

Multi-Omics Integration for Enhanced Insights into Chronic Kidney Disease: Unraveling Biological Networks and Therapeutic Targets, A Mini Review

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Chronic Kidney Disease (CKD) is a major worldwide health concern associated with a gradual decline in kidney function, cardiovascular complications, and considerable variability in clinical progression among affected individuals. Although estimated glomerular filtration rate (eGFR) and albuminuria remain central to the clinical assessment of CKD, these conventional measures provide only a limited representation of the complex molecular processes underlying the disease. In this mini review, we explore the potential integrated multi-omics approaches to improve the understanding and clinical management of CKD. Combining information from genomics, epigenetics, transcriptomics, proteomics, and metabolomics analyses can provide a more comprehensive picture of the biological mechanisms involved in disease development and progression. By providing a high-resolution, systems-level view of renal pathophysiology, multi-omics enables the discovery of novel early biomarkers, reveals distinct molecular endotypes within the CKD spectrum. We synthesize current evidence supporting the application of multi-omics in CKD, from risk prediction and early detection to precise subtyping and the guidance of personalized therapeutic strategies. We further discuss the computational and translational challenges, including data integration, validation, clinical implementation, and ethical considerations, that must be addressed to realize the promise of precision nephrology. The integration of multi-omics data into clinical workflows stands to revolutionize CKD care, shifting it from reactive management to proactive, personalized medicine. Finally, this review posits that the future of CKD therapeutics lies in targeting hubs within these identified networks, rather than single molecules, and provides a forward-looking roadmap for translating integrated network insights into clinically actionable biomarkers and rationally designed combination therapies.

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INTRODUCTION

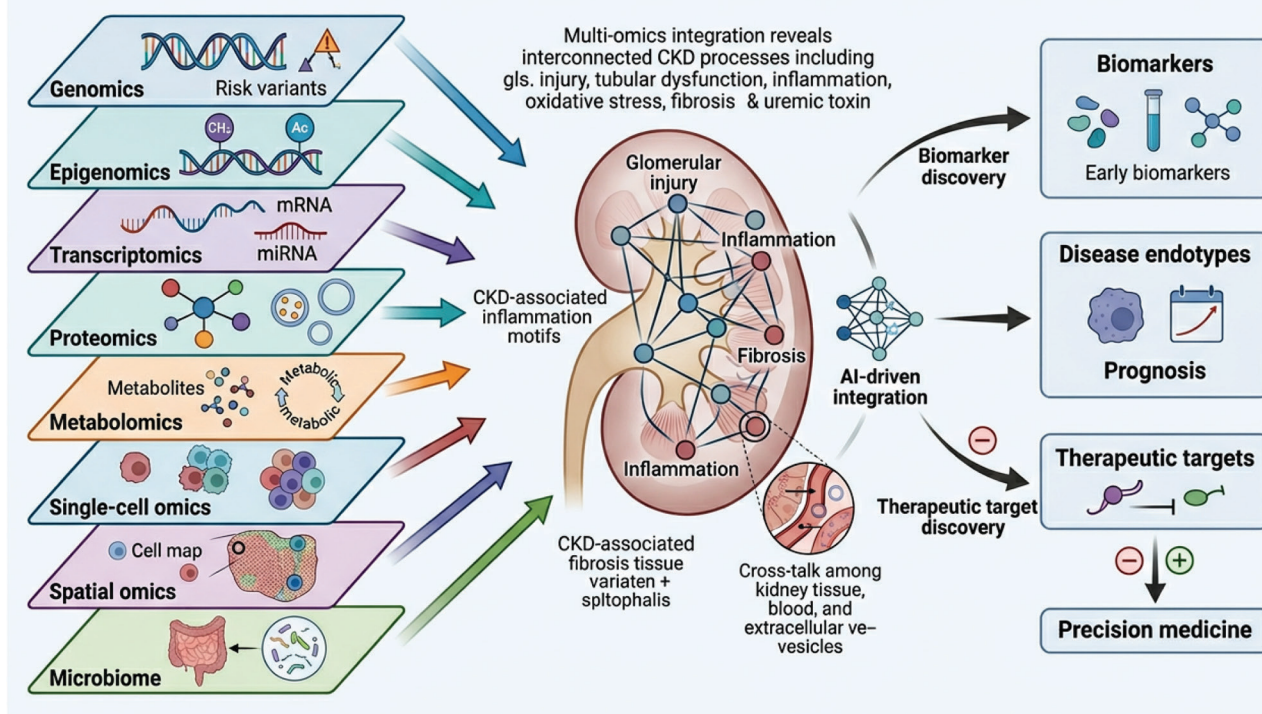
With a global burden exceeding 850 million cases, chronic kidney disease (CKD) represents a substantial contributor to illness, premature mortality, and the growing costs of healthcare.¹

