Current Pediatrics Reports (2026) 14:13
https://doi.org/10.1007/s40124-026-00387-9

REVIEW

Transcriptomic Insights into Pediatric Nephrotic Syndrome: Redefining Disease Mechanisms and Clinical Precision

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Received: 5 May 2026 / Accepted: 25 August 2026

Abstract

Purpose of the Article Pediatric nephrotic syndrome (PNS) is a clinically defined disorder characterized by proteinuria and edema but exhibits substantial biological heterogeneity that is not captured by conventional classifications. This review synthesizes current transcriptomic evidence to better understand disease mechanisms and explore its relevance for precision medicine.

Recent Findings Advances in transcriptomic technologies, including bulk RNA sequencing, single-cell and single-nucleus approaches, and spatial transcriptomics, have revealed distinct molecular signatures in PNS. Key pathways involve podocyte cytoskeletal disruption, immune and inflammatory activation, extracellular matrix remodeling, and mitochondrial dysfunction. These findings differentiate molecular profiles across phenotypes such as minimal change disease, focal segmental glomerulosclerosis, and steroid-sensitive versus steroid-resistant disease. Emerging high-resolution approaches further enable cell-type-specific and spatial insights into disease progression.

Summary Transcriptomics has redefined PNS as a spectrum of molecularly distinct endotypes and offers promising avenues for biomarker discovery and targeted therapy. However, clinical translation remains limited by small sample sizes, technical variability, and lack of longitudinal validation. Integration with multi-omics and functional studies is essential to develop reproducible, clinically actionable strategies for improving pediatric outcomes.

Keywords Pediatric nephrotic syndrome · Transcriptomics studies · Health care · Child health · Vulnerable population

Introduction

Pediatric nephrotic syndrome (PNS) is one of the most common chronic kidney disorders in children and remains a major cause of morbidity worldwide. Clinically, it is defined by massive proteinuria, hypoalbuminemia, oedema and hyperlipidaemia, but this apparently uniform presentation conceals remarkable biological heterogeneity. Children diagnosed under the same clinical label may follow vastly different courses, ranging from steroid-sensitive disease with excellent long-term prognosis to steroid resistant forms that progress to chronic kidney disease or end stage kidney failure [1, 2]. Conventional classification systems based on histopathologic findings (e.g., minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS)) and treatment response have improved risk stratification but do not fully explain the reasons for these different clinical outcomes. Furthermore, as a kidney biopsy is an invasive procedure, it is frequently avoided for use in young children; therefore, there are significant limitations in obtaining molecular insights at the very beginning of the disease process. Consequently, currently available clinical decision-making methods rely largely on trial-and-error methods for immunosuppression treatment. This gap between clinical phenotype and underlying biology underscores the need for molecular-level tools to enable a more accurate representation of the complexity of disease

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Published online: 03 September 2026

processes. Transcriptomics, which enables comprehensive analysis of gene expression patterns in relation to a range of tissues and cells, is a powerful way to study the dynamic molecular mechanisms that drive nephrotic syndrome in the pediatric population. Thus, transcriptomic approaches can provide opportunities to redefine the mechanisms of disease processes, identify early molecular alterations and produce hypotheses that are inaccessible using only traditional clinical or histological evaluations [3–5].

Transcriptomics refers to the large-scale study of RNA transcripts produced by the genome under specific conditions, reflecting active gene regulation rather than inherited variation alone. Transcriptomic profiling in paediatric nephrotic syndrome has provided a way to analyse the functional impact of podocytes, immune cells and renal tubular cells affected by injury, inflammation and therapy. Transcriptomics is sensitive to disease stage, environmental impact and treatment exposure; therefore, it is a valuable tool for analysing relapsing and remitting disorders like nephrotic syndrome, as opposed to the fixed DNA alterations that are captured with genomics [6, 7]. Advances in high throughput technologies due to the use of microarrays and RNA sequencing allow thousands of genes from kidney tissue, peripheral blood or urinary cells, to be analysed at the same time. Recent studies have produced distinctive gene expression signatures that correlate with steroid sensitivity/responsiveness, immune activation, extracellular matrix remodelling and podocyte cytoskeletal integrity. Transcriptomic data can coordinate the signals from both immune-mediated and intrinsic renal pathways, providing a platform to reconcile the previously conceptual debate regarding immune versus podocyte centric nephrotic syndrome. By having an overall view of the various complex molecular networks associated with nephrotic syndrome, the transcriptomic analysis yields a more appropriate systems-based view of paediatric nephrotic syndrome because of the multifactorial nature of the disease than approaches based on single pathway or single gene analyses alone [6, 8, 9].

The increasing interest in transcriptomics also suggests that it may have considerable translational value for the field of PNS research. Identification of molecular subtypes through gene expression signatures may help to identify patient subpopulations who are likely to respond to specific therapies or who are at an increased risk for disease progression and provide an important tool for the implementation of personalized therapeutic strategies for patients. Transcriptomic data can also identify pathways that are dysregulated within PNS and may identify novel targets for intervention, while also pointing out deficiencies in our understanding of the mechanisms underlying PNS. However, transcriptomic studies in PNS presently remain highly fragmented, with significant variability across study design, sample source and analytical approach used. Many of the reported gene expression signatures will require independent validation, functional characterisation and correlation with clinical outcomes over time before they can be used for clinical purposes [10, 11]. Additionally, given ethical and practical issues related to the availability of tissue from children, results obtained from smaller sample sizes will need to be interpreted cautiously. Given the above, it is appropriate that a comprehensive analysis of transcriptomic studies in PNS occurs at this time. By synthesising the current evidence, it will clarify what is known, what is not known and how transcriptomic research can be used more effectively to advance mechanistic understanding and ultimately improve care for children with PNS.

Pediatric Nephrotic Syndrome as a Molecularly Heterogeneous Disorder

For a long time, PNS has been recognised as a clinical syndrome comprising three main symptoms (heavy proteinuria, hypoalbuminemia and oedema), along with accompanying lab findings (e.g., hyperlipidaemia). Although the clinical triad has been a longstanding basis for the diagnosis and management of this syndrome, it does not adequately capture the complexities of the disorder at the biological level. Multiple factors contribute to the heterogeneity of disease presentations, like age of onset, frequency of relapses, sensitivities to steroid treatment, risk of progression to chronic kidney disease, long-term renal survival, etc. Furthermore, even when pathologically diagnosed with minimal change disease or focal segmental glomerulosclerosis, patients with nephrotic syndrome often exhibit a diverse range of outcomes. This variance describes a phenomenon where traditional diagnostic classifications only identify the ultimate or last common endpoint of glomerular injury [12, 13].

As evidence accumulates from genetic and molecular studies, it is becoming increasingly apparent that PNS may be better conceptualised as a spectrum of biologically distinct disorders that share similar clinical features. Ultimately, each type of disease state has its own distinct mechanism of action but will ultimately converge upon the glomerulus from different pathways through the cell and immune system, resulting in a similar outward appearance (i.e., nephrotic syndrome) as a consequence of fundamentally different and biologically distinct processes [12, 14].

At the podocyte level, patients show wide-ranging heterogeneity with respect to disrupted molecular programs. Some children show primarily transcriptional changes in programs related to actin cytoskeleton function, slit diaphragm assembly and attachment of protein complexes like nephrin and podocin, while others show evidence of cellular

stress (e.g., mitochondrial dysfunctions, impaired autophagy and programmed cell death). These two types can also be distinguished from each other based upon an increasing number of identified monogenic causes of nephrotic syndrome that include pathogenic variants in several genes like *NPHS1*, *NPHS2*, *WT1*, *PLCE1* and *ACTN4*, all of which support an endotype driven by intrinsic defects in podocytes. Early-onset forms of these genetic variants typically do not respond to corticosteroid treatment and, thus, demonstrate an underlying mechanistic independence from immune-mediated modulation. These recent findings suggest that podocytes can produce severe proteinuria in the absence of an inflammation-based trigger due to significant cellular structural or signalling abnormalities [13, 15, 16]. The variability of immune responses occurs when someone suffers from an illness resulting from dysfunction of their immune system. Aberrant signalling, along with transcriptomic changes in multiple genes, has been used to characterise a large percentage of patients diagnosed with idiopathic steroid-sensitive nephrotic syndrome and has been associated with abnormal distributions of T cell subsets, T cell receptor and cytokines. B cells may also be involved by presenting allergenic antigens to helper T cells (Th2), thus responding in an antagonistic manner to Th1-mediated activation through the action of IgE [17]. This has led to improvements in clinical outcomes when patients with FSGS have been treated with the use of rituximab, which targets B cells and depletes them for a specific time. There is emerging evidence for the role of dysregulated complement pathways in the pathogenesis of FSGS and related secondary disorders; this includes but is not limited to patients with secondary forms of focal segmental glomerulosclerosis, where dysregulation of the complement pathway is known to occur. The immune profile associated with these patients may also vary over time and additionally may interact with an underlying abnormality of podocyte susceptibility, which results in overlapping molecular expression patterns rather than defined classified categories. In addition, chronic proteinuria can result in tubular epithelial cell proliferation and may result in inflammatory and profibrotic signalling pathways being activated via transforming growth factor beta, leading to enhanced chronicity of injury and the eventual development of renal failure [18, 19].

