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Novel Biomarkers in the Early Detection of Chronic Kidney Disease: Current Evidence and Future Directions

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ABSTRACT

Chronic kidney disease (CKD) affects over 850 million individuals worldwide, with conventional markers failing to detect early renal damage until significant nephron loss occurs. This review synthesizes current evidence on emerging biomarkers—including proteomic signatures (e.g., CKD273 panel), metabolomics profiles, circulating microRNAs, APOL1 genetic variants, cell-free DNA methylation patterns, and urinary exospores that enable earlier detection of CKD. We examine multi-marker panels integrated with machine-learning algorithms, achieving high sensitivity and specificity in prospective cohorts, and assess point-of-care technologies facilitating decentralized screening. Regulatory and ethical challenges, cost-effectiveness analyses, and standardization hurdles across diverse healthcare settings are also discussed. Finally, we identify research gaps in longitudinal, multi-center validation studies and propose future directions toward precision nephrology, integrating multi-omics data with imaging and wearable sensors to shift CKD management from treatment to prevention. This comprehensive overview informs clinicians and researchers on the translational potential of novel diagnostics in combating the growing CKD burden.

INTRODUCTION

Epidemiology and Burden of CKD

Chronic kidney disease (CKD) has an estimated prevalence of 850 million people globally, roughly exceeding 10 percent of the current world population making it one of the most prevalent chronic diseases today. In Francis et al. (2023), they cite a study which states that from 1990 to 2017, the CKD prevalence increased globally by 33 percent due to population growth, aging, and the growing burden of diabetes and hypertension. Of particular concern is that Low and Middle Income Countries (LMICs) bear two-thirds of the CKD burden even though they have limited access to therapeutic and diagnostic tools aggravating the CKD situation. CKD has become the 3rd fastest growing cause of death from non-communicable diseases around the globe and is likely to be the 5th leading cause of life lost to be projected in 2040. In 2019, CKD surpasses other non-communicable diseases by causing more than 3.1 million deaths alongside hundreds of millions of disability-adjusted life years (Frank, 2024). Aside from mortality, CKD puts enormous impact individually and socially such as the kidney replacement therapies cost which served around 2.6 million in 2010 and expected to increase by 2030, also including the loss of economic productivity alongside comorbidities cardiovascular pathology (Francis et al., 2024).

Significance of Detecting a Problem Earlier Than Later

Chronic Kidney Disease (CKD) is known to be silent in the earlier stages and is not affiliated with detectable symptoms, traditionally used markers like serum creatinine and estimated glomerular filtration rate (eGFR) do not recognize any renal damage until a substantial 40-50% of nephron function has already been lost (Mizdrak et al., 2022). Some patients may even skip the pre-stage of GFR decline, albuminuria lacked in a significant proportion of patients which includes those with tubulointerstitial and hypertensive nephropathies, meaning conventional screening goes undetected for around 30% of individuals suffering from diabetic kidney disease (Mizdrak et al., 2022). The late-stage identification of CKD makes it

troublesome to incorporate protective therapies in a timely manner, sodium-glucose cotransporter-2 (SGLT2) inhibitors, mineralocorticoid receptor antagonists, and lifestyle changes which have proven to slow down its progression and cardiovascular risk if used in the early stages (Heerspink et al., 2025). Emerging novel biomarkers, including proteomic classifiers like CKD273, physiologic metabolomic panels, proteins fortified urinary exosomes, and various microRNAs in the blood showcases their potential in revealing the clinical evidence of kidney functions ahead of major operational declines (Heerspink et al., 2025; Mizdrak et al., 2022). Finding solutions earlier enables these to enforce mitigation strategies that not only help in retaining what little kidney function is still viable, but more importantly dialysis or transplant requirements, and restrictiveness of cardiovascular disease related to CKD (Zhang et al., 2025).

Aim and Scope of This Review

This review seeks to find gaps in novel biomarkers of chronic kidney disease (CKD) and its clinical translation with particular emphasis on earlier detection of CKD. We shall start with a proteomic signature of CKD known as CKD273 and its associated metabolites such as symmetric dimethyl arginine, 5-methoxytryptophan. Then, we will discuss genomic and transcriptomic markers like APOL1 variants and microRNAs, along with epigenetic changes that can be monitored via cell-free DNA (Božić et al., 2022). Followed by these indicators, focus will shift to exosomal DNA situated in urine and ensemble models combined with AI, assessing these models for sensitivity, specificity, area under curve (AUC), and overall accessibility (Zhang et al., 2025). We will also address other factors: health—economic, regulatory and ethical, even performing cost-effectiveness analyses across various healthcare contexts alongside standardization hurdles in aiding adoption strategy (Kumar et al., 2025; Di Dio et al., 2024). In the end, we detail the comparative lack of work done on longitudinal studies and multi-centered trials, where the consolidated aim is believed to be early intervention along with integrated advanced personalized strategies tailored for CKD, shifting the focus from CKD treatment to prevention, otherwise known as precision nephrology (Di Dio et al., 2024; Kumar et al., 2025).