Defined by abnormalities in structure or function



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Multi-Omics Integration in Chronic Kidney Disease



Graphical Abstract. Integrated multiomics layers, genomics, transcriptomics, epigenomics, metabolomics, proteomics, singlecell and spatial profiling, and microbiome, are fused by Al-driven analytics to reconstruct CKD biological networks (glomerular injury, inflammation, fibrosis). Extracellularvesicle crosstalk links kidney and circulation. The pipeline enables early biomarker discovery, disease endotyping/prognosis, and therapeutic target nomination toward precision nephrology.

of kidney persisting for more than three months, CKD encompasses a vast etiological spectrum, from diabetes and hypertension to glomerulonephritides and rare genetic disorders. Current clinical paradigms are heavily reliant on functional (eGFR) and structural (albuminuria) parameters. While useful, these markers are often late indicators of damage, exhibit poor correlation with underlying molecular mechanisms, and fail to predict disease progression or treatment response accurately.² Consequently, patients are diagnosed late, stratified crudely, and managed with broadly applied guidelines, leading to suboptimal outcomes.

The emergence of high-throughput “omics” technologies offers an unprecedented opportunity to deconstruct CKD’s biological complexity. Genomics identifies hereditary predispositions; transcriptomics reveal changes in gene expression over time; proteomic analysis profiles protein levels and post-translational changes; metabolomics

characterize downstream metabolic phenotypes; and epigenomics maps regulatory alterations that affect gene expression. Individually, each omics layer provides valuable but fragmented insights. However, their integrative analysis, multi-omics, facilitates the construction of comprehensive molecular networks that underlie disease pathogenesis.³

This mini-review argues for integrative multi-omics profiling as the cornerstone of a new CKD paradigm. We detail its application in: 1) Early Diagnosis: Identifying sensitive biomarkers long before eGFR decline; 2) Molecular Stratification: Moving beyond etiology to define disease endotypes based on shared biological pathways; and 3) Personalized Management: Informing targeted therapies, monitoring treatment response, and predicting complications. Finally, we outline the roadmap and hurdles for translating this research vision into clinical practice.

THE MULTI-OMICS TOOLKIT: APPLICATIONS IN CKD PATHOBIOLOGY

Genomics and Epigenomics: Unraveling Predisposition and Regulation

Genome-wide association studies (GWAS) analyses have uncovered numerous genetic variants linked to both CKD susceptibility and variation in eGFR (Figure 1), implicating pathways in podocyte function, renal development, and metabolism.⁴ For example, variants in *APOL1* confer high risk for CKD in individuals of African ancestry, illustrating a genetic basis for health disparities.⁵ Beyond common variants, whole-exome sequencing uncovers rare, penetrant mutations in diseases like atypical hemolytic uremic syndrome, directly guiding therapy with eculizumab. Epigenomics, including DNA methylation, histone modification, and non-coding RNA expression (e.g., miRNAs), mediates the interaction between genes and

environment. Hypermethylation of *RASAL1*, a suppressor of renal fibrosis, has been linked to sustained fibrotic responses in CKD.⁶ Circulating miRNAs (e.g., miR-21, miR-29) show promise as stable biomarkers reflecting renal fibrosis and inflammation.⁷

