

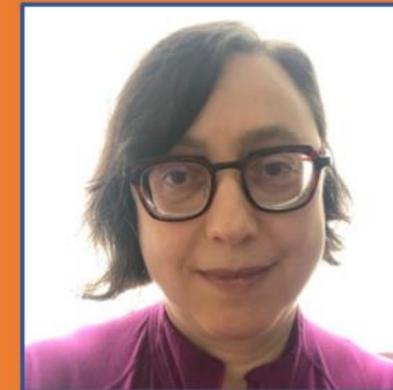
Bracketology



www.AJKDBlog.org
March 1-31, 2026

Slides Prepared by the NephMadness Executive Committee

- Matthew Sparks
- Anna Burgner
- Anna Vinnikova
- Jeffrey Kott
- Ana Catalina Alvarez-Elías
- Dia Waguespack
- Samira Farouk
- Krithika Mohan



What to do

- Review the Regions & Teams on [AJKDBlog](#)
- Submit your picks by **March 31, 2026**, on [Tourneytopia](#)
- Discuss on social media using [#NephMadness](#)
- Claim CME/MOC credit through [NKF PERC](#)



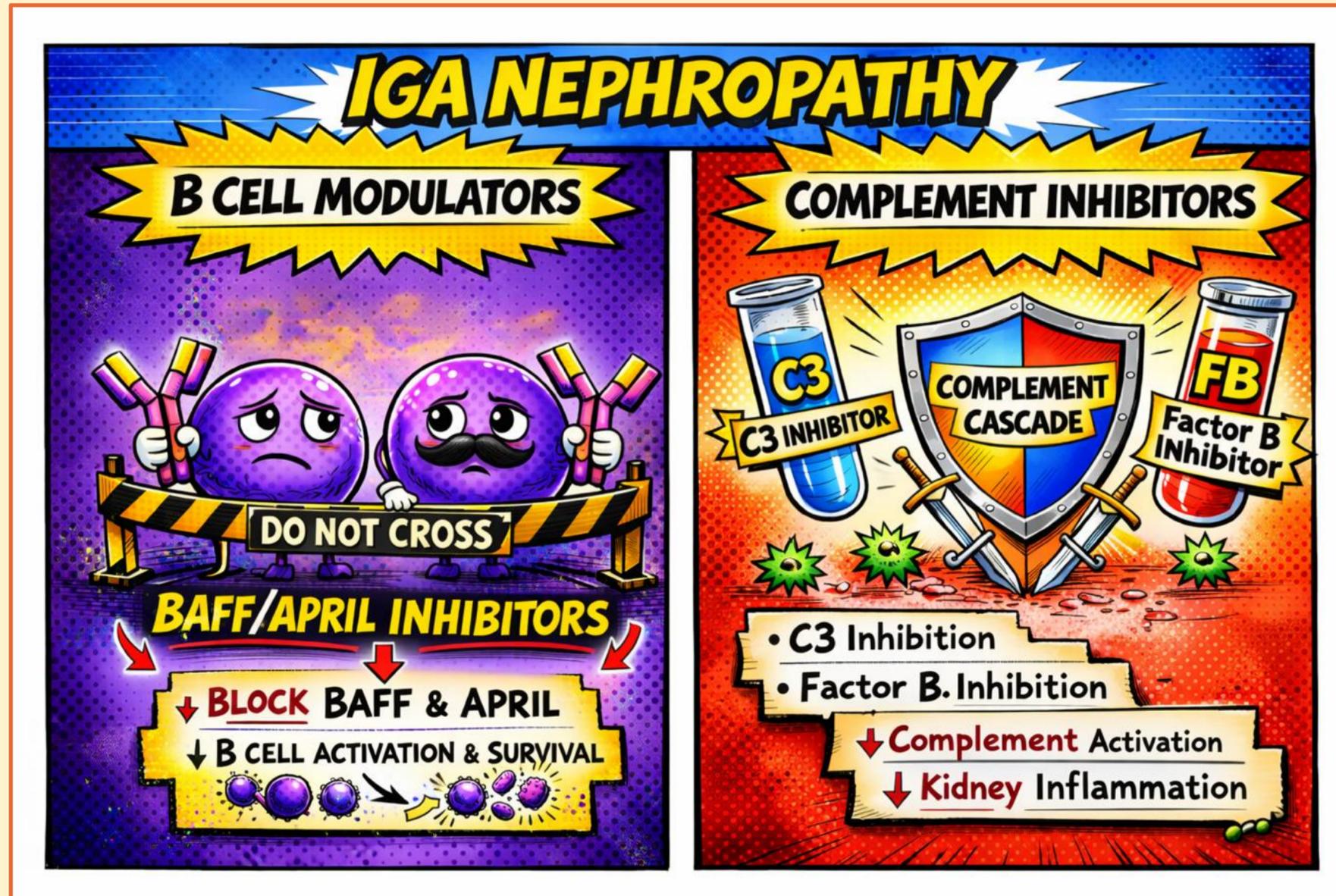
The BRP Has Chosen the Winning Bracket

To win, predict what the BRP thinks will bring the most practice change to nephrology!

- Timothy Yau
- Prabir Roy-Chaudhury
- Kirk Campbell
- Meredith Atkinson
- Lori-Ann Fisher
- William Whittier
- Yara Mouawad
- Christel Wekon-Kemeni
- Giftay Kingston



IgA Nephropathy



Writer:

Alessandra Tomasi

Expert:

Laura Mariani

Region Execs:

Matthew Sparks

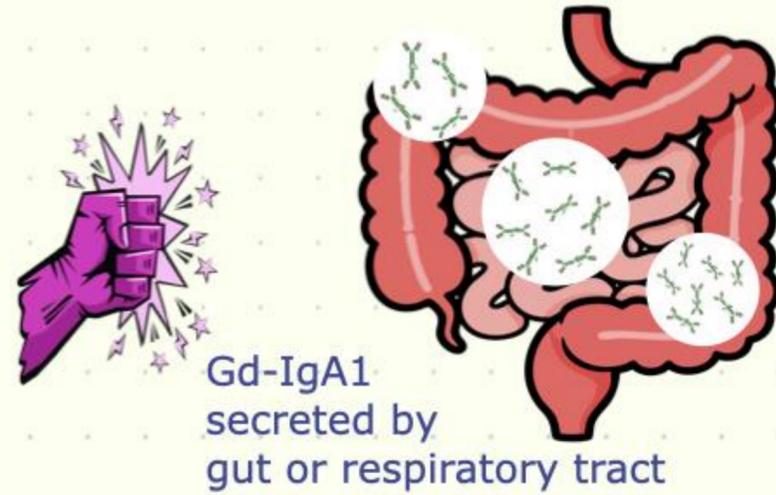
Dia Waguespack

Four-Hit Model in the Pathogenesis of IgA Nephropathy



Hit 1

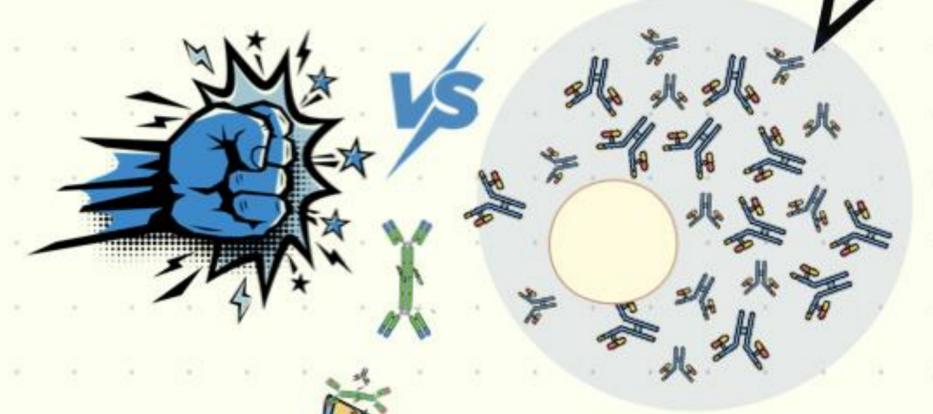
Increased production and circulation levels of a galactose-deficient IgA1 (Gd-IgA1)



Gd-IgA1 secreted by gut or respiratory tract

Hit 2

Production of auto-anti-antibodies against Gd-IgA1 (Self-antigen)



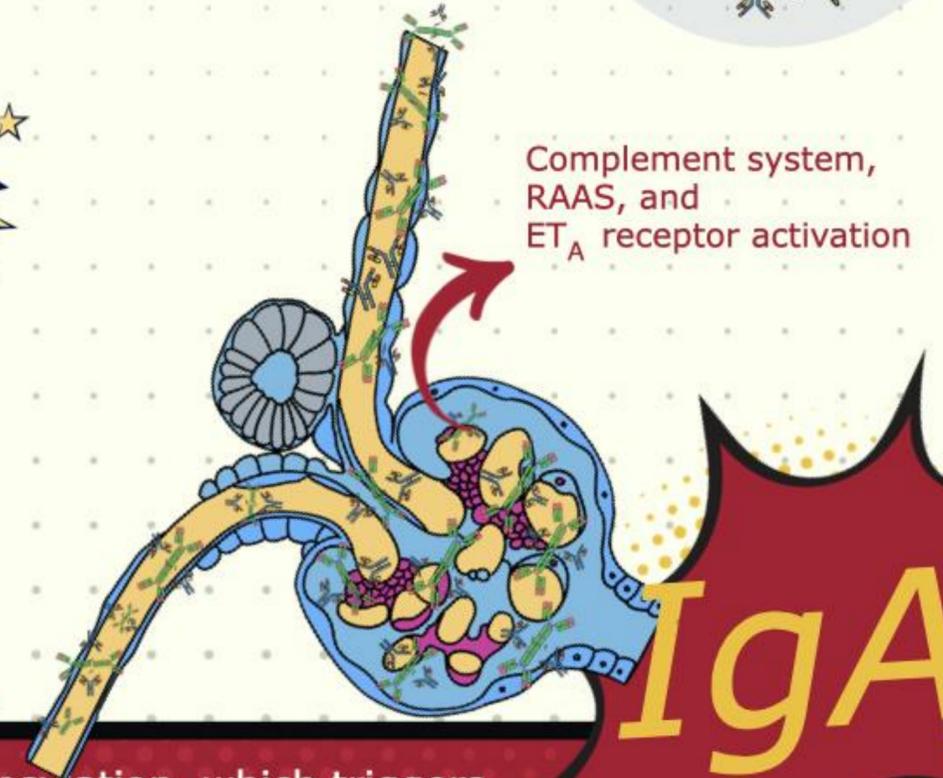
Hit 3

Formation of circulating nephritogenic immune complexes with anti-Gd-IgA1-IgG, IgA, and/or IgM



Hit 4

Binding of circulating immune complexes to mesangial cells



Complement system, RAAS, and ET_A receptor activation

RAAS,renin-angiotensin-aldosterone system; ET , endothelin receptor type A

El Karoui K.et al.,CJASN, 2024

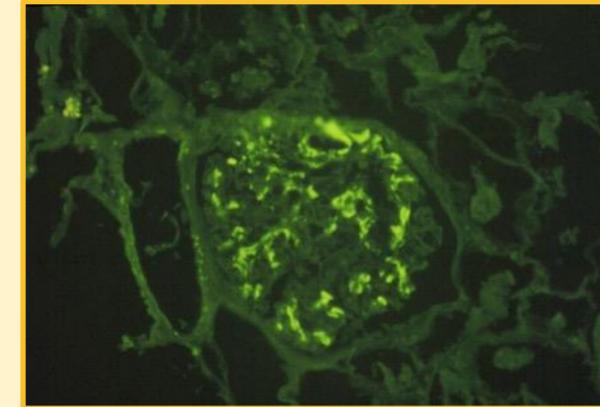
VA by **Elba Medina**

Conclusion: IgA nephropathy stems from deficient IgA1 galactosylation, which triggers a 'four-hit' process. This sequence involves Gd-IgA1 immune complex deposition in the mesangium, leading to glomerular and tubulointerstitial injury, intensified by activation of the complement system, RAAS, and endothelin pathway, ultimately provoking inflammation and fibrosis.

The Oxford classification, (MEST-C score), used as an initial assessment of disease severity.

5 key components:

- **M**esangial hypercellularity
- **E**ndocapillary hypercellularity
- **S**egmental glomerulosclerosis
- **T**ubular atrophy/interstitial fibrosis
- **C**rescent formation



International IgAN Prediction Tool to help determine prognosis in adults with IgA nephropathy for up to two years following initial biopsy

2025 KDIGO Guidelines for IgA nephropathy

1. Stopping the production of pathogenic IgA and associated immune complex formation as well as resultant kidney injury
2. Reducing glomerular hyperfiltration and proteinuria
3. Managing hypertension.

Non-disease-specific interventions to manage BP, reduce glomerular hyperfiltration, proteinuria

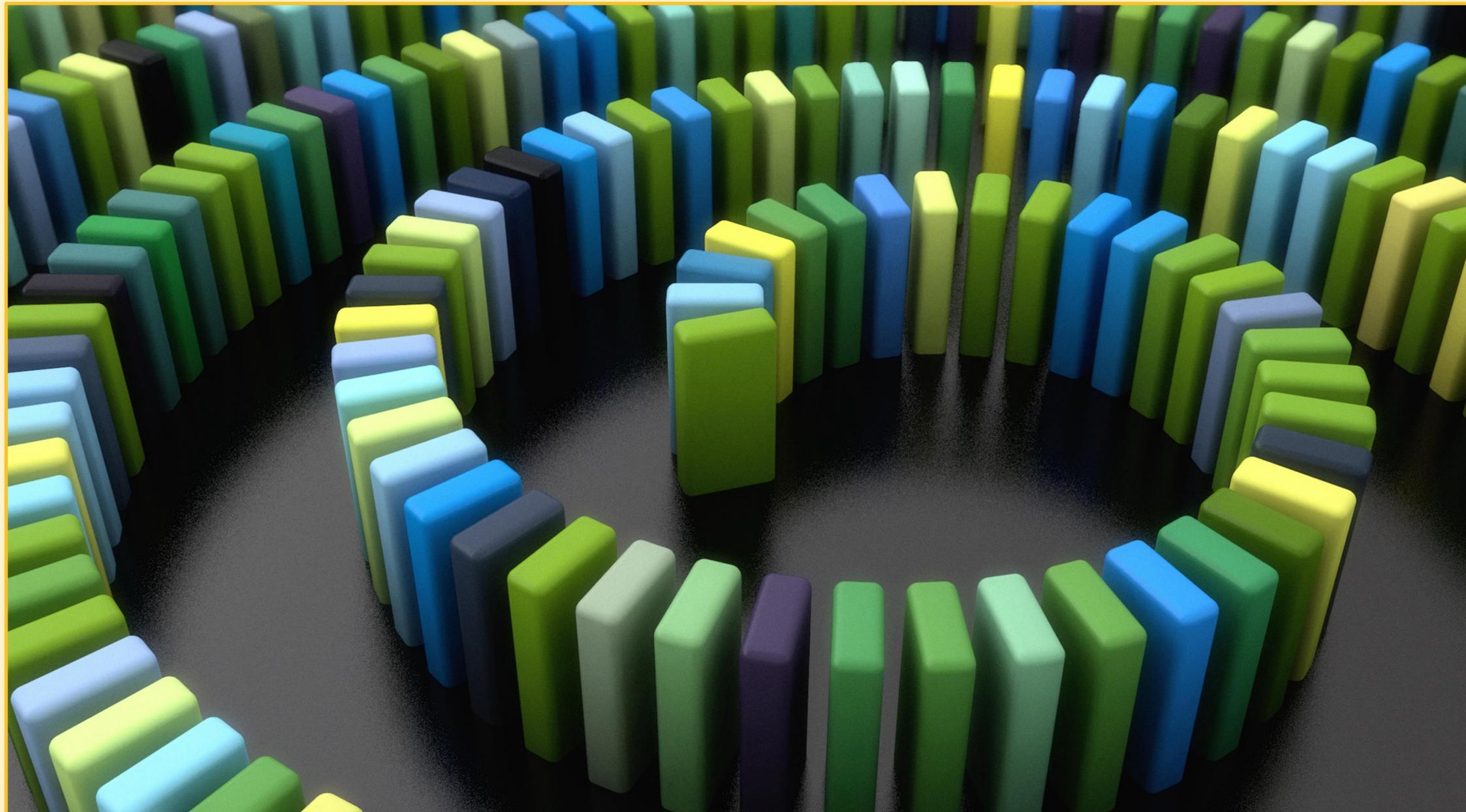
-RAS inhibitors, -SGLT-2 inhibitors, -endothelin receptor antagonists (ERAs) or

-dual endothelin angiotensin receptor antagonists (DEARAs)

Disease modifying steroids, targeted-budesonide, **B-Cell modulators**, **anti-complement**



New B-Cell Targets



Team B-Cell Modulators

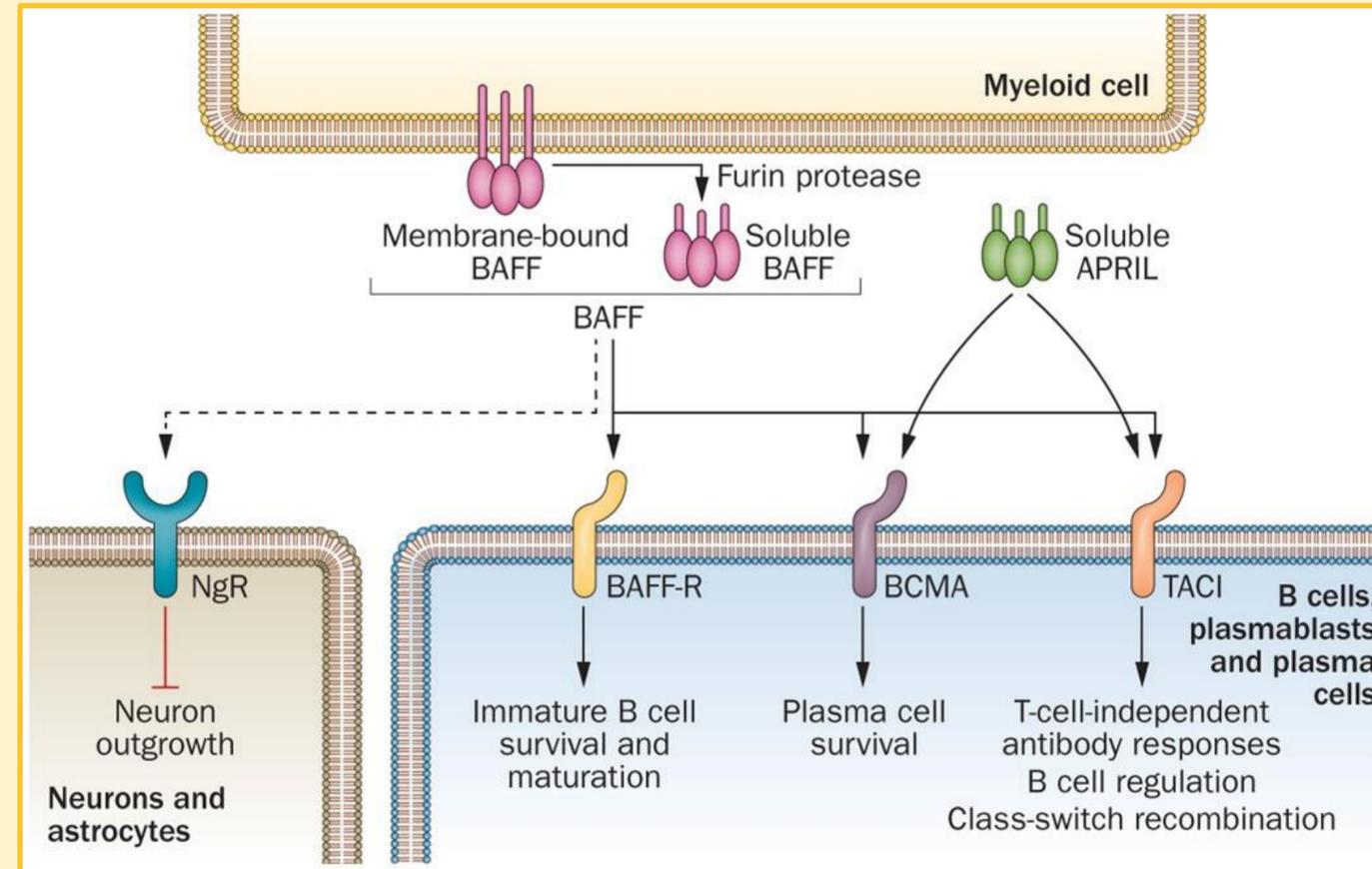
Let's meet our two cytokines that will be targeted. Both are important for B-Cell function.

BAFF- B-cell Activating Factor Family
APRIL- A Proliferation-Inducing Ligand

BAFF facilitates peripheral B cell selection and survival, as well as helps maintain follicular- and marginal-zone B cell populations.

APRIL allows for antibody class-switching and ultimately their differentiation into antibody-secreting plasma cells.

Work by reducing aberrant IgA molecule (Gd-IgA1), reduce the production of IgG and IgA autoantibodies against Gd-IgA1, and reduce the formation of immune complexes containing IgG, IgA, and Gd-IgA1.



Vincent FB, et al Nat Rev Rheumatol. 2014 PMID: 24614588.

The players

Atacicept- A fully human recombinant fusion protein provided as a once-weekly subcutaneous injection, atacicept targets both BAFF and APRIL.

Ongoing phase 3 ORIGIN trial

- 203 patients were included in this prespecified analysis (106 in the atacicept and 97 in the placebo group)
- 46% reduction in proteinuria (7% in the placebo)
- Resolution of hematuria in 81% (21% in the placebo).

The phase 2 ORIGIN trial

- 60% decrease in circulating Gd-IgA1, 36% reduction in IgG, 64% in IgA, and 75% in IgM

The phase 2b extension trial

- sustained reduction in proteinuria (by 52%), hematuria, and circulating Gd-IgA1 levels at 96 weeks
- stabilization of eGFR (mean eGFR slope 0.6 mL/min/1.73 m²).
- We are awaiting FDA approval at the time of this publication.