Pathophysiology of Chronic Kidney Disease Underlying Mechanisms

Inflammation

Low-grade chronic inflammation remains one of the key contributors to the acceleration of CKD. DAMPs such as NLRP3 inflammasome and Toll-like receptors are elicited by renal resident cells, specifically tubular epithelial cells and podocytes, of which are known to be injured. These pathways include NF-κB, JAK-STAT, and cGAS-STING which in turn induces overexpression of pro-inflammatory cytokines (TNF-α, IL-1β), and even additional chemokines that attract monocytes and T lymphocytes into the interstitium (Yuan et al., 2022; Giuliani et al., 2024). This increased inflammation drives further immunological instability which further aggravates the tumor microenvironment through incessant signals perpetuating inflammation thereby increasing M1 macrophage activity. This cycle is known to have a destabilizing effect with a continuous feedback mechanism of sustained inflammation and cell loss along with immune cell infiltration (Giuliani et al., 2024).

Fibrosis

Renal fibrosis, which is the accumulation of extracellular matrix (ECM) tissue, is the common final pathway in chronic kidney disease or CKD. Transforming growth factor-beta 1, or TGF-β1, regulates/professes as the principal fibrogenic cytokine. It orchestrates epithelial-mesenchymal transition, or EMT of tubular cells, and the activation of pericytes. Also, it causes the differentiation of interstitial fibroblasts into myofibroblasts, which secrete collagen and thus are termed 'collagen-secreting myofibroblasts' (Reiss et al., 2022). There is also compression of the peritubular capillaries due to ECM accumulation which leads to hypoxia. This lowers oxygen supply which further increases TGF-β1 release in a self-reinforcing feedback loop (Reiss et al., 2022).

Hemodynamic Changes

Particularly, hemodynamic stress such as glomerular hyperfiltration and hypertension contributes greatly to the pathology of early-stage CKD – especially in the case of diabetic nephropathy. 'Tuttle et al (2022)' stated that the overactivation of renin–angiotensin–aldosterone system (RAAS) coupled with systemic hypertension raises glomerular capillary pressure which exerts a mechanical load on the glomerular basement membrane podocyte resulting in injury which potentiates glomerulosclerosis. It is noted that pharmacologic RAAS blockade using ACE inhibitors or ARBs lowers intraglomerular pressure and mitigates nephron attrition.

Staging of CKD and Clinical Milestones

CKD is defined by persistent abnormalities in kidney structure or function for ≥3 months, irrespective of cause (KDIGO, 2024). The KDIGO classification uses GFR categories (G1–G5, with G3 split into 3a/3b) and albuminuria categories (A1–A3) to stratify risk (Vaidya & Aeddula, 2024)

Table 1

Category	GFR (mL/min/1.73 m²)	Albuminuria (ACR mg/g)
G1	≥90 + kidney damage	A1: < 30
G2	60–89	A2: 30–299
G3a	45–59	A3: ≥ 300
G3b	30–44	
G4	15–29	
G5	< 15 or dialysis	

Clinical Milestones

- **G1–G2/A1–A2**: Mostly asymptomatic; microalbuminuria may be first sign in high-risk groups (diabetes, hypertension) (Vaidya & Aeddula, 2024).
- **G3a–G3b/A2–A3**: Decline in eGFR with rising creatinine; overt proteinuria; onset of hypertension, anemia, and mineral bone disorders as GFR falls below ~45.
- **G4**: Uremic symptoms (nausea, pruritus), metabolic acidosis, hyperphosphatemia, hypocalcemia, secondary hyperparathyroidism; planning for renal replacement therapy.
- **G5**: End-stage kidney disease; initiation of dialysis or transplantation.

Early intervention—blood pressure control, RAAS blockade, SGLT2 inhibitors, and lifestyle measures—can delay progression and improve outcomes (Vaidya & Aeddula, 2024).

