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Advances in Precision Medicine for Chronic Kidney Disease: Biomarkers, Risk Stratification, and Personalized Therapeutic Approaches

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ABSTRACT

Chronic kidney disease (CKD) is a biologically heterogeneous condition with great variations in the progression, complications and treatment responses in people with the same clinical syndromes. The concept of precision medicine is to address this variability by leveraging molecular, clinical and digital data to inform individual diagnosis and treatment. This review discusses the current understanding of precision nephrology, including the role of genetic susceptibility, metabolic dysfunction, inflammation, fibrosis, and multi-omics-defined disease subtypes. It also assesses newly introduced biomarkers such as KIM-1, NGAL, suPAR, DKK3, cystatin C, extracellular vesicles and multi-omics panels to detect, diagnose, and follow-up patients early. Dynamic prediction models, interpretable machine learning, artificial intelligence, and digital health platforms are discussed as tools for improving risk stratification and identifying patients at greatest risk of kidney function decline. Personalized therapeutic approaches include biomarker-guided treatment, RAAS inhibition, SGLT2 inhibitors, GLP-1 receptor agonists, pathway-specific therapies, gene and RNA therapeutics, and precision nutrition. Despite rapid progress, clinical implementation remains limited by inadequate validation, data fragmentation, cost, regulatory uncertainty, infrastructure demands, and inequitable access. Future progress will depend on standardized assays, interoperable data systems, representative cohorts, transparent algorithms, and prospective evidence of clinical utility. Finally, the integration of multi-omics, computational medicine, and personalized treatment could help facilitate mechanism-based classification and personalized treatment of CKD.

Keywords: chronic kidney disease, precision medicine, biomarkers, risk stratification, personalized therapy

1. Introduction

CKDs have become one of the most important non-communicable diseases of the world with a significant clinical, social and economic burden on the healthcare system. CKD is defined by long-term abnormalities in kidney structure or function and in people of all ages is linked to a progressive decline in renal function, greater cardiovascular morbidity, reduced quality of life and early death. The rise in prevalence of diabetes mellitus, hypertension, obesity, population ageing and environmental risk factors has contributed to the rapid global spread of CKD, which is now a global public health priority, and necessitates new diagnostic and therapeutic techniques that go beyond the current paradigm of disease management [1]. Beyond kidney failure, the impact of CKD is widespread, impacting cardiovascular outcomes, healthcare costs and socio-economic development globally. Early disease progression is often asymptomatic, and existing disease diagnostic tools are mainly based on estimated glomerular filtration rate (eGFR) and albuminuria, which do not reflect the underlying biological processes involved in disease progression, leaving millions of people undiagnosed until the late stages of disease [2]. The clinical presentations are often similar, but the rates of renal decline, response to therapy and long-term outcomes vary significantly, highlighting the high degree of clinical heterogeneity found in CKD and its challenges in clinical management [3].

In spite of the great progress in nephrology and the implementation of evidence-based therapies, the progression of CKD is still observed in many patients. However, in spite of the great advancement of nephrology, many patients still have CKD progression after adopting evidence-based therapies. The course of the disease is affected by a complex interaction of genetic susceptibility, metabolic disturbances, immune regulation, chronic inflammation, environmental causes and lifestyle factors, which are different in different individuals [4]. The multi-dimensionality of CKD poses a threat to the prevailing "one-size-fits-all" treatment paradigm, and underscores

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the need for personalized approaches that will identify patients at the highest risk and allow for timely and targeted therapeutic interventions [5]. Over the last few years, molecular biology, high-throughput omics technologies and computational medicine have revolutionized the way CKD pathogenesis has been understood, as well as the opportunities for precision medicine. Extensive research on the genome, transcriptome, proteome, metabolome and epigenome has led to the identification of new biomarkers that more accurately reflect the activity and progression of the disease than conventional clinical markers [6]. At the same time, advancements in molecular data integration, predictive analytics, and digital health technologies have improved the potential to integrate clinical attributes with molecular data to inform more precise risk prediction and clinical decision-making at a personal level [7]. Precision medicine in nephrology is a novel paradigm that involves the use of molecular profiling, clinical phenotyping, imaging manifestations and patient history to develop personalized and effective prevention, diagnosis and treatment strategies based on the disease's molecular nature. Recent efforts such as the Kidney Precision Medicine Project have helped to propel multidimensional biological information into clinically relevant applications and to create a unifying strategy for personalized care of the kidney [8]. Simultaneously, personalized medicine is exhibiting significant potential in terms of biomarker-based therapies, patient segmentation, and therapeutic selection, still enhancing the shift from treatment algorithms to patient-specific therapeutic approaches [9].

