A Goemans-Williamson Algorithm for Subcohort Discovery in Kidney Disease

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At a Glance (Kidney Precision Medicine Project, $N = 217$):
- **Problem (Boxes 1–2):** The same eGFR or diagnosis can hide different immune pathways
- **SC1 (Box 3):** Blood IL-6 and kidney complement inflammation (mostly AKI; 7 of 9 biopsy-proven AIN)
- **SC2 (Box 4):** Diabetic/hypertensive CKD with kidney-localized interferon signal (eGFR 40 vs. 57)
- **SC3 (Box 5):** Scarred CKD: high biopsy complement RNA, blood complement not raised
- **Uses & Validation (Boxes 6–8):** Trial-enrichment hypotheses; replicates in validation patients

1. Clinical Motivation: Moving From Kidney Damage Staging to Pathway Selection

A. Why Routine Staging Dilutes Anti-Inflammatory Kidney Trials:

- Routine staging (eGFR, albuminuria) and labels (acute kidney injury, AKI; chronic kidney disease, CKD) group distinct immune mechanisms.
- Patients with the same drop in kidney filtration (eGFR) can be losing kidney function from systemic IL-6 and kidney complement inflammation or from local interferon inflammation inside the kidney.
- Kidney tissue profiling shows that patients sharing the same high-level clinical diagnosis differ in which inflammatory pathway is active (e.g., ∼27% of nephrotic syndrome [MCD/FSGS] patients form a distinct TNF-activated group with worse outcomes; **Mariani 2023**), so enrolling 100% of a broad AKI or CKD cohort dilutes drug benefit across non-responders.

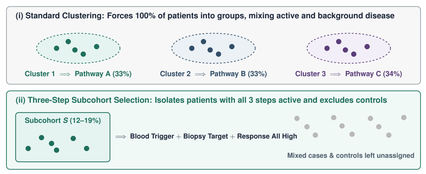
The Question: Which patients with kidney disease have an active, druggable immune pathway, and which targeted therapy does that pathway indicate?

B. What Pairing Blood & Biopsy Adds Beyond Injury Markers & Tissue Atlases:

- Tubular injury markers (NGAL, **Paragas 2011**; KIM-1, **Han 2002**) and prognostic sTNFR1/2 (**Niewczas 2012**) detect kidney stress, but cannot specify which immune pathway to block.
- Checking that the **blood trigger**, **kidney drug target**, and **tissue response** are all elevated together suggests an immune pathway is active before considering a targeted drug.
- **Poster overview (Boxes 3–5):** in KPMP, three largely distinct subcohorts emerge:
  - **SC1 (Box 3):** Acute **systemic** IL-6 **and kidney complement inflammation**, mostly in AKI (captures 78%, 7/9, of biopsy-proven AIN in this small dataset).
  - **SC2 (Box 4):** Progressive **diabetic and hypertensive** CKD with local kidney interferon inflammation while blood CRP is not raised and IL-6 is low.
  - **SC3 (Box 5): Scarred** CKD with high biopsy complement Factor B (CFB) and JAK1/2-STAT1 RNA, while blood complement and CRP are not raised (similar to controls).

Our Approach: Matching Patients to Targeted Kidney Therapies

Instead of forcing all patients into broad clusters, we isolate the 12–19% where the **blood trigger**, **kidney drug target**, and **tissue response** are all active together, to identify patients who may benefit from a targeted anti-inflammatory drug.



Schematic. Why standard clustering is not enough. Standard clustering (i) assigns every patient to a group, which fails when explaining the whole disease requires too many gene and protein dimensions. Our cut-based (Goemans–Williamson) algorithm (ii) selects only patients with all three pathway steps elevated, leaving mixed cases and controls unassigned.

2. Methods: Marker Panel, Subcohort Selection, eGFR Adjustment & Validation

A. Choosing the 20-Marker Panel Along Each Drug Pathway:

- For a pathway-targeted drug to work, having its upstream blood trigger, kidney drug target, and downstream tissue response active together is a necessary (though not sufficient) condition.
- Across 190 kidney disease patients (U) and 27 controls (V), each patient is scored on **7 biopsy drug targets** (x_i^T), **6 blood triggers** (x_i^L), and **7 pathway response markers** (x_i^R).

