Nephrogenetics Webinar Series

Grupo de trabalho em Nefrogenética
Sociedade Portuguesa de Nefrologia

Alport Syndrome

11th April 2025: 15-16h (WEST)

Speaker:

Ana Marta Gomes, ULS Gaia.

Moderators:

Claúdia Falcão Reis, ULS Santo António.

Francisco Pereira Gonçalves, Sygehus Sønderjylland.

Scientific Sponsorships

ERKNet The European Rare Kidney Disease Reference Network

Sociedade Portuguesa Nefrologia

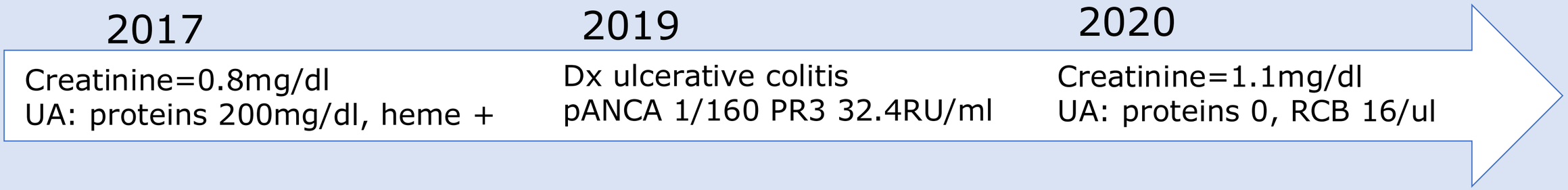
SPGH Sociedade Portuguesa de Genética Humana

SPNP Sociedade Portuguesa de Nefrologia Pediátrica

Clinical Case

Clinical history and laboratory results

- Male, 26 years old, caucasian
- Past medical history:
  - Ulcerative colitis – lost FUP 4 years ago – without R\
  - Anxiety
  - Ex-smoker
- No current medication
- Didn´t know familial history of renal disease



Clinical Case

Clinical history and laboratory results

2017
Creatinine=0.8mg/dl
UA: proteins 200mg/dl, heme +

2019
Dx ulcerative colitis
pANCA 1/160 PR3 32.4UI/ml

2020
Creatinine=1.1mg/dl
UA: proteins 0, RCB 16/ul

- No complaints
- BP=136/67mmHg P=90bpm; BMI= 24.22kg/m^2; CPA:normal; ∅ edema

- Hb= 14.8g/dl, creatinine= 1.4mg/dl, urea= 63mg/dl
- UA: proteins 100mg/dl, RBC 80/ul

  Uprot/creat= **2**g/g, RBC= **15-30**/hpf, Leuc= 5-15/hpf
- 24hurine: proteins= **5.4**g
- Renal US: RK 98mm (Some scar indentations) LK 111mm preservation of cortical thickness but attenuation of the PS differentiation. No dilation of the excretory systems

- VSR 12mm
- P-ANCA 1/80 PR3=40.5RU/ml
- Ig's, ANA, anti-GBM, complement:normal/negative

