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Review Article

Novel Biomarkers in Drug-Induced Nephrotoxicity: A Comprehensive Overview

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ABSTRACT

Pharmaceutical development after drug-induced kidney injuries becomes highly complex because this condition produces adverse results in patient therapeutic outcomes. The review examines the limitations of conventional markers sCr and BUN because these biomarkers prove ineffective for early detection of nephrotoxicity. Acute kidney injury detection should be made possible by developing new biomarkers which can identify damage during its early phases due to the late detection capabilities of renal markers sCr and BUN. The diagnostic capabilities of nephrotoxicity may be enhanced through a combination of KIM-1 with NGAL and urinary metabolomic panels which deliver improved accuracy and speed for detection. Better interpretation of risk assessment coupled with customized therapies becomes possible through the union of artificial intelligence (AI) with machine learning technologies and high-dimensional data. The successful deployment of innovative biomarkers for pharmaceutical research requires standardization of valid biomarker practices and removal of regulatory limits which enable their clinical application. Modern biomarker research presents opportunities to elevate drug security standards and renal medical practices while better supporting patient healthcare needs.

INTRODUCTION

Overview of Drug-Induced Kidney Injury (DIKI)

Kidneys function as a sophisticated biological organ which ensures three main processes including electrolyte stabilization and metabolic equilibrium maintenance and toxic substance removal from the bloodstream. The kidneys remain highly exposed to circulating toxins because they filter about a quarter of the cardiac output. Drug-induced kidney injury (DIKI) blocks such a high percentage of medications from proceeding to market availability during phase III clinical trials that it totals twenty percent. The drug-related origin accounts for 18.3% of such kidney injuries that comprise tubular renal damage along with interstitial nephritis among patient cases. The assessment of potential nephrotoxic effects in drug candidates needs to happen during

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the early stages of drug discovery work for achieving successful medication development. [1] Similar to other injuries DIKI represents a form of kidney damage triggered by specific medications. Yearly deaths because of kidney disease reached 54,358 in 2021 according to US mortality statistics which ranked it as the 10th leading cause of death in that year. The most significant contributors to death rate were nephrosis while nephrotic syndrome and nephritis brought additional substantial increases. [2] Recorded as Drug-Induced Kidney Injury (DIKI), excessive kidney damage leads to three possible medical outcomes including acute kidney damage (AKI), chronic kidney disease (CKD) and end-stage renal disease. The annual adverse events affecting 26% of Americans amount to 1.5 million such incidents. [2-4] . The healthcare field currently depends on traditional biomarkers including serum creatinine (sCr) for diagnosing and classifying AKI. As a late marker of kidney injury sCr remains a biomarker which fails to distinguish between multiple causes of AKI and provides measurements late in the identification process. The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline identifies the requirement of establishing AKI origin as essential for adequate practice. [5] Scientific evidence continues to enhance understanding of biomarker value for identifying nephrotoxicity in its preliminary stages. The research field is expanding its investigation into clinical outcome relations while developing knowledge about patient medical forecasts. A number of potential drugs are being reviewed for acute kidney injury (AKI) treatment but the availability of specific targeted therapies remains unbearably scarce. Progress toward diagnosing and treating AKI remains slow because experts identify three primary obstacles: the difficulty level and varied nature of AKI together with the absence of accepted results measurements and the dependency on serum creatinine to diagnose despite its Biomarker inadequacy. The development of kidney injury biomarkers represents a solution to present challenges in drug development pipelines. This analysis reviews contemporary research regarding biomarkers used in the diagnosis of drug-induced kidney injury (DIKI) while exploring their function in determination of clinical outcomes and drug risk assessment based on predictive measures and therapeutic drug impact assessment based on pharmacodynamic indicators. [6]

