MINIMAL CHANGE DISEASE
FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS

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Disclosure of Interests

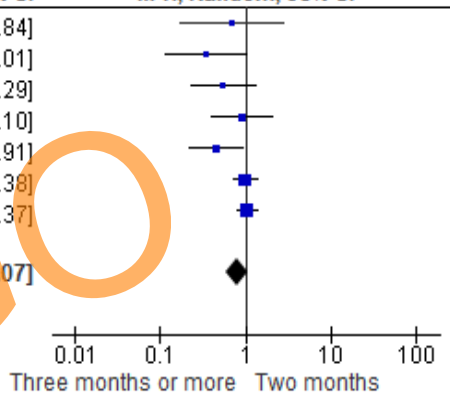
- No relevant disclosures

Minimal change disease/steroid sensitive nephrotic syndrome in children

Duration of prednisone for the initial episode of childhood SSNS: Number with FRNS at 1-2 years*

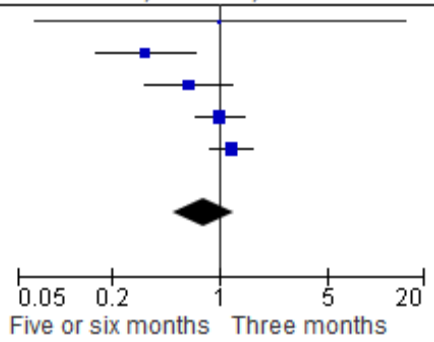
Study or Subgroup	3 months or more Events	Total	2 months therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Norero 1996	3	29	4	27	4.1%	0.70 [0.17, 2.84]
Ueda 1988	3	17	15	29	6.4%	0.34 [0.12, 1.01]
APN 1993	6	34	12	37	9.3%	0.54 [0.23, 1.29]
Bagga 1999	7	22	8	23	9.9%	0.91 [0.40, 2.10]
Jayantha 2002a	8	48	26	70	12.5%	0.45 [0.22, 0.91]
Yoshikawa 2014	45	122	46	124	27.0%	0.99 [0.72, 1.38]
PREDNOS Study 2017	59	113	54	109	30.7%	1.05 [0.81, 1.37]
Total (95% CI)		**385**		**419**	**100.0%**	**0.79 [0.58, 1.07]**
Total events	131		165			

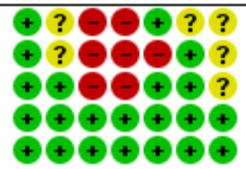
Heterogeneity: Tau² = 0.06; Chi² = 10.57, df = 6 (P = 0.10); I² = 43%
Test for overall effect: Z = 1.53 (P = 0.12)



Study or Subgroup	5 or 6 months Events	Total	Three months Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Mishra 2012	1	37	1	37	2.5%	1.00 [0.06, 15.40]
Sharma 2000	8	70	24	70	18.3%	0.33 [0.16, 0.69]
Hiraoka 2003	10	36	15	34	20.4%	0.63 [0.33, 1.20]
Sinha 2014	36	92	35	89	28.8%	1.00 [0.69, 1.43]
Teeninga 2013	38	64	31	62	30.0%	1.19 [0.86, 1.64]
Total (95% CI)		**299**		**292**	**100.0%**	**0.78 [0.50, 1.22]**
Total events	93		106			

Heterogeneity: Tau² = 0.15; Chi² = 12.05, df = 4 (P = 0.02); I² = 67%
Test for overall effect: Z = 1.07 (P = 0.28)





*Hahn D et al. CDSR 2015, CD001533

Prednisone + steroid-sparing agents to prolong time to first relapse in children with SSNS

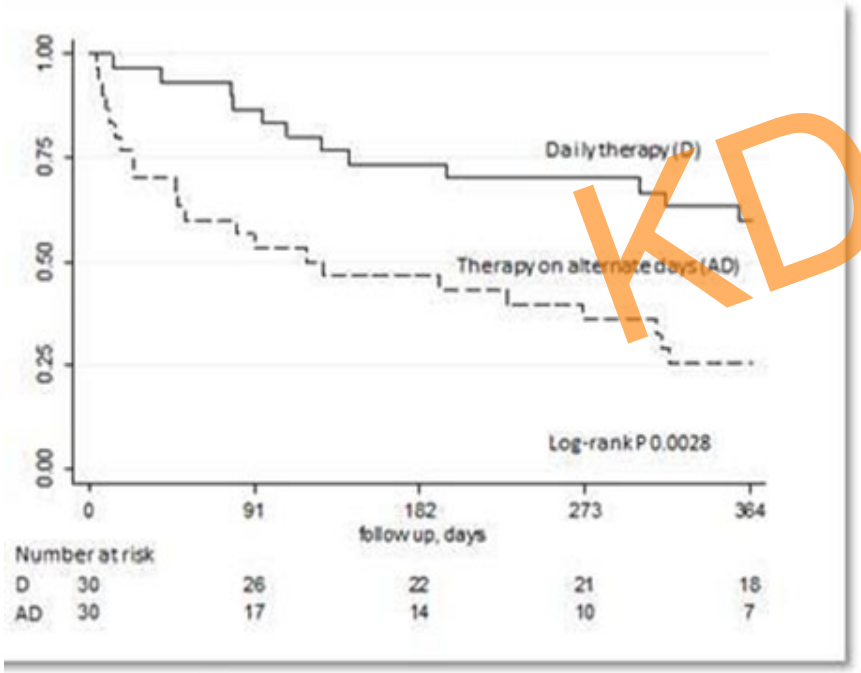
- Azithromycin (Zhang 2014). RCT
  - Intervention: Azithromycin + prednisone (106)
  - Comparator: Prednisone (105)
  - Outcome at 6 months:
    - No difference in number with relapse or FRNS at 6 months

- INTENT study (EudraCT 2014-001991-76. N=400/340; Germany). RCT
  - Intervention: Prednisone till remission, then MMF for rest of 12 week induction period. Alternate day prednisone for 2 weeks
  - Comparator: 6 weeks daily and 6 weeks alternate day prednisone
  - Outcome: First relapse within 24 months
  - 110 recruited to date. Completion expected 2020 (Dr Marcus Benz)