PNS has dynamic molecular heterogeneity that changes over time. There are shifts in gene expression due to the child's stage of illness and the therapy received (e.g., upon relapse, remission). Recent studies have also highlighted that inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) reflect underlying variability in immune activation states, further supporting the heterogeneity of disease presentations in nephrotic syndrome. Each therapy, such as corticosteroids or calcineurin inhibitors, has different transcriptional and epigenetic impacts on gene expression [8, 13]. Thus, a snapshot of molecular profiles at one time point does not provide adequate information about the progression of the disease. To adequately assess transitions between active injury and repair states, longitudinal molecular profiling needs to occur. Recent advancements in single-cell and single-nucleus RNA sequencing techniques have revealed new and previously unidentified subpopulations of podocytes, activated parietal epithelial cells and immune cell subsets associated with podocyte injury that are usually lost in bulk tissue analyses. Additionally, spatial transcriptomics enables mapping the molecular programs to the structure of the kidney to better understand cell-to-cell interactions in situ. Understanding this level of complexity and dynamic change is critical to the rational development of biomarkers, improved design of clinical trials and implementation of mechanistic-based therapies [7, 19, 20].

Key Points:

- PNS represents a molecularly heterogeneous disease spectrum.
- Transcriptomics reveals distinct endotypes beyond histopathology.

Transcriptomic Technologies Applied to Pediatric Kidney Disease

Our comprehension of renal biology and pathology has been altered by the advent of high-throughput transcriptomic technologies. These technologies offer us an incredible resource for studying how many different molecular changes lead to podocyte injury, proteinuria and disease progression in the setting of PNS. The evolution of these technologies from profiling bulk tissue to spatially resolving single cells has provided a more detailed picture of the kidney and helped us identify the mechanisms of disease, markers and targets for therapy.

Bulk RNA Sequencing Approaches

Bulk RNA sequencing (RNA-seq) is the main technique utilised in modern transcriptomic profiling. In this technique, an RNA extract from homogenised tissue, such as a renal biopsy core, is obtained, converted into a cDNA library and then sequenced to determine the relative abundance of thousands of genes simultaneously. Gene expression data provide an average gene signature across all cell types present in a given sample, which includes podocytes, tubular epithelial cells, endothelial cells and resident immune cells, as shown in (Fig. 1) [20, 21].

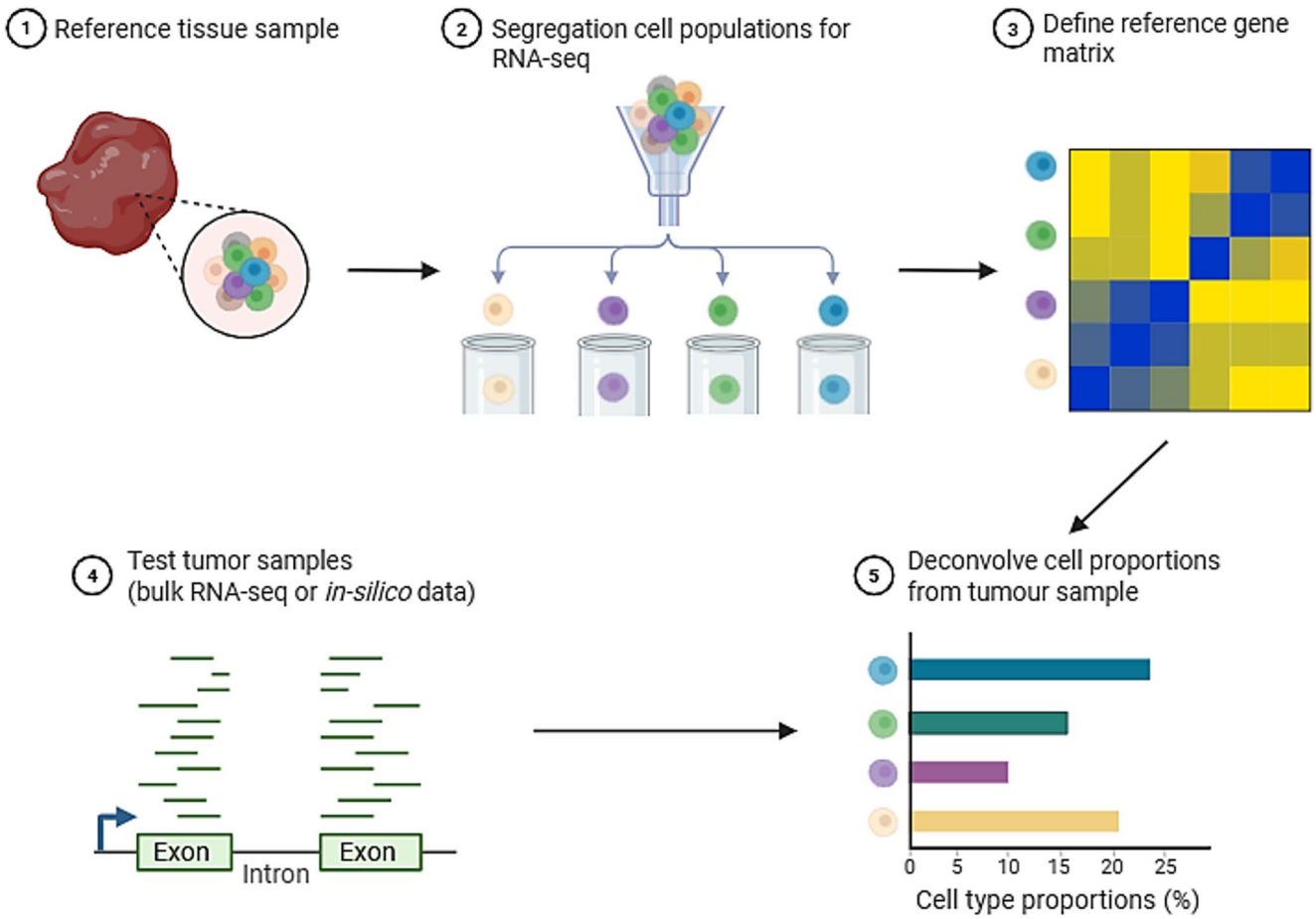

Fig. 1 Schematic diagram of the bulk RNA sequencing workflow. It illustrates the end-to-end workflow for bulk RNA sequencing, a cornerstone technology for dissecting the molecular underpinnings of PNS. The process begins with obtaining a sample from tissue or fluid and continues with isolating total RNA from that sample. After isolating total RNA, it is converted into cDNA via a reverse transcription reaction and then broken into smaller fragments to produce a cDNA library. The cDNA library is sequenced on a high-throughput sequencing platform. The millions of sequences generated are then aligned to a reference genome using computational methods to produce a matrix detailing the gene expression levels at the population level. The average RNA content in the sample is represented in the matrix and allows for identifying strong, population-level transcriptional signatures that distinguish between subtypes of disease or predict responsiveness to treatment. This type of analysis is extremely effective due to the ability to represent gene expression at the population level; however, it does sacrifice cellular resolution

In cases of pediatric kidney disease, bulk RNA-seq has been critical for the identification of transcriptional signatures associated with disease. Recent studies have used bulk RNA-seq to differentiate between the histological phenotypes of nephrotic syndrome (NS), such as MCD vs. FSGS, by showing discrete patterns of podocyte injury, extracellular matrix remodelling and immune system activation in each of these histological subtypes. Bulk RNA-seq of kidney tissue has also been used to identify major pathological pathways related to cytoskeletal organisation, slit diaphragm integrity and mitochondrial function. One important eventual clinical application of these findings is to identify RNA biomarkers in peripheral blood or urine that would provide information on the underlying renal pathophysiology and enable non-invasive monitoring of disease progression and treatment response. While useful, it is limited by not being able to provide cellular resolution; it cannot tell you specifically which cell populations are responsible for observed changes in expression, which is a major challenge in a heterogeneous organ like the kidney [22, 23], as shown in Table 1.

