Web Table I Grading of Evidence [7]

Grade	*Quality of evidence*
A	Well designed and controlled studies; meta-analysis on applicable population; true effect lies close to the estimate of the effect
B	Studies with minor limitations; consistent findings from multiple observational studies; true effect is likely to be close to estimate of the effect, but there is a possibility that it is substantially different
C	Single, few or multiple studies with inconsistent findings or major limitations; confidence in the effect estimate is limited, the true effect may be substantially different from estimate of the effect
D	Expert opinion, case reports; very little confidence in effect estimate, true effect likely to be substantially different from estimate of effect
X	Situations where validating studies cannot be performed, and benefit or harm clearly predominates
Level	*Strength of recommendation*
1	"We recommend": Most patients should receive the recommended course of action
2	"We suggest": Different choices will be appropriate for different patients

Web Table II Gene List for Targeted Panel with Features of Steroid Resistant Nephrotic Syndrome (SRNS)

Gene	*Protein*	*Inheritance*	*Accession no; OMIM*	*OMIM phenotype*	*Key clinical features*
ACTN4	Actinin, alpha 4	AD	NM_004924; 603278	Focal segmental glomerulosclerosis (FSGS), type 1	Familial and sporadic SRNS (usually adolescent and adult)
ADCK4/ COQ8B	Coenzyme Q8B	AR	NM_024876; 615573	Nephrotic syndrome, type 9	FSGS or collapsing FSGS; one patient responded to coenzyme Q10
ALG1	Asparagine-linked glycosylation 1	AR	NM_019109; 605907	Congenital disorder of glycosylation, type Ik	Neurologic impairment and dysmorphic features
ANKFY1	Rabankyrin-5	AR	NM_001330063.2; 607927		Early onset illness
ANLN	Actin binding protein anillin	AD	NM_018685; 616032	FSGS, type 8	FSGS (onset between 9-70 years)
ARHGAP24	Rho GTPase-activating protein 24	AD	NM_001025616; 610586		FSGS
ARHGDIA	Rho GDP-dissociation inhibitor alpha	AR	NM_001185078; 615244	Nephrotic syndrome, type 8	Congenital nephrotic syndrome; SRNS early onset; diffuse mesangial sclerosis on biopsy
AVIL	Advillin	AR	NM_006576.3; 618594	Nephrotic syndrome, type 21	SRNS; diffuse mesangial sclerosis on biopsy
CD151	Tetraspanin (TM4)	AR	NM_004357; 609057	Nephropathy; deafness; SRNS; epidermolysis bullosa	Pretibial skin lesions, sensorineural deafness, lacrimal duct stenosis, nail dystrophy, thalassemia minor
CD2AP	CD2-associated protein	AD/AR	NM_012120; 607832	FSGS, type 3	FSGS
CLCN5	H^+/Cl^- exchange transporter 5	XR	NM_001127898.4; 300009	Dent disease; low molecular weight proteinuria, hypercalciuria	Failure to thrive; hypercalciuria, nephrolithiasis; low molecular weight proteinuria, albuminuria; FSGS
COL4A3	Type IV collagen α3	AR, AD	NM_000091; 120070	Alport syndrome 2, AR; Alport syndrome 3, AD	Alport syndrome; FSGS
COL4A4	Type IV collagen α4	AR	NM_000092; 120131	Alport syndrome 2, AR	Alport syndrome; FSGS
COL4A5	Type IV collagen α5	XLD	NM_000495; 301050	Alport syndrome 1, XL	Alport syndrome; FSGS

