Genetic and Hereditary Kidney Diseases with Disease-Modifying Therapies: State of the Art, Clinical Evidence, and Perspectives

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Abstract

Genetic and hereditary disorders account for a substantial and increasingly recognized proportion of chronic kidney disease (CKD), particularly in young adults and in children. Over the last decade, the therapeutic landscape has been transformed by disease-modifying therapies (DMTs) — interventions that act on etiopathogenic or core pathophysiological pathways and alter the natural history of disease — moving nephrology from supportive care towards precision medicine.

We aimed to provide a structured, evidence-based narrative review of the genetic and hereditary kidney diseases for which a DMT is currently approved, in advanced clinical development, or in established off-label use; and to summarize the evidence supporting these therapies for the practicing nephrologist.

A predefined narrative-review framework was applied. Eligible conditions were monogenic or strongly heritable disorders with predominant or clinically relevant kidney involvement and at least one DMT approved by EMA or FDA, in phase 2/3 clinical trials, or with established off-label use supported by guidelines. PubMed/MEDLINE was searched (January 2010 – November 2025) and complemented by KDIGO, ERA, ERKNet and NICE guidelines, ClinicalTrials.gov and reference lists of pivotal articles. Reporting follows the principles of PRISMA 2020 adapted to a narrative review.

Twelve diseases or disease groups are reviewed under a uniform framework (definition; genetics; renal phenotype; DMT mechanism; clinical evidence; place in therapy). DMTs are classified, after Dietz, into therapies acting on (i) the primary genetic defect, (ii) downstream effector pathways, and (iii) the final common pathway of nephron loss. Approved DMTs include tolvaptan in autosomal dominant polycystic kidney disease, enzyme replacement and migalastat in Fabry disease, C5 inhibitors (eculizumab, ravulizumab) in complement-mediated thrombotic microangiopathy, pegcetacoplan and iptacopan in C3 glomerulopathy, lumasiran and nedosiran in primary hyperoxaluria type 1, RAAS inhibitors and SGLT2 inhibitors in Alport syndrome, cysteamine in cystinosis, transthyretin stabilizers and silencers in hereditary ATTR amyloidosis, and burosumab in X-linked hypophosphataemic rickets. Inaxaplin (APO lipoprotein 1 (APOL1)-mediated

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kidney disease) and several complement, ciliopathy and tubulointerstitial agents are in advanced trials. Lifestyle and non-specific renoprotective measures remain the foundation upon which DMTs are added.
Genetic kidney medicine has entered a therapeutic era. Early genetic diagnosis, structured assessment of disease-specific eligibility criteria, and integration of DMTs with evidence-based non-specific renoprotection are now central to nephrology practice.

Keywords: Amyloidosis, Familial; Apolipoprotein L1; Atypical Hemolytic Uremic Syndrome; Complement Activation; Fabry Disease; Hyperoxaluria, Primary; Hypophosphatemia, Familial; Kidney Diseases/genetics; Nephritis, Hereditary; Polycystic Kidney Diseases; Precision Medicine.

INTRODUCTION

Chronic kidney disease (CKD) affects an estimated 850 million people worldwide and ranks among the fastest-growing causes of global mortality. A genetic etiology is identifiable in approximately 10% of adults and more than 20% of children reaching kidney replacement therapy, and in up to one in four adults under 45 years of age with advanced CKD.[1] More than 600 monogenic disorders affecting the kidney have been catalogued, accounting for roughly 5% of all known genetic diseases.[1]A genetic diagnosis informs prognosis, enables family counselling and cascade screening, refines transplant and donor selection, avoids unnecessary immunosuppression and — increasingly — identifies candidates for disease-modifying therapy. The term "disease-modifying therapy" (DMT), borrowed from neurology and rheumatology, denotes an intervention that acts on the etiopathogenic or core pathophysiological mechanism of a disease and thereby alters its natural history, as opposed to purely symptomatic or supportive treatment. Following the conceptual framework proposed by Dietz, DMTs may be classified by the level at which they intervene: (i) therapies that correct or compensate the primary genetic or molecular defect (gene therapy, antisense oligonucleotides, small interfering ribonucleic acids (RNAs), pharmacological chaperones, enzyme replacement); (ii) therapies that target downstream effector pathways activated by the genetic defect (e.g., complement inhibition, fibroblast growth factor 23 (FGF23) blockade, vasopressin V2-receptor antagonism); and (iii) therapies that act on the final common pathway of nephron loss (renin angiotensin system inhibition (RAASi) or sodium-glucose cotransporter 2 inhibition (SGLT2i)).[2]
DMTs are most effective when initiated early — sometimes pre-symptomatically — because once nephron loss and interstitial fibrosis are established, they are largely irreversible. Their integration into clinical practice raises new questions: how to select patients, how to combine DMTs with non-specific renoprotection, how to monitor response, and how to manage cost and access.
This review summarizes, under a uniform framework, the genetic and hereditary kidney diseases for which a DMT is currently available or in advanced development. It is intended as a practical reference for the nephrologist.

