Clinical and Experimental Medicine (2026) 26:94
https://doi.org/10.1007/s10238-025-01989-1

REVIEW

Integrative multi-omics profiling for early diagnosis, stratification and personalized management of chronic kidney disease: a new paradigm

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Received: 17 October 2025 / Accepted: 26 November 2025

Abstract

Chronic Kidney Disease (CKD) is a progressive condition characterized by the gradual loss of renal function over time, affecting millions worldwide and representing a significant public health challenge. CKD is associated with increased morbidity and mortality, primarily due to cardiovascular complications, and its prevalence continues to rise due to factors such as diabetes, hypertension, and aging populations. Despite advances in understanding its etiology, early detection remains a challenge, and current diagnostic methods often identify the disease at advanced stages, limiting therapeutic options and impacting patient outcomes. Early diagnosis of CKD is crucial for implementing interventions that can slow disease progression, prevent complications, and improve quality of life. Consequently, there is a growing emphasis on personalized management strategies tailored to the unique molecular and clinical profiles of patients. Personalized approaches enable targeted therapies, optimize treatment efficacy, and reduce adverse effects, ultimately transforming CKD care from a one-size-fits-all model to precision medicine. Multi-omics approaches have emerged as powerful tools in modern medicine, offering comprehensive insights into the molecular landscape of diseases like CKD. By integrating data from various biological layers, such as genomics, transcriptomics, proteomics, epigenomics, and metabolomics, researchers can achieve a holistic understanding of disease mechanisms, identify novel biomarkers, and uncover therapeutic targets. This systems biology perspective enables the characterization of individual variability, facilitating the development of personalized treatment strategies. In conclusion, multi-omics has the potential to revolutionize early diagnosis, refine patient stratification, and guide the design of targeted pharmacological interventions, paving the way for a new paradigm in disease management.

Keywords CKD · Renal failure · Personalized medicine · Genomics · Transcriptomics · Proteomics · Metabolomics · Epigenomics

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Abbreviations

CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
ESKD	End-stage kidney disease
GWAS	Genome-wide association studies
DKD	Diabetic kidney disease
ADPKD	Autosomal dominant polycystic kidney disease
WES	Whole-exome sequencing
WGS	Whole-genome sequencing
CAKUT	Congenital anomalies of the kidney and urinary tract
AKI	Acute kidney injury
scRNA-seq	Single-cell RNA sequencing
MS	Mass spectrometry
PTMs	Post-translational modifications

Published online: 06 December 2025

FSGS	Focal segmental glomerulosclerosis
miRNAs	microRNAs
lncRNAs	Long non-coding RNAs
PKD	Polycystic kidney disease
SNPs	Single nucleotide polymorphisms
eQTL	Expression quantitative trait loci
mRNA	Messenger RNA
TWASs	Transcriptome-wide association studies
TNF-α	Tumor necrosis factor-alpha
IL-6	Interleukin-6
CCL2	Chemokine (C-C motif) ligand 2
MCP-1	Monocyte chemoattractant protein-1
IFN-γ	Interferon-gamma
ECM	Extracellular matrix
TGF-β1	Transforming growth factor-beta 1
MMPs	Matrix metalloproteinases
UUO	Unilateral ureteral obstruction
PBMCs	Peripheral blood mononuclear cells
ncRNAs	Non-coding RNAs
RRBS	Reduced representation bisulfite sequencing
LC-MS	Liquid chromatography-mass spectrometry
TMT	Tandem mass tags
ESRD	End-stage renal disease
hsCRP	High-sensitivity C-reactive protein
2D-PAGE	Two-dimensional gel electrophoresis
KIM-1	Kidney injury molecule-1
MR	Mendelian randomization
IS	Indoxyl sulfate
pCS	p-Cresol sulfate
ADMA	Asymmetric dimethylarginine
NOS	Nitric oxide synthase
NO	Nitric oxide
NMR	Nuclear magnetic resonance
GC-MS	Gas chromatography–mass spectrometry
PCA	Principal component analysis
ICA	Independent component analysis
ML	Machine learning
AI	Artificial intelligence
FAIR	Findable, Accessible, Interoperable, and Reusable
LUSC	Lung squamous cell carcinoma

Introduction

Chronic Kidney Disease (CKD) represents a formidable global health challenge, characterized by its progressive nature and high prevalence worldwide. Current diagnostic and prognostic methods, primarily based on estimated Glomerular Filtration Rate (eGFR) and proteinuria, often lack the sensitivity and specificity required for early detection, precise disease stratification, and individualized therapeutic interventions [1]. The molecular complexity underlying CKD pathophysiology necessitates advanced approaches to decipher its intricate mechanisms and identify novel targets for intervention. A shift towards more sophisticated, patient-centric strategies is underway, aiming to move beyond traditional symptom-driven medical practice [2].

Integrative multi-omics profiling offers a promising avenue to address these unmet needs in CKD management [3–5]. By combining data from genomics, transcriptomics, proteomics, metabolomics, and other 'omics' layers, researchers can construct a holistic view of the biological system, providing unparalleled molecular depth. This comprehensive molecular mapping facilitates the discovery of robust biomarkers for early diagnosis, enables accurate patient stratification into distinct molecular subtypes, and informs the development of personalized treatment strategies [6]. Ultimately, this approach aims to usher in a new era for pharmacological interventions in CKD, moving towards precision medicine where treatments are tailored to an individual's unique molecular signature. Chronic kidney disease affects approximately 850 million people globally, making it a substantial public health concern [7]. The condition is characterized by a gradual, irreversible decline in renal function, progressing to End-Stage Kidney Disease (ESKD) and increasing the risk of premature mortality. Patients with advanced CKD or ESKD experience a considerable burden of comorbidities, physical and mental symptoms, and a diminished quality of life. Despite advances in renal replacement therapies, such as dialysis, these interventions do not fully restore kidney function and are associated with high costs and substantial patient morbidity [8].

The limitations of conventional diagnostic markers, such as serum creatinine and proteinuria, are well documented. These markers typically reflect renal damage at a relatively advanced stage, often when significant, irreversible injury has already occurred [9]. Furthermore, CKD exhibits considerable heterogeneity in its etiology, progression, and response to treatment, which traditional markers fail to capture. This lack of precise molecular pathology-based stratification impedes the development of effective, targeted therapies and personalized management strategies, highlighting a critical gap in current nephrology practice [10]. The inherent limitations of single-marker diagnostics and the complex, heterogeneous nature of CKD underscore the necessity for more sophisticated investigative tools. Omics technologies offer deep molecular insights into biological processes, moving beyond macroscopic clinical observations to the underlying cellular and biochemical perturbations [11]. By generating vast quantities of data across multiple biological layers, these technologies enable a comprehensive understanding of disease mechanisms, rather than focusing on isolated components. Integrative

multi-omics profiling addresses the complexity of CKD by combining diverse datasets, such as genetic predispositions, gene expression patterns, protein activities, and metabolic states [12]. This integrated approach provides a more complete molecular signature of an individual's disease state, facilitating the identification of subtle early changes, predicting disease trajectories, and uncovering patient-specific therapeutic vulnerabilities. The precision medicine paradigm, which advocates for tailoring medical decisions to the individual patient, relies heavily on such comprehensive molecular profiling [13]. Integrating these molecular data with clinical information provides a robust framework for developing predictive, diagnostic, and prognostic biomarkers, guiding optimal personalized care and ultimately moving beyond a reactive, symptom-driven medical practice [14].