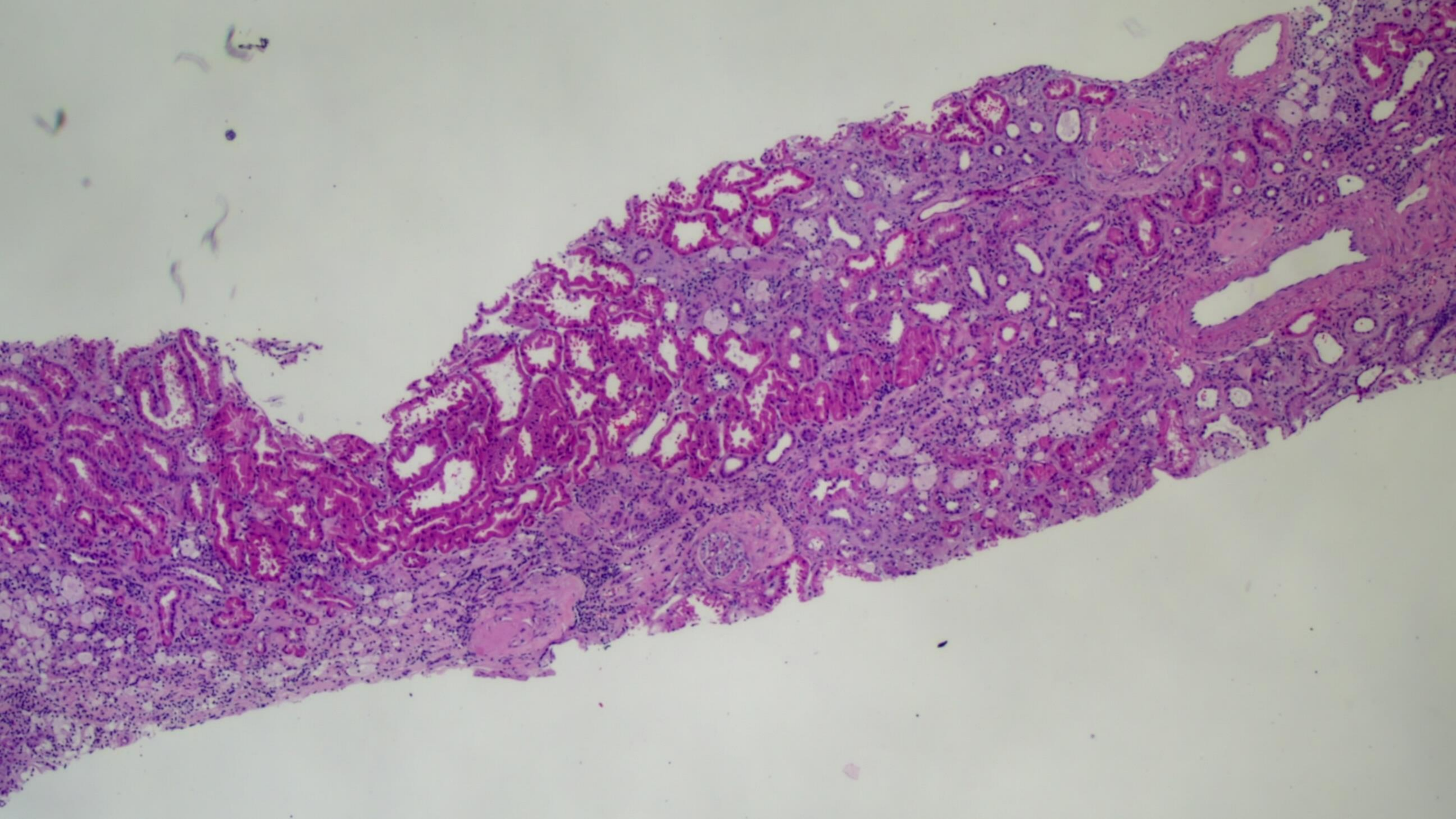
Clinical Case

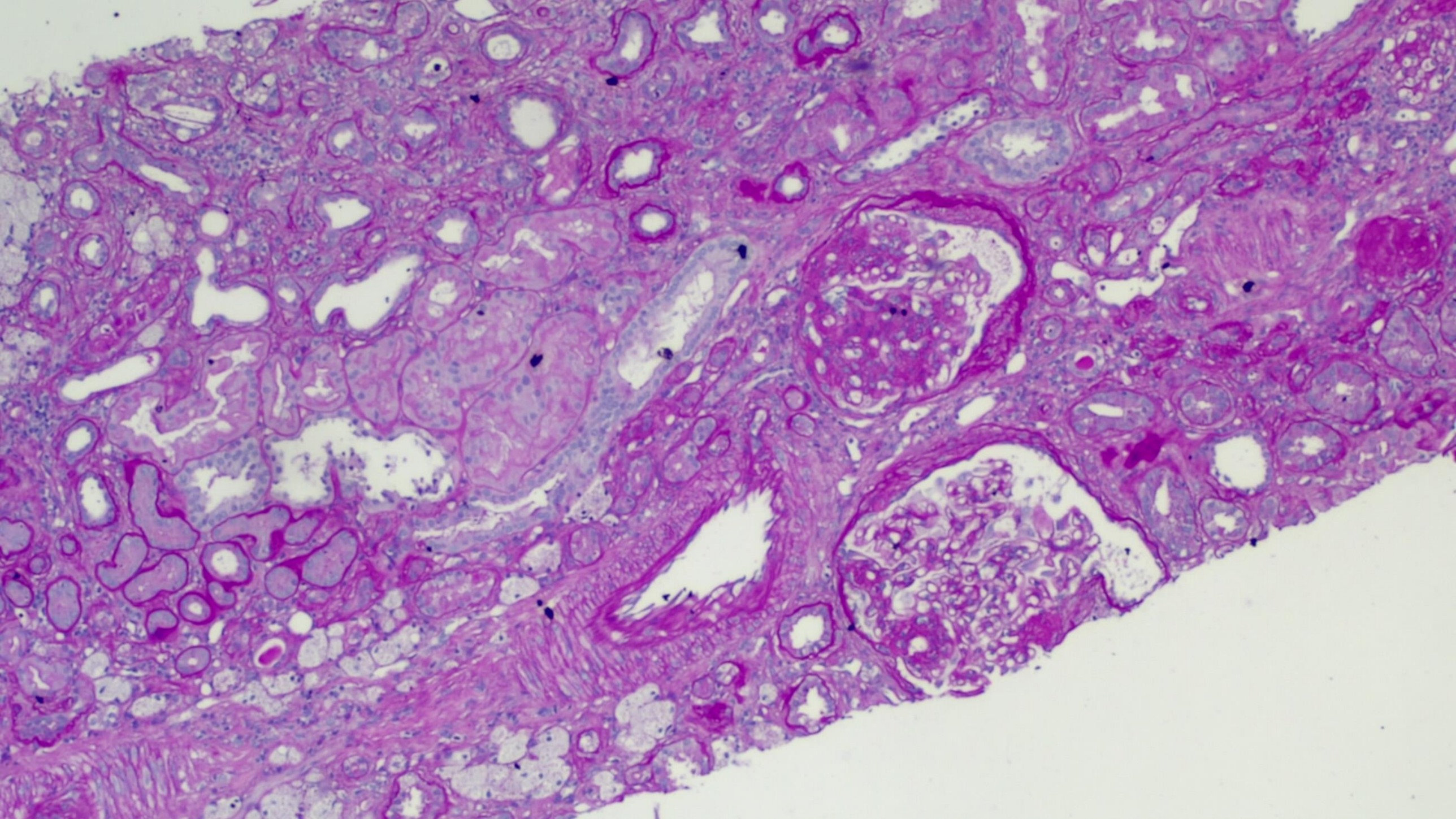
Diferential diagnosis

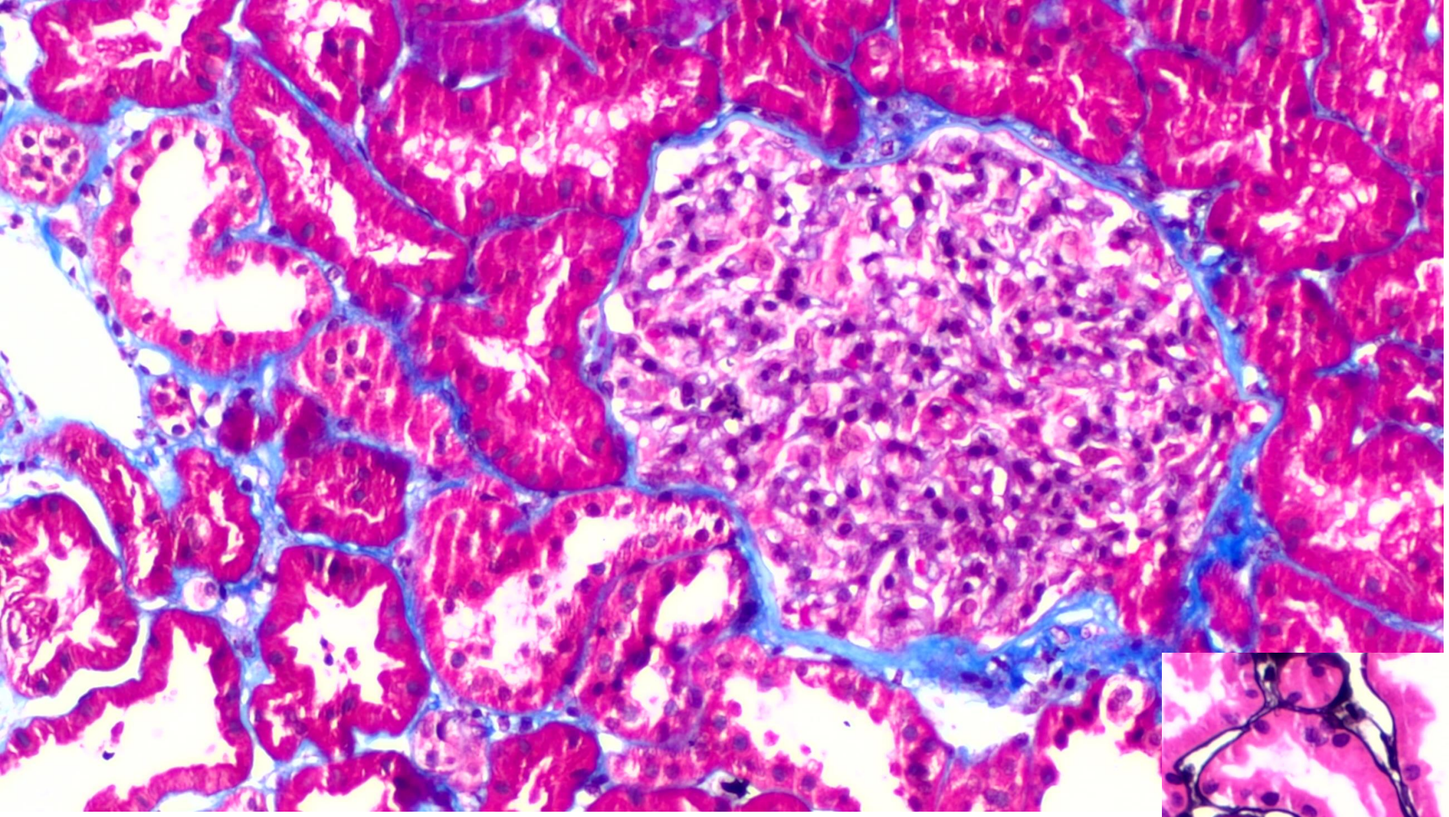
IgA Nephropathy?

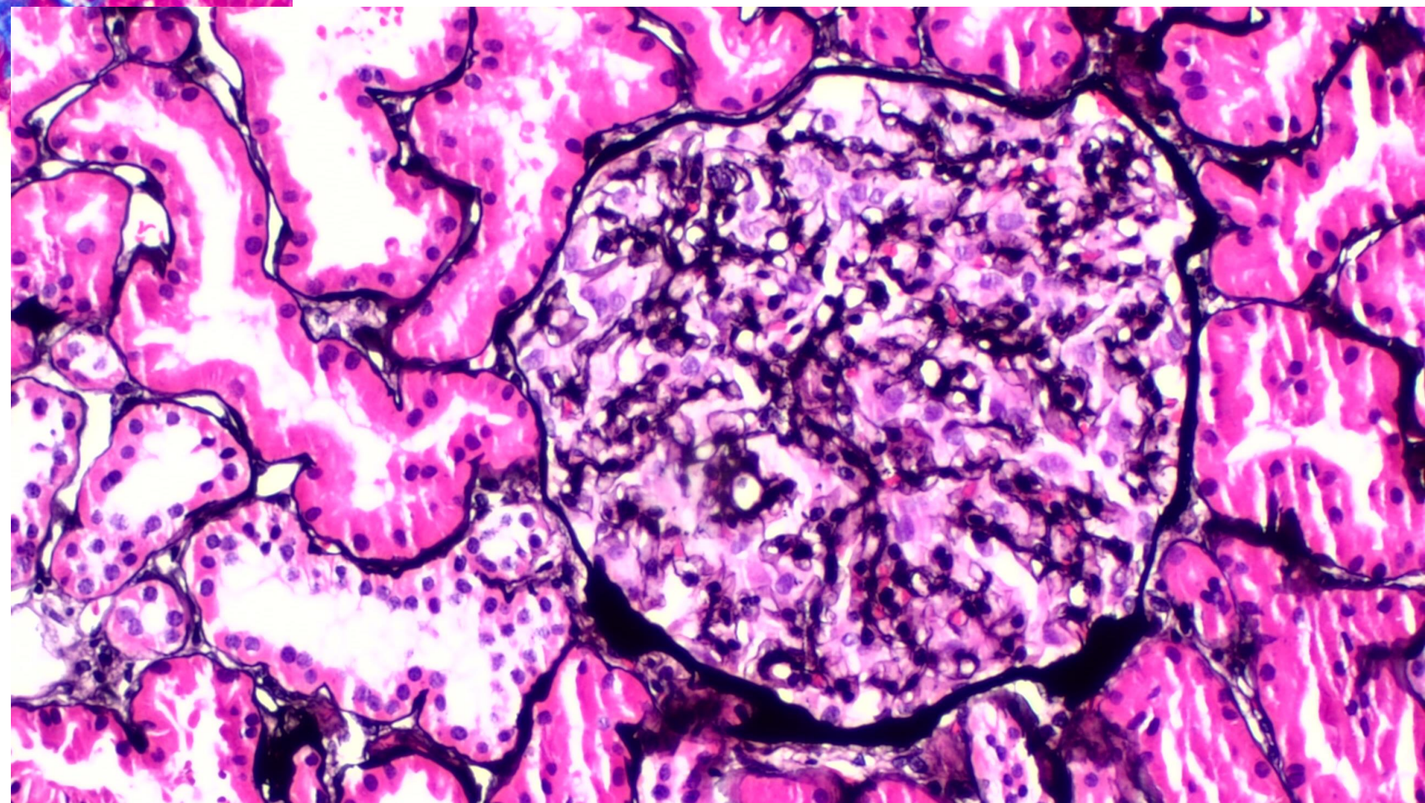
ANCA vasculitis ?

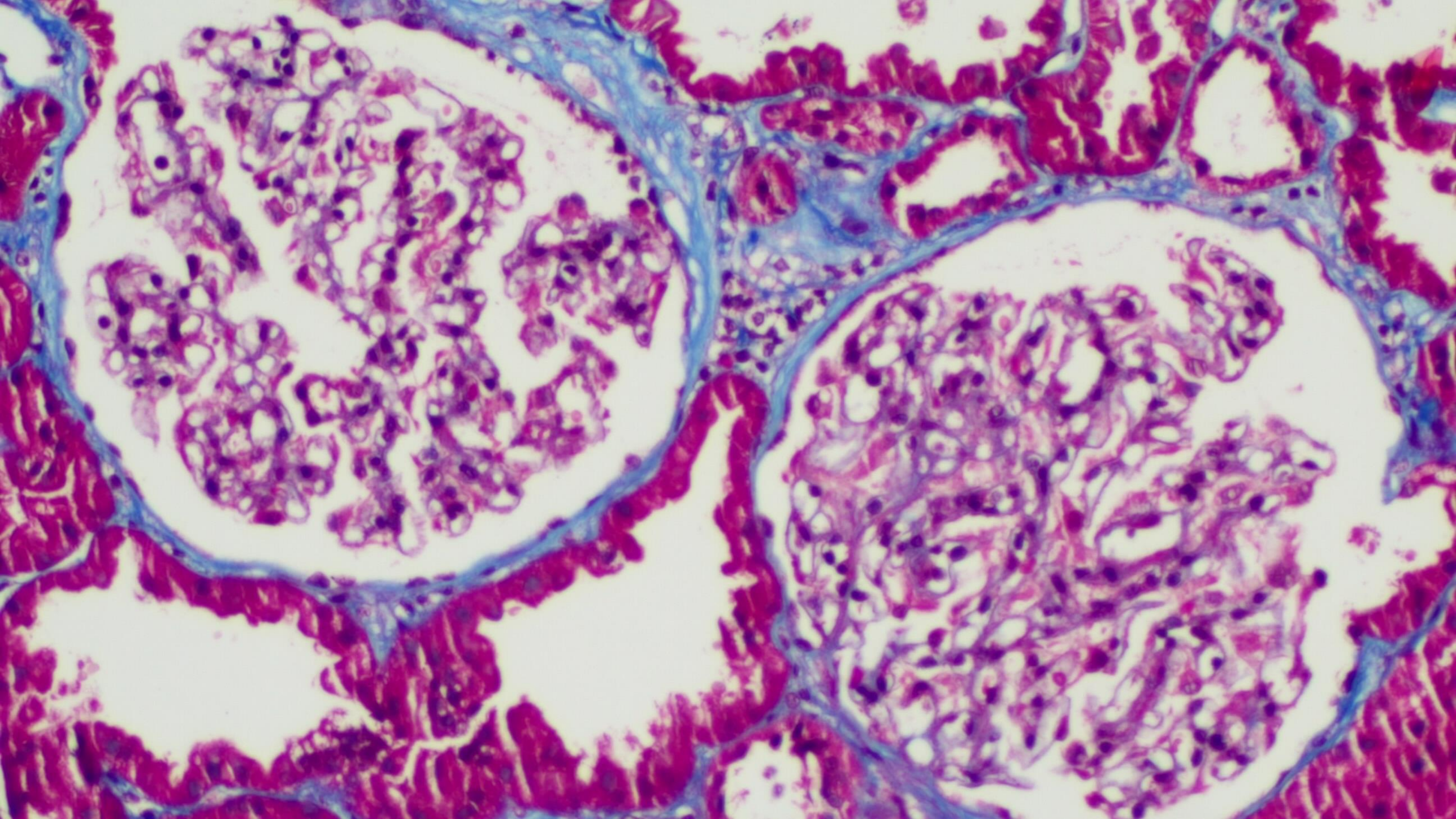
FSGS ? Genetics? UnK?