The future of bulk RNA-sequencing in pediatric nephrology is twofold: firstly, it is necessary for validating a large cohort of candidate genes and single-cell study discoveries. Secondly, their integration with other "omics," including proteomics or genomics, will yield a more thorough and complete understanding of the complete system of the affected children. Beyond this application, bulk RNA-sequencing can be used to analyse RNA contained in urinary-derived extracellular vesicles, i.e., liquid biopsies, enabling robust, non-invasive indicators as to the activity of the disease and response to therapy for children suffering from these malignancies [21, 23].

Table 1 Comparison of major transcriptomic technologies in pediatric nephrotic syndrome research. This provides a clear, concise comparison of the key technologies, especially to understand the strengths, weaknesses and specific applications of each method in the context of pediatric kidney disease

Technology	Cellular Resolution	Sample Requirement & Type	Advantages in PNS Research	Primary Constraints
Bulk RNA Sequencing	Tissue-level (averaged)	Requires fresh or frozen tissue; can use whole biopsy.	Cost-effective for large cohorts; good for identifying robust, population-level signatures; established analytical pipelines [20, 23].	Lacks cellular resolution; cannot identify cell-type specific changes; signals from rare cell populations are masked [21, 22].
Single-cell RNA Sequencing (scRNA-seq)	Single-cell	Requires fresh, viable tissue; dissociation can be challenging.	Unbiased identification of cell types and states; discovery of rare cell populations; detailed characterisation of cellular heterogeneity [21, 23].	Higher cost; requires specialised equipment and expertise; potential for dissociation-induced artefacts; limited cell numbers per sample [24, 25].
Single-nucleus RNA Sequencing (snRNA-seq)	Single-nucleus	Can use frozen tissue; suitable for archived biopsies.	Enables use of precious archived clinical samples; captures nuclear transcripts from cells difficult to dissociate (e.g., podocytes) [21, 24].	Captures primarily nuclear pre-mRNA, not full cytoplasmic transcriptome; may miss lowly expressed genes [21, 25].
Spatial Transcriptomics	Sub-cellular to multi-cellular	Requires fresh or frozen tissue sections.	Preserves spatial context of gene expression; links molecular signatures to histopathological features; enables study of cell-cell communication in situ [26–28].	Currently, lower sensitivity than scRNA-seq; higher cost; data analysis is complex; resolution is still improving [29–31].

Single-Cell and Single-Nucleus Transcriptomics

To overcome the resolution limitations of bulk RNA-seq, single-cell RNA sequencing (scRNA-seq) and single-nucleus RNA sequencing (snRNA-seq) have emerged as transformative technologies. scRNA-seq and snRNA-seq platforms are changing the way researchers can quantify gene expression from the kidneys, allowing researchers to obtain an unprecedented understanding of the cellular heterogeneity in the kidney. Clinical researchers must understand the differences between scRNA-seq and snRNA-seq, as scRNA-seq typically requires newly obtained, viable tissue, whereas snRNA-seq can be performed on previously frozen samples. This is because pediatric kidney biopsies often contain scarce amounts of viable tissue and snRNA-seq is well-suited for archived samples [21, 32].

Utilising scRNA-seq and snRNA-seq has revealed immense information regarding pediatric nephrotic syndrome (NS). Researchers are using scRNA-seq to define the specific transcriptional programming states of podocytes following injury and are able to identify the specific factors that cause foot process effacement and detachment. scRNA-seq has also helped identify pathogenic and active transcriptional programming states in parietal epithelial cells that are associated with crescent formation and segmental sclerosis in children with FSGS. In addition, these technologies have enabled a high-resolution characterisation of infiltrating immune cells, allowing researchers to determine their activation states and how they interact non-pathogenically with resident renal cells. Overall, the use of single-cell transcriptomic technologies such as scRNA-seq and snRNA-seq has allowed researchers to identify previously unseen rare cell populations and previously hidden disease-associated states that cannot be detected using bulk sequencing technology, as given in (Fig. 2) [24, 25, 32].

In order to establish a basis for developing long-term, continuous assessment of cell changes over time, it is essential that large-scale, multicentre scRNA-seq projects be performed at multiple sites to generate comprehensive cell atlases for aged and disease-associated human nephron populations representing healthy and diseased states across the spectrum of pediatric nephron age and disease. Although these findings were derived from IgA nephropathy, another glomerular disease, they provide a valuable comparative framework for understanding shared mechanisms of disease progression in NS. Utilising longitudinal sampling will enable researchers to follow cellular changes that occur as a result of therapy. Future directions include the incorporation of scRNA-seq data with other single-cell technologies (e.g., single-cell ATAC-seq to evaluate chromatin accessibility, CITE-seq to determine surface proteins) to assemble a multi-omic profile for each cellular element [24, 25]. This will permit a comprehensive understanding of the signalling pathways regulating phenotypic presentation of disease and

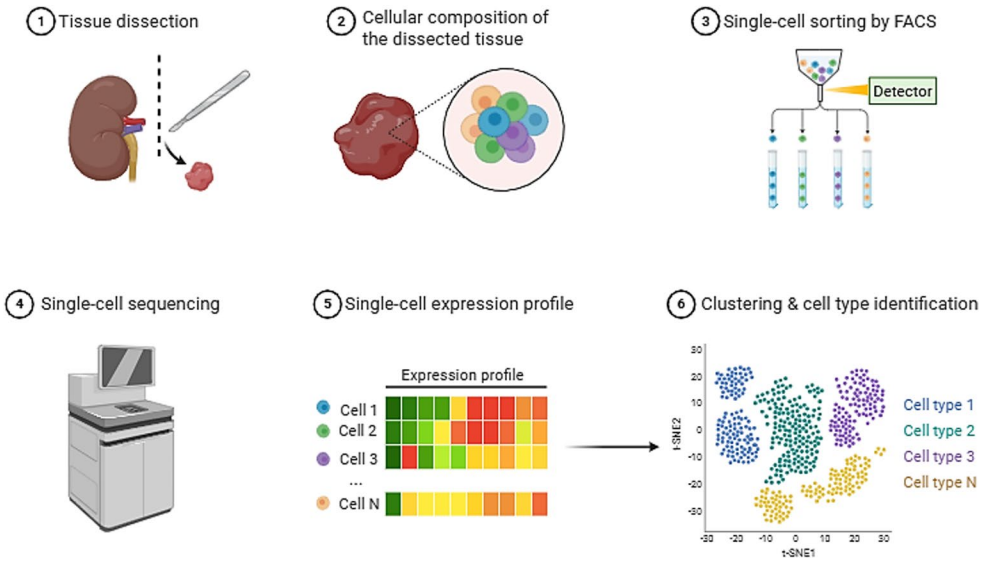

Fig. 2 Single-cell RNA sequencing workflow. It outlines the key steps in single-cell RNA sequencing. A single-cell suspension is created from a complex tissue that contains multiple cells, like those found in a kidney biopsy begins with dissociating the whole tissue into single cells and isolating each of those cells in order to capture the RNA, reverse-transcribing it and converting it to a barcoded cDNA library. The cells are then sequenced and through computational means, the cells are grouped based on similarities in their gene expression profiles. It is through this grouping that a researcher can determine whether there are distinct cell types, rare cell types or new cell states within the tissue. Single-cell sequencing represents a new methodology for overcoming the averaging of bulk RNA sequencing and can provide insight into the pathology of the cell

could provide candidates for developing precision therapies targeting previously unidentified cell surface receptors.

Spatial Transcriptomics in Renal Tissue

Single-cell transcriptomics provides information regarding the identity of specific cell populations and their gene expression patterns. Spatial transcriptomics adds the critical "where" aspect to this data by providing information about the localisation of specific cell populations within the architecture of tissue. This technique allows researchers to collect gene expression data directly from tissues, preserving the spatial context of these cells. In kidney tissues, the regulated organisation of cells within the glomerulus, tubule and surrounding tissues is essential for the organ's function and the development of disease, as shown in (Fig. 3) [26, 27].