Conventional Biomarkers and Their Limitations

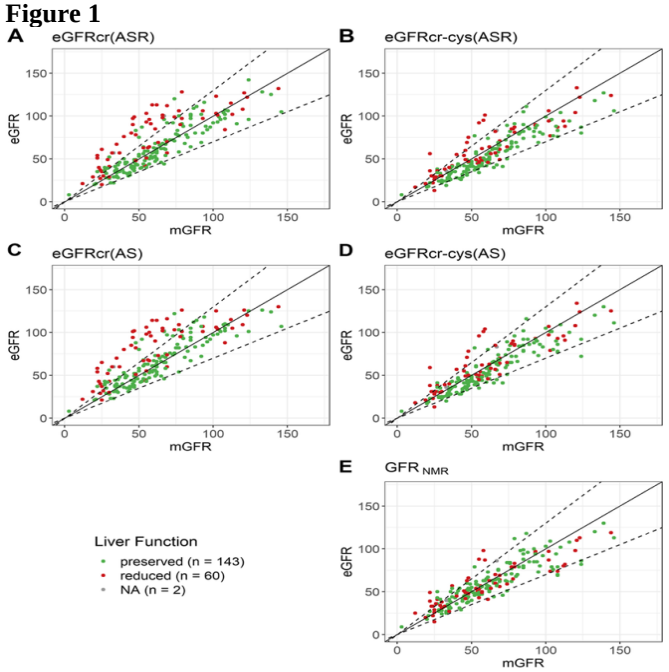
Serum Creatinine & Blood Urea Nitrogen (BUN)

The serum creatinine concentration serves as the primary marker for assessing kidney function, as it indicates the equilibrium point of muscular breakdown of creatine and glomerular filtration. It, however, is modified by non-renal changes like age, biological sex, muscle bulk, medication intake, and diet, which mask tissue damage in the kidneys (Pradeep et al., 2024; KDIGO, 2024). The same limitation applies to BUN; although it measures waste nitrogen excretion, its sensitivity to hydration status and protein intake compromises its ability to detect kidney damage when assessed independently (Pradeep et al., 2024; KDIGO, 2024).

Estimated GFR (eGFR) Equations

In the case of estimating GFR, all of the demographic variables, including age, sex, and race, are integrated into the equations MDRD, CKD-EPI, and Cockcroft-Gault because they attempt to address the issue of serum creatinine's variability. Differences in precision are observed when comparing these formulas to creatinine alone, but they still maintain a systematic underestimation of GFR at higher values and an overestimation at lower values, especially in underrepresented groups such as the elderly or those with low muscle mass (Murtagh et al.; KDIGO, 2024). The existence of numerous equations to solve a problem creates difficulty in making clinical decisions as each one functions differently across ethnicities and with preexisting diseases (Murtagh et al., 2025).

Figure 1



Urinalysis (Proteinuria)

Initial assessments for chronic kidney disease (CKD) often include a urinalysis examining protein levels, particularly albuminuria gauged through an albumin-to-creatinine ratio (ACR). Persistent proteinuria points to glomerular damage and indicates a likelihood for disease progression (Pradeep et al., 2024; Lee et al., 2024). Nonetheless, spot urine measurements can be influenced by physical activity, fever, and hydration status, and verification usually entails confirmatory testing, such repetitive 24-hour collections, or retesting to minimize the incidence of false positives (Pradeep et al., 2024; Lee et al., 2024).

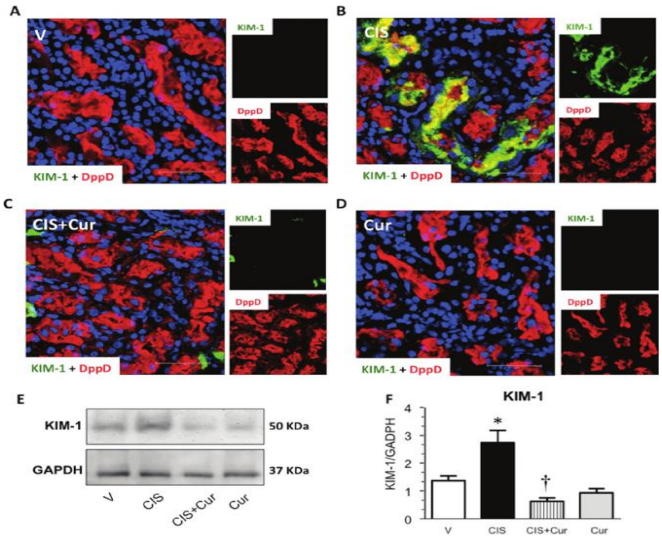
Why They Fail in Early Disease

All of the traditional markers mentioned previously only appear after significant nephron loss has occurred—and usually after 40-60% of function is already lost—which makes them unresponsive to rudimentary stages of kidney damage (Pianca et al., 2025; Shahin et al., 2024). More sensitive and specific CKD diagnostic tests are needed to enable detection at the earliest stages, as other factors like the Jaffe reaction in creatinine assays and physiological factors hinder the detection of the more sensitive traditional markers (Pianca et al., 2025; Shahin et al., 2024).