METHODS

This is a structured narrative review. A protocol was agreed by the authors prior to literature retrieval and is summarized below; reporting follows the principles of Page e*t al* (PRISMA 2020) and the guidance of Sukhera and Mak & Thomas for narrative reviews in medical education and clinical practice.[3–5]
Scope: The review covers monogenic disorders, and disorders with a major heritable contribution, in which the kidney is a predominant or clinically relevant target organ, and for which at least one DMT is (a) approved by the European Medicines Agency (EMA) or U.S. Food and Drug Administration (FDA) for the relevant indication, (b) in phase 2 or 3 clinical trials, or (c) used off-label with support from international guidelines or expert consensus. Diseases without any DMT in advanced development were excluded. Renal manifestations of multisystem disorders are included when kidney involvement is a defining or progression-determining feature (e.g., Fabry disease, cystinosis, hereditary amyloidosis).
Information sources and search: PubMed/MEDLINE was searched from January 2010 to November 2025, combining MeSH and free-text terms for each disease group with terms for "disease-modifying", "targeted therapy", "clinical trial", "approval" and "guideline". The search was complemented by manual screening of the reference lists of pivotal articles, KDIGO, ERA and ERKNet guidelines, NICE technology appraisals, the ERA Nephrology Manual, UpToDate monographs, and ClinicalTrials.gov for active trials.
Selection and prioritization: Preference was given to randomized controlled trials, prospective cohort studies, international registries, and current evidence-based guidelines. Reviews were used selectively when primary data were unavailable or when consensus terminology was required. Sources were limited to peer-reviewed journals with established impact in nephrology and genetics and to the guidelines listed above.
Data framework: For each disease, information is presented under a standardized structure: (i) definition and genetics; (ii) renal and extra-renal phenotype; (iii) DMT — mechanism of action and Dietz level; (iv) pivotal clinical evidence; (v) place in therapy, eligibility and monitoring; (vi) emerging therapies. Approved drugs are described in greater detail than those in earlier development. Human

gene symbols are written in uppercase italics in line with current HGNC nomenclature.

GENERAL PRINCIPLES: LIFESTYLE MODIFICATIONS AND NON-SPECIFIC RENOPROTECTION

Although DMTs are the focus of this review, they are added to — not substituted for — the general renoprotective measures that apply to all CKD. These include: strict blood-pressure control to KDIGO targets (systolic <120 mmHg when tolerated, measured by standardized technique); inhibition of the renin–angiotensin–aldosterone system (RAASi) for proteinuric disease; SGLT2 inhibitors in adults with eGFR ≥20 mL/min/1.73 m² and albuminuria ≥30 mg/g, supported by DAPA-CKD and EMPA-KIDNEY and now incorporated into the 2024 KDIGO CKD guideline[6–8]; non-steroidal mineralocorticoid receptor antagonism in selected patients with residual albuminuria; lipid lowering; smoking cessation; sodium restriction (<2 g/day, corresponding to 5 g of salt); generous fluid intake in concentrating defects; weight management and individualized exercise; and immunization, particularly meningococcal vaccination before complement inhibition. These measures are particularly relevant in autosomal dominant polycystic kidney disease, Alport syndrome, APOL1-mediated kidney disease and any genetic disorder in which proteinuria or hypertension drives progression, and they should be reassessed at every visit. SGLT2 inhibitors have demonstrated benefit in proteinuric monogenic disease (Alport syndrome) and are being studied in other hereditary podocytopathies.[9]

GLOMERULAR AND BASEMENT-MEMBRANE DISORDERS

1. Alport Syndrome

Definition and genetics: Alport syndrome is caused by pathogenic variants in collagen *COL4A3, COL4A4* or *COL4A5,* which encode the α3, α4 and α5 chains of type IV collagen of the glomerular basement membrane (GBM). Inheritance is X-linked (*COL4A5;* the most common form), autosomal recessive or autosomal dominant; digenic inheritance is increasingly recognised.[10–12]

Phenotype: Persistent microscopic hematuria is the hallmark; proteinuria, progressive CKD, sensorineural hearing loss and lenticonus develop in classical X-linked males and in autosomal recessive disease. Heterozygous *COL4A5* females and autosomal dominant carriers exhibit a wide phenotypic spectrum.

DMT — RAAS inhibition (Dietz level III): Ramipril delays kidney failure by approximately three years in CKD G3–G4 and by up to 18 years when initiated at first appearance of proteinuria, with consistent benefit across genetic subtypes; the EARLY PRO-TECT Alport trial confirmed safety and efficacy of early ramipril in children.[13–15] The 2024 ERKNet/ERA/ESPN guideline recommends starting RAASi at diagnosis in males with X-linked or autosomal recessive disease, in females with autosomal recessive disease, and at the onset of microalbuminuria in heterozygous *COL4A5* females and in autosomal dominant disease.[16]

DMT — SGLT2 inhibition (Dietz level III): Based on DAPA-CKD and EMPA-KIDNEY, the 2024 guideline now also recommends adding an SGLT2 inhibitor in adults with Alport syndrome and CKD G2 with category A3 albuminuria or worse despite RAASi.[6–8,16] An international observational study in 112 adults confirmed reduction of proteinuria with combined RAASi–SGLT2i.[17] Pediatric evidence is limited; the ongoing DOUBLE PRO-TECT Alport trial (10–39 years, eGFR >60 mL/min/1.73 m²) will address this gap.[18]

Emerging therapies: Phase 1–2 studies are exploring restoration of the α3–α4–α5 collagen network, correction of misfolded type IV collagen, anti-fibrotic agents and gene therapy.[19]

COMPLEMENT-MEDIATED KIDNEY DISEASES

1. Complement-Mediated Thrombotic Microangiopathy (CM-TMA)/ Atypical Haemolytic Uremic Syndrome(aHUS)

Definition and genetics: CM-TMA — the term now preferred by the National Kidney Foundation working group over “atypical HUS” — is a rare, life-threatening thrombotic microangiopathy driven by dysregulation of the alternative complement pathway.[20] It presents with microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury; approximately 25% of patients have renal-limited disease. Diagnosis requires exclusion of thrombotic thrombocytopenic purpura and secondary causes. Genetic testing of *CFH, CFI, CD46* (MCP), C3, *CFB, CFHR1*–5, *MMACHC* and *DGKE,* and screening for anti-CFH antibodies (most often associated with *CFHR1/CFHR3* deletions, predominantly pediatric) and the C5 p.R885H polymorphism (which predicts eculizumab non-response) are recommended.[20,21] Pathogenic variants are identified in 45%–70% of cases; *CFH* variants are most common (20%–30%) and confer the highest recurrence risk, followed by MCP/*CD46* (10%–15%, moderate recurrence) and rarer *CFI, C3* and *CFB* variants.[21]