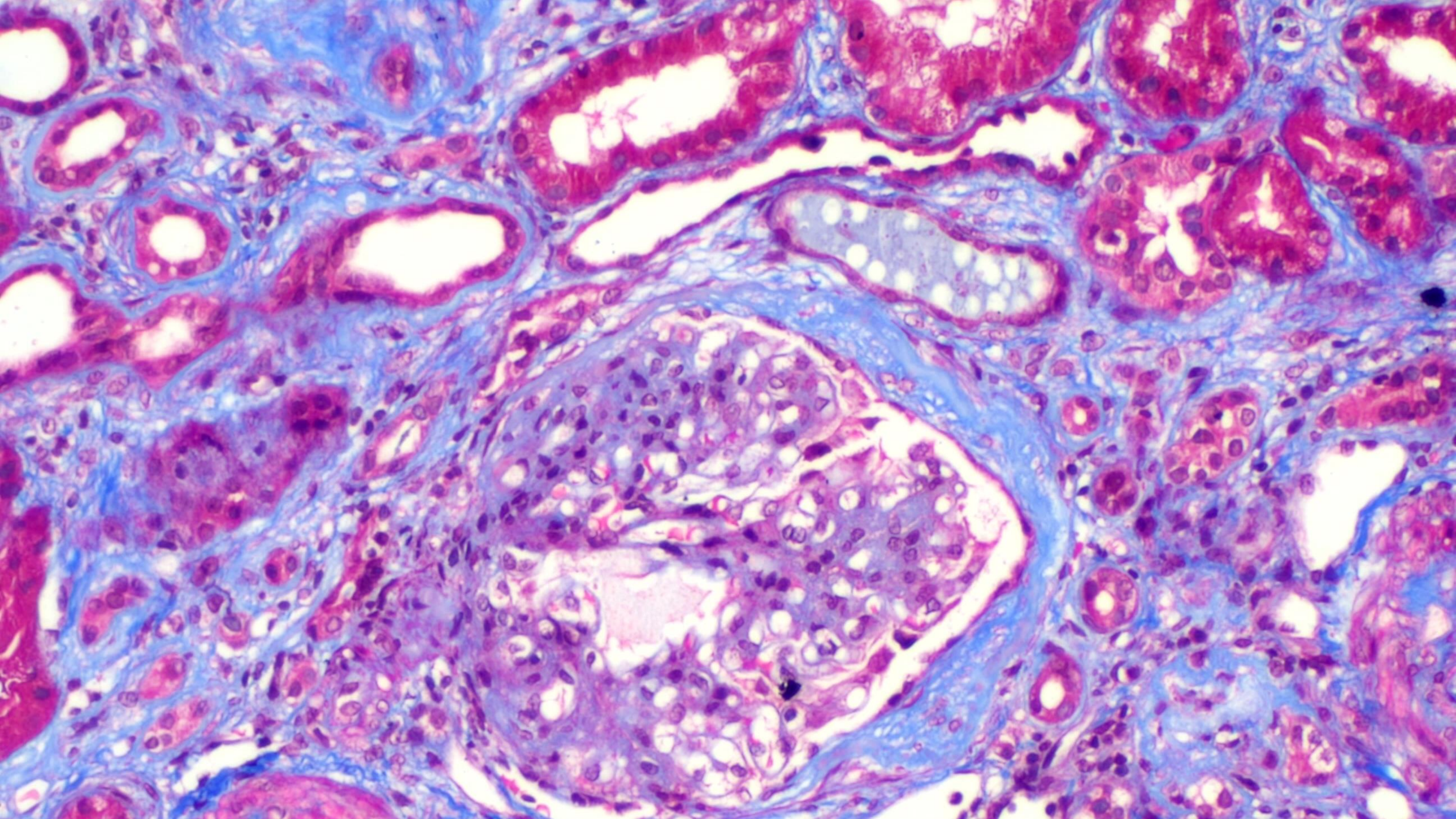


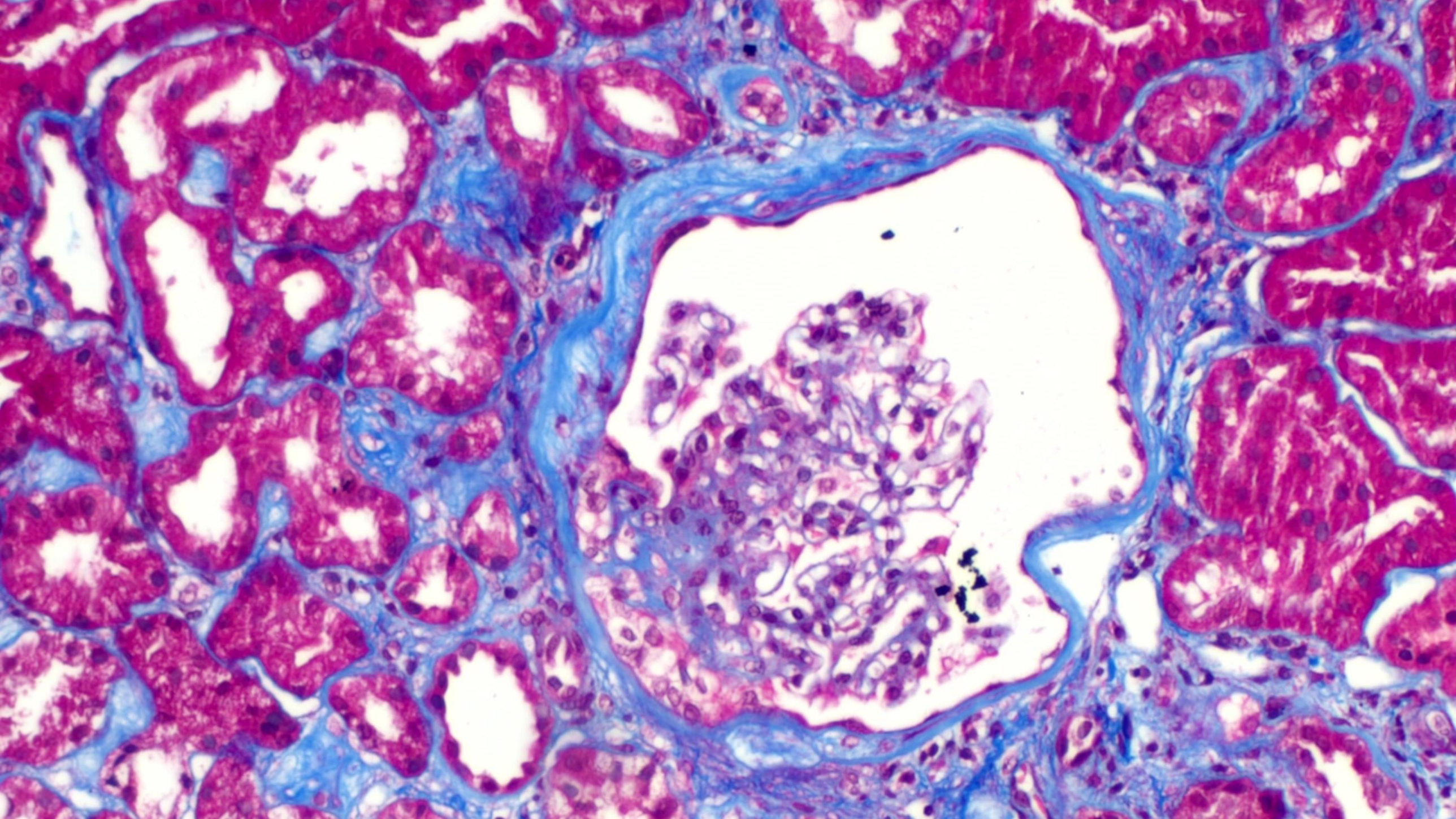


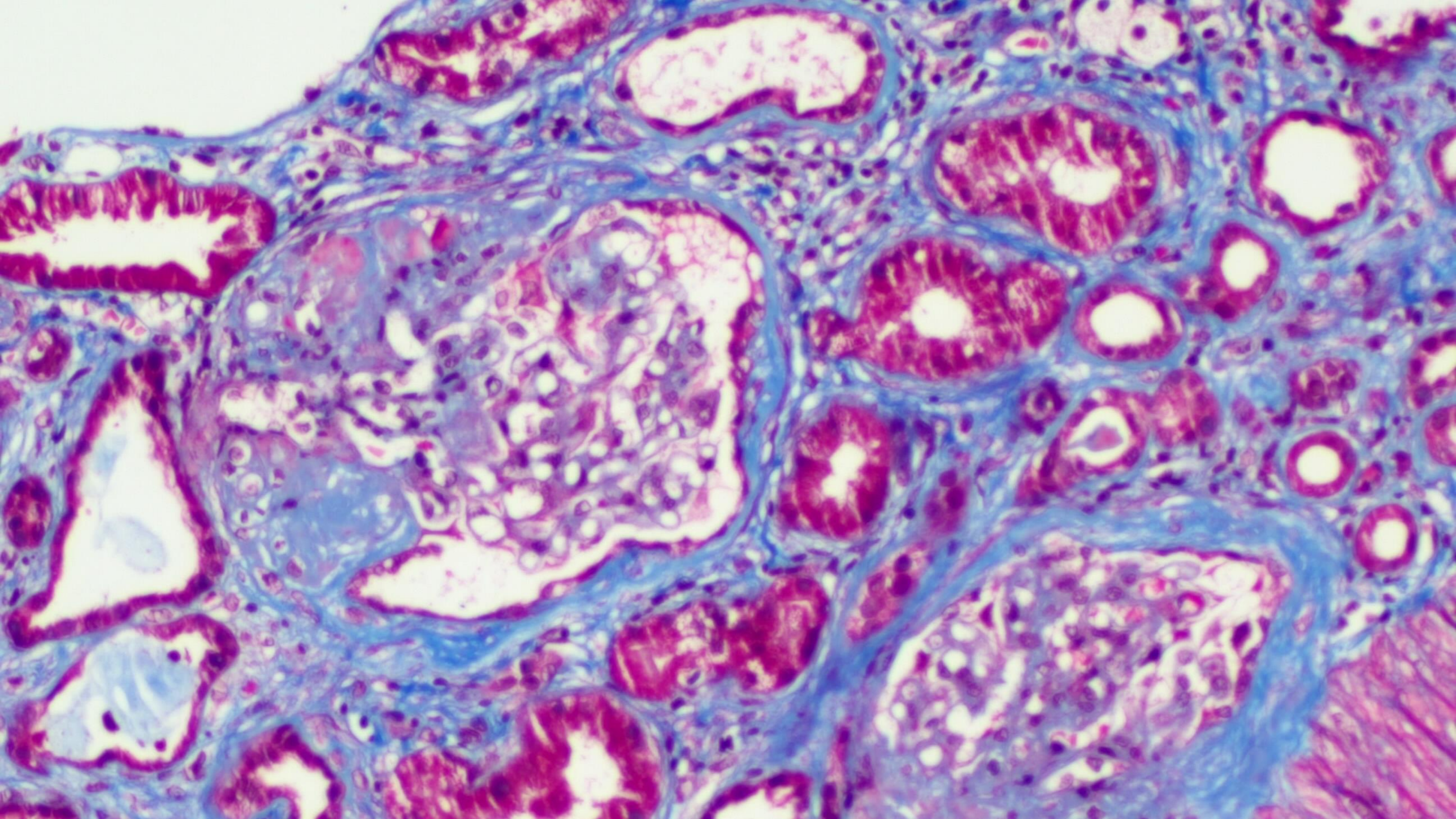


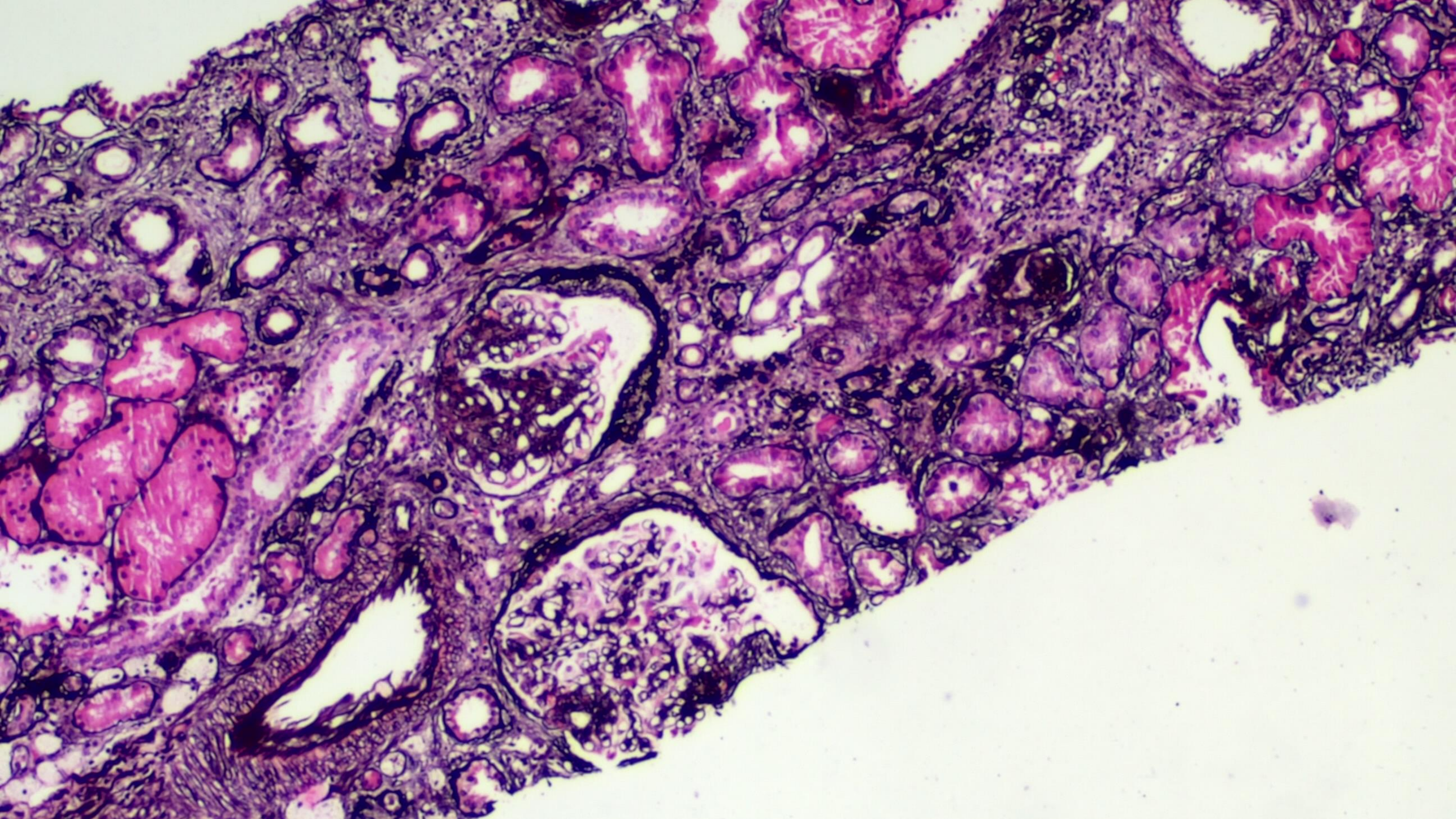


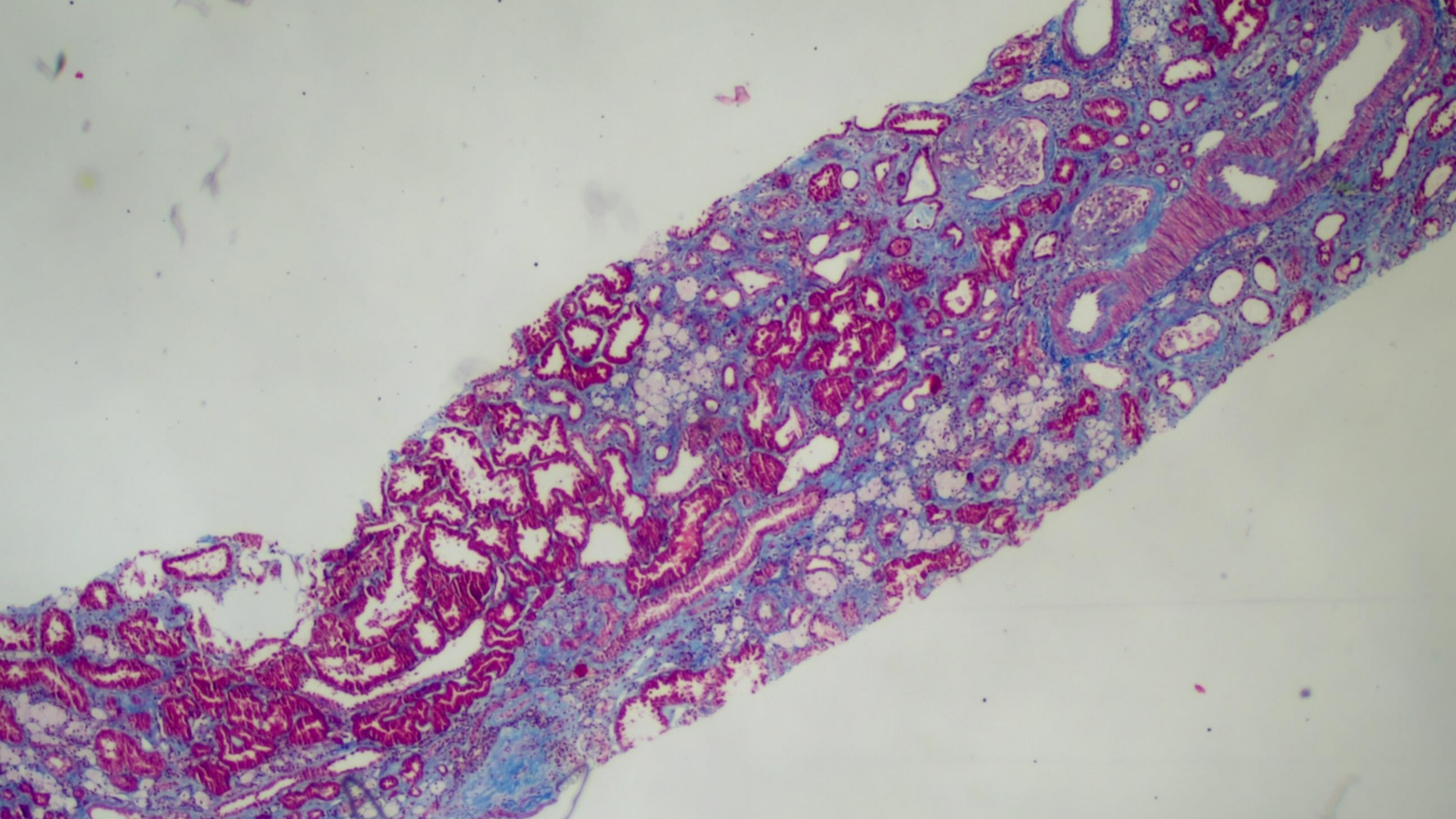


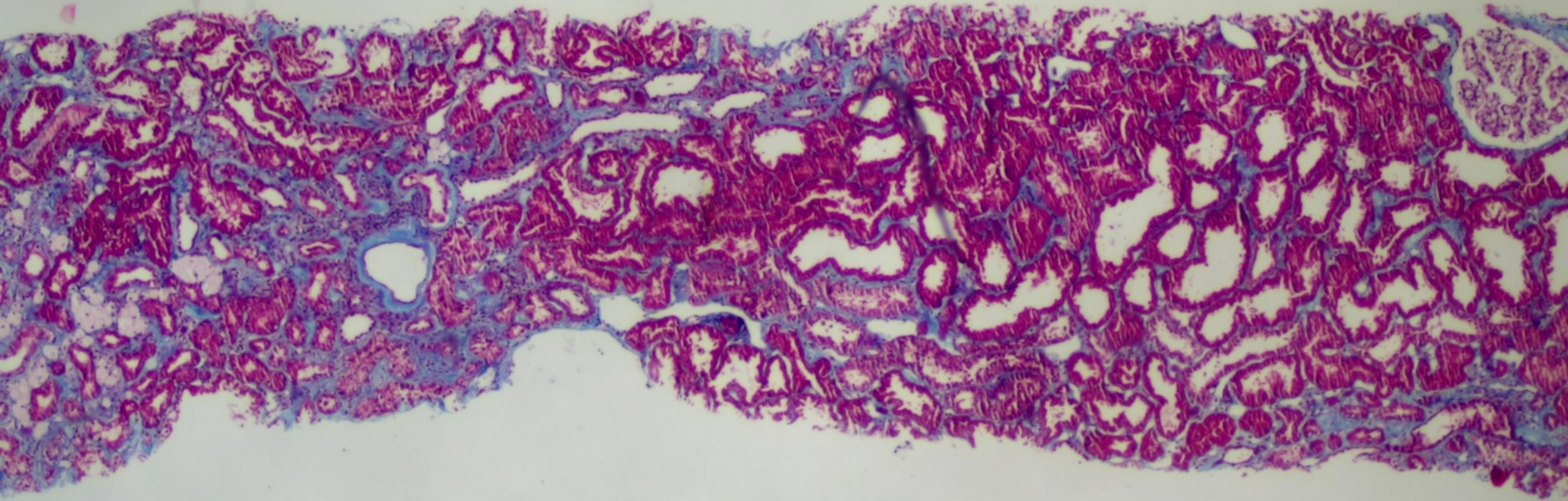