Transcriptomics and Proteomics: Capturing Active Disease States

Single-cell and bulk RNA-sequencing of kidney biopsies have revolutionized our understanding of intra-renal cellular heterogeneity and disease-specific gene signatures (Table 1). In diabetic kidney disease (DKD), transcriptomics has identified activation of inflammatory (NF- κ B) and fibrotic (TGF- β) pathways, and revealed distinct prognostic signatures beyond histology.⁸ Proteomics, particularly using mass spectrometry, analyzes the functional effector molecules. Urinary

The Multi-Omics Toolkit

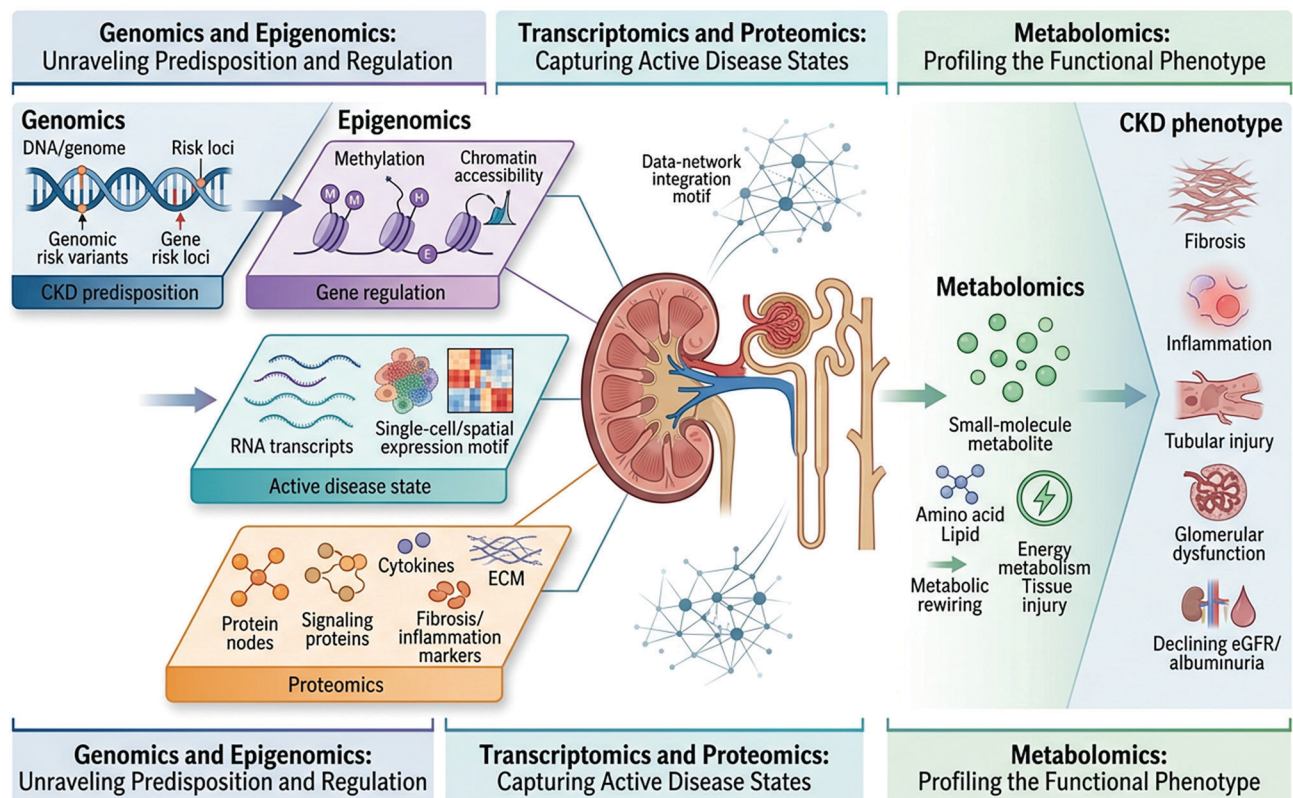


Figure 1. The MultiOmics Toolkit for CKD Pathobiology [Genomic and epigenomic features define predisposition and regulatory context; transcriptomic and proteomic layers capture cellstate and effector pathways; metabolomics profiles functional phenotype. Integrated network analytics across kidney compartments link molecular signals to CKD phenotypes including fibrosis, inflammation, tubular and glomerular injury, and declining renal function (eGFR / albuminuria).]

A Multi-Omics Framework for Target Discovery in CKD

Omic Layer (The Toolkit)	Biological Question Addressed (The Lens)	Key Technological Platforms	Application in CKD Pathobiology (The Target Discovery)	Specific Insights into Therapeutic Targets
Genomics (The Blueprint)	What is the inherited risk or fixed genetic predisposition to CKD onset and progression?	- GWAS (Genome-Wide Association Studies) - WES/WGS (Whole Exome/Genome Sequencing) - Polygenic Risk Scores (PRS)	Identifying risk alleles for CKD (e.g., APOL1 in African Americans, UMOD mutations). Discovering monogenic causes of kidney disease (e.g., collagenopathies, podocytopathies).	- Target Validation: Confirming a causal role for a gene (e.g., APOL1) provides a high level of confidence for drug development. - Patient Stratification: PRS can identify “high-risk” populations for early intervention or clinical trial enrichment.
Epigenomics (The Environmental Regulator)	How do environmental factors (diabetes, hypertension, toxins) and aging modify gene activity without changing the DNA sequence?	- ChIP-seq (Histone modifications) - ATAC-seq (Chromatin accessibility) - Bisulfite sequencing (DNA methylation)	Mapping aberrant DNA methylation patterns in kidney fibrosis. Identifying changes in chromatin accessibility in renal proximal tubular epithelial cells under metabolic stress.	- Epigenetic Therapies: Targeting “writers” and “erasers” (e.g., HDAC inhibitors, DNMT inhibitors) to reverse maladaptive transcriptional programs. - Reprogramming Potential: Identifying accessible chromatin regions that could be targeted to induce regenerative cell states.
