



**Università
di Brescia**

Dipartimento di Scienze Cliniche e Sperimentali

Dottorato di Ricerca in
«Intelligenza Artificiale in Medicina e Innovazione nella Ricerca
clinica e metodologica»

Coordinatore: Prof. Domenico Russo

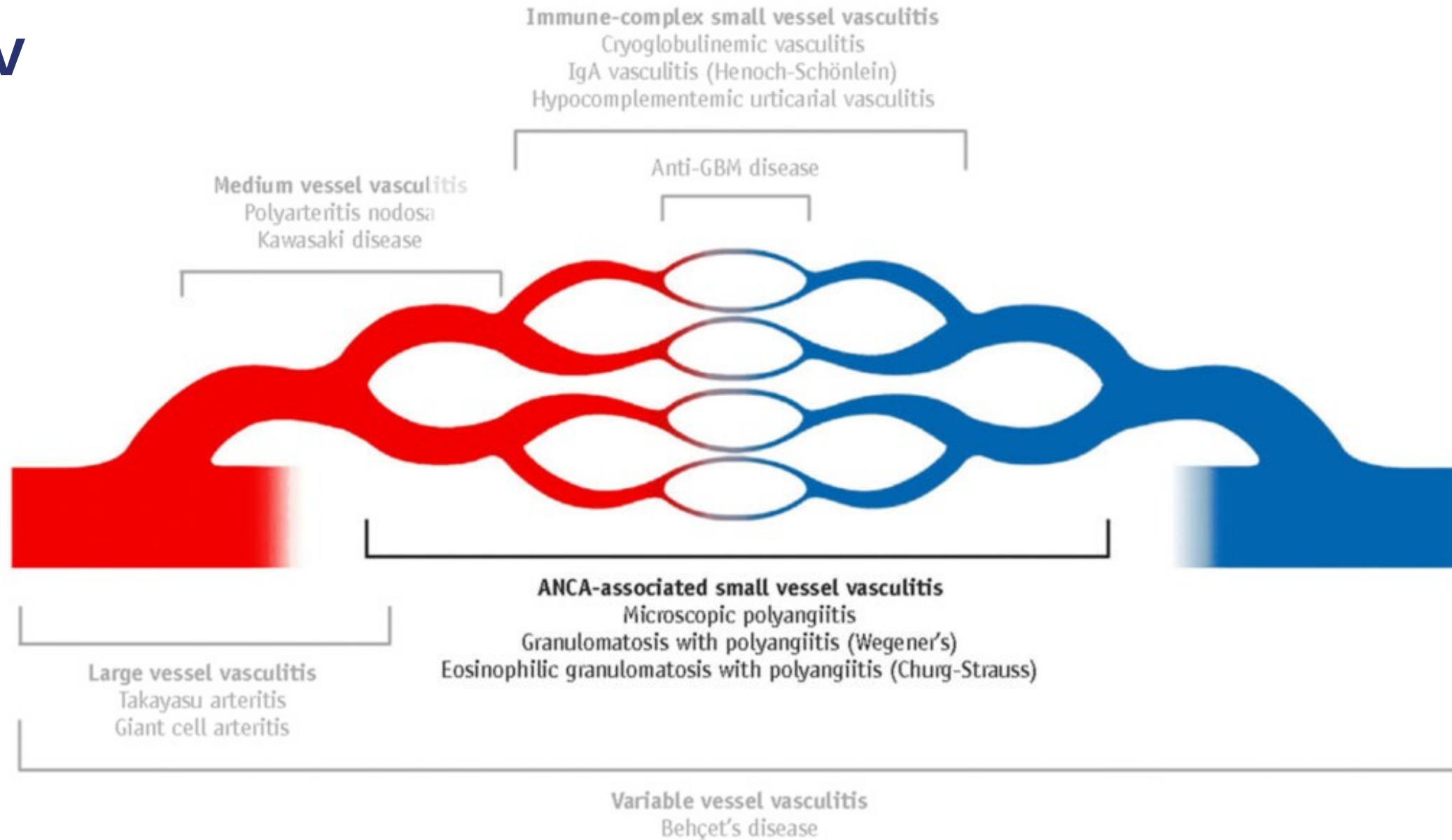
Personalizing treatment in ANCA-associated vasculitis using digital pathology

