

# Personalized Medicine in Polycystic Kidney Disease: Emerging Precision Therapeutics and Future Clinical Perspectives

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**Abstract:** *Polycystic Kidney Disease (PKD) is a hereditary, progressive kidney disease that involves the creation of numerous cysts containing fluid which progressively damage the structure and function of the kidneys. There are mainly two forms of the disease; one is Autosomal Dominant Polycystic Kidney Disease (ADPKD) and the other is Autosomal Recessive Polycystic Kidney Disease (ARPKD). Both are linked to genetic mutations in tubular cells. Treatments for conventional therapy are largely directed towards symptom control and avoiding renal failure, but in recent years, advances in genomics, molecular still life and pharmacogenomics, and biomarker research have allowed for the introduction of personalized medicine as a potential avenue for the management of PKD. One goal of personalized medicine is the targeted diagnosis, prognosis and treatment for an individual patient related to the individual patient's genetic and molecular fingerprint. This review covers the molecular bases of pathogenesis of PKD, role of genetic testing, monitoring through the use of biomarkers, targeted therapy, pharmacogenomics, and newly developed technologies like CRISPR gene editing and AI. It therefore emphasises the key challenges and prospects of precision nephrology in PKD.*

**Keywords:** Polycystic Kidney Disease, Personalized Medicine, ADPKD, Precision Nephrology, Biomarkers, Pharmacogenomics, Tolvaptan, CRISPR

## I. INTRODUCTION

Polycystic Kidney Disease (PKD) is a common hereditary renal disease in the world, and it is a very important cause of chronic kidney disease and end-stage renal failure. The disease is progressive, resulting in the presence in the kidneys of numerous fluid-filled cysts, kidney enlargement, renal damage, fibrosis and progressive failure in function. There are also several extrarenal complications associated with PKD including liver cysts, cardiovascular defects, hypertension and intracranial aneurysms. Such complications greatly impair the lives of those suffering and can produce high long-term health care costs.

There are two basic types of PKD, such as Autosomal Dominant Polycystic Kidney Disease (ADPKD) and Autosomal Recessive Polycystic Kidney Disease (ARPKD). ARPKD is more common and typically occurs in infancy or childhood, whereas ADPKD is more common and typically occurs in adulthood. Mutations in the genes that produce two proteins, PKD1 and PKD2, cause the majority of cases of ADPKD; mutations of the gene for another protein called PKHD1 cause most cases of ARPKD (Harris and Torres, 2014). Although the diseases have similar pathological features, there is a distinct genetic heterogeneity and environmental factors which account for the different severity and progression of the disease in patients (Torres et al., 2007).

Therapy for PKD is largely targeted at symptomatic treatment, including blood pressure control, pain control, dialysis and renal transplantation. But these methods are not specifically targeted at the molecular mechanisms of cyst formation and progression. With recent developments in molecular genetics, genomics, and targeted therapeutics, thus, the focus has been shifted towards personalized medicine approaches. The objective of precision medicine is to tailor



the therapies to the patient’s unique genetic makeup, molecular processes and severity of disease, which will enhance therapeutic outcome as well as minimize adverse effects (Menezes and Germino, 2019).

**II. GENETIC BASIS AND MOLECULAR PATHOPHYSIOLOGY OF POLYCYSTIC KIDNEY DISEASE**

The molecular causes of familial PKD are largely mutations of genes that maintain normal architecture of renal tubules and normal channels of cell-cell communication and signal transduction. The polycystin-1 (PKD1) and polycystin-2 (PKD2) genes encode polycystin-1 and polycystin-2 protein respectively which are localized in the primary cilia of renal epithelial cell. These proteins are involved in multiple functions including calcium signaling, mechanosensation, differentiation and tubular integrity (Harris and Torres, 2014).