Sibeprenlimab- A humanized monoclonal antibody that targets APRIL alone as a monthly subcutaneous injection. [Has received conditional FDA approval.](#)



VISIONARY: Safety and Efficacy of Sibeprenlimab in Patients with IgA Nephropathy



Multicenter
(Phase 3)



Double-blind



IgA
Nephropathy
(Biopsy proven)
n=320



RASi
SGLT2i



40 years
Mean age



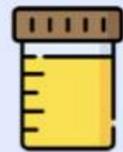
55%
Male



40% White
55% Asian



eGFR 63
Mean eGFR



1.2 g/g
Mean UPCr

1:1
R
A
N
D
O
M
I
Z
A
T
I
O
N



Month 9

Sibeprenlimab
400 mg SC/
4 weeks
n=152



Placebo
n=168



Reduction in
24 hr UPCr

PRIMARY
OUTCOME

-50%

$p < 0.001$

+2%



Adverse
Events

3.5%

No deaths

4.4%



Week 48



Gd IgA1
Levels

-67%

-1%

Reduction in
APRIL

-96%

-26%

SECONDARY OUTCOMES

* UPCr, Urine protein-to-creatinine ratio; Gd IgA1, Galactose deficient IgA1, APRIL, A Proliferation Inducing Ligand

Perkovic V, et al, NEJM, 2025

VA by **Edgar Lerma, MD**

Conclusion: Sibeprenlimab resulted in a significant reduction in proteinuria as compared with placebo in patients with IgA nephropathy

Complement Inhibition



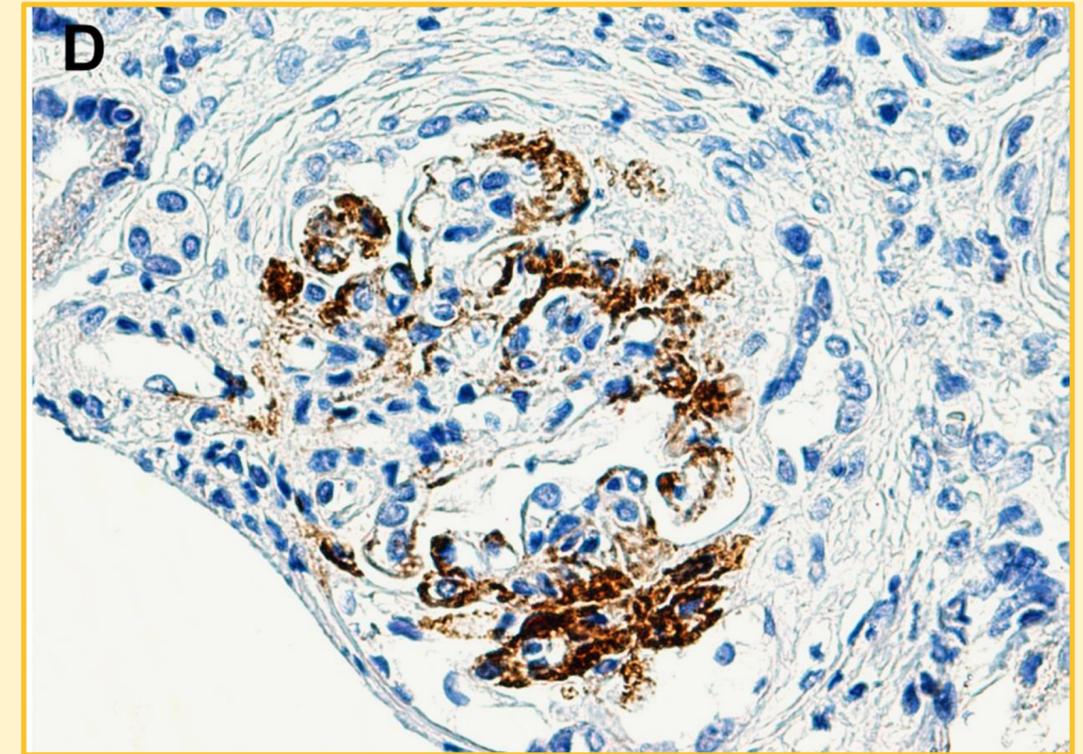
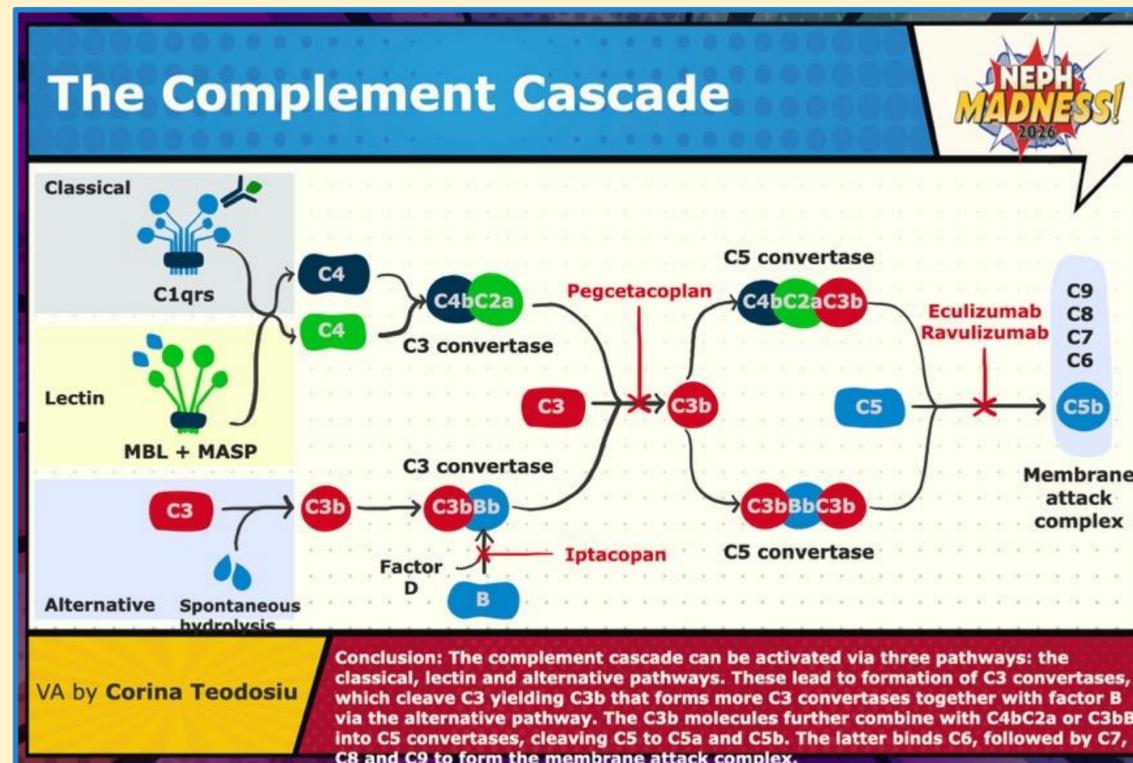
Team Complement Inhibitors

Evidence of complement deposition in glomeruli in IgA nephropathy is common.

The alternative and lectin pathways have been most implicated.

Role of complement inhibitors in the management of IgA nephropathy has gained significant traction.

Need vaccination to encapsulated bacteria- *Streptococcus pneumoniae*, *Neisseria meningitidis*



Faria B et al Am J Kidney Dis. 2020 PMID: 32439421.

Meet the players

- **Iptacopan** (ip-TAH-kopan)- An oral complement factor B inhibitor, works by blocking the alternative complement pathway, inhibiting Factor B preventing the formation of C3 convertase (C3bBb), inhibiting the cleavage of C3 dampening inflammation. Has received conditional FDA approval.
- **Pegcetacoplan** (Peg-sitta-co-plan) (a C3 inhibitor)- still under development.
- **Ravulizumab** (Rav-u-Liz-ooH-mab)(a long-acting C5 inhibitor similar to eculizumab)- Phase 3 I CAN Trial Starting



APPLAUSE-IgAN: Safety and Efficacy of Iptacopan in Patients with IgA Nephropathy



Multicenter (Phase 3)

Double-blind

IgA Nephropathy (Biopsy proven) n=443
(n=250 in interim analysis)

Prespecified Interim Analysis: When 1st 250 patients reached Month 9 or discontinued the study

RASi SGLT2i

39 years Mean age

52% Male

51% Asian

eGFR ≥30 Mean eGFR

>1 g/g Mean UPCr

1:1
R
A
N
D
O
M
I
Z
A
T
I
O
N

Month 9	Adjusted geometric Mean 24 hr UPCr	SAEs
Iptacopan 200 mg BID n=125	PRIMARY OUTCOME	
Placebo n=125	44%	8%
	38.3% <i>(95% CI 26.0-48.6) 2-sided p <0.001</i>	Mostly mild to moderate in severity and reversible
	9%	5%

The reduction in proteinuria was supported by consistent results in secondary endpoint analyses

No increased risk of infection

* UPCr, Urine protein-to-creatinine ratio; SAEs. Serious Adverse Events

Perkovic V, et al, NEJM, 2025

VA by **Edgar Lerma, MD**

Conclusion: Among patients with IgA nephropathy, treatment with iptacopan resulted in a significant and clinically meaningful reduction in proteinuria as compared with placebo.

EFFLUENT EIGHT ROUND

Pick Your Champion for the IgA Nephropathy Region

IGA NEPHROPATHY

B CELL MODULATORS

DO NOT CROSS

BAFF/APRIL INHIBITORS

- ↓ BLOCK BAFF & APRIL
- ↓ B CELL ACTIVATION & SURVIVAL

COMPLEMENT INHIBITORS

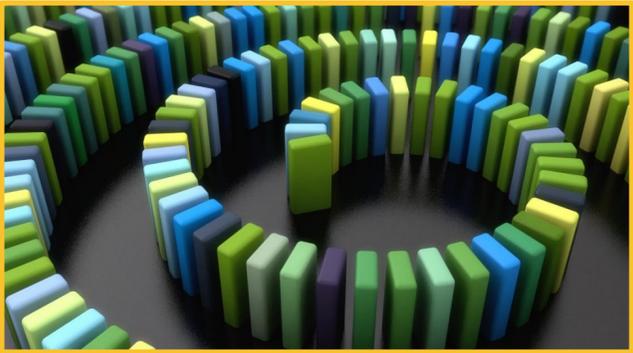
C3 INHIBITOR

COMPLEMENT CASCADE

Factor B Inhibitor

- C3 Inhibition
- Factor B. Inhibition

- ↓ Complement Activation
- ↓ Kidney Inflammation



New B-Cell Targets

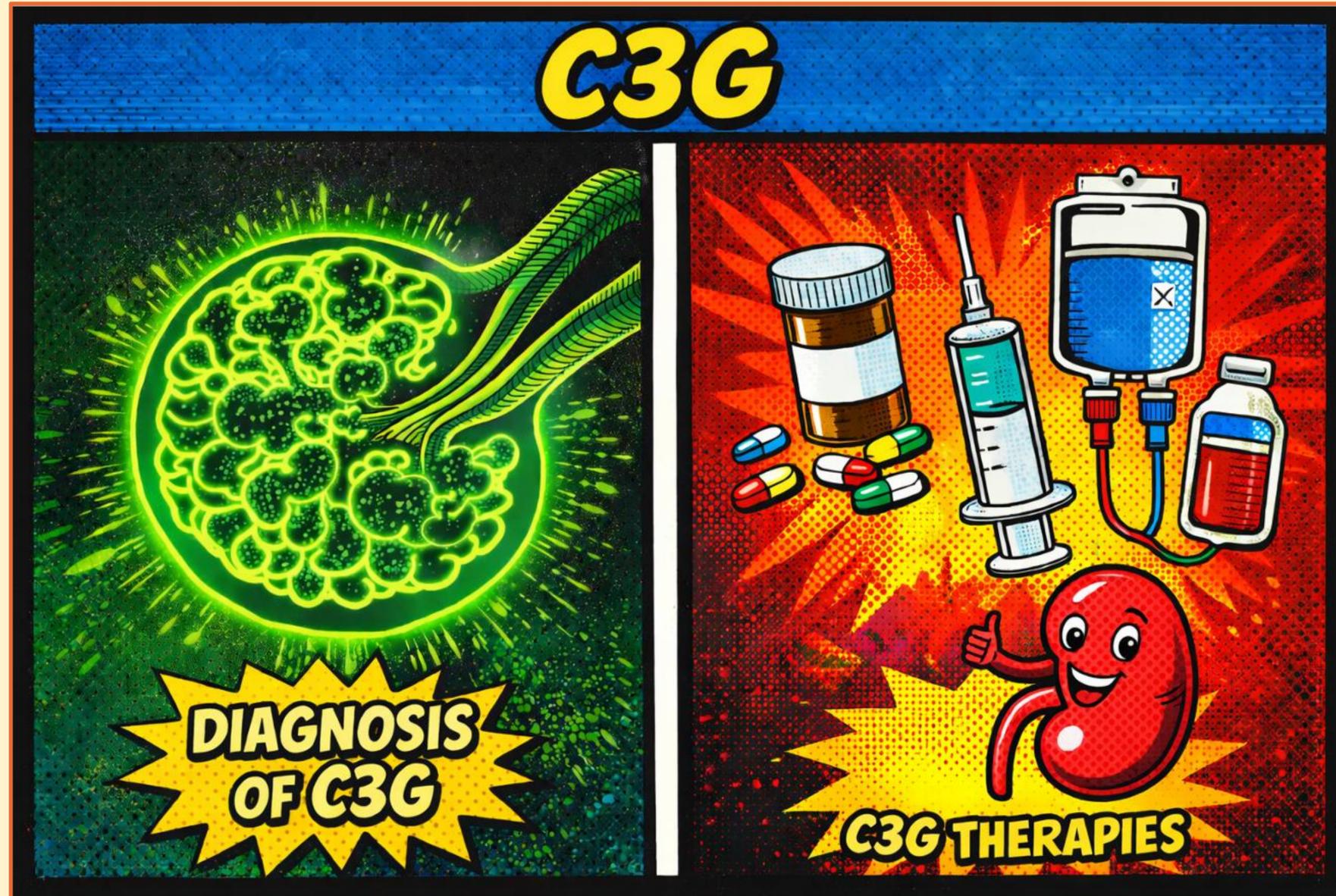
VS



Complement Inhibition



C3G



Writer:

Aarushi Varshney

Expert:

Bradley Dixon

Region Execs:

Matthew Sparks

Anna Vinnikova



C3G Region

C3 glomerulopathy (C3G) is an ultra-rare disorder that encompasses

- C3 glomerulonephritis (C3GN)
- dense-deposit disease (DDD)

Results from dysregulation of the alternative complement pathway

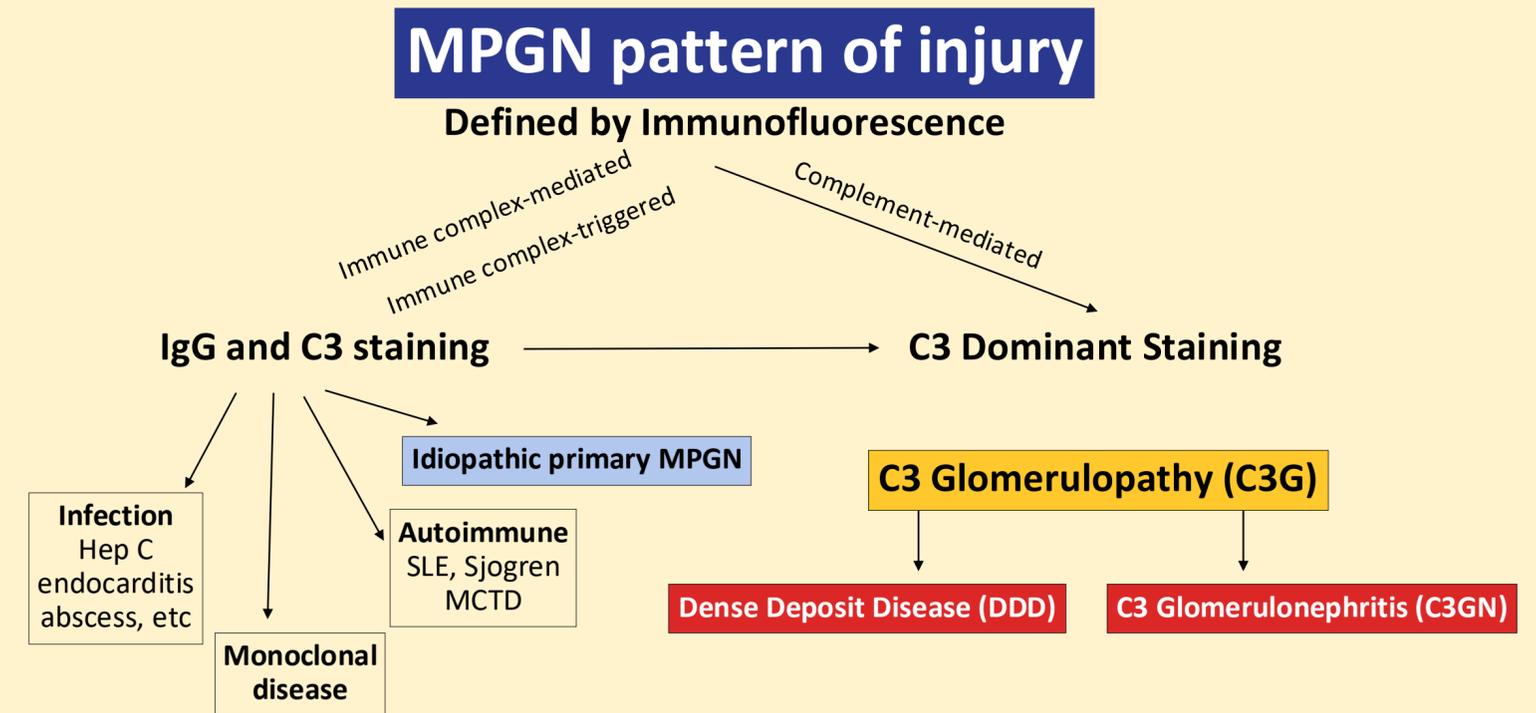
- Leads to **C3 dominant complement deposition** in the kidney
- **50% progress to kidney failure** in 10 years after diagnosis
- **High rate of recurrence** in kidney transplantation
- Usually from autoantibodies (C3/4/5 nephritic factors), for Factor B/H autoantibodies & genetic mutations (workup on next slide)

Kidney biopsy is the main diagnostic tool

- Sits at the intersection of histologic overlap, subtle immunofluorescent interpretation, inadequate complement testing, and evolving terminology. (from infection, monoclonal diseases, to autoimmune diseases) (Figure to Right)
- Which is why diagnosis is highlighted as a distinct Team

Treatment paradigm for C3G

- Past expert recommendations suggested use of MMF and steroids to dampen immune system
 - no RCTs
 - cohort retrospective studies provided mixed results
- Use of terminal (C5) complement inhibitor (eculizumab) with mixed results as well and no RCTs exist
- Use of plasma exchange and rituximab have both not demonstrated efficacy and no RCTs exist
- Recent RCTs have led to the FDA approval of two drugs, **pegcetacoplan** (C3 inhibitor) and **iptacoplan** (Factor B inhibitor)
 - pegcetacoplan- ~65% reduction in proteinuria & reduction in C3 staining,
 - iptacoplan- ~35% proteinuria reduction
- mandated to have immunization to encapsulated bacteria (meningococcal and pneumococcal vaccine)
- Guidelines are still in development, but new approved drugs will likely dramatically alter this course of this disease



Membranoproliferative glomerulonephritis (MPGN) underwent a nomenclature change in 2013 reflecting shift from morphology-based to pathogenesis-based classification. Pickering M et al. *Kidney Int.* 2013 PMID: 24172683



C3G Diagnosis



Diagnostic approach to membranoproliferative glomerulonephritis



Complement-mediated MPGN

C3GN and DDD

Low serum C3 and normal C4

IF: C3 staining at least 2 times greater than Ig
EM: Ribbon-like deposits within GBM in DDD, isolated subendothelial and mesangial deposits in C3GN



Additional tests to identify complement abnormality:

-  Autoantibody testing (C3/C4/C5 nephritic factors, factor B/H autoantibodies)
-  Genetic testing (mutations of factors B/H/I, C3, CFHR5)

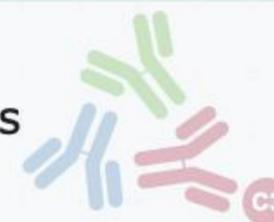
DDD associates extra-kidney manifestations (ocular drusen, partial lipodystrophy)

Immune complex/monoclonal Ig-mediated MPGN

Post-infection associated GN

Low serum C3 and C4

IF: **polyclonal Ig** and complement components



Documentation of infection (bacterial, viral, fungal, protozoal or parasitic)

Screen for autoimmune disease (systemic lupus erythematosus, Sjögren's disease, rheumatoid arthritis)

Monoclonal Ig-mediated MPGN

Low serum C3 and C4

IF: **monoclonal Ig** and complement components



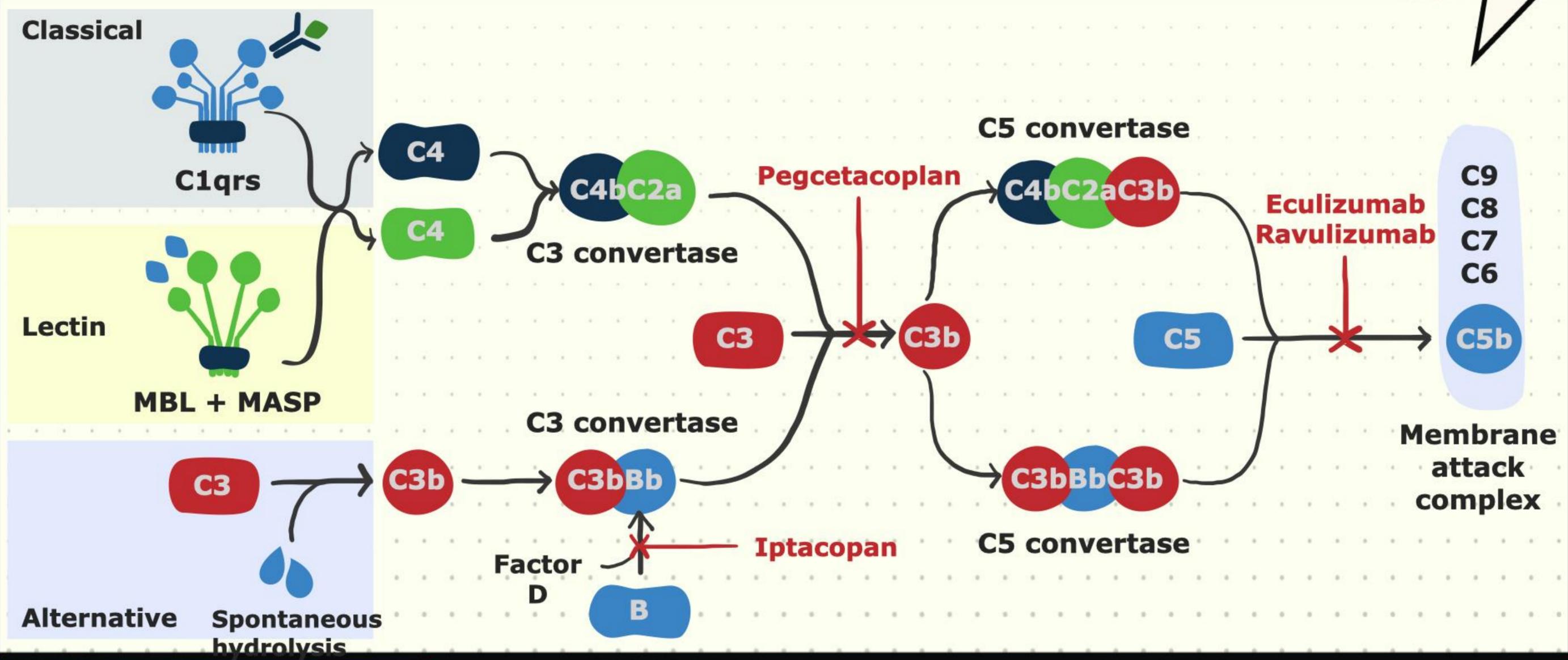
Identification of monoclonal protein (serum protein electrophoresis, serum free light chains, and/or immunofixation electrophoresis)

Bone marrow biopsy to identify plasma cell disorder

VA by **Corina Teodosiu**

Abbreviations: C3GN: C3 glomerulonephritis; CFHR: complement factor H-related; DDD: dense deposit disease; IF: immunofluorescence; EM: electron microscopy; GBM: glomerular basement membrane; Ig: immunoglobulin; MPGN: membranoproliferative glomerulonephritis

The Complement Cascade



VA by **Corina Teodosiu**

Conclusion: The complement cascade can be activated via three pathways: the classical, lectin and alternative pathways. These lead to formation of C3 convertases, which cleave C3 yielding C3b that forms more C3 convertases together with factor B via the alternative pathway. The C3b molecules further combine with C4bC2a or C3bBb into C5 convertases, cleaving C5 to C5a and C5b. The latter binds C6, followed by C7, C8 and C9 to form the membrane attack complex.