This review provides an unprecedented, holistic view of biological systems at molecular resolution, integrative multi-omics profiling is poised to revolutionize the early diagnosis, risk stratification, and personalized pharmacological management of CKD, ushering in a new paradigm for nephrology.

Overview of omics technologies in nephrology

Omics technologies encompass high-throughput methodologies designed to quantify and characterize the entirety of biological molecules within a system, providing an unbiased view of molecular landscapes. These methodologies generate extensive datasets, which are instrumental for dissecting complex biological systems. In nephrology, omics tools have revolutionized the investigation of kidney disorders, allowing for a deeper understanding of molecular mechanisms and the discovery of novel biomarkers [15, 16].

Genomics: the blueprint of kidney health and disease

Genomics, the study of an organism's complete set of DNA, has been instrumental in identifying genetic predispositions to kidney diseases. Genome-Wide Association Studies (GWAS) have pinpointed numerous genetic variants associated with common nephropathies like diabetic kidney disease (DKD) and autosomal dominant polycystic kidney disease (ADPKD) [5, 17]. These variants, often located in non-coding regions, can influence gene expression, protein function, or cellular processes critical for kidney development and maintenance. For instance, variations in genes like *APOL1* have emerged as a major risk factor for endemic nephropathies in individuals of African ancestry, highlighting how genetic background significantly impacts kidney susceptibility [18]. Furthermore, advancements in whole-exome sequencing (WES) and whole-genome sequencing (WGS) have become invaluable for diagnosing rare and monogenic kidney disorders, such as congenital anomalies of the kidney and urinary tract (CAKUT) and certain forms of glomerulonephritis [19]. Identifying the causal genetic mutations in these conditions not only provides a definitive diagnosis but also opens avenues for targeted therapies and genetic counseling. Moving forward, integrating genomic data with clinical phenotypes (genotype-phenotype correlation) will continue to refine prognostication and personalize treatment strategies [20].

Transcriptomics: the dynamic expression of kidney function

While genomics provides the static blueprint, transcriptomics offers a dynamic snapshot of which genes are actively being transcribed into RNA at a given time and in a specific cellular context. Technologies like RNA sequencing (RNA-seq) allow for the global measurement of gene expression levels within kidney tissue, cells, or biofluids [21]. This is crucial for understanding how genetic alterations or environmental insults translate into cellular dysfunction and disease. In nephrology, transcriptomics has been pivotal in dissecting the molecular mechanisms underlying various kidney diseases [22, 23]. By comparing gene expression profiles of healthy and diseased kidneys, researchers can identify differentially expressed genes that are upregulated or downregulated during disease progression. This has led to the discovery of novel pathways involved in inflammation, fibrosis, and cellular injury in conditions like CKD, lupus nephritis, and acute kidney injury (AKI) [24]. For example, transcriptomic studies have revealed critical roles for specific cytokines, growth factors, and transcription factors in driving renal fibrosis. Furthermore, single-cell RNA sequencing (scRNA-seq) has revolutionized our ability to study cellular heterogeneity within the kidney, enabling the identification of distinct cell populations and their unique transcriptional signatures in health and disease. This high-resolution approach is uncovering subtype-specific drivers of kidney pathology that were previously obscured by bulk tissue analysis [25, 26].

Proteomics: the workhorses of kidney physiology and pathology

The proteome, the complete set of proteins expressed by an organism or system, represents the functional execution of the genetic blueprint. Proteomics, employing techniques like mass spectrometry (MS), allows for the identification

and quantification of thousands of proteins simultaneously. In nephrology, proteomics is essential for understanding the protein-level changes that underpin kidney function and dysfunction. Proteomic studies have identified key proteins involved in glomerular filtration, tubular reabsorption, and interstitial processes [27]. In disease states, proteomics can reveal alterations in protein abundance, post-translational modifications (PTMs), and protein-protein interactions that contribute to pathology [28, 29]. For instance, research has identified specific protein biomarkers in urine and blood that can aid in the diagnosis and prognosis of AKI and DKD [30]. Furthermore, studying the proteomic landscape of kidney biopsies can provide insights into the cellular and molecular mechanisms driving specific glomerular diseases, such as focal segmental glomerulosclerosis (FSGS) and IgA nephropathy [31]. The identification of specific protein targets in these diseases holds promise for the development of targeted therapies. Analyzing the secretome (proteins secreted by cells) and the interactome (protein-protein interaction networks) are emerging areas within kidney proteomics that are further illuminating complex biological processes [32].

Metabolomics: the chemical fingerprints of kidney metabolism

Metabolomics focuses on the complete set of small molecules (metabolites) within a biological system. These metabolites, including amino acids, lipids, carbohydrates, and organic acids, are the end products of cellular processes and reflect the functional state of the organism. In nephrology, metabolomics provides a direct link between genotype, phenotype, and environmental factors [33]. Metabolomic profiling of serum, urine, or kidney tissue can reveal perturbations in metabolic pathways associated with kidney disease. For example, studies have identified altered levels of specific metabolites in patients with CKD, suggesting dysregulation of pathways like urea cycle, amino acid metabolism, and lipid metabolism [34]. These metabolic alterations can not only contribute to disease progression but also serve as potential biomarkers for early detection and risk stratification. Metabolomics has also been crucial in understanding the metabolic consequences of AKI and the impact of different therapeutic interventions on the kidney's metabolic profile [35]. Furthermore, the gut microbiome's influence on host metabolism and its contribution to uremic toxins has been elucidated through integrated metabolomic and microbiome studies, offering new avenues for intervention [36].

Epigenomics: the modulators of kidney gene expression

Epigenomics investigates heritable changes in gene expression that occur without alterations to the underlying DNA sequence. This includes modifications like DNA methylation, histone modifications, and non-coding RNAs. In nephrology, epigenomics is increasingly recognized for its role in mediating the long-term consequences of environmental exposures and in the pathogenesis of complex kidney diseases [37]. DNA methylation patterns, for instance, can influence gene silencing and activation, thereby impacting kidney development and the response to injury. Studies have shown that epigenetic modifications can contribute to renal fibrosis and the progression of DKD [28, 38]. Histone modifications, which alter chromatin structure, can also dictate gene accessibility and expression crucial for kidney cell function. Furthermore, non-coding RNAs, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), play significant regulatory roles and have been implicated in various kidney diseases, acting as potential therapeutic targets [39].

