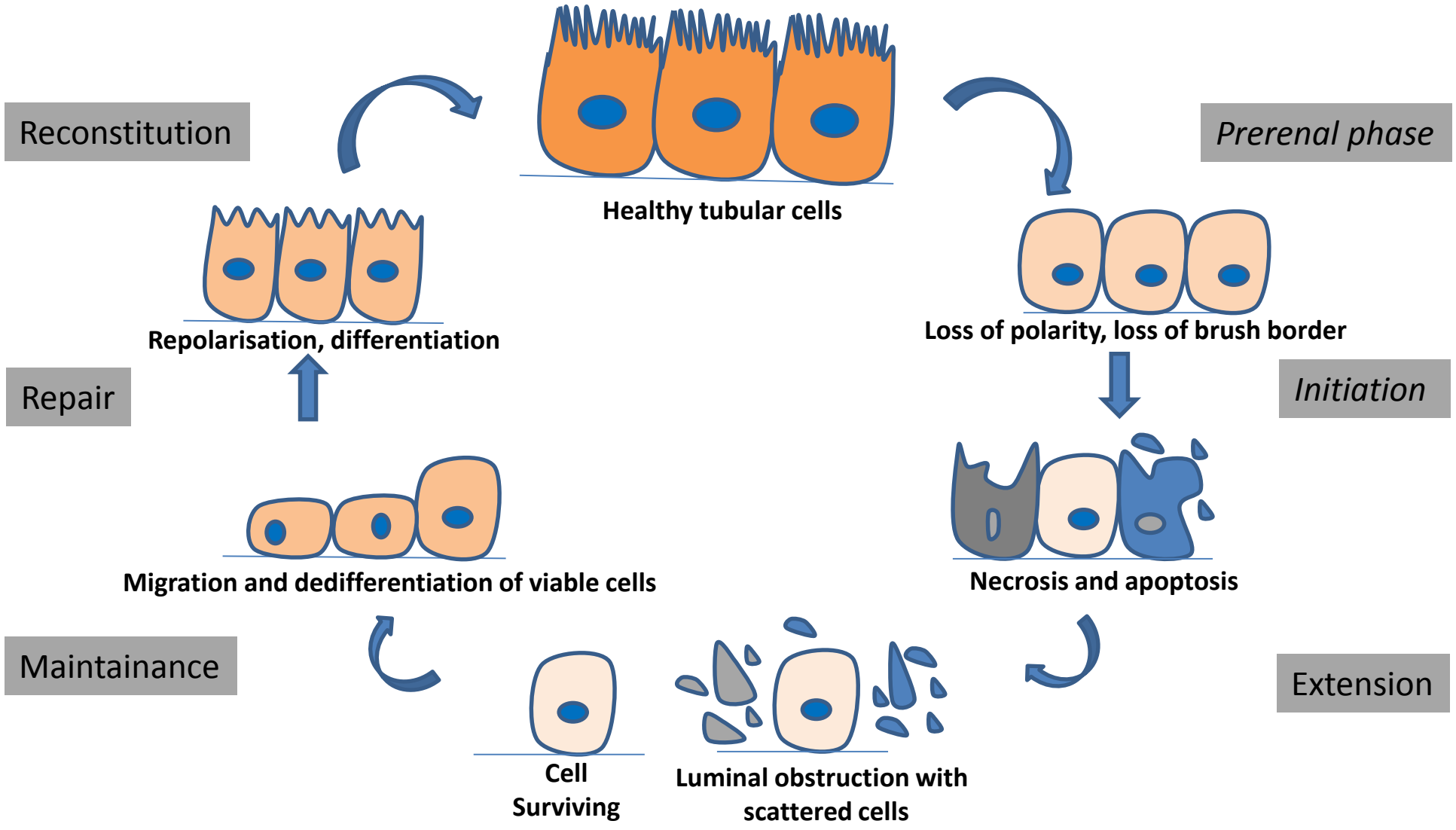


Clinical phases of AKI



Rosner & Okusa CJASN 2006; Sutton & Fisher & Molitoris KI 2002

Clinical phases of AKI



modified from Bonventre et al JCI 2011

Common problems of models for AKI

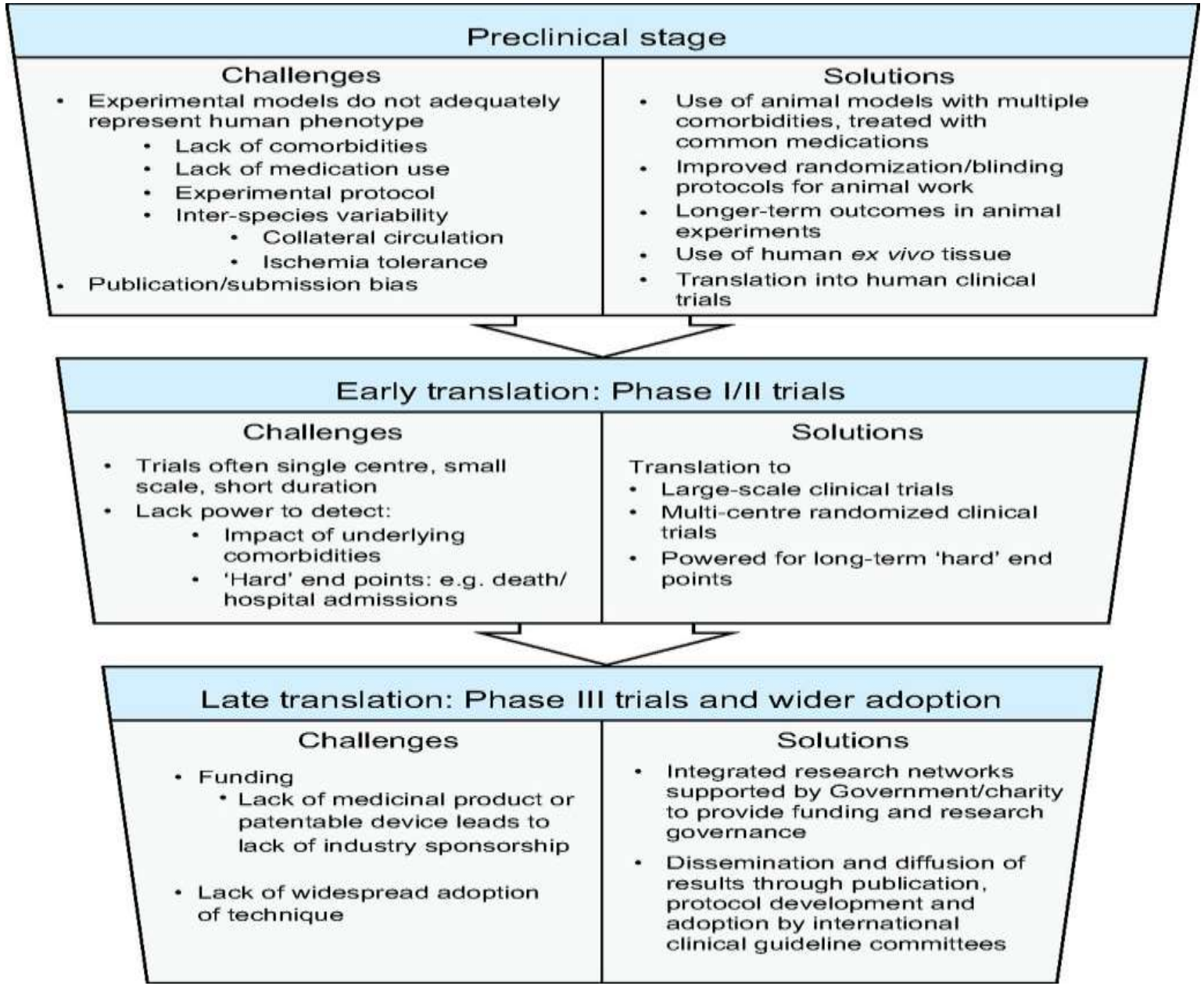
humans

- comorbidities
- mechanical ventilation
- cardio-pulmonar-arrest
- no tissue available
- medications
- older age, senescent epithelial cells

rodents

- different biology
- same diet
- same environment
- other comorbidities than humans
- young age, responsive vasculature