Common nephrotoxic drugs: - The body eliminates drugs together with their metabolites through glomerular filtration and tubular secretion methods into the urine. Main tubular transport activities that modify ultrafiltrate occur primarily in the proximal tubules. Potentially dangerous substances can be taken up by cells during nephrotoxicity through either peritubular capillaries and basolateral membrane uptake or endocytosis, pinocytosis and active and passive transport routes at the apical membrane. The absorption process of negatively charged pharmaceuticals relies on organic anion transporters (OATs) while organic cation transporters (OCTs) deal with positively charged medications and sodium dicarboxylate transporters as well as additional active transport pumps. [7] Most of the medications leading to nephrotoxic damage produce their effects through recognized pathologic mechanisms. Nephrotoxicity occurs from four main pathological pathways which include thrombotic microangiopathy and crystal nephropathy together with rhabdomyolysis and inflammation and tubular cell toxicity as well as intraglomerular hemodynamic changes. The use of both anti-angiotensin-II drugs such as ACE inhibitors together with ARBs and anti-prostaglandin drugs like NSAIDs diminishes kidney autoregulation of glomerular pressure thus lowering GFR. Patients with kidney function risks face declining renal performance when taking tacrolimus (Prograf) and cyclosporine (Neoral) along with other calcineurin inhibitors because these drugs create a measured narrowing effect on afferent arterioles. [8] Drug medications known as nephrotoxic agents have the

capacity to damage kidney tissue. The review paper investigates fresh methods to identify preliminary indications of kidney injury which result from medications. The information about this subject plays a critical role in advancing patient security and the creation of refined kidney health monitoring tools for drug therapy.

Need for Emerging Biomarkers:-

Both of the kidneys normally experience damage from injury. When kidney blood filtering ability becomes seriously compromised waste products and excess water stay within the body. The loss of kidney reabsorption abilities for various endogenous molecules such as small proteins, sugars, and metabolites leads to elevated levels of these substances in urine after renal damage happens. Six warning signs of Drug Induced Kidney Injury become evident late in the insult course even though most drugs associated with kidney injury do not lead to symptoms:

1. Blood concentrations of BUN and creatinine out of the normal range
2. Decreased glomerular filtration rate (GFR) (<60%)
3. Urine blood and/or protein
4. Increased blood pressure
5. Prolonged or painful micturition
6. Swelling in hands and feet, puffed eyelids

All these symptoms exist independently from renal damage and match other types of organ damage and diseases. A number of things prevent these "markers" from specifically detecting renal damage. Clinical trials rely on the risk, injury, failure, loss and end-stage renal disease (RIFLE) scheme for renal injury classification. [9] The development of drug induced kidney damage (DIKI) in its early stages remains asymptomatic which makes it an essential pharmaceutical concern in medicine. Serum creatinine as well as blood urea nitrogen (BUN) and urine output serve as conventional biomarkers which are still used to detect renal dysfunction. A diagnosis delay appears because initial-stage injury detection suffers from inaccurate results using these diagnosis markers. The biomarkers' poor detection capabilities prompt the critical need for biomarkers which can provide superior and predictive information about kidney function deterioration. Acute renal damage leads to diverse serum creatinine level increases that might prevent early detection of renal problems until two days post-insult occurs. Most clinicians rely on serum creatinine concentrations as the gold standard for renal function assessment in regular practice settings even when they acknowledge their measurement limits. [10] Creatinine functions as one of numerous biomarkers that lacks sensitivity while failing to distinguish different types of acute kidney damage. Medical research needs a biomarker that identifies between glomerular and tubular tissue damage because it could detect acute kidney injuries earlier than creatinine screening does. [10] Below is a comprehensive list of the variables affecting serum creatinine and BUN:-

Non-renal related causes of alteration in BUN levels:

1. Congestive heart failure (CHF) (11)
2. Heart attack (11)
3. Excessive protein levels in the gastrointestinal tract (12)
4. Gastrointestinal bleeding (13)
5. Hypovolemia (14)
6. Shock (15)
7. Dehydration (16)