Dr. Tedesco Martina

CICLO XLI

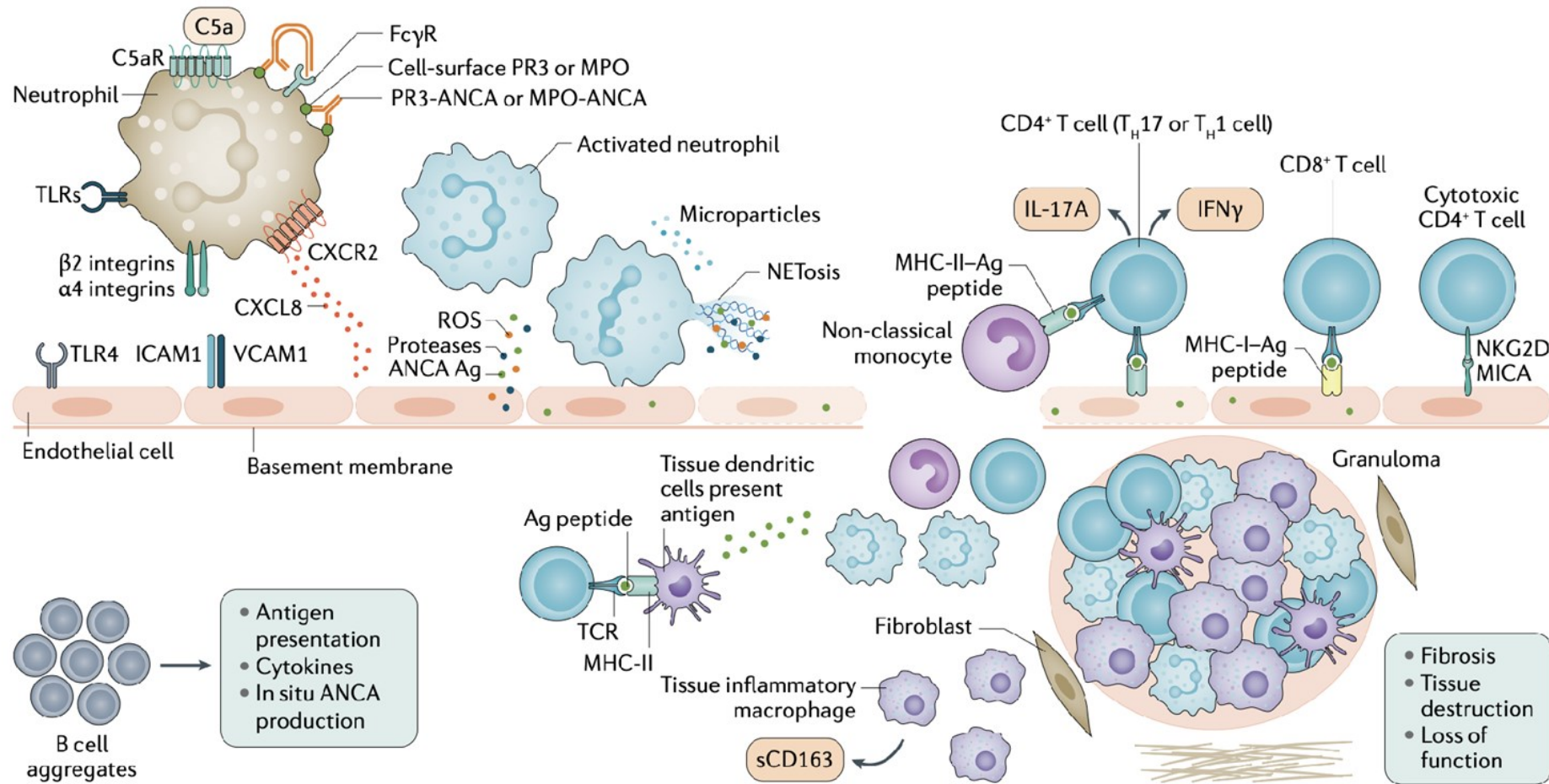
Supervisor: Prof. Federico Alberici

AAV



Adapted from Jennette C et al, Clin Exp Neph (2013)

AAV pathogenesis



AAV

Clinical features

a Granulomatosis with polyangiitis

Central nervous system

Headache, stroke, intracranial haemorrhage (0%–18%)

Heart

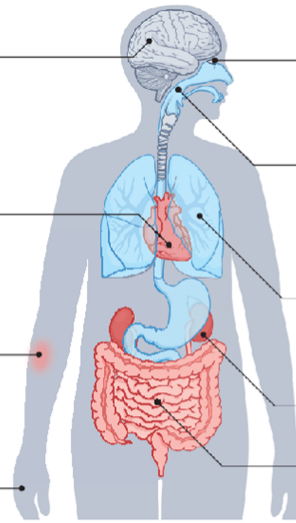
Pericarditis, pericardial effusion, cardiomyopathy, coronary artery disease, heart failure (2%–15%)

Skin

Palpable purpura, livedo reticularis (10%–50%)

Peripheral nervous system

Vasculitic neuropathy, mononeuritis multiplex (14%–40%)



Eyes

Episcleritis, uveitis, optic neuropathy, nerve palsy, retinal vasculitis (1%–9%)

Ear, nose, throat

Rhinosinusitis, chronic otitis media, sensorineural hearing loss, subglottic stenosis, saddle nose deformity after rhinosinusitis (75%–99%)

Lungs

Nodules, cavities and pulmonary infiltrates: alveolar haemorrhage and pleurisy (62%–94%)

Kidneys

Acute kidney injury with pauci-immune necrotizing glomerulonephritis (38%–85%)

Gastrointestinal tract:

Abdominal pain, bleeding, diarrhoea, pancreatitis (0%–7%)

Limited disease
(often ANCA-negative)

- Necrotizing granulomatous inflammation usually involves the upper and lower respiratory tract
- Necrotizing vasculitis predominantly affects small to medium vessels
- Necrotizing glomerulonephritis is common

b Microscopic polyangiitis

Central nervous system

Headache, stroke, intracranial haemorrhage (0%–18%)

Heart

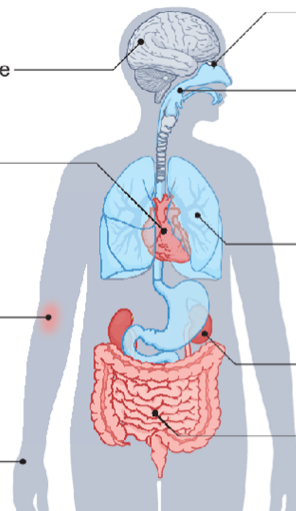
Pericarditis, pericardial effusion, cardiomyopathy, coronary artery disease, heart failure (2%–15%)

Skin

Palpable purpura, livedo reticularis, nodules, urticarial lesions (30%–60%)

Peripheral nervous system

Vasculitic neuropathy, mononeuritis multiplex (14%–40%)



Eyes

Episcleritis, uveitis, optic neuropathy, nerve palsy, retinal vasculitis (1%–9%)

Ear, nose, throat

Non-granulomatous and non-erosive sinus inflammation, sensorineural hearing loss (9%–30%)

Lungs

Diffuse alveolar haemorrhage, interstitial pneumonitis or pulmonary fibrosis (25%–66%)

Kidneys

Acute kidney injury with pauci-immune necrotizing glomerulonephritis (75%–100%)

Gastrointestinal tract

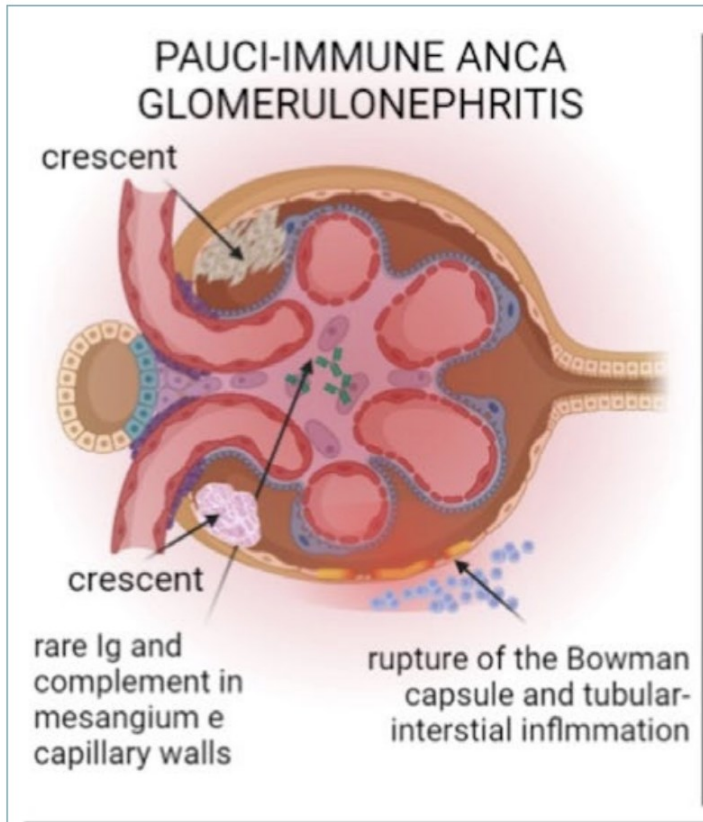
Abdominal pain, bleeding, diarrhoea, abnormal liver tests, cholecystitis, appendicitis (2%–56%)