DMT — terminal complement inhibition (Dietz level II): Before 2011, CM-TMA carried 6.7% one-year mortality and 46% progression to ESKD. Eculizumab — a humanized anti-C5 monoclonal antibody (induction 900 mg weekly ×4, then 1200 mg every two weeks) — typically normalizes platelet count within one week and recovers kidney function within the first month.[22] Predictors of renal recovery include lower presenting creatinine, younger age, shorter time to treatment, lower platelet count and lower systolic blood pressure.[21,22] Ravulizumab, an engineered

anti-C5 antibody with a four-fold longer half-life, allows eight-weekly dosing while maintaining remission, and transition from eculizumab is safe.[23] In anti-CFH disease, plasma exchange combined with immunosuppression (commonly mycophenolate mofetil for 1–2 years) achieves rapid antibody reduction and hematological remission in >90% of patients within one week; where available, eculizumab is the preferred initial therapy and immunosuppression may be added or substituted thereafter.[21] Patients on C5 inhibitors should receive meningococcal vaccination (MenB plus MenACWY) and antibiotic prophylaxis for at least two weeks after vaccination, with influenza, pneumococcal and *Haemophilus influenzae* type b vaccination; some experts continue antibacterial prophylaxis throughout therapy because of breakthrough infections.[24]

Discontinuation: Most renal recovery occurs within 90 days; continuation beyond three months should be individualized. Withdrawal appears safe when no pathogenic variant or anti-CFH is present and serum C5b-9 (sC5b-9) levels are decreasing; relapse risk is higher with *CFH* or *CD46* variants and persistently elevated sC5b-9 ≥300 ng/mL.[25,26] Lifelong therapy is rarely required, and individualized monitored discontinuation is more cost-effective.[25]

Transplantation and pregnancy: Without prophylaxis, recurrence after kidney transplantation reaches 58%–68% (5-year graft survival 51%), except in CM-TMA associated with *MCP/CD46* variants, for which the risk of post-transplant recurrence is considerably lower (low risk); prophylactic eculizumab improves three-year graft survival from 61% to 89% in high/moderate-risk variants.[21] Living-donor candidates should be screened, since donation may act as a "second hit" in carriers.[21] Eculizumab data in pregnancy are limited but reassuring.[27]

Emerging therapies: Several agents targeting earlier or alternative components of the complement cascade are in development, including iptacopan (factor B), pegcetacoplan (C3), crovalimab (alternative C5 epitope, predicted to overcome the R885H polymorphism), narsoplimab (MASP-2), avacopan (C5aR), cemdisiran (C5 siRNA) and BCX9930 (factor D); these are summarized in Table 1. Their accessibility may improve cost-effectiveness in resource-limited settings, where plasma exchange currently remains the only option.[23,28]

Table 1. Complement inhibitors approved or in clinical development for complement-mediated thrombotic microangiopathy (CM-TMA).

Molecule	Target / mechanism	Stage of development
Eculizumab	Anti-C5 monoclonal antibody	Approved (EMA/FDA)
Ravulizumab	Anti-C5 monoclonal antibody, long half-life	Approved (EMA/FDA)
Crovalimab	Anti-C5 (alternative epitope; predicted active in R885H carriers)	Phase 3
Iptacopan	Oral factor B inhibitor	Phase 3
Pegcetacoplan	C3 inhibitor	Phase 2
Avacopan	C5a receptor antagonist	Phase 3 (other indications)
Narsoplimab	Anti-MASP-2 (lectin pathway)	Phase 3
Cemdisiran	siRNA against C5	Phase 2
BCX9930	Oral factor D inhibitor	Phase 2
Ruxoprubart	Anti-factor Bb	Phase 2
KP104	Bifunctional C3/C5 inhibitor	Phase 2
Nomacopan	C5 and LTB4 inhibitor	Phase 2

2. C3 Glomerulopathy

Definition and genetics: C3 glomerulopathy (C3G) is a rare complement-mediated glomerular disease defined histologically by dominant glomerular C3 staining with absent or scant immunoglobulins and two electron microscopy patterns: C3 glomerulonephritis and dense deposit disease.[29] Disease is driven by fluid-phase dysregulation of the alternative pathway, due to genetic variants in complement regulators or acquired drivers (C3 and C5 nephritic factors, autoantibodies to complement proteins).[30]

Phenotype: Typical presentation is in children and young adults with hematuria, proteinuria (often nephrotic-range), hypertension and variable kidney dysfunction. More than half progress to kidney failure within ten years and recurrence after transplantation is frequent.

DMT (Dietz level II): KDIGO 2021 recommends supportive renoprotection for all patients and, for those with persistent proteinuria >1 g/day, hematuria and declining eGFR, mycophenolate mofetil (2–3 g/day) plus glucocorticoids tapered over 6–8 months.[31] Eculizumab has been used in refractory cases with inconsistent benefit (≈40% response in early series).[32] Two complement inhibitors targeting the alternative pathway have now produced phase-3 evidence: pegcetacoplan (anti-C3) in VALIANT (n=124, primary IC-MPGN or C3G, proteinuria ≥1 g/day, eGFR ≥30 mL/min/1.73 m²) reduced UPCR by 68% at six

months versus placebo, slowed eGFR decline (−1.5 ***vs*** −7.8 mL/min/1.73 m²) and reduced glomerular C3 deposition[33]; iptacopan (anti-factor B) in APPEAR-C3G (n=74) reduced UPCR by 35% at six months without a significant eGFR effect.[34] KDIGO Controversies output expected in 2026 will refine positioning of these agents.

