

Nano Biosensors for Early Detection of Kidney Disease Biomarkers: From Conventional Markers to Uromodulin-Based Point-of-Care Diagnostics

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Abstract:

Kidney diseases, particularly chronic kidney disease (CKD) and acute kidney injury (AKI), are major global health problems in which early structural injury may precede substantial change in conventional measures of renal function. Serum creatinine, estimated glomerular filtration rate (eGFR), and urinary albumin remain central to clinical assessment, while cystatin C provides complementary information about filtration. Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) provide information related to tubular injury. Uromodulin is particularly attractive because it is produced predominantly by renal tubular epithelial cells and may reflect tubular mass and renal parenchymal integrity. Nanobiosensors combine biological recognition with nanoscale materials and transducers to enable sensitive, rapid and miniaturized measurement. Gold nanoparticles, graphene-based materials, carbon nanotubes, MXenes, metal oxides, magnetic nanoparticles and nanozymes can enhance surface area, biomolecule immobilization, electron transfer, catalytic activity and optical responses. Recent kidney-focused studies include impedance-based uromodulin detection, optical-fiber KIM-1 sensing, electrochemical/aptamer NGAL sensing, cystatin-C nanobiosensors, and smartphone-enabled creatinine/albumin systems. This review critically examines kidney biomarkers, nanomaterial-enabled sensing mechanisms, representative recent platforms, analytical performance, sample matrices, point-of-care integration and translational barriers. Particular emphasis is placed on uromodulin as an underexplored target for nanobiosensing and on multiplex platforms combining uromodulin with NGAL, KIM-1, cystatin C, creatinine and albumin. Future systems integrating microfluidics, artificial intelligence, smartphone interfaces and wearable electronics may enable decentralized and personalized kidney monitoring.

Keywords: *Chronic kidney disease; acute kidney injury; nanobiosensor; uromodulin; NGAL; KIM-1; cystatin C; creatinine; albumin; electrochemical biosensor; point-of-care diagnostics.*

How to cite this article: Kavita Sharma¹ Dr. Bushra Fiza^{*2} Mohd Sajid³ Priya Gouri⁴ Madhu Sharma¹ Shilpa Dhameja¹ MD Aziz⁴. Nano Biosensors for Early Detection of Kidney Disease Biomarkers: From Conventional Markers to Uromodulin-Based Point-of-Care Diagnostics. *Int J Drug Deliv Technol.* 2026;16(80s):550-555. DOI: 10.25258/ijddt.16.80s.67.

1. INTRODUCTION

CKD is characterized by persistent abnormalities of kidney structure or function and may remain clinically silent during early stages. AKI can develop rapidly following ischemia, sepsis, surgery, nephrotoxic exposure or other systemic insults. In both settings, the diagnostic challenge is to identify clinically meaningful renal injury before irreversible loss of nephron function has occurred. Current clinical practice relies heavily on serum creatinine, eGFR and albuminuria. These measurements are indispensable, but each describes only part of renal biology. Creatinine is affected by muscle mass, age, sex, diet and tubular secretion, whereas albuminuria is primarily a marker of glomerular barrier dysfunction. The 2024 KDIGO CKD guideline recommends creatinine-based eGFR and supports combined creatinine-cystatin C estimation when greater accuracy is required [1]. Cystatin C is increasingly incorporated into clinical assessment because it can reduce some limitations of creatinine-based estimation [2,3]. In parallel, kidney

injury biomarkers such as NGAL and KIM-1 can provide information about tubular injury, while uromodulin provides a kidney-specific signal associated with tubular integrity and renal function [4–9].

Nanobiosensors are attractive because nanoscale interfaces can improve target capture and signal transduction while enabling miniaturization. The field has progressed from proof-of-concept sensing in buffered solutions toward urine, plasma, smartphone and point-of-care formats. Importantly, clinical translation now requires attention not only to analytical sensitivity but also to matrix effects, reproducibility, clinical cut-offs, manufacturing, validation and integration into clinical workflows [10–13].