COQ2	Coenzyme Q2	AR	NM_015697; 609825	Coenzyme Q10 deficiency, primary, 1	Mitochondrial disease; isolated SRNS
COQ6	Coenzyme Q6	AR	NM_182476; 614647	Coenzyme Q10 deficiency, primary, 6	Early SRNS; sensorineural deafness; ataxia, facial dysmorphism; FSGS, diffuse mesangial sclerosis
CRB2	Crumbs cell polarity complex component 2	AR	NM_173689; 616220	FSGS, type 9	SRNS
CUBN	Cubilin	AR	NM_001081; 261100	Megaloblastic anemia	Megaloblastic anemia; proteinuria
DGKE	Diacylglycerol kinase, epsilon	AR	NM_003647; 615008	Nephrotic syndrome, type 7	
DLC1	DLC1 Rho GTPase activating protein		NM_182643.3; 604258		Child and adult steroid sensitive illness and SRNS; partial CNI response
E2F3	E2F transcription factor 3		NM_001949.4; 600427		FSGS, mental retardation; also with partial deletion of chromosome 6
EMP2	Epithelial membrane protein 2	AR	NM_001424; 615861	Nephrotic syndrome, type 10	Childhood SRNS; steroid sensitive illness also reported
FAT1	FAT tumor suppressor homolog 1	AR	NM_005245.4; 600976		SRNS, tubular ectasia, hematuria
FN1	Fibronectin	AD	NM_212482.3; 601894	Glomerulopathy with fibronectin deposits 2	Proteinuria, hematuria; glomerulomegaly, fibronectin positive subendothelial, mesangial deposits
GAPVD1	GTPase-activating protein, VPS9-domain protein 1		NM_001282680.3; 611714		Early-onset SRNS
INF2	Inverted formin 2	AD	NM_022489; 613237	FSGS, type 5	Isolated SRNS; Charcot-Marie-Tooth neuropathy with FSGS
ITGA3	Integrin α3	AR	NM_002204; 605025	Interstitial lung disease; epidermolysis bullosa	Congenital, SRNS; interstitial lung disease; epidermolysis bullosa (congenital)
ITGB4	Integrin β4	AR	NM_000213; 147557	Epidermolysis bullosa; pyloric atresia	Epidermolysis bullosa (junctional); pyloric atresia; FSGS
ITSN1	Intersectin-1	AR	NM_003024.3; 602442		Congenital, SRNS; steroid sensitive illness reported
ITSN2	Intersectin-2	AR	NM_019595.4;		Steroid sensitive illness

			604464		(minimal change) or membranoproliferative glomerulonephritis
KANK1	KN motif ankyrin repeat domain-containing protein 1	AR	NM_015158.3; 607704		Steroid sensitive illness
KANK2	KN motif ankyrin repeat domain-containing protein 2	AR	NM_015493; 617783		Steroid sensitive illness; steroid dependence; hematuria
KANK4	KN motif ankyrin repeat domain-containing protein 4	AR	NM_0181712.4; 614612		SRNS; hematuria
KIRREL1	Kin of IRRE-like protein 1	AR	NM_018240.7; 607428		SRNS
LAGE3	EKC/KEOPS complex subunit LAGE3	XR	NM_006014.4; 301006	Galloway-Mowat syndrome 2	Early-onset SRNS; FSGS; microcephaly, gyral abnormalities; delayed development
LAMB2	Laminin, beta-2	AR	NM_002292; 614199	Nephrotic syndrome, type 5; ocular anomalies	Pierson syndrome; SRNS, microcoria, neurodevelopmental delay
LCAT	Phosphatidylcholine-sterol acyltransferase	AR	NM_000229.2; 245900	Norum disease	Proteinuria, renal failure, anemia, corneal lipid deposits
LMNA	Prelamin-A/C	AD	NM_170707; 151660	Lipodystrophy type 2, partial	Familial partial lipodystrophy; FSGS
LMX1B	LIM homeobox transcription factor 1β	AD	NM_002316; 602575	Nail-patella syndrome	FSGS; SRNS, mild ridging to hypoplasia of nails, absent, hypoplastic patella; glaucoma
MEFV	Pyrin	AD/AR	NM_000243.2; 608107	Familial Mediterranean fever	Fever, pericarditis, pleuritis, arthralgia; nephrotic syndrome
MAFB	Transcription factor MafB	AD	NM_005461.5; 166300	Multicentric carpotarsal osteolysis syndrome	Proteinuria, end stage kidney disease; skeletal disorders; mental retardation; minor facial anomalies
MAGI2	Membrane-associated guanylate kinase inverted 2	AR	NM_012301.4; 617609	Nephrotic syndrome, type 15	SRNS; FSGS
MYO1E	Myosin IE	AR	NM_004998; 614131	FSGS, type 6	FSGS; collapsing FSGS
MYH9	Myosin-9	AD	NM_002473; 155100	Macrothrombocytes, granulocyte	MYH9-related disease; Epstein, Fechtner

