Review Article

Recent Advances in Differential Diagnostic Strategies for Diabetic and Non-Diabetic Nephropathy

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ABSTRACT

Diabetic nephropathy and non-diabetic renal disease are two major causes of chronic kidney disease in patients with diabetes, often presenting with overlapping clinical features but requiring distinctly different management strategies. Traditional diagnostic approaches, especially renal biopsy, though definitive, are invasive and not feasible for routine use. Recent years have witnessed rapid progress in the development of non-invasive diagnostic models that leverage systems biology, advanced imaging, and artificial intelligence for differential diagnosis. Multi-omics platforms, including metabolomics, transcriptomics, and proteomics, have identified promising biomarker signatures capable of distinguishing diabetic nephropathy from non-diabetic renal disease. Imaging techniques combined with machine learning, particularly deep learning-assisted histopathology and renal ultrasound localization microscopy, have further improved diagnostic precision. Additionally, integrative prediction models incorporating clinical, molecular, and imaging data are being validated to offer personalized diagnostic pathways. This review comprehensively explores the latest advancements in differential diagnostic strategies for Diabetic nephropathy and non-diabetic renal disease, with an emphasis on biomarker discovery, computational model development, and translational potential. The findings aim to support a shift from invasive diagnostics toward clinically viable, non-invasive, and patient-centered approaches in nephrology.

Keywords: Diabetic nephropathy, Non-diabetic renal disease, Differential diagnosis, Biomarkers, Artificial intelligence.

INTRODUCTION

Diabetic nephropathy (DN) and non-diabetic nephropathy (NDN), also referred to as non-diabetic renal disease (NDRD), represent two distinct clinical and pathological categories of chronic kidney disease (CKD) in patients with diabetes mellitus. DN is a microvascular complication that primarily results from prolonged hyperglycemia and is characterized histopathologically by mesangial expansion, thickening of the glomerular basement membrane, podocyte loss, and glomerulosclerosis.[1,2] In contrast, NDN includes a heterogeneous group of renal diseases unrelated to diabetes, such as IgA nephropathy, membranous nephropathy, hypertensive nephrosclerosis, and tubulointerstitial nephritis.[3] These conditions differ significantly in etiology, histopathology, clinical progression, and response to therapy.

In diabetic individuals presenting with proteinuria or declining renal function, DN is often presumed without histological confirmation. However, studies have reported that a substantial proportion (up to 40%) of such patients may have NDN or mixed forms of nephropathy.[4,5] Differentiation between DN and NDN is therefore critical, as the underlying disease process guides the choice of therapy. DN management typically focuses on optimizing glycemic control, lowering blood pressure, and using renin–angiotensin–aldosterone system (RAAS) blockers and SGLT2 inhibitors.[6] In contrast, NDN may require disease-specific interventions, such as immunosuppressive therapy for glomerulonephritides or steroids for tubulointerstitial nephritis.[3,7]

The current gold standard for distinguishing DN from NDN is renal biopsy, which provides definitive histological insights. Despite its diagnostic accuracy, renal biopsy is invasive, associated with procedural risks (e.g., hemorrhage, arteriovenous fistula), and is not feasible in patients with coagulopathies, solitary kidneys, or poor general condition.[4,8] These limitations make non-invasive diagnostic strategies highly desirable for broader clinical application. Albuminuria and estimated glomerular filtration rate (eGFR) are commonly used clinical markers to assess renal function and damage in diabetes. While albuminuria (measured by the urinary albumin-to-creatinine ratio) has long been considered a hallmark of DN, recent evidence indicates that a substantial subset of patients with DN may not exhibit elevated albumin levels—a condition referred to as non-albuminuric diabetic kidney disease.[6,9] Moreover, albuminuria is not specific to DN and can occur transiently due to physical exertion, fever, urinary tract infections, or use of medications like NSAIDs and statins.[10] eGFR, though useful, is an indirect and delayed indicator of nephron loss, and is influenced by age, sex, muscle mass, and protein intake.[11]