- Necrotizing vasculitis predominantly affects small vessels (capillaries, venules or arterioles)
- Necrotizing glomerulonephritis is very common
- Pulmonary capillaritis is common

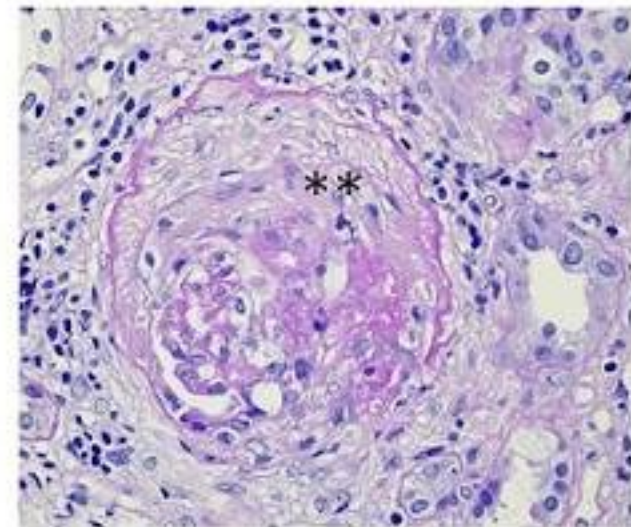
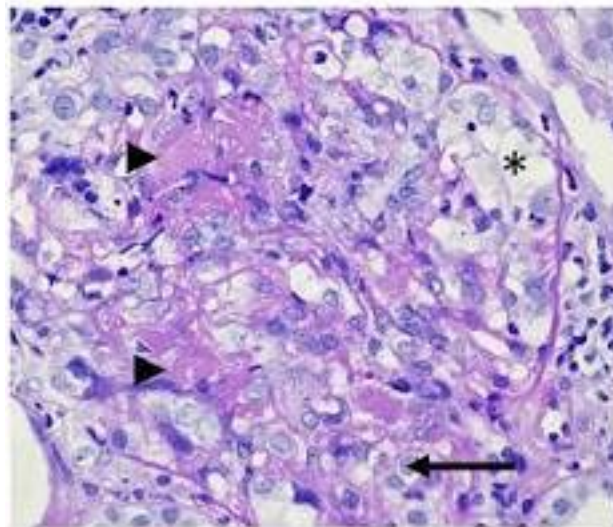
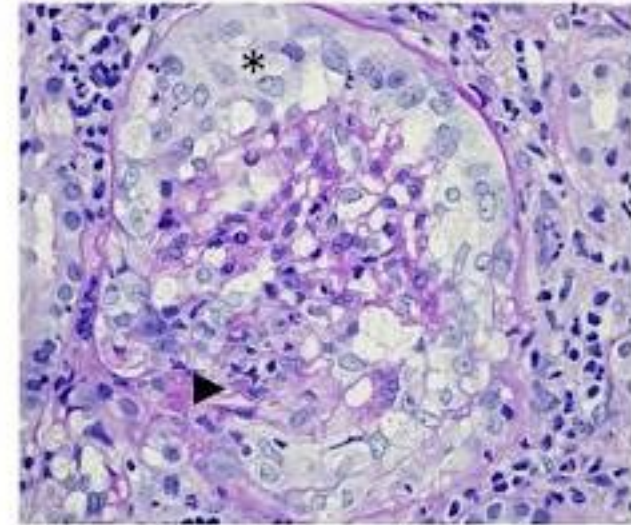
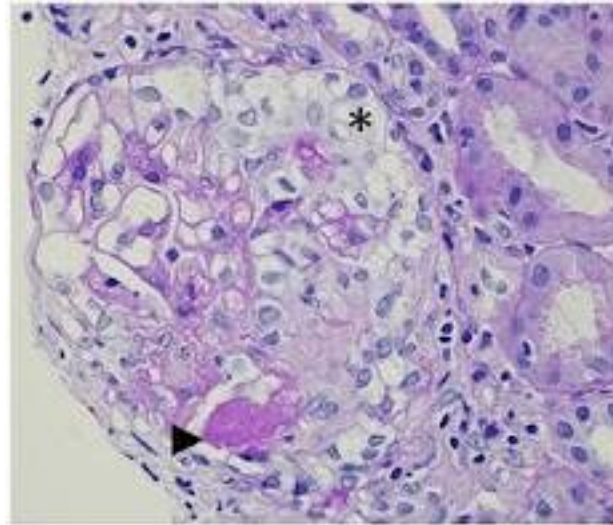
• Jennette et al, CJASN

Kitching R et al, Nat Dis Primers (2020)