Proteomic Biomarkers

Chronic kidney disease (CKD) progresses insidiously and conventional markers such as serum creatinine and albuminuria only become aberrant after considerable nephron depletion has occurred. Emerging proteomic biomarkers may enable detection of early subclinical kidney damage by monitoring the release of specific proteins into the blood or urine as a result of tubular or glomerular destruction. We focus on four leading candidates of proteomic biomarkers—NGAL, KIM-1, cystatin C and β_2-microglobulin—and present their biology, diagnostic accuracy, and possible clinical uses.

Figure 2



Neutrophil gelatinase–associated lipocalin (NGAL)

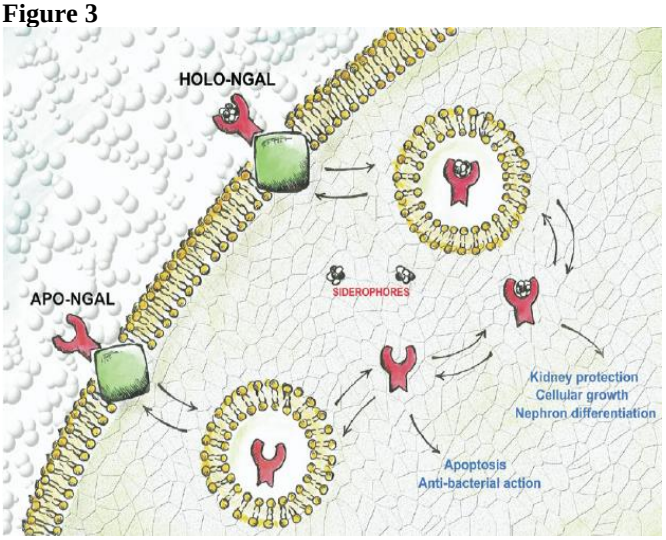
NGAL is a 25 kDa protein originally isolated from neutrophil granules. In healthy kidneys, NGAL is minimally expressed, but its synthesis is markedly upregulated in injured tubular epithelial cells. Urinary and plasma NGAL levels can rise within 2 hours of acute tubular damage, preceding creatinine elevation by up to 48 hours (Pu & Xu, 2024; Catanese et al., 2023).

In CKD, elevated baseline NGAL reflects ongoing tubular stress and correlates with faster eGFR decline. A meta-analysis showed that each doubling of NGAL associates with a 1.5-fold higher risk of progression to end-stage kidney disease (Alobaidi et al., 2025). NGAL's sensitivity for early CKD (stage 1–2) surpasses that of albuminuria, making it a potential screening tool in at-risk populations.

Key points:

- Rapid rise post-injury (< 2 h)
- Predicts CKD progression independently of proteinuria
- Readily measured by ELISA or automated immunoassays

Figure 3



Kidney injury molecule-1 (KIM-1)

KIM-1 is a transmembrane glycoprotein expressed at low levels in healthy proximal tubules. Upon injury, its ectodomain is shed into urine, where it can be quantified (Pu & Xu, 2024; Catanese et al., 2023). In diabetic kidney disease (DKD), urinary KIM-1 levels correlate with histologic tubular atrophy and interstitial fibrosis, outperforming albuminuria in predicting long-term eGFR slope (Villalvazo et al., 2025).

KIM-1 also rises in non-diabetic CKD etiologies and may help discriminate active tubular injury from chronic scarring. Combining KIM-1 with NGAL and cystatin C further enhances early detection accuracy (Alobaidi et al., 2025).

Key points:

- Marker of proximal tubular injury
- Correlates with fibrosis on biopsy
- Complements glomerular biomarkers

Cystatin C

Cystatin C is a 13 kDa cysteine protease inhibitor produced by all nucleated cells and freely filtered by glomeruli. Unlike creatinine, its serum concentration is less influenced by muscle mass, age, or diet. Elevations in cystatin C may detect mild GFR reductions earlier than creatinine (Pu & Xu, 2024; Alobaidi et al., 2025).

In longitudinal cohorts, cystatin C–based eGFR equations identified "preclinical" CKD—patients with normal creatinine but elevated cystatin C—who later progressed to overt CKD at twice the rate of controls (Catanese et al., 2023). Serum cystatin C is now recommended by several guidelines for confirmatory testing when creatinine-based eGFR is borderline (KDIGO 2020).

Key points:

- More sensitive for early GFR decline
- Incorporated into combined eGFR equations
- Reduces CKD misclassification

Other candidate proteins (e.g. β₂-microglobulin)

β₂-microglobulin (β₂M) is a 12 kDa component of MHC class I molecules, filtered by glomeruli and reabsorbed by proximal tubules. In CKD, urinary β₂M reflects both impaired reabsorption (tubular dysfunction) and increased serum load. Elevated β₂M predicts faster CKD progression and correlates with interstitial inflammation (Pu & Xu, 2024; Catanese et al., 2023).