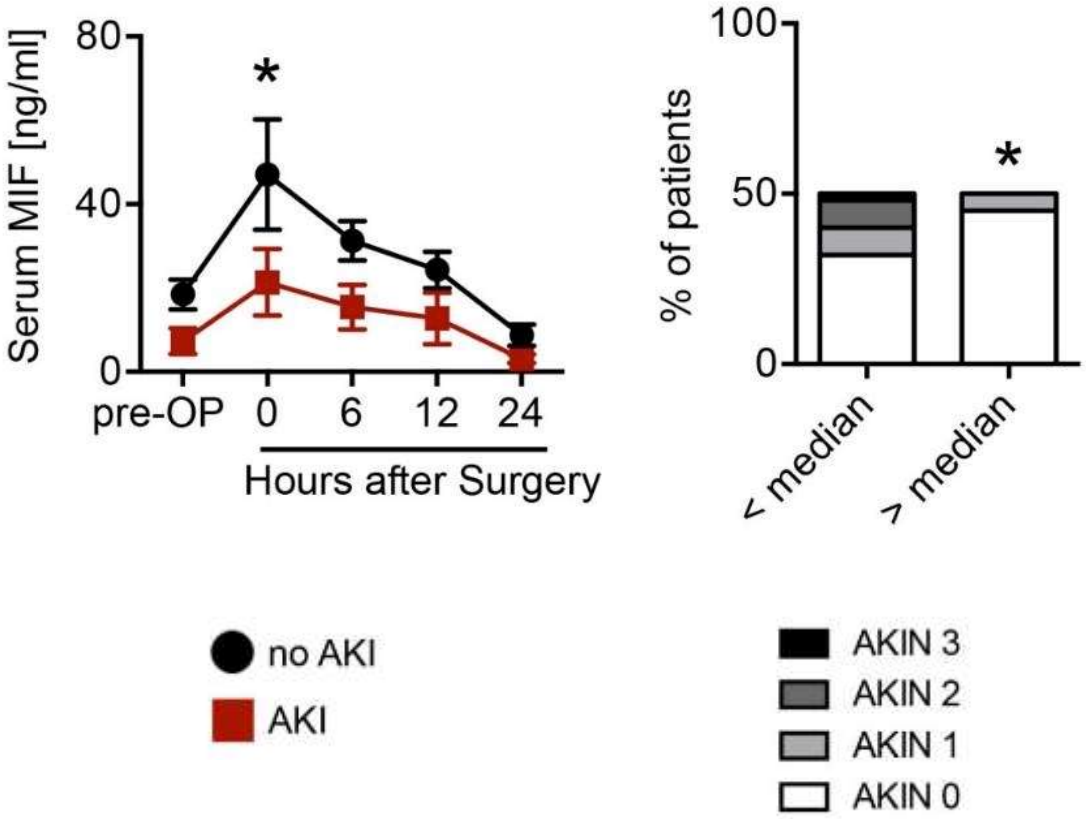
Challenges and solutions in translation



McCafferty et al 2014

Combine clinical & preclinical research - Role of MIF in AKI

Cohort studies in patients after cardiac surgery

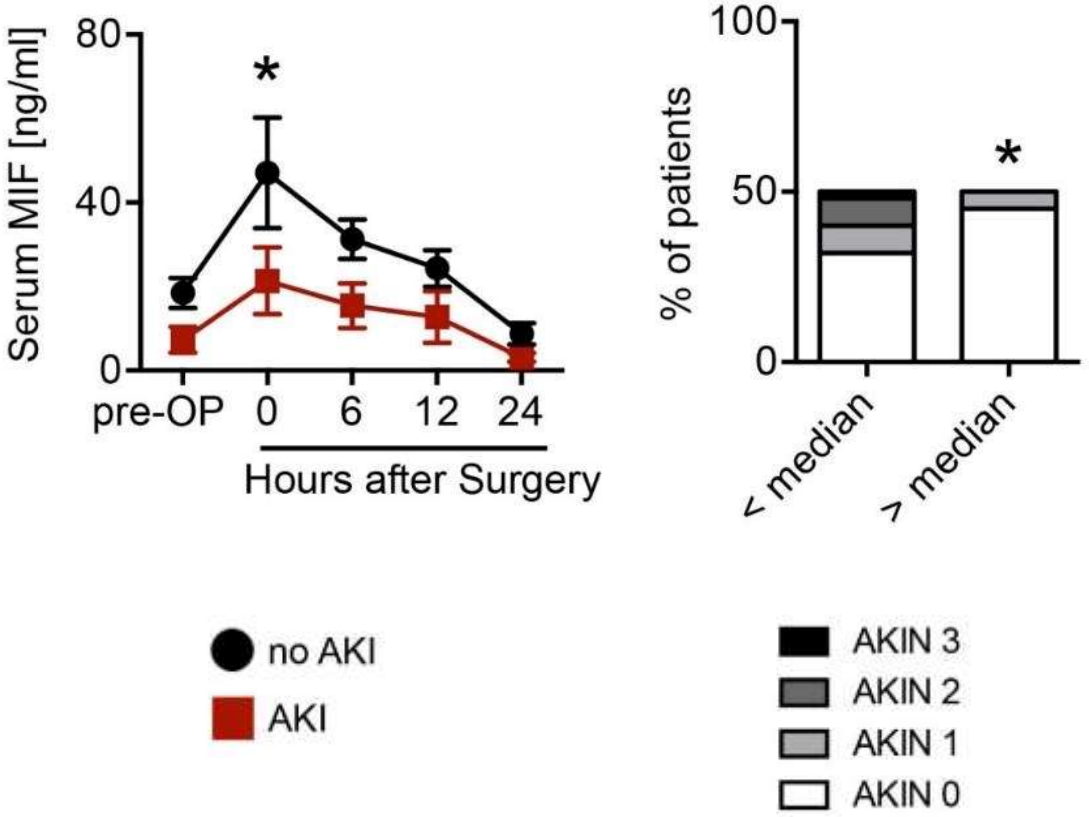


Stoppe…Boor, Sci Transl Med 2018

Combine approaches - role of MIF in AKI & tubular injury

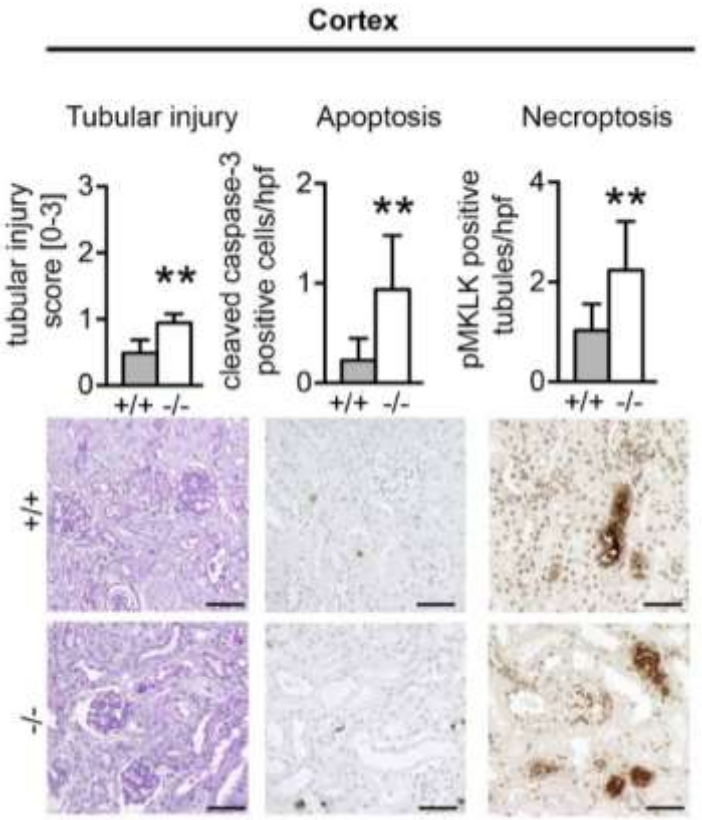
Clinical studies

patients after cardiac surgery



Preclinical studies

Different animal AKI models & interventions & in vitro mechanistic studies



Stoppe…Boor, Sci Transl Med 2018

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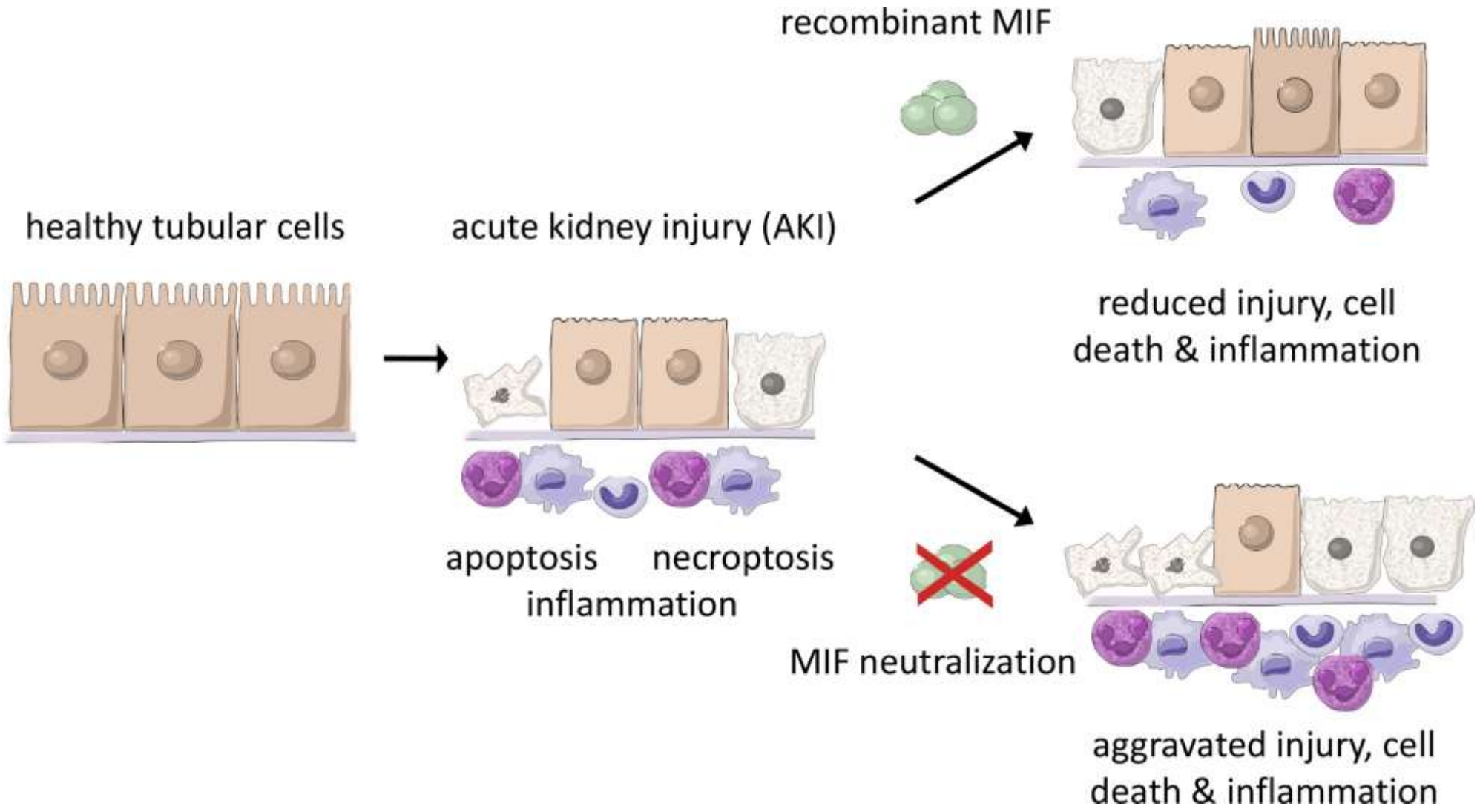
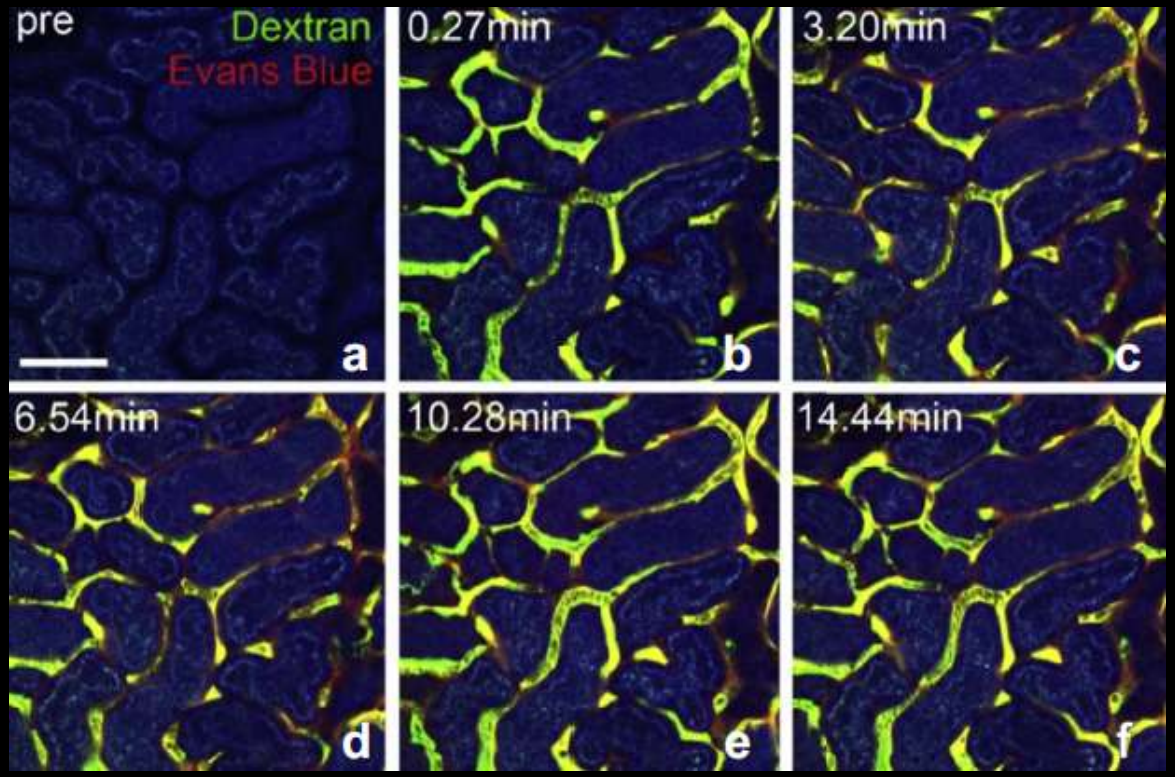


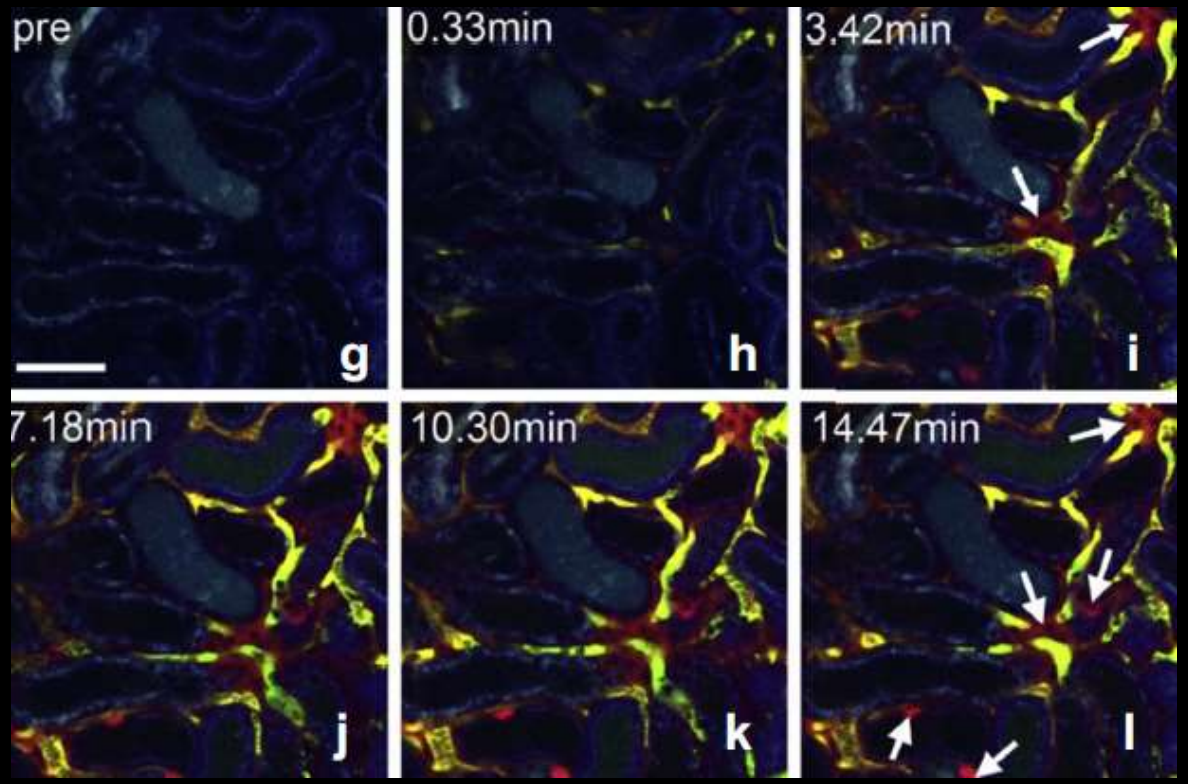
Stoppe…Boor, Sci Transl Med 2018

Other processes in AKI – microvascular dysfunction (in vivo imaging)

Kidney autofluorescence (tubular cells)
Peritubular capillaries (2000 kDa dextrane-FITC, 50 µl of 5mg/ml))
Evans blue (1µl/g BW of 1mg/ml)

sham



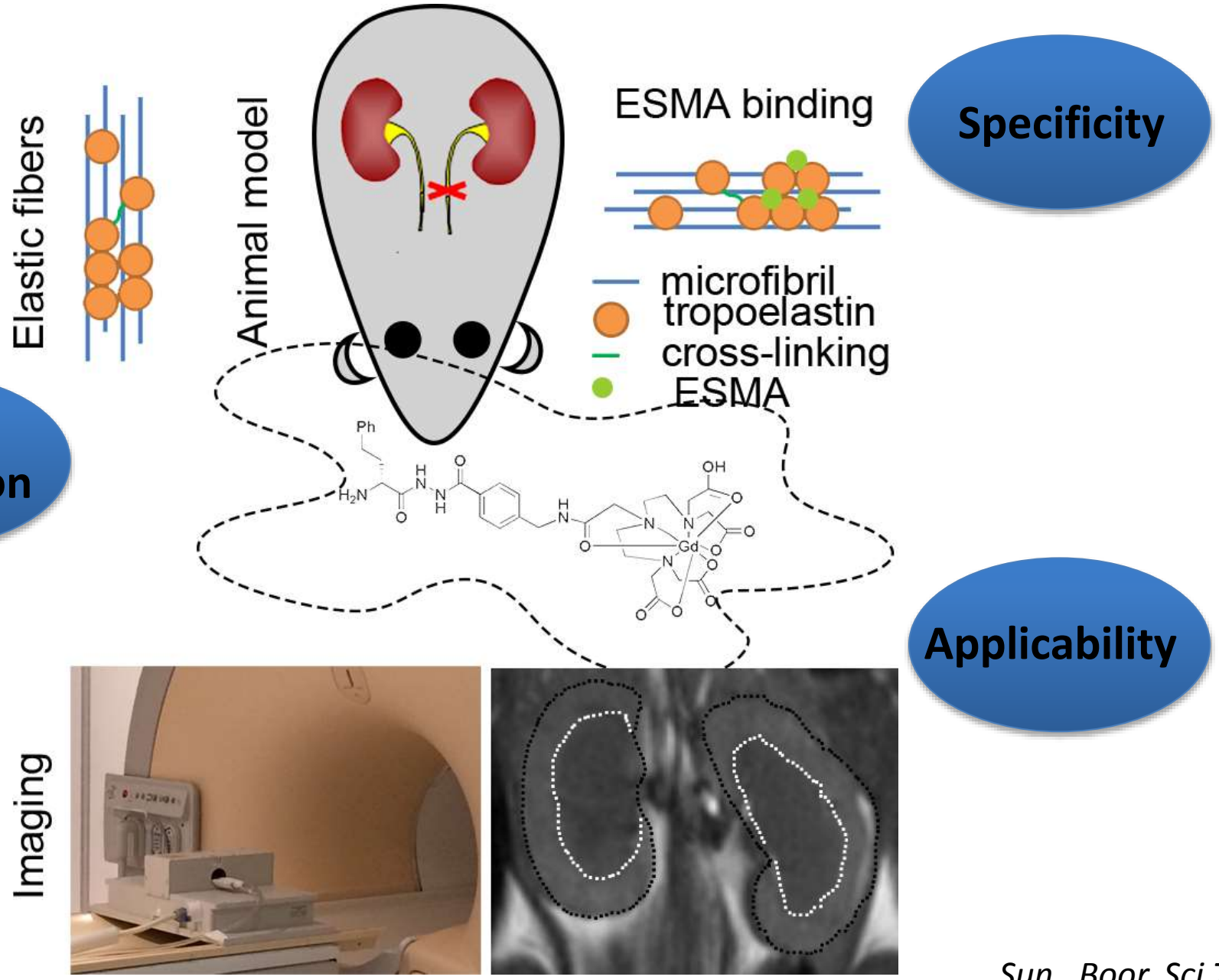


Postrenal AKI (UUO d5)