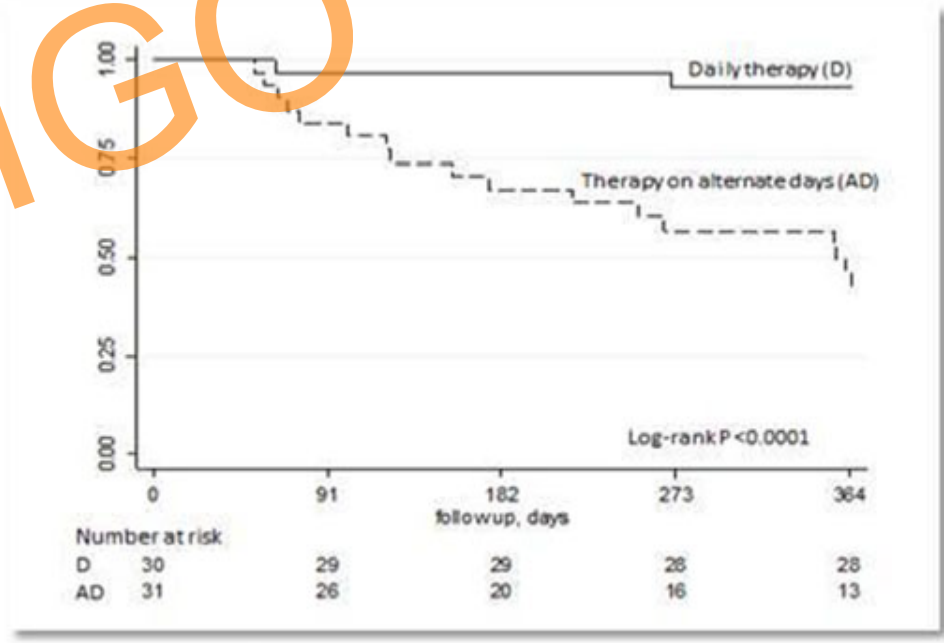
- NEPHROVIR3 study (NCT02818738. N 156: France). RCT
  - Intervention: Levamisole for 6 months after first remission
  - Comparator: Placebo for 6 months after first remission
  - Recruitment not started. Completion expected 2020

Steroid regimens to prevent relapse in children with SSNS

- Yadav et al 2016 (CTRI/2012/12/003194; Pediatric Nephrology (2016) 31:1752)
  - Open label RCT enrolling 62 children aged 1-16 years with FRNS without steroid toxicity
  - Intervention: Daily prednisone 0.2-0.3 mg/kg/day for 12 months
  - Comparator: Alternate day prednisone 0.5–0.7 mg/kg/day for 12 months



Time to first relapse

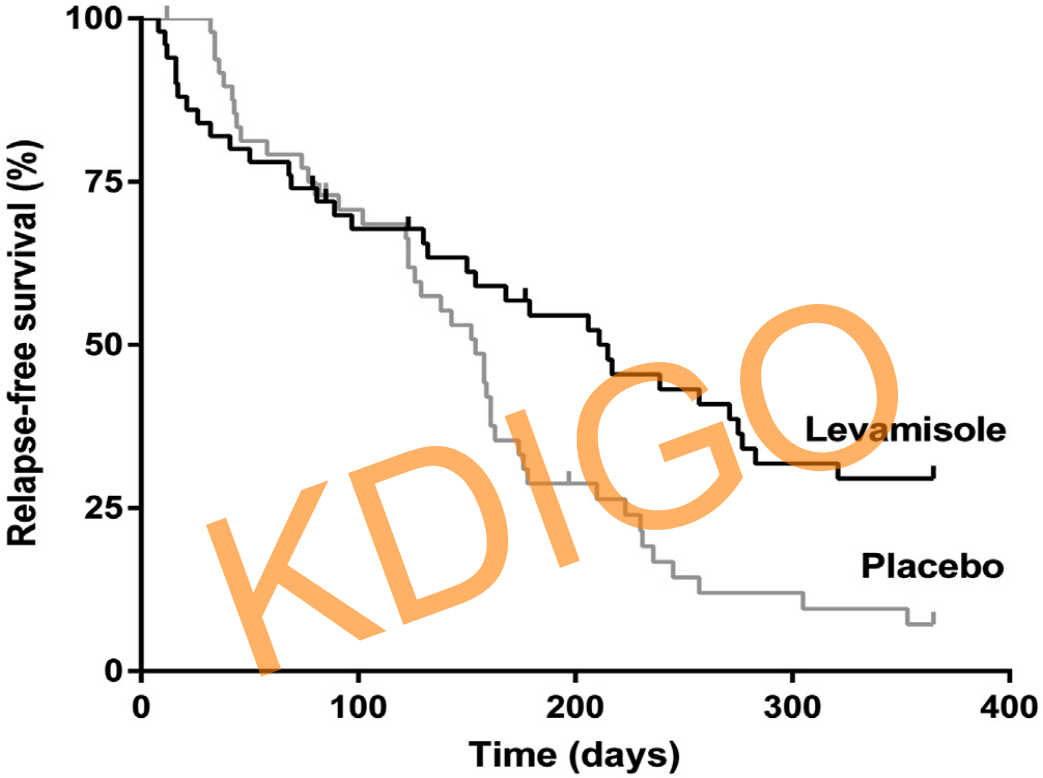


Time to therapy failure

Steroid regimens to prevent relapse in children with SSNS

- Reduced prednisone schedule vs standard schedule
  - RESTERN study 2017 (EudraCT - 2016-002430-76; *BMJ Open* 2017;7:e018148)
    - Double-blind RCT enrolling 144 children aged 1-18 years with relapse of SSNS
    - Intervention: Reduced prednisone schedule (daily till remission, alt day for 2 weeks)
    - Comparator: Standard prednisone schedule (daily till remission, alt day for 6 weeks)
    - Outcome: Time to next relapse
- Increased dose of prednisone to prevent relapse with infections
  - Abeyagunawardena 2017 (Pediatric Nephrology 32: 1377-1382, 2017)
    - Cross-over study (48 patients/33 completed) showed fewer relapses in children with FRNS (not on prednisone) given daily prednisone at onset of infection compared with placebo
  - PREDNOS 2 Study (EudraCT – 2012-003476-39)
    - RCT comparing 6 days of prednisone with placebo in children with FRNS & URTI
    - Results awaited. 295/360 patients enrolled to date (data from N. Webb)