C3G Treatment



VALIANT trial: Is Pegcetacoplan in C3 Glomerulopathy and Immune-Complex MPGN Superior to Placebo?



IC MPGN, immune complex membranoproliferative glomerulonephritis

Methods & Cohort

1:1 RCT, double blind

International

C3 glomerulopathy or primary IC MPGN
N = 124

Adolescents (12-17 YO)
Adults (≥ 18 YO)

05/2022 - 06/2024

Design

Supportive care ± MMF & low dose glucocorticoids +...

Pegcetacoplan
1080mg 2x weekly
Weight adjusted ≤ 50kg
n = 63



Placebo
n = 61

Results (at 26 weeks)

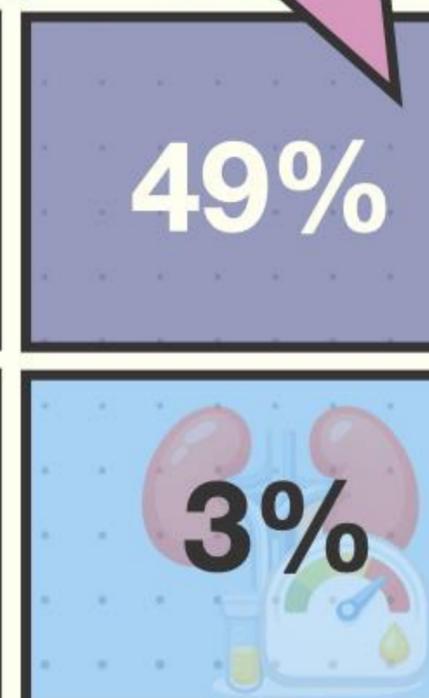
% Reduction UPCR
(95% CI)
(compared to placebo)



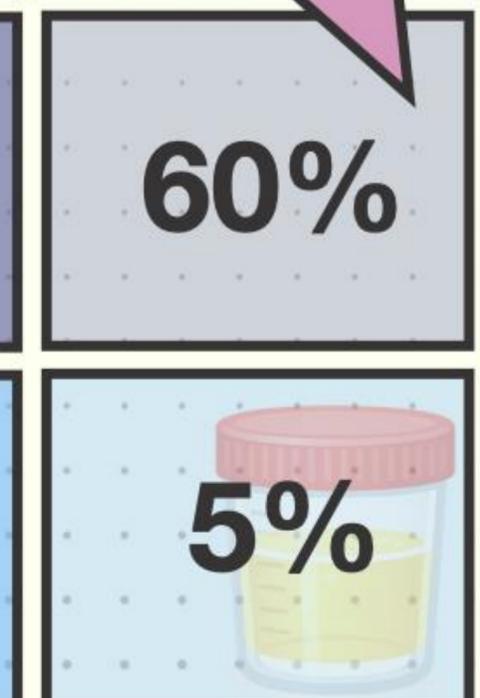
% change UPCR
(95% CI)



% Stabilized eGFR & ≥50% reduction in UPCR



≥50% reduction in the UPCR



Fakhouri F, NEJM, 2025

VA by **Sophia L Ambruso**

Conclusion: Pegcetacoplan resulted in a significantly greater reduction in proteinuria than placebo among patients with C3 glomerulopathy or primary immune-complex MPGN.

APPEAR C3G: Is Iptacopan Superior to Placebo in C3 Glomerulopathy



UPCR, urine protein creatinine ratio

Methods & Cohort

 1:1 RCT, double blind

 International

 Biopsy confirmed C3 glomerulopathy

Inclusion criteria

- C3 <77 mg/dL at screen
- UPCR 1.0 g/g at days -75 & -15 before randomization
- eGFR ≥ 30 ml/min/1.73m²

Design

 July 28, 2021- Feb 15, 2023

6 mos double blind

6 mos open label

Iptacopan
200 mg BID
n = 38

Iptacopan
200 mg BID

Placebo
n = 36

Iptacopan
200 mg BID



Results (at 6 mos)

Mean change in UPCR (g/g)
(baseline \rightarrow 6 mos)

3.33 \rightarrow 2.17

2.58 \rightarrow 2.8

% Reduction 24-h UPCR
(95% CI)
(compared to placebo)

35%
(13.8-51.1)

% change 24-h UPCR
(95% CI)

- 30%
(42.8 to -14.8)

- 8%
(-11.9 to 31.3)

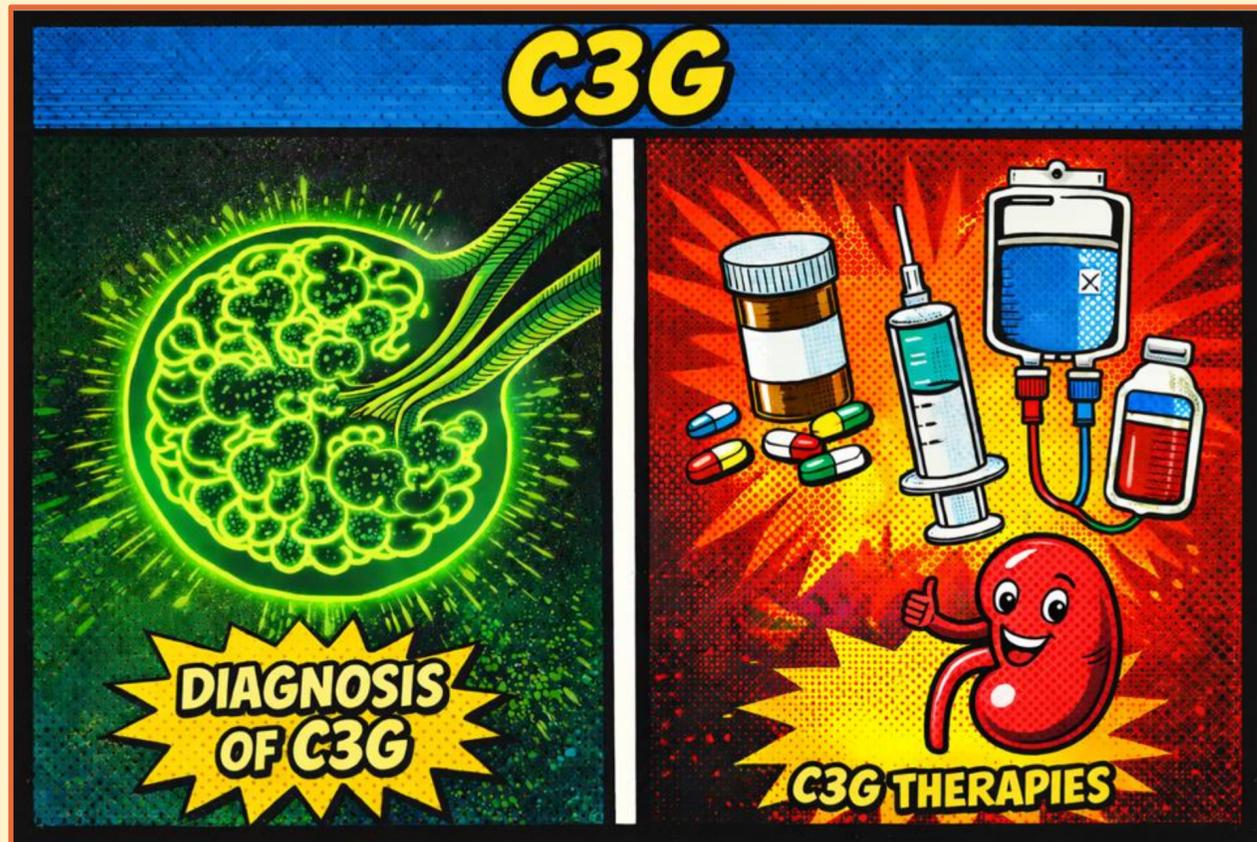
Kavanaugh D, Lancet, 2025

VA by **Sophia L Ambruso**

Conclusion: Iptacopan showed a statistically significant, clinically meaningful proteinuria reduction in addition to RAAS inhibitors and immunosuppression at 6 months. Iptacopan was well tolerated with an acceptable safety profile in patients with C3 glomerulopathy.

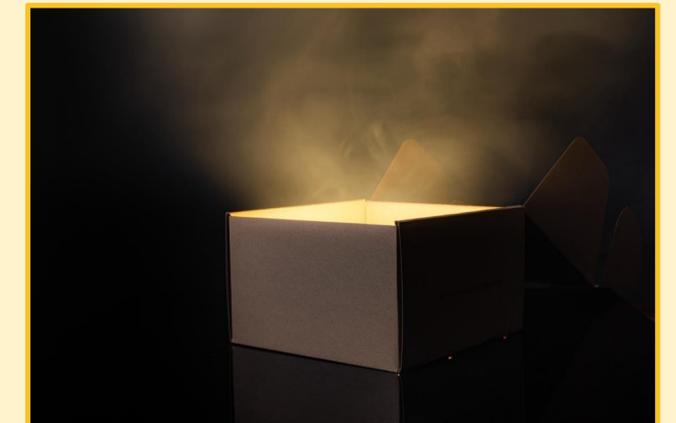
EFFLUENT EIGHT ROUND

Pick Your Champion for the C3G Region



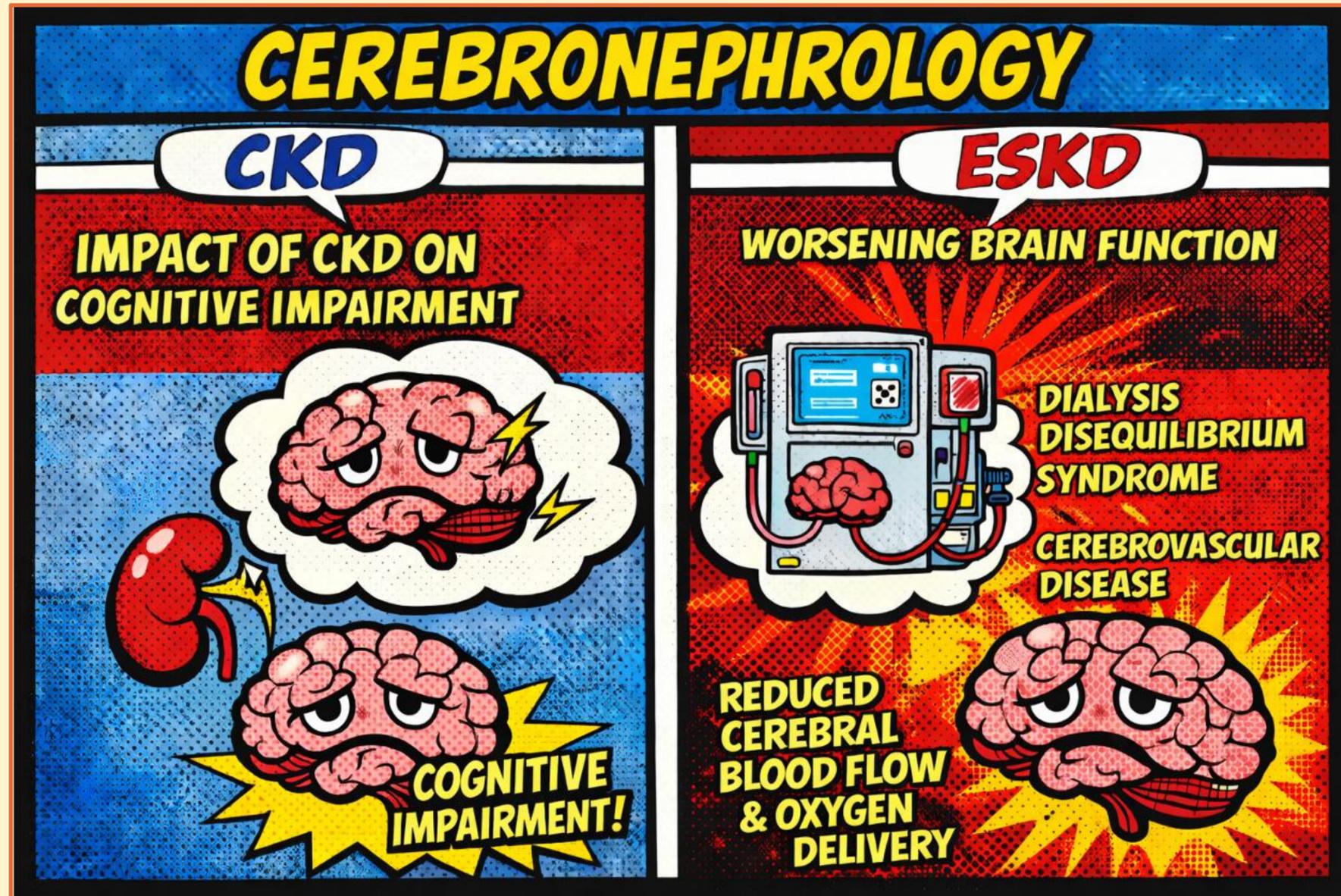
C3G Diagnosis

VS



C3G Treatment

Cerebronephrology



Writer:
Colton Jensen

Expert:
David Drew

Region Execs:
Dia Waguespack
Jeff Kott



The Brain-Kidney Axis

- **Kidney & brain share vascular design**
 - Low-resistance, high-flow organs that rely on autoregulation → vulnerable to chronic BP/vascular injury
- **Bidirectional cross-talk**
 - CKD → ↑ cerebrovascular disease, blood–brain barrier disruption, exposure to uremic metabolites
 - Brain injury → ↑ sympathetic tone; impacts Na/H₂O balance and kidney function
- **Why nephrologists should care**
 - Cognitive impairment can be an underrecognized CKD complication and impacts adherence, self-management, and outcomes

“**Team CKD**” (chronic microvascular + metabolic injury) vs “**Team ESKD**” (added dialysis-related hemodynamic/osmotic stress)



Cognition is not “extra-renal”—it’s part of CKD/ESKD care.



in CKD



Team CKD

- **What it is**

- Cognitive impairment = deficit in ≥ 1 domain (executive function, memory, attention, language, visuospatial, learning) spanning mild \rightarrow dementia

- **How common / who's at risk**

- CKD is common (especially in older adults), and cognitive impairment often goes unnoticed
- Studies highlighted in the post: $\sim 48\%$ prevalence of neurocognitive impairment in older CKD cohorts
- Risk rises with lower eGFR, higher albuminuria, and higher systolic BP

- **Pathophysiology - multifactorial**

- Cerebral small vessel disease
- Anemia/oxygen delivery mismatch: even with \uparrow cerebral blood flow, oxygenation may be impaired
- Glymphatic dysfunction (CNS waste clearance) and uremic metabolites accumulating earlier than “overt uremia”

Prevention focus:

control BP and
albuminuria



in ESKD



Team ESKD

Core concept

- Kidney replacement therapy necessarily lowers osmolality, intravascular volume, and MAP → can provoke transient ischemia + ICP fluctuations

Cerebrovascular + structural brain injury

- ESKD patients have high stroke/CVD burden
- MRI/DTI studies: more atrophy/WMH and DTI shows reduced white matter integrity
- PD vs CKD imaging: PD associated with lower gray matter volume and greater decline over 2 years

Hemodynamics during HD: often “silent” brain stress

- Near-infrared spectroscopy measurements with $\geq 15\%$ cerebral oxygen drop; most episodes asymptomatic
- Transcranial Doppler: mean flow velocity drops (~10%); correlates with UF and with subsequent cognitive/WMH signals
- ICP monitoring and MRI data: HD can raise ICP and increase cerebral water



Dialysis Disequilibrium Syndrome

What cerebral consequences of rapid solute removal?

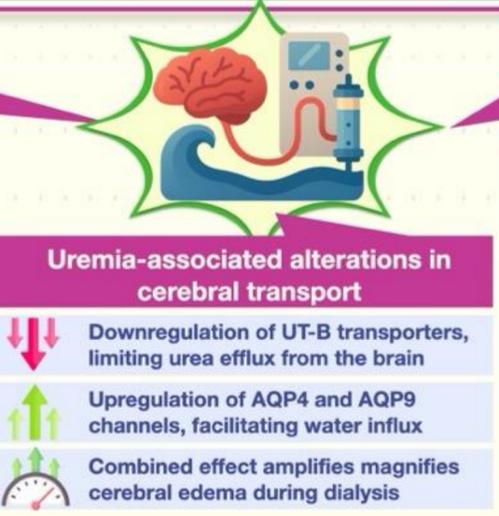
Mechanisms

Reverse urea effect (dominant mechanism)

- Rapid plasma urea removal
- Delayed urea clearance from brain/CSF
- Development of a transient blood-brain osmotic gradient
- Net movement of water into the brain, resulting in interstitial cerebral edema

Additional contributory mechanisms (context-dependent)

- Generation or persistence of idiogenic osmoles (i.e. AKI or acute hyperosmolar states)
- Rapid correction of hypernatremia or hyperglycemia
- Rapid bicarbonate correction → paradoxical CNS acidosis



Uremia-associated alterations in cerebral transport

- Downregulation of UT-B transporters, limiting urea efflux from the brain
- Upregulation of AQP4 and AQP9 channels, facilitating water influx
- Combined effect amplifies magnifies cerebral edema during dialysis

Diagnosis

- Timing: during or shortly after dialysis
- DDS= diagnosis of exclusion
- Mild**: Headache, nausea, dizziness, restlessness
- Moderate**: Vomiting, confusion, agitation, muscle cramps, hypertension
- Severe**: Seizures, coma, raised intracranial pressure, death
- CT/MRI may show cerebral edema
- Normal imaging does not exclude DDS

Prevention and management

Slow initial dialysis

- Short session (~2 h)
- Low blood flow (200–250 mL/min)
- Target urea reduction $\approx 40\%$

Maintain plasma osmolality

- Sodium modelling / higher dialysate sodium
- Consider glucose or mannitol

Modality choice

- Prefer CRRT with very high-risk (slower, continuous correction)

Identify high-risk patients

- First dialysis
- Very high BUN (no absolute threshold)
- AKI > CKD
- Children, elderly
- Metabolic acidosis
- Hypertremia / hyperglycemia
- Pre-existing neurologic disease or cerebral edema

Acute management

- Stop or slow dialysis
- Osmotherapy (mannitol)
- Supportive neurologic care
- Exclude mimics: hypoglycemia, stroke, hypertensive encephalopathy

DDS - Dialysis disequilibrium syndrome, UT-B - Urea transporter B, AQP - Aquaporin, CSF - Cerebrospinal fluid, AKI - Acute kidney injury, CKD - Chronic kidney disease, BUN - Blood urea nitrogen, CNS - Central nervous system, CRRT - Continuous renal replacement therapy

Saha M, Allon M. Clin J Am Soc Nephrol. 2017

Mistry K. Int J Nephrol Renovasc Dis. 2019

VA by **Cristina Popa**

Conclusion: Dialysis disequilibrium syndrome arises from rate-dependent disequilibrium between plasma and brain during dialysis resulting in cerebral edema. It is largely preventable through controlled solute and osmolality reduction, particularly during initial treatments.

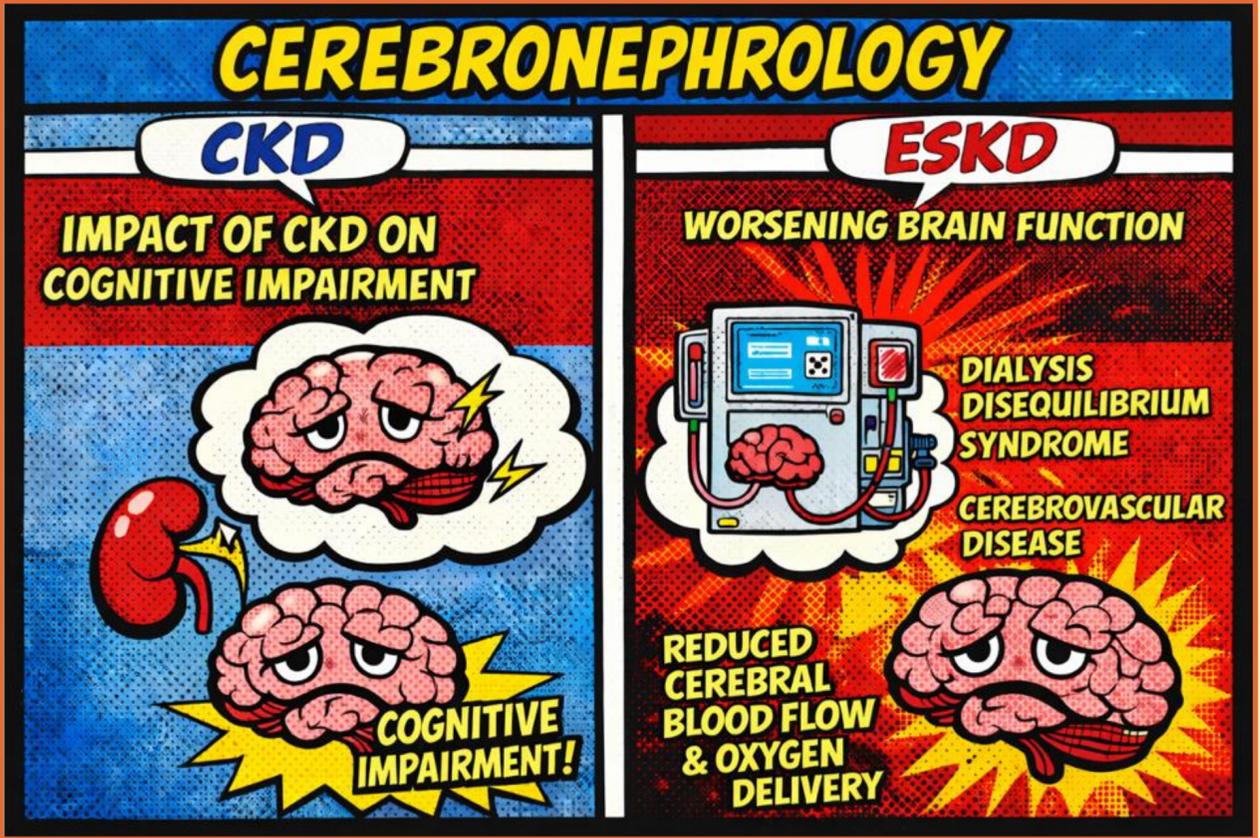


Dialysis physiology can stress the brain



EFFLUENT EIGHT ROUND

Pick Your Champion for the Cerebronephrology Region



in CKD

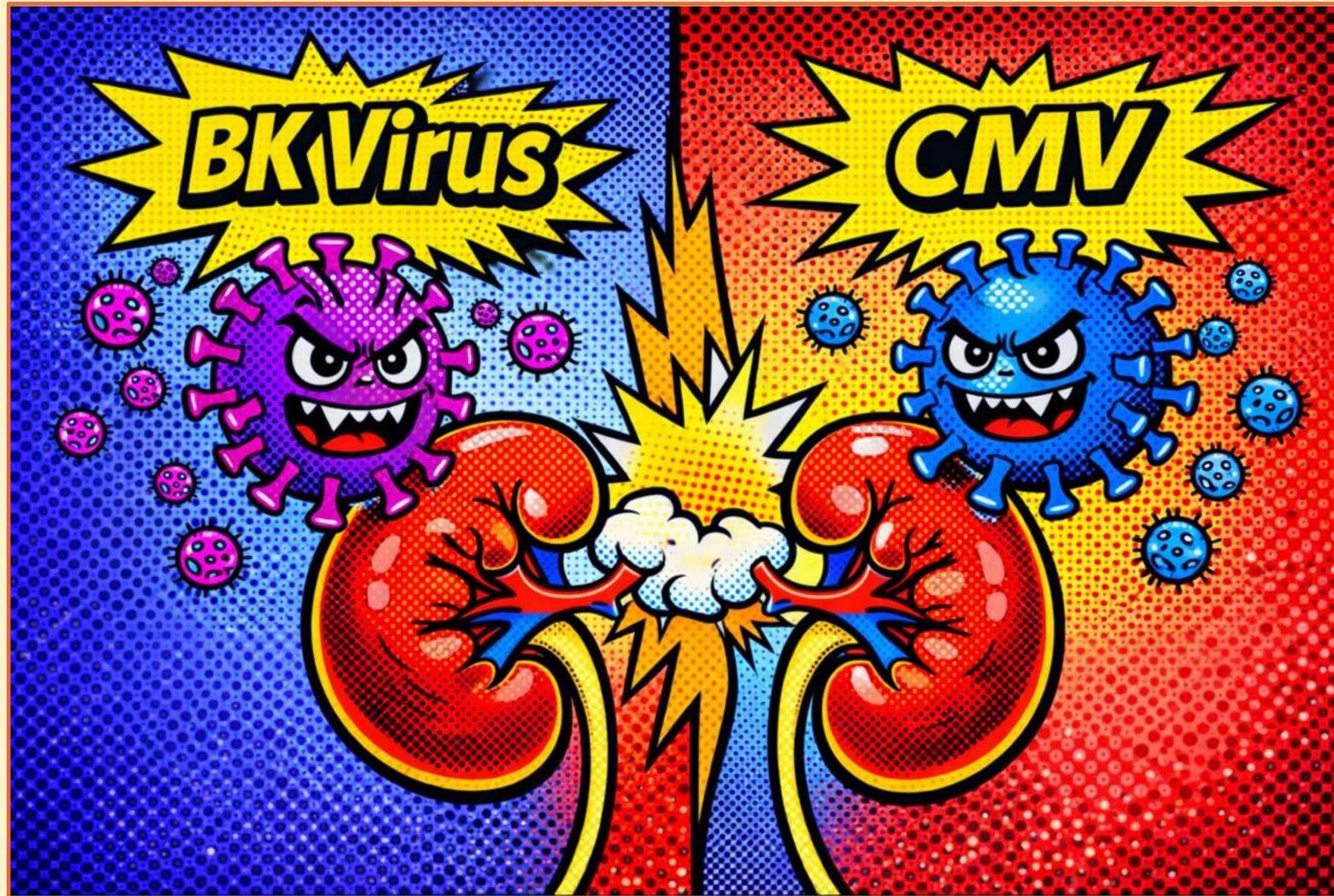
VS



in ESKD



Trolls of Transplantation



Writers:

Hariharasudan Natarajan
Caitlyn Vlasschaert

Experts:

Sam Kant
Jeannina Smith

Region Execs:

Samira Farouk
Ana Catalina Alvarez-Elías

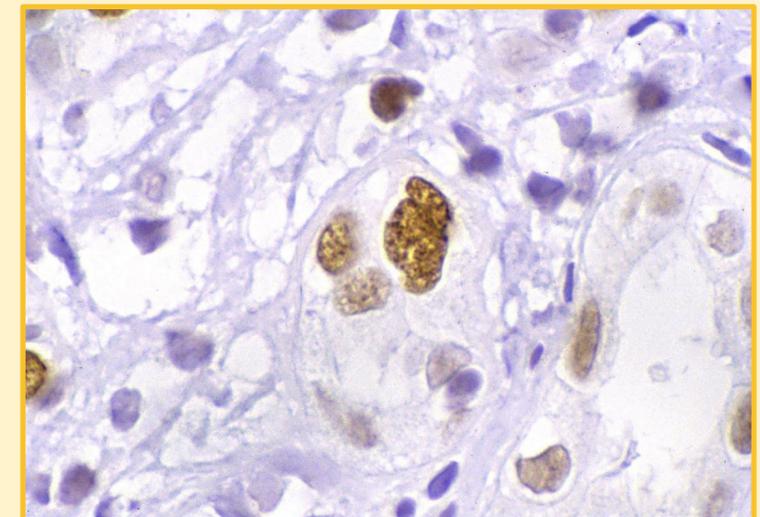
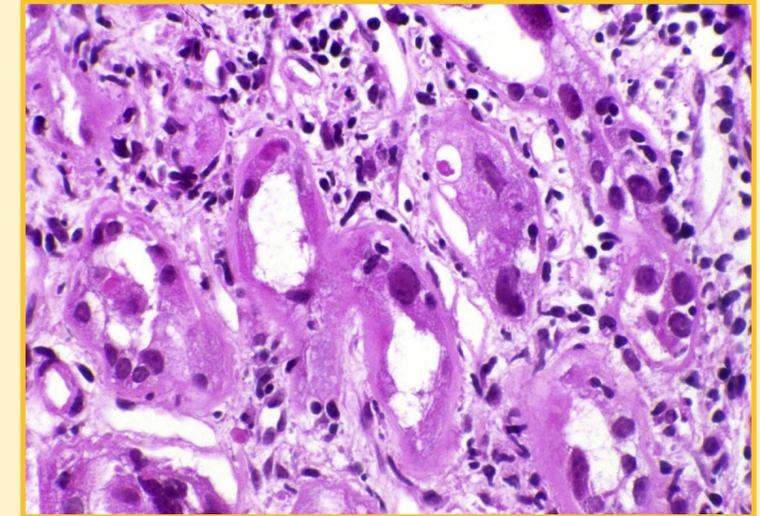


BK



BKV: A Silent Passenger With A Heavy Toll

- **Meet BK virus (BKV):** Identified in 1971 in Sudanese kidney transplant recipient (KTR) BK SD GB (*BKV = cousin of JCV: named for John Cunningham*)
- **BKV is a “sleeper”:** 90% of adults seropositive; enters urothelial & tubular cells → lifelong latency in an episomal form (*as extra-chromosomal circles of DNA tucked into the nucleus without producing viral proteins*); can awaken/reactivate in immunosuppressed host
- Recipient age, prior KT, recent rejection, specific HLA class profiles: linked to BKV reactivation
- BK viremia (*we actually measure DNA-emia 🦟*) > 10K copies = presumptive BKVAN*
- BKVAN: in up to 10% of KTR; up to 50% allograft loss
- Donor-derived cell-free DNA assays have shown promise to distinguish viral injury from alloimmune rejection.
- Antivirals that have failed: fluoroquinolones, leflunomide, cidofovir. **For now, KISS**:** just lower immunosuppression!
- **Potentially promising therapies:** viral-like particle vaccines, monoclonal antibodies (potravitug, MAU868), BKV-specific T cells (e.g. posoleucel), targeting agnoprotein & viral mRNA splicing

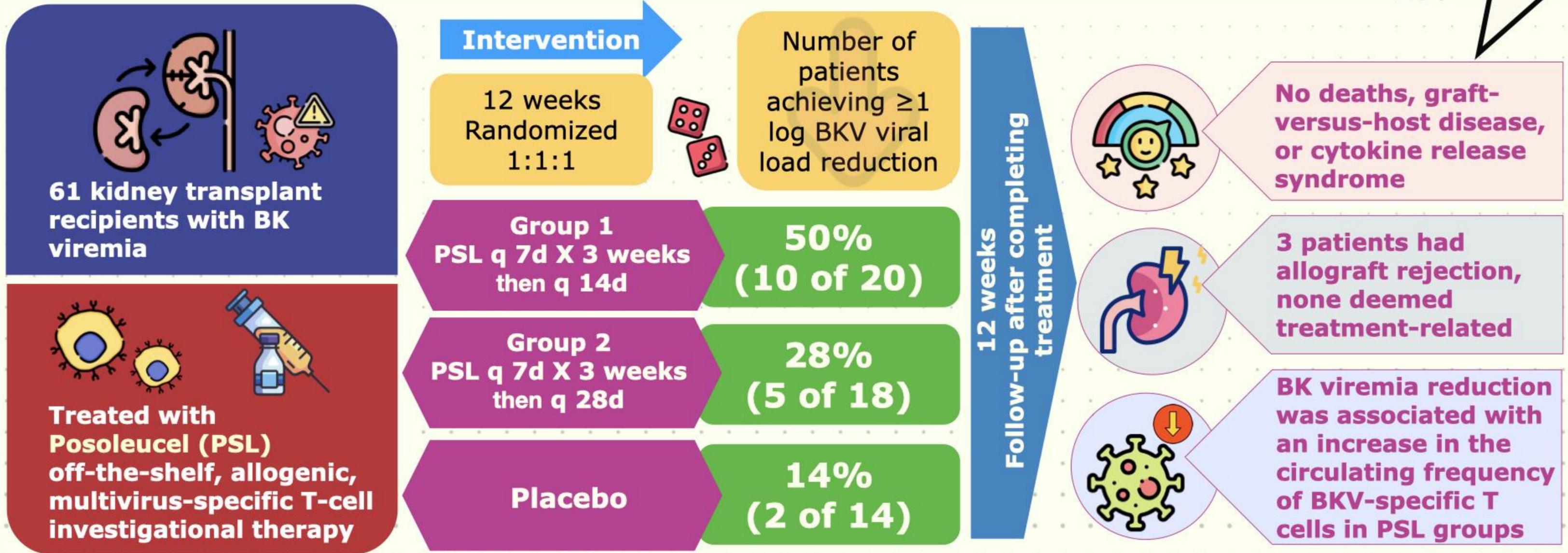


(Top) Dark purple (basophils) inclusions in tubular epithelial cells suggest BKV associated nephropathy; (Bottom) SV40 Immunohistochemistry confirms BKV. Adapted from the *AJKD Atlas of Renal Pathology*

*BKV-associated nephropathy (BKVAN)

**Keep it simple stupid

Posoleucel in Kidney Transplant Recipients with BK Viremia: Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial



Anil Chandraker et al, JASN 2024 May 1;35(5):618-629

VA by Kajaree Giri

Conclusion: Posoleucel was generally safe, well tolerated, and associated with a larger reduction of BK viremia compared with placebo. Limitations of this study include the relatively short duration of follow-up and lack of power to detect significant differences in clinical outcomes.

CMV





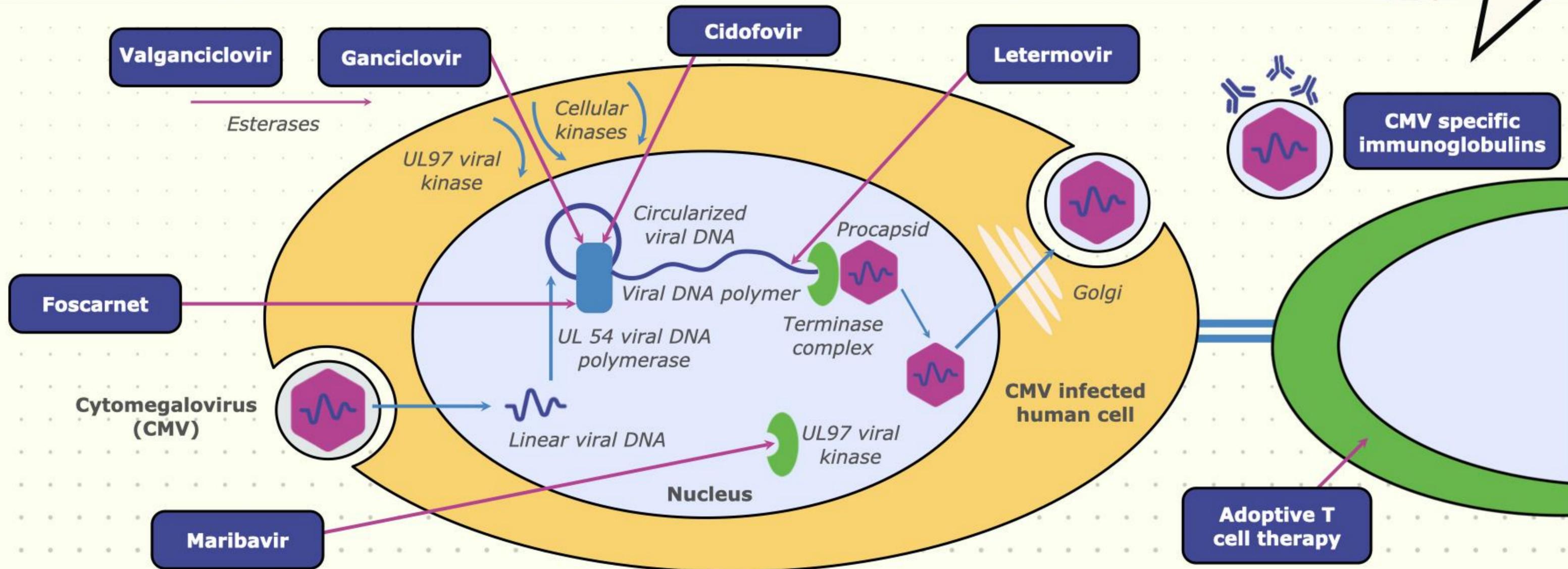
CMV: Whether Asymptomatic or Deadly, Always Harmful



- **Meet cytomegalovirus (CMV):** AKA human herpes virus 5 (HHV5); Identified in 1956 in infants
- **Most common** opportunistic infection among KTR
- **CMV genome:** highest level of genetic diversity of all known HHV → antiviral resistance is a problem
- **2 phases:** lytic (active viral replication and contagion) & latent (viral “hibernation”)
- **2 preventative strategies**
 - **Universal:** initiation on anti-viral drug for finite duration (valganciclovir or letermovir ↓ leukopenia)
 - **Preemptive:** screen for CMV DNAemia, treat if you find it
- **First line therapies:** PO valganciclovir & IV ganciclovir (both activated by CMV kinase pUL97 & inhibit DNA polymerase pUL54)
- **Options for refractory infections (+/- resistance):** pUL54 inhibitors (foscarnet, cidofovir), pUL97 inhibitor (maribavir)
- **Potential promising future therapies:** CMV-specific T-cells, vaccines, monoclonal antibodies, adoptive T-cell therapies
- **CMV-related kidney injury mimics BKV:** tubulointerstitial nephritis, intranuclear glassy, basophilic inclusions with a surrounding halo (“owl’s eye”). Collapsing FSGS has been reported



Mechanism of Action of Anti-CMV Therapies



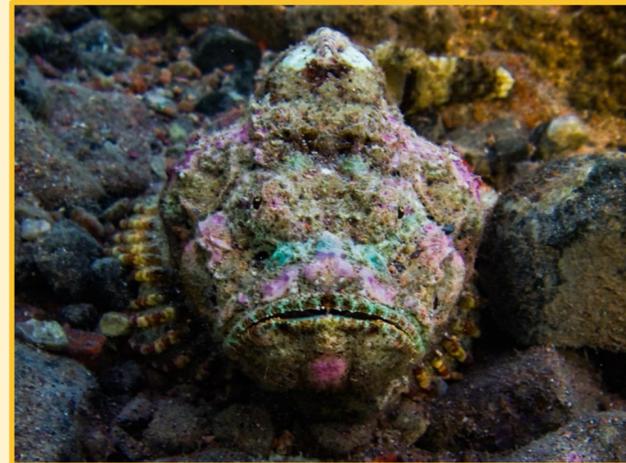
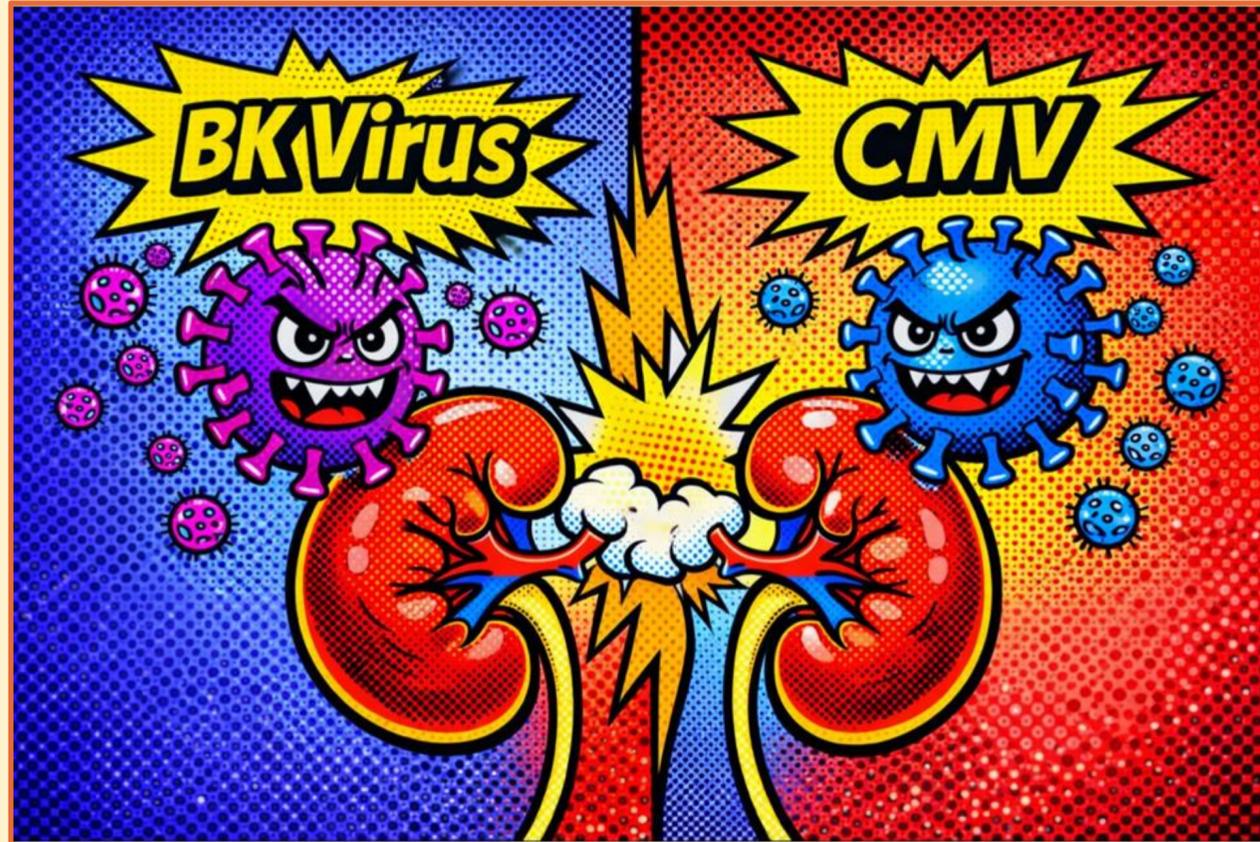
Adapted from Walti et al,
Transplant international, 2023
Oct 12;36:11785

VA by **Krithika Mohan**

Ganciclovir requires phosphorylation by UL97 for activation. Both, ganciclovir and cidofovir require phosphorylation by host *cellular phosphokinases* for activation. Both drugs inhibit the *viral DNA polymerase* (UL54) at the desoxynucleotide triphosphate binding site. Foscarnet inhibits UL54 at the pyrophosphate binding site. Maribavir inhibits UL97, & phosphorylation of viral and host cellular proteins. Letermovir inhibits binding of the newly produced viral DNA polymers to the *viral terminase complex*. CMV-specific adoptive T cells recognize CMV-infected cells via T cell receptor.

EFFLUENT EIGHT ROUND

Pick Your Champion for the Trolls of Transplantation Region



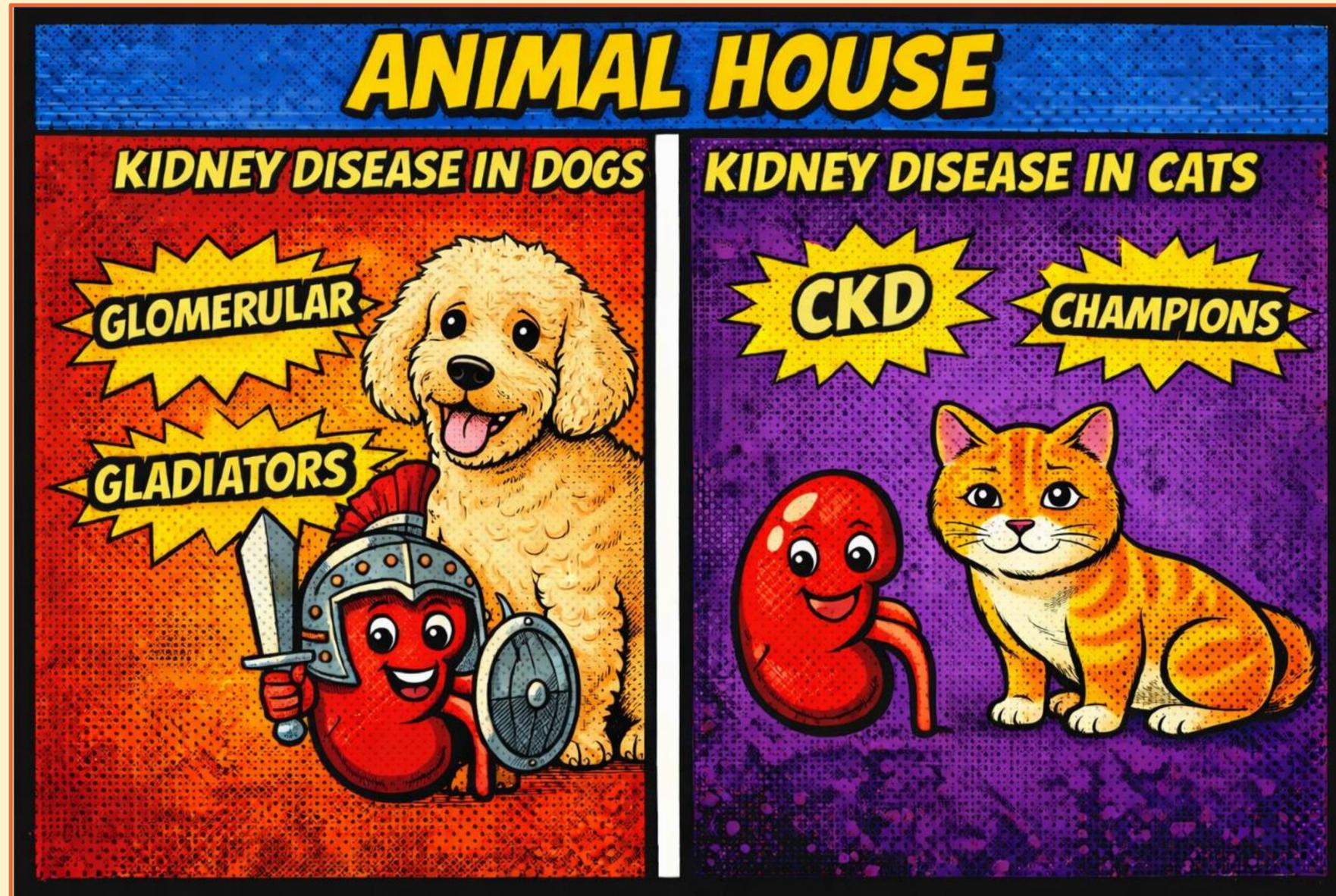
BK

VS



CMV

Animal House



Writers:

Autumn Harris

Kelly Hyndman

Experts:

Sarah Street

Susan DiGiovanni

Region Execs:

Anna Vinnikova

Matthew Sparks



Dogs



Canine Kidney - A Bystander



Dogs are proteinuric powerhouses & glomerular gladiators

Physiology

- GFR 3.5-4.5 mL/min/kg
- Typical SG > 1.030

Anatomy

Bean shape, 2.5-3.5 times size of 2nd lumbar vertebra

Susceptible to glomerular diseases

Higher GFR per unit of body weight causes greater constant pressure on glomerular filtration barrier

↓

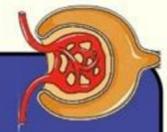
Prone to immune complex mediated glomerulonephritis (Secondary to infections, chronic inflammation & neoplasia)

↓

Cause immune complex deposition in the glomeruli activating the inflammatory cascade + decreased clearance

↓

Proteinuria + glomerular damage



Acquired

Species	Disease	Primary lesion	Inheritance pattern	Gene mutation
Samoyed	Hereditary Nephropathy	Glomerular	XR	COL4A5
English Cocker Spaniel	Hereditary Nephritis	Glomerular	AR	COL4A4
Shih Tzu, Lhasa Apso	Renal Dysplasia	Tubulointerstitial, Glomerular	AR or AD with incomplete penetrance	Unknown, potentially COX-2 mutant alleles
Bull Terrier, Dalmatian	Hereditary Nephritis	Glomerular	AD	Not fully characterized
Chinese Shar-Pei	Familial Amyloidosis	Primarily Medullary/Tubulointerstitial	Unknown, possibly AR	SAA gene variants studied, no direct link

Etiology of glomerular damage

Inherited

Hypertension dependant on RAS
Drug of choice - ARB

Common kidney stones:
Male dogs- Ca oxalate > struvite > cystine
Female dogs- Struvite >>Ca oxalate

SG specific gravity RAS renin angiotensin system XR x linked recessive AR autosomal recessive AD autosomal dominant ARB angiotensin receptor blocker

AKI, CKD and ESKD in

- **AKI:** driven by ischemic/inflammatory conditions (58%), infections (8%) unknown causes (24%) and nephrotoxins (6%)



- Common nephrotoxins are grapes, ethylene glycol, NSAIDs (especially human-use), antibiotics, vit D
- IRIS AKI grading I-V uses creatinine, urine output and RRT requirement

- **CKD:** persistent urinary abnormalities > 3 mo

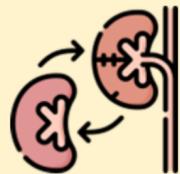
- IRIS CKD staging 1-4 uses creatinine, proteinuria and blood pressure

- **Dialysis:** treatment of severe AKI and sometimes ESKD



- Viewed as “bridge to recovery”, rarely “bridge to nowhere”(ESKD) (ethical dilemmas)
- Cost: \$3,000-5,000 for the first 2-3 treatments, \$10,000-20,000 total including ICU care
- Success rate: 50% survival to hospital discharge, higher in infections (eg. leptospirosis)
- Prognosis: fair to good for reversible AKI

- **Transplant:**



- High morbidity and mortality, rarely successful
- Intense host immune response, rapid rejection
- Requires potent, multi-agent protocols with severe side effects
- Opportunistic infections are common due to dogs’ behavior and exploration of the environment
- Cost upwards of \$20,000 + high annual drug costs

Cats



Feline Kidney - The Protagonist



Cats are desert animals, optimized for arid environments. And they are CKD champions!