Non-renal-related causes of alteration in serum creatinine levels:

1. CHF (11)
2. Shock (15)
3. Dehydration (16)
4. Eclampsia (a condition of pregnancy that includes seizures) (17)
5. Preeclampsia (pregnancy induced hypertension) (18)
6. Rhabdomyolysis (19)

Classification of DIKI: The classification of Drug-Induced Kidney Injury includes Acute Kidney Injury and Chronic Kidney Disease according to the disease onset length and pathogenic factors. The distinguishing features can be found in the following table (1).-[20-26]

Feature	Acute Kidney Injury (AKI)	Chronic Kidney Disease (CKD)
Definition	The use of nephrotoxic medicines leads to fast kidney function deterioration that lasts between hours and days.	Progressive serious kidney damage results from persistent exposure to nephrotoxic drugs which become permanent.
Onset	Immediate (between a few hours to a few days)	Rarely (months to years)
Causes (Nephrotoxic Drugs)	The list of drugs which may harm hearing abilities includes NSAIDs and aminoglycosides (such as gentamicin) and contrast media along with vancomycin, amphotericin B, and cisplatin.	The list of drugs which may harm hearing abilities includes NSAIDs and aminoglycosides (such as gentamicin) and contrast media along with vancomycin, amphotericin B, and cisplatin.
Pathophysiology	Direct tubular injury, The kidneys expose themselves to various changes in blood flow patterns and inflammatory reactions leading to either acute tubular necrosis (ATN) or acute interstitial nephritis (AIN).	Tubular atrophy, glomerulo-sclerosis, chronic interstitial fibrosis, and gradual loss of kidney function
Clinical Presentation	Increased serum creatinine, electrolyte abnormalities, or oliguric or non-oliguric renal failure	Proteinuria, hypertension, electrolyte imbalances, and a progressive reduction in glomerular filtration rate (GFR)
Reversibility	With early intervention and drug withdrawal, it is frequently reversible.	Irreversible, if left untreated, it can result in end-stage renal disease (ESRD).
Diagnostic Tests	Blood urea nitrogen (BUN), serum creatinine, urine analysis, and in some situations, kidney biopsy.	For a conclusive diagnosis, eGFR monitoring, chronic proteinuria, imaging (CT scan, ultrasound), and kidney biopsy are required.
Management	Drug withdrawal, hydration control, dialysis in extreme situations, and supportive care	Discontinuing medication, controlling blood pressure with ACE inhibitors and ARBs, and, in more severe situations, renal

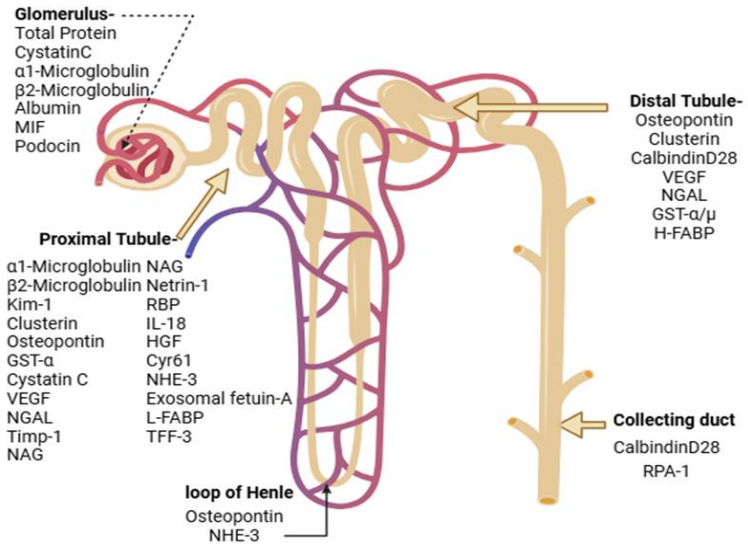

Figure1.1-Site of origin of some biomarkers of drug induced kidney injury within a nephron segments.