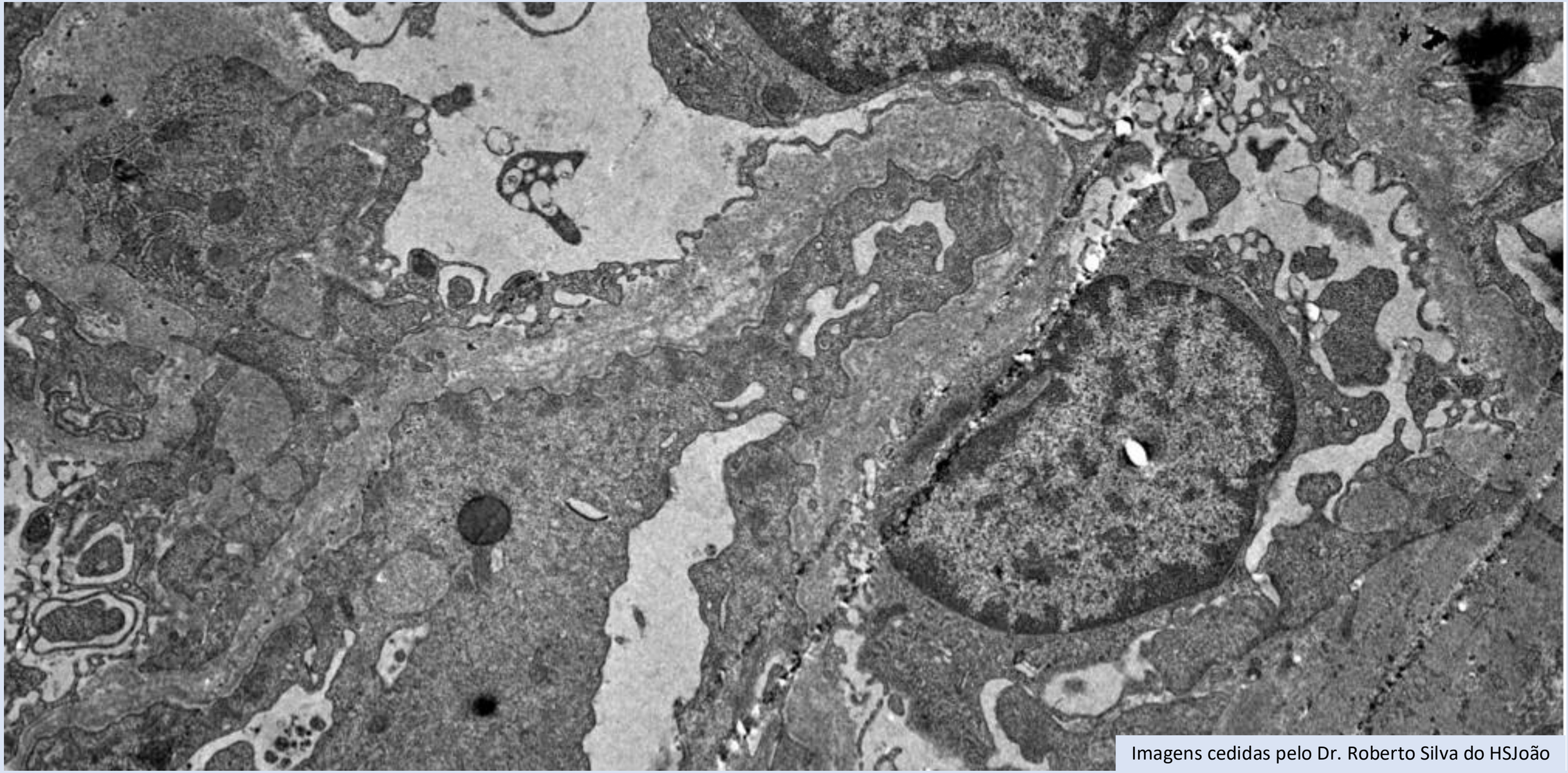




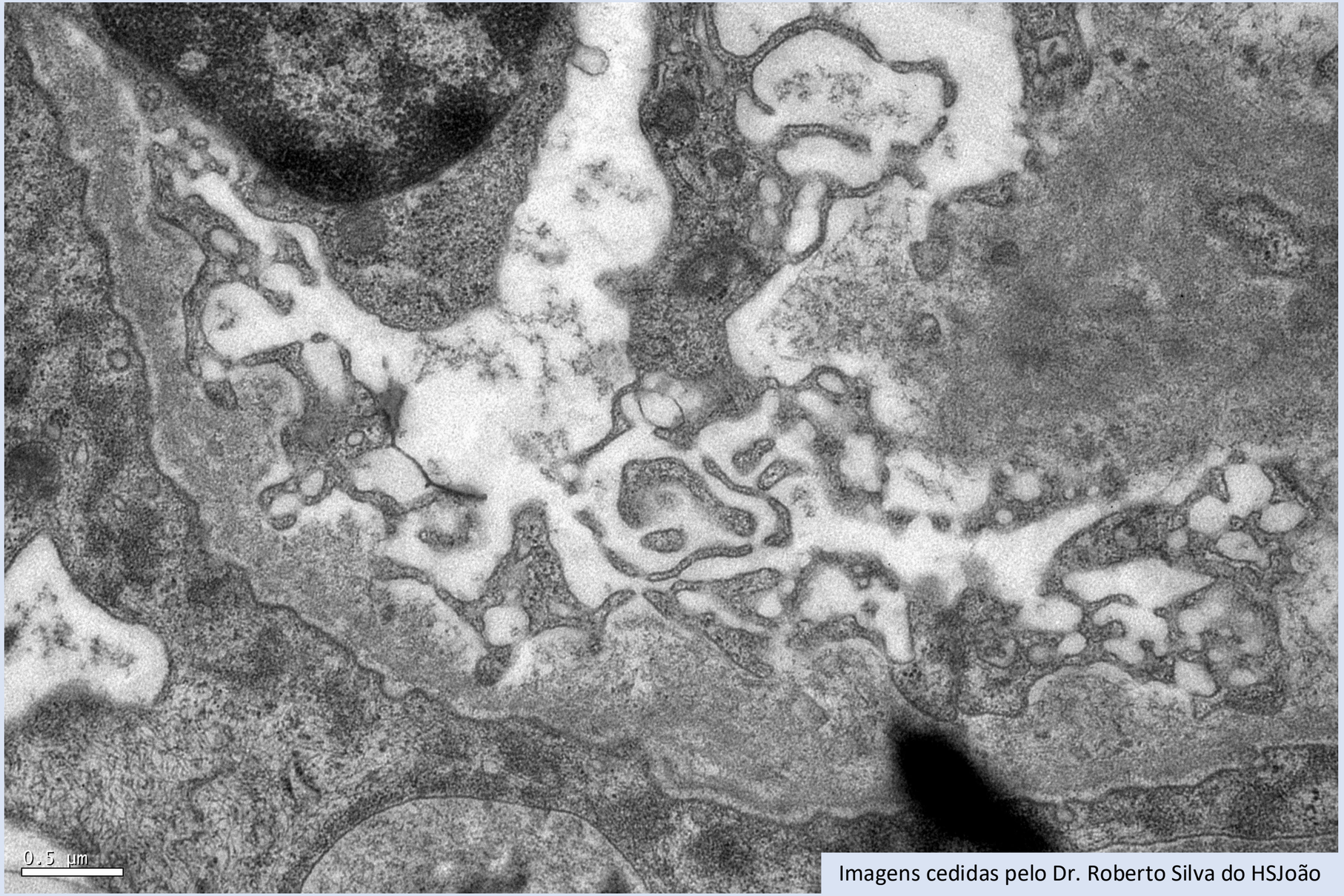
Clinical Case

Renal Biopsy

- Light microscopy: FSGS – NOS
- IF: negative



Imagens cedidas pelo Dr. Roberto Silva do HSJoão