Babickova…Boor, Kidney Int 2017

Pathological process-specific kidney imaging

Approach to molecular imaging in kidneys (renal fibrosis)



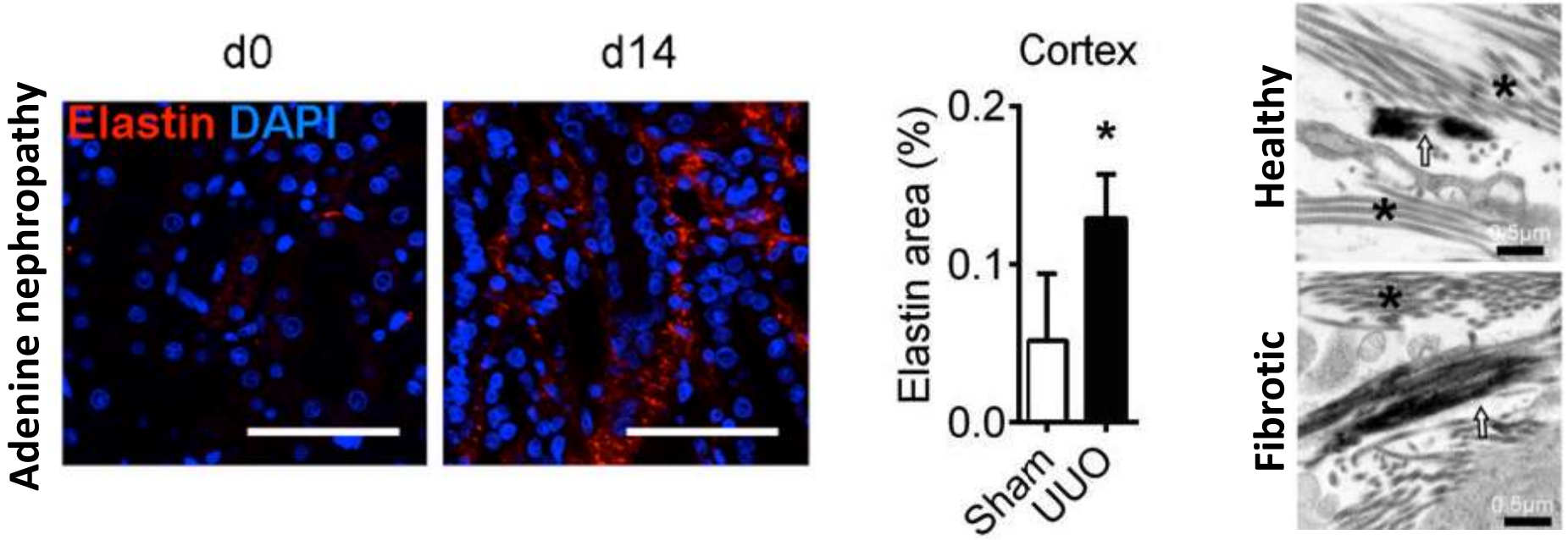
Target validation

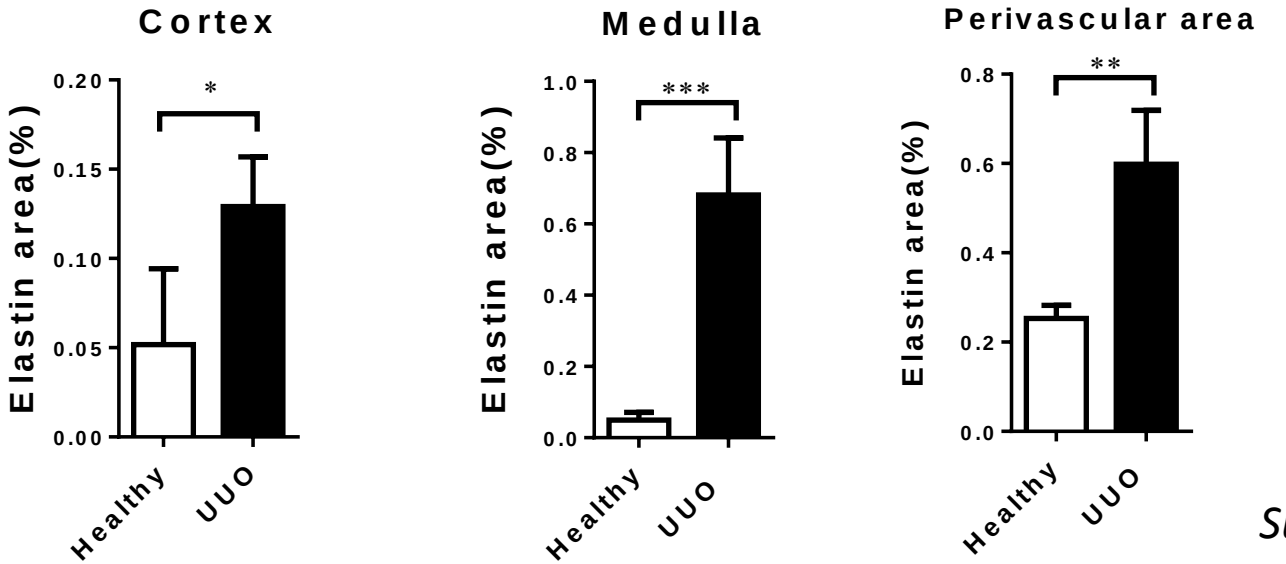
Specificity

Applicability

Sun…Boor, Sci Transl Med 2019

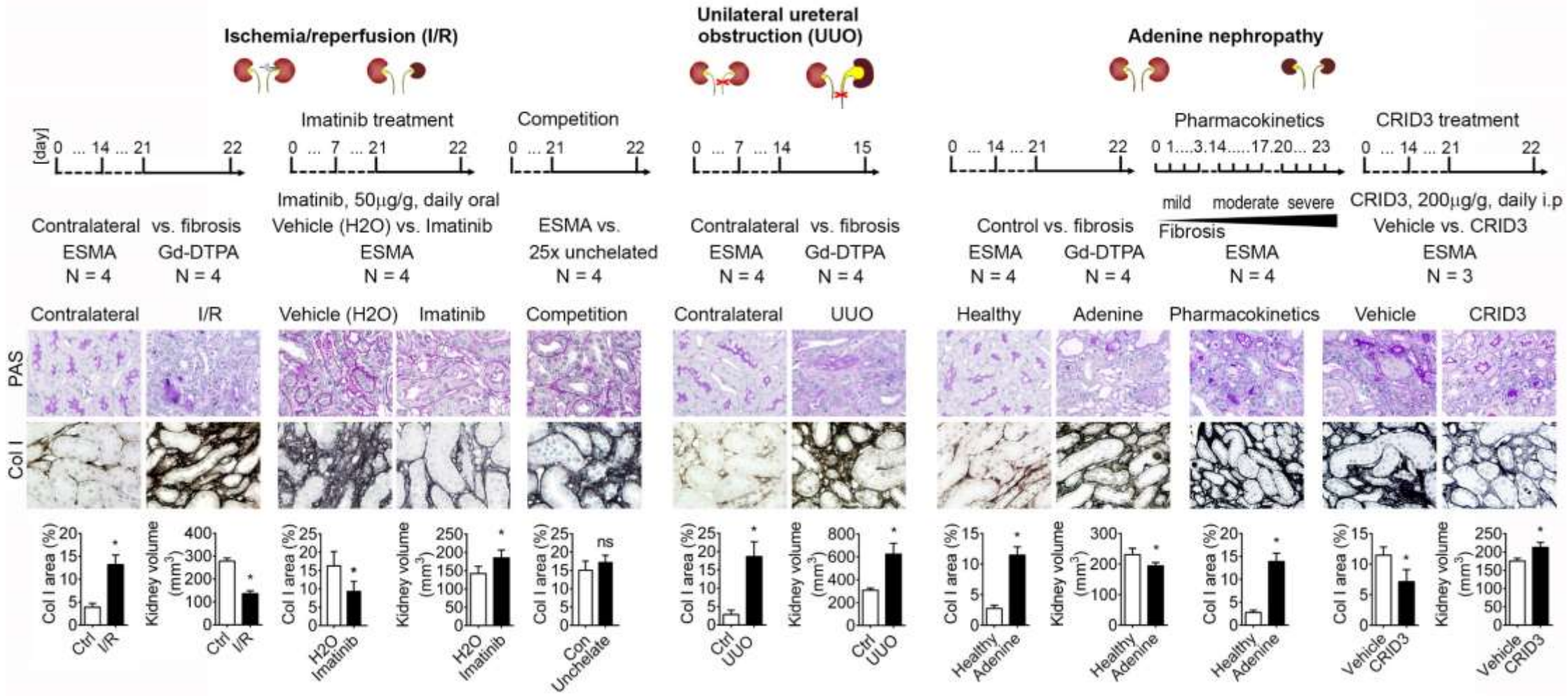
Elastin is up-regulated in models of renal fibrosis (target validation)





Sun…Boor, Sci Transl Med 2019

Confirmation in other animal models



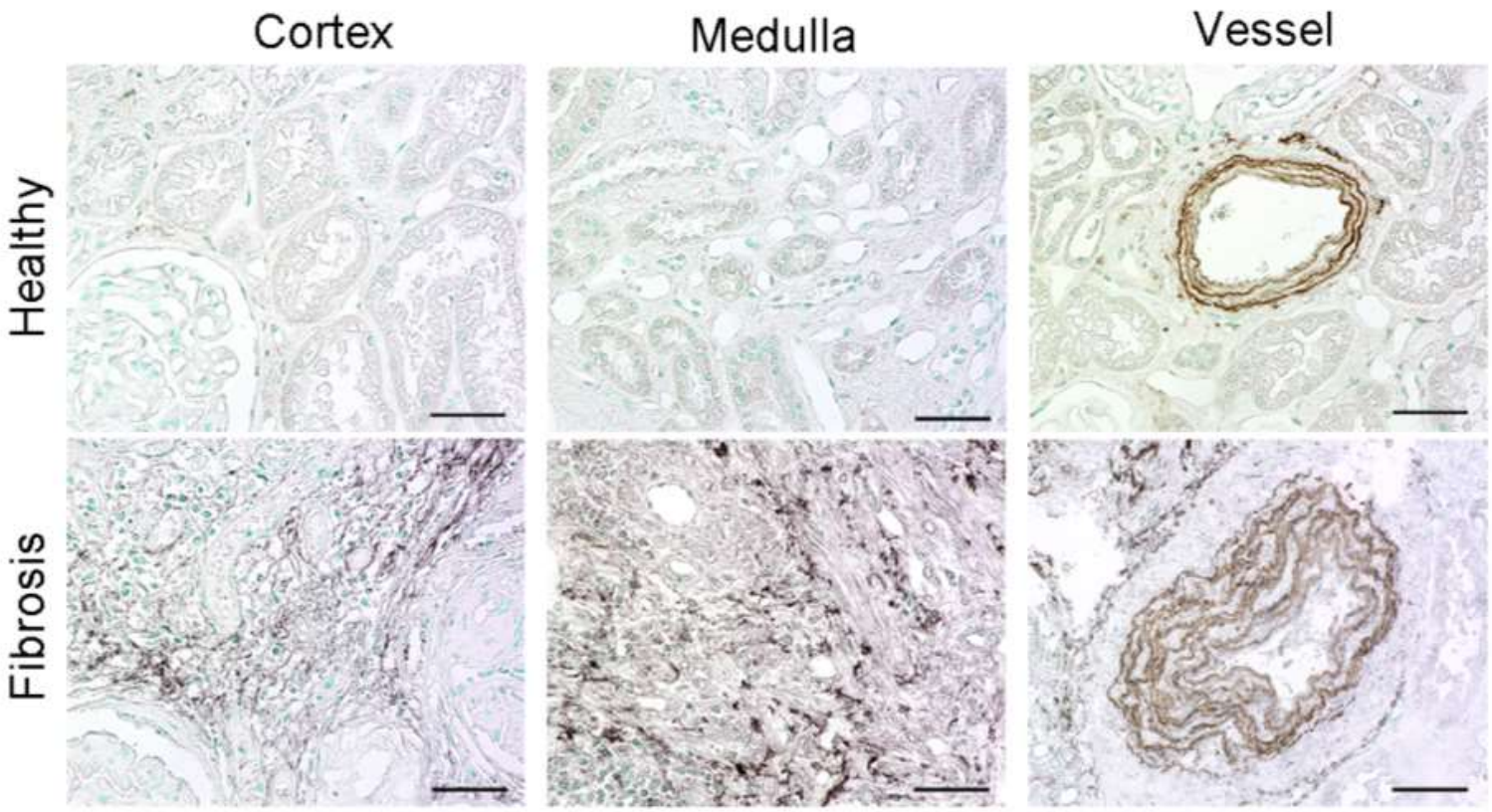
Rat: UUO, 5/6 Nx, chronic anti-Thy1.1 Nephritis, adenine nephropathy