While significant advances have been made in the discovery and development of biomarkers and in the development of personalized therapeutics, evidence is currently scattered across different molecular platforms, predictive models and clinical applications. A unifying and comprehensive synthesis that translates the new technologies of emerging biomarkers, precision risk stratification strategies and individualized therapy is currently underdeveloped and underutilized in routine nephrology practice.

Accordingly, the review offers an in-depth description of the latest advances in precision medicine in chronic kidney disease, such as the evidence of emerging biomarkers, molecular profiling, risk stratification models and personalized therapeutic approaches. It also examines the translation potential of these innovations together with the current challenges in implementation and future perspectives for the field of precision nephrology, to deliver more individualized and personalized patient care.

2. Biological Basis of Precision Medicine in Chronic Kidney Disease

Precision medicine in chronic kidney disease (CKD) is based on the notion that CKD is a complex syndrome with several different disease etiologies, molecular pathways, and clinical phenotypes. The disease onset, disease progression, treatment response and clinical outcome of patients with comparable degrees of kidney dysfunction vary widely between individuals. Such differences are a result of interactions between the genetic makeup, environment, metabolism, inflammation and adaptive responses of cells. The biological determinants are the foundation to develop individualized diagnostic and therapeutic strategies that lie beyond the traditional classification based on estimated glomerular filtration rate (eGFR) and albuminuria [10]. Biological Heterogeneity is one of the hallmarks of CKD and the scientific foundation of precision nephrology. In each case of progressive kidney injury, there are several different mechanisms, and each is different in individual patients depending on the disease process and patient characteristics. Rates of renal function decline may vary considerably, however, between individuals with similar clinical diagnosis, and not only in terms of clinical phenotype, but also in molecular activity. This heterogeneity makes it difficult to treat efficiently in a uniform way and emphasizes the need for disease-specific signatures of changes in the biology that are better predictors of disease progression and therapeutic responses [11]. This is also reflected by clinical observations demonstrating the multistate nature of the progression of CKD in the real world. Even with the best medical care, the function of some patients' kidneys declines rapidly, while others' kidney function stays stable for years. These differences represent dynamic biological processes involved in the disease process, including inflammation, fibrosis, oxidative damage, vascular injury and the activation of repair pathways that vary between individuals. This identification and characterization of these biological pathways will fine-tune patient stratification and targeted interventions to the major pathways involved in the disease process [12].

Another important determinant of susceptibility and progression of CKD is genetic variation. In addition to common genetic variants that contribute to renal function, disease severity, and response to treatment, there are many monogenic causes of kidney disease identified by advances in genomic research. The use of genetic tests has become more and more valuable in the investigation of inherited nephropathies; they also have proven their usefulness in the better classification of a disease and to inform clinical decision making, particularly when there is clinical atypicality or unexplained progressive renal failure. Therefore, genomic information plays a key role in the common clinical practice of nephrology, which is a turning point towards precision medicine [13]. There are also signs of the important role of polygenetic variation in the expression of disease, beyond single gene disorders. The clinical penetrance and severity of many monogenic kidney diseases can be influenced by many common variants acting in concert to influence a person's susceptibility to CKD. When used together with the usual clinical examination, PRS can offer an opportunity to enhance the forecasting of early risk and recognize people who may profit from more thorough surveillance or treatment at an earlier stage to prevent the development of permanent renal damage [14]. The biological understanding of CKD has been enriched by fast progress in multi-omics technologies, which allow a comprehensive characterization of molecular changes at different regulatory levels. In summary, genomics, transcriptomics, proteomics, metabolomics, epigenomics, and single-cell analyses are all employed to provide detailed information about the dysfunctions of cells and

their signaling networks through disease pathogenesis, across different tissues. These multimodality approaches provide a means to identify new subsets of molecular biology and mechanisms which are not yet seen by traditional clinical markers [15].

The incorporation of omics data has revolutionized nephrology from descriptive clinical phenotyping to the classification of diseases based on mechanisms. Extensive molecular characterization allows the identification of markers linked to a particular pathological process, treatment target and prognosis and helps to understand the mechanisms at play in various patient populations. These types of system-wide analysis are increasingly necessary to translate molecular discoveries to clinically applicable precision medicine strategies [16]. However, despite all these advances, the progression of CKD is a biologically complex process that is influenced by ongoing cross-talk between inflammation, fibrosis, metabolic dysfunction, vascular dysfunction and impaired tissue repair. These mechanisms contribute differently from person to person and underline the need for personalised approaches that can monitor the dynamic changes occurring within a molecule during the disease process, not just by conventional clinical parameters [17]. Further evidence is also emerging to show that metabolic reprogramming is a key mechanism in the progression of CKD. These changes in energy metabolism, mitochondrial function, lipid homeostasis, amino acid metabolism, and accumulation of uremic toxins lead to a sustained injury to cells, which in turn can drive kidney dysfunction. These metabolic abnormalities have been identified and will open new avenues to prevent and treat patients with a more targeted approach based on the individual's metabolic profile, further deepening the biological underpinnings of precision medicine in CKD [18]. Biological interactions involved in precision nephrology are summarised in Figure 1.