The use of spatial transcriptomics will dramatically increase our understanding of paediatric nephrology by linking molecular signatures to histopathological characteristics. Applications in which spatial transcriptomics might be utilised for this purpose include mapping the exact locations of damaged podocytes within the glomerulus and identifying the spatial relationship between activated fibroblasts and regions of interstitial fibrosis. In addition, spatial transcriptomics can be used to gain insight into cell-cell communication in situ, as given in Table 1. For instance, how infiltrating T cells interact with and/or damage tubular epithelial cells located in a specific region of the nephron [29, 30].

Higher resolution and multiomic integration will define the future of spatial transcriptomics. New technology advances are driving us toward the ability to resolve single cells and even subcellular structures, enabling accurate mapping of gene expression in large and complicated structures like the glomerulus. Ultimately, the ability to perform spatially resolved multiomic analysis with respect to the same tissue section, assessing RNA, protein and metabolite levels simultaneously, will permit creation of an integrated spatial map of a patient's kidney biopsy. Pathologists and clinicians will then be able to use this integrated spatial map of the biopsy at a molecular level to identify disease mechanisms, predict prognosis and identify the best target therapy for each child presenting with nephrotic syndrome [28, 29, 31].

Key Points:

- Single-cell and spatial approaches enhance mechanistic resolution.

Transcriptomic Signatures of Glomerular Cell Types

Advanced high-resolution transcriptomic technologies have revolutionised our understanding of the PNS by enabling researchers to interrogate specific cell types that are affected by disease-related changes on a molecular level. When looking at the glomerulus as a whole, we may envision it

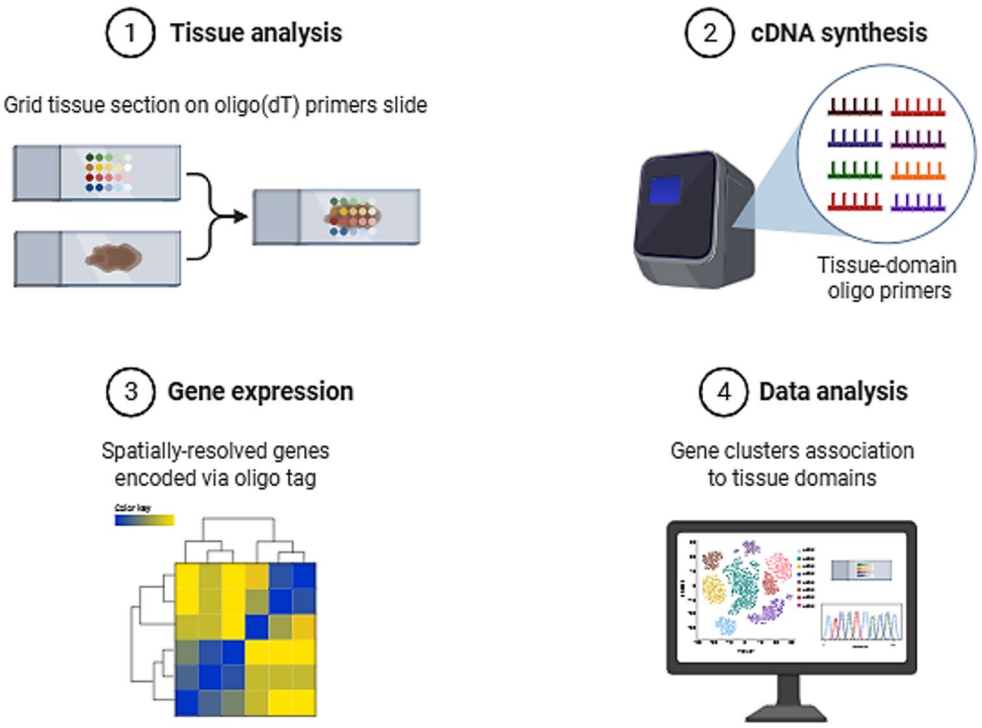

Fig. 3 Spatial transcriptomics workflow for mapping nephrotic syndrome. It describes the process of spatial transcriptomics, including how to prepare kidney biopsies by cryosectioning each sample and placing it onto a slide with spatially barcoded slides that have been permeabilised, allowing mRNA molecules to hybridise with adjacent barcoded probes. This is followed by on-slide reverse transcription, generating a cDNA library that is spatially tagged and high-throughput sequencing is performed. A bioinformatic analysis that maps the sequence results back onto the tissue image, producing a spatially resolved gene expression map. Thus, providing a valuable means of exploring the microenvironmental interactions that drive nephrotic syndrome pathology

as a single unit. Multiple transcriptomic studies have shown that the glomerulus is comprised of many different specialised cell types and each of these cells responds uniquely to cellular injury. Although podocyte loss is still the primary underlying cause for nephrotic syndrome, evidence has grown to support that all of the following cell types: parietal epithelial, mesangial, endothelial cells, as well as tubulointerstitial compartments, contribute to the development and progression of nephrotic syndrome [33, 34].

- **Podocyte Specific Transcriptional Alterations**

Studies utilising single-cell/single-nucleus RNA sequencing consistently demonstrate that podocyte injury is associated with a decrease in the expression of genes that are critical for protecting slit diaphragm integrity and for maintaining actin cytoskeletal organisation. The decreased expression of *NPHS1*, *NPHS2*, *ACTN4* and other podocyte-specific structural genes diminishes the stability of the filtration barrier and leads directly to proteinuria [33, 35].

Transcriptomic studies provide insight into additional mechanisms of injury that are specific to particular diseases. In steroid-sensitive nephrotic syndrome, which includes minimal change disease, podocytes frequently show transcriptional profiles consistent with dedifferentiation and cytoskeletal remodelling but with limited activation of apoptotic pathways. Conversely, in steroid-resistant forms of nephrotic syndrome, including FSGS, podocytes demonstrate a greater degree of transcriptional disruption with aberrant activation of genes related to the cell cycle, activation of profibrotic signalling pathways and up-regulation of genes associated with the stress response. This suggests that forced re-entry into the cell cycle results in maladaptive responses in terminally differentiated podocytes and leads to accelerated podocyte depletion [33, 36].

The identification of additional transcriptomic signatures suggests that mitochondrial dysfunction, oxidative stress and impaired autophagic flux are all contributors to progressive podocyte injury. These pathways suggest that metabolic stress is an important factor in the loss of podocytes as well as the chronicity of disease. Current translational studies are increasingly focused on identifying molecular targets and non-invasive biomarkers specific to podocytes, which include mRNA and microRNA species found in urinary extracellular vesicles, for the purposes of early diagnosis and therapeutic monitoring [34, 37].

- **Parietal Epithelial Cell Transcriptomes**

Parietal epithelial cells lining Bowman's capsule were traditionally regarded as structurally inert. However, transcriptomic profiling has redefined these cells as active participants in glomerular disease, particularly in focal segmental glomerulosclerosis. Recent single-cell analyses show that there is a population of activated parietal epithelial cells that express elevated levels of genes involved in the proliferation, migration or production of extracellular matrix. In addition, *CD44* and *PAX2* are used as markers to

identify this group of cells and both of these molecules are found to be elevated in conjunction with progressive glomerular injury [38, 39].

The transcriptional profile of activated parietal epithelial cells reflects a shift toward a mesenchymal and profibrotic phenotype. This change is thought to take place in response to the loss of podocytes. Parietal epithelial cells will try to migrate to the glomerulus and cover the exposed area of the basement membrane; however, this process promotes fibrosis by laying down a matrix to fill in the area that has lost podocytes, causing distortion to the capillary loops and causing glomerulosclerosis. Researchers are working to identify the pathways that control the change in phenotype of activated parietal epithelial cells. This includes how genes are regulated through developmental factors and those mediated by growth factors, which cause cell division [9, 36, 40, 41].

From a clinical standpoint, determining the transcripts expressed by parietal epithelial cells will help clinicians identify which patients are likely to develop progressive glomerulosclerosis. Targeting mediators of the activation pathway of parietal cells presents a new avenue for preventing glomerulosclerosis and preserving kidney function in patients with kidney disease.

- **Mesangial and Endothelial Cell Transcriptomes**

Mesangial and glomerular endothelial cells play essential roles in maintaining the structural and functional integrity of the glomerulus. Research done on transcriptomics has shown how cells in this area can undergo secondary changes that are still biologically relevant to the health of the kidney after injury has occurred to the podocyte. In particular, mesangial cells have been reported to show increased amounts of many pro-inflammatory cytokines, chemokines and extracellular matrix-related genes, which is an indicator of mesangial expansion related to specific types of nephrotic syndrome [42, 43].