Transcriptomics (The Dynamic Script)	What are the actively expressed genes and RNA networks driving the disease phenotype in specific kidney cells?	- Bulk RNA-seq - Single-cell RNA-seq (scRNA-seq) - Spatial Transcriptomics	Deconvoluting the cellular landscape of the fibrotic kidney (e.g., identification of novel pro-fibrotic fibroblast subtypes, inflammatory macrophage signatures). Mapping the “zonation” of injury along the nephron.	- Cellular Precision: scRNA-seq pinpoints the exact cell type expressing a drug target (e.g., a cell-surface receptor on an activated myofibroblast). - Biomarker Discovery: Identifying cell-type-specific secreted factors as non-invasive biomarkers of disease activity.
Proteomics (The Functional Machinery)	What are the functional proteins and signaling networks that constitute the disease’s machinery, including post-translational modifications?	- Mass Spectrometry (MS) - Proximity Extension Assay (PEA) - Antibody arrays	Profiling the urinary proteome to discover early indicators of tubular damage (e.g., KIM-1, NGAL) or the glomerular proteome to identify podocyte injury pathways. Quantifying thousands of circulating proteins associated with kidney function decline.	- Direct Druggable Entities: Proteins are the most common drug targets. Proteomics directly measures their abundance and activation state (e.g., phosphorylation). - Pathway Mapping: Identifying dysregulated signaling cascades (e.g., TGF-β, JAK-STAT) that are amenable to intervention with biologics or small molecules.
Metabolomics (The Physiological Readout)	What are the downstream metabolic consequences of kidney dysfunction, and how do metabolic derangements (uremic toxins) drive further injury?	- Nuclear Magnetic Resonance (NMR) - Liquid/Gas Chromatography-Mass Spectrometry (LC/GC-MS)	Identifying and quantifying the accumulation of uremic toxins (e.g., indoxyl sulfate, p-cresyl sulfate, TMAO). Mapping shifts in energy metabolism (e.g., fatty acid oxidation) in the diseased kidney.	- Therapeutic Intervention: Developing adsorbents to remove uremic toxins or inhibitors to block their production by the gut microbiota (e.g., targeting microbial TMA lyase to reduce TMAO). - Metabolic Reprogramming: Identifying nodes in metabolic pathways (e.g., in glycolysis or fatty acid oxidation) that, if targeted, could restore cellular energetics and slow degeneration.