RENAL CILIOPATHIES

Renal ciliopathies are disorders caused by structural or functional defects of the primary cilium, basal body or centrosome. They share common cellular consequences — dysregulated planar cell polarity, altered cAMP and Wnt signalling, and aberrant proliferation of tubular epithelium — that translate clinically into cystic, fibrocystic or tubulointerstitial kidney disease. The most common example is autosomal dominant polycystic kidney disease.[35]

1. Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Definition and genetics: ADPKD, the most prevalent monogenic kidney disease and the prototypical renal ciliopathy, is caused mainly by pathogenic variants in *PKD1* (≈85%) or *PKD2* (≈15%), and rarely in *GANAB, DNAJB11, IFT140* and others.[36] Penetrance is essentially complete by adulthood, but severity varies because of allelic heterogeneity, modifier loci and somatic "second hits" in cyst-lining cells.[37] Polycystin-1 and -2 localize to the primary cilium; their dysfunction leads to cyst formation, parenchymal compression, ischemia and progressive fibrosis. Hepatic cysts are frequently observed, its frequency increases with age and may affect over 90% of patients when MRI is used as the imaging method (in the CRISP study is 58% in participants aged 15- 24 years, 85% in those aged 25- 34 years, and 94% in those aged 35- 46 years)

DMT — vasopressin V2-receptor antagonism (Dietz level II): Tolvaptan suppresses cAMP-driven cystogenesis. In TEMPO 3:4 (n=1445; total kidney volume ≥750 mL; eGFR ≥60 mL/min/1.73 m²), tolvaptan reduced annual TKV growth (2.8% *vs* 5.5%) and slowed eGFR decline by approximately 1.2 mL/min/1.73 m² per year versus placebo.[38] In REPRISE (n≈1360; eGFR 25–65 mL/min/1.73 m²), the eGFR slope was 1.27 mL/min/1.73 m² per year better than placebo (p<0.001).[39] EMA and FDA approved tolvaptan in 2018 for adults at risk of rapid progression (maximum 120 mg/day).[39]

Eligibility, monitoring and adverse effects: Rapid-progression criteria (Mayo imaging class 1C–1E; PROPKD score; family history) should guide selection. Aquaresis (polyuria, polydipsia) is universal and dose-limiting; hepatotoxicity requires monthly liver-function testing. Tolvaptan is contraindicated in significant liver disease and pregnancy. Off-label somatostatin analogues (e.g., octreotide) modestly reduce hepatic cyst growth; mTOR inhibitors have not shown clinical benefit. Non-specific renoprotection — strict blood-pressure control (target <110/75 mmHg in young patients with preserved GFR per HALT-PKD), RAAS inhibition, sodium restriction, generous fluid intake and avoidance of nephrotoxins — remains foundational.[6–8, 36]

2. Autosomal Recessive Polycystic Kidney Disease (ARPKD)

Definition and genetics: Autosomal recessive polycystic kidney disease (ARPKD) is characterized by non-obstructive fusiform dilatation of the renal collecting ducts and varying degrees of congenital hepatic fibrosis. Estimated incidence is ≈1:20 000 live births. Most cases are caused by biallelic pathogenic variants in *PKHD1;* rarer phenocopies involve *DZIP1L* and other ciliopathy genes.[40,41]

Phenotype: Approximately one third of patients present in the neonatal period with massive nephromegaly, oligohydramnios sequence and respiratory distress; the remaining cases present in childhood, adolescence or adulthood with hypertension, impaired urinary concentrating capacity, progressive CKD, and complications of congenital hepatic fibrosis (portal hypertension, recurrent cholangitis, splenomegaly). Pulmonary and lower-extremity deformities, when present, are secondary to renal and hepatic disease.[40]

DMT and supportive care: No targeted disease-modifying therapy is currently approved for ARPKD. Management remains supportive: neonatal respiratory support, blood-pressure control with RAAS inhibition, optimization of nutrition and growth, surveillance and treatment of cholangitis and portal hypertension, and renal replacement therapy in those who progress to ESKD. Combined or sequential liver–kidney transplantation may be required in patients with concomitant advanced renal and hepatic disease.[40]

Emerging therapies: Vasopressin V2-receptor antagonism is being prospectively evaluated in pediatric ARPKD: two ongoing multinational, multicenter, open-label, non-randomized trials of tolvaptan are designed to assess safety, tolerability and efficacy — Study 204 (phase 3) enrolling infants 28 days to <12 weeks with imaging criteria suggestive of rapid progression, and Study 307 (phase 3b) enrolling subjects 28 days to <18 years.[42,43] Additional agents under preclinical or early clinical investigation include pioglitazone, statins (pravastatin, simvastatin), the miR-17 antagonist RGLS4326, bardoxolone methyl, metformin, somatostatin analogues (lanreotide, octreotide, pasireotide), and tyrosine-kinase inhibitors (tesevatinib, bosutinib), targeting cyst expansion, cell proliferation and fibrosis.[40] Genetic counselling, prenatal testing and cascade screening of at-risk family members are integral to management.