Levamisole reduces the risk of relapse in children with FRNS



RFS 26%

RFS 6%

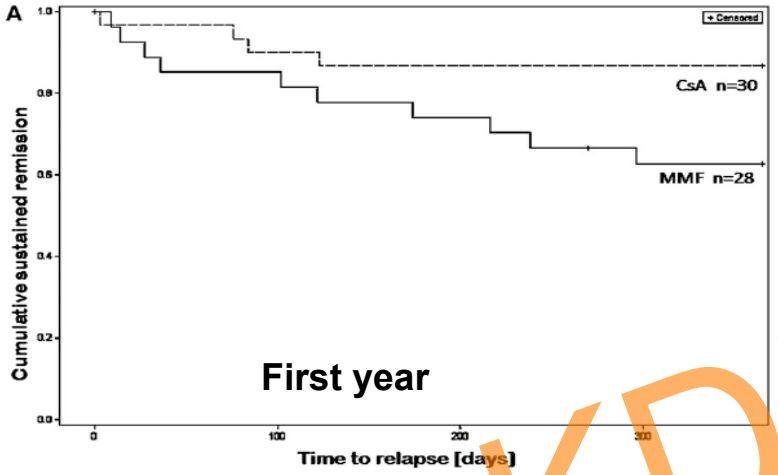
Numbers at risk

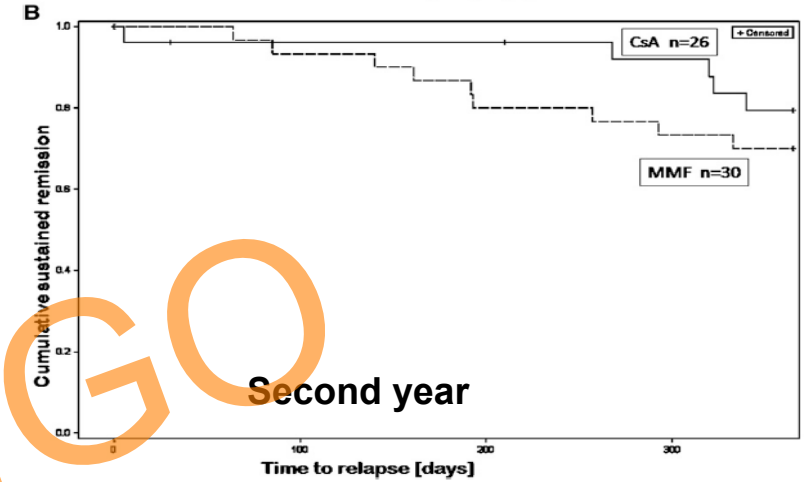
L	50	32	24	14	13
P	49	32	12	5	3

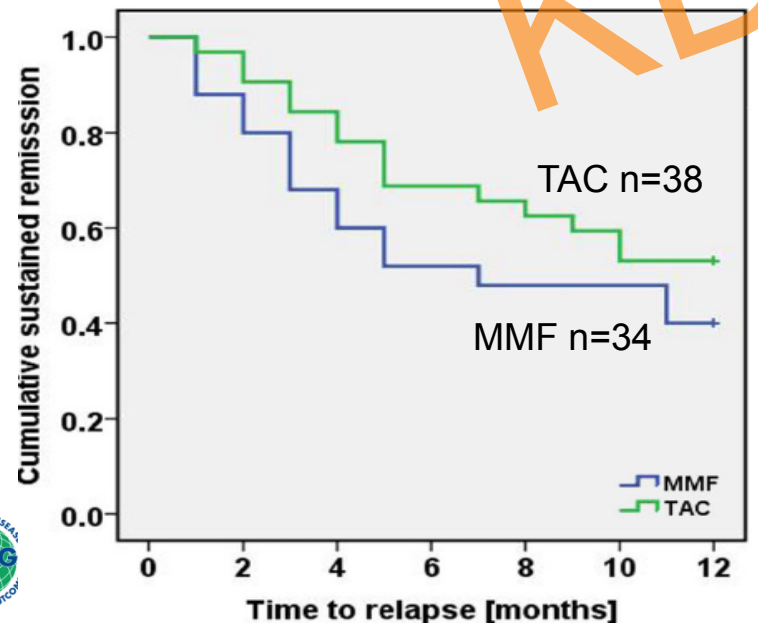
Gruppen et al. Kidney International. 2017. http://dx.doi.org/10.1016/j.kint.2017.08.011.
Eudra CT 2005-005745-18

The relative efficacies of CNIs and MMF in children with FRNS

Gellerman et al: JASN 24: 1689-1697, 2013: CSA vs MMF (RCT)

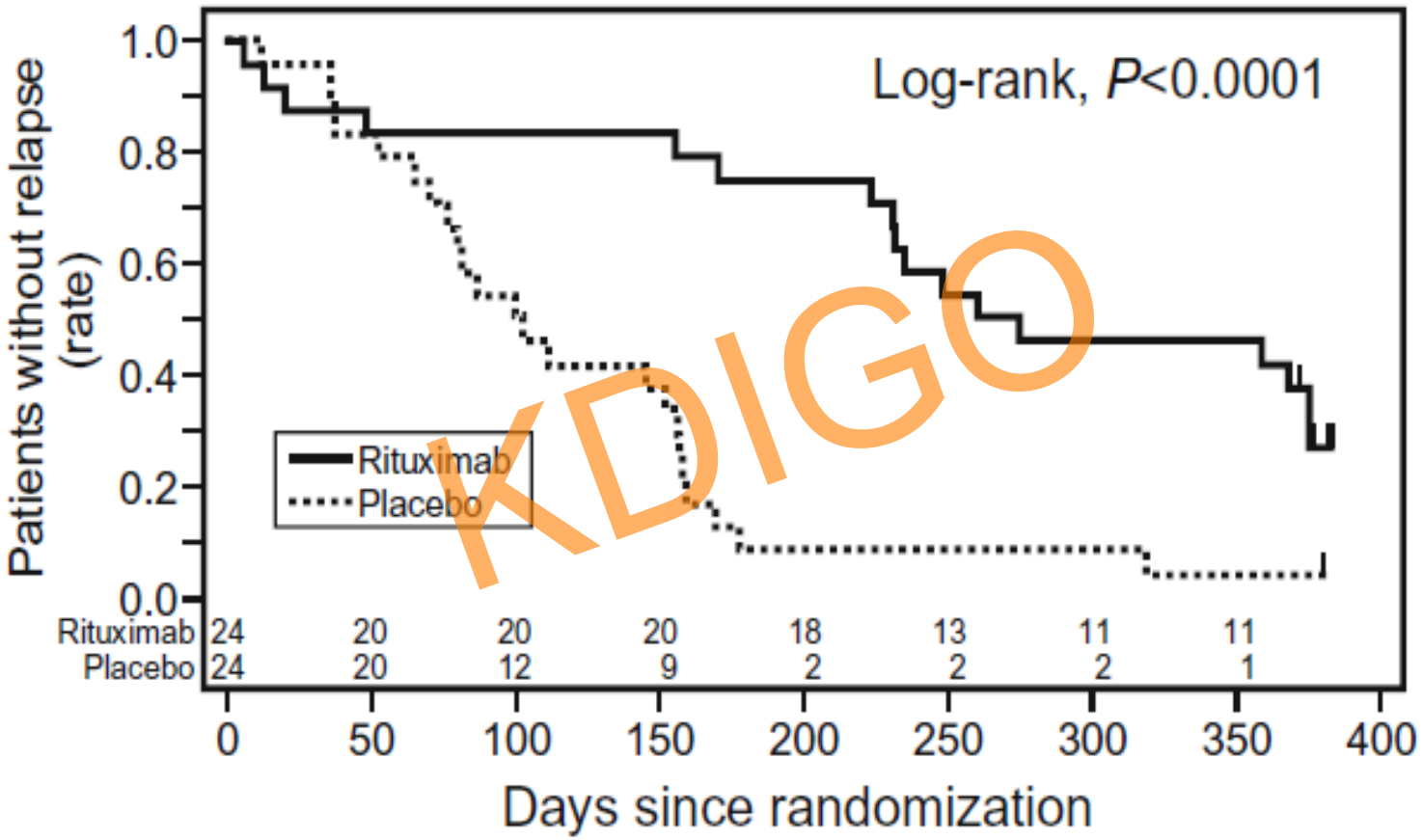






Wang et al: Nephrology 21: 21-27, 2016
MMF vs TAC
(non-randomised comparator study)