Strategies and methods for integrative Multi-Omics profiling in CKD

A broad array of omics data types contributes to a comprehensive understanding of CKD pathophysiology. Each layer offers unique insights, and their integration provides a richer context for molecular mechanisms [40].

Genomics

The genetic architecture of CKD is complex and heterogeneous, reflecting its diverse etiologies and the interplay of multiple susceptibility genes and environmental factors. Beyond monogenic inherited kidney diseases that manifest early in life, common forms of CKD are increasingly recognized as polygenic disorders where numerous small-effect genetic variants collectively contribute to disease risk [41]. Investigating these genomic data is crucial for understanding disease pathogenesis, identifying novel therapeutic targets, stratifying patients for risk assessment, and ultimately, developing effective prevention strategies. Historically, our understanding of kidney genetics was largely confined to rare monogenic forms of kidney disease [42]. Conditions like Polycystic Kidney Disease (PKD), Alport Syndrome, and FSGS caused by specific gene mutations provided early clues into the critical roles of certain genes in kidney development and function [43]. For instance, mutations in *PKD1* and *PKD2* are the primary drivers of ADPKD, characterized

Table 1 Key genes and loci implicated in common CKD (Examples from GWAS)

Gene/Locus (Symbol)	Associated phenotype(s)	Primary biological function	Potential role in CKD pathogenesis
APOL1	CKD risk, hypertension-associated nephropathy, HIV-associated nephropathy	Apolipoprotein L1; involved in innate immunity and lipid metabolism.	Specific high-risk variants are strongly associated with CKD in individuals of African ancestry. Potential mechanisms include innate immunity, podocyte injury, and inflammation [43, 44].
SHROOM3	CKD risk, hypertension-associated nephropathy	Actin cytoskeleton regulation; involved in epithelial cell polarity and tissue morphogenesis.	May disrupt podocyte structure and function, leading to proteinuria and glomerular damage [43–46].
UMOD	CKD risk, medullary cystic kidney disease, hypertension	Uromodulin (Tamm-Horsfall protein); plays a role in tubular transport of electrolytes and water.	Variants associated with altered uromodulin processing and excretion, potentially leading to tubular damage and interstitial fibrosis [44–47].
PRKAG2	CKD risk, cardiac hypertrophy	AMP-activated protein kinase subunit gamma2; involved in energy metabolism.	Dysregulation of cellular energy homeostasis in kidney cells may contribute to damage and dysfunction [44–48].
CERS2	CKD risk, eGFR	Ceramide synthase 2; involved in sphingolipid biosynthesis.	Sphingolipids play roles in cell signaling and membrane integrity; altered levels may impact podocyte health [44–49].

Table 2 Advanced genomic and multi-omics approaches in CKD research

Approach	Description	Key insights gained in CKD Research
WGS	Sequencing of the entire genome of an individual.	Identifies all types of genetic variants, including SNVs, indels, structural variants, and copy number variations. Crucial for identifying rare variants and novel mutations in both coding and non-coding regions [50, 51].
WES	Sequencing of only the protein-coding regions (exons) of the genome.	Efficiently identifies variants within genes that directly alter protein sequences. Useful for identifying causal variants in Mendelian kidney diseases and common variants with significant functional impact [50–52].
Transcriptomics (RNA-Seq)	Measures the abundance of RNA transcripts in a cell or tissue, reflecting gene expression levels.	Provides a snapshot of which genes are active and to what extent. Allows for the study of differential gene expression in diseased versus healthy kidney tissue [50–52].
Proteomics	The large-scale study of proteins, their structures, and functions.	Identifies and quantifies proteins in biological samples. Can reveal changes in protein abundance, post-translational modifications, and protein-protein interactions [51–53].
Metabolomics	The systematic study of small molecules (metabolites) in biological systems.	Analyzes the complete set of metabolites present in cells, tissues, or biofluids. Reflects the functional state of the organism [50–54].
Epigenomics (e.g., ChIP-Seq, ATAC-Seq, Bisulfite Sequencing)	Studies the chemical modifications to DNA and histone proteins that regulate gene expression.	Investigates how genetic variants influence epigenetic marks and, consequently, gene expression. Crucial for understanding the role of non-coding variants [52–54].

by the formation of renal cysts. Similarly, mutations in genes encoding collagen IV (e.g., *COL4A3*, *COL4A4*, *COL4A5*) underlie Alport Syndrome, leading to progressive glomerular damage [44].

However, the majority of CKD cases are not attributable to single-gene defects. The emergence of GWAS has been instrumental in identifying common genetic variants, primarily single nucleotide polymorphisms (SNPs), associated with increased risk of developing CKD [45, 46]. GWAS compare the genomes of individuals with and without a particular disease to pinpoint genetic loci that are statistically more frequent in the affected group. These studies have successfully identified numerous genetic loci associated with eGFR, a key indicator of kidney function, and CKD itself [47, 48] (Table 1).

These GWAS findings have revealed that many identified genes are involved in fundamental biological processes within the kidney, including glomerular filtration, tubular transport, immune regulation, and fibrosis [49]. However, the precise functional consequences of many identified SNPs remain elusive due to their presence in non-coding regions of the genome or their modest effect sizes. GWAS typically identifies regions of the genome containing multiple SNPs. Fine-mapping techniques aim to pinpoint the most likely causal variant(s) within these regions [50]. Imputation allows researchers to infer genotypes for ungenotyped SNPs based on reference panels, thereby increasing the density of genetic information [51]. Expression Quantitative Trait Loci (eQTL) analysis links genetic variants to variations in gene expression levels. By identifying SNPs that influence the mRNA levels of specific genes in kidney tissue, researchers

Table 3 Representative inflammatory genes upregulated in CKD

Gene ymbol	Protein Product	Role in CKD pathogenesis
TNF	Tumor Necrosis Factor-alpha	Potent pro-inflammatory cytokine, induces apoptosis and extracellular matrix production [59].
IL6	Interleukin-6	Pro-inflammatory cytokine, promotes immune cell activation, fibrosis, and metabolic dysregulation [59, 60].
CCL2	Chemokine (C-C motif) ligand 2 (MCP-1)	Chemoattracts monocytes and macrophages, key drivers of inflammation and fibrosis [60].
IFNG	Interferon-gamma	Activates macrophages, enhances antigen presentation, contributes to fibrosis and immune cell infiltration [60, 61].
CXCL10	Chemokine (C-X-C motif) ligand 10 (IP-10)	Attracts T cells and NK cells, contributing to immune-mediated kidney damage and fibrosis [61, 62].
TLR4	Toll-like receptor 4	Recognizes pathogen-associated and damage-associated molecular patterns, initiating inflammatory signaling pathways [61–63].