MIF **(**Macrophage Migration Inhibitory Factor), GST-α (Glutathione S-Transferase Alpha), VEGF **(**Vascular Endothelial Growth Factor), NGAL (Neutrophil Gelatinase-Associated Lipocalin), Timp-1 (Tissue Inhibitor of Metalloproteinases-1**.**), NAG (N-Acetyl-β-D-Glucosaminidase), RBP (Retinol-Binding Protein), IL-18 **(**interleukin-18), HGF (Hepatocyte Growth Factor),NHE-3 (Sodium-Hydrogen Exchanger-3), L-FABP (Liver-Type Fatty Acid-Binding Protein), TFF (Trefoil Factor Family**.**) RPA-1(Replication Protein A1)

Emerging Biomarkers of Drug-Induced Kidney Injury

A. Protein-Based Biomarkers

Neutrophil Gelatinase-Associated Lipocalin (NGAL):- The scientific discovery of Human neutrophil lipocalin (HNL) originated from lysosomes of neutrophils leading to its alternative name of neutrophil gelatinase-associated lipocalin (NGAL). [27] Research findings revealed that the renal tubular epithelium serves as one of the tissues which produces NGAL. In the setting of bacterial infection NGAL levels rise while this enhanced circulation allows medical practitioners to distinguish between bacterial and viral infections because NGAL demonstrates a specific affinity for siderophores. These high-affinity organic iron chelators. Physiological reactions to tissue damage or adaptive responses may cause NGAL concentrations to elevate because studies reveal that NGAL-siderophore-iron complexes contribute to kidney protection mechanisms. [28] Research performed analysis of NGAL as a potential biomarker to identify acute and chronic kidney injury because the molecule gets rapidly produced in nephrons when renal epithelial injury occurs with inflammation. [29] The levels of a polypeptide rise during animal studies of AKI while serum and urinary quantities also increase. The detection of AKI after cardiac catheterization now becomes possible through early assessment of elevated NGAL levels within a short period. The scientific community has employed plasma NGAL tests for predicting mortality and morbidity risks among children undergoing heart operations. A single urine test for NGAL in the emergency room proved better at assessing clinical outcomes of nephrology consultations and critical care admission as well as dialysis initiation and death than elevated serum creatinine levels according to study findings. [30]

Kidney Injury Molecule-1 (KIM-1):- After ischaemia occurs the proximal tubule drastically

increases its production of KIM-1 which is a transmembrane protein with immunoglobulin and mucin domains. [10] The biomarker exists only in cases of renal damage since it cannot be found in healthy renal tissue. The soluble human KIM-1 form presents itself as an early sign which detects proximal tubule damage in the kidneys and has been detected in urine samples from pathologically proven acute tubular necrosis cases. [31] Acute drug exposure caused proximal tubule damage which triggered elevated KIM-1 levels in urine but did not affect serum urea, creatinine or urinary NAG activity levels. This indicated that current tests showed low sensitivity to detect tubular damage. [32] Drug-induced toxicity has received recognition from both EMA and US FDA as a highly sensitive biomarker by KIM-1. [33]

Clusterin & Osteopontin:- A sulfated glycoprotein named clusterin stimulates both tissue arrangement and programmed cellular death processes. The identification of early renal damage in rats receiving cisplatin becomes possible through urine or serum clusterin evaluation. Gentamicin exposure at harmful doses induced alterations in both urine clusterin and KIM-1 and osteopontin levels. [34] Clusterin(Clu) is normal value 22-88 ug/ ml. The acidic glycoprotein osteopontin exists both inside cells and outside the cells and it maintains solubility in plasma and urine. Osteopontin has been identified as an expressed molecule across brain cells as well as bone cells and endothelial cells and smooth muscle cells and immune cells within the human body. Osteopontin levels in kidney injuries remain within the range of 31 to 200 ng/ml at the time of both acute and chronic injury evolution. When functioning as an inflammatory molecule osteopontin aids in stress reduction by providing both anti-inflammatory and pro-inflammatory properties. The cardiovascular system together with the kidneys function through osteopontin as this molecule controls the pathophysiology progress of glomerulonephritis along with kidney damage development by managing oxidative stress and inflammatory responses. [35]

