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Precision Medicine in Pediatric Nephrology: From Monogenic Diseases to Personalized Immunosuppression

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Abstract

Background: Pediatric nephrology is moving away from empirical, one-size-fits-all therapeutic strategies towards a precision medicine model. This is propelled by advanced genomic technologies that have uncovered the monogenic cause of many childhood kidney diseases and a recognition of inter-individual variation in drug response.

Aim: The purpose of this review is to summarize the present status and future prospects of precision medicine in pediatric nephrology. Two main pillars are highlighted: the use of genetic diagnosis in monogenic disease and the individualization of immunosuppressive treatment of acquired diseases.

Methods: A comprehensive review of the literature was conducted, scrutinizing peer-reviewed articles between 2010 and 2024. The synthesis integrates evidence from clinical trials, genomic studies, pharmacogenetic research, and emerging evidence on novel biomarkers to provide a composite overview for the practicing pediatric nephrologist.

Results: Genetic diagnosis, particularly through next-generation sequencing, now makes definitive diagnoses in a large proportion of steroid-resistant nephrotic syndrome (SRNS), congenital anomalies of the kidney and urinary tract (CAKUT), and ciliopathies. This directly impacts clinical care by ending diagnostic odysseys, informing prognosis and recurrence risk, and preventing futile immunosuppression. Meanwhile, pharmacogenomics, i.e., CYP3A5 genotyping to inform tacrolimus dosing, and novel biomarkers are enabling more personalized and potent immunosuppressive regimens with reduced toxicity.

Conclusion: Precision medicine is already transforming patient management in pediatric nephrology by enabling targeted diagnostics, prognostication, and therapy. While challenges surrounding accessibility, affordability, and the interpretation of genetic data remain, the application of these approaches is instrumental in advancing the field towards more effective and personalized patient management.

Keywords: precision medicine, pediatric nephrology, pharmacogenomics, monogenic disorders, immunosuppression.

1. Introduction

Pediatric kidney disease is a significant cause of morbidity and long-term disability, and a high proportion progresses to chronic kidney disease (CKD) and end-stage kidney disease (ESKD). Treatment based on traditional phenotypic classification and empirical therapy is an approach plagued by diagnostic uncertainty, heterogeneous response to treatment, and a high rate of drug-related adverse effects. The advent of precision medicine—a novel approach to disease treatment and prevention that considers variability in genes, environment, and lifestyle among individuals—promises to change this landscape (Sadowski et al., 2015). Precision medicine is most tangibly realized in pediatric nephrology in the application of next-generation sequencing (NGS) to identify monogenic disease etiologies and in the application of pharmacogenomics to rationalize drug therapy.

This review will trace the journey from syndromic diagnosis to molecular etiologies. We will first discuss how genetic discoveries have impacted our understanding of steroid-resistant nephrotic syndrome (SRNS), CAKUT, and ciliopathies. We will then enter the field of personalized immunosuppression, with a discussion of the impact of genetic polymorphisms on the metabolism and action of drugs like calcineurin inhibitors and corticosteroids. Furthermore, we will cover the role of innovative biomarkers in individualizing therapy in conditions like lupus nephritis. By integrating these facets, this review aims to provide a birds-eye view for the practicing pediatric nephrologist, illustrating that precision medicine is no longer a future aspiration but a daily practice that is refining diagnosis, prognosis, and therapeutic planning in children with renal disease.

The Genomic Revolution in Diagnosing Monogenic Kidney Disease

The development of high-throughput NGS technologies, including WES and WGS, has transformed the diagnostic yield in children with

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various forms of kidney disease. In cases where the etiology was formerly unknown, a molecular diagnosis is now possible in a considerable minority of instances, significantly altering clinical management.

Steroid-Resistant Nephrotic Syndrome (SRNS)

SRNS is a poster child for the power of genetic diagnosis. Over 60 monogenic causes of SRNS have been identified that account for 30% of childhood-onset and 10-30% of adult-onset disease (Sadowski et al., 2015). Most of these genes encode proteins of basic significance in the structure and function of the podocyte, the terminally differentiated glomerular epithelial cell. Mutations in the genes NPHS1 (nephrin), NPHS2 (podocin), WT1 (Wilms tumor 1), and PLCE1 (phospholipase C epsilon 1) are the most common (Trautmann et al., 2018).