Table 4 Key genes involved in fibrosis upregulated in CKD

Gene symbol	Protein product	Role in CKD pathogenesis
TGFB1	Transforming Growth Factor-beta 1	Master regulator of fibrosis, induces myofibroblast differentiation and ECM production [64].
COL1A1	Collagen Type I Alpha 1 Chain	Major structural component of ECM, its deposition contributes to tissue stiffening and scarring [64].
COL4A1	Collagen Type IV Alpha 1 Chain	Essential component of glomerular basement membrane and tubular basement membranes; dysregulation contributes to damage [64, 65].
FN1	Fibronectin 1	ECM protein involved in cell adhesion, migration, and matrix assembly; increased deposition is a hallmark of fibrosis [65, 66].
ACTA2	Actin Alpha 2, Smooth Muscle	Marker of myofibroblast differentiation, responsible for ECM contraction and production [65–67].
SERPINE1	Serine (or Cysteine) Peptidase Inhibitor, Clade E, Member 1 (PAI-1)	Inhibitor of fibrinolysis and a strong inducer of TGF-β signaling and fibrosis [66, 67].

Table 5 Common proteomic methodologies in CKD research

Methodology	Description	Applications in CKD	Advantages	Limitations
LC-MS/MS (Shotgun Proteomics)	Proteins are digested into peptides, separated by liquid chromatography, and then analyzed by mass spectrometry.	Large-scale identification and quantification of thousands of proteins in plasma, urine, and kidney tissue. Discovery of potential biomarkers and pathways.	High throughput, broad coverage, ability to identify low-abundance proteins.	Requires extensive bioinformatics analysis, can be complex to standardize, variability in sample preparation and instrument performance [91].
Targeted Proteomics (SRM/PRM)	Focuses on quantifying a pre-defined set of proteins or peptides of interest.	Validation of candidate biomarkers identified in discovery studies, precise quantification of specific proteins involved in disease pathways.	High sensitivity and specificity for targeted proteins, reproducible quantification.	Limited to pre-defined targets, requires prior knowledge of target peptides, less suitable for discovery [92].
Protein Arrays (e.g., ELISA, Luminex)	Utilizes antibodies to detect and quantify specific proteins in a sample.	Screening for known CKD-related proteins (e.g., cytokines, growth factors), validation of biomarkers.	Relatively simple to perform, can analyze multiple targets simultaneously.	Limited by antibody availability and specificity, may not detect novel proteins [92, 93].
2D-PAGE/MS	Proteins are separated based on isoelectric point and molecular weight, then excised and analyzed by MS.	Historically important for identifying large-scale changes in protein expression, particularly in tissue samples.	Good for visualizing global protein changes and isoforms.	Lower throughput compared to LC-MS/MS, challenges with analyzing highly hydrophobic or low-abundance proteins, labor-intensive [94, 95].

can infer that these variants may exert their functional effect by altering gene transcription [52, 53].

Transcriptomics

Transcriptomics focuses on the study of all RNA molecules, particularly messenger RNA (mRNA), within a cell or tissue. This provides insights into gene expression patterns, indicating which genes are actively being transcribed and their relative abundance [54]. In DKD, transcriptomic analysis has revealed molecular changes related to inflammation, oxidative stress, and lipid metabolism disorders [55]. Cross-tissue transcriptome-wide association studies (TWASs) further correlate gene expression levels with CKD

Table 6 Representative proteomic biomarkers identified in CKD studies

Protein Category	Example Proteins	Relevance in CKD	Sample Type
Inflammation	CCL2 (MCP-1), TNF-α, IL-6, CRP	Pro-inflammatory signaling, immune cell recruitment, progression of fibrosis and glomerular damage [96, 97].	Urine, Plasma
Tubular Injury	KIM-1 (HAVCR1), NGAL (LCN2), Clusterin (CLU)	Markers of acute kidney injury (AKI) and chronic tubular damage [97, 98].	Urine
Fibrosis	TGF-β1, Collagen I, Fibronectin, MMP-2, TIMP-1	Key mediators and markers of ECM deposition and remodeling, leading to interstitial fibrosis [97–100].	Kidney Tissue, Urine, Plasma
Oxidative Stress	Superoxide Dismutase (SOD), Glutathione Peroxidase	Proteins involved in cellular defense against reactive oxygen species; alterations can indicate increased oxidative burden [98–100].	Kidney Tissue, Plasma
Metabolism	Apo-lipoproteins, Aldolase, Urea Cycle Enzymes	Reflect systemic metabolic disturbances and impaired kidney metabolic functions in CKD [99–101].	Plasma, Urine
Endothelial Dysf.	VCAM-1, Endothelin-1	Indicators of vascular damage and dysfunction, which are prevalent complications of CKD and contribute to cardiovascular morbidity [100, 101].	Plasma, Urine

phenotypes, identifying genes such as MAP3K11 as potential therapeutic targets [56, 57]. Inflammation is a central player in CKD pathogenesis, contributing to tubular injury, interstitial fibrosis, and glomerular damage. Transcriptomic analyses have identified a significant upregulation of genes encoding pro-inflammatory cytokines, chemokines, and their receptors [58]. For instance, studies have consistently reported increased expression of: (i) Tumor Necrosis Factor-alpha (TNF-α): A potent pro-inflammatory cytokine that exacerbates kidney damage; (ii) Interleukin-6 (IL-6): Involved in both acute and chronic inflammatory responses; (iii) Chemokine (C-C motif) ligand 2 (CCL2)/Monocyte Chemoattractant Protein-1 (MCP-1): Crucial for monocyte recruitment to the injured kidney; (iv) Interferon-gamma (IFN-γ): Associated with immune cell activation and fibrotic processes [59–61].

Conversely, genes involved in anti-inflammatory pathways and immune regulation may be downregulated, further perpetuating the inflammatory cycle. Understanding these inflammatory transcriptomic signatures can aid in identifying patients at higher risk of progressive CKD and may point towards anti-inflammatory therapeutic targets [62].

Fibrosis and extracellular matrix remodeling

Kidney fibrosis, the excessive deposition of extracellular matrix (ECM) proteins, is the common endpoint of most CKD etiologies and is strongly associated with loss of kidney function. Transcriptomic studies have illuminated the cellular and molecular players driving this process [63]. Key upregulated genes include: (i) Transforming Growth Factor-beta 1 (TGF-β1): A master regulator of fibrosis, promoting the differentiation of fibroblasts into myofibroblasts, which are the primary producers of ECM; (ii) ECM components: Genes encoding collagen types I and IV (*COL1A1*, *COL4A1*), fibronectin (*FN1*), and laminin (*LAMA5*) are consistently upregulated; (iii) Matrix metalloproteinases (MMPs) and their inhibitors (TIMPs): While some MMPs involved in ECM degradation may be altered, the overall balance often favors ECM accumulation due to dysregulation of MMPs and increased expression of their inhibitors; (iv) Integrins and cell adhesion molecules: These play crucial roles in cell-matrix interactions and fibrotic signaling [64–66]. Understanding the transcriptomic regulation of fibrosis is critical for developing antifibrotic therapies.