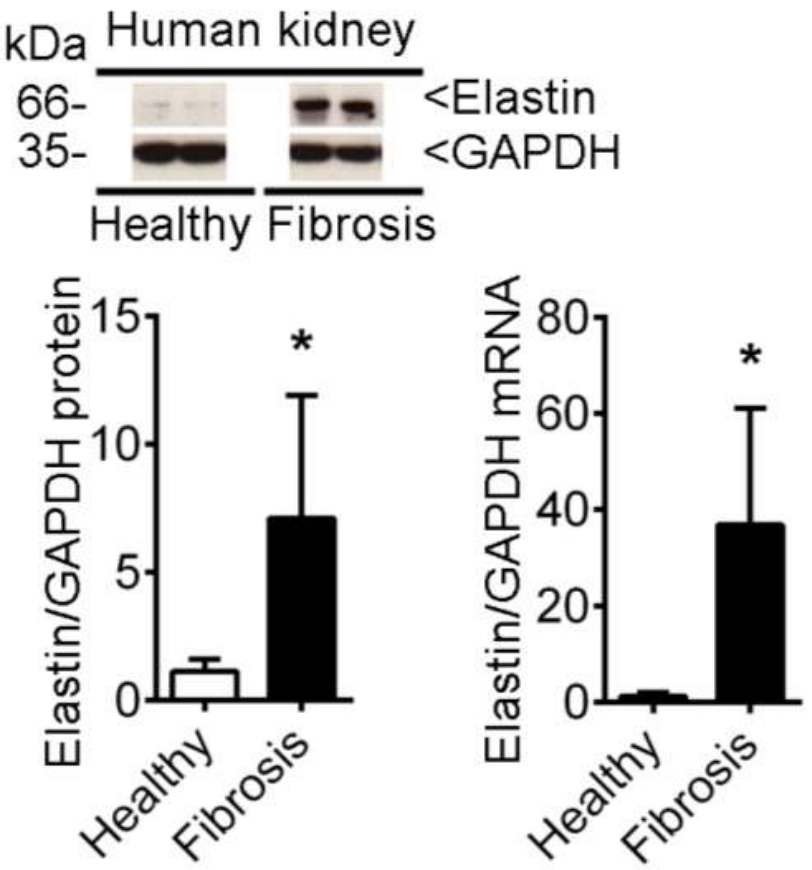
Mouse: UUO, I/R injury, NTN, Alport mice (*Col4a3*$^{-/-}$), 5/6 Nx, Folic acid nephropathy

Methods: IHC, IF, WB, qRT-PCR, electron microscopy

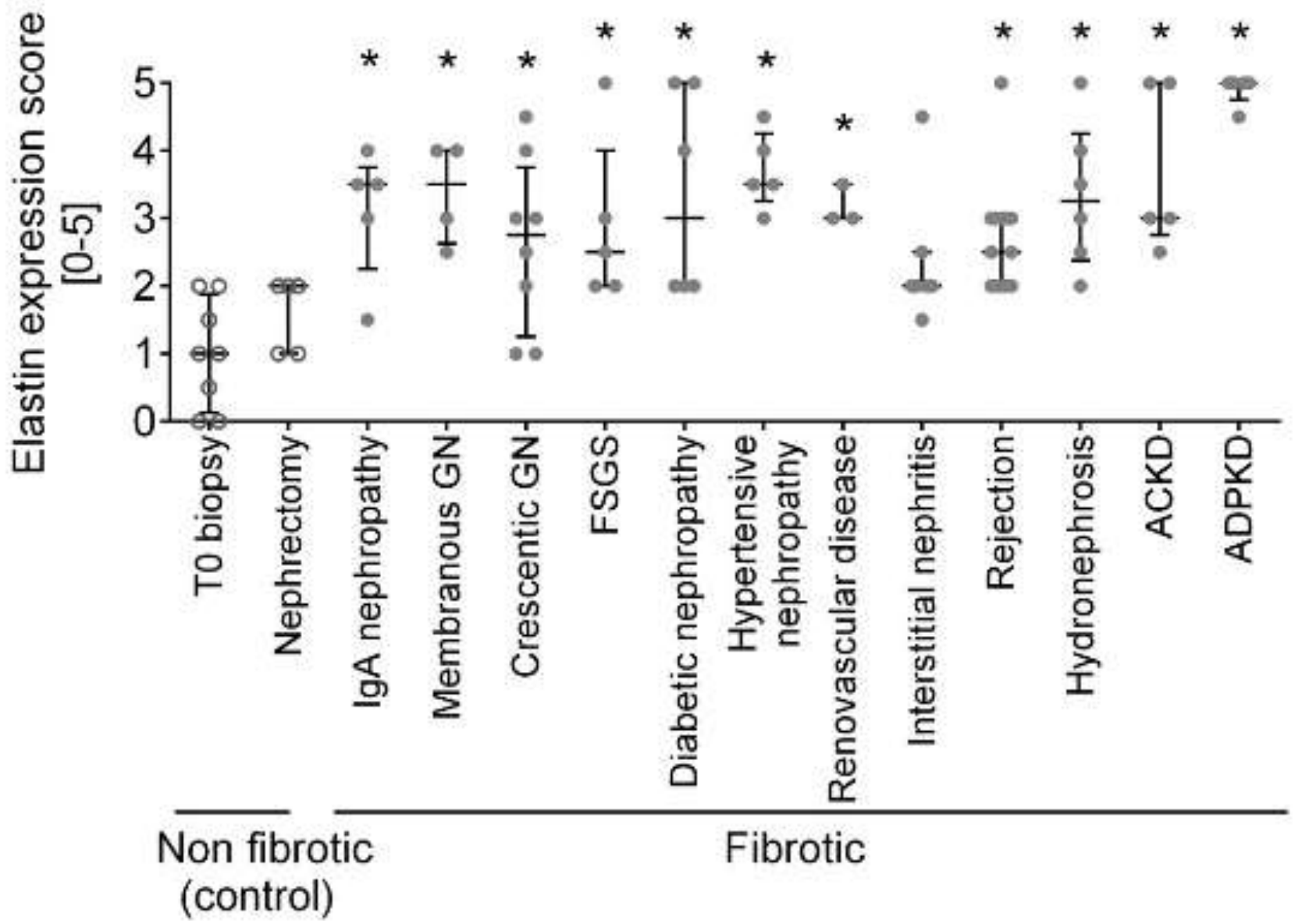
Sun…Boor, Sci Transl Med 2019

Elastin is up-regulated in patients with renal fibrosis





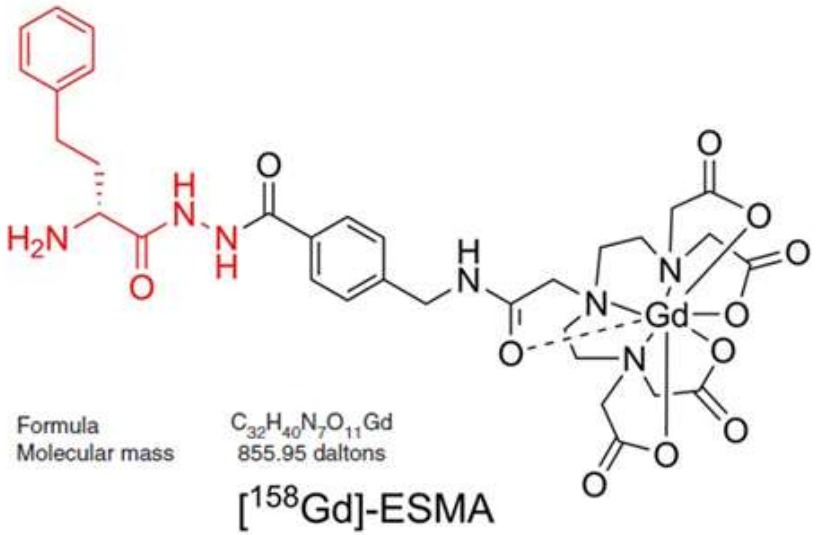
Elastin expression in human kidneys

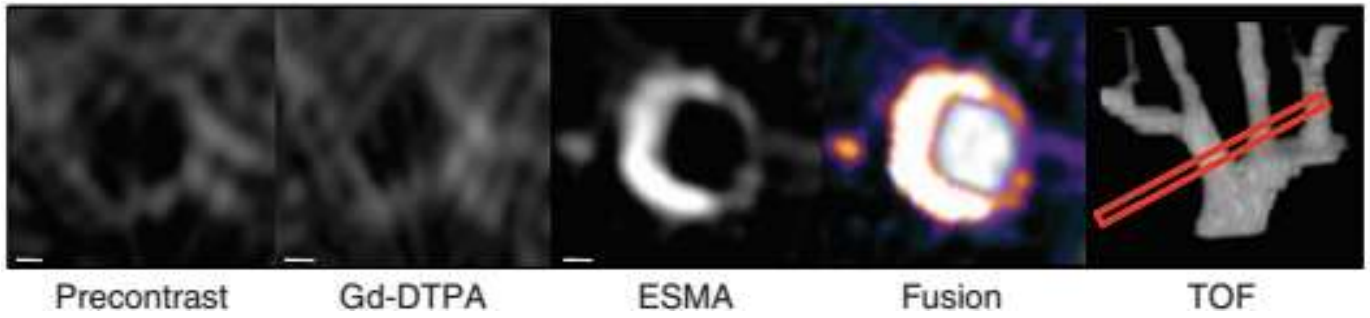


Sun…Boor, Sci Transl Med 2019

Elastin-specific magnetic resonance contrast agent (ESMA)

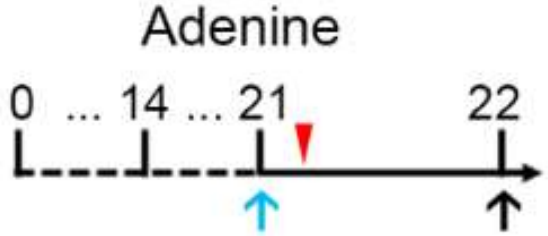
^{153}Gd-DTPA linked to D-amino acid D-phenylalanine