A genetic diagnosis in SRNS has important clinical ramifications. First, it provides a definitive etiology, putting an end to the diagnostic odyssey for families and allowing for accurate genetic counseling regarding recurrence risks (Gubler, 2011). Second, it plays a paramount role in prognosis. For instance, disease caused by NPHS2 mutations recurs in only 10-20% of transplants, whereas disease caused by NPHS1 mutations has a very high recurrence rate (>80%), necessitating pre-emptive planning (Kravets & Mallipattu, 2020; Barutta et al., 2022). Most importantly, a genetic diagnosis spares children from undergoing futile, toxic empirical attempts at immunosuppression. The majority of patients with monogenic SRNS are unresponsive to corticosteroids or calcineurin inhibitors, and the determination of a genetic etiology allows for the prompt discontinuation of these drugs, avoiding their severe side effects (Trautmann et al., 2018). Treatment can then focus on conservative, renoprotective measures and preparation for renal replacement therapy. Figure 1 shows the flow of precision medicine in pediatric nephrology

Tract (CAKUT)

CAKUT is the most common cause of CKD in children and encompasses a spectrum of malformations from renal agenesis to obstructive uropathy. While traditionally multifactorial, a genetic etiology is being identified in at least 10-20% of subjects, particularly in those with extra-renal abnormalities or family history (van der Ven et al., 2018). Genes involved in early kidney development, such as PAX2, EYA1, SALL1, and HNF1B, are frequently implicated.

An exact genetic etiology of CAKUT provides significant prognostic information. For example, HNF1B disease carries a high risk of progressive CKD, maturity-onset diabetes of the young (MODY5), and pancreatic atrophy, which warrants lifelong surveillance beyond the kidneys (Bockenhauer & Jaureguiberry, 2016). A diagnosis of a PAX2-related disorder alerts the clinician to the risk of ocular colobomas. Such knowledge provides the possibility of an anticipatory, multidisciplinary approach in care. Moreover, a diagnosis of a de novo dominant mutation can reassure about low recurrence risk for future pregnancies, while the identification of an autosomal recessive or dominant mutation with variable penetrance allows informed family planning (Sanna-Cherchi et al., 2017).

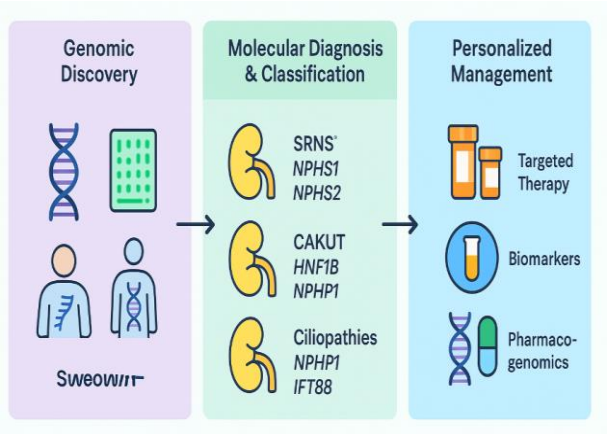

Figure 1: Precision Medicine in Pediatric Nephrology: From Genes to Treatment

Congenital Anomalies of the Kidney and Urinary Ciliopathies and Tubulopathies

Monogenic disorders also underlie a wide range of tubular and cystic kidney disorders. Ciliopathies like nephronophthisis (NPHP), Bardet-Biedl syndrome (BBS), and Joubert syndrome are caused by mutations in genes coding for proteins confined to the primary cilium, a key cellular organelle (Braun & Hildebrandt, 2017). Similarly, some tubulopathies like Bartter and Gitelman syndromes are caused by mutations in tubular transport proteins.

A genetic diagnosis in these syndromes, which may share overlapping clinical features, is often required for definitive classification. For instance, the discovery of a molar tooth sign on brain MRI in a child with CKD is very suggestive of Joubert syndrome and can guide genetic testing to implicated genes such as TMEM67 or CEP290 (Brancati et al., 2010). The diagnostic clarity provided by genetics allows for comprehensive management, e.g., screening for extra-renal manifestations (retinal degeneration in NPHP, polydactyly and obesity in BBS, and neurological issues in Joubert syndrome), which significantly impacts the child's long-term quality of life and functional outcomes (Table 1).

Table 1: Clinical Utility of Genetic Diagnosis in Selected Pediatric Nephrology Disorders

Disorder	Example Genes	Immediate Clinical Impact	Long-Term Management Implications
Steroid-Resistant Nephrotic Syndrome	*NPHS2, NPHS1, WT1, PLCE1*	Avoidance of futile immunosuppression; accurate genetic counseling.	Informs transplant planning (recurrence risk); enables family screening.
CAKUT	*HNF1B, PAX2, EYA1*	Explanation of syndromic nature (e.g., diabetes, ocular defects).	Initiates screening for extra-renal features (e.g., glucose, liver function); refines prognosis for CKD progression.
Nephronophthisis	*NPHP1, NPHP3, NPHP4*	Definitive diagnosis for progressive CKD of unknown cause.	Screening for retinal degeneration (leading to blindness) and liver fibrosis; informs family planning.
Atypical HUS	*CFH, CFI, CD46, C3*	Diagnosis guides acute therapy (initiation of eculizumab).	Determines duration of eculizumab therapy; informs transplant planning (high recurrence risk without prophylaxis).