Renal histology in AAV light microscopy

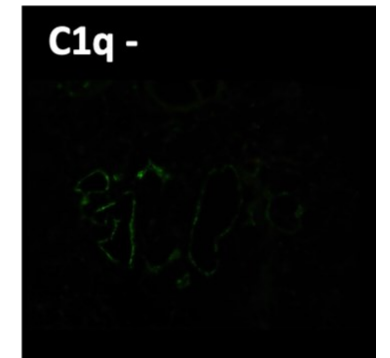
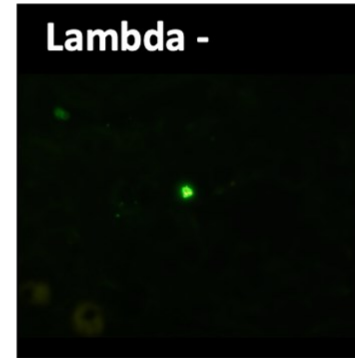
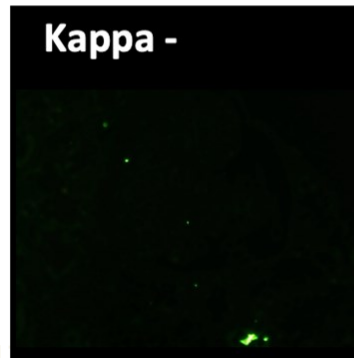
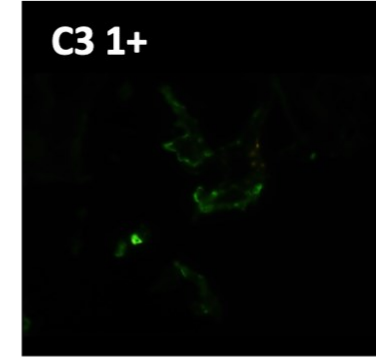
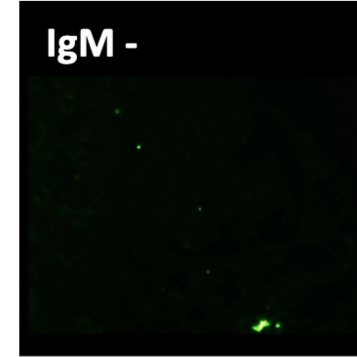
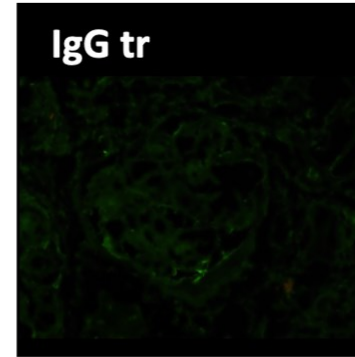
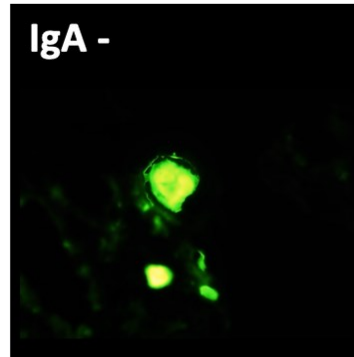
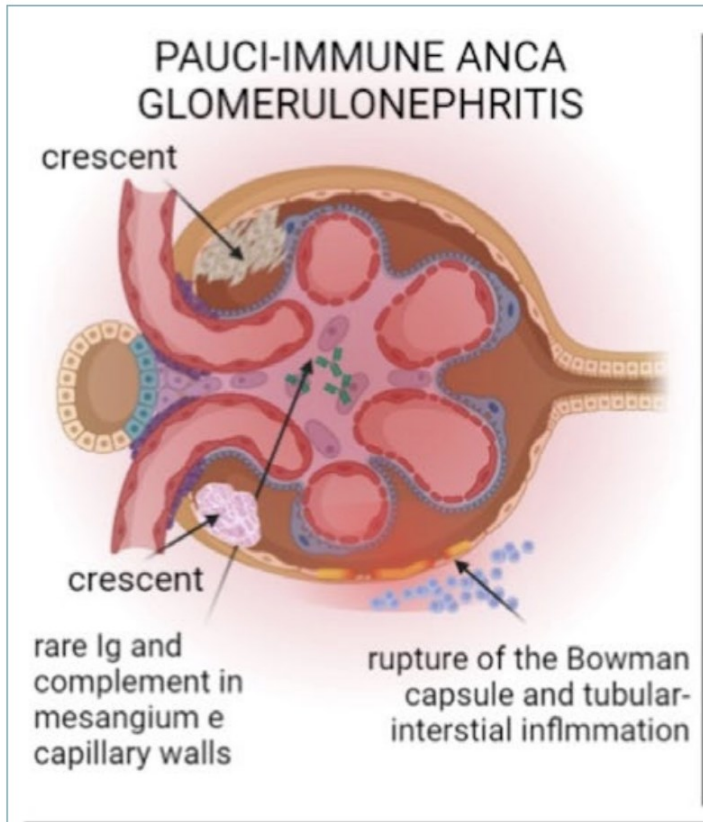


