Shaping Tomorrow's Nephrology: Insight-Driven Kidney Care
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Precision Nephrology: Insights from the KPMP and the Integration of Pathology with Transcriptomics

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The Kidney Precision Medicine Project (KPMP) is a landmark multi-institutional consortium established to redefine the molecular taxonomy of chronic kidney disease (CKD) and acute kidney injury (AKI). By integrating state-of-the-art single-cell and spatial transcriptomics, proteomics, metabolomics, and digital pathology from kidney biopsies obtained across a spectrum of disease, KPMP aims to identify novel disease subtypes, therapeutic targets, and biomarkers that transcend traditional clinicopathologic classification. The previously published KPMP Atlas V1 and the recently completed KPMP Atlas V2 represent transformative advances in the molecular cartography of human kidney disease. Atlas V2, which encompasses over 350 patients and approximately 1.7 million cells analyzed across single-cell and spatial modalities, provides unprecedented resolution of cell-type-specific transcriptional states, disease-associated cell populations, and intercellular communication networks across the nephron. Critically, it defines spatially resolved repair states and delineates the pathogenic signaling — including key transcription factor networks such as SOX4, SOX9, and NFKB1 — that drives unresolved inflammation and fibrosis. This cross-species atlas, incorporating complementary mouse multi-omic profiles, establishes a reference framework for anchoring pathological observations to their underlying molecular programs and identifies secreted biomarkers predictive of AKI-to-CKD progression. In addition, we present data integrating quantitative morphological features with transcriptomic profiles across two complementary cohorts. In KPMP, glomerular pathology descriptor scoring, a structured, observer-derived quantification of glomerular lesion severity, was correlated with glomerular transcriptomics, revealing molecular signatures that underlie discrete morphological injury patterns. Additionally, leveraging a subset of the KPMP cohort, we examine transcriptional modules associated

with arteriolohyalinosis, a lesion central to hypertensive and diabetic nephropathy whose molecular underpinnings remain incompletely understood. Finally, we extend this multimodal framework to the tubulointerstitial compartment using pathomics, the systematic, quantitative extraction of morphological features from the tubule functional tissue unit (FTU), integrated with bulk tubulointerstitial transcriptomics and Xenium spatial transcriptomics, enabling direct anchoring of pathomic phenotypes to their molecular context. Together, these findings illustrate the power of precision nephrology: by grounding molecular data in the spatial and morphological context of the biopsy, we can move toward mechanistically informed, patient-specific disease characterization with direct implications for prognosis and therapeutic targeting.

Keywords: Multimodal data integration, Chronic kidney disease, Spatial transcriptomics, Pathomics, Digital pathology

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