Physiology

- GFR 2.5-3.5 mL/min/kg
- Typical SG > 1.035
- Superior ability to concentrate urine
- Max U.Osm 3000 mOsm/kg

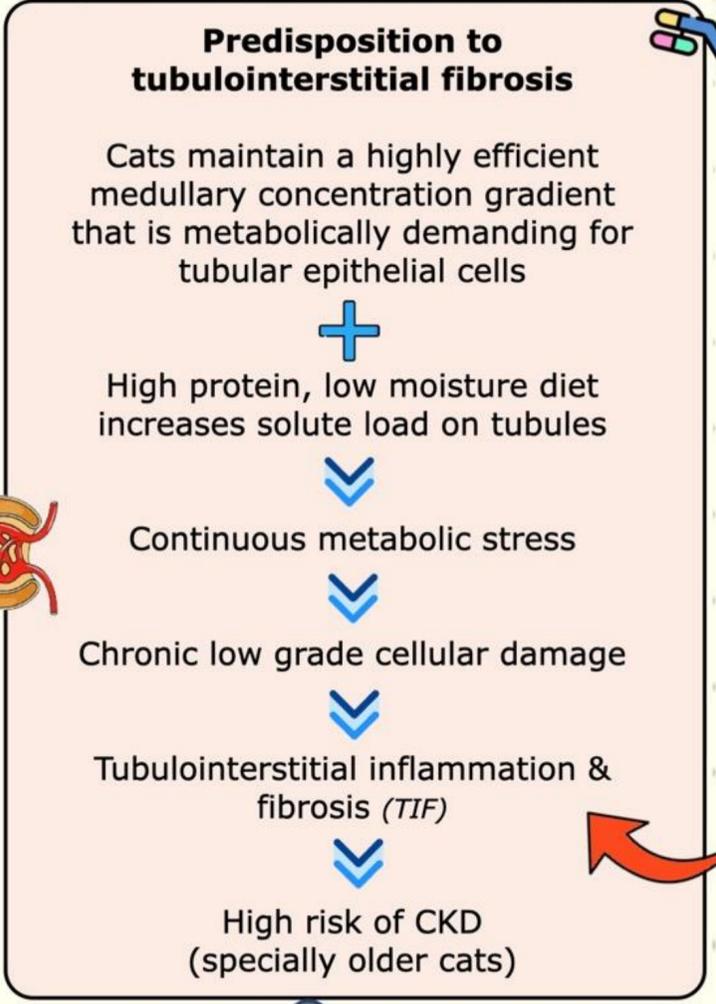


Anatomy

Rounded shape, 2-3 times size of 2nd lumbar vertebra

Microscopy

- In cats, tubular cytoplasm & nuclei are larger due to higher metabolic activity
- Tubular lumens are narrower =>
- Higher risk of tubular obstruction in AKI in cats vs dogs
- Unique feature - islands of ascending branches of loop of Henle amid densely arranged papillary ducts



Immune & genetic landscape

Cats are less commonly affected by vector-borne infections/ immune-mediated conditions

Greater genetic diversity within breeds may be contributing to natural resistance

Feline immune response targets metabolically stressed tubules > glomeruli

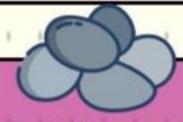


Inherited diseases

Polycystic kidney & amyloidosis replace normal tissues with cysts or deposits



More prone to kidney stones (struvite > calcium oxalate > uric acid)



Hypertension less dependant on RAS
Drug of choice - Calcium channel blockers

Glomerular diseases are less common

SG specific gravity RAS renin angiotensin system U.osm Urine osmolality

AKI, CKD and ESKD in



- **AKI:** less common than CKD

- Common causes are trauma, obstruction, volume depletion and toxins such as lilies



- **CKD Champions:** prevalence 20% in all cats and 80% in geriatric cats; treatment:

- Hydration (Hydra Care, water fountains, e-tubes)
- Antiemetics and appetite stimulants
- Darbepoetin or Molidustat for anemia
- Phosphate binders
- New: uremic toxin binders (Renaltec)

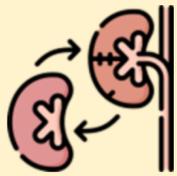
- **Dialysis:** treatment of severe AKI and intoxications

- Cost: same as in dogs
- Success rate: 50% survival to hospital discharge, less in intoxications (eg. lilies)
- Prognosis: guarded to fair



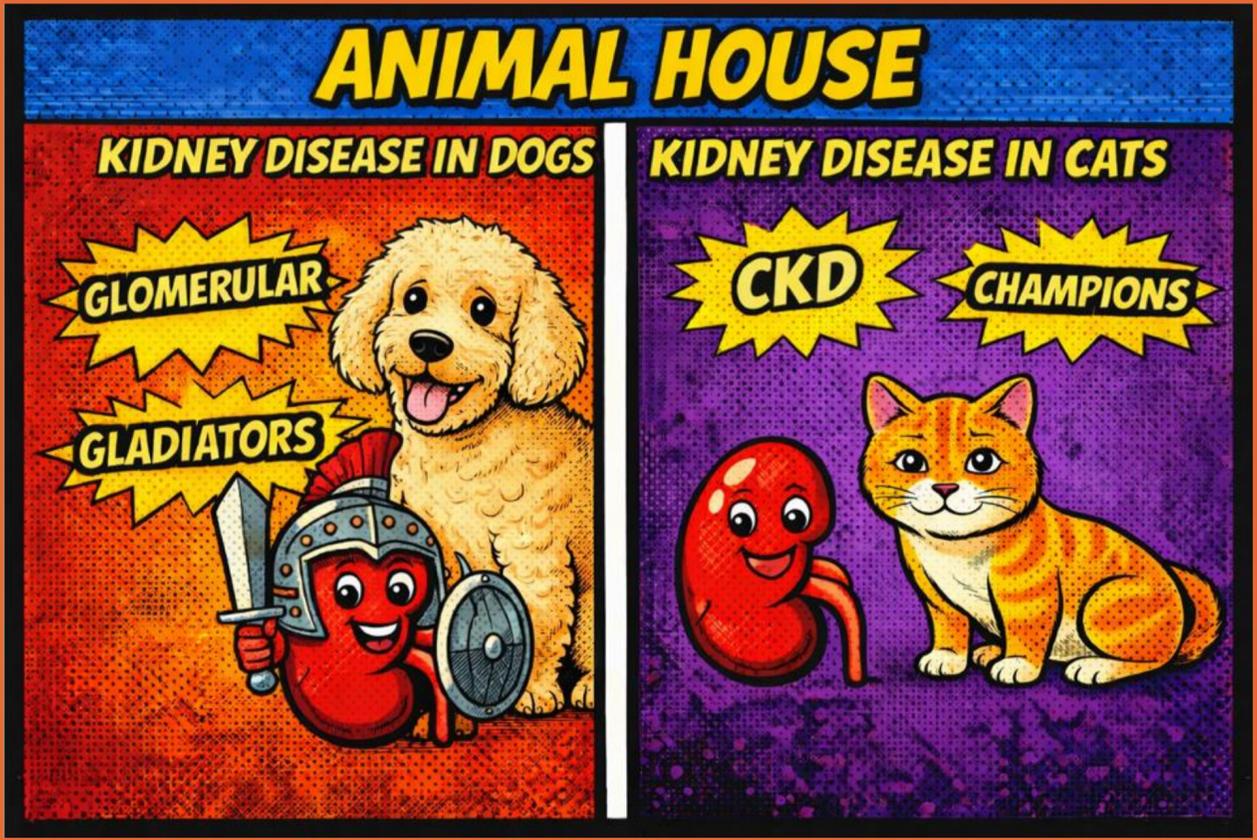
- **Transplant:**

- Survival 60-70% at 1 yr, 40% at 3 yrs
- Tolerant immune response, cyclosporine is a key component of immunosuppressive regimen
- Cost \$8,000-15,000 for surgery + \$500 - \$1,500 annually for drugs
- Ethical consensus: offered at specialized centers, donor must be adopted by recipient's owner



EFFLUENT EIGHT ROUND

Pick Your Champion for the Animal House Region



Dogs

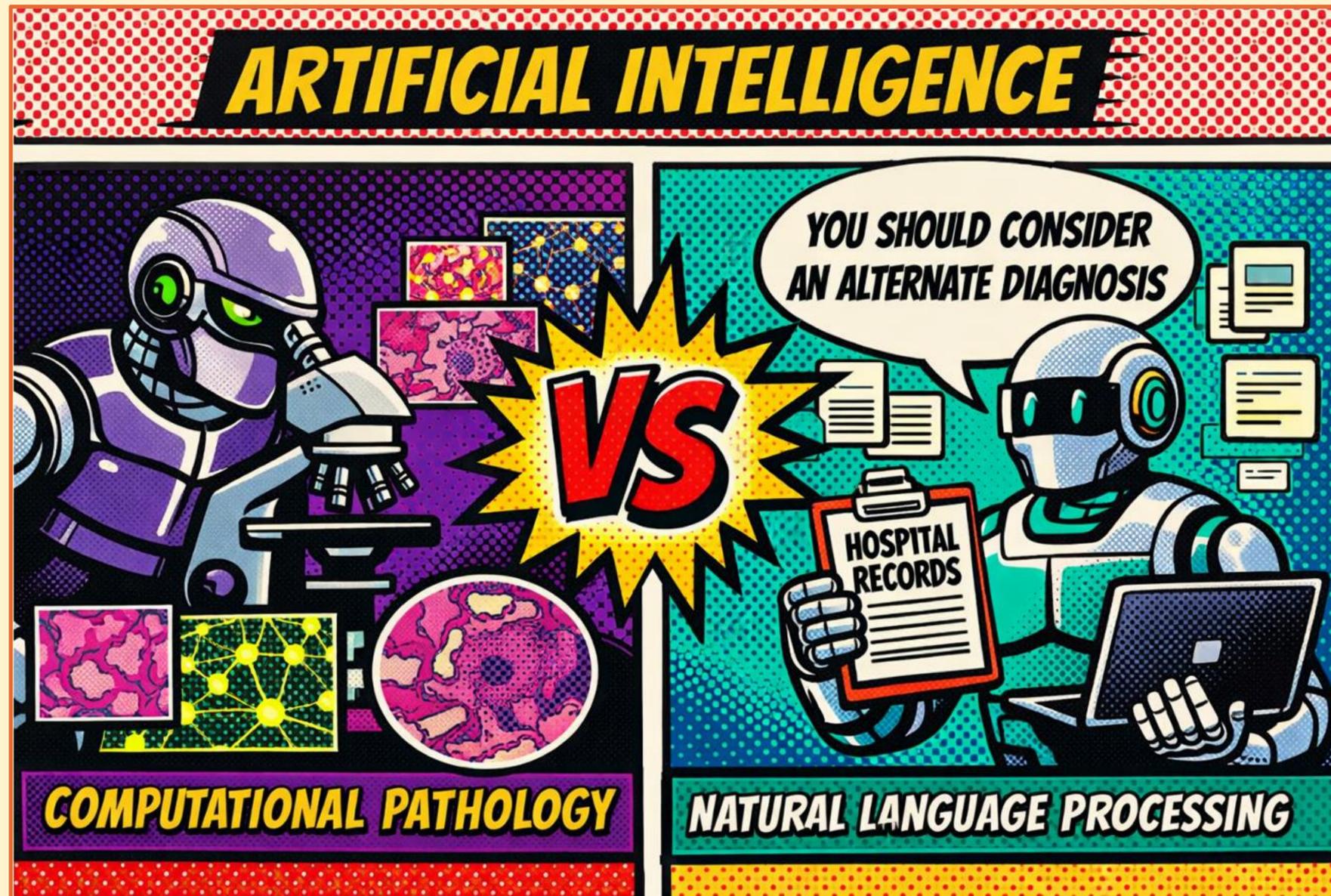
VS



Cats



Artificial Intelligence



Writers:

Neil Evans

Aditya Yelamanchi

Experts:

Lili Chan

Kuang-Yu Jen

Region Execs:

Ana Catalina Alvarez-Elías

Jeff Kott



Computational Pathology



Natural Language Processing



Artificial intelligence in nephrology

Clinical applications and real-world limits



How AI is used?

Supervised machine learning (ML)

predicts known outcomes

Deep learning

imaging, pathology, time-series

Unsupervised ML

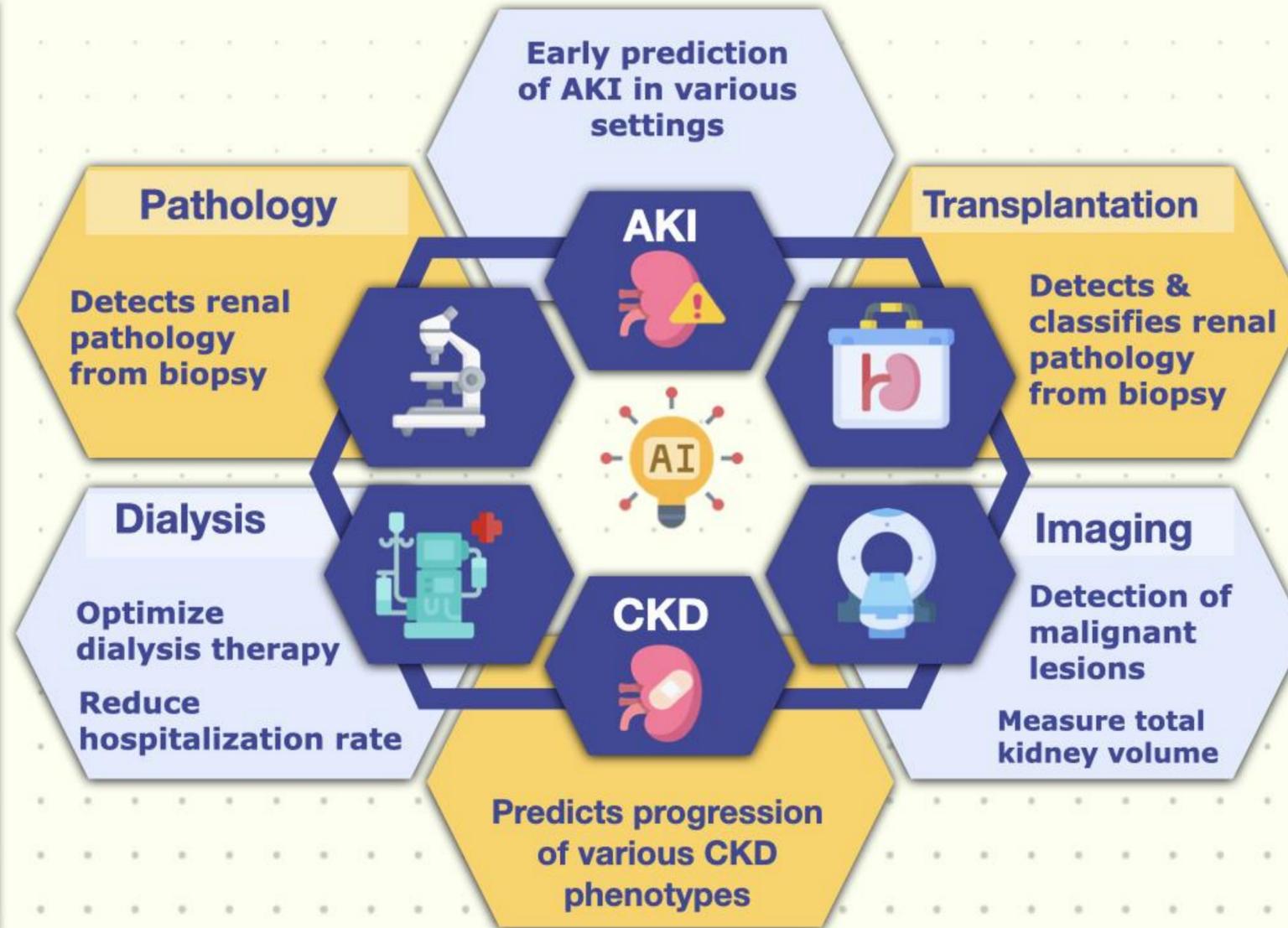
phenotypes / clustering

Natural language processing

extracts signals from clinical notes

Reinforcement learning

conceptually useful; limited by ethics/data in healthcare



AI challenges

Bias- non-representative data

Leads to inequity

Data quality

Missing/heterogenous/siloed

Black box- low transparency

Translating to low trust

Safety

Distribution shift after rollout

Standardization

EHR interoperability gaps

Medico/legal/ethics

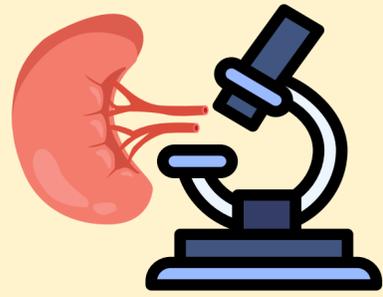
Privacy, liability, governance

Singh P et al, Kidney Med, 2024

VA by **Cristina Popa**

Conclusion: AI is already shaping nephrology by helping spot risk earlier and bring more consistency to care. It highlights patterns and does not make decisions. The danger is using it blindly. Nephrologists need to understand what AI can and cannot do, so it supports clinical judgment rather than replacing it.

Two Different Engines, Two Different Problems



Computational Pathology

Data source: Digitized histology images

Unit of analysis: Pixels → Structures

Strength: Quantification (fibrosis, lesions, segmentation)

Best for: Morphology-driven questions

Natural Language Processing (NLP)

Data source: Clinical documentation

Unit of analysis: Words → Concepts

Strength: Pattern extraction across time

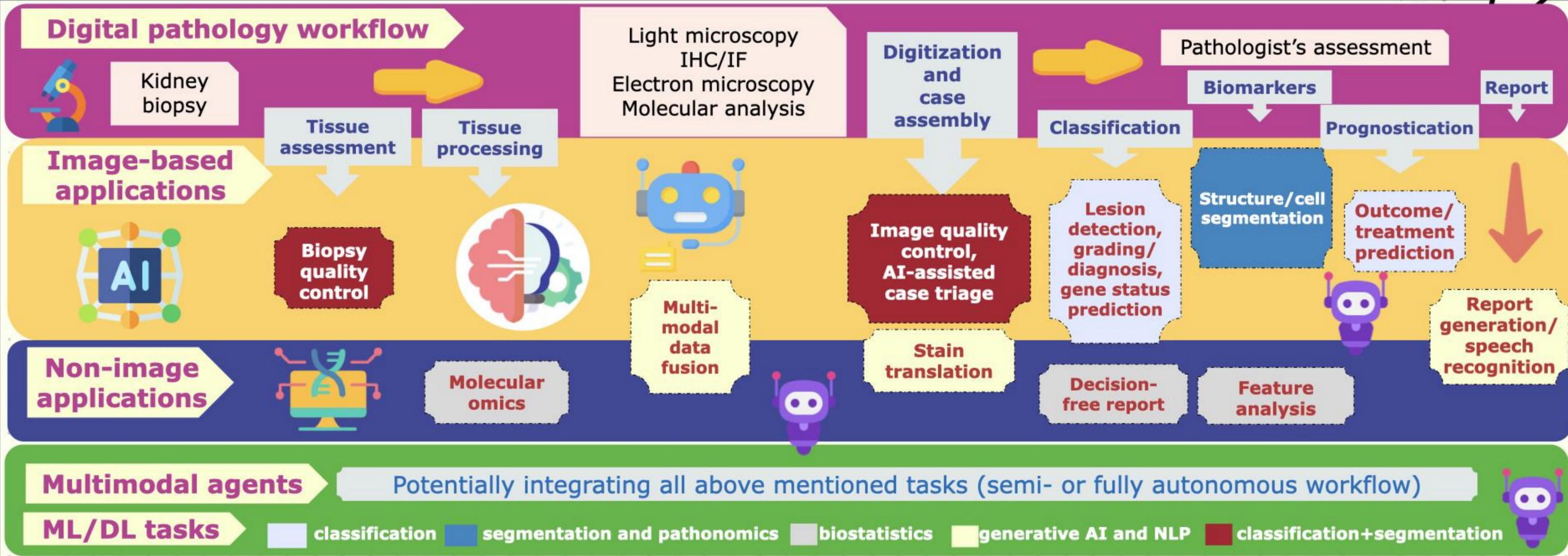
Best for: Phenotypes, medication signals, trajectories



AI in nephrology is not one tool — it is fundamentally different approaches solving different clinical problems



Advances in Computational Nephropathology: Can Integration of AI Tools Improve the Digital Pathology Workflow?



Hölscher et al,
Kidney International, 2025

VA by **Kajaree Giri**

Conclusion: Computational nephropathology is transforming our ability to analyze kidney histopathology. By integrating artificial intelligence techniques into the digital and molecular workflow, we can enhance diagnostic precision and reveal novel morphomolecular relationships.

Natural Language Processing in Nephrology Clinical Care



Tielman et al, Adv Chronic Kidney Dis, 2023

VA by **Dr PS Vali**

Conclusion: Nephrology language processing (NLP) provides a way to access data, & has been used in research in nephrology. While there are challenges to the implementation of NLP into clinical care, NLP can enable the extraction of key patient characteristics from free text & allow for the inclusion of novel predictors into risk stratification models.