The 20-Marker Panel: How We Check That an Immune Pathway Is Active Before Selecting a Drug

Step 1: Blood Trigger (6) — Is the upstream immune signal raised in the blood? IL-6, IFN-γ, IFN-α2, C3a, C5, C5a (blood protein, adjusted for eGFR)

then check →

Step 2: Drug Target (7) — Is the matching drug target expressed in the kidney biopsy? JAK1, JAK2, IFNAR1, IL6R, CFB, C3, C5AR1 (biopsy RNA, adjusted for assay)

then check →

Step 3: Response (7) — Is the downstream response raised in tissue and blood? Biopsy RNA: STAT1, SOCS3, IFI27 Blood protein: CXCL10, CRP, C3d, C5b-6

Selection Criterion: A patient is assigned to a subcohort only when ALL 3 steps are elevated together.

B. Selecting the Subcohort (Goemans-Williamson SDP):

- A Goemans-Williamson semidefinite program (**Goemans & Williamson 1995; Worah 2026**) solves for X on cross-step covariance $M_{T\text{-}L\text{-}R}$ and rounds it to unit weights (w_T, w_L, w_R) and cutoffs ($\theta_T, \theta_L, \theta_R$):

$$\max_{X \succeq 0,\, \mathrm{diag}(X)=1} \mathrm{Tr}(M_{T\text{-}L\text{-}R} X), \quad S = \{i \in U : \langle w_T, x_i^T \rangle \geq \theta_T \ \wedge \ \langle w_L, x_i^L \rangle \geq \theta_L \ \wedge \ \langle w_R, x_i^R \rangle \geq \theta_R\},$$
$$\text{subject to } \ S \cap V_{\text{deriv}} = \emptyset \quad \text{(no reference controls selected during derivation)}.$$

C. Controlling Filtration (eGFR), Biopsy Platform & Cohort Confounding:

- Low kidney filtration (eGFR) passively builds up small proteins in the blood ($r = -0.83$ to -0.87 with eGFR; **Podos 2022**), while single-cell and single-nucleus biopsy assays differ in baseline gene capture.
- All scaling and filtration adjustments are fit only on derivation patients before scoring validation patients (0/3 subcohorts replicate without adjustment):
  - **Biopsy RNA Standardization:** Log-transformed RNA counts ($\log_2(\mathrm{CPM}+1)$, counts per million) are standardized within single-cell ($n = 112$) and single-nucleus ($n = 78$) assays, raising replicate correlation from $r = 0.70$ to 0.96.
  - **Blood Filtration Adjustment:** Log-transformed blood protein levels ($\log_2$(RFU), relative fluorescence units) are standardized within each KPMP cohort ($n = 90$ and $n = 100$) and adjusted for log(eGFR).

How We Verify These Subcohorts Are Real (Out-of-Sample Validation)

We learn marker weights and cutoffs on one group of patients and test them on completely separate validation patients (random validation subsets, plus two independent KPMP patient cohorts, $n = 90$ and $n = 100$), confirming that the same disease subgroups and kidney injury patterns recur ($p < 0.05$).

3. Subcohort 1 (SC1): Acute Interstitial Nephritis & Systemic Inflammatory AKI

A. KPMP Open-Access Cohort ($N = 217$; kpmp.org; de Boer 2021; Lake 2023):

- Paired blood/urine proteins and kidney biopsy RNA from **190 kidney disease patients** (131 CKD, 46 AKI, 13 diabetes-at-risk) and **27 controls** (21 transplant, 6 nephrectomy).

Table 1. Four druggable immune pathways in the 20-marker panel. Each row follows one pathway through the 3 steps of Box 2 (blood trigger, measured as protein → biopsy target, measured as RNA → pathway response, measured as biopsy RNA or blood protein); the last column shows in which subcohort the pathway is active and which drugs target it.

