Kidney Diseases

Review Article

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Advances in Diagnosis and Treatment of Inherited Kidney Diseases in Children

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Abstract
Background: Inherited kidney diseases (IKDs) in children pose unique diagnostic and therapeutic challenges. IKD significantly impact patient quality of life, morbidity, mortality, and cost to the healthcare system. With over 150 genetic abnormalities, they account for approximately 30% of cases requiring renal replacement therapy. There is an urgent need to advance both diagnosis and treatment strategies. In this review, we present recent advances in diagnosis and treatment for facilitating personalized treatment approaches. ***Summary:*** The diagnostic landscape for IKDs have evolved significantly, emphasizing precise genetic identification and classification of these disorders. Recent advancements include the refinement of genetic testing techniques, such as whole exome sequencing, which has improved the accuracy of diagnosing specific diseases and facilitated early intervention strategies. Additionally, this review categorizes IKDs based on genetic abnormalities and clinical manifestations, enhancing understanding and management approaches. Finally, it summarizes the corresponding treatment, and lists the application of emerging therapeutic options such as gene therapy and organoids, which show promise in transforming treatment outcomes. ***Key Messages:*** This review summarizes the common types of IKDs in children, including their diagnosis and treatment advances, and provides an update on the status of gene therapy development for these disorders.

Introduction

Inherited kidney diseases (IKDs) represent a significant pediatric health challenge, encompassing over 160 distinct disorders with a prevalence of approximately 60–80 cases per 100,000 total population in Europe and the USA [1, 2]. Since the kidney is involved in vital processes including water and electrolyte balance, blood pressure regulation, acid-base homeostasis, etc. The clinical manifestations of IKDs include renal function impairments and other multisystem complications, such as hearing impairment, visual disturbances, hematological abnormalities, multiorgan cysts, and intracranial aneurysms. Compared to adults, IKDs in children

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progresses aggressively and can rapidly lead to end-stage renal disease (ESRD). The classification of IKDs remain diverse and debate and the commonly used classification system by Devuyst et al. [2], which categorizes these conditions based on abnormalities in kidney growth, structure, and function. Congenital anomalies of the kidney and urinary tract (CAKUT) and ciliopathies represent renal growth and structural abnormalities; glomerular diseases, renal tubular and metabolic diseases, and nephrolithiasis are renal function abnormalities.

Innovations in multi-omics technology have provided many new markers for kidney disease, but the diagnosis of hereditary kidney disease still primarily relies on genetic testing, including targeted gene panels, whole-exome sequencing, and whole genome sequencing. To date, more than 625 genes have been implicated in monogenic kidney diseases, with CAKUT and ciliopathies accounting for 50%, glomerular diseases and renal tubular accounting for 14%, and metabolic diseases accounting for 24% [3]. Accurate genetic diagnosis may enable better treatment beyond current symptomatic management and renal replacement therapies. Patients with early-stages IKDs generally receive symptomatic and supportive treatment, but as the disease processes to ESRD, renal replacement therapy is needed, including hemodialysis, peritoneal dialysis, and kidney transplantation [4]. In addition, nearly 80% of children and over 10% of adults who require renal replacement therapy have IKDs [2]. All these pressing issues underscore the urgent need for innovative therapeutic approaches.

With advancements in gene editing technology, gene therapy has demonstrated wider applications in genetic kidney diseases, making it a promising therapeutic approach. As a leading approach for hereditary diseases, gene therapy holds significant potential for the treatment of IKDs. This review examines current research and emerging treatments, aiming to provide a comprehensive overview of advancements in gene therapy and other promising treatment strategies.

Due to genetic heterogeneity, overlapping clinical features, and complex pathophysiology, currently, there is no internationally recognized classification system for pediatric genetic kidney diseases. This review categorizes them based on the genetic mutations leading to pathology, including congenital anomalies of the urinary system, hereditary glomerulopathies, hereditary tubulopathies and genetic metabolic disorders, ciliopathies, and pediatric nephrolithiasis (Fig. 1). This section provides a comprehensive overview of the clinical features and pathogenic genes associated with IKDs, aiming to improve clinicians' early diagnostic and differential diagnostic capabilities while minimizing the risk of misdiagnosis. Our goal is to equip urologists and nephrologists with a thorough understanding of the latest advancements in genetic testing for kidney diseases, detailing various available testing methodologies, including next-generation sequencing and gene panels, as well as the importance of genetic counseling. Additionally, we summarize online tools for analyzing the pathogenicity of mutations, which serve as valuable resources for clinicians to more effectively interpret genetic variants. Emerging advanced treatment strategies, such as gene therapy and the use of kidney organoids, are also discussed, highlighting their potential to transform patient management and treatment outcomes. By integrating detailed genetic insights with practical applications and cutting-edge treatment options, this section highlights the critical of precision medicine in the diagnosis and management of IKDs, marking a significant advancement in the field.

Common IKDs in Children

Congenital Anomalies of the Kidney and Urinary Tract

CAKUT represent a group of diverse diseases characterized by congenital malformations of the kidneys and urinary system, including renal, ureteral, bladder, and urethral structures (Fig. 1). As a significant cause of chronic kidney disease (CKD) in children, CAKUT accounts for 20–30% of all congenital malformations and occurs in about 3–6 in every 1,000 newborns. These conditions can be life-threatening during the embryonic or neonatal periods [5]. The incidence of these anomalies can be influenced by genetic factors and environmental exposures during pregnancy, such as maternal diabetes, certain medications, or nutritional deficiencies in folate and iron. Aroud 50 pathogenic genes have been identified, including PAX2, HNF1B, EYA1, SIX1, and SALL1, typically following an autosomal dominant inheritance pattern [6].