2. CONVENTIONAL AND EMERGING KIDNEY BIOMARKERS

2.1 Creatinine and eGFR

Creatinine remains the most widely used functional marker because it is inexpensive, standardized and broadly available. Its main limitation is that serum

concentration may not increase substantially until a meaningful reduction in filtration has already occurred. Nanotechnology-based creatinine sensors have therefore been investigated using electrochemical, optical, potentiometric, conductometric and paper-based architectures [14].

2.2 Cystatin C

Cystatin C is a low-molecular-weight cysteine protease inhibitor produced by nucleated cells and freely filtered by the glomerulus. Its concentration is less dependent on muscle mass than creatinine, although nonrenal influences remain possible. Cystatin C has an established role in GFR estimation and has also been investigated as an early AKI biomarker [3,15,16]. Recent reviews describe electrochemical and optical cystatin-C sensing as an expanding area, with nanostructured interfaces used to increase recognition-site density and signal amplification [17,18].

2.3 Albumin and albumin-to-creatinine ratio

Albuminuria is a major marker of glomerular barrier dysfunction and is routinely expressed as the urinary albumin-to-creatinine ratio (uACR). Sensor platforms have progressed from conventional immunosensors to dual-analyte, smartphone and microfluidic devices [19–23].

2.4 Ngal

NGAL is a rapidly induced protein associated with tubular injury. Urinary NGAL has demonstrated prognostic associations in CKD and is extensively studied in AKI [24,25]. A 2026 flow-enhanced electrochemical aptamer sensor used miniaturized gold microelectrodes and hydrodynamic flow to improve mass transport and NGAL detection in plasma [26].

2.5 Kim-1

KIM-1 is strongly induced in injured renal tubular epithelial cells and has been studied as a urinary marker of tubular injury. Foundational qualification work established KIM-1 as a sensitive renal injury biomarker [27,28]. Recent biosensor developments include an optical-fiber semi-distributed interferometer for urine KIM-1 with a reported linear range spanning 10 aM to 1 nM and a lowest reported detection limit of 13.6 aM in the study matrix [29]. A 2026 dual-readout aptasensor combined aptamer recognition, CRISPR/Cas12a signal processing and FeNi-MOF@AgNP nanzyme amplification, with urine validation against ELISA in AKI samples [30].

2.6 Uromodulin

Uromodulin, also known as Tamm–Horsfall protein, is produced predominantly in the thick ascending limb and distal nephron. It is the most abundant protein in normal urine and has important roles in tubular homeostasis, electrolyte handling and urinary tract defense [5–8]. Clinical studies have shown that serum uromodulin correlates strongly with cystatin C, creatinine and eGFR, and may change within ranges where creatinine provides limited discrimination [6]. Lower serum uromodulin has also been associated with subsequent CKD development

[9]. Urinary uromodulin has been associated with tubulointerstitial fibrosis and tubular health [31].

Uromodulin is attractive for nanobiosensing because its biological origin is highly kidney-specific. Yet the sensor literature is much smaller than for creatinine, albumin, NGAL or cystatin C. A 2023 label-free impedance biosensor used a 50-nm tantalum pentoxide passivation layer on interdigitated electrodes and detected uromodulin in artificial urine over 0.5–8 ng/mL [32]. This is an important proof of concept for compact point-of-care detection, but it also highlights the need for validation in authentic patient specimens, standardized reference ranges and direct comparison with established immunoassays.

3. NANOMATERIALS USED IN RENAL BIOMARKER BIOSENSING

Nanomaterials improve biosensor performance through large surface area, tunable surface chemistry, enhanced conductivity, catalytic activity or distinctive optical properties. The most relevant materials include gold nanoparticles, graphene/graphene oxide, carbon nanotubes, metal oxides, magnetic nanoparticles, MXenes and nanozymes.

Table 1. Nanomaterials and their renal biosensing roles.

