(p)pFSGS: what's in a name?

Rutger Maas
Workshop Nefrologie Papendal 2021

Radboudumc

Disclosures

(Potentiële) belangenverstrengeling:

n.v.t.

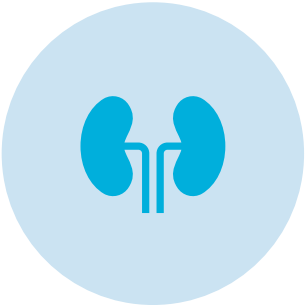
Voor bijeenkomst mogelijk relevante relaties met bedrijven:

n.v.t.

Klinische vragen bij FSGS

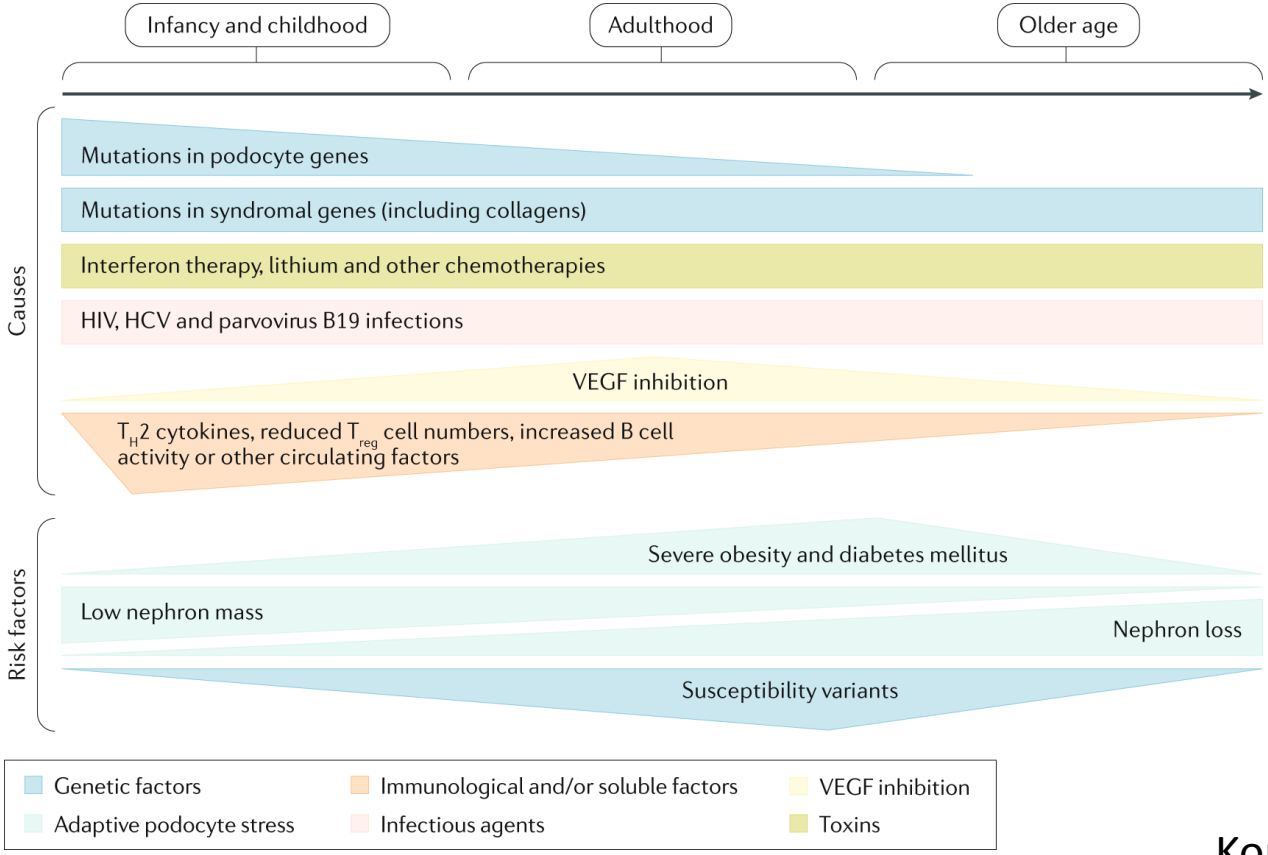
INDICATIE GENETISCH ONDERZOEK?