Personalized Immunosuppression in Acquired Glomerular Diseases and Transplantation

While genetic diagnosis is largely relevant to monogenic disease, the principles of precision medicine are equally relevant to acquired disease, where inter-individual differences in drug metabolism and immune response dictate outcomes.

Pharmacogenomics of Calcineurin Inhibitors

Calcineurin inhibitors (CNIs) like tacrolimus and cyclosporine are mainstays of immunosuppression in renal transplantation and certain glomerulopathies. Their narrow therapeutic index and extensive inter-patient pharmacokinetic variability present a major clinical challenge. One of the major sources of this variability is the cytochrome P450 family, subfamily 3A (CYP3A), and the drug efflux pump P-glycoprotein (encoded by ABCB1) (Birdwell & Chung, 2017).

The CYP3A5 gene is the most well-characterized pharmacogenetic effect on tacrolimus dosing. Individuals who express the CYP3A5 enzyme (those carrying at least one CYP3A51 allele, "expressors") have enhanced tacrolimus metabolism and require significantly higher doses to achieve target trough levels compared with "non-expressors" (CYP3A53/3 genotype) (Birdwell et al., 2012). Pre-emptive CYP3A5 genotyping can guide initial tacrolimus dosing, leading to more rapid attainment of therapeutic levels and, possibly, a lower risk of early rejection or CNI toxicity (Shuker et al., 2016). Despite compelling evidence, routine CYP3A5 genotyping in clinical practice remains variable, highlighting a translational gap between discovery and practice.

Corticosteroid Pharmacogenomics

Corticosteroids are a first-line therapy for the majority of immune-mediated renal illnesses but are also associated with considerable morbidity, including growth restriction, obesity, and metabolic syndrome. Glucocorticoid resistance also develops in a subset of patients. The biologic response to corticosteroids is influenced by polymorphisms in the glucocorticoid receptor gene (NR3C1) and in genes of the glucocorticoid pathway (Reichardt et al., 2021). For instance, some researchers have associated NR3C1 polymorphisms with a heightened risk of steroid toxicity or lower likelihood of response in idiopathic nephrotic syndrome (INS) (Pac et al., 2021; Parvin et al., 2021). While not yet ready for daily clinical practice, this research paves the way for future practice where a child's genetic profile can potentially influence the choice and dosing of steroid-sparing agents from the very beginning.

Biomarker-Guided Therapy in Lupus Nephritis

Systemic Lupus Erythematosus (SLE) and lupus nephritis (LN) are characterized by flares and remissions that are hard to anticipate. Traditional markers like serum creatinine and proteinuria are lagging indicators of disease activity. Predictive biomarkers of flare, distinction between active disease versus chronic damage, and guiding individualized therapy are desperately needed (Anders & Fogo, 2014).

Several candidate biomarkers have been proposed. Anti-C1q antibodies are extremely specific for LN and also presage renal flare (Yung & Chan, 2015). Urinary monocyte chemotactic protein-1 (uMCP-1) and urinary vascular cell adhesion molecule-1 (uVCAM-1) are markers of renal inflammation and are linked with histologic activity and response to treatment (Nie et al., 2023; Parodis & Houssiau, 2022). More recently, multi-omic investigations (transcriptomics, proteomics) have now delineated molecular endotypes within LN that are potentially predictive of response to therapies such as mycophenolate mofetil versus cyclophosphamide (Banchereau et al., 2016). The future of LN therapy likely involves the incorporation of clinical data with a panel of genomic, transcriptomic, and proteomic biomarkers to assign patients at diagnosis to the most suitable therapeutic pathway (Table 2). Figure 2 illustrates layers of personalization in immunosuppressive therapy.

Framework in Pediatric Nephrology

Future Directions and Emerging Therapeutics

The holy grail of precision medicine is not only to diagnose but to treat based on molecular findings. We are now approaching a time when this is a reality for some pediatric kidney diseases.

Table 2: Applications of Personalized Immunosuppression in Pediatric Nephrology

Domain	Target	Technology/Marker	Clinical Application
Pharmacogenomics	Tacrolimus Dosing	*CYP3A5* Genotyping	Guides initial dosing to achieve therapeutic levels faster, reducing rejection/toxicity risk.
Pharmacogenomics	Azathioprine Toxicity	*TPMT / NUDT15* Genotyping	Identifies patients at high risk for myelosuppression; mandates dose reduction or alternative drug.
Pharmacodynamics	Corticosteroid Response/Toxicity	*NR3C1* Polymorphisms	(Emerging) May predict poor response or high toxicity, prompting early use of steroid-sparing agents.
Biomarker Monitoring	Lupus Nephritis Activity	Anti-C1q, uMCP-1, uVCAM-1	Provides real-time assessment of renal inflammation, predicts flare, and monitors treatment response.
Immune Monitoring	Transplant Rejection	Donor-Derived Cell-Free DNA (dd-cfDNA)	Non-invasive marker of allograft injury; can detect rejection prior to a rise in serum creatinine.