Methodological considerations and applications

The application of transcriptomics in CKD research is diverse, encompassing various experimental models and human studies. Studies utilizing rodent models of CKD (e.g., unilateral ureteral obstruction (UUO), adenine-induced nephropathy, diabetic nephropathy models) have been instrumental in identifying early transcriptomic changes and validating findings [67]. Transcriptomic profiling of kidney biopsies from CKD patients at different stages and with various etiologies provides crucial insights into the human disease [68]. Additionally, studies analyzing peripheral blood mononuclear cells (PBMCs) or urine sediment offer the potential for non-invasive biomarker discovery [69, 70].

Epigenomics

The intricate interplay between genetic predisposition and environmental factors is well-established in CKD pathogenesis. However, traditional genetic studies have only partially explained its heritability and variability. This gap points towards the crucial role of epigenetics – heritable changes in gene expression that occur without alterations in the underlying DNA sequence [71]. Epigenomics, the comprehensive study of these epigenetic modifications across the genome, offers a powerful lens through which to investigate the complex regulatory landscape contributing to

CKD [72]. By analyzing epigenomics data, researchers aim to unravel how environmental exposures, metabolic stressors, and lifestyle choices translate into durable changes in gene activity that drive kidney damage and dysfunction [73]. Epigenetic mechanisms act as crucial intermediaries, orchestrating gene expression patterns in response to intrinsic and extrinsic cues. The primary players in this regulatory network include DNA methylation, histone modifications, and non-coding RNAs (ncRNAs) [74]. These mechanisms are not static; they are dynamic, reversible, and intimately involved in cell differentiation, tissue homeostasis, and disease pathogenesis [75].

The investigation of epigenomics data relevant to CKD involves a multi-pronged approach, leveraging advanced molecular techniques and sophisticated bioinformatics tools. WGBS, this method reduced representation bisulfite sequencing (RRBS), Methylation BeadChips (Illumina 450 K/EPIC arrays) [76]. Numerous studies have identified aberrant DNA methylation patterns in kidney tissue and peripheral blood cells from CKD patients. For instance, global hypomethylation has been observed in fibrotic kidneys, while specific promoter regions of pro-fibrotic genes like *TGF-β1* and *collagen I* often exhibit hypermethylation, contributing to their sustained expression [77, 78]. Conversely, tumor suppressor genes may become hypermethylated and silenced, potentially exacerbating kidney injury. Longitudinal studies are beginning to link specific methylation signatures to CKD progression rates and response to therapy [79]. Chromatin immunoprecipitation followed by sequencing (ChIP-seq), ATAC-seq (Assay for Transposase-Accessible Chromatin using sequencing) technique in dysregulation of histone-modifying enzymes (e.g., HDACs, HATs, HMTs) is a recurring theme in CKD [80]. For example, increased activity of HDACs has been implicated in promoting kidney fibrosis by repressing the expression of anti-fibrotic genes [81]. Conversely, certain histone methylation marks, such as H3K27me3, have been shown to be altered in diabetic nephropathy, influencing the expression of genes involved in inflammation and cellular stress. ncRNAs, particularly miRNAs and lncRNAs, are emerging as critical regulators in CKD [82]. Numerous miRNAs (e.g., miR-21, a pro-fibrotic miRNA; miR-192, linked to renal fibrosis; miR-126, involved in endothelial function) are dysregulated in various CKD etiologies, found in kidney tissue, urine, and circulating exosomes [83]. LncRNAs like *MALAT1* and *HOTAIR* have been shown to influence key processes such as EMT, inflammation, and cellular senescence in renal cells. The stability and accessibility of ncRNAs in biofluids make them attractive candidates for non-invasive biomarkers [84].

Challenges

CKD is a syndrome with diverse etiologies (e.g., diabetic nephropathy, hypertensive nephropathy, glomerulonephritis). Epigenetic signatures can vary significantly across these conditions, requiring careful stratification of patient cohorts. Epigenetic profiles are highly tissue-specific [85]. While kidney biopsies provide the most relevant data, their invasive nature limits widespread application. Surrogate tissues (blood, urine) may reflect systemic changes but might not capture kidney-specific epigenetic events accurately. The kidney is composed of various cell types (glomerular, tubular, interstitial, endothelial) [86]. Bulk tissue analysis can obscure cell-type-specific epigenetic changes, which might be crucial for understanding disease mechanisms. Single-cell epigenomics approaches are beginning to address this. Establishing causality between an epigenetic modification and disease progression is challenging [87]. Longitudinal studies and functional validation experiments are essential to differentiate epigenetic consequences from drivers of the disease [88]. Environmental factors (diet, lifestyle, medications) can significantly influence epigenetic marks, making it difficult to isolate disease-specific changes. Integrating large-scale epigenomics data with genomics, transcriptomics, proteomics, and clinical data requires sophisticated bioinformatics pipelines and multi-omics analytical frameworks [89].

Proteomics

Proteomics involves the large-scale study of proteins, including their identification, quantification, and analysis of post-translational modifications. Proteins are the primary functional molecules in cells, and their altered expression or modification directly reflects cellular processes and disease states [90]. Tandem liquid chromatography-mass spectrometry (LC-MS/MS) and Tandem Mass Tags (TMT) labeling techniques have been used to evaluate protein changes and phosphorylation sites in DKD, highlighting crucial kinases and signaling pathways [91]. Urinary proteomics can detect early molecular changes in conditions like DKD, heart failure, and coronary artery disease, offering non-invasive alternatives for diagnosis and prognostication by differentiating between glomerular and extraglomerular pathologies [92]. In End-Stage Renal Disease (ESRD), plasma levels of high-sensitivity C-reactive protein (hsCRP) and cardiac troponins (cTnT, cTnI) have demonstrated prognostic value for mortality [93]. Other techniques, such as antibody-based arrays (e.g., protein arrays, Luminex) and two-dimensional gel electrophoresis (2D-PAGE) followed by mass spectrometry, also play valuable roles depending on the research question and the sample type [94].

Key proteomic findings in CKD

Numerous proteomic studies have illuminated the molecular underpinnings of CKD. These investigations have consistently identified alterations in proteins involved in inflammation, cellular damage, and tissue remodeling [95]. Pro-inflammatory cytokines (e.g., TNF-α, IL-6), chemokines (e.g., MCP-1/CCL2), and complement system components are frequently found to be upregulated in CKD. These proteins contribute to immune cell infiltration and activation within the kidney, exacerbating tissue injury [96]. Proteins involved in antioxidant defense mechanisms (e.g., superoxide dismutases, glutathione peroxidases) and markers of oxidative damage (e.g., protein carbonyls, advanced glycation end products) are often altered. This highlights the significant role of oxidative stress in CKD pathogenesis [97]. Proteins associated with the synthesis and degradation of ECM such as collagen, fibronectin, and MMPs are differentially expressed. Increased ECM deposition leads to interstitial fibrosis and impaired kidney architecture [98]. Proteins related to epithelial cell integrity, transport processes, and mitochondrial function are altered, reflecting the functional decline of renal tubules. Proteins such as kidney injury molecule-1 (KIM-1), a known marker of tubular injury, are often detected [99]. CKD is associated with profound metabolic disturbances. Proteomic studies have identified dysregulation of proteins involved in lipid metabolism, glucose homeostasis, and urea cycle [100].