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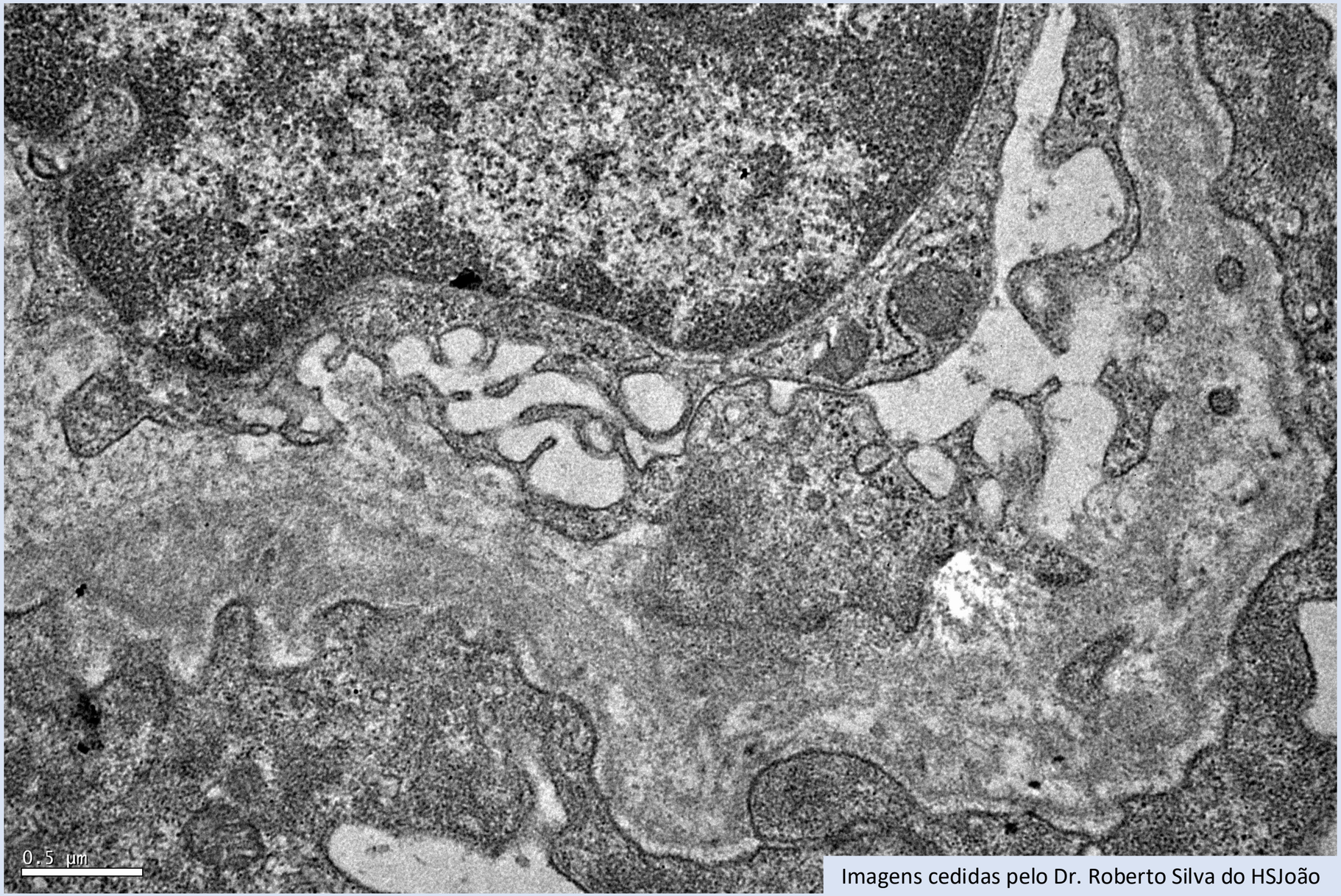


Imagens cedidas pelo Dr. Roberto Silva do HSJoão

Clinical Case

Renal Biopsy

- Light microscopy: FSGS – NOS;
- IF: negative
- EM: basement membrane changes compatible with Alport Syndrome