Nanomaterial	Key property	Potential renal biosensing role
Gold nanoparticles	Conductivity; functionalizable surface	Antibody/aptamer immobilization; electrochemical signal amplification
Graphene/graphene oxide	High conductivity; large surface; functional groups	Electrode modification and biomolecule immobilization
Carbon nanotubes	Conductive networks	Enhanced electron transfer
MXenes	2D conductivity; surface groups	High-area electrochemical interfaces
Metal oxides	Catalytic/semiconducting properties	Signal amplification; optical/electrochemical sensing
Magnetic nanoparticles	Magnetic manipulation	Target enrichment/separation
Nanozymes	Enzyme-like catalytic activity	Colorimetric/electrochemical amplification

4. MAJOR NANOBIOSENSOR TRANSDUCTION STRATEGIES

4.1 Electrochemical sensing

Electrochemical sensors are particularly attractive for point-of-care applications because electronics can be miniaturized and integrated with disposable electrodes.

Amperometric, voltammetric, potentiometric, conductometric and impedance-based methods have all been investigated. The uromodulin impedance sensor is an example of label-free non-faradaic detection [32]. A recent conductometric platform detected urinary β 2-microglobulin, EGF and CD163 with low reported detection limits and short analysis times [33].

4.2 Optical sensing

Optical approaches include surface plasmon resonance, fluorescence, optical-fiber interferometry and colorimetric sensing. The KIM-1 optical-fiber system demonstrates the high analytical sensitivity achievable with fiber-optic interferometry [29].

4.3 Colorimetric, lateral-flow and nanozyme sensing

Colorimetric methods can simplify instrumentation and are compatible with smartphone image analysis. Lateral-flow systems offer rapid operation and are attractive for decentralized testing. A 2026 multiplex plasmon-enhanced lateral-flow assay illustrates movement toward multiplex AKI diagnosis [34].

4.4 FET and transistor-based sensing

Field-effect and transistor-based biosensors enable label-free electrical detection. Early renal applications included albumin FET sensors [35]. Their potential advantages include low sample volume and semiconductor integration, although ionic screening, biofouling and reproducibility remain challenges.

5. COMPARATIVE EVIDENCE FROM RECENT RENAL NANOBIOSENSORS

Table 2. Representative recent renal nanobiosensor studies.

Biomarker	Platform	Matrix	Representative performance	Year	Ref.
Uromodulin	Impedance; Ta2O5 interdigitated electrode	Artificial urine	0.5–8 ng/mL reported measurement range	2023	[32]
KIM-1	Optical-fiber interferometer	Urine/artificial urine; clinical testing	LOD 13.6 aM; linear range 10 aM–1 nM	2025	[29]
KIM-1	CRISPR/Cas12a + FeNi-MOF@AgNP nanozyme	Patient urine	LOD 58.7 pg/mL colorimetric; 34.4 pg/mL fluorometric	2026	[30]

NGAL	Flow-enhanced electrochemical aptamer sensor	Blood plasma	Nanomolar detection; hydrodynamic flow	2026	[26]
Creatinine + albumin	Smartphone photoelectrochemical	Artificial urine	Creatinine 100–1500 μ g/mL; albumin 9.9–500 μ g/mL	2023	[20]
Albumin/creatinine ratio	Dual electrochemical sensor	Urine	One-step ACR determination	2023	[19]
β 2MG + EGF + CD163	Conductometric biosensors	Urine	100 fM; 5 pM; 10 fM reported LODs	2025/26	[33]

6. MULTIPLEX RENAL NANOBIOSENSING

Single-biomarker testing cannot fully represent kidney disease heterogeneity. A clinically meaningful multiplex panel could combine creatinine and cystatin C for filtration; albumin for glomerular barrier dysfunction; NGAL and KIM-1 for tubular injury; and uromodulin for tubular mass/integrity. Multiplexing is technically challenging because each biomarker requires selective recognition chemistry and an appropriate dynamic range, but recent multiplex biosensor work supports feasibility [19,34].

Table 3. Biological axes represented by a proposed multiplex renal panel.