Inherited Glomerular Diseases

Inherited glomerular diseases, a major form of genetic kidney diseases in pediatric and adolescent populations, are caused by genetic mutations that manifest clinically as hematuria, proteinuria, edema, hypertension, and varing degrees of renal impairment. The overall incidence of inherited glomerular diseases in children estimated be around several tens to a few hundred cases per 100,000 individuals. The most common form in children include

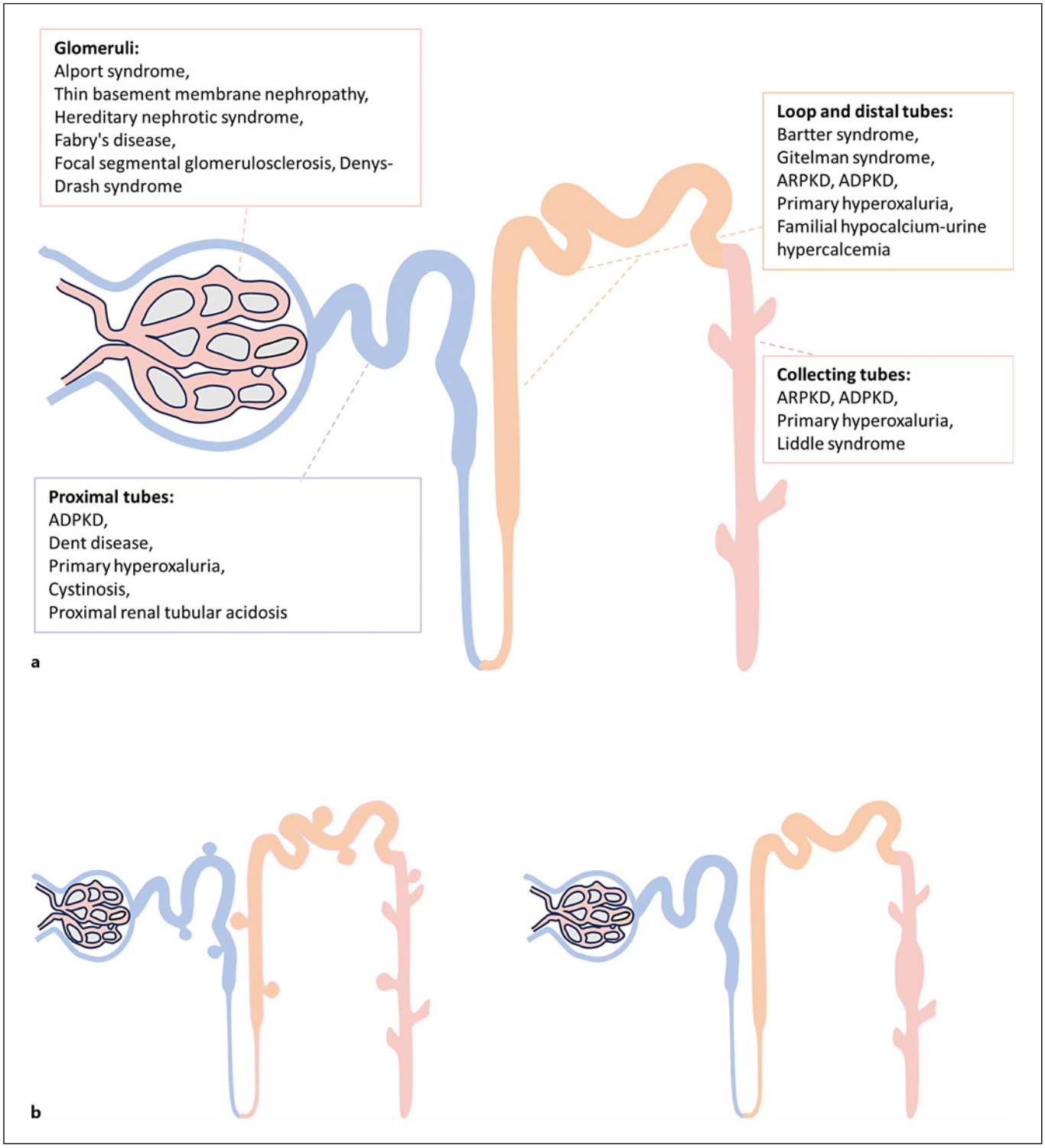

Fig. 1. Schematic catalog outlines the major IKDs in children. **a** The onset sites and pathogenic genes of common hereditary nephropathy in children. **b** The main pathogenic genes of ADPKD are *PKD1*, *PKD2*, and the main affected parts of the kidney.

Alport syndrome (AS), thin basement membrane nephropathy (TBMN) and congenital nephrotic syndrome (CNS). AS, also known as hereditary progressive nephritis, is an inherited progressive glomerular disorder that typically presents hematuria, proteinuria, and progressive renal insufficiency. AS has an incidence of 1 in 5,000 [7], accounting for 12.9% of new ESRD cases in children [8]. Based on its genetic mode, AS is divided into X-linked dominant AS (accounting for about 80–85% of cases, caused by *COL4A5* mutations), autosomal recessive AS (ARAS, accounting for about 15% of cases, caused by *COL4A3* or *COL4A4* mutations), and autosomal dominant AS (accounting for about 5% of cases, caused by *COL4A3* or *COL4A4* mutations). With the increasing emphasis on rare diseases and the expanded application of genetic testing, substantial research advances have been made in AS diagnosis and treatment in recent years.

TBMN, known as benign familial hematuria, is characterized by persistent microscopic hematuria with rare progression to kidney failure. The hallmark of TBMN is the thinning of the GBM to less than 200 nm, detectable via electron microscopy. The prevalence of TBMN in the general population is 1~2%. TBMN is typically inherited in an autosomal dominant pattern, with approximately 40% of cases involving detectable *COL4A3* and *COLA4A4* gene mutations, primarily in heterozygous form [9].

CNS, now known as podocytopathy, is a heterogeneous disease characterized by massive proteinuria, hypoproteinemia, and edema in neonatal period or within the first 3 months of life, primarily caused genetic defects in podocytes. The annual incidence of CNS undulates between 1 and 3 cases per 100,000 children, with 80% of cases is steroid-resistant nephrotic syndrome (SRNS) [10, 11]. Most patients with CNS develop proteinuria in the first few days of life and progress rapidly to ESRD between the ages of 2 and 8 years. CNS is frequently caused by mutations in genes encoding glomerular filtration barrier structural proteins or other related genes [12, 13]. Around 60 genes were associated with CNS, and 27 genes related with SRNS, including the *ADCK4* gene [14]. *NPHS1* and *NPHS2* mutations are observed in most patients, and *LAMB2*, *PLCE1*, and *WT1* mutations are prevalent in children with SRNS diagnosed within the first year of life [15].