Furthermore, glomerular endothelial cells display evidence of injury/dysfunction through gene analysis, which reflects a lack of expression of the receptors that mediate vascular endothelial growth factor signalling, suggesting that podocyte injury may, in turn, lead to stress on endothelial cells due to diminishing integrity of the capillary structures. More recently, there is evidence that the activation of complement pathways and transcriptional signatures that relate to endothelial-to-mesenchymal transition can lead to inflammation and thrombotic complications in patients with severe disease. Identifying any endothelial-specific transcriptional signature within the patient may allow for stratification of these patients and also help identify treatment options for targeting complement activation or providing protection for the endothelium [44, 45].

- **Tubular and Interstitial Transcriptional Responses**

Nephrotic syndrome is a glomerular disorder, but it is now being understood that the progression of tubulointerstitial injury has a significant impact on long-term renal prognosis. An analysis of transcriptomics on renal tubular epithelial cells exposed to prolonged periods of proteinuria revealed broad activation of inflammatory signalling pathways, including nuclear factor kappa B-mediated inflammatory response genes, markers of oxidative stress, endoplasmic reticulum stress and cellular dedifferentiation. These maladaptive processes promote interstitial inflammation and fibrogenesis [46, 47].

Single-cell transcriptomic investigations of the interstitial compartment have been able to identify activated fibroblasts and myofibroblasts that express high amounts of collagen and various other extracellular matrix components. In addition, immune cell profiling has revealed differing macrophage and T lymphocyte and other infiltrating cell populations' contributions towards either promoting tissue damage or healing. The balance among these programs of cellular biology appears to be important in determining the progression to CKD [47–49].

The clinical promise of transcriptomics from the tubulointerstitial compartment stems from its potential to provide prognostic information. The ability to detect early transcriptional patterns indicative of tubular damage and interstitial inflammation will assist with timely intervention through appropriate therapy. These types of interventions will be critical to combatting fibrosis, which remains an unfulfilled challenge in managing PNS and preventing end-stage kidney disease.

Molecular Pathways Mapped by Transcriptomic Profiling

The high-resolution nature of transcriptomic profiling has provided scientists with a clear and detailed picture of the complex molecular landscape of PNS. These analyses also consistently identify multiple dysregulated biological pathways underpinning the pathogenesis of PNS diseases. The most critical ones include those involved in the alteration of podocyte structure and function, as well as alterations in the dynamics of the extracellular matrix, alterations in immune-mediated mechanisms and alterations associated with mitochondrial dysfunction and oxidative stress signalling. Together, these molecular mechanisms define the molecular aspects of the disease.

Cytoskeletal & Slit Diaphragm Organisation

Dysregulation of gene networks involved in podocyte cytoskeletal architecture and slit diaphragm integrity has been detected by many transcriptomic analyses performed on samples from patients with PNS. The actin cytoskeleton is critical for podocyte foot process maintenance and provides an anchoring mechanism for slit diaphragm complexes that create the final barrier against protein loss. Changes in gene expression for actin-binding/regulatory proteins like ACTN4, along with components of small Rho GTPase signalling pathways such as RHOA and CDC42, have been described in patients. These molecules are also essential in the polymerisation, branching and spatial organisation of actin filaments [35, 50].

Concurrently, transcripts for proteins forming slit diaphragms, NPHS1 and NPHS2, are expressed in reduced quantities or in a non-physiological pattern within specific subgroups of PNS. Nephrin and podocin play a critical role in stabilizing cell-cell junctions and signalling between podocytes via the slit diaphragm. Therefore, any dysregulation of nephrin and podocin expression can potentially compromise the filtration barrier. Multiple studies suggest transcriptional changes may precede obvious histopathological changes associated with nephron injury, indicating that cytoskeletal junctional pathway disruptions may represent very early pathophysiological events [51, 52].

The various levels of dysregulation in cytoskeletal gene expression among patients suggest some biological variation in PNS. In patients with reversible actin reorganisation based on transcriptional patterns, this is consistent with a high rate of response to steroid treatment seen in MCD. Conversely, patients with chronic changes in pathways that regulate adhesion between cells, mechanotransduction or stability of the cytoskeleton have similar features to patients with FSGS and progressive podocyte loss. Continued activation or deactivation of Rho GTPase signalling may lead to the effacement of podocyte foot processes and subsequent detachment of podocytes from the glomerular basement membrane, both of which are important steps in producing an irreversible glomerulus injury [53, 54].

However, transcriptomic studies alone cannot distinguish whether the changes in gene expression in the cytoskeleton occurred because there is a defect in those genes or if they are due to adaptive changes as a result of immunologically or metabolically induced stress. Functional validation using experimental systems is required to determine causal relationships. However, the consistent finding of gene networks that are associated with the cytoskeleton and slit diaphragm indicates the importance of podocyte structure in the development of any form of PNS.

Extracellular Matrix Remodelling and Fibrosis

There are considerable and observable alterations in the gene expression for the ECM and the genes regulating turnover of the ECM using transcriptomic studies in PNS. The involvement of the ECM's structural matrix components, like *COL1A1* and *COL4A1*, with an increase in production of interstitial and basement membrane collagen is indicative of early remodelling processes contributing to the development of the disease by expanding both the mesangial and interstitial compartments. Upregulation of profibrotic mediators such as *TGFβ1* and *CTGF* indicates the activation of pathways that promote deposition of the ECM, cellular transdifferentiation, and blocking of ECM degradation. In addition to these findings, the changes in the expression pattern of matrix metalloproteinases and their inhibitors together indicate an imbalance between the composition of ECM and the proteolytic turnover of ECM [55, 56].

Limited remodelling of the ECM after injury may be a physiological response of the body to stabilise the injured ECM, but persistent stimulation of pathways involved in remodelling of the ECM can predispose the kidney to the development of glomerulosclerosis and tubulointerstitial fibrosis, both of which are associated with progressive chronic kidney disease. Profibrogenic gene expression signatures that are associated with ECM remodelling are more pronounced in both steroid-resistant nephrotic syndrome and in patients with an estimated glomerular filtration rate (eGFR) of $\leq$70 ml/min, suggesting that these signatures can be used as early molecular indicators for identifying chronicity. Distinguishing between adaptive repair responses and maladaptive fibrogenic responses is difficult, especially when using cross-sectional data; therefore, the importance of longitudinal sampling and integration with clinical outcomes is highlighted. This indicates that ECM-based transcriptional programs offer a mechanistic understanding of how proteinuria may ultimately convert into permanent structural damage of the kidney [56, 57].

Immune & Inflammatory Activation

In studies on the transcriptome of the PNS, researchers have repeatedly observed evidence of activation of both innate and adaptive immune/inflammatory gene expression programs. Analyses of differential gene expression revealed an enriched representation of components of cytokine signalling pathways, which include JAK1, STAT6, etc. and an increased level of transcription of complement pathway genes C3 and CFB, markers for T cell activation in addition to evidence of signature patterns of differential transcriptome gene expression in renal biopsies and urinary sediment cells, as given in Table 2. This suggests that effects of

Table 2 Key molecular pathways implicated by transcriptomics in pediatric nephrotic syndrome. The specific pathways are linked to their functional consequences in the kidney, providing a clear summary of the disease's pathophysiology

Molecular Pathway	Role in Pediatric Nephrotic Syndrome	Representative Genes Identified by Transcriptomics	Therapeutic Implications
Cytoskeletal & Slit Diaphragm Organisation	Disruption leads to foot process effacement and loss of filtration barrier integrity.	Downregulation of *NPHS1*, *NPHS2*, *ACTN4*; altered expression of RHOA, CDC42 pathway genes [35, 51].	Targeting actin dynamics (e.g., RhoA inhibitors); therapies to stabilise slit diaphragm proteins [53, 54].
Extracellular Matrix (ECM) Remodelling & Fibrosis	Excessive ECM deposition leads to glomerulosclerosis and tubulointerstitial fibrosis, driving CKD progression.	Upregulation of *COL1A1*, *COL4A1*, *TGFB1*, *CTGF*; matrix metalloproteinases genes [55, 56].	Anti-fibrotic therapies (e.g., anti-TGF-β agents); targeting specific collagen synthesis pathways [56].
Immune & Inflammatory Activation	Immune dysregulation leads to the production of permeability factors and direct podocyte injury.	Upregulation of cytokine signalling genes (*STAT6*, *JAK1*), complement genes (*C3* and *CFB*) and T-cell activation markers [58, 59].	Immunosuppressive agents; targeted biologics (e.g., anti-*CD20* rituximab); complement inhibitors [60].
Mitochondrial Dysfunction & Oxidative Stress	Podocyte energy failure and damage from reactive oxygen species contribute to injury and apoptosis.	Downregulation of mitochondrial respiration genes (*ND1*, *COX6A1*); upregulation of *NOX4*, *SOD2* [61, 62].	Antioxidant therapies: agents that improve mitochondrial biogenesis and function [62, 63].

altered immune function may have a role in the pathogenesis of disease [58, 59].