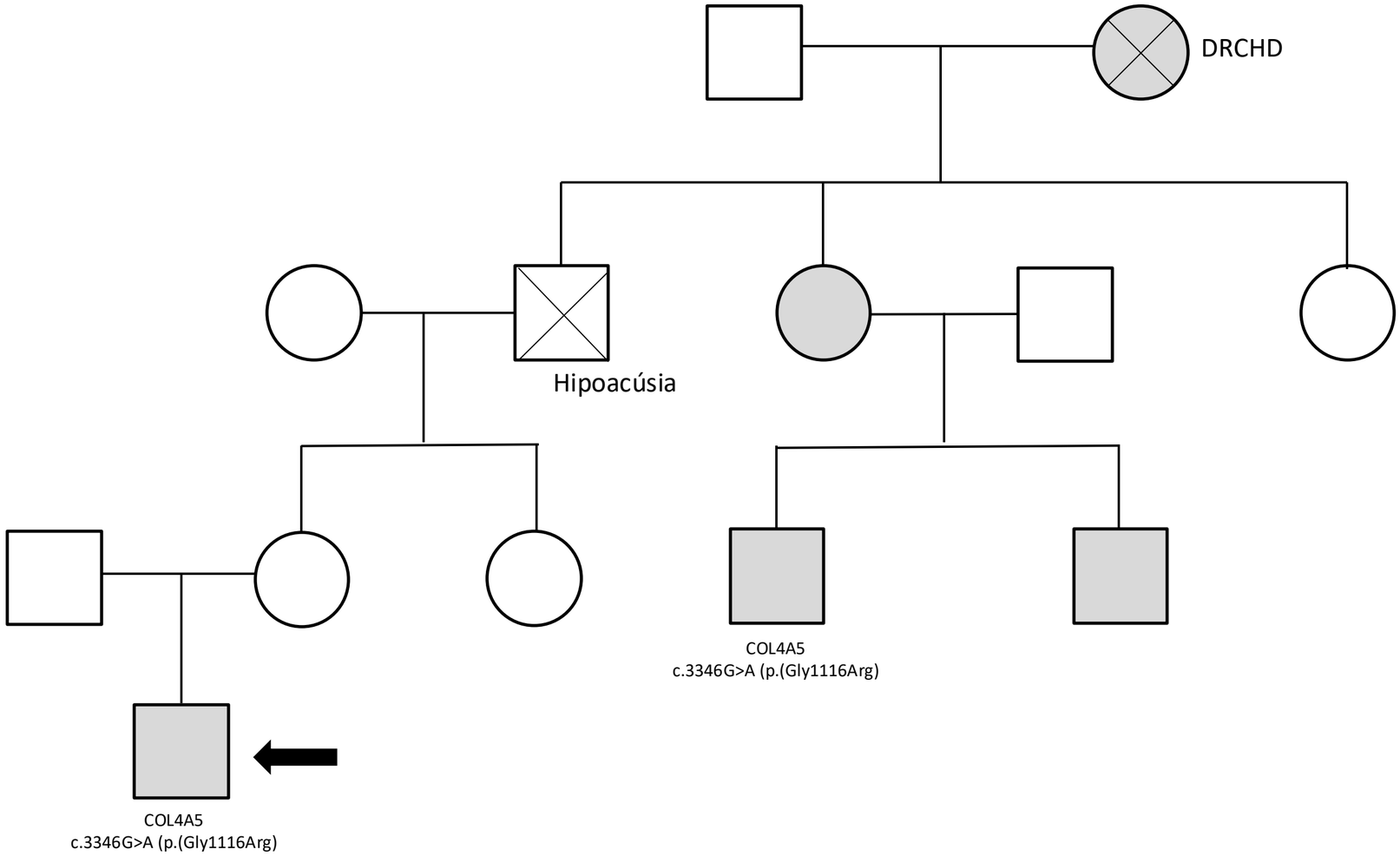
Clinical Case

Genetic Test – Panel COL4A3, COL4A4, COL4A5

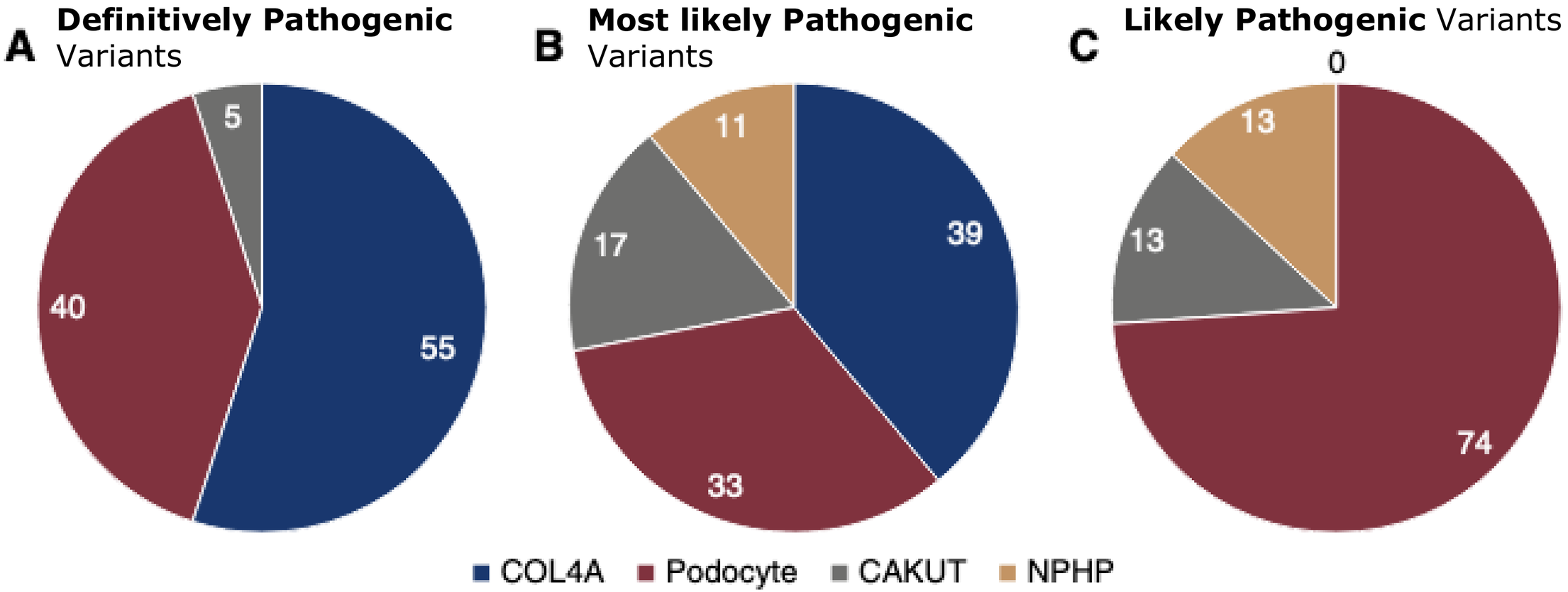
- Pathogenic variant on *COL4A5* c.3346G>A p.(Gly1116Arg)

Clinical Case

Pathogenic variant on *COL4A5* c.3346G>A p.(Gly1116Arg)