proteomics has yielded classifiers (e.g., CKD273, a 273-peptide signature) that can detect early CKD and predict progression with high accuracy, even in normoalbuminuric diabetic patients.⁹ Plasma proteomic panels are also being developed to assess cardiovascular risk specifically in CKD populations.

Metabolomics: Profiling the Functional Phenotype

Metabolomics provides a snapshot of systemic

and local biochemical processes. CKD is characterized by a profound disruption of metabolism, including the accumulation of uremic toxins (indoxyl sulfate, p-cresyl sulfate), alterations in the tricarboxylic acid (TCA) cycle, and dysregulation of amino acid and lipid metabolism.¹⁰ Specific metabolite panels can distinguish CKD etiologies and correlate more strongly with residual renal function than traditional markers.

INTEGRATIVE MULTI-OMICS: FORGING A NEW PARADIGM

The true power lies in data integration, where complementary omics layers are combined to construct causal networks.

Early Diagnosis: Beyond Creatinine

Integrative models outperform single-omics approaches. For instance, combining a genomic risk score with a urinary proteomic classifier and a panel of serum metabolites can significantly enhance the prediction of incident CKD in at-risk populations (e.g., hypertensive or diabetic patients). Such models can identify “silent” disease during the molecular injury phase, enabling preventative strategies.

Molecular Stratification: Defining Endotypes

CKD is not one disease. Multi-omics clustering can stratify patients into endotypes with shared molecular drivers, irrespective of clinical diagnosis. A seminal study in DKD identified distinct endotypes: an “inflammatory,” a “fibrotic,” and a “metabolic” cluster, each with different progression rates and potential therapeutic vulnerabilities.¹¹ Similarly, in IgA nephropathy, integrative analyses have defined subgroups with varying activity of the complement system, guiding the use of complement inhibitors.

Personalized Management: Guiding Targeted Therapy

Multi-omics can match patients to optimal treatments. A patient with a lupus nephritis transcriptomic signature dominated by interferon pathways may be a prime candidate for anifrolumab (an interferon receptor antagonist). Proteomic monitoring can reveal early response (or resistance) to therapies like SGLT2 inhibitors, allowing for timely adjustment. Furthermore, metabolomic profiling can personalize dietary recommendations and manage uremic toxin accumulation.

This table presents a layered, systems biology approach to understanding CKD pathobiology. Each “omic” layer serves as a distinct investigative tool that addresses a unique biological question, providing a multi-dimensional view of the disease. By integrating insights across these layers,

from fixed genetic risk (Genomics) to dynamic environmental responses (Epigenomics), active cellular programs (Transcriptomics), functional protein networks (Proteomics), and ultimate metabolic consequences (Metabolomics), researchers can identify and validate novel therapeutic targets with greater precision. This integrated strategy moves beyond single biomarkers to uncover the complex, interconnected networks that drive CKD progression, facilitating the development of targeted, rational therapies.