Should rituximab be used as first line steroid-sparing agent in children with SDNS?: Efficacy



Iijima et al. Lancet 384; 1273-1281, 2014

Should rituximab be used as first line steroid-sparing agent in children with SDNS?: Adverse effects

Reported in nephrotic syndrome

- Infusion reactions
- Fever, skin rash, arthritis
- Hypersensitivity in 2nd courses
- Hypogammaglobulinaemia
- Infections
- Fulminant myocarditis
- Pulmonary fibrosis
- Pneumocystitis pneumonia
- Immune-mediated ulcerative colitis
- Agranulocytosis

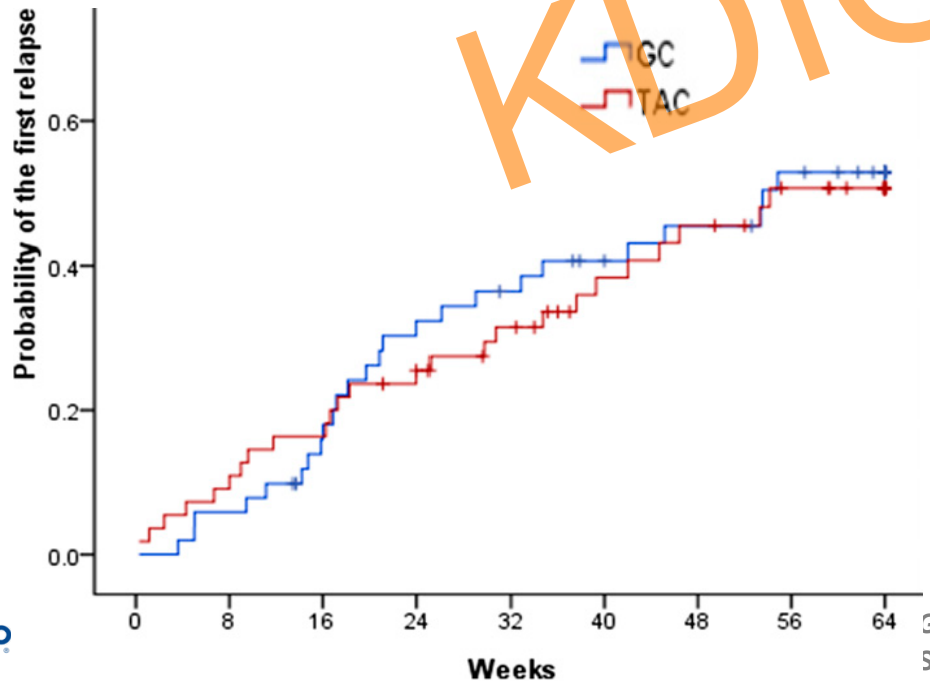
Reported in other conditions

- Reactivation of Hep B virus
- Progressive multifocal leucodystrophy
- Secondary malignancies
- Death due to infections

Minimal change disease in adults

Tacrolimus for adults with new-onset MCD

- Li et al 2017 (JASN 28: 1286-1295, 2017; ChiCTR-TRC-11001454)
  - Intervention (N=63): 10 days of IV MP, then tacrolimus for 36 week with FU to 64 weeks
  - Comparator (N=56): 10 days of IV MP, then prednisone for 36 weeks with FU to 64 weeks
  - 1er outcome: remission at 12 wks, Tac 52/56 (93%) vs pred 51/53 (96%)



2er outcome: Relapse
No relapse: TAC 55%; Pred 51%

2er outcome: SAE
TAC 2; Pred 7

Other studies of steroid-sparing agents in adults with MCD*

Table 3. Published experience for the treatment of steroid-resistant, SD, and FR MCD in adults

Medication	Evidence	Regimen	Remission Rates			Relapse Rates		
			SR[a]	SD	FR	SR[a]	SD	FR
Oral CYC	Observational series; one RCT in adults	2–2.5 mg/kg per d×8 wk	50%–80%	50%–80%	50%–80%	50%	25%–56%	25%–56%
iv CYC	Two small RCTs in adults	750 mg/m^2 per mo×6 mo + steroids	50%	77%	NA	14%	40%	NA
Cyclosporine ± prednisone	Large observational series data; one small RCT in children and one RCT in adults	3–5 mg/kg per d in divided dose×1–2 yr	45%–92%	45%–92%	45%–92%	NA	62%–75%	62%–75%
Tacrolimus ± prednisone	Small observational series; two small RCTs in adults	0.05–0.1 mg/kg per d in divided dose×1–2 yr	79%–100%	91%–100%	NA	40%	50%	NA
Mycophenolate mofetil	Small observational series; one small RCT in children	1–2 g/d in divided dose	25%	80%–100%	58%	NA	20%–50%	20%–50%