Other promising proteomic candidates include fetuin-A, uromodulin, and vitamin D–binding protein, each reflecting distinct pathophysiologic pathways (inflammation, tubular mass, protein handling) and under active investigation in multi-analyte panels (Joshi et al., 2024).

Key points:

- β₂M: marker of tubular reabsorptive capacity
- Multi-protein panels may offer superior discrimination
- High-throughput proteomics enables discovery of novel candidates

Table 2

Biomarker	Sample	Mechanism / Key Feature	Time to Rise / Diagnostic Performance	Clinical Application	Key Reference
NGAL	Urine/ Plasma	Upregulated in injured tubular epithelial cells	Rises < 2 h post–injury; AUC ~0.85 for early CKD	Early detection; risk stratification	Alobaidi et al., 2025
KIM-1	Urine	Shed ectodomain of proximal tubule glycoprotein	Increases in early tubular injury; AUC ~0.80	Distinguish active injury vs. chronic scarring	Villalvazo et al., 2025
Cystatin C	Serum	Freely filtered, less influenced by muscle mass	Detects mild GFR decline earlier than creatinine	Confirmatory eGFR estimation	Pu & Xu, 2024
β₂-Microglobulin (β₂M)	Urine/ Serum	Filtered & reabsorbed by tubules; marker of reabsorption failure	Correlates with inflammation; predicts progression	Assessment of tubular dysfunction	Catanese et al., 2023

Metabolomic Biomarkers

Chronic Kidney Disease (CKD) managing requires paying attention to small-molecule metabolites which reflect energy metabolism, as many of them display early signs of the desease. Even in early stages of CKD, gut-derived uremic toxins like indoxyl sulfate and p-cresol sulfate, promote tubular injury along with interstitial fibrosis while accumulating. Tubular injury along with interstitial fibrosis is shown by (Pandey et al., 2025) and (Morozova et al., 2023). Urine metabolomics, both targeted and untargeted techniques, reflect fluctuation in the TCA cycle. Moreover, decreased levels of succinate and citrate along with tryptophan and arginine are noticed alongside decline in eGFR and histologic injury (Morozova et al., 2023).

Changes across the stages of CKD are observable through non-targeted plasma metabolomic profiling. Myo-inositol, betaine, taurine and 5-methylthioadenosine are some of the small metabolites which observe clear differences between individuals suffering with early renal impairments and healthy individuals (Pandey et al., 2025). The application of machine learning to these metabolic outlines for predicting CKD progression funcitioned successfully in prospective cohorts with over AUC results exceeding 0.85. This proves useful when compared to relying on estimations using creatinine-based eGFR functions (Alobaidi, 2025).

Novel methods such as high temrature mass spectroscopy allow for reproducible detection of known uremic toxins like indoxyl sulfate, p-cresol sulfate, along with new and novel metabolites like 5-methylthioadenosine. These breakthroughs boost confidence that they can be turned into early detecting tests which are necessary during the preliminary stages of the disease (Morozova et al., 2023 and Pandey et al., 2025).

Genome and Transcriptome Markers

Circulating microRNA (miRNA) reflects CKD and micro-level changes in the kidney, which makes its measurement less harmful compared to other techniques. For instance, miR-21, whose expression is elevated in diabetic CKD due to albuminuria and albuminuria's rate of eGFR decline, has been verified to be downregulated in terms of fibrogenesis and epithelial-mesenchymal transition (Medina et al, 2023). Moreover, podocyte acting integrins (miR-200b/c) also belong to miR-200 family and are believed to predict early tubular damage, having advanced proposed predictive qualities of early tubular injury (Medina et al, 2023).

lncRNAs interacts with miRNAs and mRNAs forming sophisticated systems of control. Indeed, other works remark that MALAT1 and TUG1 for instance, act as pro-fibrotic miRN operons modulate influencing urine and plasma, and their shifted values comes before clinical CKD, signifying subtle change of glomeruli and dying tubules (He & Li, 2025). This earlier CKD risk modification considers single-nucleotide polymorphisms (SNPs) of greater impact. Particular high-risk variants in APOL1 (G1/G2) increase the odds for CKD in an African American population while modifying this risk are MYH9 polymorphisms (Villa-Bellosta et al., 2025). Diabetic kidney disease's genome-wide association studies have further uncovered loci like COL4A3 Asp326Tyr, AFF3, RGMA that are associated with either protective or harmful influences on the progression of diabetic CKD (Roumeliotis et al., 2024).