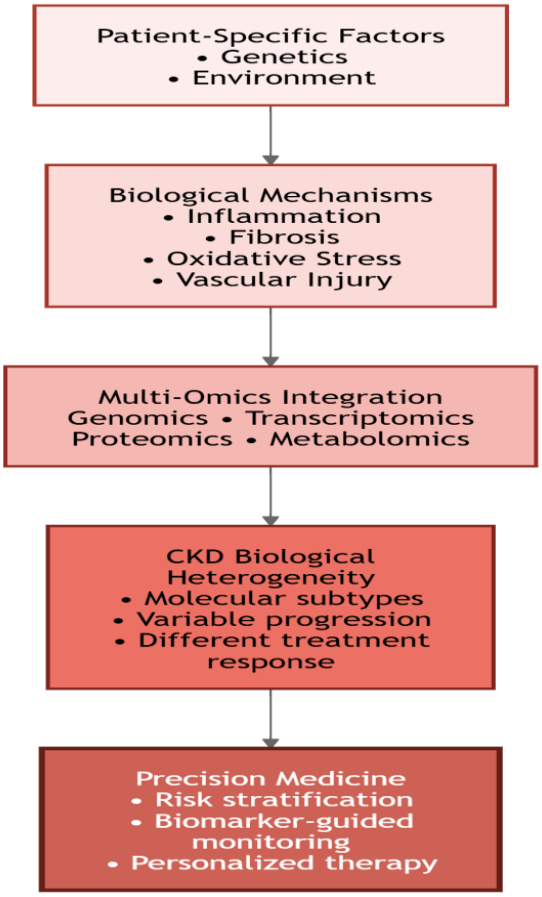

Figure 1. Biological framework of precision medicine in chronic kidney disease

3. Biomarkers for Early Detection, Prognosis, and Disease Monitoring

Much of the shift towards precision medicine has been the ability to identify kidney injury using biomarkers before it becomes clinically apparent and is irreversible. Chronic kidney disease (CKD) is traditionally diagnosed and staged using estimated glomerular filtration rate (eGFR) and albuminuria, which are still essential tools, but not always a good predictor of early pathological changes or progression of the disease. This has led to increased understanding of the biology of CKD and the need for the identification of markers reflecting the underlying biological processes and the capacity to perform individual risk assessment, prognosis and therapy monitoring [19]. Many novel biomarkers have been examined that address some of the problems associated with traditional clinical data. Whereas functional markers are mostly used to reflect established renal damage, emerging markers reflect processes like tubular injury, inflammation, fibrosis, oxidative stress, endothelial dysfunction and repair. They have the potential to enhance diagnostic accuracy, enable earlier intervention and give insights into mechanisms that can aid in personalized disease management [20]. Kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) are some of the most widely researched tubular

injury biomarkers. The expression of KIM-1 is associated with proximal tubular epithelial injury, and it is a marker of ongoing tissue damage, while the expression of NGAL is relatively quick and is related to renal stress and inflammatory activation. Both biomarkers have been shown to be useful to detect subclinical kidney injury, monitor disease activity and identify patients with a higher risk of progression of CKD before significant loss of eGFR [21].

In particular, precision biomarker strategies have gained relevance in DKD as the clinical course is highly variable but is similar in patients with the same metabolic control. New multimodal methods combine circulating markers with digital phenotypes, clinical metrics and patient longitudinal information to provide early risk assessment and personalised monitoring of the disease. These holistic approaches can help to select patients for targeted interventions, as well as to continually monitor the progression of the disease [22]. Another important biological process involved in CKD progression that has come to light is the injury of the podocytes. There has been a lot of interest in the biomarker soluble urokinase plasminogen activator receptor (suPAR) because it is a connection between systemic inflammation and glomerular dysfunction. Experimental and clinical data show that interactions of suPAR, APOL1 risk variants and podocyte integrins directly lead to kidney injury, suggesting that suPAR not only is a prognostic biomarker, but it also might be a therapeutic target for precision nephrology [23]. Across most chronic kidney disease (CKD) etiologies, fibrosis is the common end pathway associated with chronic renal function deterioration, ultimately leading to renal failure. A glycoprotein, secreted by injured tubular epithelial cells, called Dickkopf-3 or DKK3, has been identified as a potential biomarker of progressive renal fibrosis that is triggered by stress. Urinary DKK3 levels have been linked to persistent tubular stress and rapid loss of kidney function, and could help to identify patients with high risk for progressive CKD at an earlier stage in the course of disease than standard measures of kidney function [24].