Mutations in these genes affect the ability to regulate calcium levels in the internal environment and lead to activation of multiple abnormal intracellular calcium regulatory pathways that are also linked to cystogenesis. A decrease in the internal calcium triggers the cyclic adenosine monophosphate (cAMP) pathways which lead to the proliferation of the epithelial cells and a loss of fluid into the cysts. Increased levels of cAMP also open chloride channels and lead to further cystic expansion. Gradually, these cysts compress the normal nephrons, reduce blood flow and progress the renal dysfunction (Grantham, 2008).

The mammalian target of rapamycin (mTOR) signaling pathway is another one of the pathways that is involved in the progression of a case of PKD. Uncontrolled mTOR activation leads to excess cell proliferation, protein production and Cyst growth. Moreover, chronic inflammation, oxidative stress and fibrosis compounds renal damage and exacerbates the progressive loss of kidney function. The knowledge gained from these molecular mechanisms has led to important insight into the development of targeted and personalized therapeutic mechanisms for patients with PKD (Chebib and Torres, 2018).

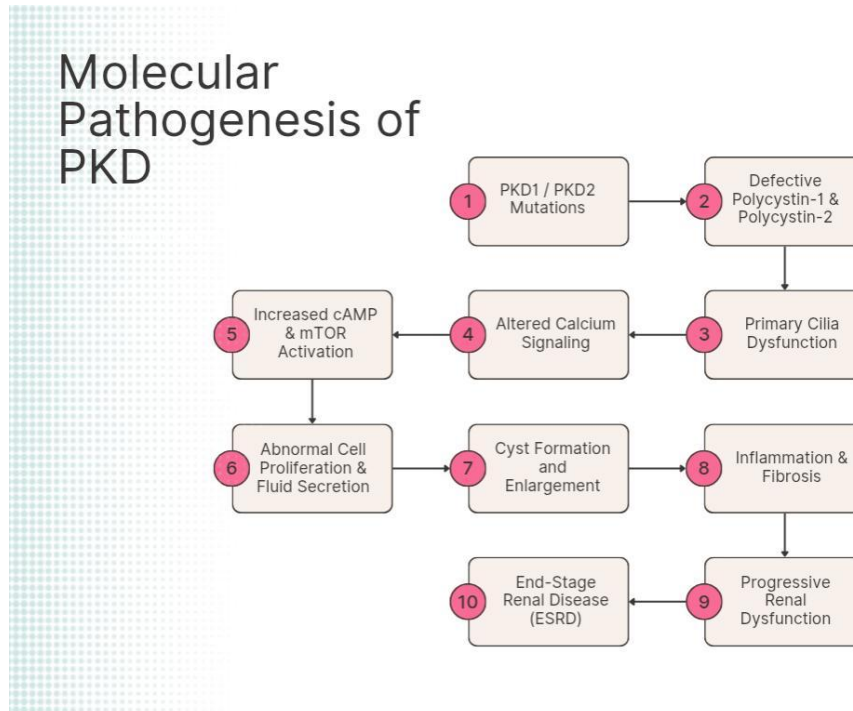


Figure 1. Molecular pathogenesis of Polycystic Kidney Disease showing PKD1/PKD2 mutations, altered calcium signaling, cAMP and mTOR activation, cyst formation, inflammation, fibrosis, and progression toward end-stage renal disease.



### **III. ROLE OF PERSONALIZED MEDICINE IN PRECISION DIAGNOSIS AND RISK STRATIFICATION OF PKD**

Personalized medicine is a patient-personalized health care strategy in which diagnosis and treatment is personalized based on a patient's genotype, molecular and physiological features. In PKD, Precision medicine has become more and more significant due to variations in disease severity and response to treatments between patients. Specific interventions based on the gene mutation can be provided, high-risk individuals identified, and progression of the disease predicted (Menezes and Germino, 2019).

Early and accurate diagnosis is one of the key benefits of personalized medicine for PKD. Genetic screening allows to detect disease-causing mutations even before clinical symptoms are observed. It is especially critical in families with a history of PKD for it to be diagnosed early so that monitoring and prevention therapies can be implemented. The ability to make a precise diagnosis also allows distinguishing PKD from other cystic kidney diseases when the clinical presentation is similar (Bergmann et al., 2018).