Metabolomics

Metabolomics is the comprehensive study of small-molecule metabolites within a biological system, representing the end-products of cellular processes and providing a direct snapshot of physiological and pathological states [101]. For example, in an adenine-induced CKD murine model, metabolomic analysis revealed how sheep milk intervention modulated metabolic processes related to proteins, lipids, minerals, and hormones, thereby exerting renoprotective effects [102]. Metabolome-wide Mendelian randomization (MR) analyses have also identified unique metabolites significantly associated with CKD and kidney function. Metabolomics studies using plasma, serum, and urine have consistently identified distinct metabolic signatures that correlate with CKD severity (stages G1 to G5) [103]. These signatures often reveal early changes missed by conventional diagnostics, suggesting utility in predicting rapid progression or identifying patients at high risk of cardiovascular complications, a major cause of mortality in the CKD population [104].

Key perturbed metabolic pathways in CKD

Metabolomics profiling has consistently flagged specific pathways that are significantly altered even in the early stages of renal decline.

Gut microbiota-derived metabolites (The Gut-Kidney Axis) One of the most critical discoveries in CKD metabolomics is the strong link between uremia and the gut microbiome [105]. Dysbiosis in CKD patients lead to the overproduction of microbial metabolites derived from the fermentation of dietary protein, which are then absorbed, conjugated by the liver, and become highly toxic when the failing kidney cannot excrete them [106]. The most prominent examples are Indoxyl Sulfate (IS) and p-Cresol Sulfate (pCS). These compounds are highly protein-bound, restricting their removal by dialysis, and act as potent uremic toxins. They have been strongly implicated in driving renal damage (tubular injury), cardiovascular disease, and endothelial dysfunction [107].

Amino acid metabolism CKD often leads to significant perturbations in amino acid homeostasis, reflecting changes in protein turnover, nutritional status, and mitochondrial dysfunction. Taurine and glycine, generally show reduced levels, possibly impacting osmoregulation and detoxification processes [108]. Arginine and citrulline changes in the asymmetric dimethylarginine (ADMA)/L-arginine ratio are highly relevant. ADMA, a competitive inhibitor of nitric oxide synthase (NOS), accumulates due to impaired renal excretion, leading to reduced Nitric Oxide (NO) bioavailability, a key factor in the development of hypertension and vascular stiffness in CKD [109, 110].

Lipid and energy metabolism Dyslipidemia is a hallmark of CKD, but metabolomics provides finer detail than simple total cholesterol/triglyceride measurements. Acylcarnitines compounds, crucial for transporting fatty acids into the mitochondria for beta-oxidation, frequently accumulate [110]. Elevated levels of long-chain and medium-chain acylcarnitines suggest impaired mitochondrial function and reduced fatty acid utilization—a potential driver of metabolic inflexibility and insulin resistance often observed in uremia [111]. Sphingolipids and phospholipids, altered ratios of various lipid classes have been correlated with

CKD progression, highlighting potential disruption in cellular membrane integrity and signaling pathways [112].

Approaches to data integration

The successful application of multi-omics profiling relies heavily on effective data integration strategies, which synthesize information from disparate sources into a coherent biological narrative. Traditional statistical methods form the bedrock of multi-omics data integration [113]. These approaches include multivariate analysis, correlation studies, and dimensionality reduction techniques like Principal Component Analysis (PCA) or Independent Component Analysis (ICA). Such methods help identify relationships and patterns within and between different omics datasets [114]. However, integrating multiple datasets, which vary in statistical power, type, size, and network coverage, presents considerable challenges. The presence of inherently high false-positive and false-negative rates in high-throughput assays, coupled with systematic biases unique to each technology, complicates accurate network reconstruction from combined data [115]. Machine learning (ML) and Artificial Intelligence (AI) have emerged as powerful toolkits for extracting knowledge and understanding underlying biological patterns from the expanded scale and complexity of omics data [116]. ML algorithms, including supervised, unsupervised, and semi-supervised learning, can handle the high dimensionality and non-linear relationships characteristic of multi-omics datasets [117]. AI-driven approaches enable predicting disease progression risks, elucidating molecular mechanisms, and supporting medical decision-making. For example, AI can integrate radiomics, genomics, and transcriptomics data to define optimal treatment allocation strategies for patients, as explored in metastatic clear-cell renal cell carcinoma [118].

Network-based integration techniques model biological systems as interconnected networks, where nodes represent biological entities (e.g., genes, proteins, metabolites) and edges represent their interactions. This approach allows for the visualization and analysis of functional connections and regulatory pathways [119]. By constructing networks from integrated multi-omics data, researchers can identify central regulatory hubs, perturbed pathways, and potential drug targets. Methodologies have been developed to integrate diverse datasets differing in statistical power and type, without requiring a curated training dataset, as demonstrated by tools like POINTILLIST. These approaches are crucial for building comprehensive molecular models that can track disease progression and identify specific disease pathways in CKD [120].

Challenges in multi-omics data integration

Despite significant advancements, multi-omics data integration faces several challenges that require ongoing research and development. High-throughput omics technologies, while powerful, inherently possess high false-positive and false-negative rates [121]. Each technology also introduces specific systematic biases, complicating the accurate integration of data from different platforms. The sheer volume and diverse formats of multi-omics data create issues with storage, processing, and computational requirements [122]. Furthermore, the rapid pace of biotechnological progress means that curated exemplar datasets, which could serve as benchmarks for data integration parameters, are often unavailable. These technical hurdles necessitate sophisticated computational methods capable of handling disparate data characteristics [123].

Standardization and reproducibility

A significant challenge in multi-omics research involves ensuring standardization and reproducibility across different studies and laboratories. Variations in sample collection, processing protocols, analytical platforms, and data analysis pipelines can lead to inconsistencies and limit the comparability of findings [124]. The development of robust, consensus-driven standards for data generation, annotation, and sharing is essential to overcome this. Adherence to principles such as Findable, Accessible, Interoperable, and Reusable (FAIR) data is crucial for maximizing the utility of omics datasets and facilitating collaborative research. Establishing standardized data repositories and analytical workflows would enhance the reliability and translational potential of multi-omics discoveries in CKD [125].

Applications of integrative multi-omics in early diagnosis and stratification of CKD

Integrative multi-omics profiling offers transformative applications for improving the early diagnosis and precise stratification of chronic kidney disease. Multi-omics approaches enable the discovery of novel molecular biomarkers that can detect CKD at its earliest stages, often before overt clinical symptoms or significant loss of kidney function are apparent [126]. By integrating genomics, transcriptomics, proteomics, and metabolomics, researchers can identify subtle molecular shifts indicative of disease onset or progression [127]. This facilitates the recognition of specific disease pathways and key events in disease development. For instance, urinary proteomics can identify early molecular changes in conditions such as diabetic kidney disease, heart

failure, and coronary artery disease, specifically detecting alterations in collagen turnover that precede extensive structural damage [128]. These non-invasive biomarkers offer a substantial advantage over traditional methods, supporting proactive interventions and potentially reducing the need for invasive procedures like renal biopsies [129].