In response to the limitations of conventional biomarkers, recent research has focused on identifying novel, non-invasive biomarkers for early and accurate discrimination between DN and NDN. Urinary biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), monocyte chemoattractant protein-1 (MCP-1), liver-type fatty acid-binding protein (L-FABP), and serum markers like TNF receptor-1 and -2 have shown promise in early-stage detection and differential diagnosis.[12,13] Multi-omics technologies have further

advanced the field by enabling simultaneous analysis of metabolomic, transcriptomic, and proteomic data to identify disease-specific molecular signatures. Recent studies have demonstrated that integrated omics-based panels, when combined with clinical parameters, can significantly enhance diagnostic precision. Luo *et al.* (2024) employed LC-MS-based metabolomic profiling and identified unique low-molecular-weight metabolites associated with early diabetic kidney injury.[14] In parallel, transcriptomic studies have revealed the differential expression of genes involved in inflammation, oxidative stress, and fibrosis in DN compared to NDN.[15]

Artificial intelligence (AI) and machine learning (ML) have also been increasingly adopted to develop predictive diagnostic models that integrate clinical, biochemical, and imaging data. Deep learning algorithms applied to digital renal biopsy images have achieved high accuracy in identifying interstitial fibrosis and tubular atrophy, key indicators for DN staging.[16] ML models using routine clinical parameters combined with omics-derived biomarkers have shown high discriminatory performance, with some achieving area under the receiver operating characteristic curve (AUC) values exceeding 0.95.[17] Advancements in renal imaging techniques, including contrast-enhanced ultrasound and novel MRI-based methods, offer additional opportunities for non-invasive assessment of renal structure and function. Recent progress in ultrasound localization microscopy, capable of visualizing the renal microvasculature, may further aid in distinguishing between DN and NDN based on vascular integrity and perfusion patterns.[18]

Modern Biomarkers

In ND, biomarkers mirror key pathophysiological mechanisms such as hyperglycemia-induced oxidative stress, inflammation, glomerular injury, and tubular damage. For instance, markers like albuminuria indicate glomerular permeability changes, while KIM-1 (Kidney Injury Molecule-1), NGAL (Neutrophil Gelatinase-Associated Lipocalin), and TNFR1 (Tumor Necrosis Factor Receptor 1) reflect tubular injury and systemic inflammation. The biomarkers used in ND are listed in Table 1. Emerging biomarkers such as soluble urokinase plasminogen activator receptor (suPAR) and specific urinary metabolites offer earlier detection of kidney damage before conventional clinical indicators such as eGFR decline or overt proteinuria. These biomarkers help enhance diagnosis, predict progression, and guide therapeutic interventions in DN patients.[19-21] The typical mechanism of biomarkers in diabetic neuropathy is illustrated in Figure 1.

Table 1: Modern biomarkers used in diabetic nephropathy.

Category	Biomarker	Biological Source	Clinical Relevance	References
Inflammatory markers	TNF receptor 1 (TNFR1)	Serum	Predicts DN progression and ESRD risk	[22]
	Interleukin-6 (IL-6)	Serum	Elevated in DN; reflects inflammatory status	[23]
Tubular injury	Kidney Injury Molecule-1 (KIM-1)	Urine	Sensitive early biomarker for tubular injury in DN	[24]
	Neutrophil Gelatinase-Associated Lipocalin (NGAL)	Urine	Indicates tubular damage before albuminuria onset	[25]
Fibrosis markers	Transforming Growth Factor-β1 (TGF-β1)	Urine/Serum	Promotes fibrosis; elevated in progressive DN	[26]
Oxidative stress	8-Hydroxy-2'-deoxyguanosine (8-OHdG)	Urine	Marker of oxidative DNA damage in renal cells	[27]
Endothelial dysfunction	Endothelin-1 (ET-1)	Plasma	Associated with glomerular endothelial injury	[28]
Metabolomics	α-Ketoglutarate, 3-Hydroxybutyrate	Urine/Serum	Discriminative in DN vs NDN classification using ML	[20]
Proteomics	Soluble Urokinase Plasminogen Activator Receptor (suPAR)	Serum	Elevated in glomerular damage and progressive DN	[19]
Genomic markers	ELMO1, SLC2A1 gene polymorphisms	DNA	Linked to DN susceptibility and progression	[29]
Transcriptomics	miR-21, miR-29a	Blood/Urine	Regulate fibrosis and inflammation-related pathways	[30]