B. Metabolomic and Urinary Biomarkers

Urinary metabolite profiling: - The kynurenine pathway sustains the development of kidney disease so urinary metabolite profiling emerged as an important technology to identify early symptoms of kidney toxicity. The kynurenine pathway shapes tryptophan metabolism to generate products that show close links to oxidative stress and inflammation as well as immunological functions. Recent studies demonstrate that kynurenine metabolism together with its metabolites quinolinic acid and kynurenic acid show correlation with acute kidney injury (AKI) and chronic kidney disease (CKD). [36] Research shows that kidney-related toxic situations lead to decreased tryptophan blood levels along with elevated kynurenine metabolites in urine as signs of disturbed kidney filtration and metabolic activity. [37] The connection of nephrotoxic conditions to disturbances in renal filtration and metabolic processes has been shown by decreased tryptophan levels together with elevated kynurenine metabolites found in urine samples. [38] The evaluation of kynurenine pathway metabolism through LC-MS testing of urine samples proves capable of detecting kidney damage caused by drugs thus enabling early therapeutic interventions. [39] These promising results need to overcome barriers for clinical application mainly because of inconsistent validation practices and individual-specific changes in metabolite concentrations. Good results from kynurenine pathway metabolite testing require additional research in order to establish them as reliable diagnostic tools for kidney toxicity assessment and medication safety evaluations.

Metabolomic changes in DIKI:-. Research indicates that fast diagnosis of DIKD can potentially occur through the monitoring of

metabolomic indicators. Scientists analyzed the urinary and kidney tissue metabolomic changes of rats that received cisplatin and gentamicin and tobramycin treatment as known agents causing proximal tubule damage. [40] Metabolomics provides quick and accurate biological process testing through tests that depend only on small volumes of plasma or urine samples. [41] Sprague-Dawley rats received a treatment of Gentamicin 40 mg/kg and cisplatin 0.5 mg/kg together with tobramycin 40 mg/kg. The research team collected urine and kidney samples at day 1, day 5 and day 28 to analyze 547 metabolites detected in kidney tissue and 657 metabolites present in urine using GC/MS and LC/MS techniques. The approach of metabolomics shows potential to identify DIKD early with precision. Metabolic profiling can detect DIKD enabling healthcare workers to start early interventions by removing offending medications and making dose reductions and treatment modifications and initiating mitigation therapy. [42]

Cystatin C – Cystatin-C (Cys-C) represents a member of the cysteine protease inhibitor super family whose 13-kDa non-glycosylated protein has a serum standard range between 0.6 and 1 mg/L. [41] Even though glomerular cells do not produce this protein the substance easily passes through filtration and obtains almost full absorption until its breakdown in proximal tubule cells completes. Studies have demonstrated that urinary cystatin C detects acute kidney damage more effectively than serum creatinine (sCr) and plasma cystatin C and the blood levels of cystatin C do not change because of age, gender, or muscle mass. Investigation of serum cystatin C's clinical value for kidney function measurement and GFR surrogate has been the focus of multiple research studies. Research shows that serum cystatin C detection begins early because it appears one to two days ahead of creatinine elevation which makes it relevant in acute renal failure diagnosis. Blood cystatin C measurements occurred before serum creatinine detection yet failed to indicate kidney conditions and proved comparable to creatinine when detecting kidney damage after extensive kidney damage occurred. [43]