Where Do They Add Value?

Clinical Domain	Computational Pathology		Natural Language Processing (NLP)	
Tissue-level diagnosis		Strong		Limited
Longitudinal risk detection		Emerging		Strong
Workflow efficiency		Lab-based		System-wide
Standardization		High reproducibility		Dependent on documentation

Different scalability paths:

Pathology AI = specialized centers, digital infrastructure

NLP = health system-wide deployment

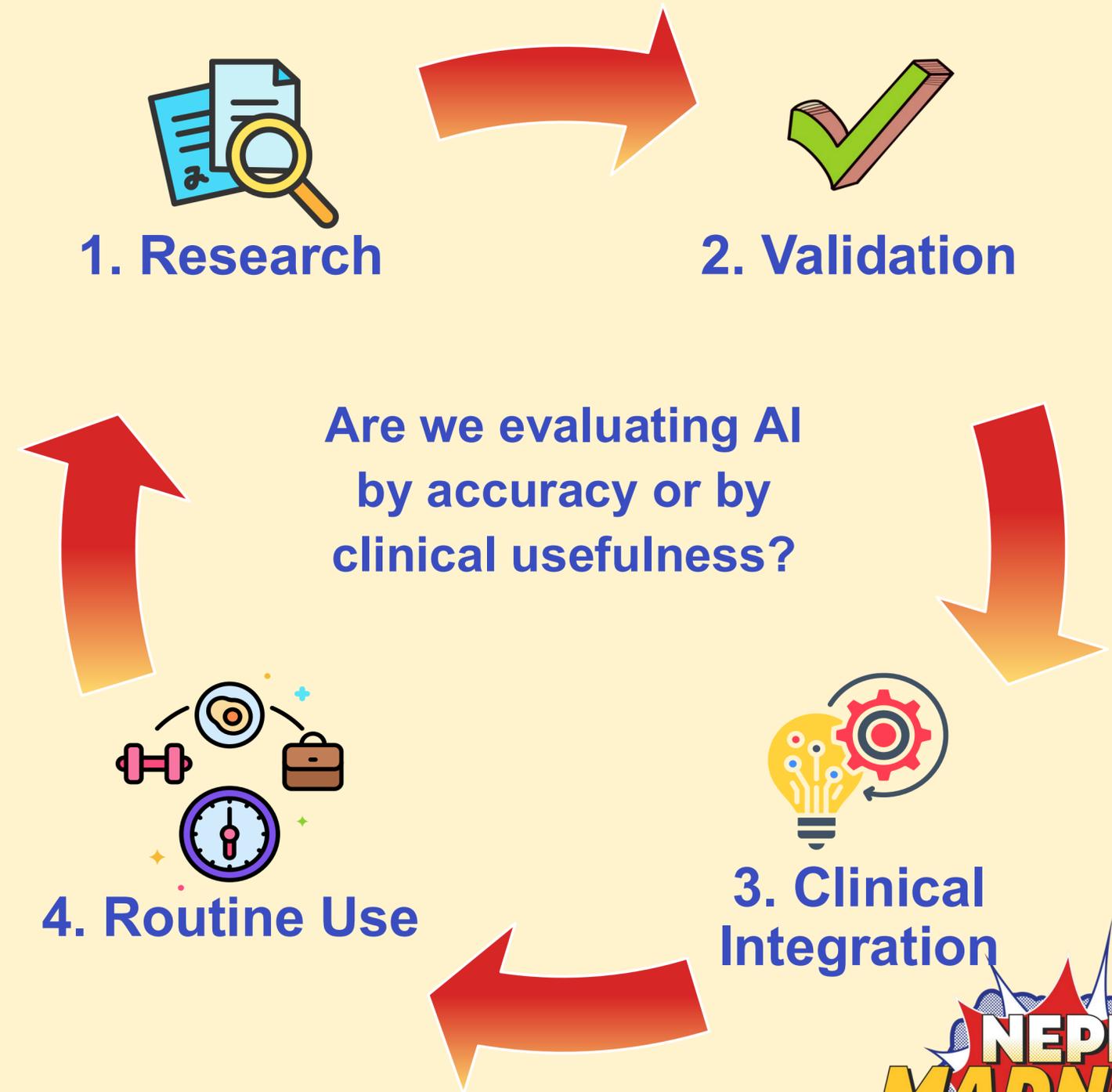


From Innovation to Implementation

Shared implementation requirements for Computational Pathology and NLP:

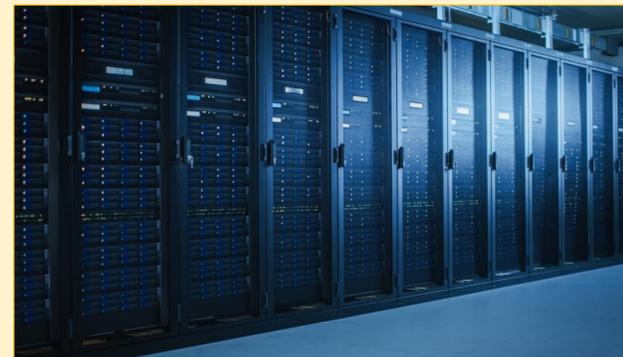
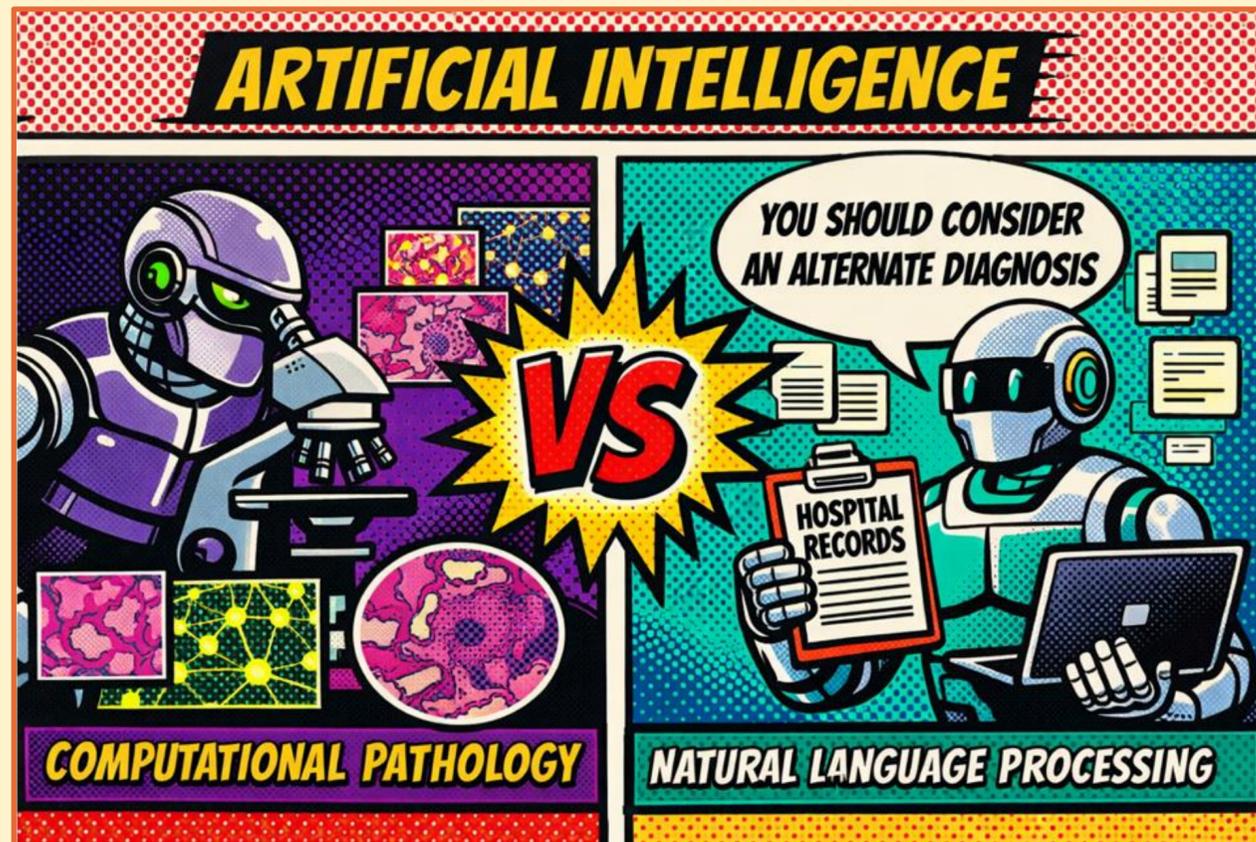
- External validation
- Bias Detection
- Data Governance
- Workflow integration
- Clinical Interpretability

Computational pathology and NLP are **complementary**, but **neither replaces clinical reasoning**. Both must earn trust before routine adoption.



EFFLUENT EIGHT ROUND

Pick Your Champion for the Artificial Intelligence Region



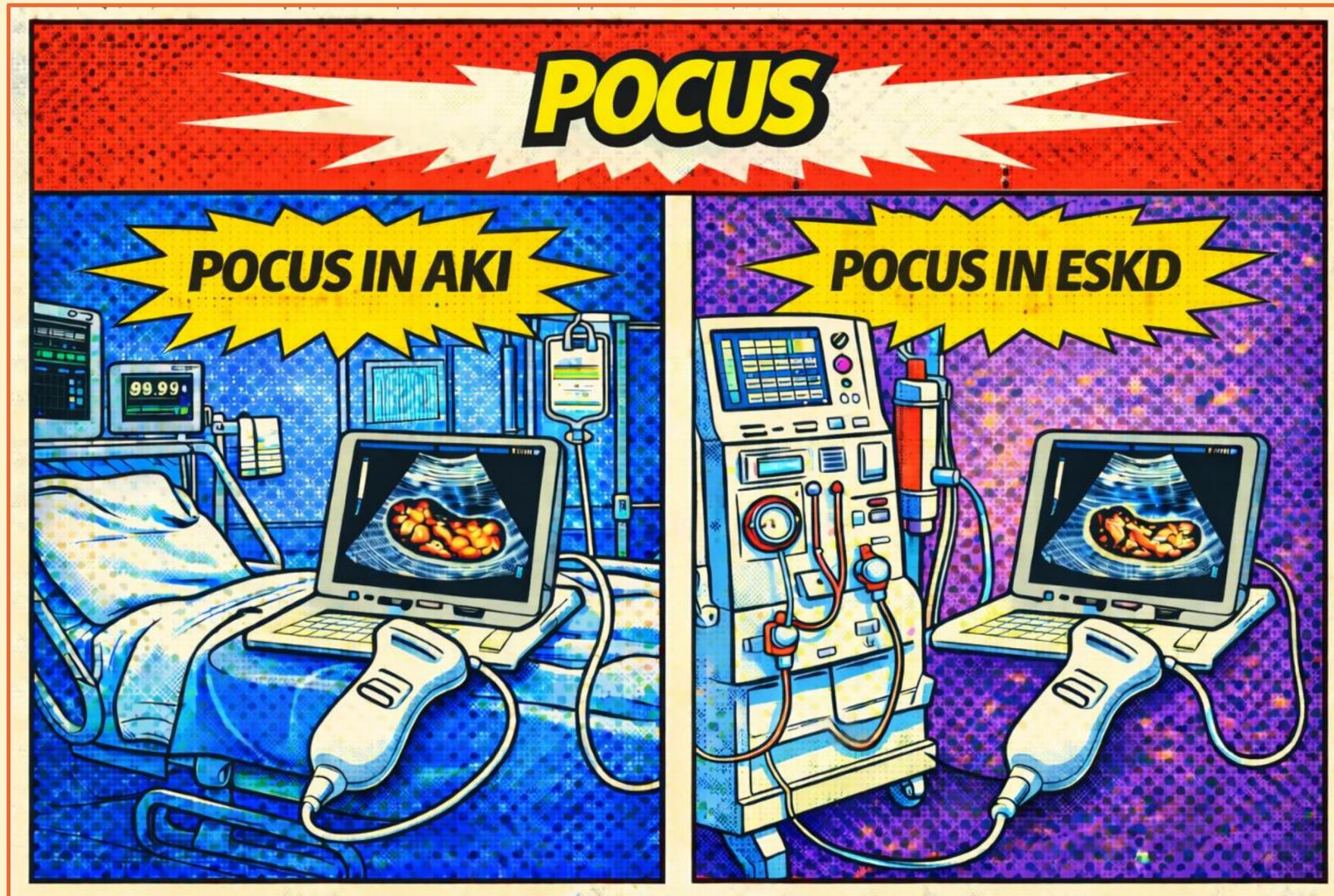
Computational Pathology

VS



Natural Language Processing

POCUS



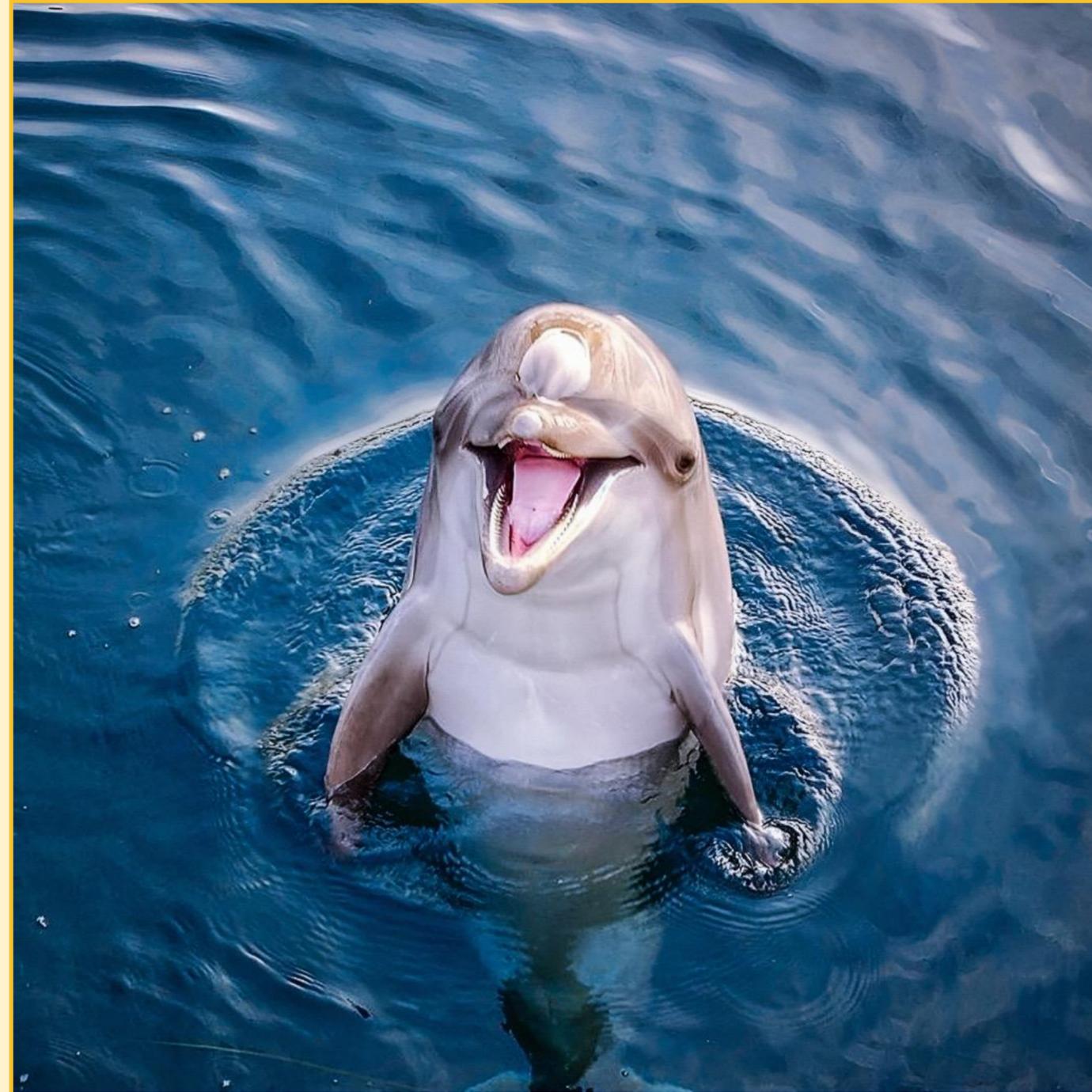
Writer:
Priyal Sakhuja

Experts:
Mohamed Hassan Kamel
Vandana Niyyar

Region Execs:
Jeff Kott
Anna Burgner



POCUS in AKI



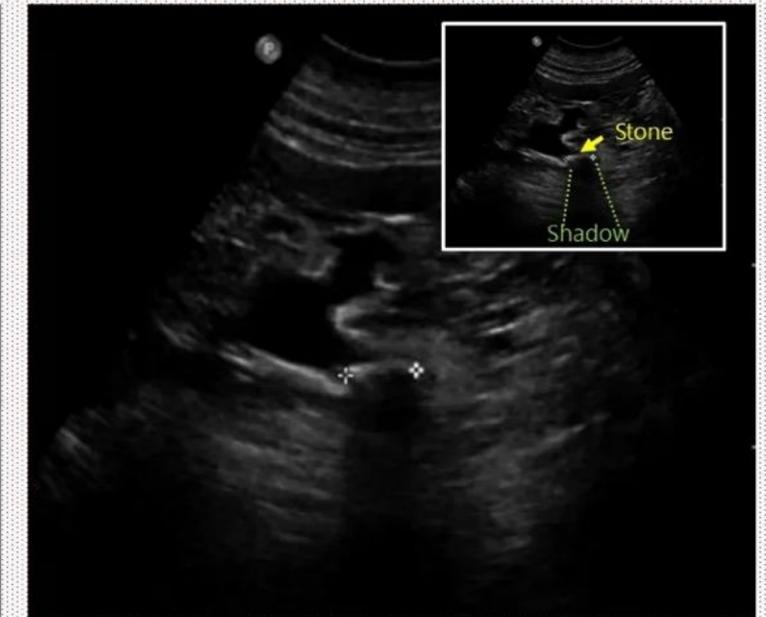
POCUS for Acute Kidney Injury

POCUS for Obstruction

- Obstructive Nephropathy Accounts for 5-10% of AKI
 1. Formal renal-bladder ultrasounds can be unnecessary and costly in low-risk patients
- POCUS of the Kidney can provide data regarding
 1. Hydronephrosis
 2. Bladder Distention/Post-Void retention
 3. Kidney Size (can give clues of acute vs chronic kidney disease)
 4. Cortex Size and Echogenicity (acute vs chronic kidney disease)
 5. Nephrolithiasis (echogenic focus with acoustic shadowing)
- Kidney POCUS has been demonstrated to be:
 1. sensitive and specific (~90%) at identifying obstruction in the AKI population as Gold standard Studies (Renal Bladder Ultrasound and CT Abdomen)
 2. Significantly faster at identifying obstruction
 3. Particularly accurate in moderate – high risk patients

False negatives for obstructive Nephropathy may occur in early obstruction, volume depletion or retroperitoneal fibrosis

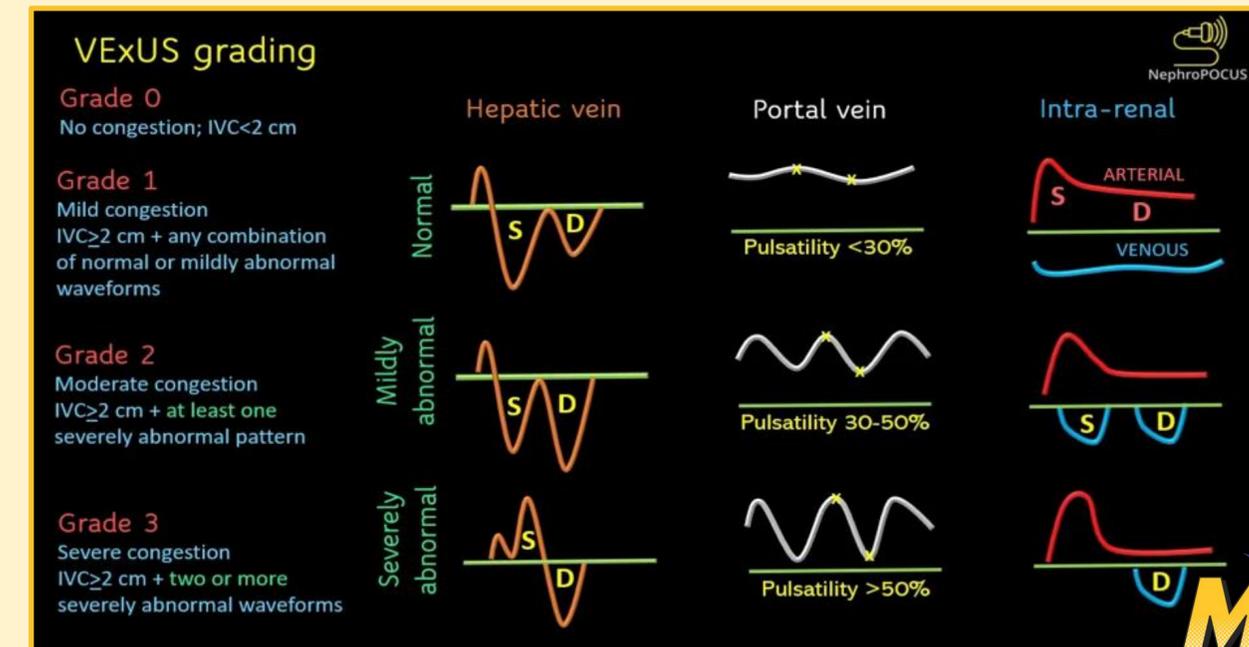
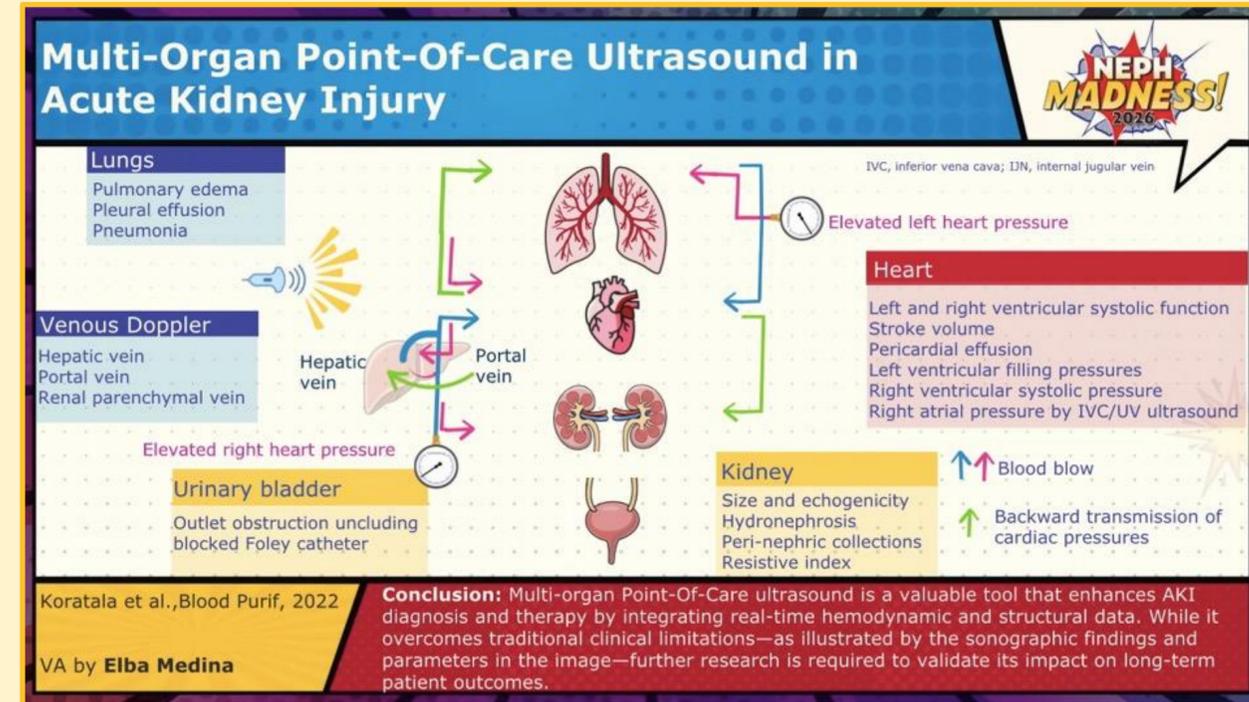
Hydronephrosis with UPJ stone