Secondly, risk stratification is crucial component in precision nephrology. Several items of clinical data (mutations, total kidney volume, hypertension and renal function) are used for disease prediction. In general, patients with mutations of the genes PKD1 are more aggressive than those with mutations of the gene PKD2. Personalized risk assessment thus serves as a tool to allow the clinician to choose a suitable therapy and to gain the best possible for the long-term management of patients (Cornec-Le Gall et al., 2016).



Figure 2. Framework of personalized medicine approaches in Polycystic Kidney Disease (PKD) including genomics profiling, imaging biomarkers, molecular biomarkers, artificial intelligence, risk stratification, precision therapeutics, and patient-centered care.

### **IV. GENETIC TESTING, PHARMACOGENOMICS AND MUTATION-SPECIFIC THERAPEUTIC APPROACHES**

The use of genetic testing is a significant and important method in the management of PKD. Improvements in next-generation sequencing (NGS) technology have greatly aided identification of pathogenic mutations for inherited renal diseases. Typical genes that are often studied are: currently, PKD1, PKD2, PKHD1, GANAB, and DNAJB11 can be studied. Genetic testing can help with early diagnosis, prenatal screening, family counseling and prognosis (Bergmann et al., 2018).



Another key factor in personalized medicine is pharmacogenomics, which looks at genetic differences among people and how it affects their reactions to drugs. In PKD, pharmacogenomic research provides clues to identify patients who are likely to respond to a more targeted approach like those with Tolvaptan. Such methods enhance the effectiveness of the therapy but reduce any negative side effects of the medications. Patient-specific selection of drugs can be particularly crucial because effective treatment is long-term and patient responses and side-effects may change over time (Gansevoort et al., 2016).

Precision nephrology is also a research area where mutation-specific therapeutic strategies are also being discussed. This study is looking at drugs that will be targeted towards specific molecular pathways that individuals with the genetic change are altering. These might give better disease control than conventional blanket treatment. New technologies have progressed, and mutation-directed treatments are likely to play an important role in the treatment of PKD in the future (Ong et al., 2015).

#### **V. BIOMARKER-GUIDED MONITORING AND IMAGING-BASED PRECISION ASSESSMENT IN PKD**

In personalized medicine the identification of biomarkers is important to assess disease activity, drug efficiency, or the disease outcome. There have been two main types of molecular biomarkers and imaging-based biomarkers which are both commonly used for disease monitoring in PKD. Magnetic Resonance Imaging (MRI) has been identified as one of the most reliable and widely-used imaging techniques for estimating Total Kidney Volume (TKV); which is also one of the best players to predict disease progression (Perrone et al., 2017).

Other biochemical markers such as serum creatinine, neutral gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and cystatin C have also been studied as markers of progression of PKD. These biomarkers are very useful for the evaluation of renal function, tubular damage, and inflammatory response linked with cystogenesis. An increased concentration of one or more vasopressins and inflammatory cytokines has also been associated with increasing disease activity (Chebib and Torres, 2018).

Microbiological monitoring of treatment effectiveness occurs via biomarker monitoring which can be used to change the therapeutic management of the treatment. A personalized approach is crucial as disease course is very variable from one patient to another. Therefore, combination of molecular biomarkers with image technologies could provide a better early diagnosis and prognosis, as well as optimize personalised treatment approaches for clients with PKD (Chapman et al., 2015).

#### **VI. TARGETED THERAPEUTICS AND PERSONALIZED DRUG DEVELOPMENT IN PKD MANAGEMENT**

Targeted therapeutics have revolutionized the way that you approach treating PKD. Unlike standard treatments (which are more likely to focus on relieving symptoms), targeted drugs will focus, directly, on blocking molecular pathways that can stimulate the formation of cysts and their progress. The development of the vasopressin V2 receptor antagonist, Tolvaptan, which is approved to slow the progression of ADPKD, is one of the greatest windfalls of this field (Torres et al., 2012).