Renal Ciliopathies

Renal ciliopathies are caused by mutations affecting primary cilia, which are essential for tissue development and signal transduction, leading to kidney and systemic abnormalities. Renal ciliopathies typically manifest in the form of kidney dysfunction and cyst development [16, 17]. The primary types of renal ciliopathies in children include polycystic kidney disease (PKD), nephronophthisis (NPHP), Bardet-Biedl Syndrome (BBS), and Meckel-Gruber Syndrome (MKS) [18]. Over 950 cilia-related genes have been discovered, and over 180 established ciliopathy-associated proteins have been linked to renal ciliopathies, including *PKD1-PKD2, BBS1-BBS18, MKS1, TMEM67, CEP290, RPGRIP1L* and *NPHP1-NPHP13*.

PKD is a common class of inherited cystic kidney diseases, including autosomal recessive (ARPKD) and dominant polycystic kidney (ADPKD) according to different inheritance patterns. ARPKD typically present with symptoms in early childhood, marked by widespread dilation of renal collecting ducts and associated liver fibrosis [19]. The incidence of ARPKD is approximately 1:10,000 [20], patients with ARPKD with 50% developing renal failure before the age of 10 years and 75% developing hypertension within neonatal period [21]. PKHD1 is the only known causative gene for ARPKD, with a population carrier rate of approximately 1 in 70 [22]. Studies have shown that prenatal diagnosis is the most effective way to avoid birth defects with ARPKD. ADPKD typically presents in adulthood and is the most common renal ciliopathy and one of the leading causes of ESRD. ADPKD is characterized by diverse clinical manifestations, such as progressively enlarging renal cysts, hypertension, and various extrarenal complications [21]. The incidence rate of ADPKD is approximately 1:400–1:1,000 [20], and male tend to exhibit more severe outcomes. Studies have shown that *PKD1* and *PKD2* gene mutations are the underlying cause of ADPKD [23]. Nearly 75–85% of ADPKD cases are caused by *PKD1* mutations with mild symptoms [24].

NPHP is characterized by progressive atrophy and fibrosis of the renal tubules, resulting in a gradual decline in renal function. It is a major cause of childhood-onset CKD, and estimated to account for 5%–15% of cases of childhood ESRD. Over 25 different genes are identified with NPHP, accounts for only 1/3 of the clinical-confirmed NPHP. *NPHP1* is one of the most common genes associated with NPHP, and *NPHP2-7/INVS* have also been found to be associated with NPHP [25]. BBS is characterized by a wide spectrum of clinical features, including retinal degeneration, obesity, polydactyly, renal abnormalities, intellectual disability, and genital anomalies. BBS is rare, with an estimated incidence of approximately 1 in 100,000 to 160,000 births worldwide. 25 genes are identified with BBS, including *BBS1-12* [26]. MKS is characterized by a combination of

multiple congenital anomalies, primarily affecting kidney function, often fatal in the perinatal period. The incidence of MKS is approximately 1 in 13,250 to 140,000 births worldwide. MKS is genetically heterogeneous, with mutations identified in several genes related to ciliary function, including *MKS1, TMEM67, CEP290, RPGRIP1L, CC2D2A*, and *B9D1*.

Hereditary Renal Tubular and Metabolic Diseases

Hereditary renal tubular and metabolic diseases arise from genetic mutations affecting the ion channels or transporters of renal tubular epithelial cell membrane [27], leading to various clinical manifestations, including polydipsia, polyuria and abnormal bone metabolism [28]. According to the different lesions of the renal tubules, hereditary renal tubular disease can be divided into Dent disease, congenital hereditary Fanconi syndrome (CHFS), cystinuria (proximal tubule); Bartter syndrome (BS, the loop of Henle); Gitelman syndrome (GS, distal tubule); and Liddle syndrome (collecting duct). Common hereditary metabolic diseases affecting the kidneys include Fabry disease (FD), glycogen accumulation disease, cystinosis, etc., hundreds of genes being implicated in these diseases, such as *SLC12A3*, *KCNJ1*, *CLCNKB*.

Dent disease, a rare X-linked recessive tubular disease, is characterized by low molecular weight proteinuria (LMWP), hypercalciuria, nephrocalcinosis, and progressive renal failure, typically presenting in childhood or adolescence, predominantly in men, and milder onset in women [29]. Dent disease is primarily categorized three types: type I caused by *CLCN5* (accounting for approximately 65%), type 2 caused by *OCRL1* (accounting for approximately 15%), and type 3 [30]. A primary hypercalciuria feature of Dent disease leads to the formation of kidney stones. 30~40% of patients with Dent disease progress to kidney stones. Dent disease type 2 is a mild Lowe syndrome in which extrarenal involvement is milder than Lowe syndrome, and symptoms typically include muscle weakness, ocular abnormalities, and mild mental retardation.

BS is characterized by refractory hypokalemia, metabolic alkalosis, and hyperreninemic hyperaldosteronism. In recent years, BS cases have been increasing, with an incidence of approximately 1 in 100,000 [31]. BS is more common in childhood, and it can also occur as early as the fetal period. BS is autosomal recessive and mainly divided into type I caused by *SLC12A1* (accounting for approximately 60~70%), type 2 caused by *KCNJ1* (accounting for approximately 15~20%), type 3 caused by *CLCNKB* (accounting for approximately 5~10%), and type 4 caused by *BSND* (accounting for approximately 5~10%). Other remaining pathogenic genes of BS are *CLCNKA, MAGE-D2*, and *CASR*, most of which are ion transporter gene mutations in epithelial cells of renal tubules (mainly the thick ascending limb of the loop of Henle).