Beyond early detection, integrative multi-omics profiling enhances the ability to predict disease progression risks and unravel the heterogeneity within CKD patient populations. By combining clinical data with molecular profiles, machine learning algorithms can be trained to forecast individual patient trajectories and identify subgroups at higher risk of rapid decline [130]. For example, in AKI, the integration of plasma and urine biomarkers allowed for the identification of two molecularly distinct AKI subphenotypes, which exhibited differing risks for long-term adverse kidney events, independent of conventional staging criteria [131]. This molecular stratification provides a more granular understanding of disease subtypes, enabling targeted preventative strategies and more accurate prognoses compared to relying solely on serum creatinine levels [132]. The translational potential of integrative multi-omics in CKD is increasingly demonstrated through various clinical applications and case studies. For example, specific urinary peptide patterns can differentiate between glomerular and extraglomerular pathologies, aiding in the diagnosis of specific kidney diseases and predicting CKD progression and heart failure development [133]. While not specific to CKD, the development of a multi-omics signature for lung squamous cell carcinoma (LUSC) illustrates how integrating gene expression, DNA methylation, genomic mutations, and clinical data can predict patient prognosis and guide immunotherapy selection [134]. This LUSC multi-omics signature (LMS) demonstrated superior predictive performance over existing biomarkers, identifying high- and low-risk patient groups and potential therapeutic options like dasatinib [135]. Analogously, in renal digital pathology, AI-driven image recognition, integrated with omics data, offers advanced high-throughput approaches for capturing implicit molecular features and improving diagnostic accuracy. These examples underscore the capability of multi-omics to refine diagnostic processes and provide actionable insights in clinical settings [136].

Integrative multi-omics profiling for personalized management of CKD

Personalized management of CKD represents a paradigm shift from a one-size-fits-all approach to treatments tailored to individual patient characteristics. Integrative multi-omics profiling is central to achieving this goal. One of the primary benefits of integrative multi-omics is its capacity to stratify CKD patients into distinct molecular subtypes [137]. This stratification moves beyond clinical symptoms and traditional markers to uncover underlying biological differences that influence disease trajectory and treatment response [138]. For complex diseases, patients often fall into subgroups with differing molecular profiles, dictating varying responses to therapies. In kidney transplantation, systems biology approaches integrating multi-omics data are crucial for stratifying patients and predicting their responses, thereby optimizing long-term graft function and survival [139]. This molecularly driven patient stratification is essential for choosing the ideal first-line systemic treatment, as explored in oncological studies integrating genomics, transcriptomics, and radiomics with AI to guide therapy allocation [140]. By identifying specific molecular signatures for each patient or disease subtype, multi-omics profiling enables the tailoring of treatment strategies for improved efficacy and reduced adverse effects. Artificial intelligence, when integrated with multi-omics data, can provide real-time, patient-specific insights to optimize patient outcomes [141]. This allows clinicians to make informed decisions regarding drug choice and dosage, moving towards a truly personalized medicine approach. For example, in silico medicine, which leverages computational analysis of human data and omics platforms, offers reliable predictions to suggest optimal, case-specific treatments for kidney diseases [142]. This integration of diverse data points guides therapeutic decisions, potentially preventing unnecessary treatments and enhancing cost-effectiveness through early detection and precise intervention [143].

A new paradigm for Pharmacological approaches in CKD

The pursuit of effective therapeutic targets and precision pharmacology in CKD has traditionally faced obstacles due to the disease's molecular complexity. Integrative multi-omics profiling is forging a new paradigm, offering unprecedented opportunities for drug discovery and personalized treatment [144].

Identification of therapeutic targets using multi-omics data

Integrative multi-omics data provides a rich source for identifying novel therapeutic targets by unraveling complex disease mechanisms and aberrant signaling pathways. Systems biology approaches, utilizing omics data, can generate molecular models that elucidate specific disease pathways and recognize key events, thereby facilitating target

discovery [145]. In diabetic kidney disease, integrated proteomic and transcriptomic analyses have highlighted the significance of the RAS, RAP1, AMPK, PPAR, and HIF-1 signaling pathways as crucial for pathogenesis, suggesting these as promising targets [146]. Furthermore, cross-tissue transcriptome-wide association studies and Mendelian randomization have identified genes such as MAP3K11 and critical inflammatory proteins like FGF5 as potential therapeutic targets for CKD and kidney function. The identification of potential targets must be followed by robust validation. Integrated omics approaches, combining computational predictions with functional and clinical studies, provide a powerful framework for this validation [147]. For instance, cell experiments are routinely used to confirm the functional roles of model genes, as demonstrated in the validation of SERPINB13 as a potential oncogene in lung squamous cell carcinoma. Such integrated validation processes strengthen the confidence in identified targets, moving them closer to clinical application [148].

Drug repurposing and precision pharmacology in CKD

Multi-omics data can significantly accelerate drug repurposing efforts, identifying existing drugs that could be effective for CKD based on their molecular interactions. This approach reduces the time and cost associated with de novo drug development [149]. For example, in cancer research, whole-genome sequencing has been applied to identify mutated genes that could be targeted by already FDA-approved drugs. Similarly, in lung squamous cell carcinoma, multi-omics analysis suggested dasatinib as a promising therapeutic option for specific tumor subtypes [150]. The discovery that PARP inhibitors are effective in small cell lung cancer also illustrates how omics data can identify therapeutic vulnerabilities and guide the repurposing of drugs to enhance chemotherapy efficacy. Applying these strategies to CKD allows for the identification of existing compounds that interact with newly discovered disease-driving pathways or targets [151].

Molecular modeling and personalized drug response prediction

Molecular modeling, driven by integrated omics data, enables the prediction of individual patient responses to specific drugs. Systems biology and visualization tools create dynamic molecular models that track disease progression and elucidate specific drug-target interactions [152]. Molecular docking analyses, for example, can predict the binding affinity of small molecules to identified protein targets, as shown with capsaicin and its promising interactions with CKD-related targets. In silico medicine, integrating omics platforms and computational analyses, offers reliable computer predictions to suggest optimal treatments in a case-specific manner [153]. This capability to forecast drug efficacy and potential adverse effects based on an individual's molecular profile is a cornerstone of precision pharmacology, aiming to maximize therapeutic benefit while minimizing harm in CKD patients [154].