2017

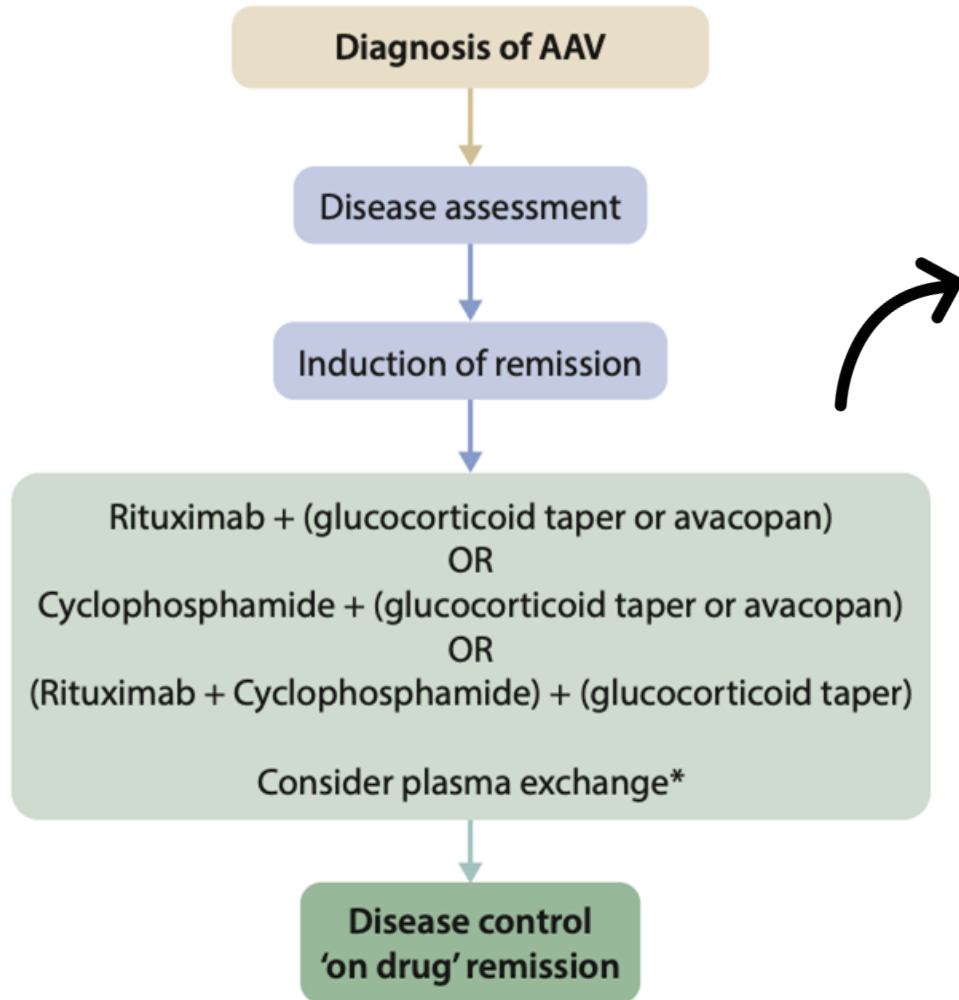


Renal histology in AAV

indirect immunofluorescence



AAV treatment – induction phase

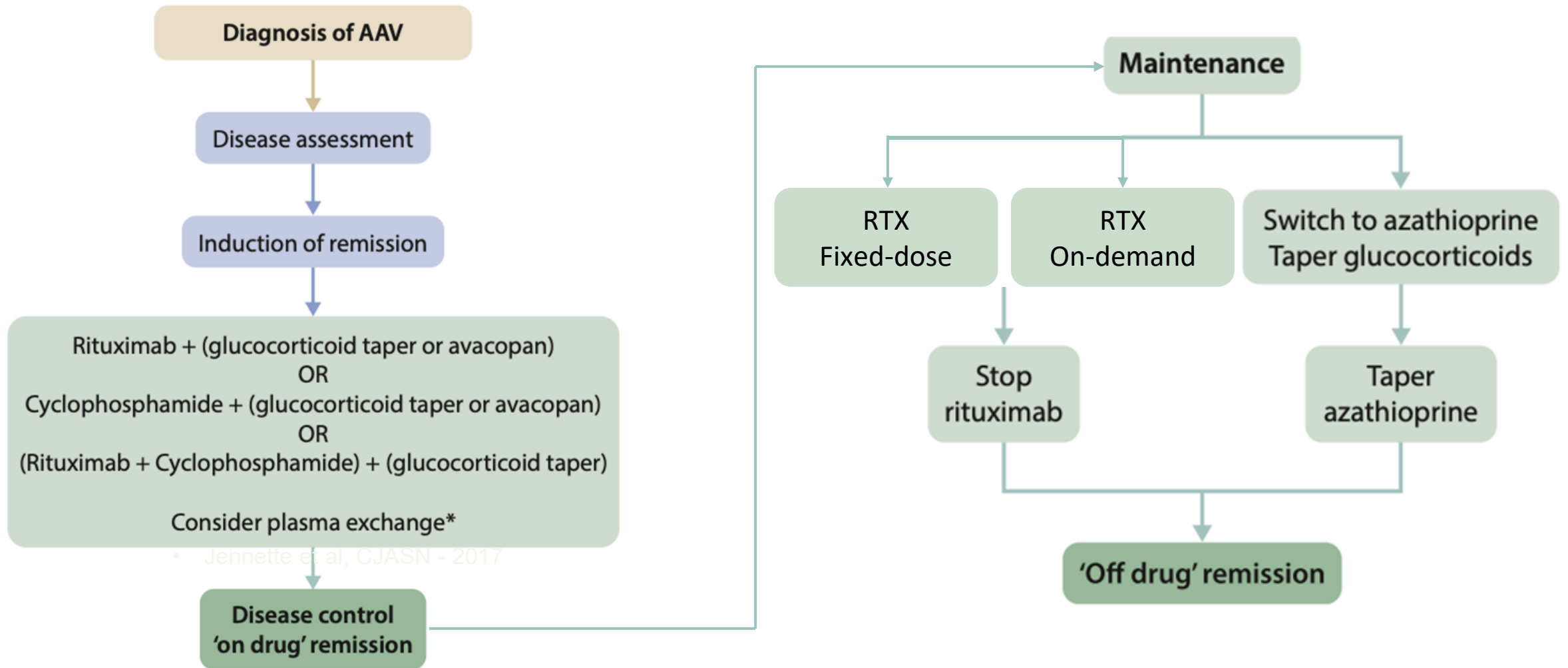


Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Pre-menopausal women and men concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3–ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 µmol/l])*

Figure 7 | Factors for consideration when choosing between rituximab and cyclophosphamide for induction therapy of AAV.

*A combination of 2 intravenous pulses of cyclophosphamide with rituximab can be considered. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; GN, glomerulonephritis; PR3, proteinase 3; SCr, serum creatinine.

AAV treatment – maintenance phase



Adapted from Floege J et al, KI (2024)

Renal histology predicts kidney survival in AAV

Casal Moura M et al, Nat Rev Rheum (2025)

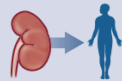
End-stage kidney disease incidence

Overall 175/848 (21%)



Dialysis

n = 140 (80%)



Transplant

n = 35 (20%)

Factors associated with end-stage kidney disease



Age > 65 years

1.68

(1.18–2.41)



eGFR

0.97

(0.93–0.99)



Haemoglobin

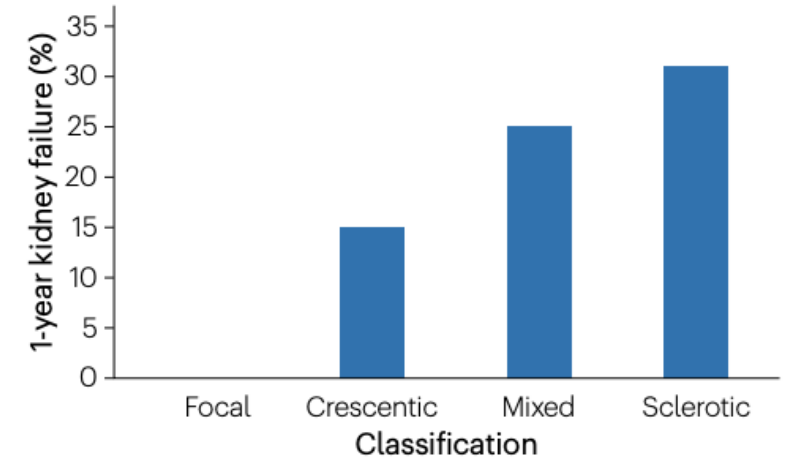
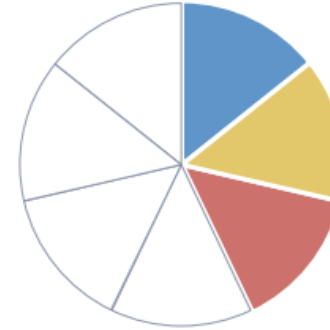
0.88

(0.78–0.98)

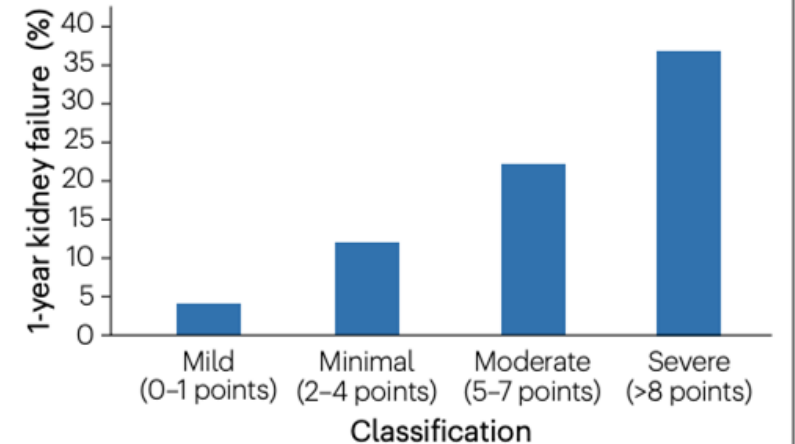
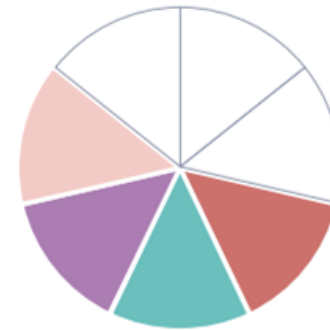
Hazard ratio
(95% CI)