GS is an autosomal recessive salt-losing renal tubular disorder and characterized by hypokalemia, hypomagnesemia, hypocalciuria, metabolic alkalosis, and hyperrenin-angiotensin-aldosterone [32]. GS occurs in approximately 1–10 cases per 40,000 and is usually detected in adolescence or adulthood due to relatively mild or nonspecific symptoms [33]. GS is primarily caused by inactivating mutations in the *SLC12A3* gene encoding the thiazide-sensitive NaCl cotransporter. Studies also found that dysfunction of the *CLCNKB* gene can be another cause, which makes the differential diagnosis of GS and classic BS difficult [34].

CHFS is a rare disorder characterized by the impaired reabsorption of electrolytes and nutrients in the proximal renal tubules, leading to hypophosphatemia, glycosuria, aminoaciduria. Some genes associated with CHFS, such as *SLC34A1*, *SLC34A3*, *EHHADH*. Cystinuria is an inherited disorder characterized by the defective reabsorption of cystine and other dibasic amino acids (lysine, ornithine, and arginine). Cystinuria is primarily classified into two types: type A caused by *SLC3A1* (accounting for approximately 70~80%), type B caused by *SLC7A9* (accounting for approximately 20~30%). 80% of patients with cystinuria progress to cystine stones [35].

FD is an inherited progressive lysosomal storage disorder caused by *GLA* gene mutations located on the X chromosome (Xq22.1), resulting in defects in lysosomal hydrolase α-galactosidase (α-GalA) activity. Deficiency of α-GalA leads to the accumulation of globotriaosylceramide (GL-3 or GB3) and associated glycosphingolipids (Lyso-GL-3) in various cell types throughout the body, particularly in kidneys, heart, and nervous system. The common clinical features of FD include proteinuria, cardiac conduction abnormalities, peripheral neuropathy, corneal opacities, etc., and women are generally less affected than men. The global incidence in surviving men ranges from 1:40,000 to 1:117,000 [36, 37].

Glycogen accumulation diseases are metabolic disorders characterized by abnormal glycogen metabolism. Just like FD, glycogen accumulation diseases affect multiple organ systems. They potentially leading to renal failure and proteinuria. Due to their rarity, the incidence of glycogen accumulation diseases in children is challenging. As for cystinosis, potentially leading to the formation of cystine stones, we would describe in next section.

Nephrolithiasis

Given their common involvement in abnormal kidney function and electrolyte balance, hereditary renal tubular and metabolic diseases and nephrolithiasis often exhibit significant clinical overlap. The aforementioned diseases will not be described here. Kidney stones are caused by a variety of factors, including genetic, environmental, and dietary factors. Approximately 15% of kidney stones are attributed to monogenic disorders [38]. Common hereditary kidney stones in children mainly include primary hyperoxaluria (PH) and cystinosis.

PH is caused by genetic mutations that result in excessive liver-produced oxalate and subsequent urinary tract stones and nephrocalcinosis, which progresses to CKD. In addition, oxalate can subsequently deposit in all tissues, particularly in bone, resulting in multiple organ damage [39]. In general, PH is autosomal recessive and is divided into three types: PH1 (*AGXT,* accounting for approximately 80%), PH2 (*GRHPR*), and PH3 (*HOGA1*), while pathogenic genes of some monogenic cases remain unclear [40, 41]. The prevalence of PH is 1 in 38,630 to 1 in 120,000 based on region. Cystinosis is an autosomal recessive lysosomal storage disorder caused by mutations in the *CTNS* gene encoding cystine [42]. Cystinosis typically causes damage to the renal proximal tubules within the first year of life, and if left untreated, progressive glomerular injury and ESRD develop in childhood. The incidence is approximately 1 in 100,000 to 1 in 200,000, depending on ethnicity and geography [43]. Cystinosis manifests three clinical phenotypes: infantile nephropathic cystinosis (90%), adolescent nephropathic cystinosis (5%), and nonnephrotic ocular cystinosis (5%) [44]. In summary, many hereditary kidney diseases share similar clinical features, which can often lead to misdiagnosis if solely based on clinical presentation. Accurate diagnosis is crucial for these conditions to ensure appropriate management and treatment.

Diagnosis of Common IKDs in Children

Pediatric genetic kidney diseases encompass a broad range of conditions, most of which are rare and pose significant challenges to the clinical knowledge of nephrologists. These conditions affect different parts of the kidneys and often lead to severe dysfunction in extrarenal organs. Due to the typically insidious onset of kidney diseases, many patients do not initially present to nephrologists, which significantly increases the likelihood of misdiagnosis. Specialized laboratory tests, including advanced urine and blood analysis, are crucial to detect any abnormal kidney function markers. In contrast to more common kidney diseases, diagnosing genetic conditions depends heavily on identifying specific genetic mutations, necessitating sophisticated and costly genetic testing [45, 46]. Because of the considerable phenotypic overlap among IKDs, genetic testing is a critical step in obtaining a definitive diagnosis for affected individuals. Advances in genetic testing techniques, like whole-exome sequencing and genome sequencing, have significantly improved the detection and confirmation of these diseases. The diagnostic process typically starts with a thorough collection of patient and family histories to pinpoint hereditary patterns indicative of a genetic disorder [47]. This genetic assessment is crucial for diagnosing children who present with characteristic clinical phenotypes and familial patterns. However, the choice of testing methods, along with considerations of cost, benefits, and limitations, significantly influences the diagnostic outcomes. Interpreting variants of uncertain significance remains one of the most significant challenges in analyzing genetic test results. Table 1 summarizes several websites Table 1used for predicting the pathogenicity of diseases, providing clinical practitioners with tools and methods to understand these mutations. This is complemented by clinical examinations that look for physical indicators of kidney dysfunction.

Additionally, imaging techniques such as 3D ultrasound or molecular imaging provide detailed insights into the structural and functional aspects of the kidneys [48, 49]. These imaging methods help visualize congenital abnormalities and other malformations associated with genetic conditions [48]. A kidney biopsy is often performed when the diagnosis remains uncertain [50]. This procedure, enhanced by specialized staining techniques and electron microscopy, allows for microscopically detailed examination of kidney tissue, revealing structural abnormalities characteristic of specific genetic disorders [51]. Moreover, multiomics is crucial for understanding IKDs by analyzing how genes interact within the genome and how they influence the disease process. Technologies like proteomics and metabolomics provide insights into the biochemical and molecular pathways affected by genetic mutations, offering a deeper understanding of the disease phenotypes [52], and can also detect biomarkers and metabolic signatures that indicate kidney dysfunction to help tailor personalized treatment approaches [53]. The comprehensive diagnostic approach outlined above facilitates a precise diagnosis of kidney disease, enabling more effective treatment interventions.