3. Nephronophthisis (NPHP), NPHP-Related Ciliopathies and Bardet–Biedl Syndrome

Nephronophthisis results from biallelic variants in genes encoding ciliary, basal-body or centrosomal proteins, with progression to end-stage CKD (ESKD) typically before 20 years of age. Approximately 20% of patients have extra-renal features (retinitis pigmentosa, cerebellar, hepatic or skeletal anomalies), defining NPHP-related ciliopathies

(Senior–Løken, Joubert, Meckel–Gruber, Sensenbrenner and Jeune syndromes[44]). No disease-specific therapy is approved. Supportive measures include adequate hydration and salt intake, treatment of anemia and CKD-MBD, and growth hormone in selected children. Recurrence after kidney transplantation does not occur. Pre-clinical data support prostaglandin E_2 receptor agonists as a potential therapeutic class for both renal and extra-renal manifestations.[45] Bardet–Biedl syndrome (autosomal recessive, >20 implicated genes) features retinitis pigmentosa, obesity, polydactyly, hypogonadism and progressive kidney disease. Setmelanotide, a melanocortin-4 receptor agonist, is approved for syndromic obesity in patients aged ≥2 years and improves weight and quality of life.[46]

AUTOSOMAL DOMINANT TUBULOINTERSTITIAL KIDNEY DISEASE (ADTKD)

Definition and genetics: ADTKD is a group of autosomal dominant disorders that, contrary to earlier classifications, are not ciliopathies and are reported as a separate entity. They are caused by pathogenic variants in *UMOD, MUC1, REN, HNF1B, SEC61A1* and *DNAJB11.*[47,48] ADTKD is now recognized as the third most common monogenic cause of kidney failure (≈5% of monogenic CKD[48]).

Phenotype: Bland urinary sediment, slowly progressive CKD, family history of kidney disease, and progression to kidney failure typically by the fifth decade (range 20–80 years). *UMOD* and *REN* variants are associated with hyperuricemia and gout; *REN* variants additionally cause anemia and risk of acute kidney injury during volume depletion or NSAID exposure.

DMT and supportive care: No targeted approved therapy currently exists. Allopurinol prevents gout and may be initiated in adolescence in ADTKD-*UMOD* with early hyperuricemia or family history; symptomatic hyperuricemia is treated with allopurinol or febuxostat. In ADTKD-*REN,* fludrocortisone reverses hyperkalemia and acidosis and is better tolerated than alkali therapy.[49] SGLT2i and RAASi have not shown specific benefit in this group.[47] Living donors should be screened, since related donors may carry the gene; ADTKD does not recur in the allograft.

Emerging therapies: BRD4780 and other TMED9-targeting small molecules clear misfolded MUC1 from the ER–Golgi intermediate complex in pre-clinical models, defining a novel proteinopathy-targeted approach.[50,51] Mesencephalic astrocyte-derived neurotrophic factor (MANF) and autophagy-promoting agents are in pre-clinical development.[52]

LYSOSOMAL STORAGE DISORDERS

1. Fabry Disease

Definition and genetics: Fabry disease is an X-linked lysosomal disorder caused by pathogenic variants in *GLA,* encoding α-galactosidase A.[53] Classical hemizygous males have <1% residual enzyme activity and develop multisystem disease; heterozygous females and patients with milder mutations show variable, often later-onset phenotypes.

Phenotype: Progressive lysosomal accumulation of globotriaosylceramide (Gb3) and lyso-Gb3 in vascular endothelium, podocytes, cardiomyocytes and neurons leads to neuropathic pain, angiokeratomas and gastrointestinal symptoms in childhood, and to proteinuric CKD, hypertrophic cardiomyopathy, arrhythmia and stroke in adulthood.[54]

DMT — enzyme replacement therapy (Dietz level I): Recombinant intravenous α-galactosidase A (agalsidase alfa, agalsidase beta) clears Gb3 from endothelium and stabilizes or modestly improves kidney and cardiac function when started early; late initiation may not arrest progression.[55] EMA and FDA approve both agents for symptomatic males and symptomatic females; key adverse effects include infusion reactions and anti-drug antibodies, especially with agalsidase beta.

DMT — pharmacological chaperone (Dietz level I): Migalastat, an oral chaperone approved in 2016, stabilizes amenable mutant α-galactosidase A. In ATTRACT (n=57; 18 months), migalastat 123 mg every 48 h maintained kidney function comparably to ERT and significantly reduced left-ventricular mass index (–6.6 g/m²; $p<0.05$).[56] It is restricted to amenable mutations (≈30–60% of patients, defined by a validated assay) and avoids biweekly infusions.

Emerging therapies: Pegunigalsidase alfa (PEGylated ERT, monthly dosing; phase 3), substrate-reduction therapy with oral lucerastat, and *ex-vivo* and *in-vivo* gene therapy studies are in clinical development.[57]

2. Cystinosis

Definition and genetics: Cystinosis is a rare autosomal recessive lysosomal storage disorder caused by biallelic pathogenic variants in *CTNS* (17p13.2), encoding the lysosomal cystine transporter cystinosin. Three clinical forms are recognized by age of onset: infantile nephropathic (≈95% of cases, most severe), juvenile nephropathic, and ocular non-nephropathic.[58]

DMT — cysteamine (Dietz level II): Cysteamine, the only approved disease-modifying therapy, depletes intralysosomal cystine and is administered lifelong; long-term studies in treatment-naïve children showed sustained reduction in leukocyte cystine, improved growth and increased measured GFR.[59,60] Delayed-release cysteamine improves tolerability.[61] Therapy should target leukocyte cystine ≤0.5 nmol half-cystine/mg protein and continue lifelong with multidisciplinary monitoring of renal and extra-renal complications.[62] Although cysteamine slows progression, it is not curative; emerging therapies aim to address inflammation, oxidative stress, impaired autophagy and dysregulated cell death implicated in residual disease progression.[63]

9. INHERITED METABOLIC DISORDERS WITH RENAL INVOLVEMENT

1. Primary Hyperoxaluria Type 1

Definition and genetics: Primary hyperoxaluria is an autosomal recessive disorder of hepatic glyoxylate metabolism. Type 1 (PH1), the most common and severe, is caused by biallelic pathogenic variants in *AGXT,* encoding peroxisomal alanine-glyoxylate aminotransferase; in PH2 and PH3 the defects involve *GRHPR* and *HOGA1* respectively.[64] In PH1, glyoxylate is shunted to oxalate, producing massive oxalate overproduction.