Sanchez-Alamo B et al, NDT (2024)

Berden classification

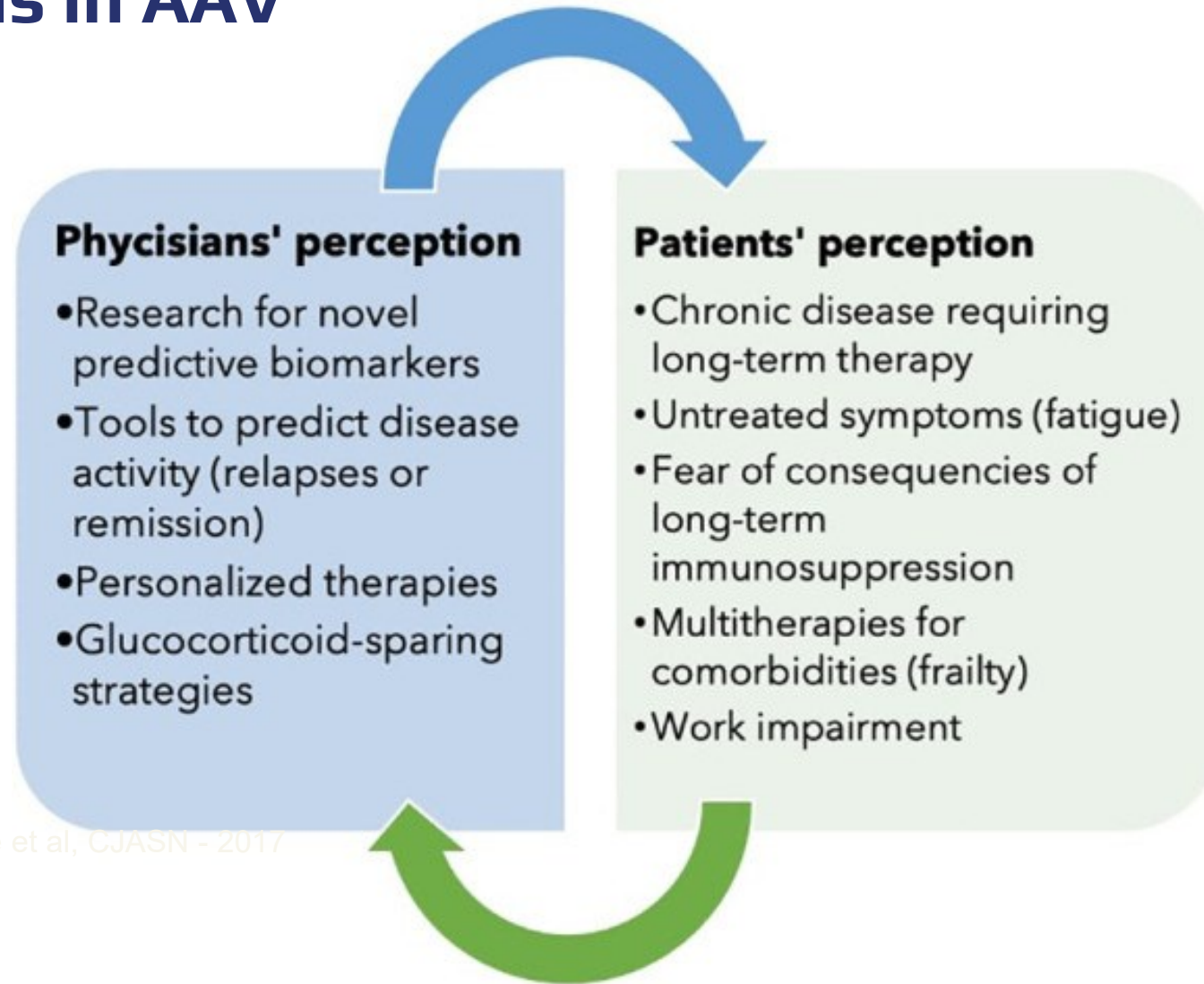


MCCS



- Normal glomeruli
- Glomerular crescents
- Glomerular sclerosis
- Serum creatinine
- Interstitial fibrosis
- Tubular atrophy
- Arteriosclerosis
- Absent compartments

Unmet needs in AAV



• Jennette et al, CJASN - 2017

Kidney Outcomes in ANCA-Glomerulonephritis According to Induction Immunosuppression & Histopathology



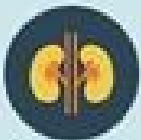
Multicentric
retrospective



Biopsy proven ANCA
glomerulonephritis



n=304



Median eGFR
20 ml/min/1.73m²

Berden classification



Mixed	33.2%
Crescentic	31.6%
Focal	23.3%
Sclerotic	11.8%



Induction Treatment

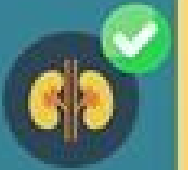


Cyclo	59%
Rituximab	17%
Cyclo + ritux	24%

Kidney outcomes

eGFR Recovery
at 6 months

50%

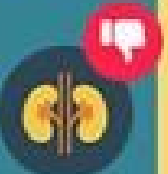


Crescentic group
Ritux vs Cyclo

OR 0.23 (0.05-0.98)

Kidney Failure
median follow-up 42 months

19.4 %



Crescentic group
Ritux vs Cyclo

HR 3.42(1.03-11.35)