Treatment of Common IKDs in Children

Most IKDs are incurable, and treatment methods mainly include 4 types: symptomatic supportive, surgical, renal replacement, and gene therapy. Early intervention is

Table 1. Tools to predict the outcome of genetic mutations

Analytical tools	Content of the forecast	Applicable mutation types
PredictSNP	Provide predictions for all chosen tools and the collective forecast by PredictSNP for each selected mutation, discerning between deleterious and neutral variants while indicating the confidence level of these predictions	Missense mutation
iStable	Predicts alterations in protein stability and presents the analysis results using the abbreviations D for Decrease and I for Increase	Missense mutation
Align GVGD	Provides classifications from class 0, deemed neutral, to class 65, regarded as deleterious	Missense mutation
MAGPIE	Analyzes the pathogenicity of the mutation and outputs a number from 0 to 1, where 0 means benign mutation and 1 means highly pathogenic mutation	Missense mutation, nonsense mutation, frameshift mutation, and inframe mutation
HOLE	Generates an exhaustive report which encompasses detailed results, animations, and illustrative figures	Missense mutation

critical, as it significantly enhances treatment efficacy. Among them, surgical treatment is the fundamental treatment for CAKUT; renal replacement is the preferred option when progresses to ESRD. In this section, we will discuss the corresponding treatment methods for each classification of genetic kidney diseases outlined above (Table 2). For CAKUT, particularly obstructive CAKUT, surgical treatment is essential.

Inherited Glomerular Disease

Currently, AS remains incurable, and its treatment goal is mainly to delay the disease progression and improve quality of life. First-line therapy consists of angiotensin-converting enzyme inhibitors (ACEIs), with angiotensin receptor blockers (ARBs) and aldosterone receptor antagonists as secondary options [54]. These agents can improve urine protein and delay the progression of renal lesions [55]. Emerging treatments include Methylba dolostone, RG-012, AnimiR-21, and potential therapies targeting IL-11 (detailed in Table 2). In the absence of a cure, patients with TBMN typically require regular monitoring of blood pressure, proteinuria, and renal function. Treatment is generally unnecessary for patients with only hematuria but normal blood pressure and renal function; however, ACE inhibitors are recommended for those with proteinuria or elevated blood pressure [56].

The clinical phenotypes of CNS are highly variable, necessitating individualized treatment approaches. Unfortunately, CNS carries a poor prognosis. Without treatment, most patients do not survive beyond the first year of life due to complications arising from infection or severe renal failure. When surviving to 2–3 years old, patients often die of uremia. The primary management strategies for CNS during the first month of life include securing intravenous access, frequent albumin infusions, diuretics, infection prevention, and nutritional support to control edema and possibly uremia [57]. During the disease progression, ACEIs and indomethacin or anti-urine protein therapy to reduce protein excretion; and prompt use of anticoagulant drugs (e.g., aspirin, didamole, or warfarin) to prevent thrombosis. Moreover, optimal nutrition and appropriate thyroid hormone replacement therapy ensure the children grow normally. Kidney transplantation is often the only effective therapy for CNS. Additionally, emerging therapeutic strategies specifically targeting ADCK4 mutations show considerable promise. These include gene-specific therapies aimed at enhancing mitochondrial function or gene therapies designed to restore normal podocyte function [58]. Encouraging preliminary clinical trials utilizing PCSK9 inhibitors and gene therapy inducing nephrin expression in animal models have shown promising results in mitigating the progression of CNS disease [59].

Renal Ciliopathies

In the absence of effective treatment, most patients with PKD often progress to ESRD in childhood or adolescence, requiring renal replacement therapy. The main treatment goals of PKD are to inhibit the growth of cysts and control infections. Although ~24% of children with ARPKD are diagnosed prenatally, the mean age of kidney

Table 2. Treatments of common IKDs in children

	Symptomatic supportive treatment		Gene therapy
	major management	advances in drug therapy (Clinical Trials)	
AS	Improve renal function and ACEI as first-line drug therapy	Methylbadoxolone, RG-012, AnimiR-21, interleukin, englizin	CRISPR/Cas9 gene editing(preclinical studies), microRNA-21 (preclinical studies), antisense oligonucleotides (ASOs) (animal model stage)
TBMN	Monitor for blood pressure, and proteinuria, and protect renal function, ACEI necessarily		
CNS	Obtain intravenous access, frequent albumin infusions, diuretics, infection and thrombosis prevention, and nutritional support	PCSK9 inhibitors, sparsentan (NCT05003986)	
ADPKD	Inhibit cyst growth, protect the remaining normal nephron, improve renal function, and tackle complications (anemia, hypertension, growth retardation	rapamycin/sirolimus (NCT00346918), everolimus (NCT00414440), tesevatinib (NCT01559363), pasireotide (NCT01670110), metformin, nicotinamide, lixivaptan(NCT04064346), tolvaptan, risivaptan, pioglitazone (NCT02697617), simvastatin, bardoxolone (NCT03918447), bosutinib, lanreotide (NCT01354405,NCT01616927), octreotide-LAR (NCT01377246, NCT00309283)	CRISPR/Cas9 technology knockout (animal model stage), antisense oligonucleotides (ASOs) (preclinical studies), MicroRNA17 (miR-17) inhibitor RGLS4326 (preclinical studies)
ARPKD	Monitor renal function and manage complications (neonatal respiratory distress, hypertension, portal hypertension and recurrent cholangitis)	Torvaptan, risivaptan, pioglitazone, rapamycin/sirolimus, bosutinib, EGF inhibitor, octreotide, paretide, rocovitin, menadione (vitaminK3), tesevatinib (NCT03096080), tolvaptan (NCT04782258, NCT04786574)	Antisense oligonucleotides (ASOs) (preclinical studies)
BS	Lifelong electrolyte replacement therapy and improve quality of life	Indomethacin, acetazolamide (NCT03847571)	
GS	Lifelong electrolyte replacement therapy and improve quality of life	Spironolactone, COX inhibitors, ACE/ARB, hydrochlorothiazide (NCT00822107)	
Dent disease	Reduce urinary calcium excretion, reduce renal calcification and tubulointerstitial fibrosis	Rapamycin and statin, Alpelisib, 4PBA and 2-NOAA, phosphorus supplement (NCT02016235), hydrochlorothiazide (NCT00638482)	CRISPR-Cas9 technology (animal model stage)
FD	Enzyme replacement therapy (galactosidase-β and galactosidase-α)	Lucerastat (NCT02930655), AMT-191 (NCT06270316), AL01211 (NCT06114329), pegunigalsidase-alfa (NCT06095713)	Gene therapy mediated by adenovirus (animal model stage)
PH	Liquid replacement, alkalinization of urine (oral potassium citrate), and inhibitors of calcium oxalate crystallization (e.g., vitamin B6), combined hepatorenal transplantation necessarily	Lumasiran, vitamin B 6 (NCT01281878), stiripentol (NCT03819647), oxabact OC5 capsules (NCT02012985), nedosiran (NCT05993416), DCR-PHXC (NCT04042402)	AAV virus-mediated CRISPR/Cas9 gene editing technology (animal model stage)