Immune Pathway	1. Blood Trigger (protein)	2. Biopsy Target (RNA)	3. Pathway Response	Active Subcohort & Drugs
IL-6 Signaling	IL-6	IL6R	Blood protein CRP; biopsy RNA SOCS3	**SC1 only** (ziltivekimab, tocilizumab)
Complement	C3a, C5, C5a	CFB, C3, C5AR1	Blood protein C3d, C5b-6	**SC1** (secondary: iptacopan, eculizumab)
JAK–STAT / IFN-γ	IFN-γ	JAK1, JAK2	Blood protein CXCL10; biopsy RNA STAT1	**Active in SC1** *(blood IFN-γ is low in SC2)*
Type-I Interferon	IFN-α2	IFNAR1 *(+ shared JAK1)*	Biopsy RNA IFI27 *(+ shared STAT1)*	**Active in SC2** (baricitinib, a JAK1/2 inhibitor)

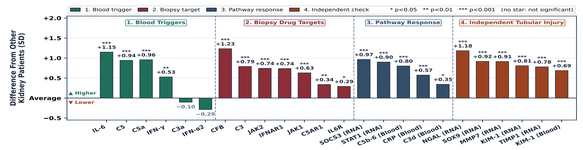


Figure 1. SC1 profile (36/190 patients; 22 AKI, 14 CKD; 7/9 AIN cases, $p = 0.00014$). Each bar shows how much higher or lower a marker is in SC1 than in the average kidney patient. Blood triggers, biopsy targets, pathway responses, and independent injury markers (groups 1–4) are mostly raised together.

B. An Inflammatory AKI Subgroup Enriched for Acute Interstitial Nephritis (AIN):

- **Context:** Acute interstitial nephritis (AIN, often drug-induced) looks like routine tubular injury (ATI) on blood creatinine, and the classic triad of fever, rash, and eosinophilia appears in under 10% of cases.
- **Finding: SC1** patients (18.9%, 36/190) have high blood IL-6 (+1.15 SD), even compared with other AKI patients. Blood complement (C5a/C5b-6, +0.80 to +0.96 SD) is also high, but to a similar degree as in other AKI. In the kidney, biopsy CFB (+1.23 SD) and JAK1/2-STAT1 are raised, and biopsy and urine show tubular injury (NGAL and MMP-7 up, protective uromodulin [UMOD] down).
- **Evidence: SC1** includes 78% (7/9) of biopsy-proven AIN in this small dataset ($p = 0.00014$), along with 12 of 26 ATI cases. In an independent validation cohort, it included all 5 AIN cases (vs. 18 of 85 other patients; $p = 0.0008$). The subgroup was identified in all 10 repeated random derivation/validation divisions of the cohort and reproduced in validation patients more often than expected by chance ($p < 0.001$).

Clinical Implication: How SC1 Could Guide Early AIN Triage & Targeted Trials

Because blood IL-6 and urine NGAL/MMP-7 are elevated together in **SC1**, they provide candidate non-invasive markers for hidden AIN (7/9 cases) to prompt earlier biopsy or drug withdrawal, while active IL-6 signaling nominates ziltivekimab/tocilizumab, with kidney Factor B and C5 activity suggesting iptacopan or eculizumab as secondary candidates, when steroids fail.

4. Subcohort 2 (SC2): Progressive CKD With Local Kidney Interferon Inflammation

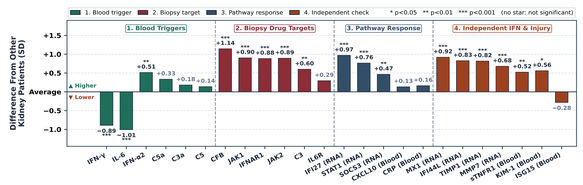


Figure 2. SC2 profile (23/143 patients remaining after excluding SC1; 22 CKD, 1 AKI; median eGFR 40.4 vs. 56.9, $p = 0.00015$). Unlike SC1, routine blood IFN-γ and IL-6 are lower than average (far left), while blood IFN-α2, biopsy interferon/JAK1/2 targets, kidney response genes, and independent injury/scarring markers are all higher.

A. Subclinical Kidney Inflammation in Stage 3 (Mostly 3b) Diabetic & Hypertensive CKD:

- **Context:** Diabetic and hypertensive CKD patients with normal blood CRP and IL-6 are usually assumed to have non-inflammatory kidney decline.
- **Finding: SC2** patients (16.1%, 23/143 non-**SC1** patients; 96% CKD: 9 diabetic, 9 hypertensive) have strong local Type-I interferon (IFNAR1, +0.88 SD), JAK1/2-STAT1 (+0.76 to +0.90 SD), and scarring (TIMP1/MMP7) activity inside the kidney biopsy despite low blood IL-6 (−1.01 SD) and IFN-γ (−0.89 SD).
- **Evidence: SC2** patients have worse kidney function (median eGFR 40.4 vs. 56.9, $p = 0.00015$) and higher blood IFN-α2, sTNFR1, and KIM-1 ($p \leq 0.010$). The subgroup was identified in 19 of 20 repeated random derivation/validation divisions of the cohort and reproduced in validation patients more often than expected by chance ($p = 0.00032$).
- **NGAL vs. KIM-1:** Blood KIM-1 is raised in both SC1 and SC2 (+0.69 vs. +0.56 SD), but NGAL is raised mainly in SC1 (biopsy +1.18 vs. +0.40 SD; blood +0.55 vs. +0.05 SD), consistent with NGAL marking acute injury (SC1 is mostly AKI, SC2 mostly CKD).