Epigenetic Cell-free DNA Biomarkers

Changes in epi-markers, especially those affecting DNA methylation that can be extracted from blood and urine, have been suggested to develop into classifying markers for earlier stages of CKD. Different genome-wide analyses of methylation has associated specific difference in methylation patterns (CpG) with the disease on accounting the genes involved in fibrosis and inflammation in blood of stage 1 CKD patients undergoing eGFR decline or surge in albuminuria (Zhong et al., 2024; Chen et al., 2024). Such changes in methylation in cellular sediment of urine are reproducible in independent cohorts and reliably predict progression to renal failure (Patel et al., 2024).

Alongside epigenetic profiling, the analysis of circulating cell-free DNA (cfDNA), which includes both nuclear cfDNA and cell-free mitochondrial DNA fragments, has emerged as a non-invasive biomarker for chronic kidney disease (CKD). Increases in plasma levels of total cfDNA and cf-mtDNA are associated with heightened inflammation, tubular injury, and increased all-cause mortality in CKD cohorts (Berezina et al., 2023). Changes in the levels of cfDNA before and after dialysis have shown additional prognostic power in patients with end-stage kidney disease (Zhang et al., 2024). Early research is focusing on developing targeted kidney nanoparticles aimed at cleaving cfDNA, suggesting both significant diagnostic and therapeutic potential in CKD management.

Exosome-Derived Urinary Biomarkers

Urinary exosomes are nanosized extracellular vesicles secreted by renal epithelial cells which contain proteins, RNAs, and other bioactive material and thus mirror intrarenal physiology and pathology (Liu et al., 2025). Methods of isolation like size-exclusion chromatography and immunoaffinity capture yield high-purity vesicles that undergo ultracentrifugation, making them suitable for proteomic and transcriptomic analysis (Zheng et al., 2024).

Elevated levels of aquaporin-1, podocalyxin, and KIM-1 (kidney injury molecule-1) have been noted in the proteomic assessments of urinary exosomes for patients with chronic kidney disease (CKD), often preempting the more traditional serum creatinine and albuminuria benchmarks. This suggests the possibility of earlier detection of both tubular and glomerular damage (Liu et al., 2025; Cao et al., 2025). Also, the capture of exosomal microRNAs is statistically related to pro-fibrotic gene expression and miR-21, miR-29 family, and miR-200b correlate strongly with histologic severity, surpassing protein quantification in driving CKD's predictive outcomes (Cao et al., 2025). These captured results advocate for exosomes derived from urine as a non-invasive "liquid biopsy" for both the detection and monitoring of CKD.

Table 3

Summary of Novel Epigenetic and Exosomal Biomarkers in Early CKD

Biomarker Category	Specific Marker(s)	Sample Matrix	Detection Method	Clinical Utility
DNA Methylation	Differentially methylated CpG sites	Blood, urine	Bisulfite sequencing / arrays	Early prediction of eGFR decline (Zhong et al., 2024)
Cell-free mtDNA	cf-mtDNA copy number	Plasma	qPCR	Correlates with tubular injury and inflammation (Berezina & Berezin, 2023)
Total cfDNA	Nuclear cfDNA fragments	Plasma	PicoGreen assay, digital PCR	Mortality risk stratification in CKD (Zhang et al., 2024)
Exosomal Proteins	KIM-1, aquaporin-1, podocalyxin	Urine (exosomes)	LC-MS/MS, ELISA	Detects tubular/glomerular injury before creatinine rise (Liu et al., 2025)
Exosomal miRNAs	miR-21, miR-29 family, miR-200b	Urine (exosomes)	qRT-PCR	Predicts fibrosis severity and progression (Cao et al., 2025)

Multi-Marker Panels & Machine-Learning Approaches

Rationale for combining biomarkers

Chronic kidney disease (CKD) is a heterogeneous syndrome involving inflammatory, fibrotic, and metabolic pathways. Single biomarkers often reflect only one aspect of renal injury, limiting sensitivity and specificity in early stages. By combining multiple markers—each reflecting distinct pathophysiological processes—multi-marker panels can capture a more complete molecular signature of early CKD. This integrative strategy improves diagnostic accuracy and allows detection of subclinical changes before conventional measures (e.g., creatinine or eGFR) become abnormal (Alobaidi, 2025; Mitra et al., 2025).

Examples of Biomarker Panels (e.g., CKD-273)

One of the most extensively studied panels is CKD-273, a urinary peptidomic signature comprising 273 peptides linked to extracellular matrix remodelling and inflammation. In the CRIC cohort, CKD-273 distinguished individuals who progressed to CKD Stage 3 over five years with an AUC of 0.85 (Alobaidi, 2025). Other panels combine plasma proteins such as NGAL, KIM-1, cystatin C, suPAR, and FGF-23—each reflecting acute tubular injury, glomerular filtration, immune activation, and mineral metabolism dysregulation, respectively (Badran et al., 2024).