The intensity and composition of immune activation vary across patients, with some exhibiting predominance of T cell-mediated responses and others demonstrating stronger innate inflammatory or complement-related patterns. It is also important for researchers to note that all immune-related transcripts are seen in renal resident cells (podocytes and tubular epithelial cells), which indicates renal resident cells are also actively involved in the inflammatory response and are not just a target. Increased expression of antigen presentation pathways, as well as pattern recognition receptors within the kidney, indicates that there are many locally amplified immune responses occurring within the kidney microenvironment. When immunosuppressive therapies are started, many of the transcriptional programs associated with an activated immune system may be attenuated; however, a significant number of residual immune activations may remain after immunosuppressive therapies are completed and can possibly contribute to relapse or incomplete remission. A detailed understanding of how the systemic immune system signals and the intrinsic renal mechanisms of injury interact will require the combination of immune gene expression data with cell-type-specific and spatial transcriptomic methodologies [59, 64].

Mitochondrial Dysfunction & Oxidative Stress

Transcriptomic analyses in PNS have identified perturbations in genes regulating mitochondrial respiration and redox homeostasis, particularly in steroid-resistant and progressive forms of disease. The maintenance of cytoskeletal organisation and slit diaphragm integrity in podocytes is dependent on oxidative phosphorylation. The decreased expression of genes encoding components of the electron transport chain, including mitochondrial respiratory subunits, such as *ND1* and *COX6A1*, indicates reduced ATP production and impaired bioenergetic capacity. In parallel to this, the increased transcription of oxidative stress-related genes such as *NOX4* and *SOD2* indicates that there is increased production of reactive oxygen species (ROS) and that the antioxidant defence mechanism has been activated [61, 62], as seen in Table 2.

Although *SOD2* functions as a mitochondrial scavenger of superoxide, the up-regulation of *SOD2* is frequently a compensatory response to oxidative stress rather than a mechanism of protection. The accumulation of excess ROS can interfere with actin dynamics, damage mitochondrial DNA and activate pro-apoptotic signalling pathways, all of which can lead to injury of podocytes and their subsequent detachment. Additionally, persistent mitochondrial dysfunction may impair mitophagy and further amplify cellular damage caused by oxidative stress. The molecular signatures discussed above correlate with histopathologic findings of segmental glomerulosclerosis and with the decline in renal function, reinforcing their association with disease progression. While transcriptomic data alone cannot establish causality, they do identify Mitochondrial bioenergetics and redox regulation as potential biological contributors to the susceptibility of podocytes and as potential therapeutic targets for selected molecular subtypes of PNS [59, 64].

Transcriptomic Differences Across Pediatric Nephrotic Syndrome Phenotypes

PNS encompasses a range of clinical and histopathological phenotypes that share common diagnostic features yet differ markedly in treatment response and long-term outcome. Traditional methods of diagnosing patients with kidney diseases have used phenotypic descriptions like minimal change disease, focal segmental glomerulosclerosis and steroid responsiveness to help determine the patient's treatment regimen, but have not had much success determining the underlying biological mechanisms of disease. Alternatively, conducting transcriptomic analyses offers an additional means to identify how gene expression programs differ between similar and dissimilar phenotypes, thereby providing insights into the molecular pathways that are shared or distinct between these phenotypes. The characterisation of transcriptomic expression variation between phenotypes may assist in improving disease classification and may also help to explain the rationale for why multiple biological pathways lead to similar clinical presentations. The majority of data that is currently available for transcriptomic analyses has been generated from studies with small sample sizes using a cross-sectional approach. Nonetheless, emerging transcriptomic data provide valuable insight into the biological basis of phenotypic diversity seen among patients with PNS [6, 7, 65].

Minimal Change Disease

Minimal change disease is the most common cause of PNS and is classically defined by the absence of overt structural abnormalities on light microscopy. Research using transcriptomic analyses has demonstrated that minimal-change disease is not simply a normal histological view of disease without molecular change. Profiled gene expressions show that there are alterations in the pathways that mediate podocyte cytoskeletal dynamics, signal transduction and activation of stress responses, even though histology appears normal. Minimal change disease usually has relatively minor transcriptional changes compared to other phenotypes; however, minimal change disease does have some pathways that are activated in response to fibrosis and inflammation. However, the transcriptional changes of immune-related genes are the most often seen, particularly in relation to T cell signal transduction and the cytokine cascade, suggesting that an immune-driven disease model exists [65, 66].

Additionally, many of the transcriptional changes observed appear to be reversible, with partial normalisation occurring during remission. This molecular plasticity corresponds to the good clinical outcome and excellent steroid responsiveness exhibited by most children with minimal change disease. Nevertheless, there is evidence of heterogeneity within this phenotype; some patients continue to experience recurrent episodes or require prolonged use of steroids. Differences in gene transcripts between subgroups indicate that minimal change disease is likely to comprise several molecular subtypes rather than being a single continuum. Thus, findings support the proposition that minimal change disease is more than a purely functional disorder and highlight the role of transcriptomic data in defining the underlying molecular complexity of such diseases [66, 67].

Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis represents a more heterogeneous and clinically severe phenotype of PNS, characterised by segmental scarring of glomeruli and a higher risk of progression to chronic kidney disease. Pathways involved in extracellular matrix remodelling, fibrosis and cellular stress are more frequently activated than in minimal change disease, according to transcriptomic studies. When looking at gene expression profiles, there is evidence of upregulation of collagen production, matrix-modulating enzymes and profibrotic signalling pathways, indicating both structural damage and maladaptive repair mechanisms. In addition, downregulation of podocyte-specific transcripts associated with differentiation/survival suggests that there may be irreversible podocyte loss or dysfunction [4, 68].

There are also gene expression programs associated with immune/inflammatory responses, but these are seen co-activated with the intrinsic renal injury pathways rather than being the dominant features of the sample. The wide range of transcriptomic heterogeneity within focal segmental glomerulosclerosis reflects the diversity of underlying causes, such as genetic, adaptive and immune-mediated mechanisms. Some of the expression patterns are similar to those that have been observed in steroid-resistant disease, whereas others are more comparable to milder forms of disease. Molecular variability provides further explanation for the differences in responses to treatment and outcomes among patients diagnosed with the same histological type. The data obtained from transcriptomic profiling further suggests that focal segmental glomerulosclerosis represents a group of injury types with several underlying molecular causes instead of a single disease process [68, 69].

Steroid-sensitive versus steroid-resistant disease

Steroid responsiveness is one of the most clinically relevant distinctions in PNS and transcriptomic studies provide insight into the molecular basis of this divergence. Steroid-responsive diseases are usually linked with transcriptional

signatures that indicate immune modulation, preservation of podocyte structure and limited activation of fibrotic pathways. Genes that have a role in glucocorticoid signalling, immune regulation and cellular stress responses are often dynamically regulated with the administration of glucocorticoids, suggesting intact regulatory mechanisms. By contrast, steroid-resistant disease has distinct transcriptomic profiles associated with continued activation of fibrosis and extracellular matrix-related pathways. Commonly observed include downregulation of podocyte differentiation markers and upregulation of inflammatory transcripts even at the earliest stages of the disease [69, 70].

The differences between steroid sensitivity and resistance suggest that steroid resistance may be due to fundamentally differing molecular drivers, rather than simply a failure of treatment. There are some patients who have identified an overlap between the two conditions, who may have intermediate or evolving transcriptional patterns. As such, the existence of an overlap necessitates caution in making overly deterministic conclusions from the transcriptomic data alone. Although differences in transcriptomic patterns between steroid sensitivity and steroid resistance continue to be defined, further validation, longitudinal data collection and integration with clinical and genetic data are necessary before translating these findings into predictive tests.