B. Replication in an Independent Validation Cohort:

- **Context:** KPMP measured blood proteins in two separate patient cohorts (2022: $n = 90$; 2024: $n = 100$), so subcohort cutoffs learned in one cohort can be tested on patients in the other.
- **Finding:** Derived on the 2022 cohort and tested on the 2024 cohort, the algorithm identified largely the same patients as deriving directly on the 2024 cohort ($p = 0.037$) and selected 0/11 reference controls; deriving on 2024 and testing on 2022 gave $p = 0.053$.
- **Evidence:** In validation patients, biopsy interferon genes (IFI44L, MX1) outside the 20-marker panel were raised in both cross-cohort tests ($p \leq 0.011$), and blood sTNFR1 and KIM-1 were raised when testing on the 2024 cohort, while the blood interferon protein ISG15 was not.

Clinical Implication: Kidney-Localized Inflammation in CKD & JAK1/2 Therapy

SC2 patients have stage 3 (mostly 3b) diabetic or hypertensive CKD (median eGFR 40.4) with kidney inflammation that routine blood CRP and IL-6 miss. Blood IFN-α2, sTNFR1, and KIM-1 are candidate markers to select them for trials of baricitinib (JAK1/2), which cut albuminuria by 41% in Phase 2 diabetic CKD.

5. Subcohort 3 (SC3): Scarred CKD With Biopsy CFB Without Blood Activation

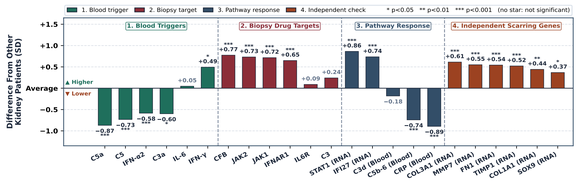


Figure 3. SC3 profile (26/190 patients; 21 CKD, 5 AKI; median eGFR 50.4). Biopsy Factor B (CFB), JAK1/2, and kidney scarring genes are higher than average, whereas blood complement triggers (C5a/C5) and blood C5b-6/CRP are lower than in other kidney disease patients and similar to reference controls, so blood complement is not raised.

A. High Biopsy Complement mRNA Without Systemic Complement Activation:

- **Context:** High complement gene expression on a kidney biopsy could be read as active complement-mediated injury.
- **Finding:** In **SC3** patients (13.7%, 26/190; 21 CKD, 5 AKI: 11 diabetic, 6 hypertensive; median eGFR 50.4), the picture differs: biopsy CFB, JAK1/2-STAT1, and matrix fibrosis genes are high, but blood complement proteins and CRP are not raised (similar to reference controls).
- **Evidence:** Biopsy CFB (+0.77 SD), JAK1/2-STAT1 (+0.72 to +0.86 SD), and scarring genes (COL3A1/FN1/MMP7/TIMP1, +0.52 to +0.61 SD, $p \leq 0.00018$) rise with mild blood IFN-γ (+0.49 SD, $p = 0.035$), whereas blood C5, C5a, C5b-6, and CRP are lower than in other kidney disease patients (−0.73 to −0.89 SD, $p \leq 0.00032$) and similar to reference controls.

B. Why Biopsy Complement RNA Alone Can Mislead:

- **Finding:** Scarred biopsies co-express CFB mRNA alongside STAT1 ($r = 0.66$) and fibrosis genes even when blood complement is not activated.
- **Comparison:** Biopsy CFB mRNA is high across **SC1**, **SC2**, and **SC3**, yet blood terminal complement (C5a/C5b-6) is raised only in **SC1** and is not raised in **SC3**.
- **Implication: SC3**'s IFN-γ/JAK1/2 signal did not replicate in validation patients (median $p = 0.13$ across random splits; unchanged blood CXCL10), so **SC3** serves mainly as a caution against choosing complement or JAK drugs from biopsy RNA alone.