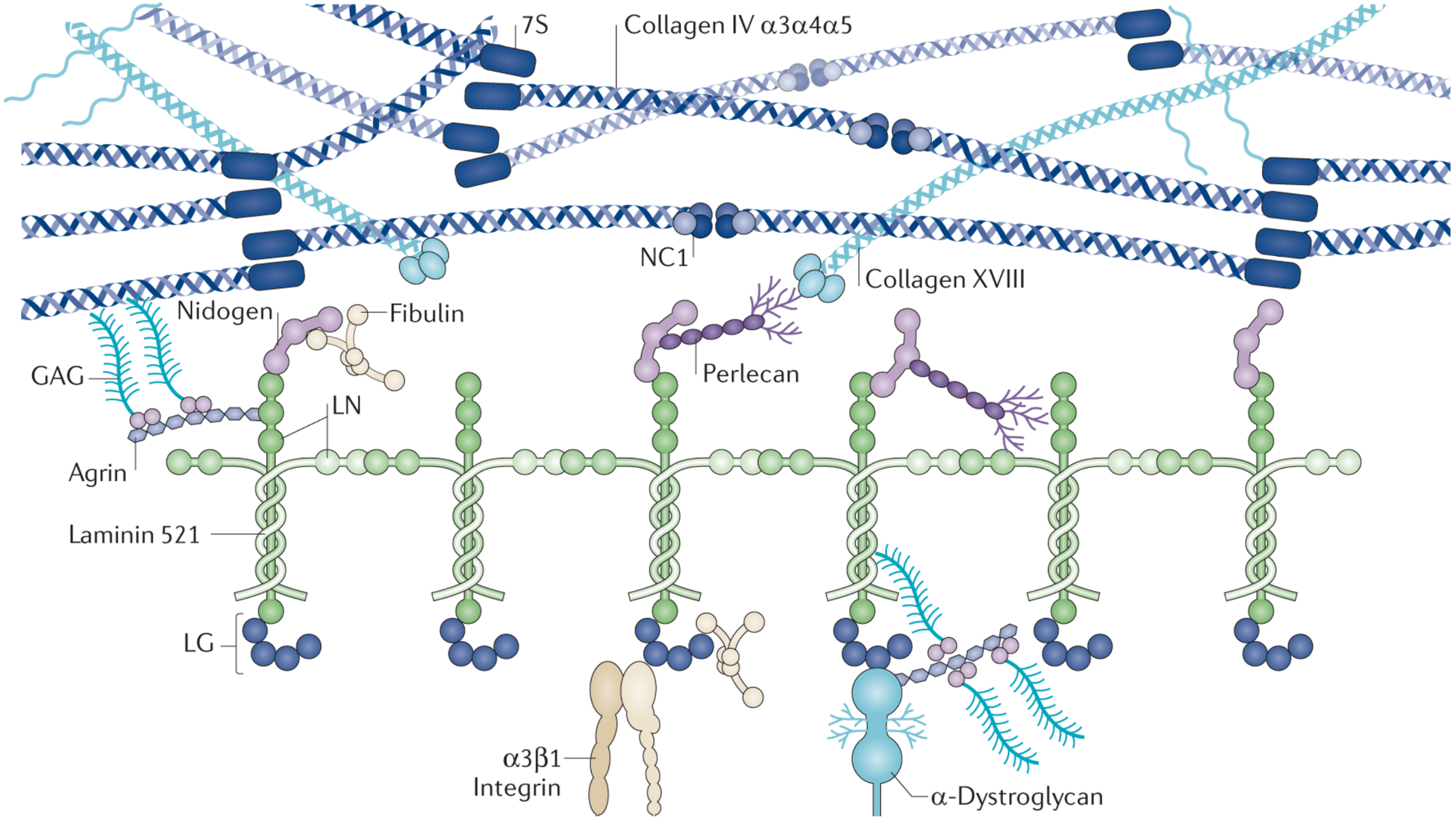


FSGS and Alport Syndrome

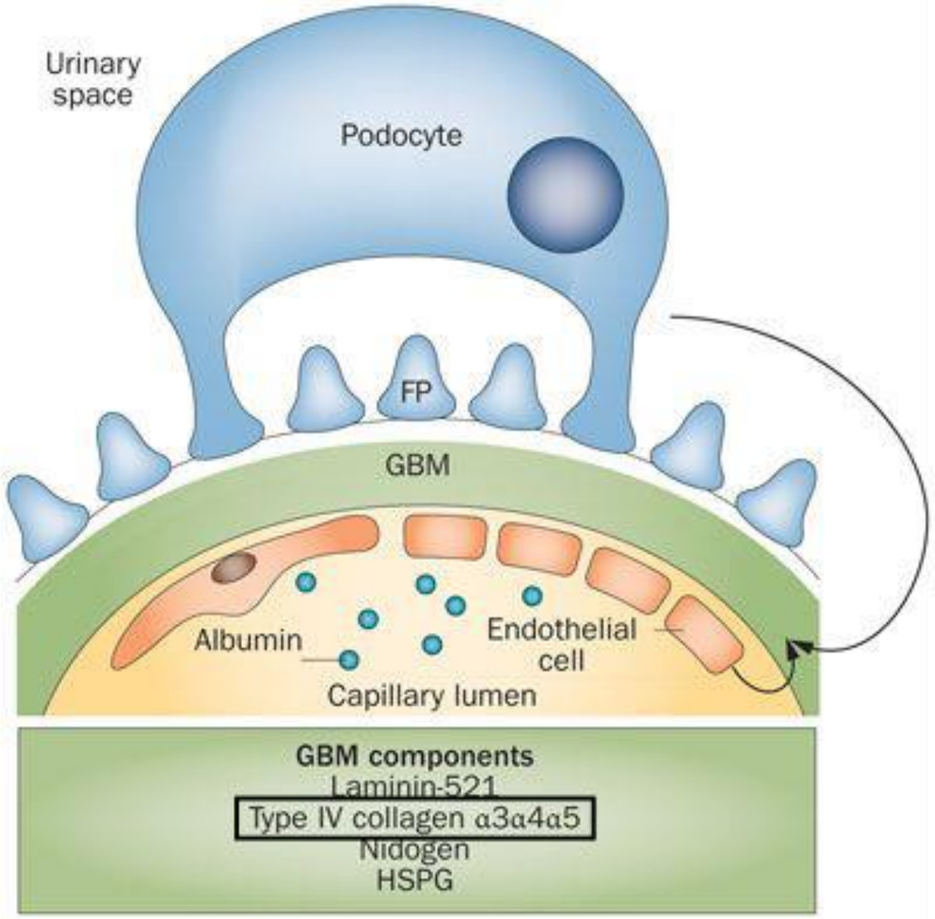


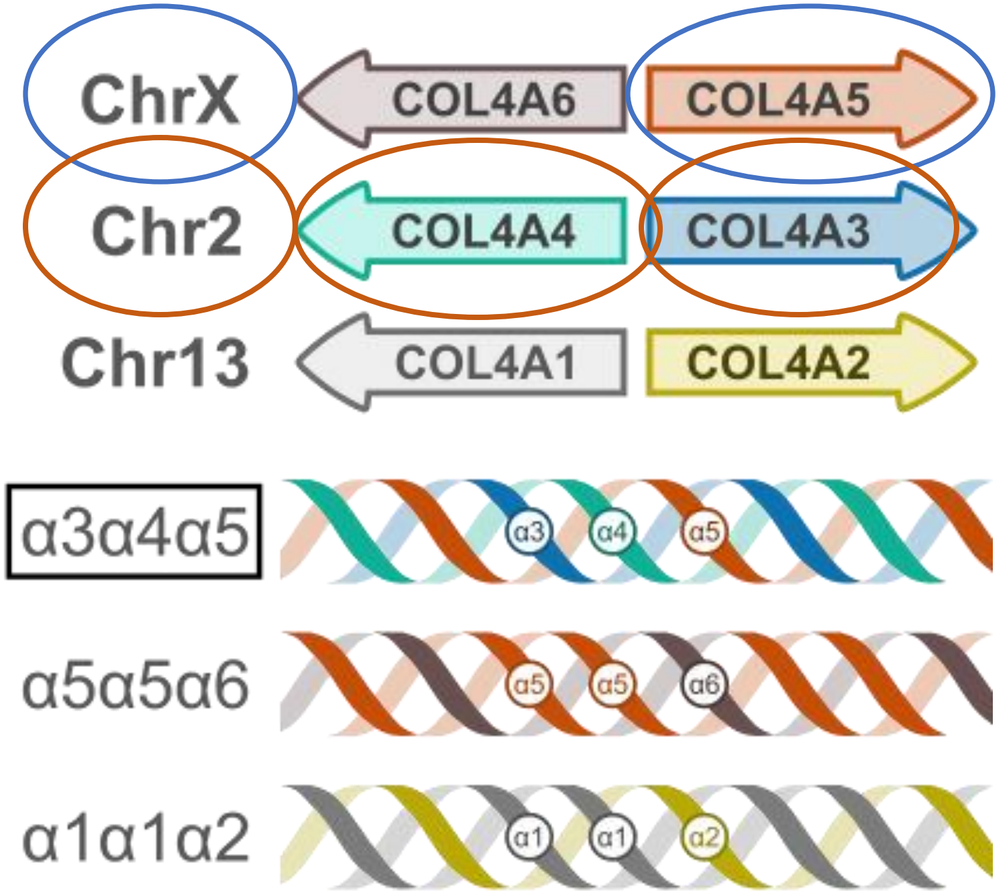
Clin J Am Soc Nephrol. 2019;14: 213–221

Glomerular Basement Membrane



COL4


Urinary space
Podocyte
FP
GBM
Albumin
Endothelial cell
Capillary lumen
GBM components
Laminin-521
Type IV collagen α3α4α5
Nidogen
HSPG


ChrX
COL4A6
COL4A5
Chr2
COL4A4
COL4A3
Chr13
COL4A1
COL4A2
α3α4α5
α3
α4
α5
α5α5α6
α5
α5
α6
α1α1α2
α1
α1
α2

Spectrum Disease

- Phenotypic heterogeneity
- Multiple modes of inheritance
- Variable expressivity and penetrance

Familial Benign Hematuria
(A3/A4 +/-)

Thin basement membrane, can progress
(A3/A4 +/-)

Women AS XL
(A5 +/-)

FSGS, CKD, ± extra-renal involvement
(A3/A4 +/-)

CKD late in life, ± extra-renal involvement
(A3/A4 +/- or -/-; A5 -/Y)

Early CKD, com extra-renal involvement
(A3/A4 -/-; A5 -/Y)

Adaptaded Kidney Int. 2014; 86: 1081-1083
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COL4A5 – X linked (1:2320)

Clinical manifestations

XY

- 100% ESKD, 90% after 40 years
- 70% SN deafness
- Severe phenotype: delections, frameshift, nonsense variants

XX

- 95% hematuria, sometimes intermittent
- 25% CKF, 15-30% at 60 years, 40% 80 years
- Random inactivation X chromosome

Kidney Med. 2020: 2(5):639-649
Am J Kidney Dis. 2021 Feb;77(2):272-279
Kidney Int. 2018 May;93(5):1045-1051
Eur J Hum Genet. 2021 Aug;29(8):1186-1197
Clin J Am Soc Nephrol. 2021; 16: 1101-1109

COL4A3-4 – Autosomal Recessive

Clinical manifestations

- Men=Female
- Phenotype ≃♂ X-linked
- Consanguinity
- Microscopic hematuria in the parents
- Genotype-phenotype correlaction not clear

Kidney Int. 2018 May;93(5):1045-1051

COL4A3-4 – Autosomal Dominant (1:106)

Clinical manifestations

(777 patients, 258 families)

- 94.8% hematuria
- 8.5% macroscopic hematuria
- 46.4% proteinuria
- 29% CKD
  - 52.3% (15.1%total) CKF
- Median age CKF: 52.8 years
- 16.5% hearing changes
- 3% ocular changes
- Intra and inter family heretogeneity
- RB: 86.8% thin BM; 39% FSGF, MPGN, IgA

Variants

- COL4A3 53.5%, COL4A4 46.3%
- Age CKF
  - Missense 55.2 years
  - Nonsense 47.1 years

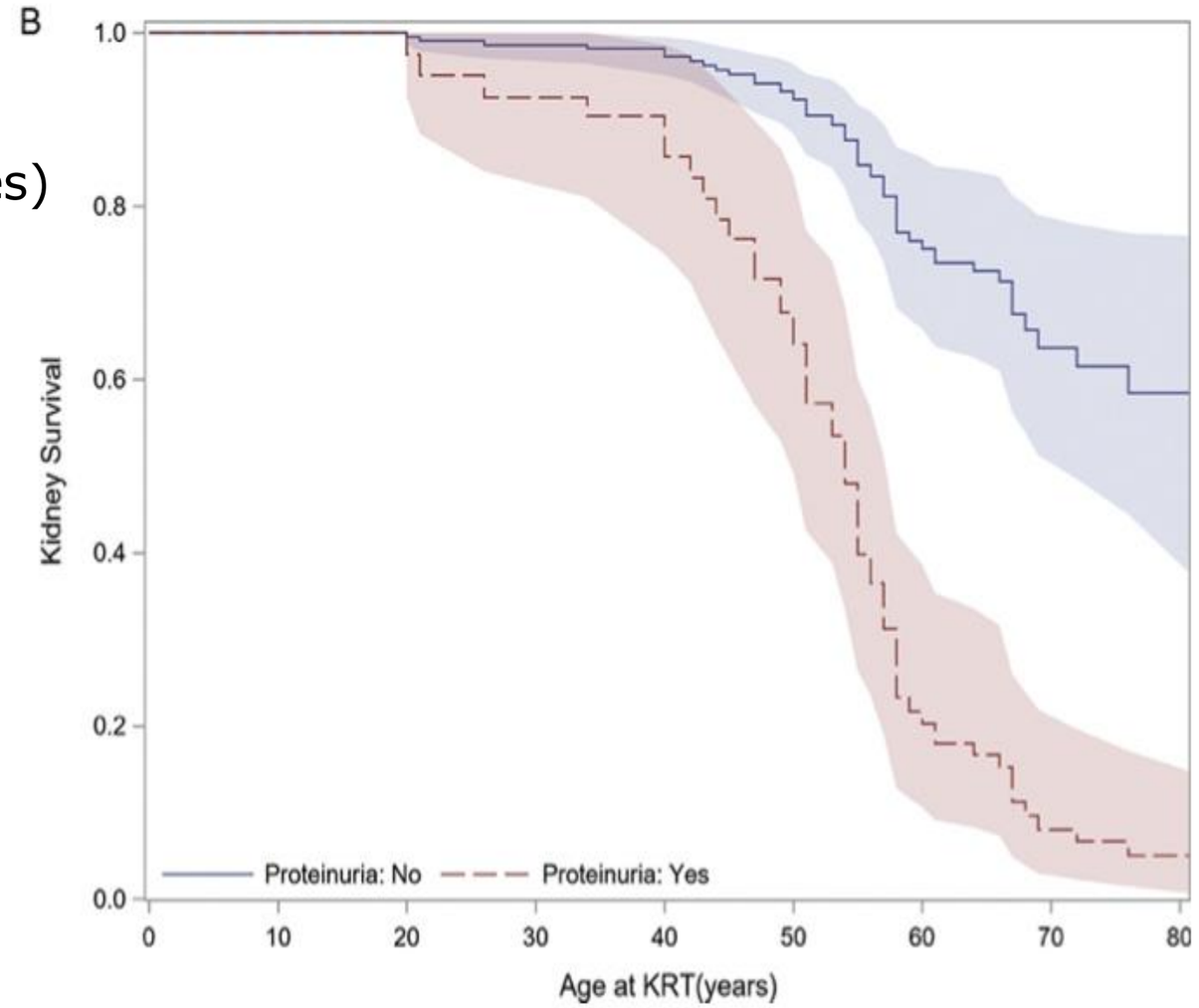
Clin Kidney J. 2020 Feb 10;13(6):1025-1036