Phenotype: Recurrent calcium-oxalate nephrolithiasis and nephrocalcinosis present in childhood and progress to CKD and ESKD; with falling GFR, systemic oxalosis develops with bone, retinal, cardiovascular and skin involvement.

DMT — RNA interference (Dietz level I): Lumasiran, a small interfering RNA targeting hepatic glycolate oxidase *(HAO1),* reduces glyoxylate substrate. In ILLUMINATE-A (PH1, eGFR ≥30 mL/min/1.73 m²), lumasiran reduced 24-hour urinary oxalate by approximately 65% at six months versus placebo (p<0.001), with sustained benefit through 30 months[65]; in ILLUMINATE-C (eGFR <45 mL/min/1.73 m² or on dialysis), plasma oxalate fell by approximately 33%–42%.[66] EMA- and FDA-approved lumasiran in 2020 for PH1 of all ages. Long-term effect on CKD progression is not yet defined. A second siRNA, nedosiran (targeting hepatic LDH) received its first approval in 2023 in the USA to lower urinary oxalate levels in children aged ≥ 9 years and adults with PH1 and eGFR ≥ 30 mL/min/1.73m^2.[67]

Adjunctive and definitive therapy: Pharmacological pyridoxine reduces oxalate production in approximately 30% of PH1 patients with vitamin-B6–responsive genotypes; high fluid intake (>3 L/m²/day in children) and oral citrate are essential. Combined liver–kidney transplantation has long been the only curative option in ESKD; isolated liver transplantation and kidney-only transplantation under RNAi coverage are under investigation.[68]

2. Cystinuria

Definition and genetics: Cystinuria is an autosomal recessive disorder of proximal tubular and intestinal transport of the dibasic amino acids cystine, ornithine, lysine and arginine, caused by biallelic pathogenic variants in *SLC3A1* (encoding the heavy subunit rBAT) or *SLC7A9* (encoding the light subunit b,$^+$AT) of the heterodimeric amino-acid transporter. Rare digenic and pseudo-dominant inheritance patterns are described.[69–71]

Phenotype: The clinical hallmark is recurrent cystine nephrolithiasis, typically beginning in childhood, adolescence or early adulthood. Cystine is poorly soluble at physiological urinary pH, so when urinary cystine concentration exceeds solubility, crystals and stones form. Recurrent obstruction, urinary tract infection, repeated urological interventions and cumulative parenchymal damage can lead to chronic kidney disease. Extra-renal manifestations are generally absent, reflecting the kidney-restricted clinical impact of the transport defect.[72]

DMT — supersaturation control (Dietz level III): No targeted molecular therapy is approved. Disease-modifying management aims to reduce urinary cystine concentration and increase its solubility, and rests on three pillars: (i) high fluid intake distributed across the 24 hours to maintain urinary cystine concentration well below the solubility threshold; (ii) urinary alkalinization to pH 7.0–7.5 with potassium citrate (preferred over sodium-containing alkali, which increases cystine excretion); and (iii) moderation of dietary sodium and animal protein intake.[72,73] Where these measures are insufficient, thiol-binding agents — tiopronin and D-penicillamine — form soluble mixed disulfides with cystine but require monitoring for hematological, hepatic, renal and proteinuric toxicity.[74] Captopril has cystine-binding properties and is occasionally used off-label, particularly when hypertension or proteinuria coexist; evidence is limited and it should not be considered first-line.[74]

Monitoring and transplantation: Recommended monitoring includes 24-hour urine volume, cystine excretion or cystine capacity where available, urine pH, sodium excretion, imaging for stone burden, kidney function and adherence.[73] Kidney transplantation is rarely required solely for cystinuria, and cystinuria does not recur in an allograft from an unaffected donor as the tubular transport defect is corrected by the graft.

3. Mitochondrial Cytopathies with Renal Involvement

Definition and genetics: Mitochondrial cytopathies are a heterogeneous group of disorders caused by pathogenic variants in mitochondrial (mtDNA) or nuclear DNA that impair the respiratory chain and oxidative phosphorylation.[75] Because the kidney is among the most energy-demanding organs, mitochondrial dysfunction produces a wide spectrum of renal phenotypes.[76] Causal genes include mtDNA variants (e.g., m.3243A>G, large-scale deletions) and nuclear genes encoding respiratory-chain subunits, CoQ10-biosynthesis enzymes (*COQ2, COQ6, COQ8B/ADCK4, PDSS1, PDSS2*) and mitochondrial translation or mtRNA-processing proteins (e.g., *FASTKD2*).[77]

Phenotype: Renal involvement is often subtle and underrecognized, particularly in adults, and warrants a high index of suspicion when there is a maternal-line family history, consanguinity, or multisystem disease (notably involving the central nervous system, skeletal muscle, heart or endocrine organs). The most frequent renal phenotype is proximal tubular dysfunction, including full Fanconi syndrome with glycosuria, generalized aminoaciduria, phosphaturia, bicarbonate wasting and growth failure, typically linked to mtDNA deletions or nuclear respiratory-chain defects. Less common but well-documented phenotypes include chronic tubulointerstitial nephritis (often associated with

m.3243A>G), glomerular disease — most commonly steroid-resistant focal segmental glomerulosclerosis or a podocytopathy linked to CoQ10-biosynthesis defects — and, rarely, cystic kidney disease.[78–80] Adult renal involvement is frequently masked by coexisting diabetes, deafness, neurologic features or cardiorenal syndrome. Variants in nuclear *FASTKD2* have been associated with young-adult-onset autosomal recessive mitochondrial podocytopathy.[81]