AI/ML Models for Risk Stratification

Machine-learning (ML) techniques—random forests, support vector machines, and gradient boosting—excel at integrating high-dimensional biomarker data. For instance, a supervised random forest model trained on five multi-omic markers achieved 95.5% accuracy and 92.0% accuracy using support vector machines in classifying CKD stages 1–5 (Gomez et al., 2024). In another study, an SVM incorporating CKD-273 peptides, TIMP-2, and IGFBP7 yielded an AUC of 0.88 for predicting rapid eGFR decline (Zhang et al., 2025) . These AI-driven approaches enable real-time risk prediction and can be embedded in electronic health records for automated flagging of high-risk patients.

Clinical Validation & Key Study Summaries

Overview of Major Prospective/Retrospective Cohorts

Several large cohorts have validated multi-marker and AI-driven approaches. The Chronic Renal Insufficiency Cohort (CRIC) enrolled over 3,000 adults with mild to moderate CKD, providing longitudinal data on biomarker trajectories (Alobaidi, 2025). Pediatric CKD studies (e.g., plasma metabolomics in children) have tested untargeted panels to detect early renal dysfunction (Benito et al., 2018) – though most focus is on adult cohorts (Mitra et al., 2025). Retrospective analyses of biobank samples have further assessed predictive performance across diverse etiologies, including diabetic nephropathy and hypertensive kidney disease.

Sensitivity, Specificity, AUC Values

- **CKD-273 panel**: AUC 0.85 (95% CI 0.82–0.88), sensitivity 78%, specificity 80% for progression to Stage 3 over 5 years (Alobaidi, 2025).
- **NGAL + KIM-1 + cystatin C**: sensitivity 82%, specificity 88%, AUC 0.90 in a cohort of 450 adults with normoalbuminuria at baseline (Zhang et al., 2025) .
- **FGF-23**: AUC 0.78, sensitivity 72%, specificity 75% for early decline in eGFR in a diabetic CKD cohort (Mitra et al., 2025).
- **Multi-omic ML model**: Random forest achieved 95.5% accuracy, SVM 92.0% accuracy in classifying CKD stages 1–5 (Gomez et al., 2024).

These studies collectively demonstrate that multi-marker panels, especially when coupled with ML algorithms, outperform traditional diagnostics in early CKD detection and risk stratification.

Table 4

Biomarker Panel / Model	Study (Author et al., Year)	Sensitivity (%)	Specificity (%)	AUC (95% CI)	Accuracy (%)
CKD-273	Alobaidi et al., 2025	78	80	0.85 (0.82–0.88)	—
NGAL + KIM-1 + Cystatin C	Zhang et al., 2025	82	88	0.90	—
FGF-23	Mitra et al., 2025	72	75	0.78	—
Multi-omic ML (Random Forest)	Gomez et al., 2024	—	—	—	95.5
Multi-omic ML (SVM)	Gomez et al., 2024	—	—	—	92.0

– "—" indicates that the metric was not reported for that particular model.

Assay Development & Point of Care Technologies

The diagnosis of chronic kidney disease is becoming easier and more manageable with the introduction of point of care technologies. With the use of nanoparticle labels and their signal-amplifying membranes, Lateral flow tests are now able to detect low-abundance proteins such as uromodulin and osteopontin with a less than 10 ng/mL limit of detection. Ease of use is also being enhanced as reviews suggest these paper-based LFTs can be manufactured using inexpensive materials, making them perfect for low resource areas (Nguyen et al. 2023).

From the work done in immunochromatography, other forms of biosensors are also being worked on extensively. These include the development of electrochemical and optical biosensors for advanced multiparameter chronic kidney disease testing. Using small sample sizes of whole blood or urine, live monitoring of various substances including creatinine and cystatin C can be performed with the use of enzyme-linked and aptamer recognition layers (Nguyen et al. 2023). The use of microfluidics has also been shown enable quantitative assessment through cloud-connected smartphones which greatly improves measurement error and allows remote monitoring (Martin et al. 2024 Lee et al. 2024). New test runs are proving the feasibility of the development of tele-medicine linked wrist-worn sensors and paper-fluidic chips, highlighting the potential for enhanced self-monitoring and self-management of chronic kidney disease.

Health-Economic and Implementation Considerations

Economic scrutiny has recurrently validated that POC screening for CKD among high risk cohorts like diabetics and hypertensive patients is cost-effective, noting ICERs of USD 10,000 to 30,000 for QALY gained (Lee et al., 2024; Ramirez et al., 2023). These analyses incorporate savings from downstream costs associated with dialysis and hospitalization because early stage CKD detection enables long term health value modeling by delaying ESKD.