COL4A3-4 – Autosomal Dominant (1:106)

Clinical manifestations

- 252 patients (82 families)
- Spain

- 92.1% Hematuria
- **65.2% Proteinuria**
- **24.2% CKF**
- Renal survival 67 years



-1.78 ml/min/1.73m^2

- 0.97 ml/min/1.73m^2

Am J Kidney Di. 2021; 78(4):560-570

COL4A3/4/5 - Digenic

- 2 variants in two 2 (of 3) genes – more commum *COL4A3* e *A4*
- *In cis (*same Chr) – ADAS
- *In trans* (≠ Chr)
- Age of onset of CKF intermediate between XLAS/ARAS and ADAS

Clin J Am Soc Nephrol. 2022; 17: (1) 143-154
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Nomenclature

Alport syndrome: a unified classification of genetic disorders of collagen IV α345. a position paper of the Alport Syndrome Classification Workin Group

- Diseases Associated with Collagen IV
- Alport Syndrome
  - X-linked (XLAS)
  - Autosomal Recessive (ARAS)
  - Autosomal Dominant (ADAS)
  - Digenic Inheritance
- Diagnosis and Early Initiation of Treatment
- **Thin Basement Membrane – A histological finding; should not be used as a diagnosis**
- **Women with X-linked Alport Syndrome and Heterozygous AS – At risk of developing CKD**

Kidney Int. 2018 May;93(5):1045-1051

Expert consensus guidelines for the genetic diagnosis of Alport syndrome

- **Do not use the term "ADAS" – it may cause anxiety and implies a different prognosis**.
- The term "**thin basement membrane" is maintained, but its limitations are acknowledged**.

Pediatr Nephrol. 2019 Jul;34(7):1175-1189

“There is an ongoing discussion on better defining the naming for this entity”

“benign should no longer be used”

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Renal Biopsy and Alport Syndrome

Kidney Biopsy Findings

- **LM:**
  - normal
  - minimal change disease
  - mesangioproliferative
  - FSGS
  - membranous nephritis
  - tubular atrophy
- **IF:** IgA deposits mimicking IgA
- **EM: thinning, splitting, lamination, basket-weaving, wrinkling or thickening of the GBM**

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Renal Biopsy and Alport Syndrome

AS diagnosis by biopsy

- electronic microscopy ESSENTIAL

- FSGS always think about AS

- mesangial hypercellularity can be present

Indications for renal biopsy in AS

- **not need in male XLAS or ARAS**

- can sometimes be useful in **ADAS, female X-linked**

Unexpected disease course:

- sudden nephrotic syndrome

- unexplained AKI

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Molecular Diagnosis of Alport Syndrome - first

- **Children and young adults** (especially females of childbearing age) with **isolated persistent glomerular** (dysmorphic) **haematuria**
- Individuals with **persistent haematuria** and **family history** of either well-documented haematuria or unexplained CKF (at least in one first or second degree relative)
- **Kidney biopsy with characteristics findings**
- Individuals with **persistent haematuria** and **high tone sensorineural hearing loss**
- Individuals with **persistent haematuria** and **certain ocular findings (fleck retinopathy and anterior lenticonus)**

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Molecular Diagnosis of Alport Syndrome

- **Panels that should include *COL4A3A4A5* gene analysis**
- **Kidney panels**
  - Persistent haematuria
  - Proteinuric kidney disease
  - Focal segmental glomerulosclerosis
  - Podocytopathies
  - DRC of unknown origin
- **Inner ear hearing loss**

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COL4A3-4 – Autosomal Dominant (1:106)

- **Phenotype**
- **Imaging**
- **Kidney biopsy?**
- **Large gene panels?**

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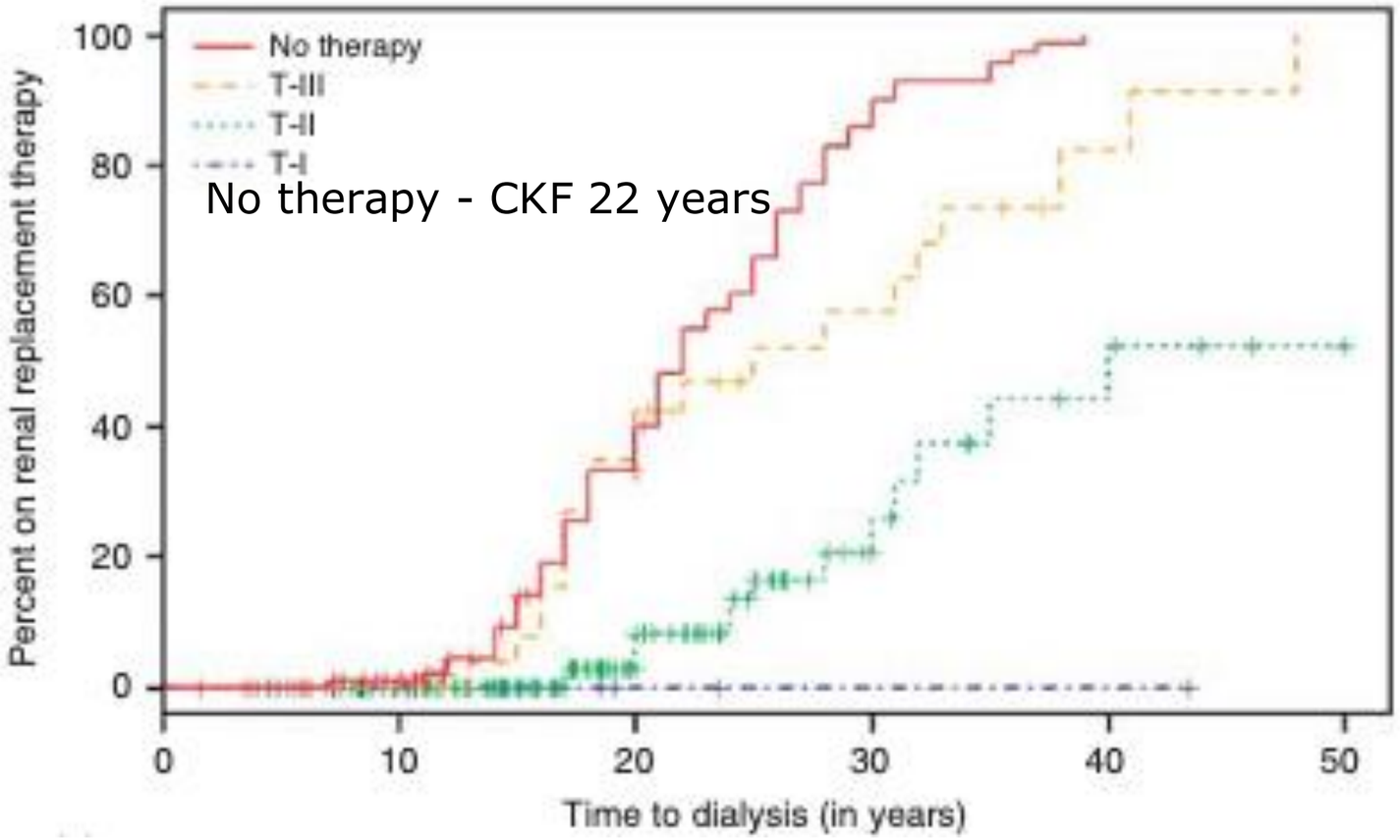
Early Intervention in Alport Syndrome



Start RASi 22y
Delay CKF 3y

Start RASi 13y
Delay CKF 18y

Start RASi 8y
Any at CKD stage 3

Kidney Int. 2012; 81: 494–501

Alport Syndrome - treatment

- ACEi/ ARAII

  - at dx: men X-linked and AR (>2 years)

  - proteinuria present: female X-linked and AD

- SGLT2i

  - 5 pediatric patients (10,4years), GFR>60ml/min

    22% proteinuria reduction in 12 weeks

  - DOUBLE PRO-TECT Alport

  - DAPA-CKD – 6 patients AS

  - observational, multicentric, international study

    122 patients (58 X-linked), age 38±14ys, eGFR 63±35ml/min/1.73m^2, FUP 32m

    After initiation SGLT2, >30% UACR reduction, mean loss GFR at 1year 9±12ml/min

Pediatr Nephrol. 2021; 36:711-9
Nephr Dial Transplant 2024 gfae265
Kid Int Reports. 2024; 9: 3490-3500

Alport Syndrome – FUP and extra-renal assessement

	Renal	Ear (audiometry)	Eye
Male-X linked	According to proteinuria, CKD stage evolution and treatment	• 1st evaluation – 4 years old/diagnosed • Yearly until 50 ys, after that according to symptoms	• At diagnosis
ARAS	According to proteinuria, CKD stage evolution and treatment	• 1st evaluation – 4 years old/diagnosed • Yearly until 50 ys, after that according to symptoms	• At diagnosis
ADAS (Female X-linked)	• **Children (persistent hematuria)** ▪ UA w/ UACR 1-4 ys from 4-6ys old • **Adults asymptomatic** ▪ Blood pressure yearly ▪ UA w/UACR 1-2 ys ▪ Individualized age, familial history and comorbities • **Adults microalbuminuria** ▪ eGFR and microalbuminuria 6m-yearly ▪ According to proteinuria, CKD stage evolution and treatment	• **ADAS:** Only if hearing loss • **Female X-linked** ▪ At diagnosis ▪ Absence of symptoms 5-5ys	• Rare

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Alport Syndrome – living donors

- **ADAS and females X-linked**
  - **Last possible resource**
  - **Not advisable**

    Under 40ys

    At any age if albuminuria reduced eGFR or histological evidence of renal damage
  - **Over 40ys**, **absence** albuminuria or reduce eGFR – consider kidney biopsy

    Risks/benefits for that individual/family

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Síndrome de Alport

- Hereditary Nephropathy Associated with Type IV Collagen
- Most common hereditary glomerulopathy
- Second leading cause of monogenic end-stage kidney disease
- Variable clinical spectrum:
  - Benign hematuria
  - Proteinuria
  - CKD/End-stage renal disease
- Variability in extra-renal manifestations – ocular involvement, non-syndromic hearing loss
- Different histological presentations
- Effective early treatment