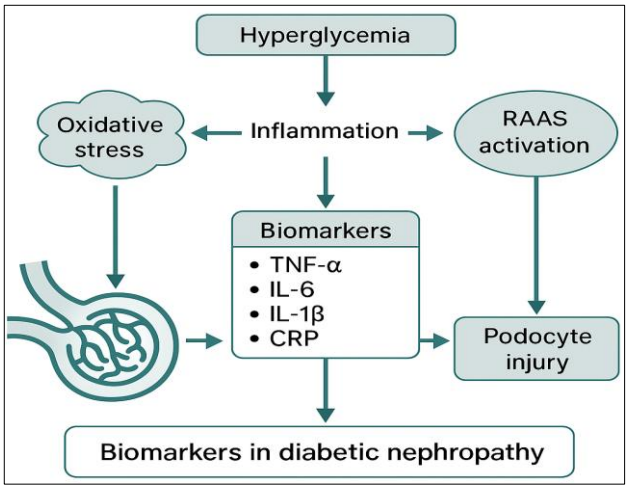

Figure 1: Biomarkers in diabetic neuropathy

Recent advances in metabolomics have revealed its value in identifying early metabolic alterations associated with ND. Yuanyuan Luo *et al*. (2024) conducted a comprehensive review of studies between 2011 and 2023, highlighting how low-molecular-weight metabolites, identified via LC-MS and NMR, provide non-invasive biomarkers capable of differentiating DN from NDRD.[14] Key findings include dysregulation of α-ketoglutarate and disturbances in glycolysis and the tricarboxylic acid (TCA) cycle, which appear consistently in DN but not in NDRD.[31] These metabolic patterns may precede overt changes in estimated glomerular filtration rate (eGFR) or albuminuria, positioning metabolomics as a powerful tool for early diagnosis and disease stratification.

Chronic low-grade inflammation plays a pivotal role in the pathogenesis of DN. Inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) have been found to correlate positively with disease severity in DN.[32] Elevated NLR has been associated with increased albuminuria and glomerular injury, with an adjusted odds ratio of approximately 1.88 for DN risk in diabetic patients.[33] Similarly, both SII and SIRI have demonstrated independent predictive value for all-cause and cardiovascular mortality in patients with diabetic nephropathy, with hazard ratios reaching 1.49 and 1.62, respectively, and SIRI showing a particularly strong association with kidney disease mortality (HR = 2.74).[32]

Secretory leukocyte protease inhibitor (SLPI), an anti-inflammatory molecule secreted by renal epithelial cells, is gaining attention as a novel biomarker. SLPI levels have been shown to correlate with declining eGFR and increased proteinuria in DN, suggesting its role in tubular protection and injury response.[34] Vascular endothelial growth factor (VEGF), a key mediator of angiogenesis and endothelial permeability, is often elevated in DN and is associated with poor glycemic control and disease progression, particularly in elderly patients with type 2 diabetes.[35] Together, NLR, SII, SLPI, and VEGF represent a composite panel of systemic inflammatory biomarkers with emerging relevance in DN diagnosis and prognosis.

Recent genetic studies have focused on polymorphisms in the interleukin-6 receptor (IL6R) gene, especially the rs2228145 variant, about DN susceptibility. A 2023 case-control study showed that AC and CC genotypes of IL6R rs2228145 were significantly more frequent in DN patients compared to healthy controls (24.1% and 9.3% vs. 10.7% and 6.7%, respectively), with the C allele conferring a nearly twofold increased risk.[36] This single nucleotide polymorphism affects IL-6 signaling, a cytokine pathway intricately involved in glomerular inflammation and fibrosis, thus supporting its use in genetic risk stratification for DN.

The IL-6 gene polymorphisms such as rs1800796 (GG genotype) and rs1524107 (CC genotype) have been significantly associated with an increased risk of diabetic nephropathy progression in type 2 diabetes patients, with adjusted hazard ratios of 2.02 and 2.08, respectively, in a prospective 5.3-year cohort study.[37]

Genetic and transcriptomic models

Differentiating DN from NDN is clinically complex due to overlapping renal manifestations. As renal biopsy is invasive and not feasible for all patients, genomics and transcriptomics are gaining attention for non-invasive, molecular-level diagnosis. **Single-cell RNA sequencing (scRNA-seq)** offers unprecedented resolution to identify disease-specific signatures in individual renal cell types. In 2019, Wilson *et al*. demonstrated that DN kidneys exhibit distinct transcriptional changes in podocytes, proximal tubular cells, and endothelial cells, including early activation of stress-response genes such as *TXNIP*, and adhesion molecules like *VCAM1*, which were absent in normal kidneys.[38] These markers represent early disease activity before clinical symptoms manifest. Further refining this approach, Lu *et al.* (2022) used scRNA-seq to explore immune cell profiles in DN and revealed macrophage-specific overexpression of *EIF4B*, *PRKCB*, and *RICTOR*, indicating the involvement of mTOR/AKT signaling in diabetic kidney inflammation and fibrosis.[39] These insights allow researchers to define not just gene markers but also pathways that could guide targeted therapy, distinguishing DN from common NDNs such as IgA nephropathy or minimal change disease.