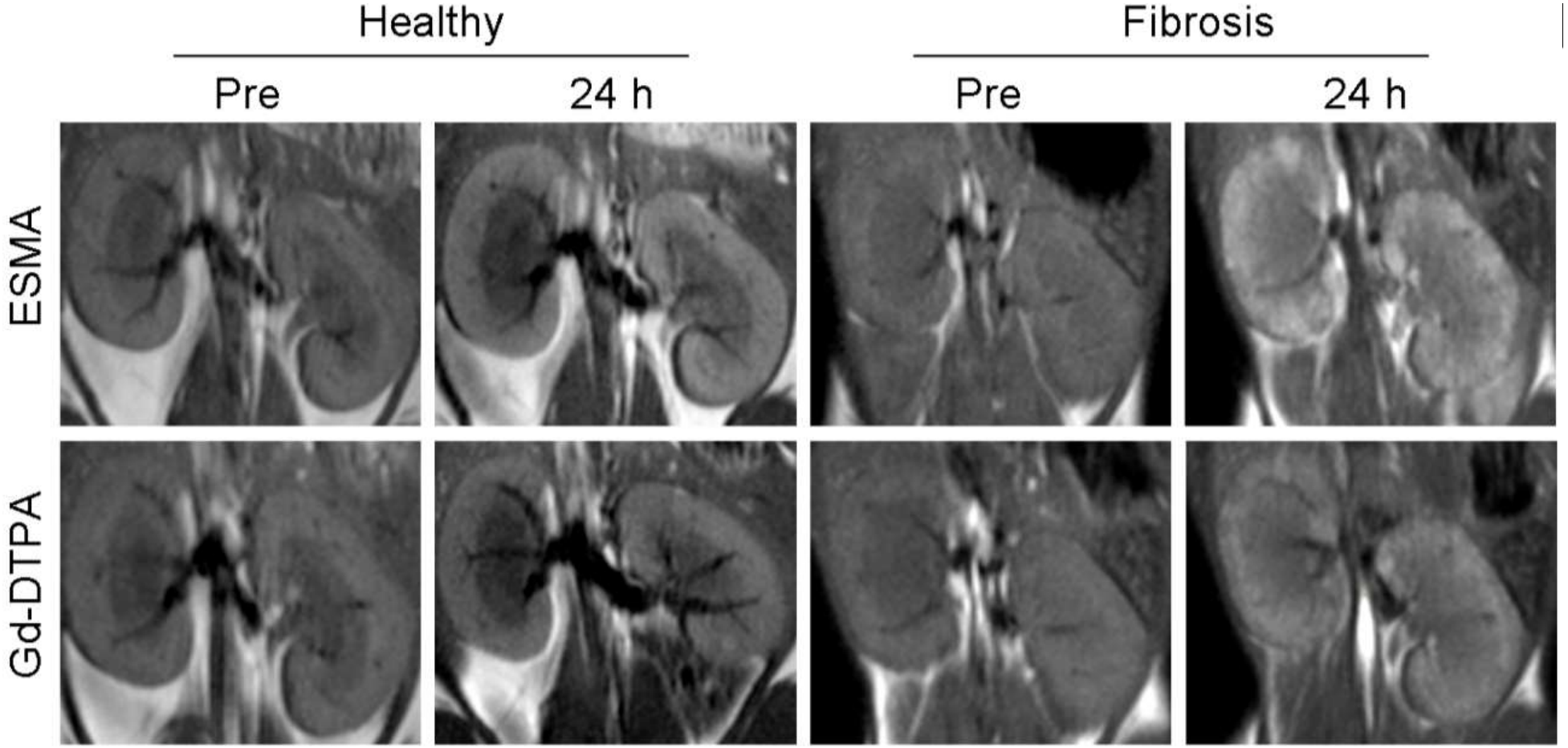
Makowski et al. Nat Med 2011

ESMA MRI in adenine nephropathy

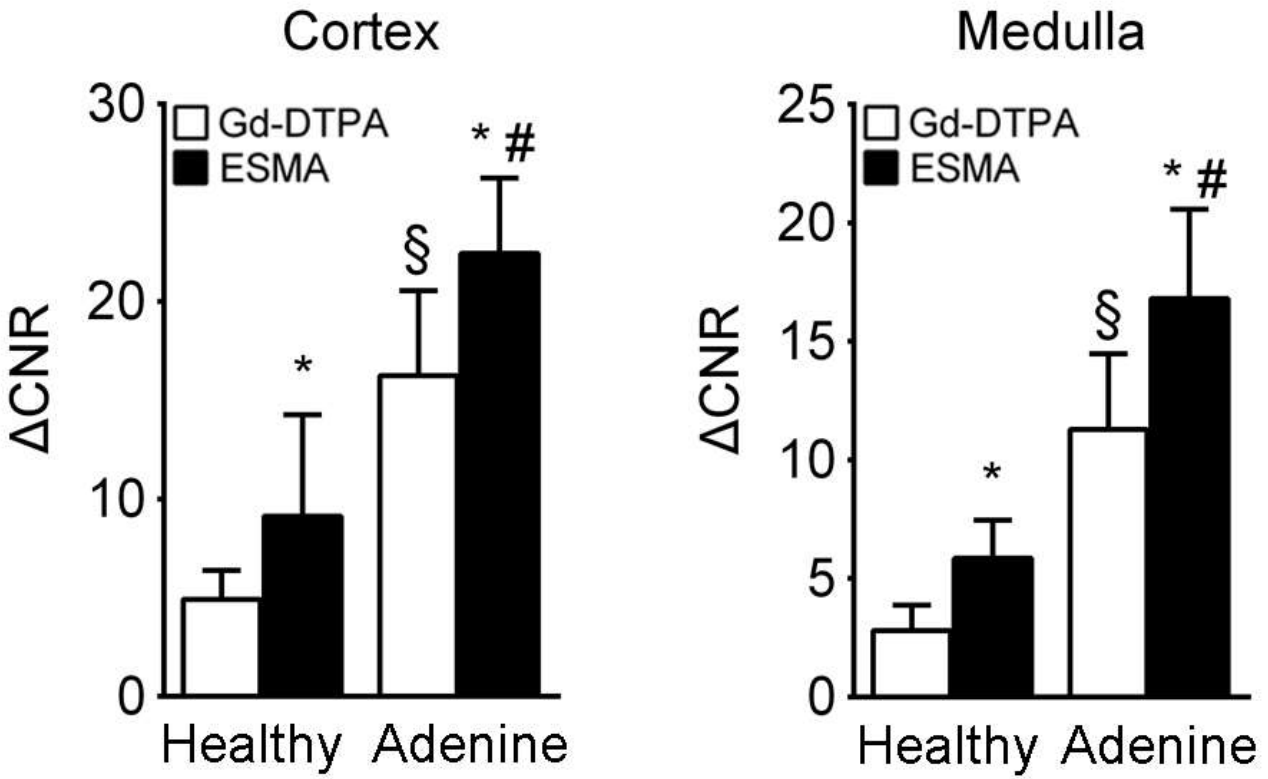


Control vs. fibrosis

ESMA	Gd-DTPA
N = 4	N = 4



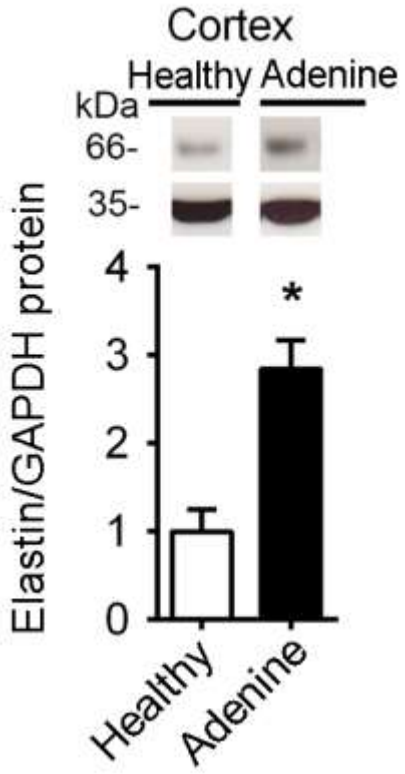
ESMA MRI in adenine nephropathy



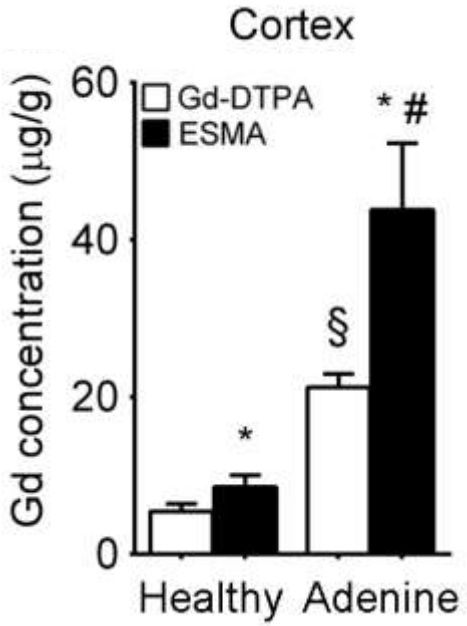
Sun…Boor, Sci Transl Med 2019

Specificity

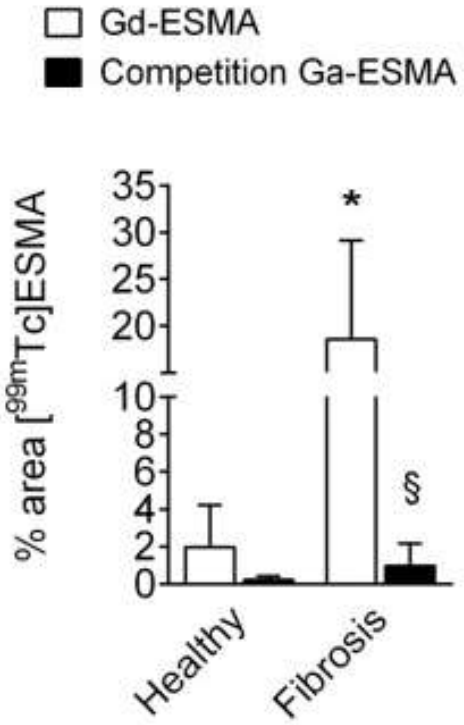
Elastin expression



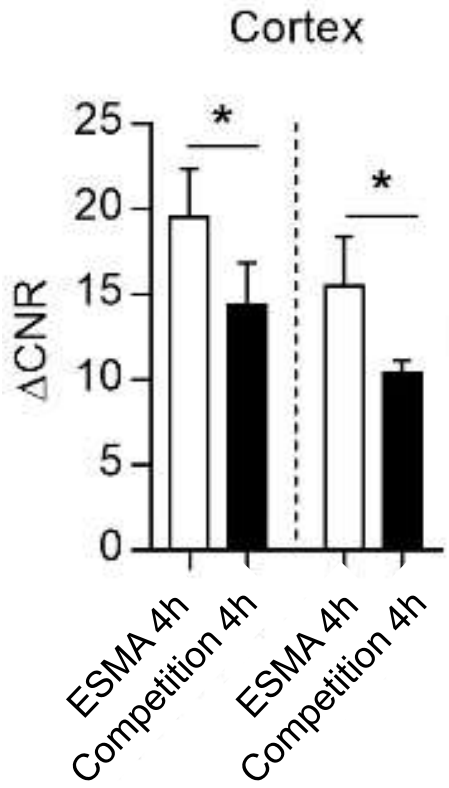
Renal Gd-content



ex vivo competition



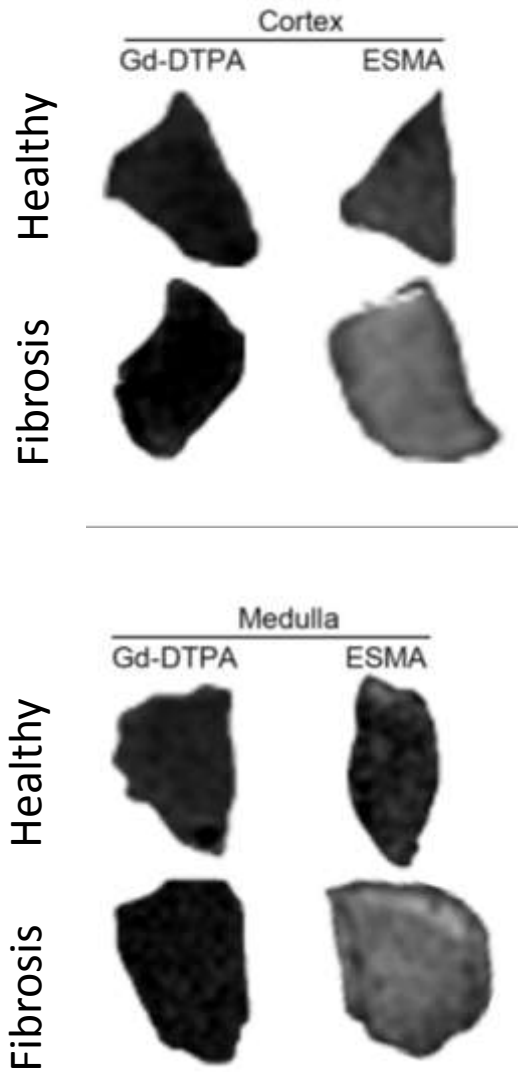
in vivo competition

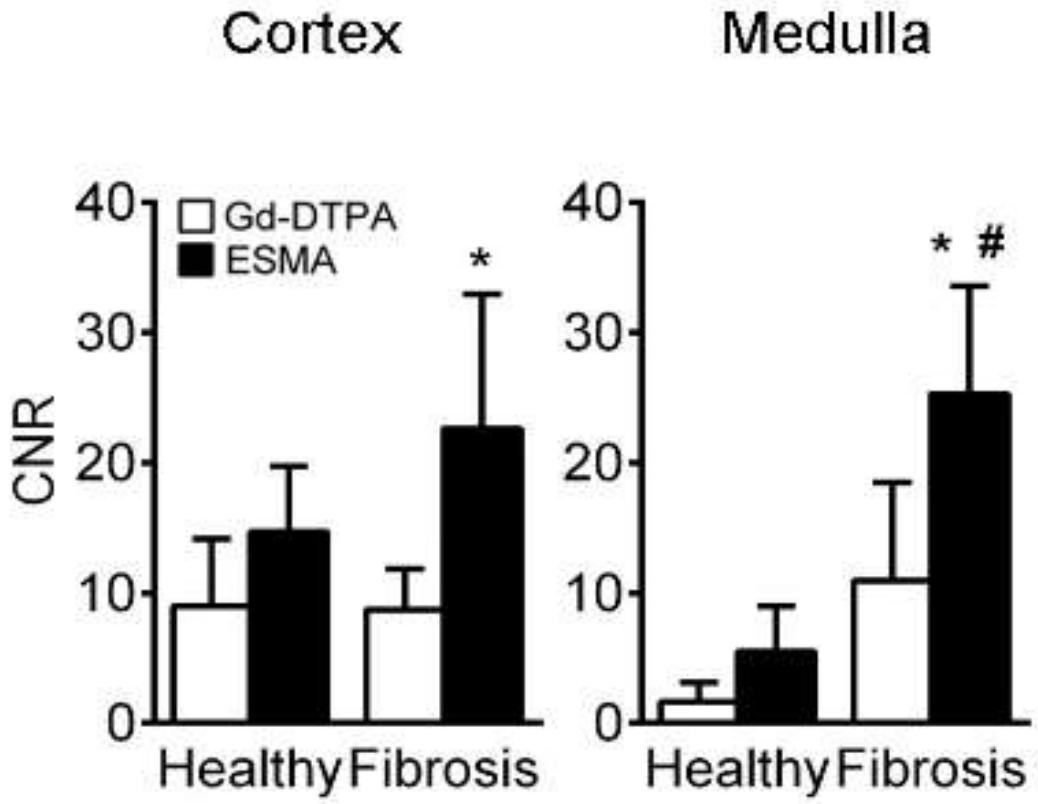


(laser ablation) inductively coupled plasma mass spectrometry – LA-ICP-MS