In spite of positive economics, bottom-up implementation contends with several difficulties. Infrastructure limitations like the absence of consistent electricity and cold chain for reagents stifle progress in rural clinics (Gupta et al., 2023). Community Point of Care Testing in Diagnosing and Managing Chronic Kidney Disease (2024) notes the addition of workforce limits and training required for new device operation and quality control amplification delays. Reimbursement policies are frequently out of sync with POC paradigms and regulatory routes for assay approvals are inconsistent across geographies which adds risk for manufacturers and health systems. It will take multi stakeholder initiatives to overcome these gaps through standardizing assay outcomes, developing telehealth frameworks, and incentivizing payment structures that enable POC CKD screening.

Compliance, Ethical & Legal Issues of Industrial Standards

The process of implementing a biomarker in clinical practice requires meticulous compliance with accompanying regulations. In the United States, the FDA runs a Biomarker Qualification Program which provides a formal submission pathway where a sponsor can put forward a biomarker together with relevant documents for qualification in the context of value chain processes. In the same way, the EMA has a Qualification of Novel Methodologies procedure that enables scientists to seek qualification of biomarkers for capturing milestones in clinical trials or for use as surrogate

endpoints (Alobaidi et al., 2025). Both require comprehensive evidence claiming that the biomarker is analytically validated (accurate, precise, reproducible) and clinically validated (predictive of decisive clinical outcomes) in the proclaimed context of use.

Pre-analytical and analytic fragmentation remains a major challenge. Variability in sample collection such as choice of anticoagulants, processing delays, and storage temperatures differences in the assay platform used (ELISA vs mass spectrometry), and absence of universal reference materials results in reproducibility challenges among labs (Pu & Xu, 2024). Several international consortia such as the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and Clinical & Laboratory Standards Institute (CLSI) are working towards publication of standard operating protocols and reference calibrators for key CKD biomarkers such as NGAL, KIM-1, and cystatin C to enable enhanced measurement reproducibility across sites and studies.

Future Directions & Research Gaps

Recent developments in lipidomics and glycomics are particularly promising for the discovery of new biomarkers for chronic kidney disease (CKD). Dysregulated lipid species associated with early renal dysfunction can now be detected via lipidomic profiling, while changes in protein glycosylation related to fibrosis and inflammation are becoming evident through glycomic analyses (Gupta et al., 2024). The addition of other omics datasets such as genomics, transcriptomics, proteomics, and metabolomics will certainly improve reconstructive attempts for multi-marker panels by providing deeper mechanistic understanding, sensitivity, and specificity. Longitudinal multi-center studies with diverse patient populations and CKD etiologies are of utmost importance for validating the identified markers and panels. Such studies should target at-risk populations, like the diabetic population with albuminuria, tracking the longitudinal biomarker changes against hard clinical endpoints like dialysis dependency or cardiovascular events to determine predictive value (Villalvazo et al., 2025).

In combination with existing biomarkers, non-invasive sensors such as continuous blood pressure and bioimpedance monitors, as well as contrast-enhanced ultrasound or MRI-based renal fibrosis mapping, provide a more holistic approach to early CKD detection. Merging real-time biomarker measurements with imaging and physiologic signals using AI-enabled systems may deliver unparalleled insights into personalized nephrology and foster dynamic risk-adjusted early intervention strategies.

CONCLUSION

To sum it up, new techniques that enable the early identification of chronic kidney disease (CKD) based on unique markers have the potential to revolutionize patient care—from treatment after symptoms appear to prevention prior to symptom manifestation. This goal is made possible with clear regulatory pathways like the FDA's Biomarker Qualification Program or the EMA's Qualification of Novel Methodologies that guarantee thorough scrutiny of every proposed marker for analytical validity, clinical importance, and practical utility. Additionally, the consolidation of international guidelines and reference materials for standard procedures across laboratories is essential to guarantee uniform and reproducible results.

There will be greater sensitivity and specificity in the creation of biomarker panels with more comprehensive proteomics, metabolomics, and machine learning algorithms through the automated processing of multi-omics data. These panels need to be tested in various longitudinal, multi-center cohorts where diverse prospective validation is performed to establish prognostic thresholds that predict with dependable accuracy the onset of dialysis or cardiovascular events. The integration of imaging and wearable sensors with AI systems offers a comprehensive and continuous assessment of renal functionality. Achieving these objectives will depend on how well the researchers, clinicians, industry, policy makers, and advocates for patients work together—enabling the standardization of the procedures, the sharing of the data, and the accelerating of the application of innovations into everyday nephrology practice.

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