				inclusions; nephritis, deafness	syndromes: nephritis, deafness, thrombocytopenia, giant platelets
NEU1	Sialidase-1	AR	NM_000434.4; 256550	Sialidosis, type I/II	SRNS; FSGS; hepatomegaly, corneal clouding, cherry red spots (nephrosialidosis)
NPHS1	Nephrin	AR	NM_004646; 256300	Nephrotic syndrome, type 1	Congenital, SRNS
NPHS2	Podocin	AR	NM_014625; 600995	Nephrotic syndrome, type 2	Congenital, SRNS
NUP85	Nucleoporin, 85-kDa	AR	NM_024844.5; 618176	Nephrotic syndrome, type 17	SRNS; FSGS
NUP93	Nucleoporin, 93-kDa	AR	NM_014669; 616892	Nephrotic syndrome, type 12	SRNS; FSGS
NUP107	Nucleoporin, 107-kDa	AR	NM_020401; 616730	Nephrotic syndrome, type 11 Galloway-Mowat syndrome-7	SRNS
NUP133	Nucleoporin, 133-kDa	AR	NM_018230.3; 618177; 618349	Nephrotic syndrome, type 18 Galloway-Mowat syndrome-8	Isolated FSGS
NUP160	Nucleoporin, 160-kDa	AR	NM_015231.2; 618178	Nephrotic syndrome, type 19	SRNS
NUP205	Nucleoporin, 205-kDa	AR	NM_015135; 616893	Nephrotic syndrome, type 13	Early onset SRNS
NXF5	Nuclear RNA export factor 5	XR	NM_032946; 300319		FSGS co-segregating with heart block
OCRL	Inositol polyphosphate 5-phosphatase	XR	NM_000276; 309000	Lowe syndrome	FSGS; absence of proximal tubular dysfunction reported
OSGEP	Probable tRNA N6-adenosine threonylcarbamoyltransferase	AR	NM_017807.4; 617729	Galloway-Mowat syndrome 3	SRNS
PAX2	Paired box protein 2	AD	NM_003987; 616002	FSGS, type 7	FSGS without extrarenal manifestations
PDSS2	Decaprenyl diphosphate synthase subunit 2	AR	NM_020381; 610564	Leigh syndrome	Mitochondrial disorder; proteinuria
PLCe1	Phospholipase C, epsilon-1	AR	NM_016341; 610725	Nephrotic syndrome, type 3	Congenital, SRNS

PMM2	Phosphomannomutase 2	AR	NM_000303; 212065	Disorder of glycosylation, type Ia	Psychomotor retardation, peripheral neuropathy with SRNS
PODXL	Podocalyxin	AD	NM_005397; 602632		FSGS
PTPRO	Protein-tyrosine phosphatase, receptor-type O	AR	NM_030667; 614196	Nephrotic syndrome, type 6	SRNS
SCARB2	Lysosome membrane protein 2	AR	NM_005506; 254900	Myoclonic epilepsy, 4; renal failure	Progressive myoclonic epilepsy; SRNS; FSGS
SGPL1	Sphingosine-1-phosphate lyase 1	AR	NM_003901.4; 617575	Nephrotic syndrome, type 14	Primary adrenal insufficiency, neurologic abnormalities; SRNS
SMARCAL1	SMARCAL1	AR	NM_014140; 242900	Schimke immunoosseous dysplasia	Spondyloepiphyseal dysplasia; immune deficiency, neurological features; FSGS
SYNPO	Synaptopodin	AD	NM_007286; 608155		Sporadic FSGS (promoter mutations)
SYNPO2	Synaptopodin-2	AR	Not available		Congenital childhood onset, SRNS
TBC1D8B	TBC1 domain family, 8B	XR	NM_017752.3; 301028	Nephrotic syndrome, type 20	Early-onset SRNS with FSGS
TNS2	Tensin 2	AR	NM_170754.3; 607717		Steroid dependence (minimal change, FSGS, diffuse mesangial sclerosis)
TP53RK	EKC/KEOPS complex subunit TP53RK	AR	NM_033550.4; 617730	Galloway-Mowat syndrome 4	Early onset SRNS
TPRKB	EKC/KEOPS complex subunit TPRKB	AR	NM_001330389.1; 617731	Galloway-Mowat syndrome 5	Early-onset SRNS
TRPC6	Transient receptor potential channel, subfamily C member 6	AD	NM_004621; 603965	FSGS, type 2	Familial and sporadic SRNS (chiefly adult)
TTC21B	Tetratricopeptide repeat protein 21B	AR	NM_024753; 613820	Nephronophthisis 12	Late onset FSGS; tubulointerstitial fibrosis and tubular atrophy; Joubert syndrome
WDR4	tRNA (guanine-N7-) methyltransferase subunit WDR4	AR	NM_001260475.1; 618347	Galloway-Mowat syndrome 6	Early-onset SRNS