Multi-omics technologies have greatly expanded the discovery of biomarkers by applying genomic, transcriptomic, proteomic, metabolomic and epigenomic data to create comprehensive molecular profiles. These multidimensional datasets can be leveraged to achieve better identification of biomarker panels that describe disease heterogeneity, more accurately predict disease progression and individualised therapeutic decision-making. Artificial Intelligence also aids this process by recognizing intricate biological patterns that are hard to uncover with statistical methods [25]. Liquid biopsy is an emerging, low-invasive method to assess molecular changes that are organ-specific. Proteins, nucleic acids, lipids and metabolites in EVs, especially those secreted by renal cells (exosomes), represent the pathological processes occurring in the kidney at the time of their secretion. They provide excellent opportunities for early diagnosis, disease monitoring, and evaluation of the therapeutic response and decrease the need for invasive renal biopsy procedures [26]. As the biology and molecular characterization of exosomes continue to develop, their use in the area of diagnostic and therapeutic precision medicine continues to grow in kidney disease [27]. With the growing amount of big clinical and molecular data, artificial intelligence (AI) and machine learning (ML) have taken center stage in risk prediction using biomarkers. The integration of multiple and heterogeneous clinical, laboratory, imaging, and omics data with the use of AI algorithms can be used to detect network relationships that are more complex and nonlinear, which improves predictive value over classical statistical models, as linked to the progression of CKD [28]. Different machine learning methods have been compared, and they show promise of improving early detection of CKD, improving prediction, and supporting individual clinical decision-making, but there is still a need to validate these in a larger clinical setting before they can be widely adopted [29]. Emerging biomarkers represent different aspects of CKD pathologies and may help identify the disease in earlier stages, assess prognosis, and monitor the disease over time, in addition to eGFR and albuminuria, as outlined in Table 1.

Table 1. Emerging biomarkers for precision assessment of chronic kidney disease

Biomarker/ platform	Biological process	Sample type	Potential clinical use
KIM-1	Proximal tubular injury	Urine, blood	Early injury detection and monitoring
NGAL	Tubular stress and inflammation	Urine, blood	Early detection and progression assessment
suPAR	Systemic inflammation and podocyte injury	Blood	Glomerular risk stratification
DKK3	Tubular stress and fibrosis	Urine	Prediction of progressive kidney decline
Cystatin C	Glomerular filtration	Blood	Refined kidney function estimation
Multi-omics panels	Integrated molecular dysfunction	Blood, urine, tissue	Molecular phenotyping and prognosis
Extracellular vesicles	Cell-specific molecular signaling	Urine, blood	Liquid biopsy and treatment monitoring

4. Precision Risk Stratification and Predictive Modeling

Precision risk stratification is the identification of patients with chronic kidney disease (CKD) who are more likely to be clinically stable versus those with a higher risk of rapid progression, kidney failure, cardiovascular disease and/or premature death. While the estimated glomerular filtration rate, albuminuria, age, diabetes mellitus and

blood pressure are some of the common factors used for conventional risk assessment, these factors are only a partial reflection of the biological and temporal complexity of CKD. Predictive modelling is therefore now a key part of precision nephrology as it integrates clinical, laboratory, molecular and longitudinal data to make a personalised prediction of the disease course, and to enable timely therapeutic intervention [30]. Dynamic prediction models are a step up from static risk estimates, and continuously adjust prognosis with the acquisition of new clinical information. Risk estimates can be based on repeated measures of kidney function, albuminuria and other clinical parameters, thus being not only based on baseline parameters but also on changes in disease activity. These models could detect relevant changes in progression risk over time in follow-up and facilitate treatment intensification, nephrology referral, vascular access planning and planning for kidney replacement therapy [31].

Combining multi-omics data provides a chance to improve the risk classification over simple clinical phenotypes. Molecular pathways linked to inflammation, fibrosis, tubular injury, immune dysfunction and metabolic dysfunction can be uncovered from the genomic, transcriptomic, proteomic, metabolomic and epigenomic profiles. These molecular signatures, together with clinical and histopathological data, could help identify biologically distinct subgroups of CKD with similar clinical and pathological features, but variable mechanisms of progression, prognosis and treatment response [32]. Machine learning has also helped to take predictive modelling a step further by capturing the complex and non-linear relationships that exist between many variables. There are several reasons why interpretable machine-learning techniques are especially relevant to the field of CKD: firstly, in order to be clinically useful, the model must be highly predictive, but also enable clinicians to understand which factors underlie an individual person's risk score. Explainable models can be used to measure the impact of factors like kidney failure, protein loss in the urine, anaemia, metabolic abnormalities and comorbid disease, etc., which can enhance transparency and enable clinicians to better interpret the outputs of algorithms and make defensible decisions about their care and management [33].