*Hogan & Radhakrishnan JASN 24: 702-711, 2013

Observational studies of steroid sparing agents in relapsing MCD in adults

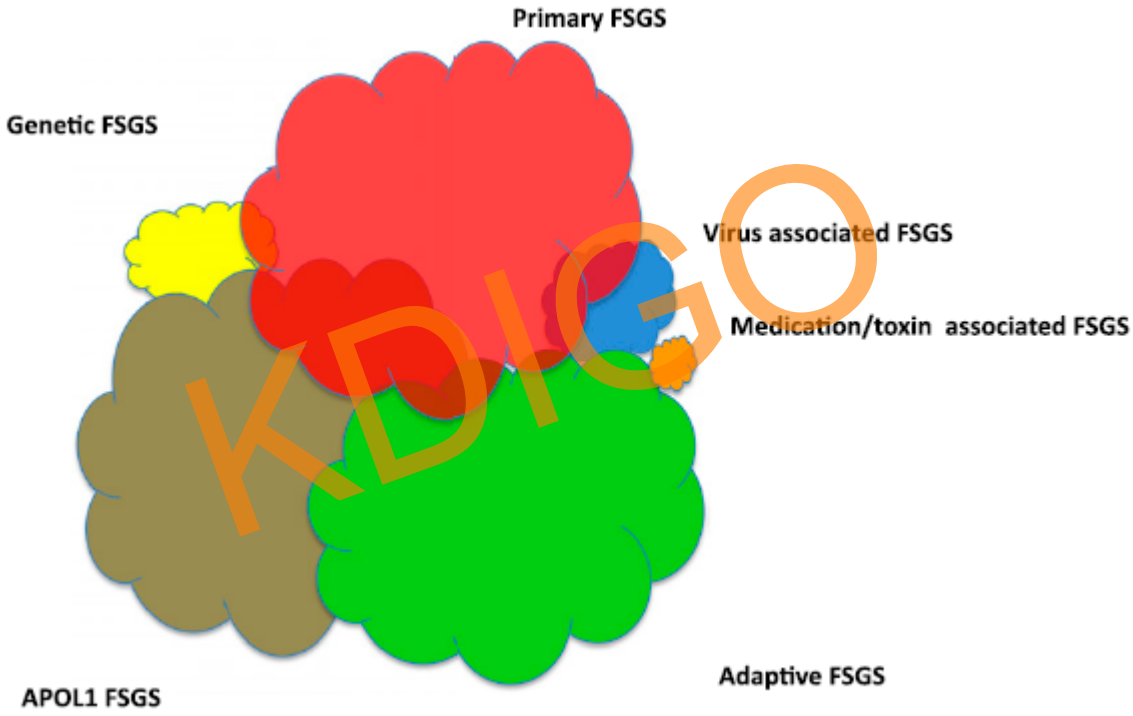
- Sandoval 2017: Mycophenolate mofetil/sodium (MF) + prednisone
  - Report of 29 adults with FRNS/SDNS
  - Remission in 27 (25 CR, 2 PR)
  - Medication ceased after 12-49 months in 20; 9 relapsed & achieved continued remission with further pred/MF
- Guitard 2014: Rituximab
  - Report of 41 adults with SDNS; variable dosing; 21 in remission & 20 in relapse
  - Remission in 32 (25 CR, 7 PR); 18 (5 PR) relapsed after 3-36 mths & 17 re-treated with remission in all (13 CR, 4 PR)
- Ruggenenti 2014: Rituximab
  - Report of 20 adults & 10 children with FRNS/SDNS; 1 or 2 doses
  - At one year, all in remission & 15 never relapsed

Investigational treatment for MCD

- Angiopoietin-like protein 4 (Angptl4) is a secretory glycoprotein that is essential for maintenance of the negative charge of GBM.
- Glomerular expression of Angptl4 is glucocorticoid sensitive
- Rats overexpressing Angptl4 develop nephrotic proteinuria, loss of GBM charge and foot process effacement
- Podocyte-secreted hyposialylated Angptl4 appears to mediate proteinuria in MCD
- N-acetyl-D-manosamine (ManNAc) converts hyposialylated Angptl4 to sialylated protein and it reverses proteinuria in experimental models
- Phase 1 study (NCT02639260) of ManNAc commenced 2015; will enrol 12 adult subjects with MCD, FSGS, MN in relapse

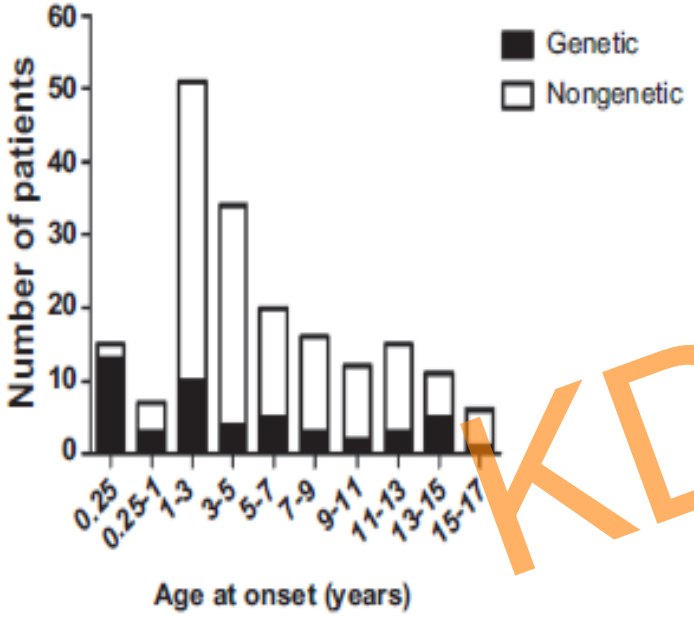
FSGS/SRNS in children and adults

The six forms of FSGS: prevalence among US adults*



*Rosenberg and Kopp. CJASN 12: 502-517, 2017

Genetic FSGS: Studies of causative mutations in 187 children with SRNS/CNS*



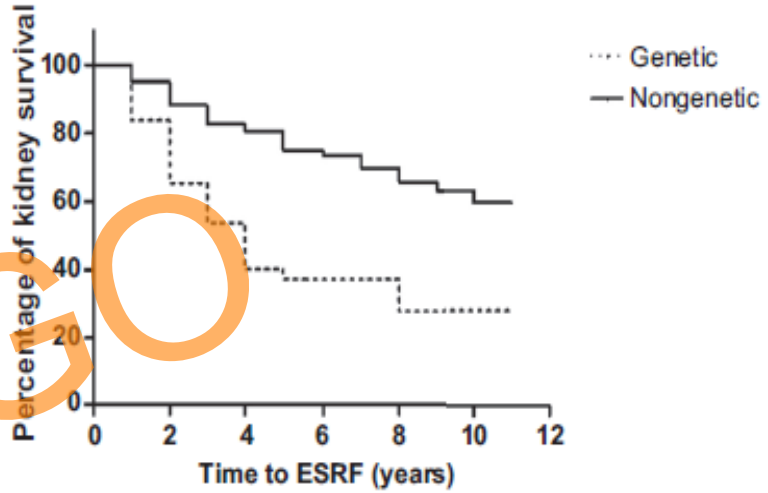


Figure 1 | Kaplan-Meier plot showing percentage of kidney survival in the genetic and genetic mutation negative group of patients. Demonstrating faster rate of progression to end-stage renal failure (ESRF) in genetic versus nongenetic cases. Log-rank (Mantel-Cox) test ($P < 0.0001$).