The mechanism of action of tolvaptan is inhibiting the accumulation of intracellular cAMP in renal tubular cells, which results in inhibition of the growth of the cysts and a delay in kidney enlargement. Tolvaptan has been shown to slow ONRF and to slow the progression of the disease in certain patients in the clinical studies. Side effects that can be associated are also polyuria, thirst and liver toxicity, so monitoring should be on an individual basis during treatment (Gansevoort et al., 2016).

Other therapeutic targets include mTOR inhibitors, somatostatin analogues, and activators of the AMP-activated protein kinase (AMPK), like metformin. These agents inhibit the abnormal proliferation of cells, curb the excessive production of fluid, and enhance metabolism control. While certain treatments are still being studied, precision drug development offers great potential for the development of more personalized approaches to treating PKD (Chebib and Torres, 2018).



**Table 1. Personalized Therapeutic Approaches and Clinical Applications in Polycystic Kidney Disease**

Personalized Approach	Description	Clinical Importance in PKD
Tolvaptan Therapy	Tolvaptan blocks vasopressin V2 receptors and reduces intracellular cAMP levels responsible for cyst enlargement.	Helps slow kidney cyst growth and delays progression toward renal failure in ADPKD patients.
mTOR Inhibitor-Based Therapy	Drugs such as sirolimus and everolimus target abnormal mTOR signaling involved in cellular proliferation.	May reduce cyst expansion and improve disease control in selected patients.
Metformin and AMPK Activation	Metformin activates AMPK pathways that regulate cellular metabolism and suppress cystogenesis.	Considered a potential supportive therapeutic strategy for long-term PKD management.
Genetic Testing and Mutation Analysis	Identification of PKD1, PKD2, and other associated mutations using genomic sequencing technologies.	Enables early diagnosis, family screening, and personalized risk assessment.
Biomarker-Guided Monitoring	Biomarkers such as TKV, NGAL, KIM-1, and cystatin C are used to evaluate disease progression.	Assists clinicians in monitoring renal injury and therapeutic response.
CRISPR-Cas9 Gene Editing	Advanced genome editing technology designed to correct disease-causing mutations.	Represents a promising future approach for mutation-specific PKD therapy.
Artificial Intelligence and Machine Learning	AI-based tools analyze imaging and genomic data for prediction of disease progression.	Supports precision diagnosis and individualized treatment planning.
Patient-Centered Precision Care	Combines genetic profile, clinical symptoms, imaging findings, and lifestyle factors for individualized management.	Improves treatment effectiveness and enhances quality of life in PKD patients.

## VII. EMERGING ROLE OF GENE EDITING, CRISPR TECHNOLOGY AND RNA THERAPEUTICS IN PKD

Precision nephrology has brought ways of Precision genome editing technology and gene therapy as revolutionary approaches. CRISPR-Cas9 technology has the potential to make precise changes to disease-causing genes to correct mutations seen with PKD. The scientists are now studying what is needed to repair the mutations that cause PKD1 and PKD2 to form cysts and cause the disease, and to prevent the mutations from occurring.

As antisense oligonucleotides and RNA interference (RNAi) therapies become known, they are also now gathering interest in the field of PKD. These treatments try to block the process of abnormal gene expression and to block the cystogenic pathways on the molecular level. RNA therapeutic based agents can also be more selective and have less systemic side effects than traditional pharmacologic therapies (Devuyst et al., 2014).

These cutting-edge technologies are still mostly in developmental stages, but are the exciting steps in personalized medicine. There needs to be more research and clinical trials to check long-term outcomes, safety and ethical implications of gene editing therapies in humans (Menezes and Germino, 2019).



## **VII. ARTIFICIAL INTELLIGENCE, MULTI-OMICS TECHNOLOGIES AND FUTURE PRECISION NEPHROLOGY**

Artificial Intelligence (AI) and machine learning technologies are becoming more and more embedded in nephrology and the improvement of diagnosis, prognosis and therapeutic decision-making. AI-driven systems can scan massive amounts of imaging data and identify early signs of cyst formation, as well as analyze the total kidney volume and more accurately predict the course of the disease than traditional approaches.