AI models have demonstrated significant promise in predicting the progression of CKD from EHR data combined with demographic, clinical, laboratory and imaging features, which are routinely collected. They could detect at an earlier stage of the disease those patients who are at risk, and they can help to allocate specialist care and preventive resources more efficiently. However, their performance will require representative training data sets, strict external validation, proper calibration and ongoing surveillance to ensure that they provide unbiased and reliable predictions for a wide range of patient types [34]. Longitudinal clinical information is also useful because the progression of CKD is a dynamic process and can have periods of stability, slow or rapid decline. Models may be informed by changes in laboratory parameters, treatment history and repeated clinical assessments; these may facilitate the separation of static risk from growing risk and provide a better picture of the evolution of the disease. Dynamic prediction, therefore, provides for repeated assessment during the course of follow-up and earlier identification of patients with a course of progression different from the typical clinical course [35]. Digital health technologies are becoming more and more connected with predictive models to support continuous and decentralized risk monitoring. The patient's information captured by EHRs, wearable devices, mobile health applications, home monitoring and remote laboratory surveillance is real-time and can be leveraged by predictive algorithms. This integration enables automated risk alerts, personalised follow-up timelines, timely therapeutic adjustment and more patient engagement, while enabling precision-based clinical decision-making outside of the traditional healthcare environment [36]. There are a variety of currently available precision-risk approaches that vary in the data they require, their interpretability and ability to inform dynamic clinical decisions, as shown in Table 2.

Table 2. Data sources and approaches for precision CKD risk stratification

Approach	Main inputs	Principal output	Clinical value	Key limitation
Conventional risk models	eGFR, albuminuria, age, comorbidities	Kidney-failure risk	Simple and clinically accessible	Limited biological detail
Dynamic prediction models	Repeated clinical measurements	Updated progression risk	Tracks changing disease trajectory	Requires longitudinal data
Multi-omics classification	Genomic and molecular profiles	Molecular CKD subtype	Mechanism-based stratification	High cost and complexity
Interpretable machine learning	Clinical and laboratory variables	Individualized risk estimate	Explains major risk drivers	External validation required
AI-based prediction	Electronic health record data	Early high-risk identification	Processes complex data patterns	Bias and calibration concerns
Digital health monitoring	Wearables and home measurements	Continuous risk updates	Supports remote management	Interoperability and access issues

5. Personalized Therapeutic Strategies in Chronic Kidney Disease

In chronic kidney disease (CKD), personalized therapeutic strategies have emerged as a major focus of precision medicine and are moving beyond standardized guidelines based treatments to treatments that are individualized based on the molecular profile, disease mechanism, and expected therapeutic response of the individual. Despite using conventional treatments to slow CKD in many patients, there is still a great deal of variability in the effectiveness of treatment and outcome of the disease. The combination of biomarkers, molecular phenotyping and clinical parameters in the therapeutic decision-making process provides an opportunity to select the most appropriate therapy, maximize therapeutic efficacy, reduce potential side effects and enhance renal outcomes in the long term [37]. Biomarker-based therapy is a considerable step forward in personalized CKD therapy. New circulating and urinary markers give information regarding the current pathological event (such as glomerular damage, tubular damage, inflammation and fibrosis) and can help guide clinicians to the therapeutic intervention that is most likely to be beneficial for the patient. In addition to enhancing the quality of diagnosis, these biomarkers enable the monitoring of treatment, prediction of therapeutic response, and early detection of disease progression, which help to ensure more accurate clinical decision-making over the course of disease. [38] Renin–angiotensin–aldosterone system (RAAS) inhibitors are still the mainstay of renoprotection therapy due to their beneficial effects on intraglomerular pressure, proteinuria and progressive renal fibrosis. The therapeutic response, however, is highly variable between patients, depending on the etiology of the disease, baseline renal function, genetic makeup and activation of compensatory molecular pathways. Precision medicine strategies aim to recognize patients who benefit most from treatment with RAAS inhibitors and to avoid side effects like hyperkalemia and acute kidney function decline in these individual patients [39].