Diagnosis: True prevalence is unknown; variants of individual mitochondrial proteins are rare. The m.3243A>G pathogenic variant in the *leucine tRNA* gene is the most frequent mtDNA defect. Diagnostic confirmation typically requires the combination of clinical suspicion, biochemical evaluation, electron microscopy of tissue biopsies and targeted or broad genetic testing.[77, 80]

DMT and supportive care: Coenzyme Q10 (CoQ10)-biosynthesis defects constitute the most clinically relevant treatable subgroup, in which oral coenzyme Q10 supplementation can halt or partially reverse proteinuria and CKD progression when initiated early; this is a paradigmatic example of a Dietz level I targeted, mechanism-based therapy in mitochondrial nephrology.[77] For *FASTKD2*-related combined oxidative phosphorylation deficiency, m.3243A>G-related cytopathies and most other mitochondrial nephropathies, no targeted therapy is currently available. Supportive care includes standard CKD management, RAAS blockade, avoidance of known mitochondrial toxins (aminoglycosides, certain antiretrovirals, valproate), and multidisciplinary follow-up. Renal replacement therapy and transplantation are appropriate in advanced disease, with attention to the systemic implications of the underlying mitochondrial disorder and the potential mitochondrial toxicity of immunosuppressive regimens. Genetic counselling — including discussion of maternal transmission for mtDNA variants and recurrence risk for nuclear genes — is an integral component of management.[81]

10. *APOL1*-MEDIATED KIDNEY DISEASE

Definition and genetics: The 2010 discovery that two coding variants in *APOL1* — G1 (the linked p.S342G/p.I384M missense pair) and G2 (a two-amino-acid p.delN388/Y389 deletion) — are major genetic contributors to the excess CKD burden in people of recent African ancestry has redefined a class of genetic kidney disease.[82,83] High-risk genotypes (G1/G1, G1/G2, G2/G2) markedly increase the risk of focal segmental glomerulosclerosis, hypertension-attributed nephropathy, HIV-associated nephropathy and other CKD; a single risk allele confers smaller risk. The disease spectrum is now termed *APOL1*-mediated kidney disease (AMKD).[84] Although approximately 10%–15% of African Americans carry high-risk genotypes, only ≈15%–20% develop CKD, supporting a "second-hit" model in which interferon-driven states (SLE, HIV, SARS-CoV-2), modifier genes (notably the protective p.N264K variant) and environmental factors are required for disease.[85]

DMT (Dietz level I–II): No therapy is currently approved. In a phase 2a trial of inaxaplin (VX-147), a small-molecule *APOL1* channel inhibitor, 13 weeks of treatment in 16 patients with two *APOL1* risk variants and proteinuric kidney disease produced a 47.6% reduction in proteinuria with preserved GFR.[86] A phase 3 study is ongoing. *APOL1*-targeted antisense oligonucleotides (e.g., AZD2373/ION532) and small-molecule channel blockers (VX-840, MZE829) are in early clinical development; baricitinib (JAK–STAT inhibitor) is in phase 2 (Table 2). Genotyping for the protective N264K variant should accompany G1/G2 testing in research and transplantation.[87]

Non-specific renoprotection and transplantation: Standard hypertension targets apply. In murine models, lisinopril reduced proteinuria and glomerulosclerosis in a genotype-specific manner (greater benefit in G1/G1), supporting RAAS inhibition; hydralazine and dapagliflozin had no effect in the same model.[88] *APOL1* high-risk genotypes raise donor ESKD risk and graft failure; counselling and selective testing of potential donors of African ancestry should be considered.[87–89]

Table 2. Investigational therapies for APOL1-mediated kidney disease (AMKD).

Molecule	Mechanism	Stage of development
Inaxaplin (VX-147)	***APOL1*** channel inhibitor (small molecule)	Phase 3
VX-840	***APOL1*** channel blocker	Phase 1
MZE829	***APOL1*** small-molecule inhibitor	Phase 1
MZ-301	***APOL1*** pore-function inhibitor	Pre-clinical
AZD2373 / ION532	Antisense oligonucleotide reducing ***APOL1*** mRNA	Phase 2b
Baricitinib	JAK1/2 inhibitor (interferon pathway)	Phase 2

11. HEREDITARY RENAL AMYLOIDOSIS

Definition and genetics: Amyloidoses are diseases of extracellular deposition of misfolded, fibrillar proteins. Of 42 currently recognized amyloidogenic proteins in humans, 19 cause systemic disease and 16 affect the kidney.[90] Renal amyloidosis is rare (1%–4% of native biopsies) but causes substantial kidney dysfunction.[91] Most cases (>80% in Western series) are AL (immunoglobulin

light-chain) amyloidosis; AA amyloidosis (7%–14%) complicates chronic inflammatory disease; ALECT2 is the third most frequent (3%–4%).[92] Hereditary renal amyloidosis — caused by autosomal dominant variants in *TTR* (ATTRv), *FGA* (AFib), *GSN* (AGel), ***LYZ*** (ALys), and *APOA1, APOA2, APOA4, APOC2* and *APOC3* — account for less than 5% overall but, in Portugal and Europe, AFib and ATTRv are the most common hereditary forms, followed by AApoAI and ALys.[93,94] Phenotypic features by precursor protein are summarized in Table 3.

Table 3. Phenotype of hereditary renal amyloidosis by amyloidogenic precursor protein.