Clinical Implication: Biopsy Complement RNA Without Blood Activation

In SC3, high biopsy CFB mRNA is not accompanied by raised blood C5/C5a/C5b-6 or CRP. If molecular biopsy panels enter practice, complement RNA should be read alongside blood markers and standard C3 immunofluorescence.

6. Four Potential Clinical Applications (Hypotheses to Test in Prospective Trials)

1. Hypothesis: Earlier Detection of Acute Interstitial Nephritis (SC1):

- **Context:** In hospitalized AKI, blood creatinine rises similarly in routine tubular injury (ATI) and acute interstitial nephritis (AIN, often drug-induced; treated by stopping any culprit drug plus steroids), while the fever, rash, and eosinophilia triad appears in under 10% of AIN.
- **Proposal:** Blood (IL-6, CRP) and urine (NGAL/MMP-7) markers raised in **SC1** are candidates for a future non-invasive test to prioritize biopsy, which would need separate validation.
- **Evidence: SC1** includes 78% (7/9) of biopsy-proven AIN in this small dataset ($p = 0.00014$) and all 5 AIN cases in an independent validation cohort (vs. 18 of 85 other patients; $p = 0.0008$).

2. Hypothesis: Detecting Hidden Kidney Inflammation in Diabetic & Hypertensive CKD (SC2):

- **Context:** Diabetic and hypertensive CKD patients with normal blood CRP and IL-6 are assumed to have non-inflammatory decline, because routine blood tests only reflect systemic acute-phase inflammation.
- **Finding:** Paired profiling reveals active Type-I interferon (IFNAR1) and JAK1/2-STAT1 signaling and matrix scarring (TIMP1/MMP7) confined to the kidney biopsy in 16.1% (23/143) of patients remaining after excluding **SC1** (96% CKD).
- **Evidence: SC2** patients have lower kidney filtration (median eGFR 40.4 vs. 56.9, $p = 0.00015$) and elevated blood IFN-α2, sTNFR1, and KIM-1 ($p \leq 0.010$), providing candidate blood markers to flag this subgroup for targeted trials (Box 7.2).

3. Hypothesis: Interpreting Biopsy Complement RNA Cautiously (SC3):

- **Context:** If molecular biopsy panels enter practice, high complement Factor B (CFB) mRNA could be misread as a reason for complement blockers (iptacopan, eculizumab).
- **Finding:** Checking blood proteins alongside the biopsy separates systemic complement activation from STAT1-linked stress gene expression ($r = 0.66$) in scarred biopsies.
- **Evidence:** Although biopsy CFB mRNA is high in **SC1**, **SC2**, and **SC3** (+0.77 to +1.23 SD), blood C5/C5a/C5b-6 and CRP are not raised in **SC3** (similar to controls), so CFB RNA alone does not confirm active cleavage without biopsy C3 staining.

4. Hypothesis: Enriching Kidney Trials for Patients Whose Target Pathway Is Active (SC1–SC3):

- **Context:** Kidney trials of targeted anti-inflammatory drugs typically enroll broad AKI or CKD labels, although tissue profiling identifies distinct pathway-active subgroups within the same diagnosis (e.g., ∼27% TNF-activated in nephrotic syndrome [MCD/FSGS], with worse outcomes; **Mariani 2023**), whose benefit is diluted by broad enrollment.
- **Approach:** After adjusting for eGFR and biopsy platform, our three-step selection criterion separates pathway-active patients from the majority of common diabetic and hypertensive CKD patients without active immune signaling.
- **Evidence:** Each subcohort spans 12–19% of kidney disease patients (28% of CKD in **SC1**/**SC2**, 39% across **SC1**–**SC3**); **SC1** and **SC2** were reproduced in validation patients more often than expected by chance ($p < 0.001$) and in an independent validation cohort ($p = 0.013$–0.037). By design, no reference controls are selected during derivation, and only 0–3 reference controls were selected in validation patients.

Clinical Takeaway: How Pairing Blood & Biopsy Could Change Patient Management

Routine blood tests (CRP, IL-6) miss local interferon inflammation in diabetic/hypertensive CKD (**SC2**), while biopsy complement RNA alone could be misread as active complement attack in scarred CKD (**SC3**); pairing blood and biopsy could guide diagnosis, drug choice, and trial enrollment, pending prospective trials.