POCUS for Acute Kidney Injury

POCUS for Volume Assessment

- Volume assessment is physiologically complex, POCUS offers a comprehensive framework but requires understanding of the test strengths/limitations.
1. Cardiovascular Ultrasound – To assess left and right sided pressure/function
 2. Lung/Abdominal Ultrasound– To assess for extravascular fluid
 3. IVC ultrasound - marker for central venous pressure rather than fluid responsiveness.
 4. VExUS– Assesses doppler flow patterns in larger proximal veins in liver/kidneys to assess for organ impacts of venous congestion
- VExUS > 2 has been validated in the post-cardiac surgery population as a risk factor for Acute Kidney Injury due to venous congestion
 - A decrease in VExUS score in the critically ill population has shown improved kidney outcomes and lower in-hospital mortality in small prospective cohort studies



Modified Venous Excess Ultrasound :

A Dynamic Tool to Predict Mortality in Acute Decompensated Heart Failure



METHODS



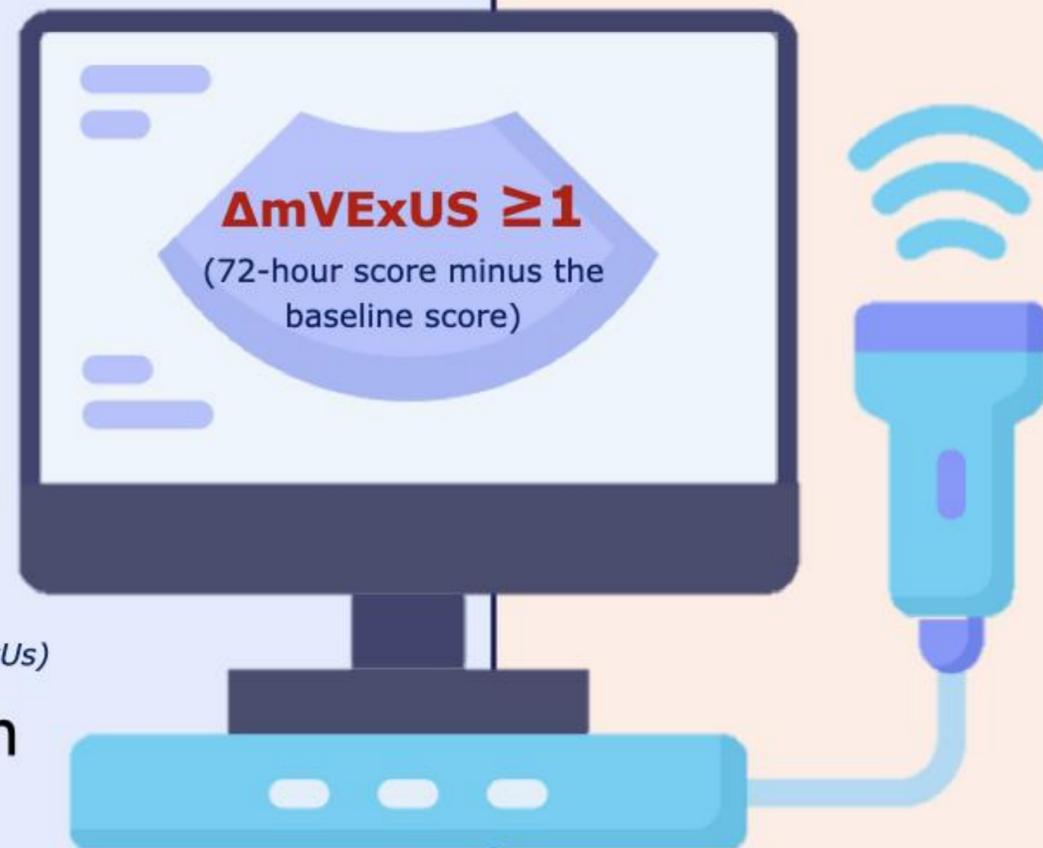
Prospective Cohort Study



ADHF with LVEF <50%
(n = 104)



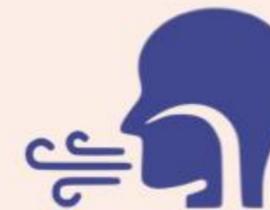
Modified VExUS (*mVExUs*)
at **≤24h** of admission
& at **72h**



FINDINGS



↑ **Weight loss & Urine output**



Better Clinical Congestion Score & Creatinine reduction



↓ **In-hospital mortality**

aOR 0.31, 95% CI (0.14–0.68);
p=0.004

Saadi et. al, JASE, 2025

VA by **Renz Pasilan**

Conclusion: A ≥ 1 -point reduction in mVExUS over the first 72 hours ($\Delta VExUS \geq 1$) was independently associated with lower in-hospital mortality in patients with ADHF and LVEF <50%. This improvement tracked with more effective decongestion supporting serial mVExUS for bedside risk stratification and monitoring.

POCUS in ESKD



POCUS for End Stage Kidney Disease

POCUS for Volume

- Dry Weight determination remains imprecise
- 1. BP and Intradialytic weight gain are crude surrogates
- 2. No universally accepted gold standard.

VEXUS

1. No studies looking to date at long-term outcomes
2. One small cohort study showed that ultrafiltration did improve VExUS score over the course of a single dialysis session
3. Case reports have detailed how VExUS can guide Ultrafiltration in overloaded, hospitalized patients

IVC Ultrasound

1. Due to its limitations in interpretation, has only been studied in the critically ill dialysis population

POCUS for vascular access is accessible and may lead to earlier cannulation with improved patient experience and outcomes

- Is used for perioperative vein assessment
- May lead to earlier cannulation
- 1. One study found POCUS led to a a quicker time to cannulation for AVFs with a diameter >6mm, <6mm deep, and >6mm long when compared standard of care with no difference in complications between groups
- May lead to better AVF/AVG related outcomes, patient satisfaction and is Is teachable to dialysis unit staff

Lung Ultrasound (LUS)

1. Lung Ultrasound guided ultrafiltration has shown improve both dry weight/BP and cardiac parameters
2. A multicenter RCT (LUST Trial) evaluated a LUS guided UF protocol vs Standard of Care and found no significant difference in major adverse cardiovascular events between groups despite improved relief of lung congestion.



Does POCUS shorten arterio-venous fistula cannulation time and CVC exposure?

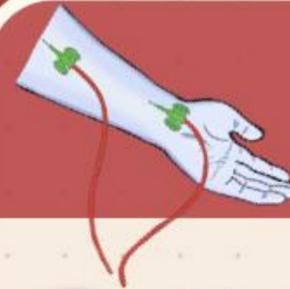


Single-center mixed design

- ▶▶ Prospective POCUS cohort
- ◀◀ Retrospective non-POCUS controls
- 👥 Population: Incident AVFs
- 📅 Follow-up: 1 year

Intervention

POCUS within 3–4 weeks post-surgery



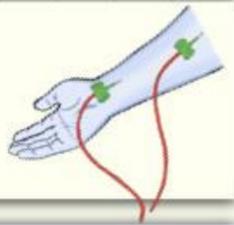
Cannulation criteria

- Diameter >6 mm
no >20% focal narrowing
- Depth <6 mm
- Cannulation length >6 cm
- ✗ **No flow measurements used**

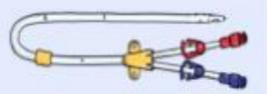


With POCUS...

Earlier AVF cannulation
36 vs 63 days



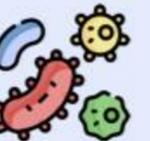
Shorter CVC exposure
68 vs 98 days



No increase in early or late complications



Fewer infections observed with POCUS
not statistically significant



POCUS- Point-of-Care Ultrasound, CVC-Central Venous Catheter, AVF- Arterio-Venous Fistula

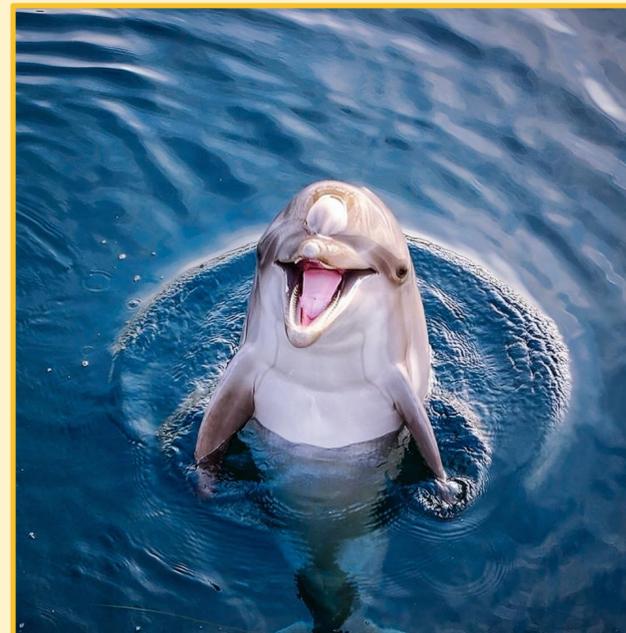
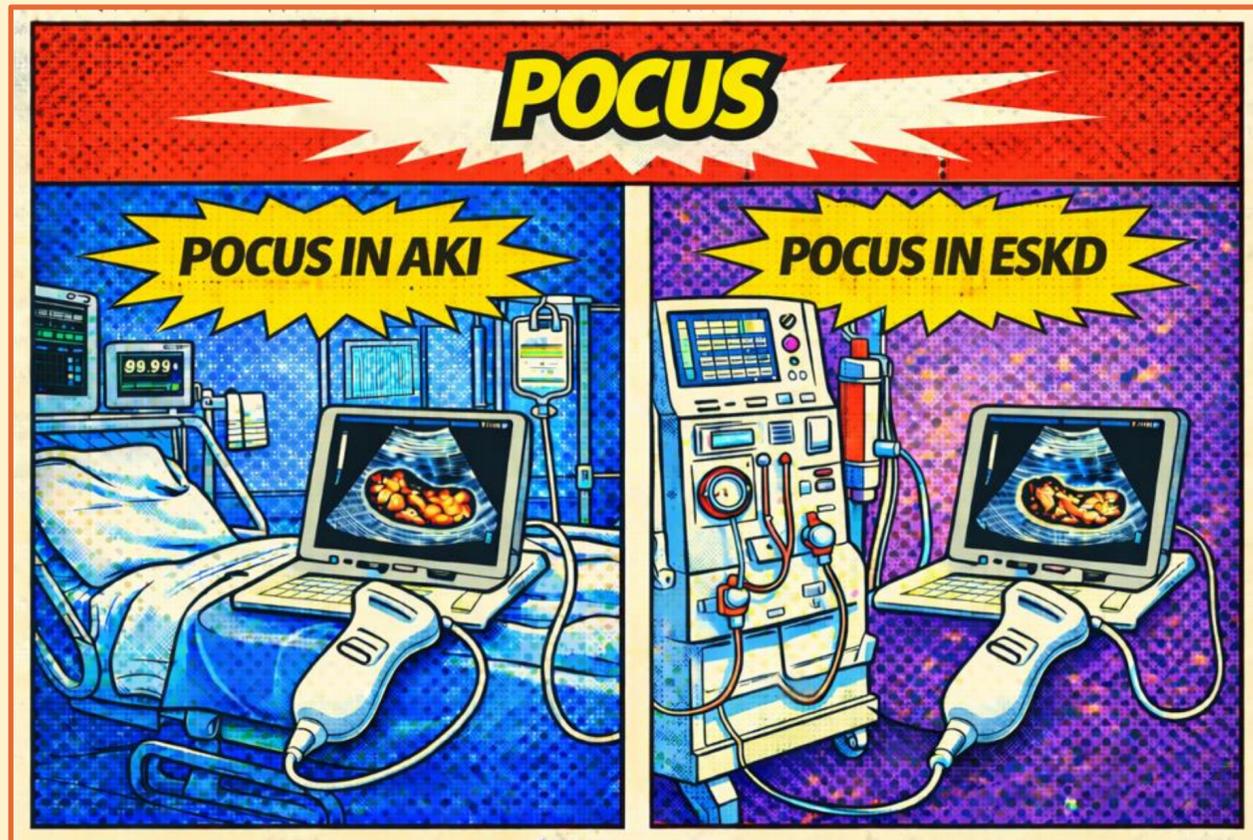
Coritsidis GN et al, J Vasc Access, 2020

VA by **Cristina Popa**

Conclusion: POCUS-guided assessment was associated with earlier AVF cannulation and shorter CVC duration, without increased complications. Due to the study's small size, single-center setting, and non-randomized design, effects on infection rates and long-term access outcomes cannot be definitively established.

EFFLUENT EIGHT ROUND

Pick Your Champion for the POCUS Region



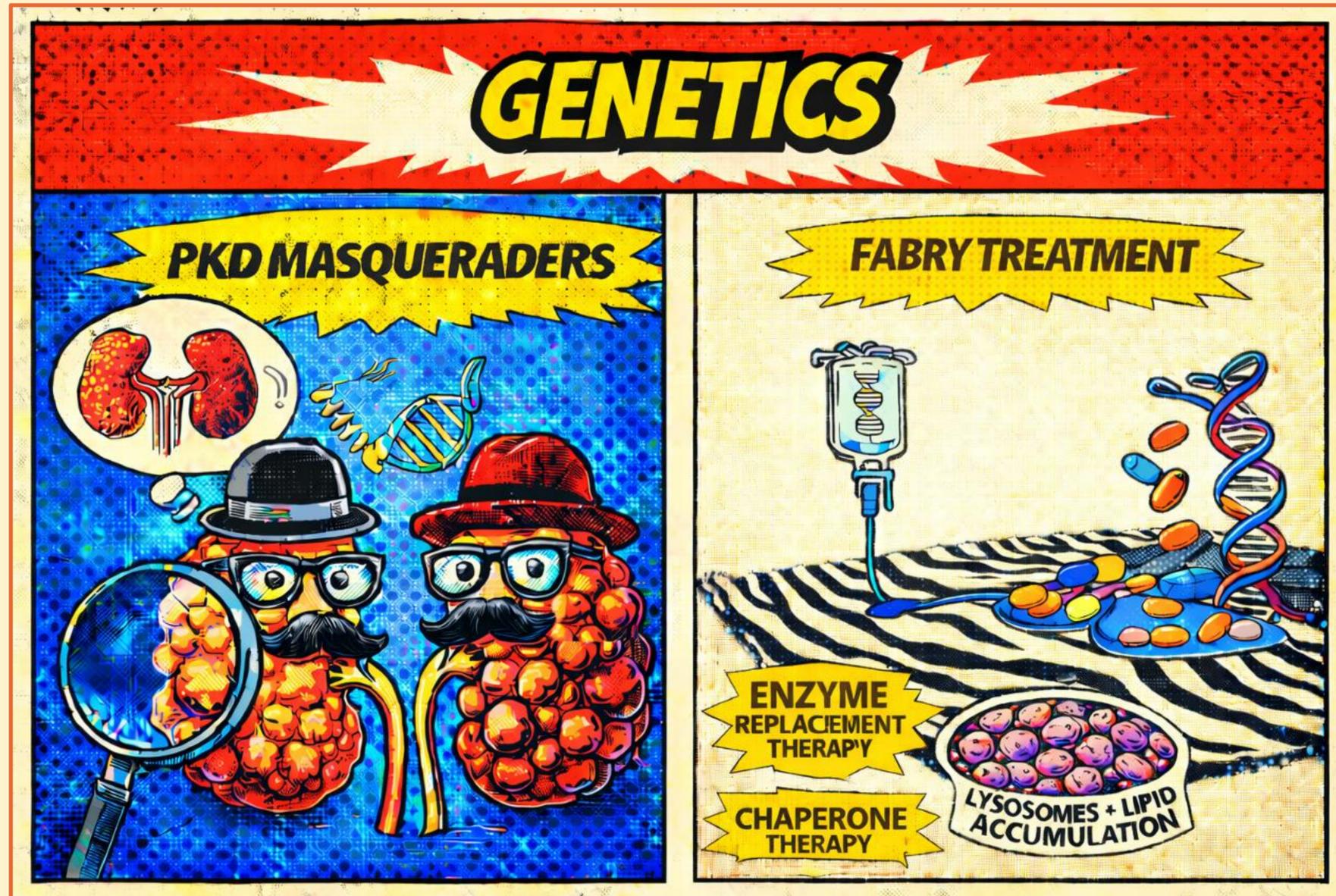
POCUS in AKI

VS



POCUS in ESKD

Genetics



Writers:
Steven Clapp
Alyssa Steitz

Expert:
Eric Wallace

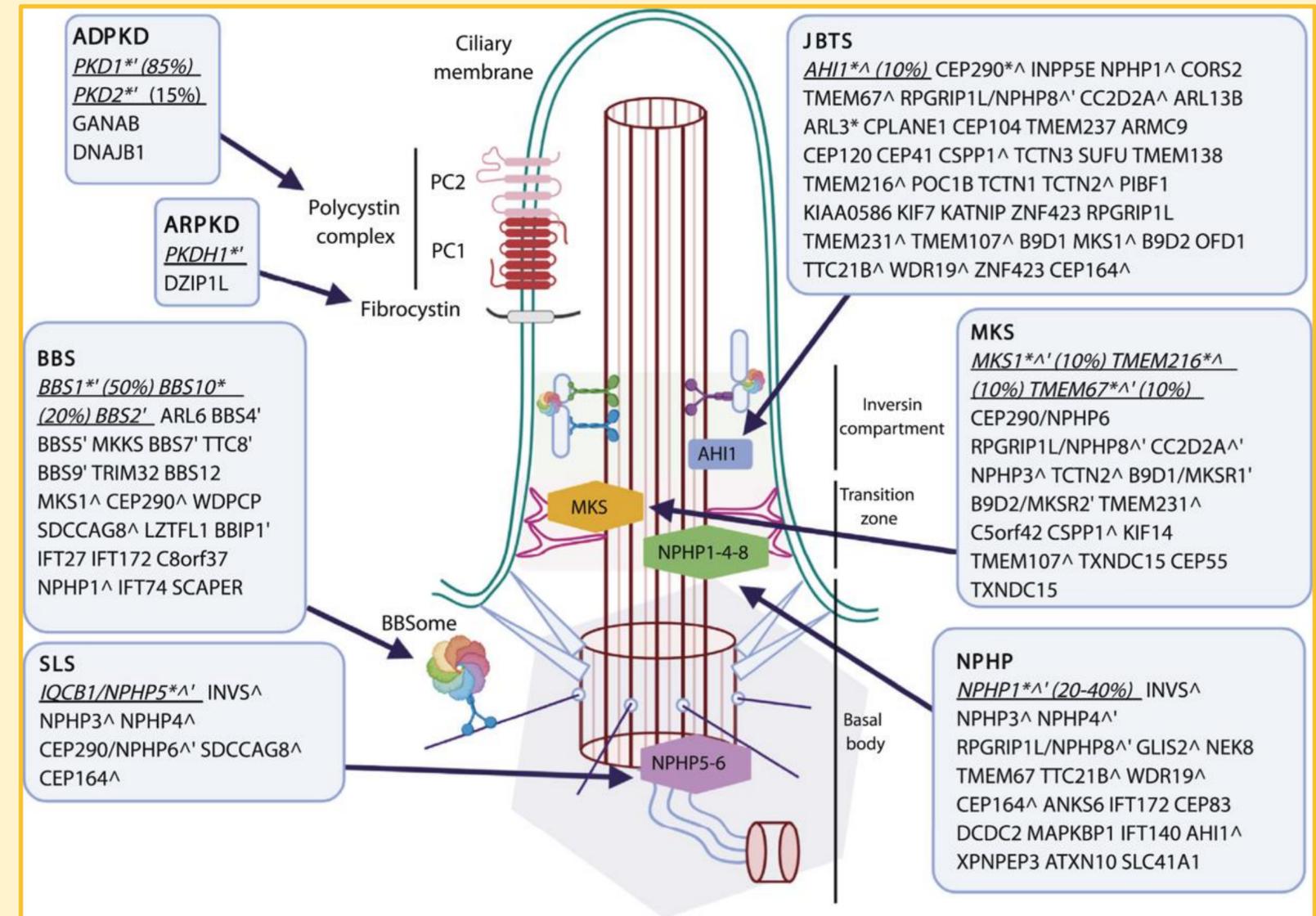
Region Execs:
Anna Burgner
Samira Farouk

PKD Masqueraders



Ciliopathies and Their Cystic Kidney Diseases

- Cilia are hair-like organelles found on nearly all eukaryotic cells
 - Key roles in development including proliferation, differentiation, and migration.
 - Cilia Dysfunction → Ciliopathies are associated with diseases of multiple organ systems
 - Ciliopathies in the kidneys are associated with cystic kidney disease
- Polycystic Kidney Disease Masqueraders
 - Autosomal Dominant PKD
 - Autosomal Recessive PKD
 - Nephronophthisis
 - Medullary Sponge Kidney
 - HNF1B related Autosomal Dominant Tubulointerstitial Kidney Disease



Our Understanding of the Genetics of Cystic Kidney Disease is Evolving

- Autosomal Dominant Polycystic Kidney Disease (ADPKD)
 - Mutations in the *PKD1* and *PKD2* genes are the most common cause
 - Threshold model → cyst formation is triggered if polycystin is reduced below a critical threshold in tubular epithelial cells
 - Leading to the discovery of multiple other gene mutations found that can cause ADPKD
 - *GANAB*, *DNAJB11*, *ALG8*, *ALG9*, *PRKCSH*, *SEC63*, and *SEC61B* among others
- *HNF1B* mutations
 - Also known as renal cysts and diabetes (RCAD) syndrome and HNF1B-MODY or MODY5
 - Kidney manifestations are highly variable, even within a family! (See next slide) →. the exact mutation doesn't predict the kidney disease!



How broad is the renal spectrum in HNF1B nephropathy?