C. Genomic and Epigenetic Biomarkers

microRNAs (miRNAs) in DIKI :- Short RNAs which fall under the category of MiRNAs serve as non-coding molecular agents, they show evolutionary preservation through their development from 20 to 25 nucleotide sequences. The regulatory role of MiRNAs works by managing the cellular expression of targeted genes post-transcriptionally. The translation-limiting mechanism operates through the ribonucleoprotein complex miRISC where they recognize specific sequences present in target mRNAs located in their 3′-untranslated regions. Scientific research has fully studied the processes of miRNA maturation and miRISC integration along with subsequent mRNA binding. [44] Extracellular miRNAs fulfill all the FDA-described biomarker criteria including 1) stability along with 2) simple availability in multiple bodily fluids and 3) universal species conservation and 4) tissue or disease-state specificity and 5) precise measurement methods. The distinctive properties of miRNAs make them highly suitable for use as non-invasive biomarkers. Our laboratory played a role in initial miRNA extraction from urine supernatants alongside demonstrating that miR-21 and miR-155 existed at distinct levels in AKI and gentamicin-induced AKI rat urine samples. [45]

DNA methylation changes in nephrotoxicity: - DNA methylation modifications serve an essential role in nephrotoxicity through their action of disrupting patterns of gene expression which connect to renal injury along with inflammation and fibrosis development. Nephrotoxic medications and oxidative stress along with environmental toxins can initiate DNA methylation problems that break essential protective genetic functions. Research shows that glyphosate-surfactant herbicides along with other

nephrotoxic agents create detectable DNA methylations in kidney cells which also raise renal biomarker levels. **[46]** The epigenetic modifications are directly linked to cellular repair breakdown which advances CKD progress. DNA methylation changes in nephrotoxicity conditions have potential as diagnostic and therapeutic markers because epigenetic managers can demonstrate reverse silencing of methylated genes. New research needs to validate DNA methylation profiles as predictors of nephrotoxicity biomarkers while developing epigenetic treatment approaches to stop kidney injury.

D. Inflammatory and Immune Biomarkers

Interleukin-18 (IL-18) – The protein contributing to ischemic acute tubular necrosis development is interleukin-18 (IL-18) which exists at 460 pg/ml in its standard format. Research proves Interleukin-18 to be an excellent marker for quick and precise cheap detection of early acute kidney injury yet prediction accuracy shows significant variation. [47] The median urinary IL-18 levels among ATN patients considerably surpassed those of patients with pre-renal azotemia, urinary tract infection, CKD and nephrotic syndrome and healthy controls. Urinary IL-18 median values within the initial 24h after organ transplantation showed elevation only in individuals receiving cadaveric kidneys with delayed graft function compared to patients with cadaveric kidneys featuring immediate graft function and living donor kidneys showing immediate graft function**.** [48]

Tumor Necrosis Factor-α (TNF-α) – Functional among pro-inflammatory cytokines is Tumor Necrosis Factor-alpha (TNF-α because it regulates drug-induced nephrotoxicity (DIN) processes. The renal injuries caused by nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics (e.g., aminoglycosides) together with the chemical agents (cisplatin and doxorubicin) and immune-suppressants are mediated through TNF-α pathways. Renal tissue toxicity occurs through TNF-α action after the protein activates inflammation and apoptosis processes in combination with oxidative stress. High TNF-α levels in renal cells trigger both an increase in inflammatory cell infiltration and NF-κB activation with subsequent enhancement of cytokines IL-6 and IFN-γ production. The sequence of events leads to renal damage which appears as elevated BUN and Cr levels in addition to noticeable tissue alterations. Acetaminophen leads to kidney damage through oxidative stress combined with TNF-α production but arjunolic acid works as an effective treatment by blocking these inflammatory processes. [49] Studies demonstrate that TNF-α activation leads to cisplatin-induced acute kidney injury but researchers discovered that antioxidant use of curcumin and melatonin lowers TNF-α expression to protect kidney tissue. [50-51] The drug class of TNF-α inhibitors used for autoimmune diseases contains infliximab which has demonstrated nephrotoxic effects in select cases thereby demonstrating that TNF-α operates through multiple pathways affecting renal pathophysiology. [52]Research has established that both ciprofloxacin antibiotics and anti-tubercular agents cause oxidative stress and renal inflammation because of TNF-α-dependent pathways yet studies demonstrate Brahmi and melatonin can counteract these effects. **[52].**Researchers have extensively studied the complete mechanism that leads to TNF-α-induced nephrotoxicity via drug-induced acute interstitial nephritis (AIN) and granulomatous interstitial nephritis which use TNF-α-mediated immune responses to cause renal impairment deterioration. Research now studies the potential use of TNF-α antagonists in drug-induced renal damage prevention but their efficacy remains under active investigation. The key inflammatory mediator TNF-α functions in drug-induced nephrotoxicity so its inhibitory mechanisms demonstrate therapeutic promise.