Type	Gene	Renal involvement	Renal phenotype	Predominant compartment	Extra-renal phenotype
ATTRv	TTR	~30%	CKD (often cardiorenal); proteinuria >1 g/day in <20%; nephrotic-range in <10%	Interstitial (medulla), then vascular and glomerular	Cardiomyopathy, peripheral neuropathy, autonomic dysfunction, bilateral carpal tunnel, biceps tendon rupture
AApoAI	APOA1	~18%	Tubular proteinuria, mild nephrogenic diabetes insipidus	Medullary-predominant	Heart, liver, GI tract, peripheral neuropathy, retina, skin, larynx, testis
AApoAII	APOA2	High	Variable proteinuria, often nephrotic	Glomerular-dominant	Rare heart, liver, spleen, adrenal, pancreas
AApoAIV	APOA4	~35%	Slow CKD progression with mild or absent proteinuria	Medullary-predominant	Heart
AApoCII	APOC2	~100%	Nephrotic-range proteinuria	Glomerular-dominant	Absent
AApoCIII	APOC3	High	Mild proteinuria with slow CKD progression	Vascular-dominant	Salivary gland, heart, liver, spleen, hypotriglyceridaemia
AGel	GSN	~52%	Nephrotic syndrome and progressive CKD	Glomerular-dominant	Corneal lattice dystrophy, cutis laxa, cardiac, neurological
ALys	LYZ	~20%	Mild proteinuria, slow CKD progression	Tubulointerstitial and perivascular	Heart, GI tract, liver, peripheral neuropathy, sicca, bleeding diathesis
AFib	FGA	~93%	Nephrotic-range proteinuria, progressive CKD	Glomerular-dominant	Systemic atheromatosis, autonomic neuropathy

Adapted from Allinovi M, et al. Nephrol Dial Transplant. 2025;40:1826-37.[93]
CKD = chronic kidney disease; ESKD = end-stage kidney disease.

Diagnosis: Hereditary amyloidosis should be suspected with unexplained proteinuria, nephrotic syndrome or progressive CKD, particularly with family history, early onset or extra-renal features. Acquired forms (above all AL) must first be excluded. Histological confirmation and amyloid typing — ideally by laser microdissection and tandem mass spectrometry, the current gold standard — are essential before genetic analysis.[95] Genetic testing of all ATTR cases is mandated to distinguish wild-type from variant TTR.[96] In suspected hereditary cases without a known family variant, targeted panels covering *APOA1, APOA2, APOA4, APOC2, APOC3, FGA, GSN, LYZ* and *TTR* are recommended; whole-exome/whole-genome sequencing is reserved for unresolved cases.

DMT (Dietz level I): Hereditary ATTR amyloidosis has been transformed by therapies that target the amyloid precursor: tetramer stabilizers (tafamidis, acoramidis) and gene-silencing agents — the small interfering RNAs patisiran and vutrisiran, and the antisense oligonucleotide eplontersen — lower circulating TTR and slow disease progression in pivotal trials in *TTR* amyloid cardiomyopathy and polyneuropathy.[97,98] Non-neuropathic hereditary amyloidoses (AFib, apolipoproteins) currently lack disease-specific therapy and are managed with renal protection. In AFib, combined liver–kidney transplantation can replace the mutant precursor; isolated kidney transplantation has low recurrence in selected cases. The choice between isolated and combined transplantation should be individualized in ATTRv, AFib and AApoAI.[99]

12. HEREDITARY HYPOPHOSPHATAEMIC RICKETS

Definition and genetics: This is a heterogeneous group of disorders of renal phosphate handling and the FGF23 axis. The most common form is X-linked hypophosphataemia (XLH), caused by inactivating variants in *PHEX,* leading to elevated FGF23, reduced renal phosphate reabsorption and inappropriately low or normal 1,25-dihydroxyvitamin D.[100] Autosomal dominant forms result from gain-of-function *FGF23* variants; autosomal recessive forms involve *DMP1* and *ENPP1.*[100]

Phenotype: Chronic hypophosphataemia, defective bone mineralization, growth failure and rickets in children, and persistent musculoskeletal pain, fractures and dental abnormalities in adults. Nephrocalcinosis is frequent, especially under conventional therapy with oral phosphate and calcitriol; secondary and tertiary hyperparathyroidism are intrinsic and treatment-related complications.[101]

DMT — anti-FGF23 monoclonal antibody (Dietz level II): Burosumab restores renal phosphate reabsorption and

normalizes calcitriol production while avoiding hypercalciuria, with sustained improvement and favourable renal safety in phase-3 trials in children and adults.[102,103] Where burosumab is unavailable or contraindicated, oral phosphate plus calcitriol remains an alternative but requires intensive monitoring of serum and urinary calcium, phosphate, creatinine and parathyroid hormone, with periodic renal imaging.

13. REAL-WORLD IMPLEMENTATION, ETHICS AND PERSPECTIVES

Genetic testing has reshaped the diagnosis and management of hereditary kidney disease, but access remains uneven, constrained by socioeconomic disparities, laboratory capacity and timely referral related to medical and patient literacy. Disease-specific registries, multidisciplinary networks (e.g., ERKNet) and digital platforms enable scalable outcome monitoring and equitable access to precision nephrology. Genomic analysis and DMT decisions raise ethical issues around informed consent, incidental findings, data privacy, reproductive choice and pre-symptomatic treatment of family members; these must be balanced against patient autonomy, family benefit and the substantial cost of many DMTs. Genetic and phenotypic heterogeneity limit predictability, and surrogate endpoints (proteinuria, total kidney volume, biomarker reduction) may not always capture long-term clinical benefit. Continued investment in registries, real-world evidence and equity-focused policies will be essential to ensure that the therapeutic revolution in genetic nephrology reaches all eligible patients.

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