7 families
13 patients with genetically confirmed HNF1B nephropathy

Genetic testing

- Targeted NGS panel + MLPA for whole-gene deletion
- Segregation analysis

- Systematic clinical, laboratory, imaging, and extrarenal phenotyping



Renal phenotypes

- Renal cysts and diabetes
- ADPKD-like cystic disease
- ADTKD ± hyperuricemia/gout (most common; bland urine, IF/TA)
- Congenital anomalies of kidney and urinary tract
- Nephrogenic diabetic insipidus with early polyuria

Marked inter-/intrafamilial variability

Cysts in ~92%

Novel phenotype: medullary sponge kidney in 17q12 whole-gene deletion family

Genetics

6 novel variants (3 frameshift, 2 missense, 1 nonsense) + whole-gene deletion

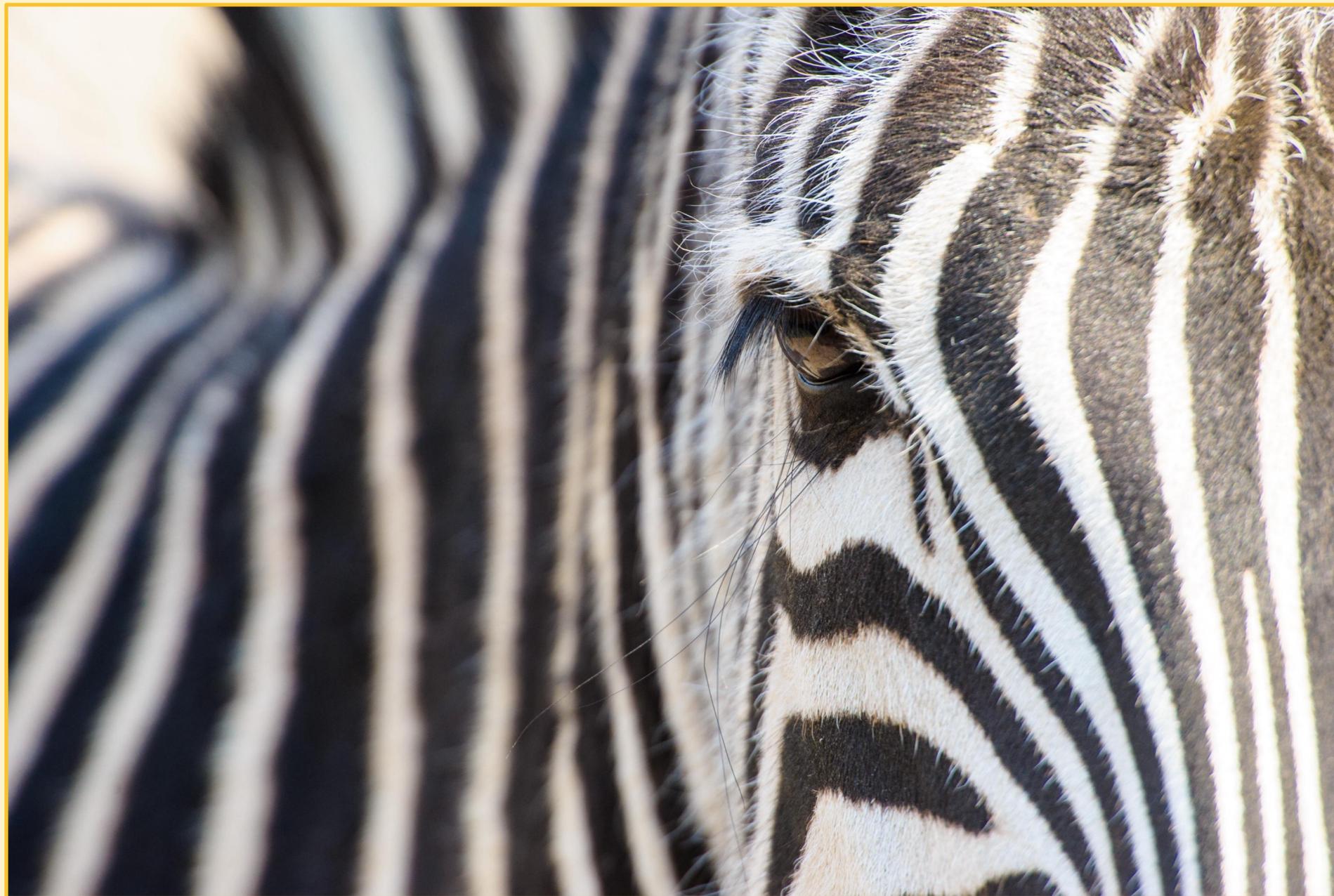
HNF1B- Hepatocyte nuclear factor-1β, ADPKD- Autosomal dominant polycystic kidney disease, ADTKD- Autosomal dominant tubulointerstitial kidney disease, NGS- Next-generation sequencing, MLPA- Multiplex ligation-dependent probe amplification. IF/TA- Interstitial fibrosis / tubular atrophy

Izzi C, et al, Kidney Int Rep, 2020

VA by **Cristina Popa**

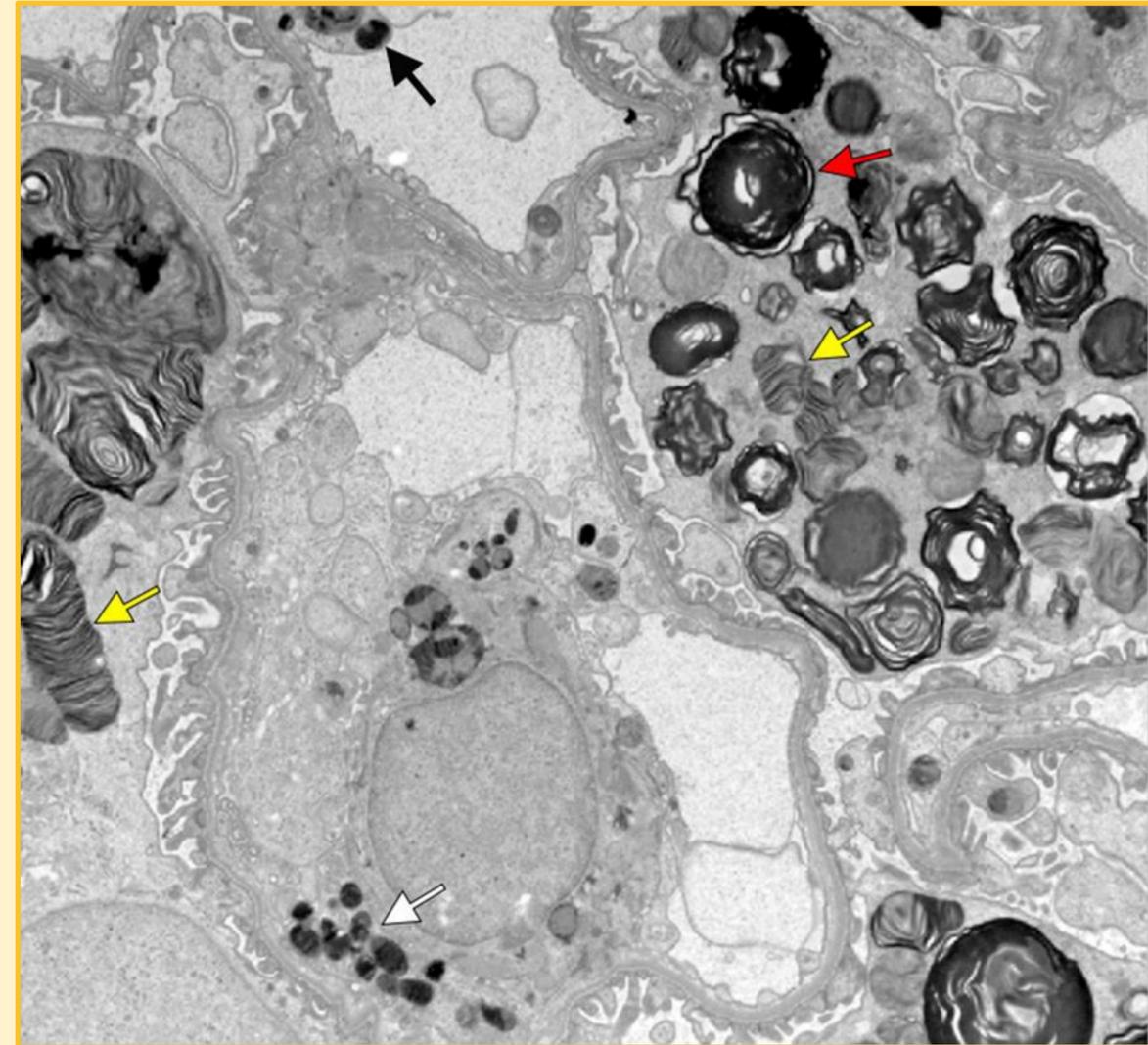
Conclusion: Extreme renal phenotypic variability characterizes adult HNF1B nephropathy, now expanded to include medullary sponge kidney. The allelic spectrum is further broadened by newly identified pathogenic variants.

Fabry Treatment



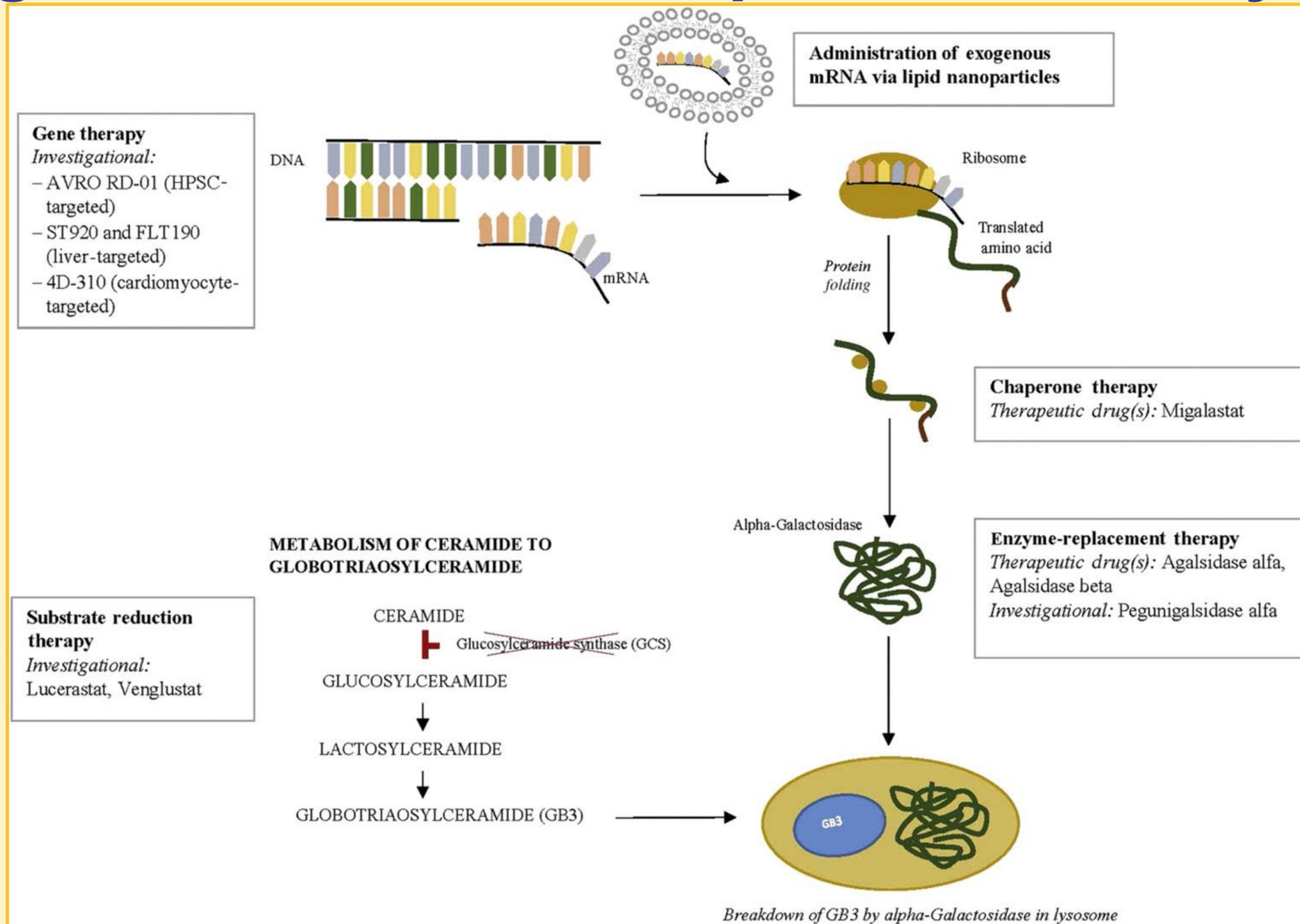
Fabry Disease

- X-linked lysosomal storage disorder caused by mutations in the galactosidase A (GLA) gene
- Deficiency of lysosomal enzyme alpha galactosidase A → accumulation of lysosomal Gb3
- End Organ Disease
 - Proteinuric kidney disease → kidney failure
 - Cardiomyopathy
 - Stroke
 - Neuropathy
 - Skin lesions (angiokeratomas)
- Other noteworthy symptoms:
 - Severe debilitating pain, irritable bowel syndrome-like symptoms, and anhidrosis (leading to heat intolerance)



Classic Zebra Bodies in Podocytes
(Yellow Arrow)

Growing List of Treatment Options for Fabry Disease

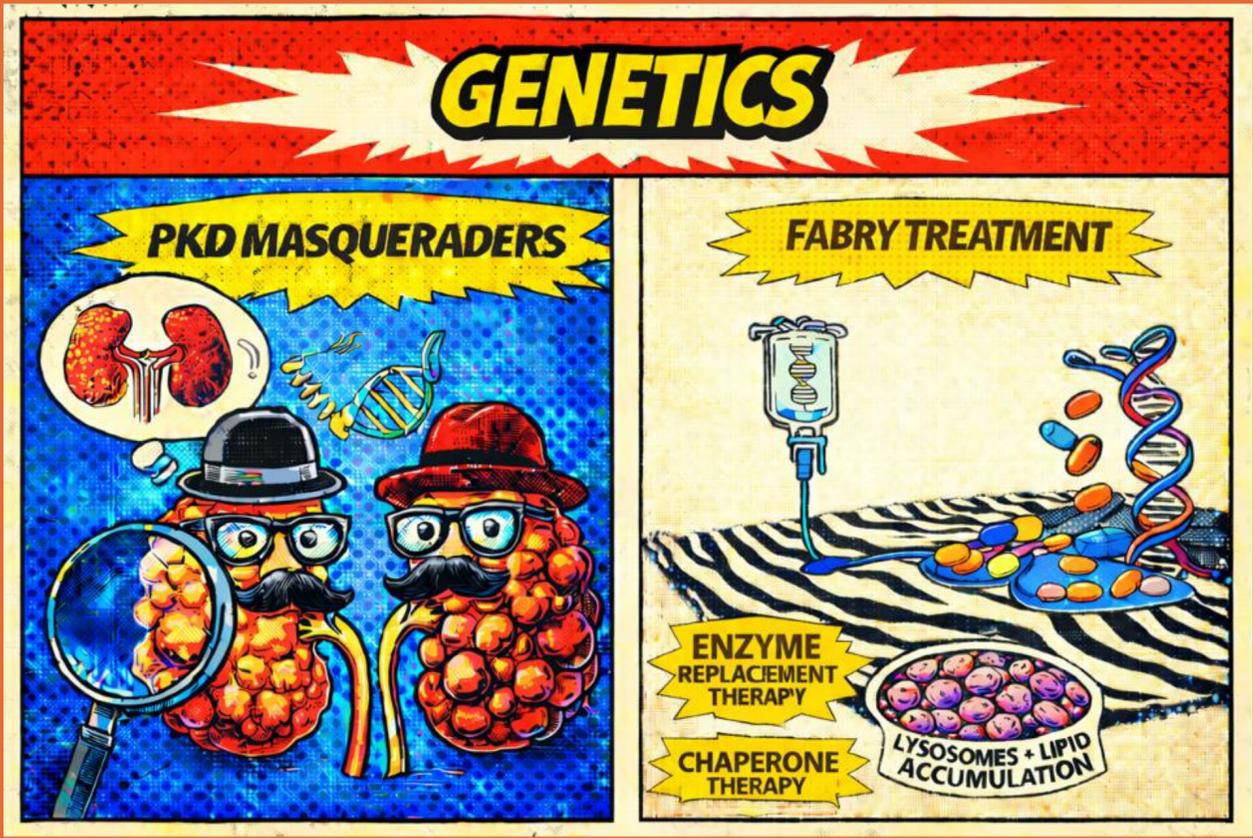


Felis A, Whitlow M, Kraus A, Warnock DG, Wallace E. Current and Investigational Therapeutics for Fabry Disease. *Kidney Int Rep.* 2019 Dec 6;5(4):407-413



EFFLUENT EIGHT ROUND

Pick Your Champion for the Genetics Region



**PKD
Masqueraders**

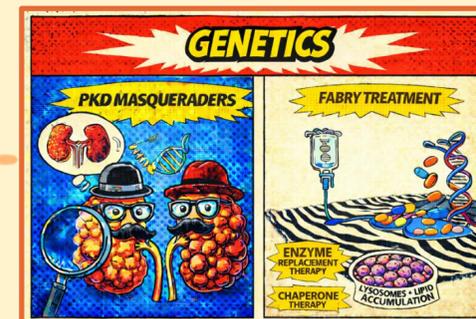
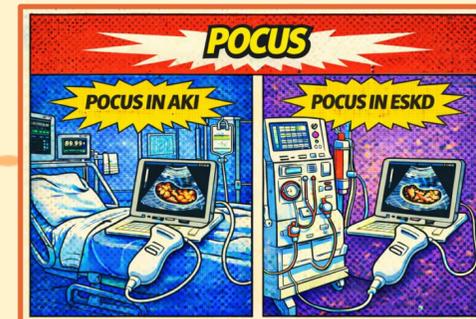
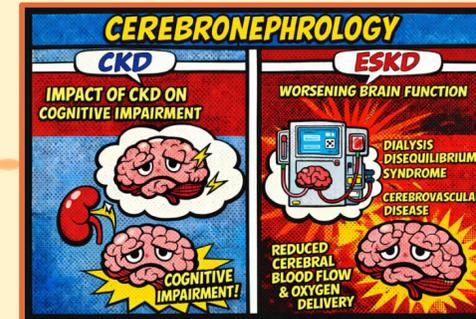
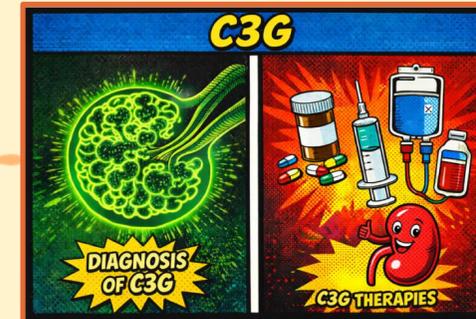
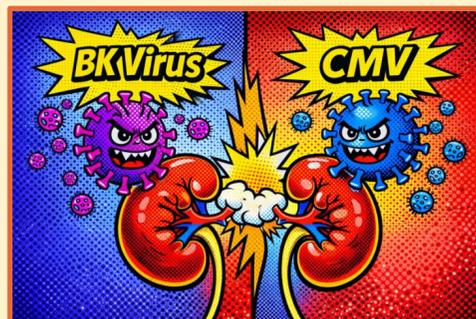
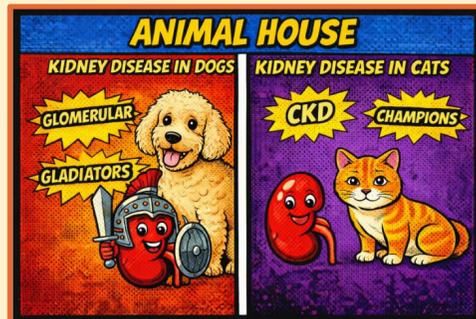
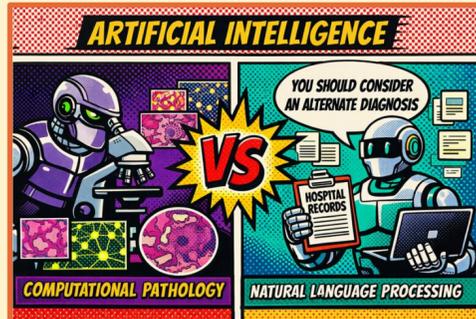
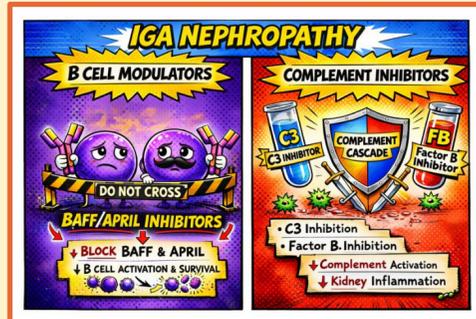
VS



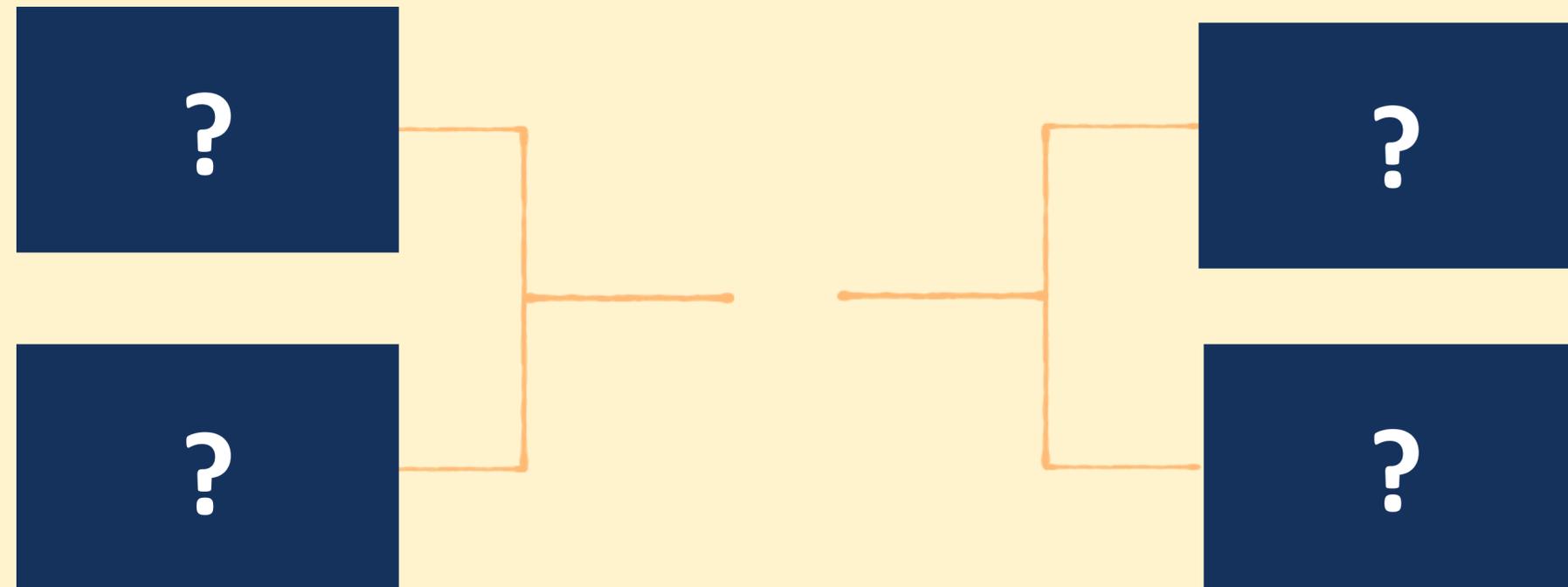
Fabry Treatment



From your Effluent 8, pick your Filtered 4



**From your Filtered 4,
pick your Left and Right Kidneys**



**Crown your
NephMadness 2026
CHAMPION:**



Thanks for playing and good luck!

- Submit brackets by March 31, 2026 on [Tourneytopia](#)
- Claim CME and MOC credit through [NKF PERC](#)
- Discuss on social media using [#NephMadness](#)

Important Dates:

March 1, Sunday (7:00 am Eastern): Bracket entry opens

March 31, Tuesday (11:59 pm Eastern): Deadline for entering contest

April 2, Thursday: Effluent 8 results

April 6, Monday: Filtered 4 results

April 8, Wednesday: Left & Right Kidney results

April 10, Friday: NephMadness Champion crowned