There has been a significant expansion of the therapeutic setting for CKD since the advent of glucagon-like peptide-1 receptor agonists (GLP-1RAs). These agents were first developed as glucoregulatory drugs but have been shown to have strong renal and cardiovascular protective properties associated with mechanisms of improved metabolic control, decreased inflammation, decreased oxidative stress, and modulation of renal hemodynamics. Evidence is now beginning to emerge to support their personalized use, especially in patients with an elevated cardiometabolic risk profile, type 2 diabetes, and/or overweight or obesity, where treatments can be tailored to the patient's clinical features and coexisting conditions [40]. Sodium-glucose cotransporter-2 (SGLT2) inhibitors have had a revolutionary impact on the management of CKD, offering proven renoprotective effects beyond their glucose-lowering properties. They act in various ways, such as decreasing glomerular hyperfiltration, enhancing tubular function, reducing inflammation, and maintaining structural integrity of the kidney. In the precision medicine context, patient phenotype and other factors such as comorbid conditions, renal function, cardiovascular risk, and concurrent therapies enable selection and optimization of treatment for various CKD patient populations [41]. Identification of disease-specific molecular pathways has not only accelerated the translation of targeted therapies but has also paved the way for drugs that can disrupt disease processes that cause the progression of CKD. New therapeutic strategies do not only aim to achieve generalized hemodynamic control but also address fibrosis, immune dysfunction, oxidative stress, mitochondrial dysfunction, complement activation and cell signaling pathways. An important principle of precision nephrology is the selection of the right therapeutic target based on the prevailing pathogenic mechanism, which will enhance therapeutic effectiveness and reduce the need for unnecessary exposure to therapy [42].

With the development of molecular medicine, there is increasing interest in gene-based therapy for inherited and acquired kidney diseases. Gene editing, gene replacement and vector-mediated gene delivery provide the opportunity to correct the genetic abnormalities present in a pathogenic organ or to alter disease-associated molecular pathways before the onset of irreversible structural abnormalities. While most are still in preclinical and/or early clinical development, they are a promising avenue for personalized treatment of genetically defined kidney disease [43]. RNA therapeutics is another rapidly advanced field of precision medicine. New technologies such as small interfering RNA, antisense oligonucleotides, messenger RNA and microRNA-targeted therapies allow for the specific control of the expression of disease-associated genes. All of these may inhibit pathogenic pathways, without impairment of normal cellular function, providing a very selective way to treat CKD at the molecular level [44]. Circulating ncRNAs have also been revealed to play a therapeutic role by modulating inflammatory, fibrotic, vascular injury and metabolic dysfunction, not only as promising biomarkers, but as targets throughout CKD pathogenesis in parallel [45]. Precision nutrition is an integral part of an individualized CKD treatment plan, along with lifestyle modification. Individual dietary recommendations based on kidney function, metabolic profile, electrolyte balance, nutritional status, comorbid conditions and genetic variability can help optimize metabolic control, decrease disease progression, and improve quality of life. Personalized nutrition is therefore a complementary approach to pharmacological and molecular treatments, meeting the patient-specific physiological needs and complementing the holistic precision-based kidney care [46]. As detailed in Table 3, increasing numbers of clinical phenotypes, molecular mechanisms, comorbidities, and predicted treatment response are being combined together and used for guiding treatment choices for personalized care in CKD.

Table 3. Personalized therapeutic strategies in chronic kidney disease

Therapeutic strategy	Main target or mechanism	Suitable patient profile	Precision application
RAAS inhibitors	Intraglomerular pressure and proteinuria	Albuminuric CKD	Adjusted to response and hyperkalemia risk
SGLT2 inhibitors	Glomerular hyperfiltration and tubular stress	Diabetic and non-diabetic CKD	Selected by kidney and cardiovascular profile
GLP-1 receptor agonists	Metabolic and inflammatory pathways	Type 2 diabetes, obesity, high cardiovascular risk	Aligned with cardiometabolic phenotype
Biomarker-guided therapy	Active injury pathway	Molecularly stratified CKD	Treatment selected by biomarker pattern
Pathway-targeted therapy	Fibrosis, immunity, complement or oxidative stress	Mechanism-defined CKD subgroup	Target matched to dominant pathway
Gene therapy	Pathogenic genetic variant	Monogenic kidney disease	Variant-specific correction or replacement
RNA therapeutics	Disease-associated gene expression	Genetically or molecularly defined CKD	Selective transcript regulation
Precision nutrition	Metabolic and nutritional imbalance	Patients with individualized dietary needs	Diet adapted to stage and metabolic profile