Single gene mutations identified in **26%** of 187 children aged < 19 years in 17/53 known SRNS genes. Mutations in 59% (13/22) familial SRNS and 22% (36/164) non-familial SRNS

*Bierzynska et al. Kidney International. (2017) 91, 937-947

FSGS in African Americans associated with mutations in *APOL1* (encodes apolipoprotein L1)

- NIH study*
  - FSGS in African Americans associated with homozygous or compound heterozygotes of G1 and G2 variants of *APOL1* (OR 16.9 (95% CI 11–26.5)*
  - Two renal risk alleles associated with earlier age of onset of FSGS & faster progression to ESKD
  - **BUT** – no difference in response to corticosteroids (8 weeks)
    - 29% (2 renal risk alleles)
    - 33% (0-1 risk alleles)
- FSGS-CT**
  - 94/138 genotyped for *APOL1* renal risk alleles; 27 had 2 risk alleles
  - Two risk alleles associated with lower kidney function, more rapid progression to ESKD, more glomerulosclerosis and interstitial fibrosis
  - **BUT** – no difference between 2 renal risk alleles and 0-1 renal risk alleles in response to treatment (cyclosporin, MMF, dexamethasone)

* Kopp et al. *J Am Soc Nephrol* 22: 2129–2137, 2011; **Kopp et al. *J Am Soc Nephrol* 26: 1443–1448, 2015

Differentiation between primary and secondary (adaptive) FSGS*

Table 2. Clinical and histological characteristics of primary versus secondary FSGS[a]

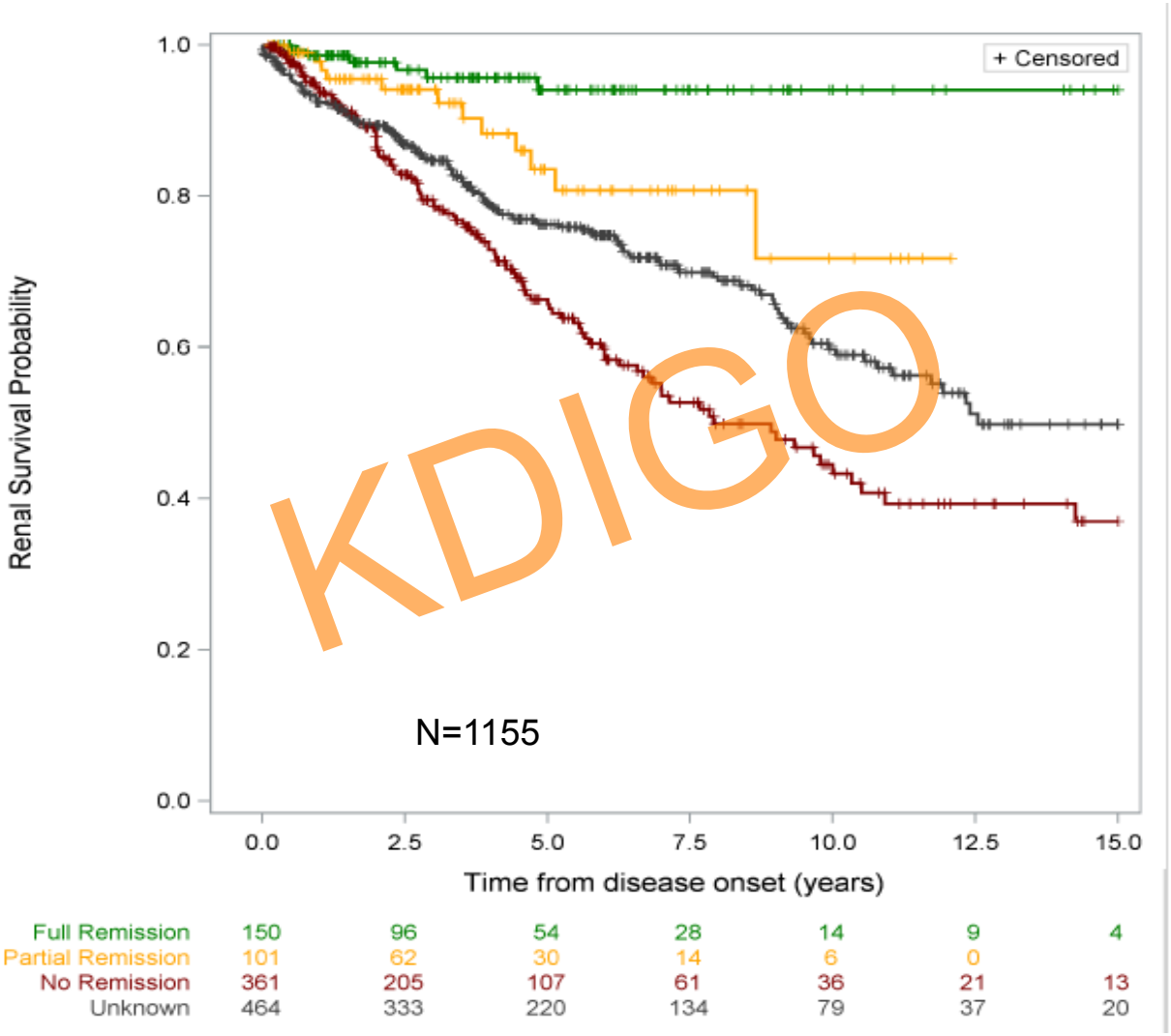
Characteristics	Primary FSGS	Secondary FSGS
Clinical presentation	Acute onset	Proteinuria develops gradually
Serum albumin	<3.5 g/dL[b]	≥3.5 g/dL
Proteinuria	≥3.5 g/24 h	Variable but can be >3.5 g/24 h
Nephrotic syndrome	Common	Uncommon
Edema	Common	Uncommon
Glomerulomegaly	Less common (30%)	Common (70%)
Foot process effacement[c]	Diffuse (>80%)	Segmental (<50%)
Clinical course	Dependent on response to immunosuppressive therapy	Slowly progressive

[a]Excluding collapsing FSGS.
[b]Usually at presentation or developing shortly after if proteinuria persists at >3.5 g/24 h.
[c]Provided patients are not receiving immunosuppressive therapy previously or at the time of renal biopsy.