Table 2 (continued)

	Symptomatic supportive treatment		Gene therapy
	major management	advances in drug therapy (Clinical Trials)	
Cystinosis	Replacement of urinary loss compounds, nutritional support, hormone replacement therapy, and cystine wasting therapy with cysteamine	Cysteamine bitartrate, RP103 (NCT01733316)	Bone marrow transplantation, hematopoietic stem-progenitor cells encoding normal CTNS genes injection into CTNS(−/−) mice (animal model stage)

transplantation remains 12 years due to the lack of effective pharmacological drugs [19]. Li et al. have proved that antisense oligonucleotides (ASOs) could correct gene expression and mRNA splicing defects associated with ARPKD, highlighting their potential as a therapeutic strategy [60]. Additionally, ongoing preclinical experiments have shown promise in delaying ARPKD cystic lesions with various drugs, such as tolvaptan, ricivapitan, pioglitazone, rapamycin/sirolimus, tevatinib, bosutinib, EGF inhibitors, octreotide, pasireotide, roskovitine, menadione (vitamin K3), as detailed in Table 2. Fortunately, Tolvaptan, a vasopressin V2 receptor antagonist, remains the only targeted FDA-approved therapy for ADPKD caused by *PKHD1* gene. While Tolvaptan's side effects and high costs present significant challenges [61]. Clinical studies have demonstrated that Tolvaptan effectively slows the rate of kidney cyst growth and delays the decline in kidney function, thereby improving the quality of life for patients. Moreover, several drugs for ADPKD, including tolvaptan, pioglitazone, pravastatin, simvastatin, RGLS4326, and bardoxolone methyl, are showing promise in clinical trials (detailed in Table 2). Compared to PKD, BBS and MSK have lower incidence rates and less in-depth research, with clinical management primarily focused on symptomatic treatment. However, insights from clinical treatments of PKD may potentially provide new perspectives for innovative therapies in BBS and MSK in the future.

Hereditary Renal Tubular and Metabolic Diseases

No cure is currently available for Dent disease. The treatment goals of Dent disease are to limit urinary calcium excretion, reduce renal calcification and tubulointerstitial fibrosis, and delay the onset of renal insufficiency. The main treatment measures for Dent disease include reducing the intake of a high-calcium, high-sodium, high-oxalate diet, alongside increasing water intake to reduce urinary calcium and prevent urinary stone formation. This is typically combined with drug, including oral thiazides, ACEIs, and citrate, to promote urinary calcium reabsorption and delay the progression of nephropathy. However, a low-calcium diet may negatively affect bone health. In cases where complications such as osteoporosis, osteomalacia, or rickets are present in patients with Dent disease, prompt vitamin D supplementation, phosphate therapy, and, if necessary, growth hormone therapy are requireded [62]. Recent experimental therapies for Dent disease show promise. Wild-type bone marrow transplantation in *Clcn5* knockout mouse models has improved tubular dysfunction [63]. Targeting specific pathways with rapamycin, statins, and alpelisib in Dent disease type 2 mouse model have been beneficial, alongside small molecules (4-phenylbutyrate, 2-naphthoxyacetic acid) enhancing *CLCN5* gene expression and function in Dent disease type 1 mouse models [64, 65].

Without a cure, the treatment for BS mainly focuses on correcting electrolyte imbalances and improving the quality of life. BS management involves lifelong electrolyte replacement therapy, including intravenous electrolytes and fluids, dietary changes, and potassium-sparing diuretics when necessary. The biggest breakthrough in the treatment of BS in recent years has been the application of cyclooxygenase inhibitors, such as indomethacin (the most widely used for good efficacy, rare allergic reactions, and mild gastrointestinal adverse reactions), aspirin, and ibuprofen. Moreover, failure to thrive is a common complication in children BS, and early intervention with increased caloric intake and growth hormone supplementation is essential to promote growth [66]. Additionally, Mazaheri, M. et al. found that a 4-week course of acetazolamide significantly reduced serum bicarbonate and increased serum potassium levels while lowering serum aldosterone and plasma renin levels. This suggests that acetazolamide can be used as an adjunct therapy for BS.

Similar to the condition of BS, the main treatment goals of GS are to correct serum electrolyte imbalances

and improve quality of life. The standard treatment of GS is quite similar to that for BS, such as potassium-sparing diuretics (e.g., spironolactone), COX inhibitors (e.g., indomethacin), and ACEIs/ARB. For GS patients, long-term consequences such as CKD, growth retardation osteoarticular changes, abnormal glucose metabolism, secondary hypertension, and arrhythmias need be considered. Early and appropriate treatment can significantly reduce sequelae and restore normal life for the child. As for the treatment of CHFS and Cystinuria, they share common approaches such as hydration, electrolyte management, and dietary modifications. While CHFS treatment is more focused on correcting proximal tubular dysfunction and its systemic effects, whereas Cystinuria treatment is primarily aimed at preventing cystine stone formation and managing related complications.