6. Clinical Translation: Opportunities and Challenges

Implementing precision medicine in the context of regular chronic kidney disease (CKD) care is built on the conviction that new biomarkers, predictive equations, and customized treatment options are reliable and have statistically and clinically significant impact. Before precision tools have an impact on treatment decisions, they must be established as being analytically, clinically, and clinically valid. Multi-biomarker algorithms are examples of this, as they integrate molecular signals with computational modelling to identify patients with a greater risk of progressive kidney function decline and are dependent on the ability to be reproducible, standardized in the laboratory, and perform across different clinical populations [47]. One of the big problems in CKD research is translating discovery of mechanisms to clinical use. Experimental research has revealed multiple inflammatory, fibrotic, vascular, metabolic and tubular damage pathways; however, only a limited number of findings have moved forward to being proven in diagnostic tests or treatments. To successfully translate basic science, clinical investigation, development of biomarkers, and therapeutic trials, study designs should reflect the heterogeneous nature of CKD and not be considered as a single entity [48]. The use of big data has opened new potential avenues for precision nephrology in the clinical setting. Big data from electronic health records, imaging databases, proteomic data, genomic data, and longitudinal laboratory data can be combined to enable predictive and prescriptive analytics for patient care. However, fragmented data sources, interoperability problems, poor data quality, and the need for analytical frameworks that are transparent and can be reliably embedded into daily clinical practice are challenges to successful implementation [49].

Standardization of diagnostic strategies is another clinical translation element that is important. Recent advances in the use of more biologically appropriate and equitable approaches for assessing kidney disease include the development of race-independent estimated glomerular filtration rate equations, the use of genetic data and an increased use of cystatin C. Before these innovations can be widely adopted, however, they need to be standardized in the lab, have validated clinical thresholds, and be interpreted consistently across patient cohorts [50]. Although significant advances have been made in science, there remains a great gap between the evidence and day-to-day nephrology practice. Many patients encounter a number of problems when it comes to the diagnosis of their disease and access to specialist support, failure to access evidence-based treatment and poor access to advanced molecular diagnostics. Health system constraints, health system infrastructure differences, and the lack of integration of precision medicine in clinical pathways are major barriers to precision medicine adoption for individualised CKD management [51].

There are also new regulatory and ethical issues to address with the clinical use of precision medicine. Rigorous testing of biomarkers, standardized reporting and transparency in regulation is required prior to widespread clinical use of biomarker assays, genomic testing, and AI-powered decision support systems. Besides, there are issues regarding patient privacy, patient informed consent, algorithmic bias, data management, and access to care to consider when implementing precision medicine in healthcare systems. One of the obstacles to widespread use is economic and operational difficulties.. Multi-omics profiling, advanced molecular diagnostics and digital health technologies have significant financial requirements and require specific infrastructure and trained personnel. Further, the lack of standardized clinical workflow, reimbursement policies, laboratory harmonization, and clinician education can help to limit the implementation of precision approaches in standard nephrology practice. Together, these challenges highlight the need for both scientific innovation and comprehensive validation, standardization, regulation, and healthcare

access and sustainability for the successful clinical adoption of precision medicine. Overcoming these barriers is crucial for facilitating the widespread use of precision approaches in different CKD patient populations. Figure 2 shows the key steps required to bring precision medicine to the bedside of the nephrologist.

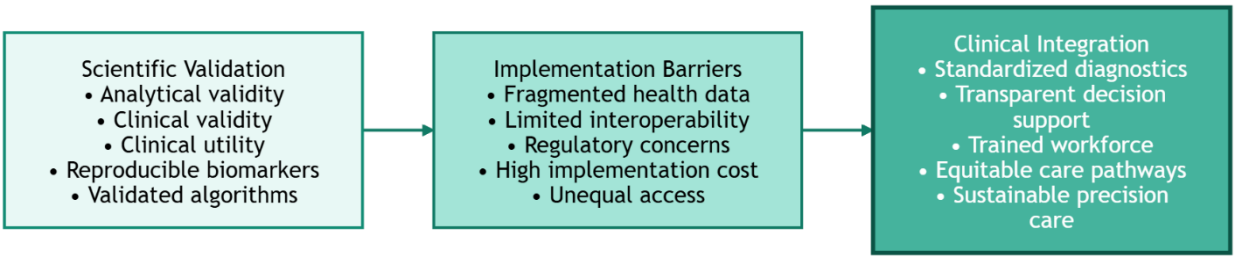

Figure 2. Clinical translation pathway for precision medicine in chronic kidney disease