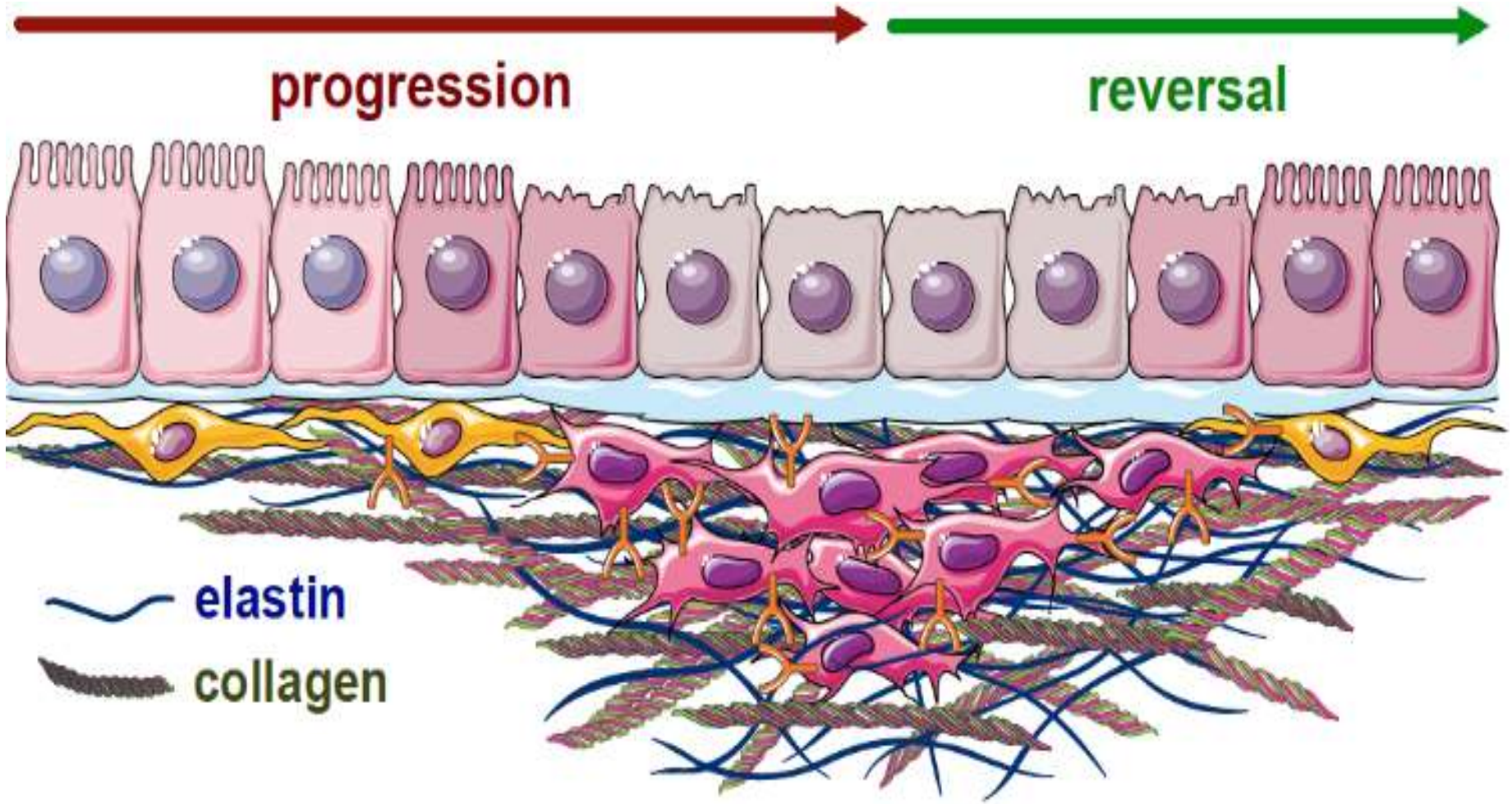
Sun…Boor, Sci Transl Med 2019

ESMA binds to human kidney *ex vivo*



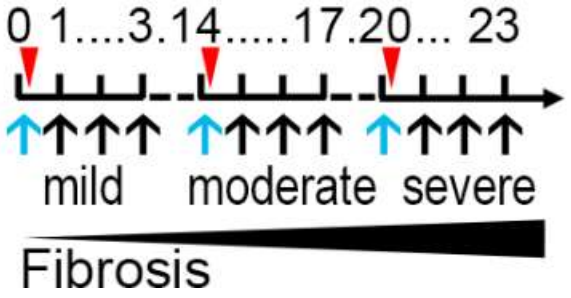


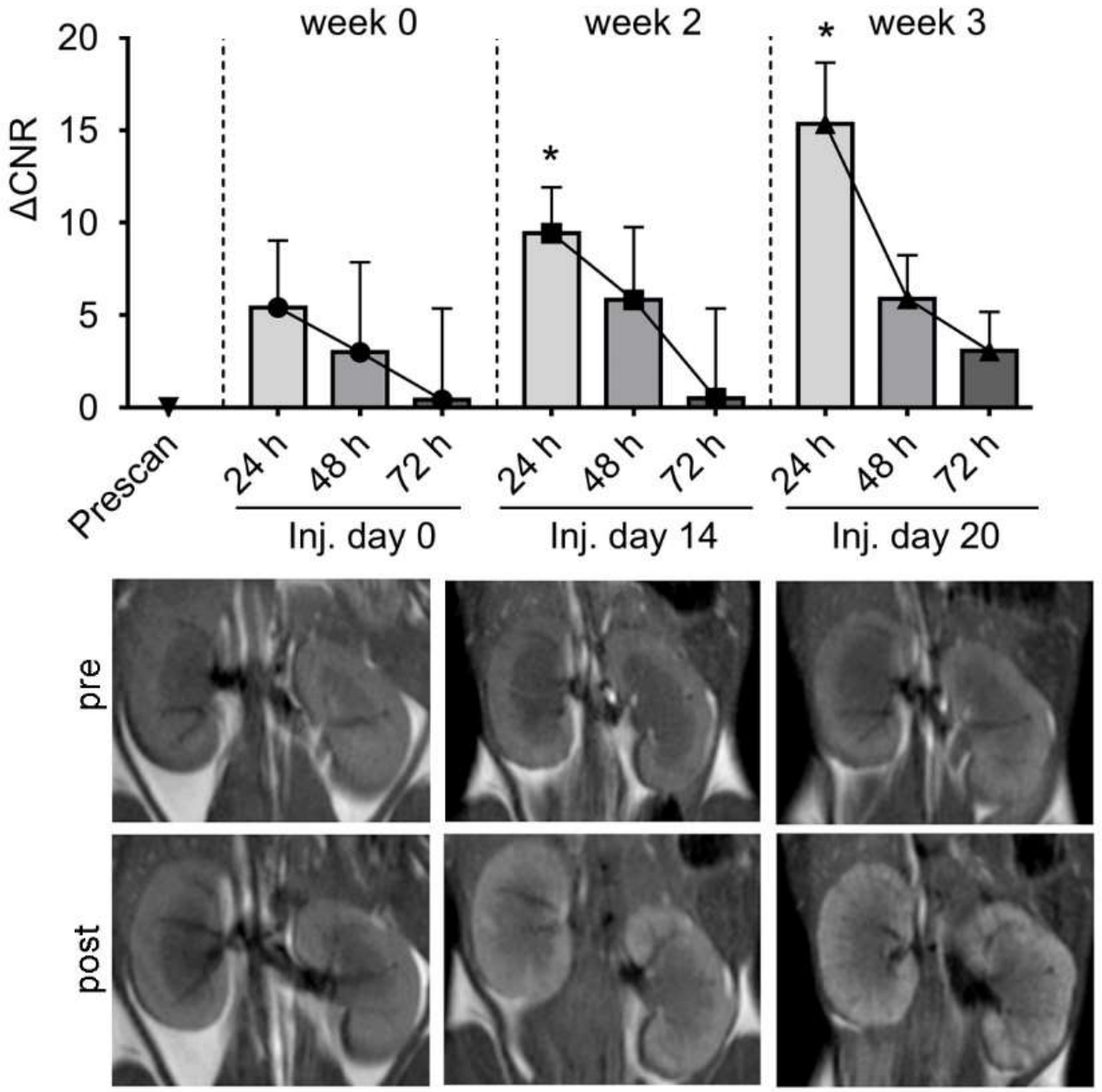
Renal Fibrosis



Baues…Boor et al., Adv Drug Deliv Res 2018

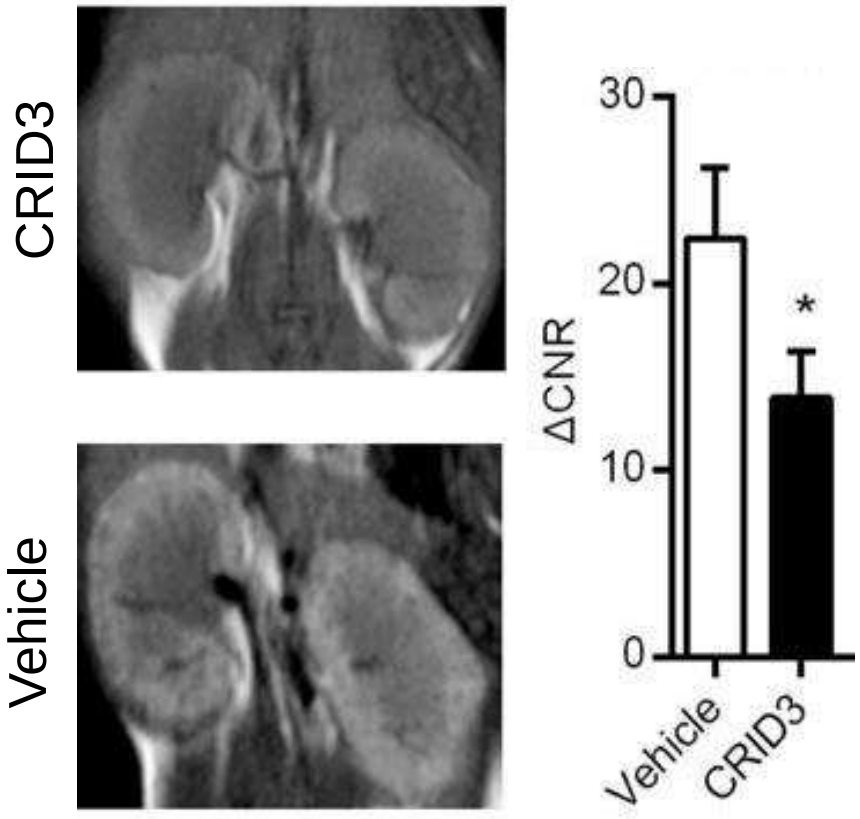
ESMA pharmacokinetics & longitudinal measures



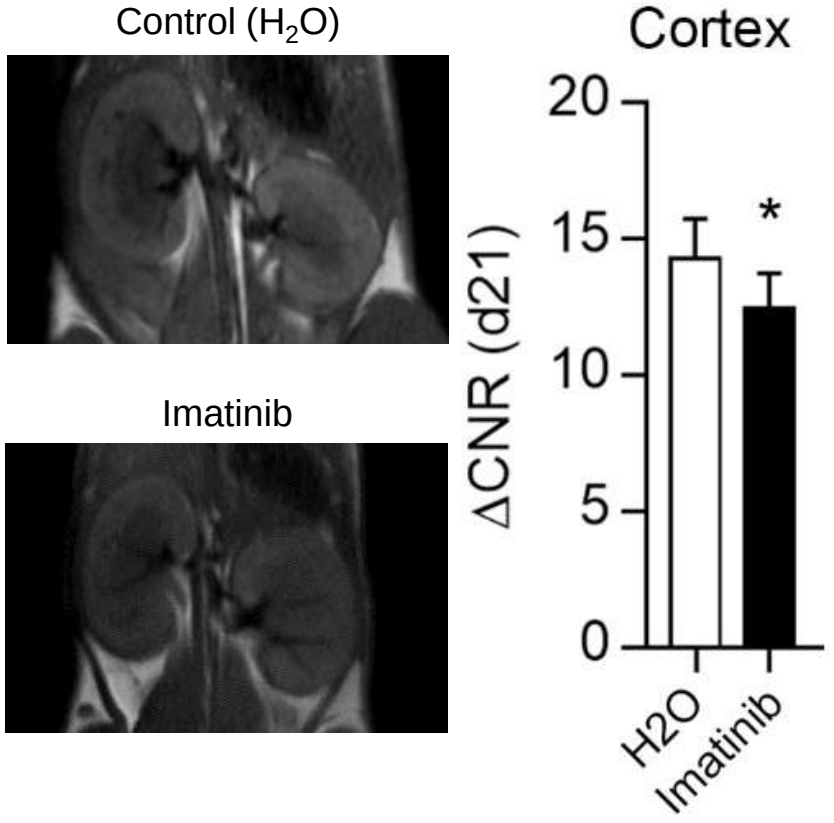


ESMA imaging monitors anti-fibrotic therapy efficacy

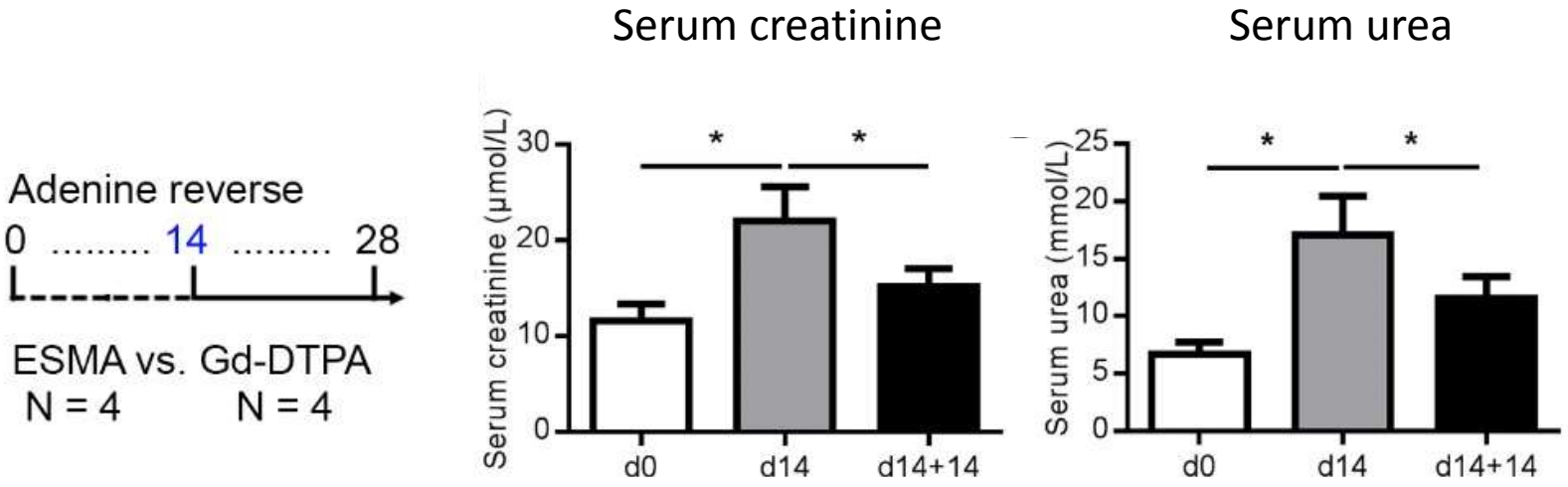
CRID3 in Adenine nephropathy



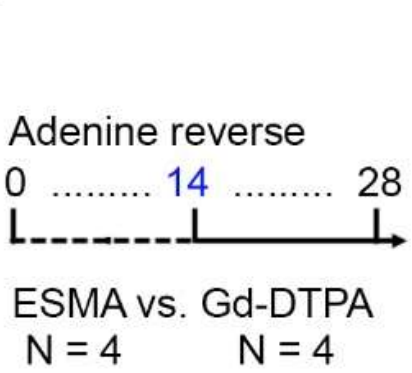
Imatinib in I/R



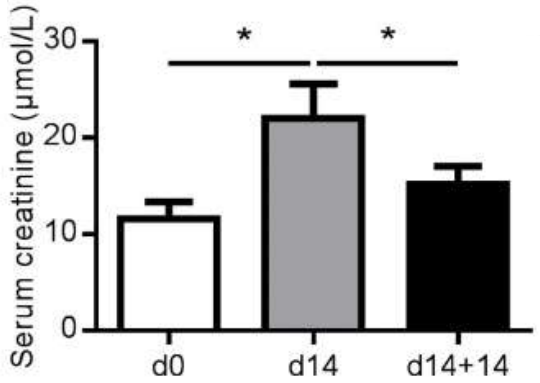
ESMA imaging - just another surrogate for GFR?