Clinically, for FD, the standard symptomatic treatments include pain management, gastrointestinal symptom relief, renal protection, and cardiac management. Additionally, the gold standard for treatment is enzyme replacement therapy with alactosidase-β and galactosidase-α. There are also chaperone therapies that stabilize the α-galactosidase A enzyme, which are used in specific mutants. Similar to the condition of FD, the treatment of glycogen accumulation diseases also include supportive therapies and alglucosidase-α – enzyme replacement therapy.

Nephrolithiasis

Treatment of hereditary nephrolithiasis includes symptomatic supportive care (rehydration, alkalinization of urine, drug therapy, etc.), and renal replacement therapy, generally without surgery. In addition, management of associated complications is crucial. Drug options vary based on the different metabolic types of stones. The goal of treatment is to reduce the recurrence of kidney stones and delay the decline of kidney function.

The prognosis of PH is very poor, and early therapy is crucial to delay the progression to ESRD. Symptomatic supportive care includes fluid replacement, alkalinization of urine (oral potassium citrate), and inhibitors of calcium oxalate crystallization (e.g., vitamin B6). Combined hepatorenal transplantation is currently the ideal therapy for PH1 with CKD, which should be performed before systemic oxalate toxicity and related complications occur [67]. Recent advancements include Lumasiran, an RNA interference (RNAi)-based therapy that inhibits calcium oxalate crystallization, showing significant efficacy in clinical trials [68]. Lumasiran has been approved by the FDA for the treatment of PH1 in both children and adults. Another RNA interference therapeutic, Nedosiran, is currently in phase 3 clinical evaluation, offering hope for future treatments (detailed in Table 2). If these emerging therapies prove effective and safe for dialysis patients and kidney transplant recipients, liver transplantation may not be necessary in the future.

The goals of supportive treatment for Cystinosis include restoring electrolyte and acid-base balance, preventing rickets, and promoting growth. Symptomatic support for Cystinosis includes managing urinary losses, nutritional and hormonal support, and cystine-depleting therapy, especially with cysteamine bitartrate, which delays ESRD progression and improves growth [43]. Taken together, traditional treatments for hereditary kidney diseases, such as symptomatic care, dialysis, and transplantation, provide essential management but are associated with limitations. Dialysis provides temporary relief without replacing the kidney's endocrine functions, leading to high mortality. Transplantation offers a better quality of life but is hindered by donor scarcity and post-transplant complications [69]. Advances in genomic sequencing and personalized medicine are paving the way for new therapies to solve the dilemma (Table 3).

Advance Treatment of Gene Therapy and Kidney Organoids in IKDs

Gene therapy emerges as a promising avenue by replacing or repairing faulty genes, offering potential cures and insights into the pathogenesis of certain unclear IKDs, driven by advances in genetic testing and molecular diagnostics. Broadly, gene therapy is divided into in vivo and in vitro methods, with stem cells serving as ideal targets for the latter. In vitro gene therapy often involves the genetic modification of stem cells outside the body, followed by their reintroducing into the patient. This approach leverages the regenerative potential of stem cells to repair or replace damaged tissues. Building on these advancements, organoid technology offers a novel approach by closely mimicking kidney structure and function for disease modeling and pharmacological testing. By using gene-edited stem cells, researchers can generate kidney organoids that not only replicate human kidney development and disease but also allow for precise genetic interventions.

In vivo Gene Therapy

In vivo gene therapy has shown promise in mouse models for IKDs, by introducing or reactivating normal genes to repair damaged cells and reverse disease

Table 3. Traditional versus gene therapy and organoid

Therapies	Advantages	Limitations
Symptomatic treatment	Economical and convenient	Adverse reactions and failure to fully recover kidney function
Renal replacement therapy	Dialysis: quickly removes metabolic waste and maintains internal environmental homeostasis	Dialysis treatment: high requirements for medical conditions, the painful treatment process is painful, and uncomplete kidney function restoration
	Renal transplantation: kidney function can be completely restored	Renal transplantation: lack of kidney source, immune rejection, high costs, surgical complications, etc.
Gene therapy	Precise	Off-target effects, delivery vector efficiency, safety and ethics, and viral vector selection
Organoid	Application potential is large	Insufficient safety and not mature technology

pathology. CRISPR/Cas9 technology has been identified for its accuracy and effectiveness in editing genes, showing promise for disease modeling and treatment of conditions like AS, ADPKD, and FD. CRISPR/Cas9 gene editing, microRNA-21, and ASOs are under research for AS therapeutic potential [70–72]. FDs, particularly using adeno-associated virus (AAV5 for AMT-191, AAV2/6 for ST-920) vectors, shows promising clinical potential, utilizing EF1α promoter to facilitate prolonged expression in hematopoietic stem/progenitor cells [73, 74]. However, many therapies remain in the experimental phase, facing hurdles related to safety and effectiveness.

Dong et al. [75] demonstrated that gene therapy has a clear therapeutic effect on ARPKD and has the potential to reverse ADPKD lesions even after cystic lesions have formed in the kidneys of mouse models. In mice with the induced Arg140Gln NPHS2 mutation, podocin expressing AAV 2/9 after the onset of albuminuria also reduced albuminuria, and they demonstrated the feasibility of AAV gene therapy for CNS [76]. CRISPR/Cas9 technology facilitated the development of a Dent disease mouse model, showing symptomatic improvements following the introduction human *CLCN5* cDNA via lentiviral vectors, indicating gene therapy's potential efficacy [77]. Additionally, CRISPR/Cas9 have been applied to reduce uric oxalic acid levels and kidney stone formation in mouse models, presenting a potential novel approach for treating PH [78]. Experiments involving bone marrow transplantation in cystinosis mouse models have shown improvements in kidney function, reduction of cystine crystals in the cornea, and enhanced thyroid function [79]. Gene therapy has emerged as a promising avenue for cystinosis treatment.