WDR73	WD repeat domain 73	AR	NM_032856; 616144	Galloway-Mowat syndrome 1	SRNS
WT1	WT1 transcription factor	AD	NM_024426; 256370	Nephrotic syndrome, type 4	Isolated SRNS; Frasier & Denys-Drash syndromes
XPO5	Exportin 5	AR	NM_020750; 607845		Childhood SRNS
ZMPSTE24	CAAX prenyl protease 1 homolog	AR	NM_005857; 608612	Mandibuloacral dysplasia, type B lipodystrophy	FSGS; skeletal anomalies, dysplastic nails; skin pigmentation; calcified skin nodules
APOL1	Apolipoprotein L-I		NM_003661; 612551	FSGS, type 4	G1, G2 risk alleles: Susceptibility to FSGS; end stage kidney disease in African, Hispanic Americans

OMIM Online Mendelian Inheritance in Man; AR autosomal recessive; AD autosomal dominant; CNI calcineurin inhibitors; XR X-linked recessive, XL X linked
Phenocopy genes (OMIM no.; phenotype): NPHP4 (606966; nephronophthisis 4); CLCN5 (300009; Dent disease 1); CTNS (219800; cystinosis); DGKE (615008; hemolytic uremic syndrome); NPHP13 (614377; nephronophthisis 13); GLA (301500; Fabry disease); FN1 (601894; glomerulopathy with fibronectin deposits 2); PAX2 (120330; papillorenal syndrome); COL4A3 (104200; Alport syndrome); COL4A4 (203780; Alport syndrome); COL4A5 (301050; Alport syndrome); AGXT (259900; primary hyperoxaluria type 1); FAT4 (612411; Van Maldergem syndrome 2); WDR19 (614377; nephronophthisis 13).

Web Table III Corticosteroid Response and Kidney Failure in Children with Genetic and Non-Genetic Forms of Steroid-Resistant Nephrotic Syndrome

Author, yr [Ref]	*Genetic cause, %**	*Complete, partial remission*		*Kidney Failure^*	
		Non-genetic, N	*Genetic, N*	*Non-genetic, N*	*Genetic, N*
Trautmann, 2018 [28]	373/1554 (24%)	159/387	10/74	113/501[^1]	116/241[^1]
Landini, 2020 [29]	37/64 (57.8%)[$1]	13/17	1/19[$2]	3/6[^2]	11/25[^2]
Nagano, 2020 [30]	69/230 (30%)	41/158	2/37	79/158[^3]	52/69[^3]
Mason, 2020 [18]	81/271 (29.9%)	69/149	9/26	41/149[^4]	16/26[^4]
Total[#]	1086/3902 (27.8%)[#]	282/711 (39.7%)	22/156 (14.1%)	236/814 (29.0%)	195/361 (61.5%)
Genetic versus non-genetic disease		*Odds ratio*	*95% confidence interval*		*P*
Non-response		4.00	2.52, 6.51		<0.0001
Kidney failure		2.87	2.22, 3.72		<0.0001