KI REPORTS

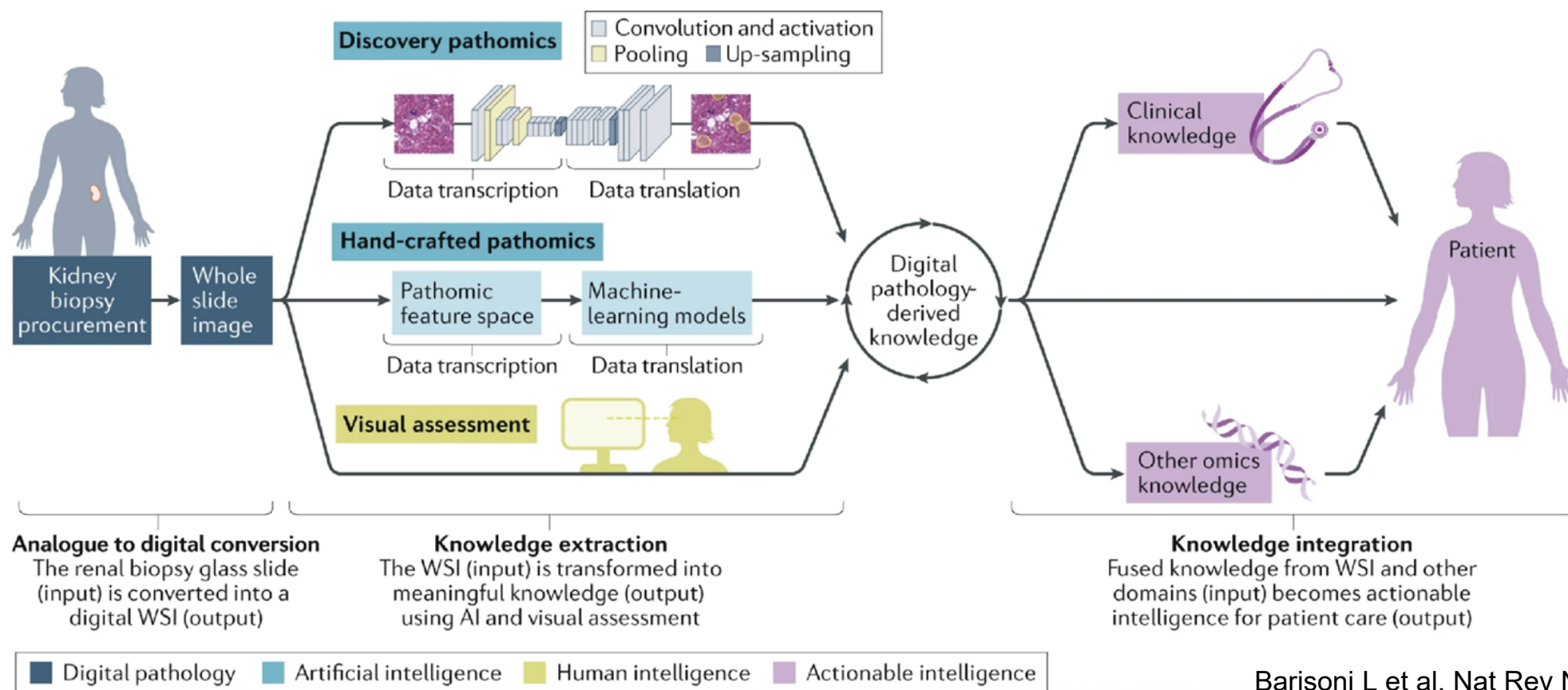
Kidney International Reports®

Conclusion: Patients with crescentic class ANCA-glomerulonephritis receiving RTX monotherapy may have worse kidney outcomes than those treated with CYC-based regimens.

Uzzo M et al, 2026. VA by Pallavi Prasad, MD, DNB(nephrology)

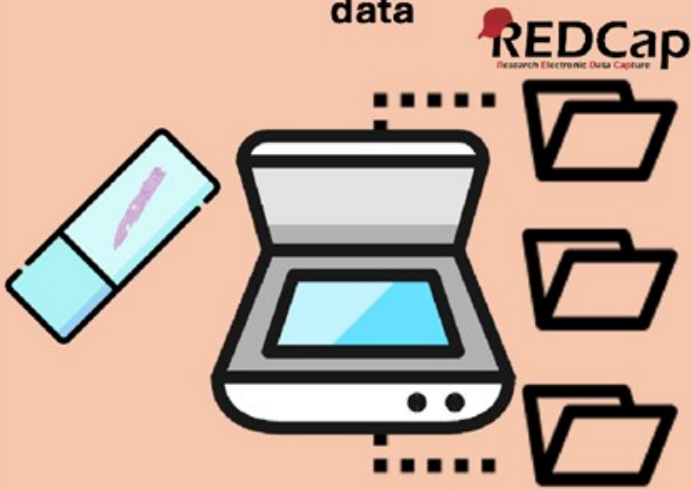
Study goal

To identify histopathological predictors of efficacy and safety across different induction regimens in patients with AAV and biopsy-proven renal involvement using deep learning

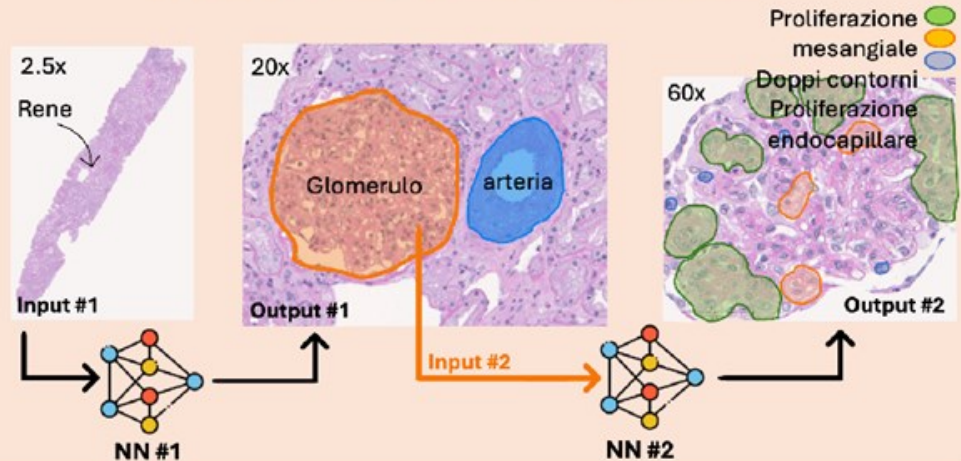


STUDY WORKFLOW

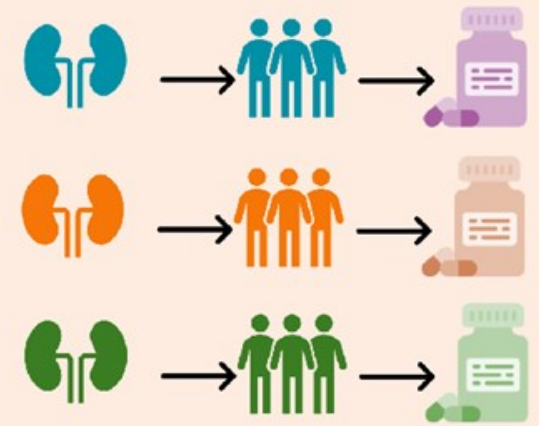
To develop a granular repository of whole-slide digital images and clinical data



To train and validate neural network pipeline to recognize distinct histological features across multiple magnifications