*Zand et al: Nephrol Dial Transplant (2017) 32: i14-i21

Renal survival by response to immunosuppressive agents in children with SRNS (*PoDoNet cohort)

*Trautmann et al. JASN. 28: 3055-3065, 2017



Problems with treatment studies in FSGS/ SRNS*

- Heterogeneous population
  - Recruitment of patients with adaptive FSGS, including patients with proteinuria without nephrotic syndrome
  - No requirement for EM in studies so the extent of foot process effacement not known
  - Inclusion of patients with FH of nephrotic syndrome; lack of genetic studies
  - Inclusion of patients with primary and delayed steroid resistance
  - Inclusion of patients with MCD and MesPGN
- Inadequate patient recruitment so the studies are underpowered to detect a difference between treatment groups

*Zand et al: Nephrol Dial Transplant (2017) 32: i14-i21

Interventions for SRNS (FSGS/MCD): RCTs

Author	N	Intervention	Control	Duration (mths)	Remission (Complete + Partial)	RR (95% CI) for remission	Conclusion
FSGS-CT 2011	138 A+C	Cyclosporin	MMF + dexamethasone	12	33 (46%) vs 22 (33%)	1.35 (0.90-2.10)	No significant difference
Ren 2013	33 A	Tacrolimus + prednisone	IV CPA + prednisone	6	10 (67%) vs 10 (56%)	1.20 (0.69-2.07)	No significant difference
APN 2008	32 C	Cyclosporin + prednisone	IV CPA + prednisone	3	9 (60%) vs 3 (18%)	3.40 (1.12-10.28)	Remission CSA > CPA
Gulati 2012	124 C	Tacrolimus + prednisone	IV CPA + prednisone	12/6	53 (80%) vs 28 (43%)	1.80 (1.34-2.42)	Remission Tac > CPA
Magnasco 2012	31 C	Rituximab/ Cyclosporin/ prednisone	Cyclosporin/ prednisone	3	3 (19%) vs 3 (20%)	0.94 (0.22-3.94)	No significant difference
Sinha 2017	60 C	Tacrolimus + prednisone	MMF + prednisone	12	28 (90%) vs 13 (45%)	2.01 (1.32-3.07)	Maintains Remission Tac > MMF

Other immunosuppressive treatments for FSGS

- mTOR inhibitors
  - Evidence that mTOR inhibitors can exacerbate FSGS
- ACTH gel (Hogan. CJASN 8: 2072-2081, 2013; NCT01155141; NCT01129284)
  - Report of 24 patients with FSGS (6 steroid dependent; 15 steroid resistant) treated with ACTH gel (80 units twice weekly sc for variable duration).
  - 7 showed response (CR 2, PR 5) including 5 with SRNS; 5 had sustained response (range 23-104 weeks) and 2 relapsed
  - 21 had adverse effects; 23 episodes of corticosteroid-like adverse effects
- ACTH gel in children
  - NCT02972346: RCT in China comparing ACTH gel with no specific treatment in ages 3-12 years for SDNS/SRNS
  - NCT02132195: RCT in USA comparing ACTH gel with no specific treatment in ages 2-20 years for FRNS/SDNS with FSGS or MCD; SRNS excluded

Investigational treatments for primary FSGS*

- Blocking TGF-β reduces fibrosis in experimental CKD
  - Fresolimumab (monoclonal antibody against 3 isoforms of TGF-β)
    - Phase 1 study: 3/16 had ≥ 50% reduction in proteinuria
    - Phase 2 study: 2/36 achieved PR. (Vincenti et al *Kid Int Rep* (2017) 2: 800-810; NCT01665391)
- TNF-α can mediate proteinuria and fibrosis in FSGS
  - Adalimumab is a monoclonal antibody against TNF-α
    - FONT Study (1): 4/10 had 50% reduction in proteinuria
    - FONT Study (2): 0/7 had any reduction in proteinuria
- Blocking B7-1 (CD80) expression with abatacept
  - Remission in 4 patients with rFSGS & 1 with primary FSGS; all had B7-1 staining of podocytes (Yu 2013)
  - Response in 1 of 25 other reported patients with rFSGS
  - Crossover RCT comparing abatacept with placebo in 90 patients (adults/children with MCD or FSGS; not post Tx recurrence) commenced in 2016; results in 2020 (NCT02592798)

*Trachtman 2017: Expert Opinion on Investigational Drugs 2017; 26: 945-952

Investigational treatments for primary FSGS*

- Angiotensin type 1 & endothelin receptors type A promote vasocontriction & extracellular matrix accumulation
  - DUET study: RCT comparing sparsanten with irbesartan for 8 weeks in 96 patients with FSGS (Trachtman ASN abstracts 2016, 2017: NCT 01613118)
  - UPC <1.5 g/g in 28% SPAR vs 9% IRB
  - Benefit persisted for 48 weeks in extension study
- Binding of circulating factors
  - Galactose can bind circulating factors
  - 0/7 children on galactose achieved CR or PR (Sqambat 2013; NCT01113385)
  - 2/7 treated with Galactose and 2/7 treated with standard therapy achieved PR (FONT 2, 2015: NCT00814255)

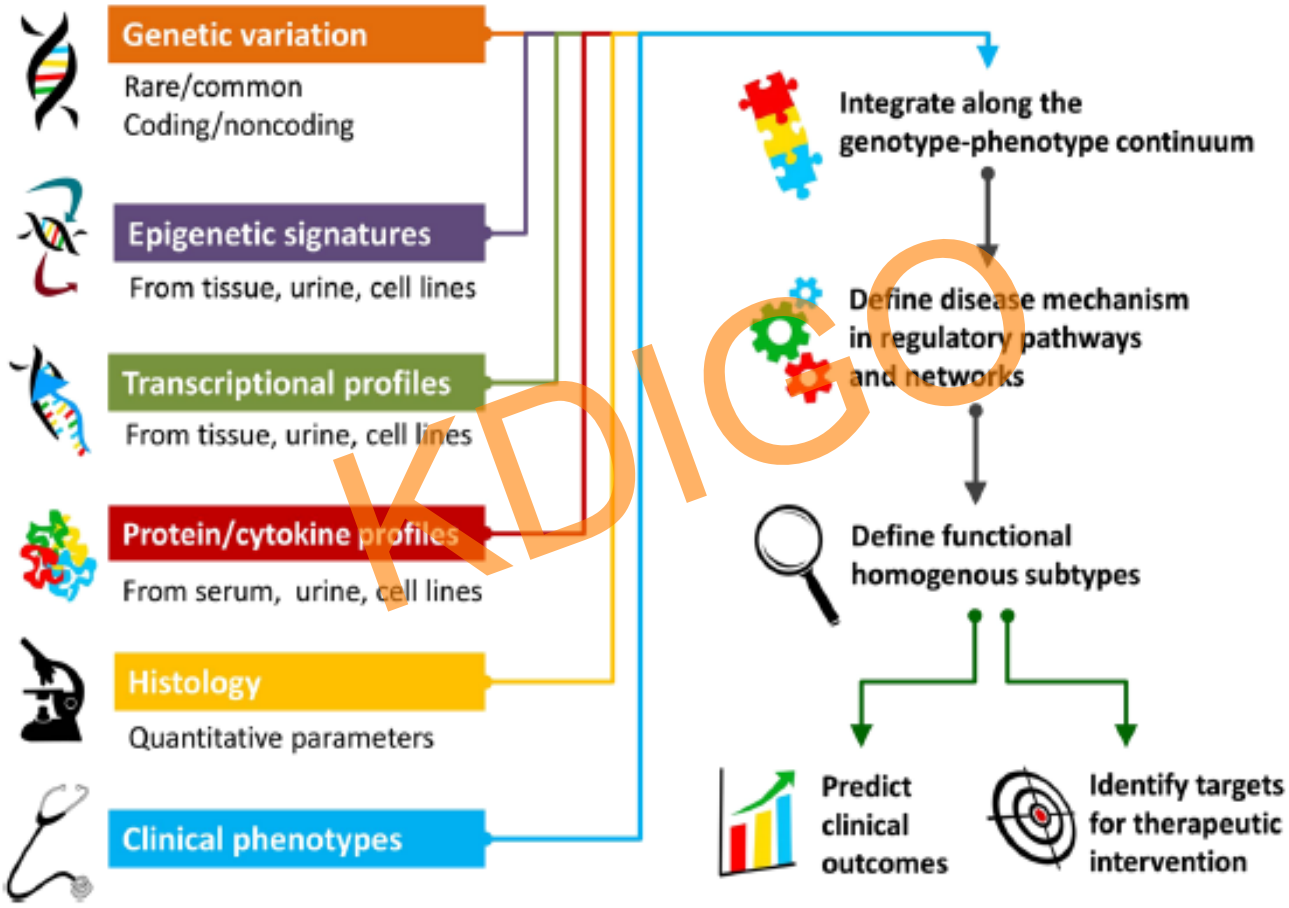
*Trachtman 2017: Expert Opinion on Investigational Drugs 2017; 26: 945-952