Only includes reports based on next-generation sequencing; latest or largest report for units with multiple papers

**Congenital nephrotic syndrome not excluded, except by Trautmann et al*

[#] Includes 526 of 1783 families tested by Sadowski et al [26]

[^] Numbers at [1]last follow up; [2]at 10-yr; or extrapolated from Kaplan Meier analysis, at [3]last follow up or at [4]10-yr

[$1] Includes and [$2]excludes 18 patients with phenocopies

Web Table IV Important Drug Interactions of Cyclosporine and Tacrolimus

Medication	*Effect*	*Management*
Drugs that decrease levels		
Anticonvulsants: Phenytoin, carbamazepine, phenobarbitone	Enzyme induction leads to lower levels; risk of non-response or relapse	Increase medication by 30%; monitor trough levels following change of dose or discontinuation of anticonvulsant
Antibiotics: Rifampin; caspofungin (only with tacrolimus)		Monitor trough levels following addition, change of dose or discontinuation of medication
Drugs that increase levels		
Erythromycin, clarithromycin Fluconazole, ketoconazole, voricanazole	Enzyme inhibition results in high levels and risk of nephrotoxicity	Monitor trough levels following addition, change of dose or discontinuation of medication Monitor serum creatinine, electrolytes, liver function tests
Diltiazem, verapamil		
Pharmacodynamic interactions		
Aminoglycosides, amphotericin B, nonsteroidal anti-inflammatory drugs	Risk of nephrotoxicity	Avoid if alternative options are available Monitor creatinine and electrolytes frequently
HMG-CoA reductase inhibitors	Myalgia, rhabdomyolysis	Start with low dose of statins; monitor for toxicity
Nifedipine, amlodipine, phenytoin (only with cyclosporine)	Higher incidence and severity of gingival hyperplasia	Avoid long-term combined use; change to alternative agent Dental and oral hygiene; regular dentist visits

Web Box I Management of Allograft Recurrence of Nephrotic Syndrome

Monitor proteinuria by urine protein to creatinine (Up/Uc) ratio
Daily for 1 week; weekly for 4-weeks; monthly for 1-yr; then every 3-6 months
Renal biopsy, especially if low grade proteinuria or graft dysfunction
Treatment of Recurrence
Plasma exchange
Membrane filtration or centrifugation based; heparin or citrate anticoagulation
Replacement fluid: 5% albumin; fresh frozen plasma
Schedule: Plasma exchange 1.5 times plasma volume (60-75 mL/kg) per session on alternate days for 2-weeks; single volume (40 mL/kg) once per week for 4-6 weeks
Medications
IV methylprednisolone 250 mg/m^2/day for 3 days; taper to previous dose of oral prednisolone
Increase dose of calcineurin inhibitors: Tacrolimus trough 8-12 ng/mL; cyclosporine trough 150-200 ng/mL
Rituximab 375 mg/m^2 two doses, one-week apart
Add angiotensin converting enzyme inhibitor once allograft function established with stable estimated GFR
Consider therapy with oral cyclophosphamide for 3 months in place of mycophenolate mofetil

Recurrence: Urine protein to creatinine ratio (Up/Uc) ≥1 mg/mg if anuric before transplant; or increase in Up/Uc by ≥1 mg/mg if proteinuria at time of transplant

Web Box II Evaluation of Patients with Congenital Nephrotic Syndrome

Extra-renal features: Dysmorphic features, eye, urogenital abnormalities; large placenta
Urinalysis; urine protein to creatinine ratio
Complete blood counts
Blood creatinine, protein, albumin, electrolytes, calcium, phosphate
Transaminases, alkaline phosphatase, 25-hydroxyvitamin D
Lipid profile, free thyroxine, thyroid stimulating hormone
Renal ultrasonography
Kidney biopsy: Not necessary, except if a genetic diagnosis is not established
Identifying the cause
Exome sequencing (*Web Table* II)
Serology for intrauterine infections (TORCH), syphilis, hepatitis B and C, HIV
Karyotyping (infants with ambiguous genitalia, extra-renal features)