7. Future Perspectives

Smooth integration of molecular biology, computational science and patient-oriented clinical care will be key to the future of precision medicine in chronic kidney disease (CKD). Despite significant progress in the discovery of new biomarkers, the prediction of risk and personalized treatment, the next steps of precision nephrology will need more holistic solutions that can address the bio-molecular complexity of CKD on several levels. It is expected that continued innovations will change disease classification from "phenotype-based" to "mechanism-based" precision care [52]. The convergence of multi-omics technologies with cutting-edge machine learning holds promise as an emerging direction. Concurrently analyzing genomic, transcriptomic, proteomic, metabolomic, epigenomic and single-cell data could unravel the mechanisms of the disease and uncover novel molecular subtypes of CKD. These high-dimensional datasets are thought to be interpreted by applying machine learning algorithms, which will lead to better disease classification, earlier identification of progression pathways, and identification of personalized therapeutic targets depending on the underlying biology, not traditional clinical parameters [52]. AI is expected to be a more integral part of the continuum of CKD management as well. In the future, AI-powered platforms could incorporate electronic health records, lab results, imaging, outputs from wearables, medication adherence, patient-reported outcomes, and other data to deliver real-time clinical decision support. These smart systems can be used to enhance diagnostic capabilities, automate risk stratification, guide therapeutic choices, aid with personalised follow-up, and support providers with interpretable and constantly updated predictive tools [53]. More innovations will be developed to bring precision medicine to the rest of the kidney diseases, including rare and inherited kidney diseases. The growing ability to sequence the genome and international collaborative studies will help elucidate common molecular pathways in various renal diseases, enable earlier diagnosis, more precise disease classification and the development of specific therapies. More harmonization of clinical registries and global research networks can help to further accelerate evidence generation for patient populations which have been underrepresented in clinical studies [54]. Another avenue of potential precision nephrology is regenerative medicine. Stem cell, tissue engineering, organoid, EVs, and cell-based approaches to repair renal tissue rather than just slowing down the disease have the potential to develop. While these treatments are still in their early stages, advances in cell engineering, biomaterials, and translational research could eventually lead to novel therapies that are personalized to repair kidney structure and function in specific patient subsets [55]. The major innovations to emerge in the future of precision nephrology are shown in Figure 3.

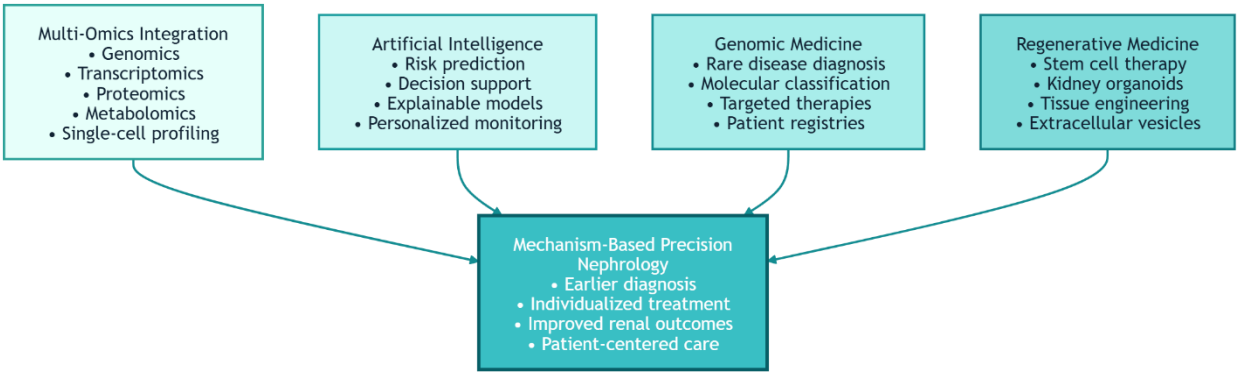

Figure 3. Emerging directions shaping the future of precision nephrology

All of these developments point towards a future of CKD management that goes beyond the prediction of risk status for an individual to a precision medicine of the future. The multi-omics technologies, the artificial intelligence, genomic medicine and regenerative therapeutics are poised to revolutionize disease classification, therapeutic options, and prognosis in the long run. To realize this vision will require a multidisciplinary approach, clinical validation, equitable implementation and continued integration of scientific innovation into clinical nephrology.

8. Conclusion

Precision medicine is a paradigm shift in the way that CKD could be treated in the future because of its biological and clinical heterogeneity. New biomarkers, multi-omics profiling and liquid-biopsy techniques can be used in conjunction with traditional methods to detect disease earlier, to classify it mechanistically, and to monitor the disease more accurately. They could be better integrated with dynamic risk models, artificial intelligence and with other longitudinal clinical data, for better prediction of kidney function decline and to identify patients who need more rigorous monitoring or targeted intervention. In addition, the shift from standard treatment to personalized treatment options such as biomarker-driven pharmacotherapy, pathway-specific drugs, gene and RNA therapeutic, and precision nutrition are complementary to the personalization of care. Despite these advances, the regular use of RUs in clinical practice is still hindered by the lack of external validation, disjointed data management, regulatory concerns, cost, infrastructure requirements, and access issues. Standardized assays, interoperable platforms, clinically representative patient cohorts, transparent algorithms, and prospective evidence of clinical utility and cost-effectiveness will thus be required in the process of translation. It is possible that molecular science, informatics and patient-centred care may transform the management of CKD in the future, but this will require scientific rigor, clinical relevance and the effective translation of precision tools into the health care system irrespective of its context.

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