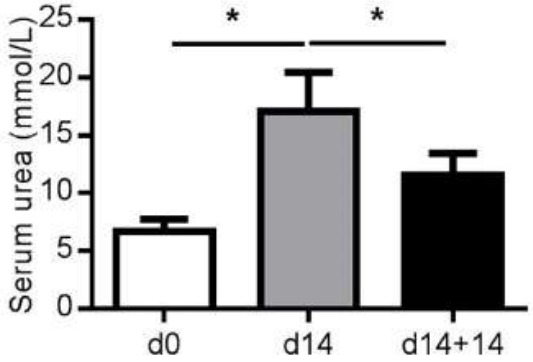
ESMA imaging in reversible adenine nephropathy



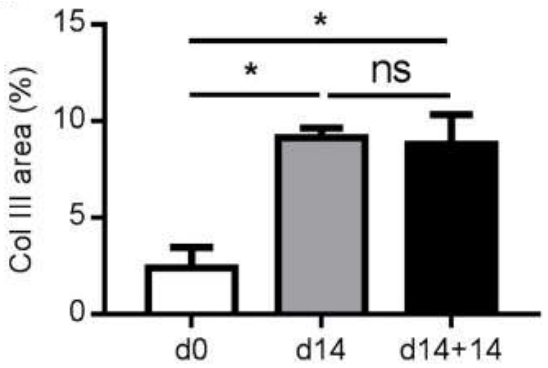
Serum creatinine



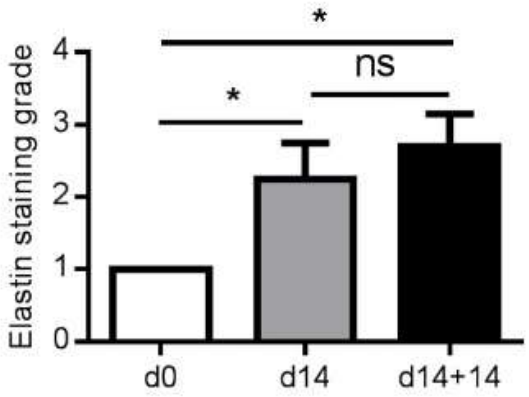
Serum urea



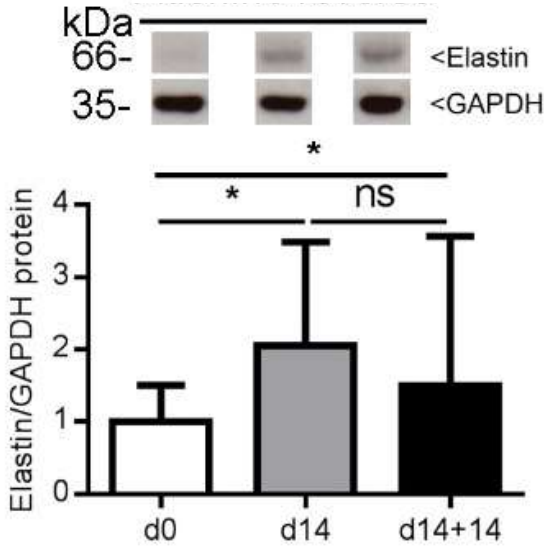
Collagen 3



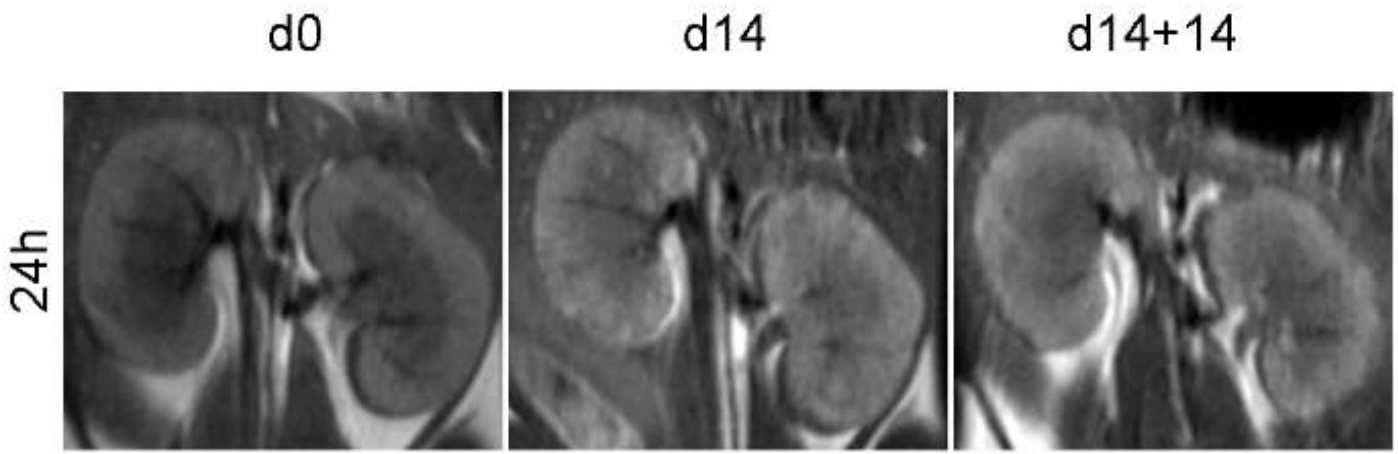
Elastin IF

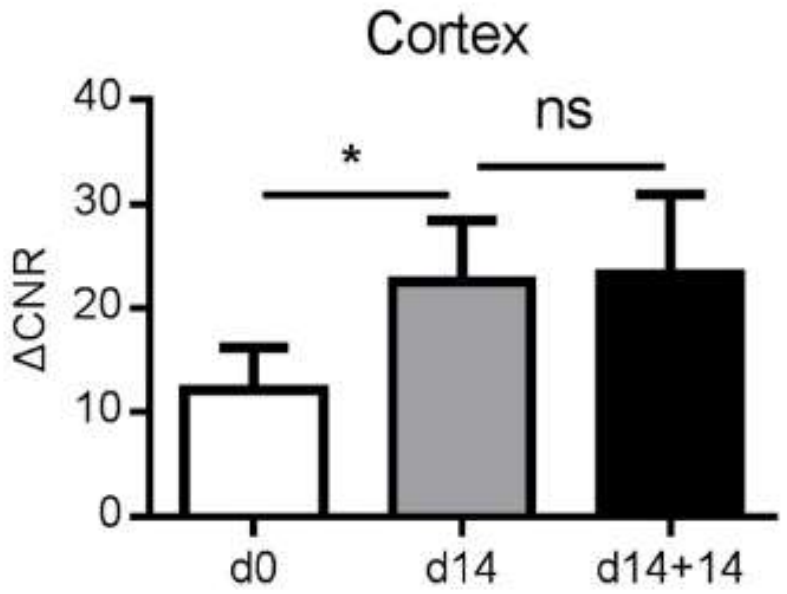


Elastin WB

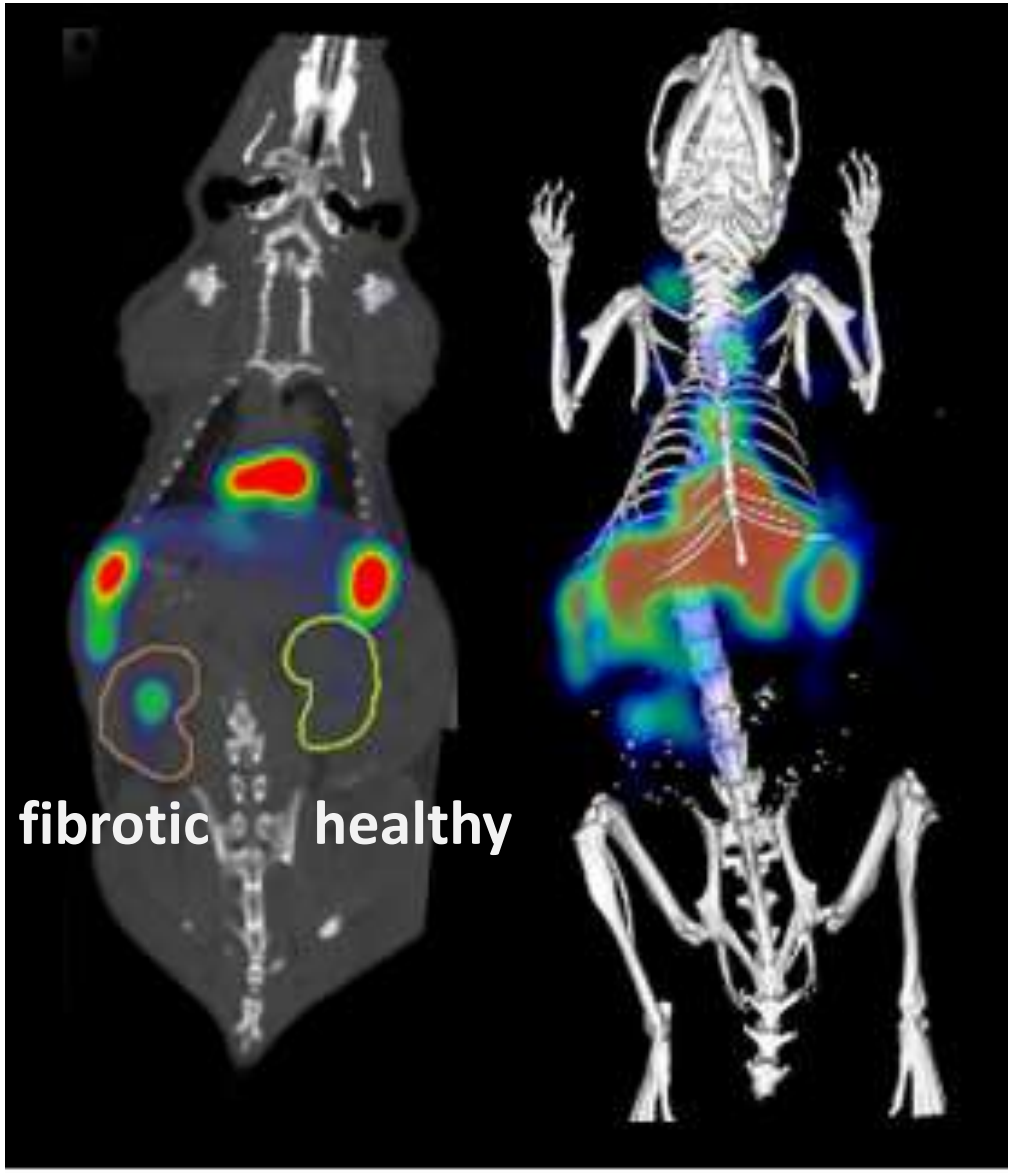


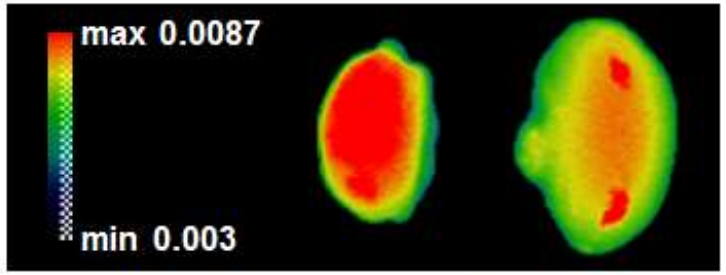
Elastin imaging identifies residual renal fibrosis not detectable using routine kidney function measurement