7. Clinical Implications: Trial Enrichment Hypotheses & Therapeutic Caveats

1. Acute Interstitial Nephritis & Inflammatory AKI (SC1, 18.9%; 7/9 AIN Cases):

- **Current care:** Standard treatment for AIN is stopping any culprit medication and giving steroids, but patients who do not recover lack targeted drug options.
- **Rationale:** Because **SC1** patients have high blood IL-6 (even compared with other AKI patients) and kidney IL6R, IL-6/IL6R blockers (ziltivekimab, tocilizumab) are the first candidates; kidney CFB and C5AR1 suggest Factor B (iptacopan) or C5 (eculizumab) blockers as secondary candidates.
- **Supporting data:** On-target blockade is established in chronic kidney cohorts (ziltivekimab cut high-sensitivity CRP 77–92% in CKD, **Ridker 2021**; iptacopan cut proteinuria 38.3% in IgA nephropathy, **Perkovic 2025**), though neither has been tested in AKI or AIN.

2. Progressive CKD With Local Kidney Interferon Inflammation (SC2, 16.1%*; Median eGFR = 40.4):

- **Current care:** Standard care for diabetic and hypertensive CKD (RAAS blockade, SGLT2 inhibitors, finerenone, GLP-1 agonists) does not target interferon/JAK signaling, leaving local kidney inflammation untreated in patients with normal blood CRP.
- **Rationale:** Because **SC2** patients have local kidney IFNAR1 and JAK1/2-STAT1 activity despite low blood IL-6, baricitinib (JAK1/2) is a candidate, with blood IFN-α2, sTNFR1, and KIM-1 (but not NGAL, which is essentially unchanged in **SC2**) as candidate selection markers.
- **Supporting data:** This is consistent with Phase 2 diabetic CKD data, where high-dose baricitinib cut 24-week albuminuria by 41% while lowering urine CXCL10 and blood sTNFR1/2 (**Tuttle 2018**); a Phase 2 pilot trial (**JUSTICE**, NCT05237388) studies baricitinib in APOL1-associated hypertensive CKD and FSGS.

3. Biopsy Complement RNA Without Blood Activation (SC3, 13.7%):

- **Context:** If molecular biopsy panels enter practice, high complement or JAK RNA alone could be misread as a reason to give complement or JAK drugs.
- **Implication:** In **SC3**, blood complement (C5/C5a/C5b-6) and CRP are not raised and biopsy C5AR1/IL6R are flat despite high biopsy CFB mRNA, so CFB RNA alone does not confirm active cleavage without biopsy C3 staining.
- **JAK signal: SC3**'s IFN-γ/JAK1/2 signal did not replicate in validation patients, so JAK inhibitors are not supported either.

Table 2. Candidate therapies by subcohort. Each row summarizes a subcohort's blood and biopsy pattern, the candidate therapy, and the main caveats.

Subcohort	Blood & Kidney Biopsy Profile	Candidate Therapy	Main Caveats
SC1 (18.9%)	Mostly AKI (22 AKI, 14 CKD; 7/9 AIN): high blood IL-6 (also vs. other AKI) & complement with active kidney CFB, C5AR1 & IL6R	ziltivekimab / tocilizumab (IL-6/IL6R); iptacopan (Factor B), eculizumab (C5)	Test against standard AIN care (stopping culprit drug + steroids)
SC2 (16.1%*)	Diabetic/hypertensive CKD (eGFR 40.4): blood CRP not raised, low IL-6, active kidney IFNAR1 & JAK1/2	baricitinib† (JAK1/2)	Missed by routine blood CRP/IL-6; Phase 2 CKD data is albuminuria-only so far
SC3 (13.7%)	Scarred CKD (eGFR 50.4): high biopsy CFB, JAK1/2 & scarring genes, but blood complement & CRP not raised	None from RNA alone (require biopsy C3 stain)	Biopsy CFB mRNA reflects STAT1 ($r = 0.66$) and scarring; urine complement tested in only 10/26 patients (not raised)

**Note: SC2 is 23/143 (16.1%) of patients remaining after excluding the 47 patients assigned to SC1 across random splits (12.1% of all 190). All drug matches are trial-enrichment hypotheses requiring randomized trials. †Baricitinib requires dose reduction at eGFR 30–60 (avoid below 30); JAK inhibitors carry an FDA boxed warning (serious infection, cardiovascular events, thrombosis, malignancy).*