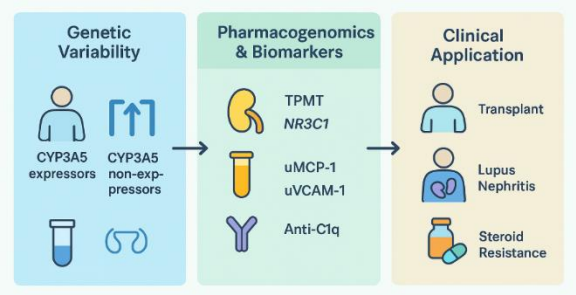

Figure 2: Personalized Immunosuppression

Targeted Therapies for Monogenic Disorders

The prime example is in atypical hemolytic uremic syndrome (aHUS), where over 60% of cases are linked to alternative complement pathway dysregulation. Identification of mutations in genes like CFH, CFI, and C3 directly led to the successful use of eculizumab, a terminal complement C5-inhibiting monoclonal antibody (Noris & Remuzzi, 2009). This therapy has transformed the prognosis of aHUS, preventing ESKD and reversing what were once life-threatening complications. Similarly, for cystinosis, the exact molecular defect in the CTNS gene allows for specific treatment with cysteamine that depletes lysosomal cystine accumulation (Nesterova & Gahl, 2013).

Novel therapies consist of small-molecule therapies, such as the use of oral galactose for certain GLA mutations in Fabry disease to stabilize the mutant enzyme (Benjamin et al., 2017), and gene-targeted therapy for specific COL4A mutations for Alport syndrome, currently in clinical trials (Savige, 2020). In diseases like ADTKD-UMOD from UMOD mutations, chemical chaperones to facilitate correct protein folding and trafficking are in the pipeline (Dvela-Levitt et al., 2019).

Gene Therapy and Advanced Molecular Interventions

The future holds even greater revolutionary promise with gene therapy. Although still largely experimental, early clinical trials are underway for diseases like X-linked Alport syndrome (Kashtan, 2022). Approaches include gene replacement (delivering a normal copy of the gene), gene editing (using CRISPR-Cas9 to correct the mutation), and RNA interference (to silence mutant alleles) (Peek & Wilson, 2023; Stein et al., 2023). Successful application of these technologies will represent the pinnacle of precision medicine, with the potential for a cure for monogenic kidney disease.

Challenges and Ethical Considerations

The integration of precision medicine into clinical practice is not without challenges. The cost and absence of insurance coverage for NGS and novel targeted therapies are among the factors perpetuating disparities in access (Manolio et al., 2019). The single interpretation of genetic variants of uncertain significance (VUS) remains a substantial diagnostic challenge, typically causing uncertainty as well as distress among clinicians and families (Richards et al., 2015). The discovery of incidental or secondary findings—a cancer predisposition, for example—complicates the ethics of what to tell whom, especially in the pediatric setting when the child is not able to give consent for adult-onset conditions (Kalia et al., 2017; Skrahin et al., 2023). Furthermore, robust data on the long-term successes and cost-effectiveness of precision medicine approaches still need to be generated to warrant their widespread adoption. One of the critical remaining tasks is making sure that these innovations do not exacerbate existing health disparities and that diverse populations are included in

genomic studies so that the variants and pharmacogenetic relationships are generalizable across the board (Popejoy & Fullerton, 2016).

Conclusion

Precision medicine has irrevocably changed the future of pediatric nephrology. The ability to diagnose monogenic causes of SRNS, CAKUT, and tubulopathies has provided diagnostic clarity, prognostic value, and diverted patients from ineffective and toxic treatments. Meanwhile, personalization of immunosuppression through pharmacogenomics and biomarker monitoring is also individualizing drug therapy in pediatric acquired glomerular disease and kidney transplantation, optimizing efficacy and minimizing toxicity. As we move forward, the pipeline from genetic discovery to targeted therapy is accelerating, with the potential for disease-modifying therapies and even cures. For the pediatric nephrology consultant, embracing this new paradigm is not optional. It requires a working understanding of the modalities of genetic testing, the interpretation of their results, and the pharmacogenetic and biomarker tools that are increasingly available. Although challenges of cost, equity, and ethics still exist, the way forward is clear: the future of pediatric nephrology lies in providing the right diagnosis and the right treatment to the right child, at the right time.

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