Other investigational treatments for FSGS*

- Blocking JAK/STAT pathway
  - Rationale: JAK/STAT inhibitor reverses increased glomerular permeability to albumin after exposure to FSGS plasma or cardiotrophin-like cytokine factor-1 (CLCF-1)
- Retinoic acid treatment (NCT00098020)
  - Rationale: Retinoids restore podocyte phenotype and reduces proteinuria
  - Phase 1 study of isotretinoin in 10 adults with MCD/FSGS for 6 months completed
- Blocking Notch 1
  - Rationale: Significant activation of Notch 1 in FSGS
  - Signature of this pathway in FSGS patients could identify patients for trials of Notch 1 inhibitors
- Complement antagonists
  - Rationale: 5 of 19 patients in FSGS-CT showed complement activation
  - Demonstrating complement activation could allow eculizumab use in a subset of FSGS patients
- Infusion of mesenchymal stem cells
  - Rationale: Improvement in experimental models of kidney disease
  - NCT02382874 currently recruiting

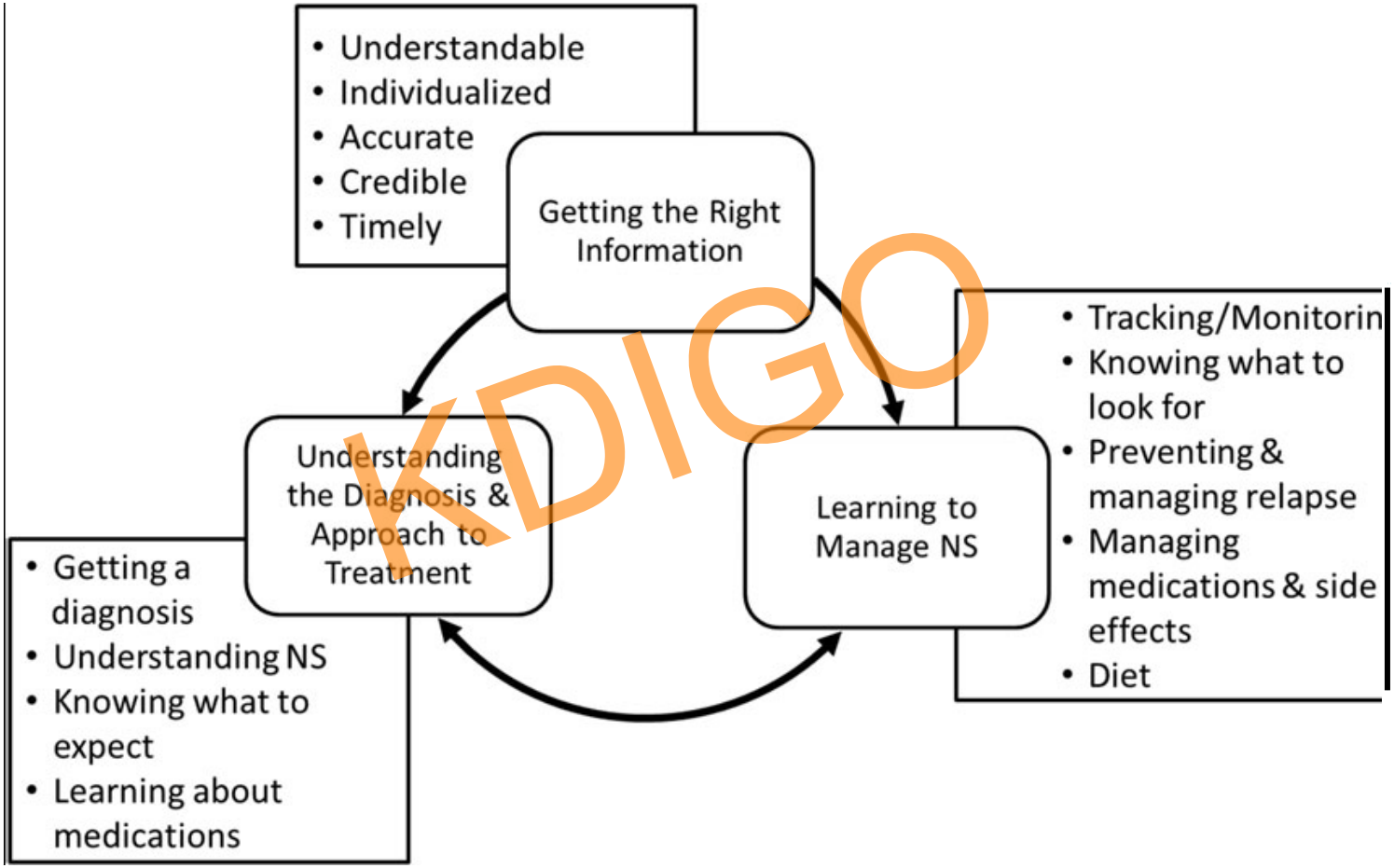
*Trachtman 2017: Expert Opinion on Investigational Drugs 2017; 26: 945-952

"Neptune" schema for integrative genomics of nephrotic syndrome*



*Sampson et al. Pediatric Nephrology (2015) 30: 51-63

Remember the child/adult/family with nephrotic syndrome*



*Beanlands NDT (2017) 32: i98 - i105

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