Bulk RNA sequencing studies also provide valuable transcript-level comparisons between DN and NDN. In 2011, Woroniecka *et al*. first reported overexpression of extracellular matrix genes (*COL4A1*), chemokines (*CCL2*), and inflammation-associated genes (*SERPINA3*) in glomerular tissues from DN patients.[40] In a comparative study by Dong *et al*. showed that *IL1B*, *TGFB1*, and *CXCL10* were significantly elevated in DN relative to membranous nephropathy (a typical NDN), while podocyte injury markers like *PLA2R1* were more specific to NDN.[41]

These molecular distinctions have diagnostic potential in biopsy-sparing cases. In 2023, Guo et al. developed a transcriptomic diagnostic model consisting of 14 hub genes, including *SPP1*, *TGFBI*, and *TIMP1*, achieving an AUC of 0.92 in differentiating DN from other glomerular diseases.[42]

These genes were validated using qRT-PCR and immuno histochemistry in biopsy specimens, suggesting future applications in liquid biopsy or urinary mRNA assays.

Polygenic risk scores (PRS) offer a genomic lens into DN susceptibility. In 2018, Sandholm *et al.* conducted a GWAS in type 1 diabetes cohorts, identifying risk loci such as *COL4A3*, *UMOD*, and *ELMO1*, which are associated with basement membrane integrity and tubulointerstitial fibrosis in DN.[43] In the CREDENCE trial (n=3080), higher HbA1c variability in T2D patients with CKD was independently linked to increased cardiovascular and renal risks. This aligns with meta-analyses by Xu *et al*. and Li *et al*., supporting its prognostic value beyond mean HbA1c. Unlike prior studies, greater variability was observed in younger patients, possibly due to advanced CKD or unstable control. While current KDIGO guidelines overlook variability, agents like SGLT2 inhibitors, as shown in EMPA-REG OUTCOME, may reduce associated risks. Overall, HbA1c variability shows promise as a clinical risk marker in this population.[44] However, Jung *et al*. (2025) emphasized the importance of population-specific calibration, noting reduced PRS utility in Asian populations without allele-frequency adjustments.[45] Integrative models are emerging as a comprehensive solution. In 2024, Li *et al.* conducted a multiomics analysis integrating scRNA-seq, kidney cortex proteomics, pQTL, GWAS, and metabolomics data to identify key molecular drivers of diabetic kidney disease (DKD).

Using data from the Kidney Precision Medicine Project and the Diabetes Heart Study, they identified *AKR1A1* as a central biomarker, with consistent downregulation across transcriptomic and proteomic layers in proximal tubule cells. This integrative approach highlights *AKR1A1* as a potential molecular hub implicated in DKD progression via multiple intersecting pathways.[46] This represents a shift toward systems-level, precision nephrology.

Imaging and histopathologic advances

The distinction between DN and NDN has benefited greatly from recent innovations in imaging and histological interpretation, particularly with the integration of AI and high-resolution microvascular imaging. Traditional histopathology, though central to diagnosis, suffers from interobserver variability and limited reproducibility, which new technologies are addressing. Deep learning (DL) approaches using convolutional neural networks (CNNs) have shown high accuracy in detecting glomerular features characteristic of DN.[47]

Weis *et al.* developed a CNN model that identified nine glomerular morphologies, including mesangial expansion and capillary loop thickening, with inter-rater agreement exceeding κ=0.84 [49]. Similarly, Juang *et al*. used an Xception-based architecture to classify glomerular sclerosis, achieving a 94.7% accuracy and 93.8% F1-score.[37] In 2019, **Ginley *et al*.** developed a computational pipeline integrating CNNs and unsupervised learning to classify renal biopsies in DN. The model segmented glomerular structures, including nuclei, capillary lumina, and Bowman's spaces, achieving **93% balanced accuracy** in boundary detection, **94% sensitivity and 93% specificity** for nuclei, and **95% sensitivity and 99% specificity** for other glomerular components. Diagnostic concordance with expert pathologists reached **Cohen's κ of 0.55–0.68,** demonstrating that algorithmic interpretation can match expert-level histopathology and reduce interobserver variability in DN assessment.[50]