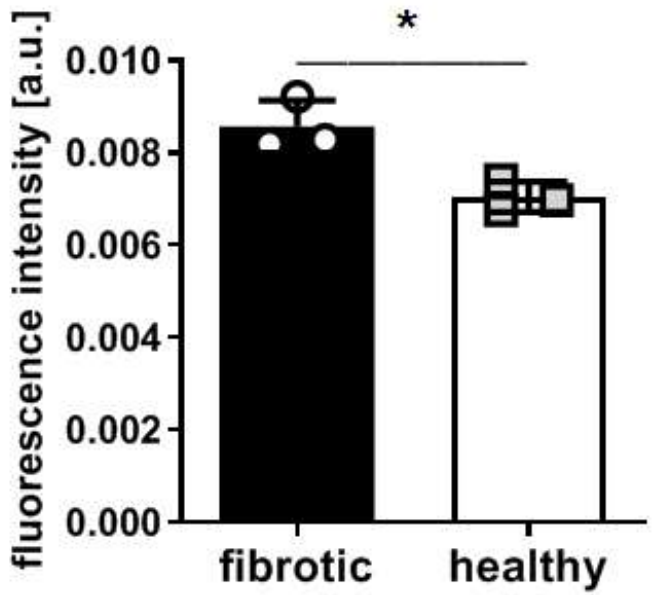




Collagen imaging in renal fibrosis

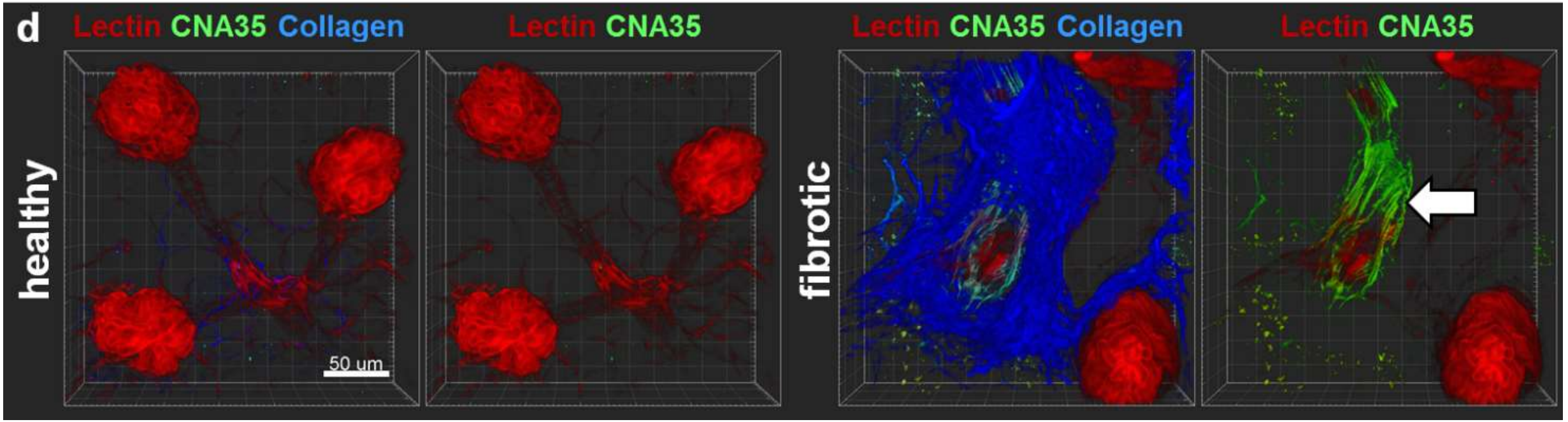


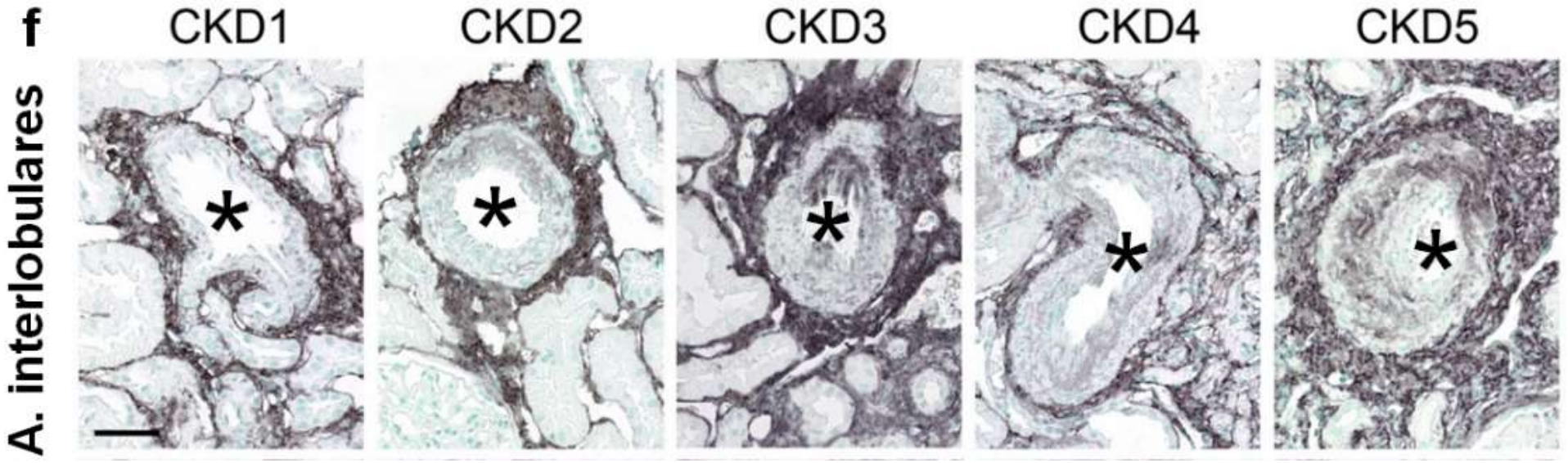




Baues…Boor, Kidney Int 2019

Collagen imaging in renal fibrosis



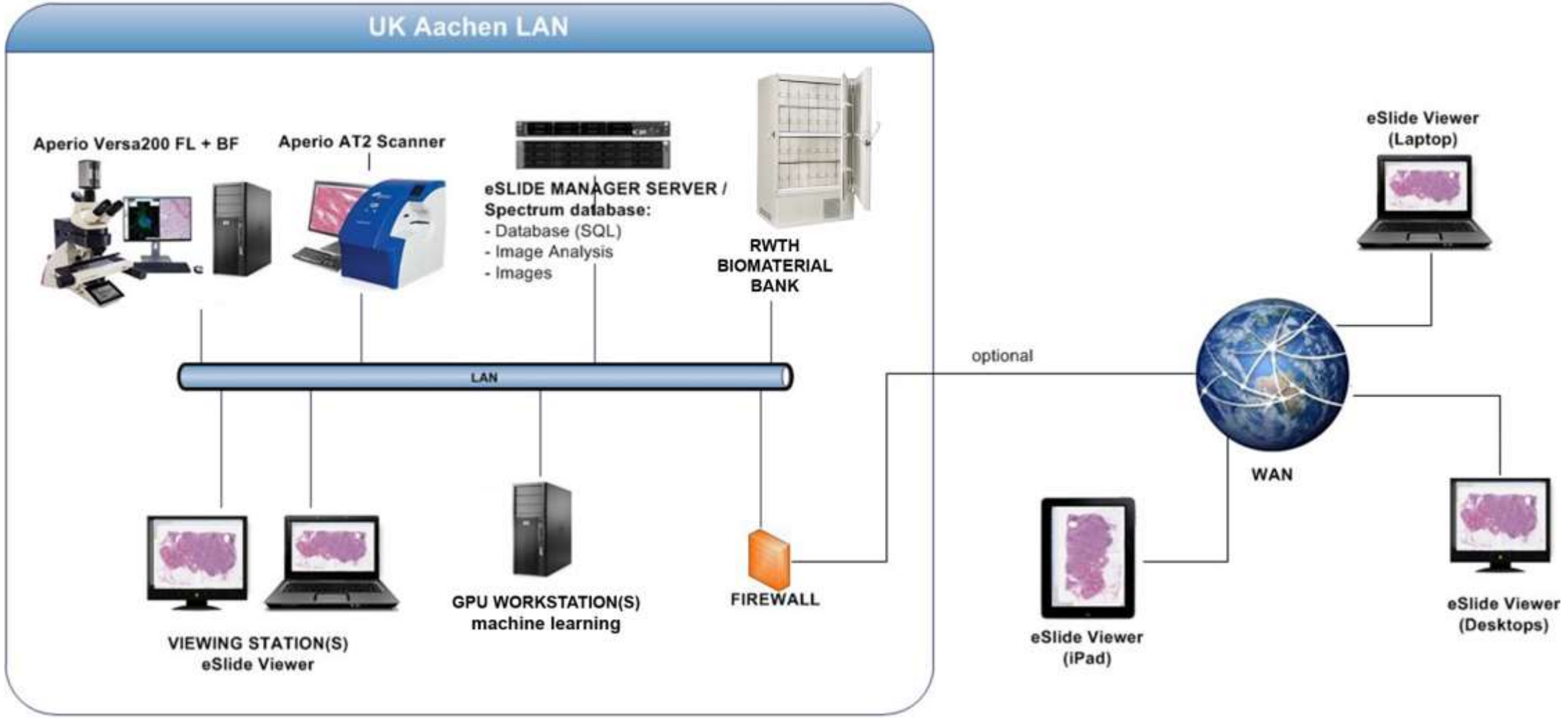


Baues…Boor, Kidney Int 2019

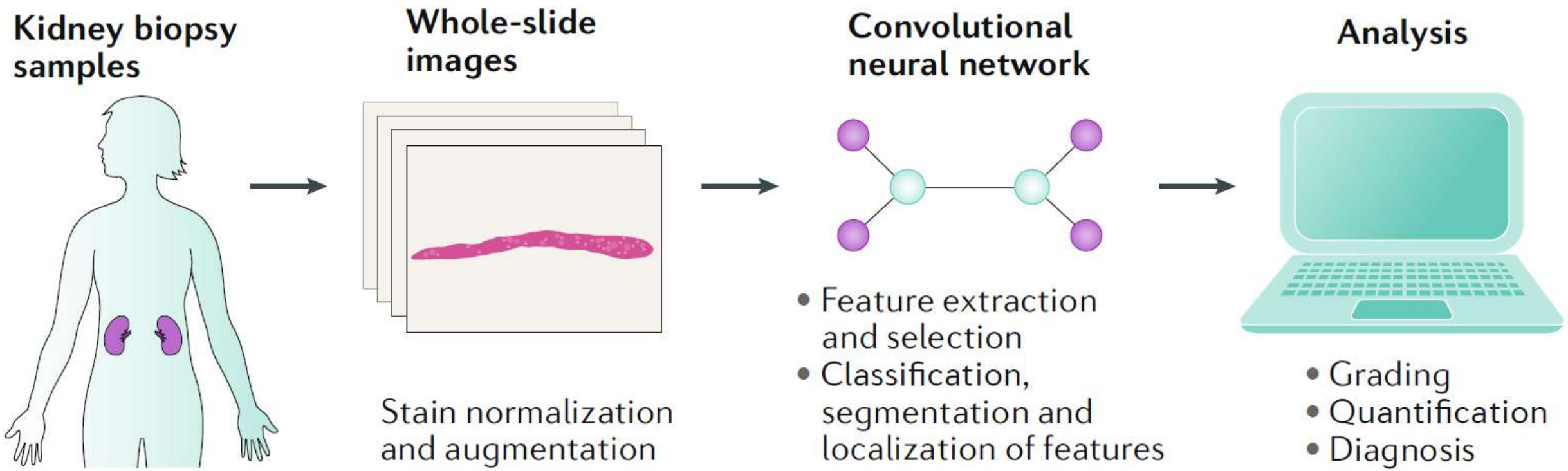
Will pathology be needed with all the non-invasive diagnostic??

Yes – perhaps more than ever…

Digital & Computational Pathology

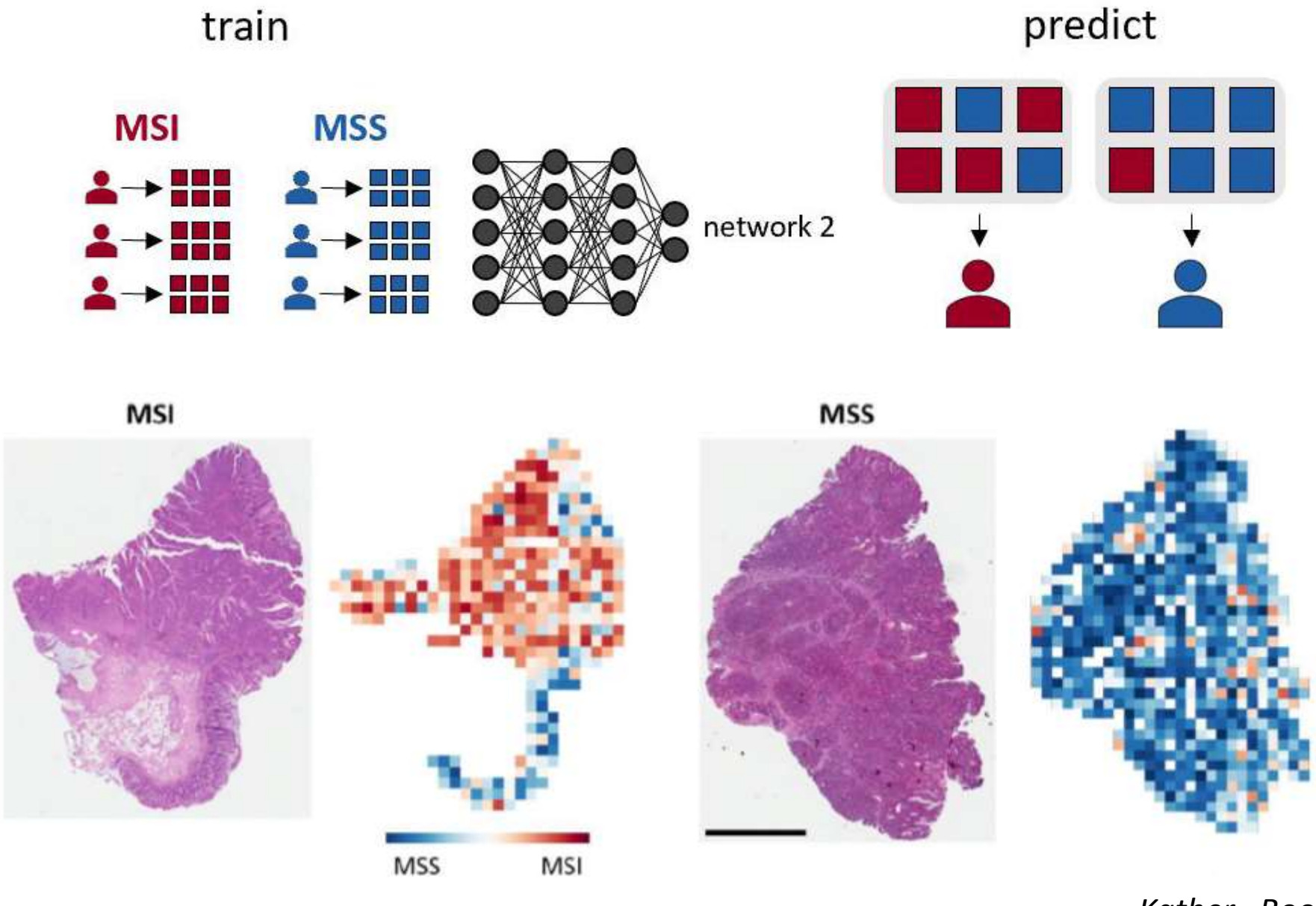


Digital Pathology – augmented by deep learning



Boor Nat Rev Nephrol 2019

Digital Pathology – augmented by deep learning



Kather…Boor et al., Nat Med 2019

Conclusions

Acute Kidney Injury

- common & relevant disease
- pathophysiology mainly from animal models (relevance?)
- limited data from human kidney tissue
- hallmark - tubular injury (variable degree)
- various other processes involved (microvascular dysfunction…)
- non-invasive & disease process-specific biomarkers needed

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