Biomarker	Biological axis	Potential role
Creatinine	Filtration/function	Established functional marker
Cystatin C	Filtration/function	Complementary filtration marker
Albumin	Glomerular barrier	Albuminuria/uACR
NGAL	Tubular injury	Early injury/stress
KIM-1	Tubular epithelial injury	Structural injury
Uromodulin	Tubular integrity/mass	Kidney-specific tubular marker

7. MICROFLUIDICS, SMARTPHONE READOUT AND WEARABLES

Microfluidics can integrate sample handling, filtration, biomarker capture and detection within a small cartridge. Smartphone-based systems can provide imaging, data

processing and wireless communication. A 2023 smartphone photoelectrochemical platform simultaneously measured urine creatinine and albumin using a g-C₃N₄/chitosan nanocomposite electrode [20]. A 2022 microfluidic paper-based ACR device used a Raspberry Pi for optical interpretation [23]. A 2024 review of wearable electrochemical renal biomarker sensors highlights the possibility of non-invasive monitoring in sweat, but also the need to establish clinically meaningful relationships between sweat and blood/urine concentrations [36].

8. ARTIFICIAL INTELLIGENCE AND DIGITAL INTERPRETATION

AI can assist with signal denoising, baseline correction, multiplex pattern recognition, calibration, classification and risk prediction. For a multiplex renal sensor, the output need not be a single concentration; it can be a structured renal phenotype. Such interpretations require large, representative datasets and prospective validation.

9. CLINICAL TRANSLATION: FROM ANALYTICAL SENSITIVITY TO CLINICAL UTILITY

A recurring problem in biosensor literature is that very low limits of detection may be emphasized without demonstrating whether the analytical range overlaps the clinically relevant disease range. A translationally useful renal biosensor should demonstrate accuracy, precision, specificity, interference resistance, stability, reproducibility and performance in real patient samples. It should be compared directly with a reference method and evaluated across clinically relevant stages. Recent CKD biosensor reviews explicitly identify clinical translation, ethics, trial design, alternative body fluids, manufacturing and workflow integration as major challenges [12,13].

10. Key Research Gaps

- Limited number of uromodulin-specific nanobiosensors compared with creatinine, albumin, NGAL and cystatin C.
- Limited validation of uromodulin sensors in authentic serum or urine from well-characterized CKD cohorts.
- Lack of standardized biosensor calibration ranges linked to clinically meaningful uromodulin thresholds.
- Limited head-to-head comparison of nanobiosensors with ELISA or reference laboratory methods.
- Limited multiplex platforms combining kidney-specific and injury biomarkers.
- Insufficient longitudinal studies showing whether sensor-derived changes predict clinical outcomes.
- Need for standardized reporting of matrix effects, interference, recovery, precision, stability and batch reproducibility.
- Need for clinical-economic evaluation and regulatory strategies before routine point-of-care implementation.

11. Proposed Uromodulin-Centered Multiplex Renal Nanobiosensor

A particularly promising research direction is a uromodulin-centered multiplex platform. The proposed

architecture combines uromodulin with NGAL and KIM-1 to represent tubular biology, cystatin C and creatinine to represent filtration, and albumin to represent glomerular barrier dysfunction. A microfluidic cartridge could divide the sample into parallel sensing chambers, while a smartphone or dedicated potentiostat could collect and normalize signals. AI could then convert the six-dimensional biomarker pattern into a renal risk profile.

12. Future Perspectives

Future renal nanobiosensors are likely to move toward multiplexing, microfluidic automation, smartphone connectivity, wearable sampling and AI-assisted interpretation. Uromodulin is especially attractive because it is closely linked to the kidney and may capture tubular information not represented by creatinine alone. The most valuable next-generation platform will not simply achieve the lowest detection limit; it will provide clinically interpretable information using a small sample, short turnaround time, robust calibration and reproducible performance.

CONCLUSION

Nanobiosensors provide a promising route for earlier and more decentralized detection of kidney disease biomarkers. Current evidence supports electrochemical, impedance, optical, colorimetric, lateral-flow and transistor-based strategies. NGAL and KIM-1 provide information about tubular injury, cystatin C and creatinine reflect filtration, and albumin reflects glomerular barrier dysfunction. Uromodulin adds a kidney-specific tubular signal and represents an important underexplored target for nanobiosensor development. The strongest translational opportunity is a multiplex platform integrating uromodulin with NGAL, KIM-1, cystatin C, creatinine and albumin, provided that future studies establish clinical validity, reproducibility and utility.

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