8. Out-of-Sample Cohort Validation, Longitudinal Dynamics & Limitations

A. Reproducibility in Validation Patients & an Independent Validation Cohort:

- **Approach:** We evaluated subcohort selection in two ways: on random validation subsets of patients, and by deriving marker cutoffs in one KPMP cohort and validating them in the other.
- **Finding:** In validation patients, subcohorts derived independently on each subset identified the same patient subgroups more often than chance ($p < 0.001$), and selected patients again had raised kidney injury and scarring markers ($p = 0.005$). Figure 4 shows the cross-cohort test:

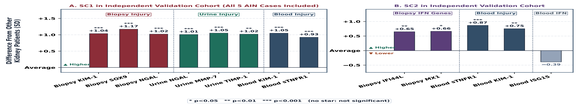


Figure 4. Cross-cohort validation on an independent KPMP cohort. Patients assigned to SC1 in the validation cohort (A) have injury markers in biopsy, urine, and blood 0.9–1.2 SD above other patients (all 5 AIN cases included). Patients assigned to SC2 (B) have biopsy interferon and blood injury markers 0.65–0.87 SD above average, while the blood interferon protein ISG15 is not raised.

B. Following the Same Kidneys Over 1 Year: Repeated Transplant Biopsies (GEO GSE126805):

- **Why We Checked a Second Study:** Because KPMP biopsies each patient only once, a single biopsy cannot show whether acute kidney inflammation heals on its own or turns into permanent scarring over time.
- **What Was Done:** We analyzed a separate study (**Cippà 2018**) that biopsied the same 42 human transplanted kidneys 4 times over 1 year (163 biopsies: before surgery, right after surgery, and at 3 and 12 months; derived in 25 patients, validated in 17):
  - **Acute SC1-Like Inflammation Heals Completely:** Acute complement (C5AR1) and IL-6 receptor (IL6ST) signaling rises sharply right after surgery (30–65% of validation kidneys) and **drops to 0% by 3 and 12 months** as acute injury heals.
  - **Chronic Scarring Inflammation Appears Late:** In contrast, macrophage (CSF1R) and interferon-JAK (JAK1/IFNAR1/STAT1) scarring inflammation is absent right after surgery but **emerges at 3 to 12 months (21–43% of kidneys)** despite standard maintenance immunosuppression (including steroids, which do not directly inhibit CSF1R or JAK1/2).

Study Limitations & Clinical Interpretation

- **Sample Size:** The dataset is small (190 patients, 27 controls), and each validation test included only 8–26 subgroup patients. Figures 1–3 pool all 190 patients (descriptive summaries, not held-out validation tests).
- **Study Design:** All results are retrospective analyses of existing KPMP samples; prospective trials are needed before any clinical use.
- **Reference Controls:** Pre-perfusion transplant (21/27) and nephrectomy (6/27) biopsies are used, not healthy donors.
- **Clinical Data:** Only RAAS blockade is recorded; AIN etiology/subtype and steroid/anti-inflammatory use are unrecorded.
- **Assay Scope:** Urine protein levels are not corrected for urine creatinine, and biopsy RNA is averaged over all cells in the sample, so it reflects the mix of cell types.

AI Use Statement: AI was not used to design and implement the variant of the Goemans-Williamson algorithm from Worah 2026, but was used for data preprocessing, validation scripts, literature auditing, and poster layout.

References: de Boer et al. (*Kidney Int.* 2021); Lake et al. (*Nature* 2023); Tuttle et al. (*NDT* 2018); Ridker et al. (*Lancet* 2021); Perkovic et al. (*NEJM* 2025); Podos et al. (*Am. J. Nephrol.* 2022); Paragas et al. (*Nat. Med.* 2011); Niewczas et al. (*JASN* 2012); Han et al. (*Kidney Int.* 2002); Mariani et al. (*Kidney Int.* 2023); Cippà et al. (*JCI Insight* 2018); Goemans & Williamson (*J. ACM* 1995); Worah (*AISTATS* 2026).

Data Attribution: Results are in whole or part based upon data generated by the Kidney Precision Medicine Project (accessed Nov 1, 2026; https://www.kpmp.org; NIDDK grant U24DK114886 et al.); content is solely the author's responsibility and does not necessarily represent official NIH views.