CHALLENGES AND FUTURE DIRECTIONS

Despite its promise, several hurdles remain: i) Technical & Computational: Integrating heterogeneous, high-dimensional datasets requires advanced bioinformatics (AI, machine learning) and robust statistical frameworks to avoid overfitting. A major computational challenge in multi-omics studies is the risk of overfitting, particularly when high-dimensional molecular datasets are analyzed in relatively small clinical cohorts. Models may capture noise or cohort-specific patterns rather than robust biological signals, resulting in poor generalizability to new patients. Therefore, rigorous feature selection, appropriate regularization, cross-validation, and, importantly, testing in independent external validation cohorts are essential to establish model robustness and clinical utility.^{12,15,17} In addition, batch effects arising from differences in sample processing, analytical platforms, laboratory procedures, or study sites can introduce systematic variation across multi-omics datasets. Careful experimental design, standardized protocols, and appropriate computational batch-correction strategies are consequently required to distinguish true biological signals from technical variation; ii) Validation and Standardization: Discoveries must be validated in large, diverse, prospective cohorts. Assay standardization and quality control are critical for clinical adoption; iii) Clinical Implementation and Ethics: Integrating multi-omics into electronic health records, demonstrating cost-effectiveness, and training clinicians are major tasks. Ethical issues surrounding data privacy, incidental findings, and equitable access must be proactively addressed;¹⁵⁻⁸ iv) Economic Feasibility: The high cost of comprehensive multi-omics profiling remains an important barrier

to routine clinical implementation. Future research should therefore evaluate the cost-effectiveness of multi-omics-guided care and focus on translating broad multi-omics discoveries into targeted, clinically validated panels containing a smaller number of informative biomarkers. Such lower-cost approaches may provide a more scalable and practical strategy for incorporating molecular profiling into routine CKD management, particularly in resource-limited settings; v) Biological Sample Access: While urine and blood are accessible, kidney tissue provides the most direct insight. Biopsy biobanking and non-invasive methods to assess tissue status are vital. Although kidney tissue provides direct information about intrarenal molecular changes, repeated biopsy is invasive and may not be feasible for longitudinal monitoring. Liquid biopsy approaches, including circulating cell-free DNA and urinary extracellular vesicles, may offer a minimally invasive means of capturing molecular signals associated with ongoing renal injury. Serial assessment of these biomarkers could complement tissue-based analyses by enabling repeated monitoring of disease progression and treatment response. However, their clinical utility still requires rigorous validation, standardization, and correlation with tissue-level molecular findings¹²⁻²⁰.

CONCLUSIONS

The integrative multi-omics approach represents a paradigm shift in nephrology, moving from a phenotype-based to a mechanism-based understanding of CKD. By defining the molecular features that drive CKD heterogeneity, multi-omics may not only support earlier disease detection and mechanistic patient stratification but also help predict how individual patients will respond to established therapies, including SGLT2 inhibitors and mineralocorticoid receptor antagonists, thereby enabling more informed and personalized treatment decisions. While significant translational challenges exist, coordinated efforts across research, clinical, and computational domains are paving the way for a future where CKD management is proactive, predictive, and precisely tailored to the individual patient's molecular profile. The era of precision nephrology, grounded in multi-omics, is on the horizon.

DECLARATIONS

Conflict of Interest

The author declares that there are no competing interests that could have influenced the preparation or content of this manuscript.

Generative AI Statement

The authors declare that generative artificial intelligence (GenAI) tools and large language models (LLMs) were used during the preparation of this manuscript. Tools including InstateX, Wordvice, and DeepL were used to assist with language refinement, structural editing, and improvement of the clarity and overall quality of the written text. The authors remain fully responsible for the content, interpretation, and conclusions presented in the manuscript.

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Author Contribution

I confirm that the submitted author list is complete and that the authors are presented in the correct order. I acknowledge that any subsequent modification to the authorship, including adding or removing authors or changing their order, must be formally submitted to the editor and approved in writing by all authors.

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Data Availability

This study did not involve the generation or analysis of any new data.

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