In vitro Gene-Cell Therapy

In vitro gene-cell therapy, particularly stem cell therapy using mesenchymal stem cells (ESCs) and iPSCs, presents a promising approach to IKDs and ESRD. This therapy offers an alternative to traditional transplantation, potentially avoiding immunosuppressants and reducing rejection risks by promoting immune tolerance [80, 81]. A 2021 study demonstrated that CRISPR/Cas9 gene editing on iPSC-differentiated cardiomyocytes from FD patients corrected cardiomyocyte hypertrophy and reduced GL-3 deposits, highlighting the transformative potential of nonviral gene-editing approaches ifor addressingg genetic components of the disease [82]. Similarly, injecting hematopoietic stem progenitor cells with the normal *CTNS* gene into mice resulted in stable cell engraftment, functional gene expression, decreased cystine levels in tissues, and improved kidney function [83]. Additionally, combining cysteamine with everolimus in a renal organoid model has been validated as an effective treatment strategy [84]. Although these strategies remain in the laboratory research stage, they offer hope for future clinical applications.

Limitations of Gene Therapy

Homologous recombination technology, marking an early and significant advancement in eukaryotic gene editing, allows for precise DNA modifications to replace or repair defective genes. This method is crucial for specific gene inactivation, correction, or base changes, proving instrumental in treating IKDs. CRISPR/Cas9 has been preferred for its simplicity, precision, and reduced cytotoxicity among current gene-editing technologies [85]. Despite its promise, gene editing for kidney faces potential challenges like

off-target effects and the difficulty of editing terminally differentiated kidney cells and complex kidney structure, underscoring the need for further technological advancements to overcome these obstacles [86]. To effectively deliver these genetic modifications into the target cells, transgenic vectors play a pivotal role. Transgenic vectors are categorized into viral and nonviral types. Viral vectors, including adenovirus, lentivirus, and AAV, are favored for their efficiency and stable gene expression but present challenges related to large-scale production and safety assurance. Nonviral vectors, like nanocarriers, offer advantages in safety, cost, and ease of production, presenting a viable alternative for gene delivery. For the gene-cell therapy, challenges in ensuring these cells reach and affect target tissues effectively limit their efficacy, particularly in kidney treatments where only a small fraction of administered cells reach the desired sites. In addition, we also found that organoid technology has great application potential in the field of IKDs, and the research method on iPSCs opens a new research direction for future treatment. As highlighted in Table 3, organoid models have significant advantages over traditional methods, such as providing a more accurate representation of human kidney physiology and allowing for precise genetic interventions. However, they also have limitations, including the complexity of development and limited long-term stability.

Prospects for Organoids

Organoids are in vitro 3D culture systems derived from tissue stem cells, which can mimic the structure and specific functions of organs in vivo. They can be derived from various cells, such as iPSCs, organ-specific adult stem cells (ASCs), and ESCs [87]. Kidney organoids show great promise as disease models, particularly for early-onset diseases. They have been used to study the effects of gene mutations, drug screening, and disease mechanisms, providing a valuable platform for discovering new treatments.

Recent advancements have highlighted the successful application of kidney organoids in modeling a variety of IKDs, including renal ciliopathies and glomerular diseases [59, 88]. Research into ARPKD and ADPKD kidney organoids, along with analyses of various inhibitors on hiPSC-derived kidney organoids from PKD patients, indicates significant advancements in treatment approaches, highlighting the potential of organoid technology and gene therapy in managing these conditions [89, 90]. Studies also show that iPSC-derived type IV collagen α5-expressing kidney organoids can model AS and reveal functional defects associated with he disease [91]. These organoid models are proving valuable for simulating disease states.

Beyond modeling diseases, organoids are instrumental in toxicity testing, providing a relevant context for evaluating the safety and efficacy of new therapeutic agents. In the realm of regenerative medicine, advancements have been made in generating functional nephrons from renal progenitor cells derived from organoids [92].

Moreover, emerging gene-editing technologies, such as CRISPR-Cas9, are being applied to organoids to correct genetic defects associated with IKDs, such as patient-derived *NPHS2* mutant organoids, showcasing their potential in future therapeutic strategies. Preliminary studies have indicated that organoids can be utilized to explore gene therapy approaches aimed at restoring normal podocyte function and mitigating disease progression. In summary, organoids stand at the forefront of innovative research and therapeutic strategies for IKDs. Their ability to model kidney pathology, facilitate drug discovery, and explore novel therapies makes them invaluable tools for addressing complex kidney diseases.

Limitations of Organoids

Despite the potential of iPSC-derived kidney organoids, several obstacles remain such as missing organ-specific structures, variable differentiation, and imcomplete maturity [93]. Integration of vasculature and whole urinary tract systems in organoids remains a challenge. Nephron organoids contain nephrons that are not connected to each other, ureteral buds and collecting ducts organoids lack nephrons, and the combination of the two types of organoids fails to form a complex structure of a functional kidney in vivo [94]. On the other hand, in some of the currently constructed organoids, challenges and risks include off-target cell population and teratomas development [95].

Conclusion

Next-generation sequencing (NGS) and other genomic approaches are now more accessible and affordable, revolutionizing clinical diagnostics for kidney diseases. This review highlights the key gene diagnostics and treatment aspects of common IKDs in children, across various categories like CAKUT,

glomerular disease, renal ciliopathy, renal tubular and metabolic diseases, and nephrolithiasis. Currently, treatment primarily involves symptomatic and supportive care, with renal replacement therapy reserved for ESRD. Advancements in molecular biology and an enhanced grasp of kidney disease pathogenesis are anticipated to push forward new treatment methodologies, particularly through the innovative application of gene therapy and organoids, promising a new horizon in the management of IKDs.

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Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

Lidan Hu and Jianhua Mao conceived, designed, and supervised the research. Guozhen Wang, Mengqiu Liao, and Lidan Hu wrote the manuscript. Danny Junyi Tan, Xiangjun Chen, Pan Li, Ran Chao, Yifan Zhu, and Yuelin Guan drew the figure and charts. All authors have read and approved the final version of the manuscript.

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