Further, projects like NEPTUNE and KPMP have developed whole-slide image analysis systems for glomerular counting, peritubular capillary assessment, and inflammation grading, facilitating standardized, scalable biopsy evaluations.[51] To overcome limited datasets, generative adversarial networks (GANs) are now used to synthetically augment rare pathology slides, enhancing model robustness. The GAN are powerful tools in digital histopathology, enabling realistic image synthesis, stain normalization, and virtual staining. They reduce reliance on annotated data and can simulate rare patterns, enhancing diagnostic workflows. However, concerns about bias, authenticity, and ethical regulation must be addressed to ensure safe clinical integration.[52]

Parallel advancements in **ultrasound localization microscopy (ULM)** have redefined vascular imaging. ULM, unlike conventional Doppler ultrasound, enables sub-capillary resolution using microbubble tracking. Qiu *et al*. demonstrated ULM's ability to reveal altered blood flow dynamics in hypertensive nephrosclerosis, a typical NDN model, not detectable by standard ultrasound.[53] In humans, Huang *et al*. used clinical ULM to visualize microvascular flow within 10 sec per scan, improving resolution six-fold and establishing feasibility in real-time nephrology assessments.[54] Enhanced signal processing methods such as deep-learning-based deconvolution and geometric localization have further improved ULM accuracy, even under high microbubble load.[55,56] Patterns observed through ULM, such as uniform rarefaction in NDN *vs* heterogenous perfusion in DN, may serve as future diagnostic signatures. These technologies, when combined with AI-powered histopathology, could offer a dual-modality framework for distinguishing renal pathologies.

While additional imaging techniques such as functional MRI, diffusion tensor imaging, and contrast-enhanced ultrasound show promise in mapping fibrosis and oxygenation, their clinical integration remains limited due to cost and technical complexity.[57,58] In contrast, AI histopathology and ULM are rapidly progressing toward routine clinical use, and their synergy may soon become central to non-invasive nephropathy classification and monitoring. The relative advantages and diagnostic caveats of histological, imaging, and biomarker-based modalities for distinguishing DN from NDN are summarized in Table 2.

Table 2: Advantages and Limitations of Diagnostic Modalities for DN vs. NDN.

Diagnostic Approach	Main Advantages	Limitations	Clinical Readiness	References
Renal Biopsy	Gold standard, histopathological confirmation	Invasive, contraindicated in some patients	High	[3]
Albuminuria and eGFR	Widely available, non-invasive	Low specificity for DN vs. NDN	High	[59]
Proteomic Biomarkers (CKD273)	Early detection, non-invasive	Cost, limited access in LMICs	Moderate	[60]
Metabolomic Panels	High sensitivity for early-stage DN	Expensive platforms, inter-lab variability	Moderate	[21]
AI-Based Models (XGBoost, Random Forest)	High accuracy, integrates complex data	Requires standardization, low interpretability	Low to Moderate	[61]
Deep Learning Histopathology	Quantitative, scalable tissue feature detection	Requires digital infrastructure, data volume	Low to Moderate	[62]

AI-driven clinical prediction models

AI and machine learning are rapidly transforming the diagnostic landscape in nephrology by enabling non-invasive, high-accuracy differentiation between DN and NDN. Traditional approaches, such as logistic regression, have gained renewed strength through integration with advanced feature selection algorithms like Boruta.[63] Comparative diagnostic performance (AUROC or accuracy) of recent biomarker, omics, and AI-based models in differentiating DN from NDN **are picturized in Figure 2.** In a retrospective study using real-world data from the DARWIN-Renal cohort, Dei Cas *et al*. (2024) developed a Boruta-assisted logistic regression model incorporating clinical, laboratory, and treatment variables. The model achieved an **AUROC as high as 0.98**, demonstrating excellent discriminative ability for predicting clinically meaningful eGFR decline in patients with diabetes.[64] Beyond logistic regression, machine learning models such as XGBoost, random forests, and deep neural networks have been explored. In 2022, Wang et al. demonstrated the application of the XGBoost algorithm in predicting type 2 diabetes using clinical, lifestyle, and demographic variables from a Beijing-based population. Compared to conventional machine learning models like SVM, Random Forest, and K-NN, XGBoost achieved the highest predictive performance, with an AUROC of 0.9182 and accuracy of 89.1%. The study emphasized XGBoost's robustness, efficiency, and superior generalization, positioning it as a highly effective tool for early diabetes risk stratification and potential clinical deployment.[65] Inn 2022, Hao *et al*. developed a multi-focus video fusion method combined with YOLOv4 (You Only Look Once version 4) deep learning to detect urine red blood cells for diabetic nephropathy diagnosis, achieving a mean average precision of 0.915 and improved diagnostic accuracy over traditional threshold methods.[66]