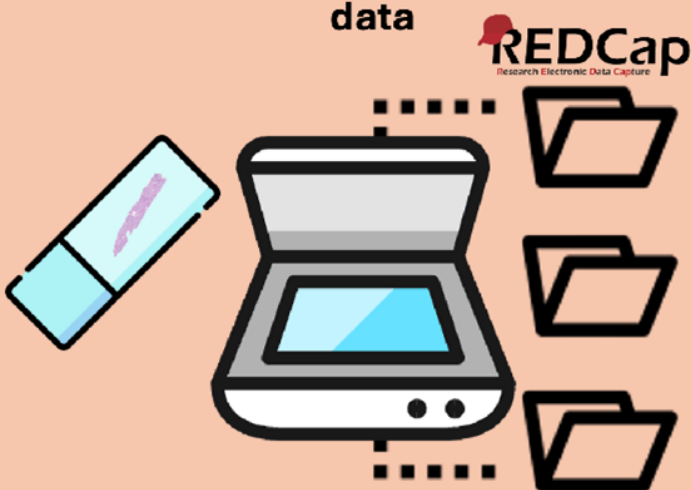


To identify clinical-histological phenotypes and correlate them with response to induction treatment regimens



STUDY DESIGN: Phase I

To develop a granular repository of whole-slide digital images and clinical data



Multicenter (multinational)

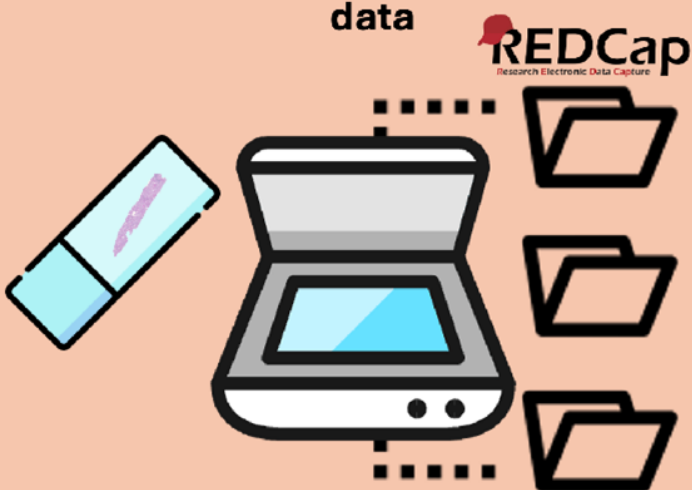
Mixed retrospective-prospective observational study

9 participating centers (+2 on the way)



STUDY DESIGN: Phase I

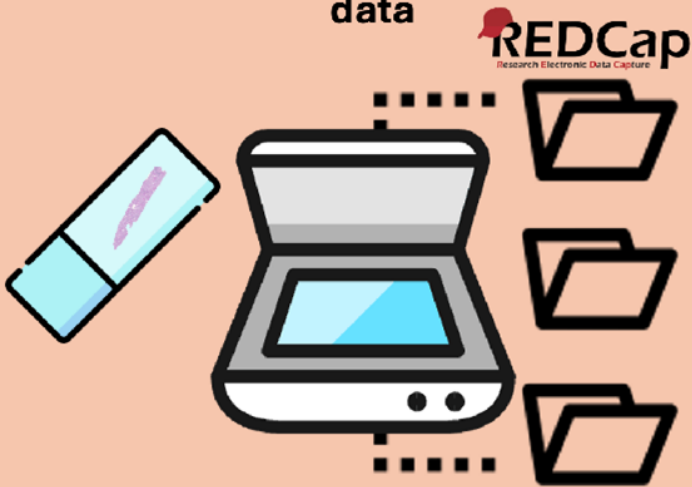
To develop a granular repository of
whole-slide digital images and clinical
data



Age at diagnosis ≥ 18 yo
and
ANCA-positive MPA or
GPA
and
Biopsy-proven AAV-
glomerulonephritis

STUDY DESIGN: Phase I

To develop a granular repository of whole-slide digital images and clinical data



Instrument name	Fields
AAV REDCap Cover	2
Demographic Features And Habits (Baseline)	10
Charlson Comorbidity Index and other comorbidities (baseline)	15
Neoplasia (baseline)	6
Pharmacological exposure (baseline)	2
Family history (baseline)	3
AAV features (baseline)	58
Kidney biopsy (baseline)	37
Lab tests (baseline)	68
Other Biopsies (baseline)	8
Infectious diseases (baseline)	5
Aav Therapy After Diagnosis	198
Aav Escalation Therapy	246
Kidney biopsy (repeat biopsies)	38
Adverse events and Follow-up	21
Hospitalizations (follow-up)	5
Cardiovascular Events (follow-up)	4
Neoplasia (follow-up)	5
Infections (follow-up)	7
Laboratory exams (follow-up) - ALL	39
Laboratory exams (follow-up) - TIMEPOINTS	13
ESKD and CKD (Outcome)	7
Death (Outcome)	5
Notes	1

- Modular structure:

- Relevant clinical data (baseline)
- Labs
- Histological features
- Treatment modules
- Adverse events and outcome

- Validated scores:

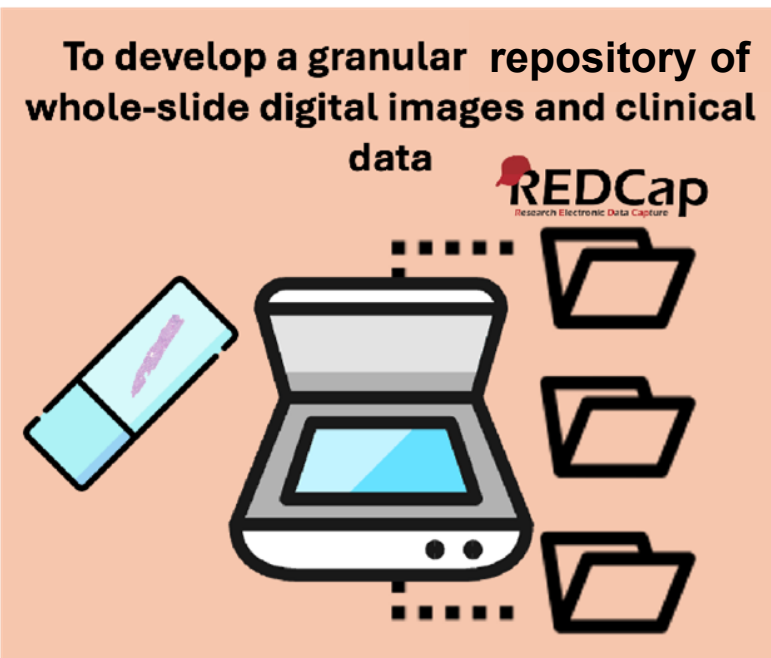
- Charlson comorbidity index
- BVAS v3.0
- Berden classification
- Mayo Clinic chronicity score

- Automated laboratory data capture

- Clear data dictionary

- REDCap built-in features

NEXT STEPS...



- Obtain ethics for other participating centers
- Expand the clinical dataset
- Develop the workflow for WSI scanning