Developmental and Age-Specific Transcriptional Context in Pediatric Nephrotic Syndrome

To accurately interpret transcriptomic data in the postnatal kidney, it is necessary to evaluate findings based on the normal development of the kidney. Completion of nephrogenesis occurs in humans during the last trimester of gestation (approximately between 34 and 36 weeks) and no additional new nephrons are generated after birth, as shown in Table 3. However, existing nephron structures will continue to mature and function during infancy and childhood through changes to glomerular size and podocyte foot process maturation, slit diaphragm composition refinement and glomerular filtration rate increase during the first years of life. Gene expression within these developing nephron structures also changes with age, including the expression of genes that encode cytoskeletal proteins, extracellular matrix proteins and transporter proteins. Therefore, the reference transcriptome of an infant's kidney differs greatly from that of an adolescent. Using non-age-matched controls in pediatric transcriptomic studies could lead to misidentifying developmental genes as being part of a pathological process. Rigorous pediatric transcriptomic studies will need to incorporate stratified analyses and the integration of developmental reference datasets to differentiate disease-associated dysregulation from physiological maturation [71, 72].

In congenital nephrotic syndrome (CNS) and infantile nephrotic syndrome (INS), the developmental environment is very important. CNS occurs in the first 3 months of life, while INS occurs between 3 months and 1 year. The majority of nephrotic syndrome types are caused by monogenic variants of genes essential for the development of the glomerular filtration barrier, such as *NPHS1*, *NPHS2*, *WT1*, *LAMB2* and *PLCE1*, as mentioned in Table 3. These genes code for structural and regulatory proteins important in podocyte differentiation and slit diaphragm formation. Transcriptomic studies on infants with disease show patterns consistent with podocyte damage, such as abnormal actin cytoskeletal regulation, cell adhesion pathways and stress-response signalling, as well as evidence of immune activation that is more prominent in the later childhood form of nephrotic syndrome but is less prominent in the monogenic type. Expression profiling can be used in combination with molecular genetic testing to identify patterns consistent with primary structural podocyte disease. Identifying a developmental genetic cause is very important clinically because most of the monogenic types do not respond to steroids or other immunosuppressive agents [72, 73].

In contrast, minimal change disease, which accounts for the majority of nephrotic syndrome cases in children

Table 3 Age-specific transcriptional and etiological drivers in pediatric nephrotic syndrome. The critical link between a child's age, the likely underlying cause of the disease and the corresponding molecular profile

Age of Onset	Predominant Etiology	Transcriptomic Features	Representative Genes/ Pathways
Congenital/Infantile (< 1 year)	Monogenic/Structural Podocytopathy	Primary podocyte developmental arrest, ER stress, defective slit diaphragm assembly.	*NPHS1*, *NPHS2*, *WT1*, *LAMB2*; unfolded protein response pathways [72, 73].
Early and Late Childhood (2–12 years)	Immune-mediated	T-cell and B-cell activation, cytokine-mediated podocyte dysfunction.	Genes in Th2 pathways (*GATA3*, *IL4*), B-cell activation (*CD79A*) [72, 74].
Adolescence (> 12 years)	Heterogeneous (Genetic, Immune, Secondary)	Mixed profile: podocyte injury, oxidative stress, fibrosis and immune activation.	Genes related to oxidative stress (*NOX4*), fibrosis (*TGFβ1*) and complement activation [62, 75].

between two and twelve years of age, occurs during a period of dynamic immune system maturation. In this phase, adaptive immunity continues to develop; specifically, the T cell subclasses and the antibody response are being refined through ongoing evolution of both biological systems. There is evidence of increased gene expression related to T cell activation, cytokine signalling and immune regulation in children with steroid-sensitive nephrotic syndrome. While a single, definitive circulating permeability factor remains unidentified, the current model underlines that alterations to podocyte function are due to immune-mediated processes rather than primary structural abnormalities. The strong steroid-treatment response rate amongst this age group correlates well with the prevalence of immune-associated transcriptional signatures [72–74].

Adolescence represents an important period of transition and the potential for shared characteristics of nephrotic syndrome with focal segmental glomerulosclerosis seen in adults. Transcriptomic analysis in older children and in adolescents shows an increase in the representation of pathways associated with oxidative stress response mechanisms, ECM remodelling and *transforming growth factor beta (TGFβ)* signalling; all three are implicated with glomerulosclerosis development and progressive kidney injury. The potential contribution of genetic susceptibility, combined with other environmental and sex-related hormonal influences during puberty, may change the expression levels of these pathways. As such, age-appropriate stratification of molecular expressions is critical for accurate interpretation of mechanisms and for risk assessment and therapy decisions at every phase through the continuum of childhood nephrotic syndrome [74, 75].

Challenges in Pediatric Transcriptomic Studies

Progress in pediatric transcriptomic research is constrained by the limited availability of biologically relevant samples and the relatively low incidence of severe disease phenotypes. Steroid-resistant nephrotic syndrome represents a small fraction of pediatric kidney disorders, which restricts cohort size and reduces statistical power. There are ethical issues that limit the use of invasive procedures in children, adding to the existing problem. Invasive kidney biopsy, the main source of glomerular tissue used for molecular analysis, is only performed when clinically indicated. Therefore, only selective access to glomerular and podocyte-specific RNA exists and the volume of this RNA is often very low. Many researchers use peripheral blood mononuclear cells or urinary sediment as surrogate sources of RNA because they are easier to obtain and allow longitudinal sampling; however, neither of these properly mimics the transcriptional profile of glomerular cells [6, 47].

Using circulating immune signatures may reflect systemic inflammation rather than direct renal injury and transcripts in urine can represent all nephron segments. This creates a biological gap such that there may be biomarkers with statistical association but without mechanistic relevance to podocyte pathology. The continued existence of small sample sizes, combined with a poor representation of the tissue available for study, is one of the primary methodological impediments to conducting pediatric transcriptomic studies [6, 74].

Technical variability in the processing and analysis of samples was the most significant source of non-biological variation when compared with biological differences between patients from different laboratories. Some causes of technical variability include differences in RNA extraction protocols, differences in library preparation methods, differences in sequencing depth and differences in the bioinformatic pipelines used to interpret the sequencing data. These technical artefacts often add to or distort the actual biological signal present in the sample being analysed, resulting in viable gene expression signals resembling those associated with disease. Additionally, laboratory instruments may have fluctuations in the calibration or the lot of reagents used that can introduce variation into the results produced using the same technology platform. The difficulty increases when combining gene expression-related datasets from different methods of gene expression analysis, such as arrays and RNA-seq, since arrays have varying levels of sensitivity, dynamic range and matching of transcriptional coverage compared to RNA-seq and therefore cannot be directly compared [47, 76].

Although statistical methods have improved for normalising and adjusting for batch effects and technical noise, they cannot remove all technical noise, particularly in smaller cohorts. Lack of control of the source of technical variability leads to lower reproducibility and difficulties in merging results completed by different institutions. Thus, for transcriptomic signatures generated by studies of PNS, standardised procedures for sample processing, sequencing and data processing, along with a commitment to consistently disclose the methods used to analyse samples [6, 67].

There are many challenges associated with the application of transcriptomic findings to clinically relevant diagnostic tests. Despite being powerful for use in discovery, whole transcriptome sequencing is both expensive and difficult to conduct, which makes it impractical for use as a routine diagnostic test. Therefore, a reduced set of candidate gene signatures that includes a manageable number of transcripts is needed to retain predictive accuracy when

assessed on diagnostic platforms commonly used in clinical laboratories, such as quantitative polymerase chain reaction or digital hybridisation assays. In addition, analytical validation of any transcriptomic biomarker will require proof of analytical precision, sensitivity, specificity and inter-laboratory reproducibility within a regulated laboratory environment [6, 65].

Likewise, in order for any transcriptomic biomarker to receive clinical validation, it must first be prospectively evaluated in large independent cohorts that are ethnically diverse to confirm prognostic/predictive value. Furthermore, the regulatory approval processes impose strict standards of evidence on the applicant, requiring that the applicant demonstrate that the proposed test will improve clinical decision-making beyond currently available testing options. Lastly, before being able to adopt any new test, clinicians will be required to interpret molecular laboratory results in the context of patients' overall clinical status to ensure that they do not misapply these findings. Taken together, the scientific, regulatory and systemic barriers to translating transcriptomic biomarkers from research settings into routine clinical practice in pediatric nephrology highlight the numerous complexities associated with these efforts.