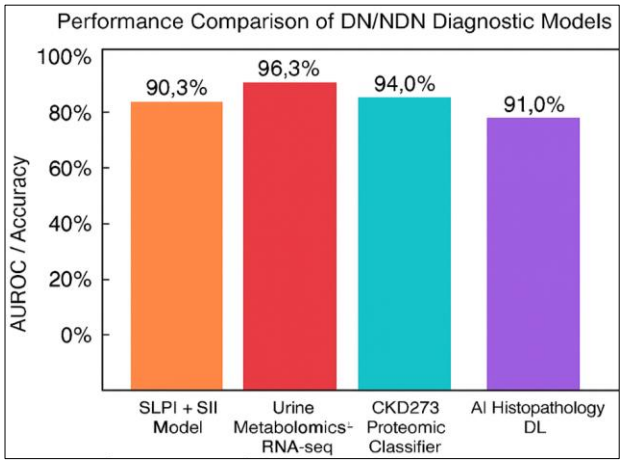

Figure 2: Comparative diagnostic performance (AUROC or accuracy) of recent biomarker, omics, and AI-based models in differentiating DN from NDN

Interpretability remains central to clinical adoption. SHapley Additive exPlanations (SHAP) have been used to elucidate variable influence on predictions, with studies showing NLR and metabolomic indices contributing most to DN classification, while urinary KIM-1 and TNFR1 pointed to NDN. These models unify heterogeneous data types, clinical, molecular, imaging into actionable, interpretable diagnostic outputs.[67,68] A 2025 study by Raza *et al.* integrated kidney injury biomarkers KIM-1 and TNFR1 (plus ACR) into a multiparametric panel, achieving AUC 0.98, with 90% sensitivity and 96.7% specificity for early DKD detection. The authors proposed combining these markers with ML models (e.g., XGBoost with SHAP) to enhance early detection.[69] Despite these advances, challenges remain. Model generalizability across populations, data standardization, regulatory approval for software-based diagnostics, and real-world integration must be addressed.

The emerging non-invasive diagnostic modalities for diabetic *vs* non-diabetic nephropathy are illustrated in Figure 3.

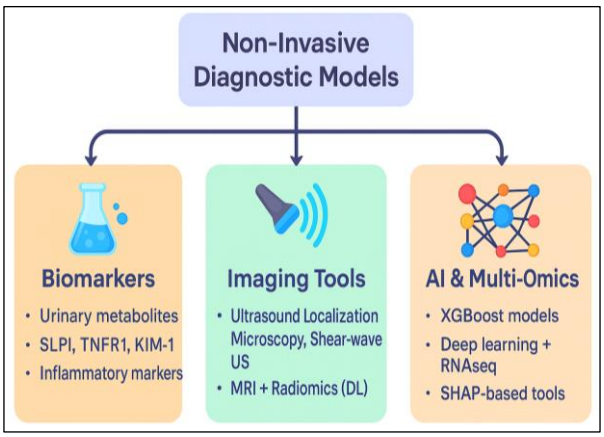

Figure 3: Emerging non-invasive diagnostic modalities for diabetic *vs* non-diabetic nephropathy

Clinical Translation and Challenges

Despite substantial progress in developing omics-, imaging-, and AI-based diagnostic models for differentiating DN from NDN, their clinical translation remains limited due to key practical and systemic challenges. A major limitation is the lack of external validation and data standardization. Many models are built using retrospective, single-center datasets, which restrict their generalizability across diverse populations. When applied to external cohorts, performance often diminishes due to demographic heterogeneity, differing disease prevalence, and variations in clinical data collection.[21,70] Sample processing variability, such as metabolomic platform differences or inconsistent imaging protocols which further undermines reproducibility and clinical adoption.