Precision nephrology is also undergoing a revolution with the advent of multi-omics technologies, such as genomics, transcriptomics, proteomics, metabolomics and epigenomics. These methods can offer fully detailed information regarding the molecular mechanisms involved in PKD, and enable the identification of new therapeutic targets. Seamless integration of multi-omics data with “AI” based computational models could help refine risk stratification and treatment planning for patients (Bergmann et al., 2018).

Long-term disease management is further enhanced by digital health technologies, like telemedicine platforms, wearable monitoring devices and remote patient management systems. These technologies can improve patient engagement, enable ongoing monitoring and aid in delivering personalized healthcare. Hence, the convergence of AI and omics technologies is anticipated to pave the way for transformative precision medicine strategies in the future for PKD (Chapman et al., 2015).

## **VIII. CHALLENGES, ETHICAL CONCERNS AND CLINICAL LIMITATIONS OF PERSONALIZED MEDICINE IN PKD**

Despite all the great strides, there are still some challenges to overcome in implementing personalized medicine in PKD. One of the significant challenges is the costs associated with genetic testing, molecular diagnostics and targeted therapeutics. In developing countries, many of the advanced precision based technologies are not available to patients due to lack of financial resources and health care infrastructure.

Ethical issues are important challenges in genomic medicine as well. The genetic testing also poses questions on the subjects of patient confidentiality, data protection, informed consent and genetic discrimination. Early genetic diagnosis can cause psychological stress that can influence patients and families as well. Thus, ethical principles and governance structures are crucial to the safe clinical use of precision medicine (Devuyt et al., 2014).

One additional drawback is that there are disparities in patient responses to treatments. This is because there are differences in the type of mutation, environmental exposure, and disease severity which are present in not everyone. Further, there are a number of promising new treatments, such as the CRISPR-based therapeutics, that have yet to be fully evaluated in clinical trials for widespread use. These will need to be bridged for the successful integration of personalized medicine into everyday nephrology care (Ong et al., 2015).

## **IX. FUTURE PERSPECTIVES AND CLINICAL TRANSLATION OF PERSONALIZED MEDICINE IN PKD**

The prospect of personalized medicine in PKD is very promising, as rapid progress in the fields of genomics, molecular therapeutics and computational biology continues. Current studies aim to discover new markers for diagnosis, as well as new drugs against mutations and new markers for mutation-specific diagnosis. Treatment strategies to come will likely be multimodality, attacking several molecular targets at once.

Other important topics of research interest in the field of PKD include stem cell therapy and regenerative medicine. These methods could contribute to restoring the damaged kidney tissues and to improved renal function in those who are affected. Regenerative nephrology is still in an early stage of development, but promising results may benefit treatment in the long-term (Chebib and Torres, 2018).

The use of AI-driven diagnostics, gene editing technologies, and multi-omics analysis will be instrumental in advancing the journey toward personalized healthcare. Precision medicine can one day help doctors forecast disease and prevent



complications with the utmost accuracy and offer the most effective and safest treatment for a particular patient (Menezes and Germino, 2019).

### X. CONCLUSION

Personalized Medicine has become a revolutionary practice in the diagnosis and treatment of Polycystic Kidney Disease. The genome, molecular biology, pharmacogenomics, biomarker discovery, targeted therapeutics and the use of artificial intelligence (AI) have brought many advances in understanding disease mechanisms, and new possibilities for patient care tailored to individual needs.

Precision medicine approaches such as genetic testing, biomarker use, targeted drug therapy, and gene editing techniques could help slow the progression of the disease, minimize complications and enhance quality of life for people living with PKD. Developing patient-specific therapeutic approaches is still a long way from being achieved, with a number of scientific, ethical and economic hurdles yet to be resolved, but continuous progress in precision nephrology holds promise of further advances in the near future. Personalised medicine is thus a key step forward for the future treatment of inherited renal diseases.

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