Future Directions: From Descriptive Transcriptomes to Functional Validation

Transcriptomic studies in PNS have generated reproducible gene expression signatures associated with steroid resistance, relapse and progression. However, differential expression alone does not establish causality. Many transcripts identified through high-throughput analyses may represent downstream consequences of injury rather than primary drivers of disease. The next phase of investigation, therefore, requires systematic functional interrogation of prioritised genes. Genome editing technologies, particularly CRISPR Cas9-based approaches, provide a precise method to disrupt or modify candidate genes in cultured human podocytes. Loss-of-function and gain-of-function experiments allow direct assessment of effects on cytoskeletal organisation, slit diaphragm integrity, cell survival and permeability characteristics. Complementary transcriptomic and proteomic profiling of edited cells can clarify downstream signalling pathways and identify compensatory mechanisms. Rigorous experimental design, including the use of multiple guide RNAs and appropriate controls, is essential to minimise off-target effects. Through this iterative process, candidate transcripts can be stratified into those with mechanistic relevance and those serving primarily as biomarkers. Establishing causation at the cellular level is a critical step before considering therapeutic targeting [76, 77].

Robust functional validation also relies on using model systems that accurately recapitulate human podocyte biology. Traditional immortalised podocyte cell lines offer a controlled setting for performing mechanistic studies, but do not exhibit the genetic variation that is present in patients. Induced pluripotent stem (iPS) cell-derived podocytes provide an additional means of replicating genetic diversity by producing patient-specific podocytes from iPSCs. The iPSC-derived podocytes retain the genetic background of the patient, allowing for the investigation of how disease-associated variants affect cellular phenotype. Advances in podocyte differentiation methods have resulted in the improved structural and functional maturity of iPSC-derived podocytes, including expression of correlative slit diaphragm proteins. Three-dimensional kidney organoids take this a step further by modelling multicellular interactions within a structured/ordered microenvironment [78, 79].

While organoids cannot fully duplicate the structure and function of a mature glomerulus, they provide opportunities to study cell-to-cell signalling and extracellular matrix dynamics. In vivo models remain critical for validating pathologic mechanisms. Zebrafish models enable the rapid generation of genetically modified animals and the visualisation of glomerular filtration, whereas murine models approximate human kidney architectural features more closely. The integration of both approaches provides an established tiered schema for translating transcriptome candidates into validated biological pathways [40, 80].

Future studies should combine transcriptomic information with other molecular levels in order to establish a systems-level framework of disease beyond gene-specific investigation. Messenger RNA abundance is not always an accurate measure of protein levels, as post-transcriptional regulation, differences in translation and protein degradation affect protein levels. Quantitative proteomics will clarify which transcriptional changes lead to functional changes in proteins. Additionally, metabolomic profiling will reveal changes in cellular energy use and oxidative stress pathways, which contribute to podocyte dysfunction. Finally, epigenomic analysis of DNA methylation and chromatin accessibility will provide insight into how environmental and inflammatory stimuli regulate gene expression patterns. By integrating these data sets using network-based computational models, we can identify central regulators, rather than single genes, as key contributors to disease mechanistic pathways. This type of network analysis is especially useful for complex diseases in which many pathways contribute to the pathological state. Thus, a multi-omics approach narrows down candidate genes and provides direction toward the most promising targets for therapeutic intervention [9, 47, 81].

The ultimate objective of functional validation and integrative molecular analysis is the development of mechanism-based therapeutic strategies. One promising avenue is computational drug repurposing, in which disease-specific transcriptional signatures are compared with publicly available databases of drug-induced gene expression profiles. Compounds predicted to reverse pathogenic signatures can be prioritised for preclinical testing, potentially accelerating translation because their safety profiles are already established. Functional assays in edited podocyte models and organoids can then assess whether these agents restore cytoskeletal stability or reduce protein permeability. Molecular stratification also enables more precise clinical trial design. Rather than enrolling heterogeneous patient populations, trials can target children whose molecular profiles indicate activation of the pathway being inhibited [82–85].

Such enrichment strategies increase statistical power and reduce exposure of unlikely responders to experimental therapies. Through careful progression from descriptive transcriptomics to validated mechanisms and targeted interventions, pediatric nephrology can move toward a rational and individualised treatment paradigm grounded in biological evidence rather than empirical escalation.

Conclusion

Transcriptomic investigation has redefined the scientific understanding of PNS by illuminating molecular heterogeneity that is not apparent through conventional clinical classification. Expression profiling has clarified that children who appear similar at presentation may harbour distinct biological processes, ranging from predominant immune activation to structural podocyte stress and maladaptive repair pathways. These insights have strengthened the rationale for moving beyond response-based labels toward biologically informed stratification. Yet gene expression data must be interpreted with appropriate caution. Altered transcription reflects dynamic cellular states that may represent upstream drivers, downstream consequences or adaptive responses to injury. Without complementary functional validation, expression signatures alone cannot establish causation or define therapeutic targets. Practical limitations, including restricted access to kidney tissue, inter-study variability and the demands of analytical and clinical validation, further constrain immediate clinical translation. For transcriptomics to meaningfully influence patient care, identified signatures must demonstrate reproducibility across diverse populations and provide actionable information that improves outcomes beyond existing standards. Integration with proteomic, genomic and epigenomic data will strengthen biological inference and reduce the risk of oversimplified conclusions. Ultimately, transcriptomics should be regarded as a powerful interpretive framework that refines diagnostic precision and generates mechanistic hypotheses. When combined with rigorous experimental validation and carefully designed clinical studies, this approach offers a realistic pathway toward individualised therapy that aligns treatment selection with the molecular architecture of disease while maintaining scientific restraint and clinical responsibility.

Abbreviations

PNS	Pediatric Nephrotic Syndrome
NS	Nephrotic Syndrome
CKD	Chronic Kidney Disease
MCD	Minimal Change Disease
FSGS	Focal Segmental Glomerulosclerosis
ECM	Extracellular Matrix
NPHS1	Nephrosis 1 - Nephrin
NPHS2	Nephrosis 2 - Podocin
WT1	Wilms Tumour 1
PLCE1	Phospholipase C Epsilon 1
ACTN4	Alpha Actinin 4
LAMB2	Laminin Subunit Beta 2
ScRNA Seq	Single Cell RNA Sequencing
SnRNA Seq	Single Nucleus RNA Sequencing
ATAC Seq	Assay for Transposase Accessible Chromatin with Sequencing
CITE Seq	Cellular Indexing of Transcriptomes and Epitopes by Sequencing
CD44	Cluster of Differentiation 44
PAX2	Paired Box Gene 2
RHOA	Ras Homolog Family Member A
COL1A1	Collagen Type I Alpha 1 Chain
COL4A1	Collagen Type IV Alpha 1 Chain
TGFβ	Transforming Growth Factor Beta
CTGF	Connective Tissue Growth Factor
eGFR	Estimated Glomerular Filtration Rate
JAK1	Janus Kinase 1
STAT6	Signal Transducer and Activator of Transcription 6
CFB	Complement Factor B
ND1	NADH Dehydrogenase 1 (Mitochondrially Encoded)
COX6A1	Cytochrome C Oxidase Subunit 6A1
NOX4	NADPH Oxidase 4
SOD2	Superoxide Dismutase 2
ROS	Reactive Oxygen Species
GATA3	GATA Binding Protein 3
CRISPR Cas9	Clustered Regularly Interspaced Short Palindromic Repeats associated protein 9
iPSC	Induced Pluripotent Stem Cell

Acknowledgements We sincerely express our gratitude to our college and department for providing the essential facilities, guidance and encouragement that made this work possible. We are deeply thankful to our families and friends for their unwavering love, support and inspiration throughout this journey. We also thank the editors and reviewers for their valuable suggestions, which helped in the improvement of this research work.

Author Contributions S.G.M designed the study, collected the data and analysed the data. G.D.J.D., G.S. and M.C.D revised the manuscript. All authors have contributed to the article.

Funding Award of the Founder Chancellor, Shri N.P.V. Ramasamy Udayar Research Fellowship granted by Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethical Approval and Consent to Participate IEC-NI/26/02/115/33. Approved by the Institutional Ethics Committee of Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.

Consent for Publication Not applicable. Individual's data was not used for this study.

Competing interests The authors declare no competing interests.

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