Innovative strategies in CKD treatments

The integration of multi-omics technologies with extracellular vesicles (EVs), particularly exosomes, analysis promises to revolutionize CKD biomarker discovery and reflect kidney-specific pathological changes like inflammation, fibrosis, and tubular injury. Their non-invasive accessibility via urine or plasma positions them as promising biomarkers for early detection, progression monitoring, and risk stratification in CKD, where traditional markers (e.g., eGFR, albuminuria) often fail to identify disease until advanced stages [155]. Specific urinary EV-miRNAs, such as miR-21, miR-192, miR-200 family members, and miR-34a, have been implicated in various CKD etiologies (e.g., diabetic nephropathy, lupus nephritis, IgA nephropathy) [156]. miR-21, often upregulated in CKD, is linked to fibrosis and inflammation, while others like miR-192 are involved in TGF-β signaling and EMT [157]. The stability of miRNAs within EVs makes them particularly robust biomarkers, reflecting kidney injury and potential therapeutic responses. Beyond cell-specific markers, EV-proteomics can identify proteins involved in pathways critical for CKD progression, such as inflammation (e.g., cytokines, chemokines), oxidative stress (e.g., superoxide dismutase), extracellular matrix remodeling (e.g., matrix metalloproteinases, collagens), and metabolic dysfunction [158]. For example, EVs from patients with diabetic nephropathy might carry a distinct proteomic profile associated with glucose metabolism dysregulation, while those from hypertensive nephropathy could show markers of endothelial injury or vascular remodeling [159].

The true power lies in the convergence of CRISPR-Cas9 with multi-omics, creating an unprecedented framework for precision medicine in CKD. Multi-omics serves as the "intelligence" that guides the "surgical precision" of CRISPR-Cas9 [160]. Multi-omics data can pinpoint the exact genetic targets for CRISPR intervention. Genomic sequencing of patients with monogenic CKDs (e.g., Autosomal Dominant Polycystic Kidney Disease (ADPKD) caused by *PKD1* or *PKD2* mutations, Alport Syndrome due to *COL4A* mutations, or certain forms of Focal Segmental Glomerulosclerosis (FSGS)) directly identifies the pathological mutation requiring correction [161, 162]. For complex, polygenic

CKDs, transcriptomic and proteomic analyses can reveal aberrantly expressed genes or proteins strongly correlated with disease progression (e.g., profibrotic factors like TGF-β or inflammatory cytokines), identifying them as prime candidates for CRISPR-mediated downregulation or knockout [163]. Epigenomic profiling can uncover dysregulated epigenetic marks that silence protective genes or activate deleterious ones, which could be targeted by CRISPR-mediated epigenetic editing tools to restore healthy gene expression patterns [164]. Beyond direct therapy, CRISPR-Cas9, guided by omics, is invaluable for creating sophisticated in vitro and in vivo CKD models. Human induced pluripotent stem cells (iPSCs) can be differentiated into kidney organoids or specific renal cell types (e.g., podocytes, tubular epithelial cells). CRISPR-Cas9 can then introduce specific disease-causing mutations (identified by genomics) into these models or knock out/in genes (identified by transcriptomics/proteomics) to study their functional consequences [165, 166].

Pitfalls, limitations, and opportunities for advancement

Despite its promise, integrative multi-omics profiling faces several inherent limitations. Technical issues related to data heterogeneity, such as varying statistical power, type, and systematic biases across different omics platforms, pose significant challenges to accurate data integration. The absence of universally curated exemplar datasets further complicates the estimation of optimal integration parameters [167]. Ensuring standardization and reproducibility across studies remains a critical bottleneck, necessitating robust protocols for sample collection, processing, and data analysis, along with adherence to FAIR data principles [168]. Moreover, the clinical translation of multi-omics discoveries is often hampered by the need for rigorous validation in large, diverse patient cohorts. Ethical considerations surrounding data privacy and the equitable application of precision medicine also represent important areas for ongoing deliberation [169]. Opportunities for advancement include the continuous development of sophisticated computational tools and AI algorithms capable of handling complex, high-dimensional data, as well as the establishment of standardized, publicly accessible multi-omics repositories [170]. Greater emphasis on prospective clinical trials that integrate multi-omics alongside traditional diagnostics will be essential to demonstrate the real-world impact and cost-effectiveness of these approaches [171].

Emerging technologies and prospects for clinical translation

The trajectory of multi-omics research points toward increasingly refined technologies and broader clinical applicability. Advanced in silico medicine, combining computational analysis with omics data, offers growing potential for personalized treatment predictions and understanding kidney physiology at a multiscale level [172]. The continuous evolution of biological databases, serving as knowledge sources and data-sharing platforms for genes, transcripts, proteins, and metabolites, will further support clinical decision-making, leading to faster diagnoses and more preventive, personalized care [173]. Looking ahead, the integration of real-time, patient-specific insights derived from multi-omics with electronic health records and wearable technologies could revolutionize patient monitoring and intervention strategies [174]. There is also an ongoing need to integrate patient-reported outcomes and psychosocial factors with molecular data, providing a truly holistic view of patient health and well-being, as highlighted by studies on barriers and facilitators to self-care in dialysis patients [175]. Furthermore, the continued development of non-invasive liquid biopsy methods, which can longitudinally evaluate tumor evolution through circulating cell-free DNA and extracellular vesicles, holds promise for monitoring CKD progression and treatment response without invasive procedures. These advancements collectively pave the way for a more precise, predictive, and personalized approach to CKD management [176, 177].

Conclusion

Integrative multi-omics profiling represents a profound advancement in understanding and managing CKD. By synthesizing information from diverse biological layers such as genomics, transcriptomics, proteomics, epigenomics, and metabolomics, this approach transcends the limitations of traditional diagnostics, offering an unprecedented depth of molecular insight. The integration of these vast datasets, often empowered by artificial intelligence and machine learning, enables the discovery of novel biomarkers for early and accurate disease detection, precise patient stratification into molecularly defined subtypes, and the identification of individualized risk profiles. This comprehensive molecular understanding provides a robust foundation for developing personalized therapeutic strategies, moving away from generalized treatments towards interventions tailored to each patient's unique biological signature. It facilitates the identification of novel drug targets by unraveling complex disease pathways, supports the repurposing of existing

drugs for new indications, and enables personalized drug response prediction through sophisticated molecular modeling. As the field advances, integrating multi-omics data into clinical workflows promises to support personalized medicine, reduce adverse effects, and improve the efficacy of treatments. This new paradigm aligns with the broader movement toward precision healthcare, offering hope for better disease control and improved quality of life for CKD patients.

Acknowledgements Not applicable.

Author contributions Soroush Taherkhani design, conceptualization; Khusniddin Saidov, Marhabo Matniyozova wrote the main manuscript and Soroush Taherkhani and Yue Li Revise it. All authors read final version of manuscript.

Funding No funding was received.

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests that may have influenced in this manuscript.

Generative AI statement The authors declare that Gen AI and large language model (LLM) were used in the creation of this manuscript. Generative AI items like instatext, wordvice, and DeepL were used for structural editing and improve handwriting of the text.

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