Another barrier is the integration into routine clinical workflows. Most healthcare infrastructures are not equipped to handle high-dimensional data inputs like transcriptomic profiles or AI-derived risk probabilities. Current electronic health records (EHRs) are seldom optimized for incorporating omics data or AI tools, and nephrologists may lack training to interpret machine learning outputs effectively.[71] Ethical and equity concerns add further complexity. The use of genomic and proteomic data raises issues related to data privacy, consent, and long-term security. Additionally, AI models trained on unbalanced datasets may perpetuate diagnostic bias, especially in underrepresented ethnic groups. Without proper transparency and fairness audits, there is a risk of worsening disparities in renal care .[72]

Cost-effectiveness and scalability remain pressing concerns. Advanced technologies like RNA sequencing, proteomics, and ULM require specialized infrastructure and trained personnel, which may not be feasible in low-resource settings. Moreover, reimbursement for such diagnostics is unclear, limiting incentive for institutional adoption. Health economic analyses are urgently needed to support policy and reimbursement decisions.[73] The regulatory framework for AI-enabled diagnostics is also evolving. Regulatory agencies like the FDA and EMA have begun addressing software-as-a-medical-device (SaMD) models, but most nephrology-focused AI tools have yet to undergo full regulatory evaluation. Challenges include dynamic model retraining, lack of real-time validation, and insufficient reporting of clinical performance in prospective settings.[74] Furthermore, real-world applicability remains limited. While multi-modal models have shown strong performance in academic studies, their use in community nephrology or primary care remains rare. Prospective trials, clinician training, and implementation infrastructure are essential to bridge the translational gap.

Future Directions

Future research in the differential diagnosis of ND and NDN should focus on building large, longitudinal multi-omics cohorts with biopsy-proven diagnoses. Most current studies rely on cross-sectional or retrospective data, which limits understanding of disease progression and hinders biomarker validation. Long-term follow-up of diverse patient populations using integrated clinical, transcriptomic, proteomic, metabolomic, and imaging data could help identify early diagnostic signatures and mixed disease phenotypes.[21,75] Translating these signatures into clinical tools requires the development of regulatory-grade assays and point-of-care (POC) diagnostics. Although biomarkers like TNFR1, KIM-1, and urinary metabolites show strong discriminatory potential, few are available in validated diagnostic formats. There is an urgent need to convert promising multi-omics biomarkers into cost-effective, rapid tests suitable for clinical laboratories or decentralized settings.[76]

AI models also need to become more transparent and clinically embedded. Current black-box algorithms often lack interpretability, reducing clinician confidence. Techniques like SHAP and LIME can enhance transparency and support clinical validation. Moreover, integrating these models into EHRs and clinical decision support systems (CDSS) would facilitate real-time application, helping nephrologists stratify patients non-invasively at the point of care. Additionally, mobile diagnostics, wearable sensors, and cloud-based platforms may contribute to real-time risk monitoring, enabling more personalized and continuous management of renal function. Future efforts must ensure that these innovations are equitably accessible and validated across global patient populations.[77-79]

CONCLUSION

The differential diagnosis between DN and NDN is critical for ensuring optimal clinical management in patients with diabetes-related renal impairment. Traditional diagnostic tools, including albuminuria levels, estimated glomerular filtration rate (eGFR), and renal biopsy, are limited by their invasiveness and diagnostic ambiguity. In contrast, recent advancements in molecular profiling such as metabolomics, transcriptomics, and proteomics which have identified

novel biomarkers that significantly enhance diagnostic specificity. Complementary progress in imaging modalities and deep learning–based histopathologic analysis has enabled non-invasive, automated tissue assessment, while AI-driven predictive models show high diagnostic performance using clinical, imaging, and omics data. Despite these innovations, real-world translation is hindered by challenges related to model validation, standardization, ethical concerns, and integration into clinical infrastructure. Moving forward, precision nephrology will require the development of longitudinal, multi-omics cohorts, regulatory-grade diagnostic assays, and interpretable AI models embedded into electronic health systems. Achieving this vision will depend on multi-disciplinary collaboration to deliver personalized, non-invasive, and scalable diagnostic solutions that improve outcomes across diverse patient populations.

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