Clinical Applications and Validation of Biomarkers: -The clinical confirmation of drug-induced nephrotoxicity biomarkers shows substantial progress since many biomarkers participate in testing during clinical trials to detect toxicity earlier and classify risk levels. Early detection requires novel biomarkers beyond standard renal markers serum creatinine and blood urea nitrogen (BUN) since they do not work well for early identification thus kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), clusterin, and osteopontin serve as better detection markers..[53] The U.S. Food and Drug Administration (FDA) approved specific biomarkers from the urinary composition including KIM-1 and NGAL to enhance drug safety and protect patients from severe kidney damage during clinical usage.[54] Implementation of biomarkers for clinical use faces three main barriers caused by regulatory hurdles alongside variable test responses and unstandardized validation methods. To advance biomarker thresholds for wider adoption experts need to conduct major clinical studies across different patient types alongside established drug development procedures. The collaboration among pharmaceutical firms with regulatory bodies and medical experts leads to establishing dependable and repeatable biomarker-based kidney toxicity evaluations which can function throughout different clinical settings. [55]

Future Directions and Challenges:- Future DIN biomarker research depends on the standardization effort that leads to routine clinical validation of biomarkers. The challenge of implementing promising biomarkers KIM-1 as well as NGAL and urinary metabolomics panels into medical practice exists due to patient outcome variations and absent standardized diagnostic accuracy standards. [56] Multiple biomarkers obtained from genomic and proteomic and metabolomic data show promise to enhance nephrotoxicity detection while improving the diagnosis speed and patient care results. [57] The search for biomarkers becomes more successful because artificial intelligence (AI) and machine learning analyze high-dimensional information patterns which leads to individual risk evaluation and enhanced renal toxicity assessments.[58] Management strategies for renal toxicity combined with optimal medication dosing receive improvements through the deployment of individual genetic information with personalized biomarkers [59] The clinical adoption of these methods depends on the solution of regulatory barriers along with extensive validation requirements and clinical process technology integration problems. Research improvement for medication safety evaluations together with patient care requires standardizing biomarker validation processes and expanding AI-driven nephrotoxicity detection while promoting scientific and medical-agency collaborative research.

Conclusion: - Many patients have kidney disease without showing symptoms until the severe stages of the condition when substantial kidney damage or even death becomes possible if patients do not receive proper screening and treatment. Medical experts use serum creatinine tests as a biomarker to detect kidney disease since their first application was about 80 years ago. [30]. Renal disease diagnosis remains highly specific with creatinine because we base our kidney disease definitions on its levels yet its detection ability fails to meet needs when treating common clinical conditions. The development of new renal biomarkers stands vital for the improvement of drug safety regarding renal elimination and nephrotoxic drugs. Pharmacists now have the chance to use cystatin C and [TIMP-2], [IGFBP7] as foundations for drug monitoring and dosing plans which represents a modern innovative approach to pharmacy care delivery. The identification of potential operational problems from early adoption of these innovative models will generate improved methods to transfer medical knowledge into practice. [60].

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