INDICATIE / DUUR IMMUNOSUPPRESSIEVE THERAPIE?



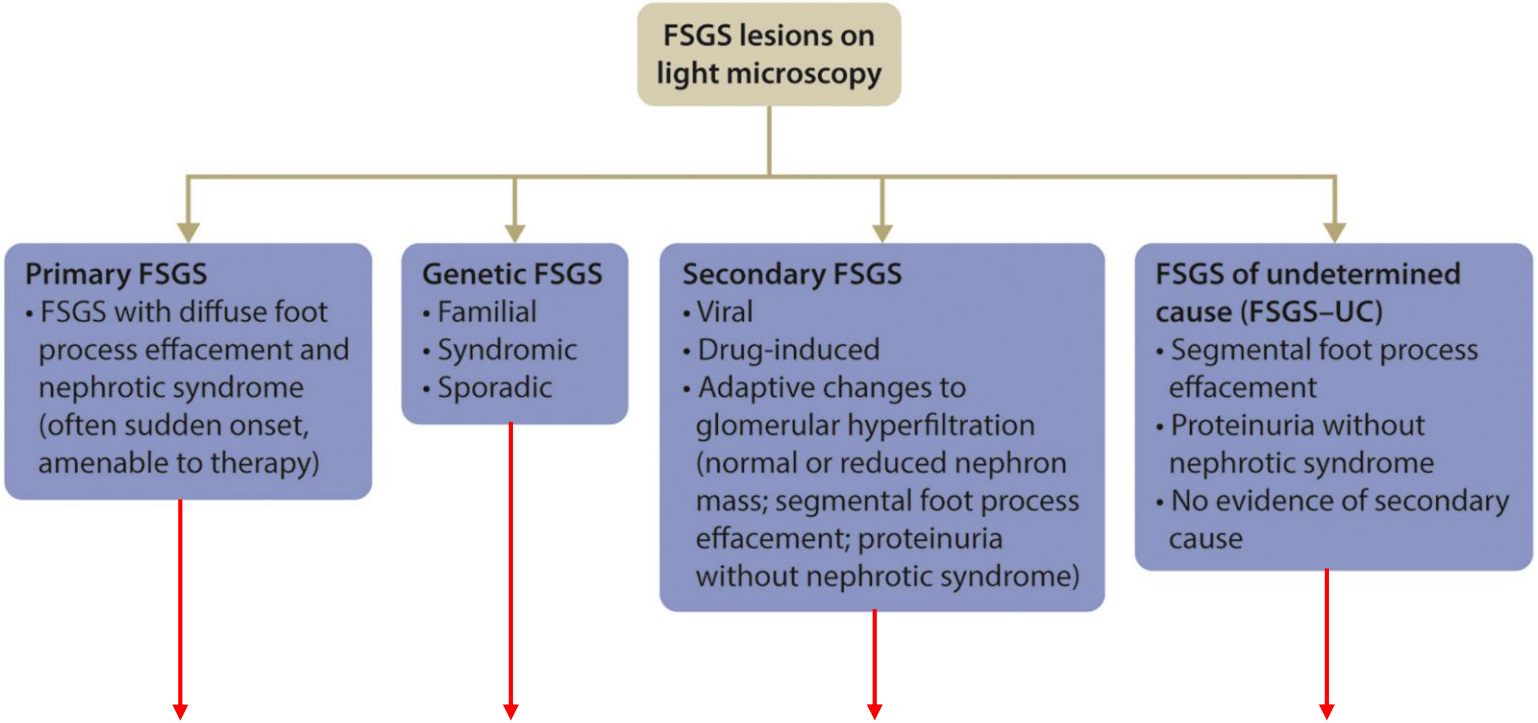
ROL VAN PERMEABILITY FACTOR / RECIDIEF NA NTX?

Oorzaken van FSGS



Kopp, Nat Dis Primers 2020

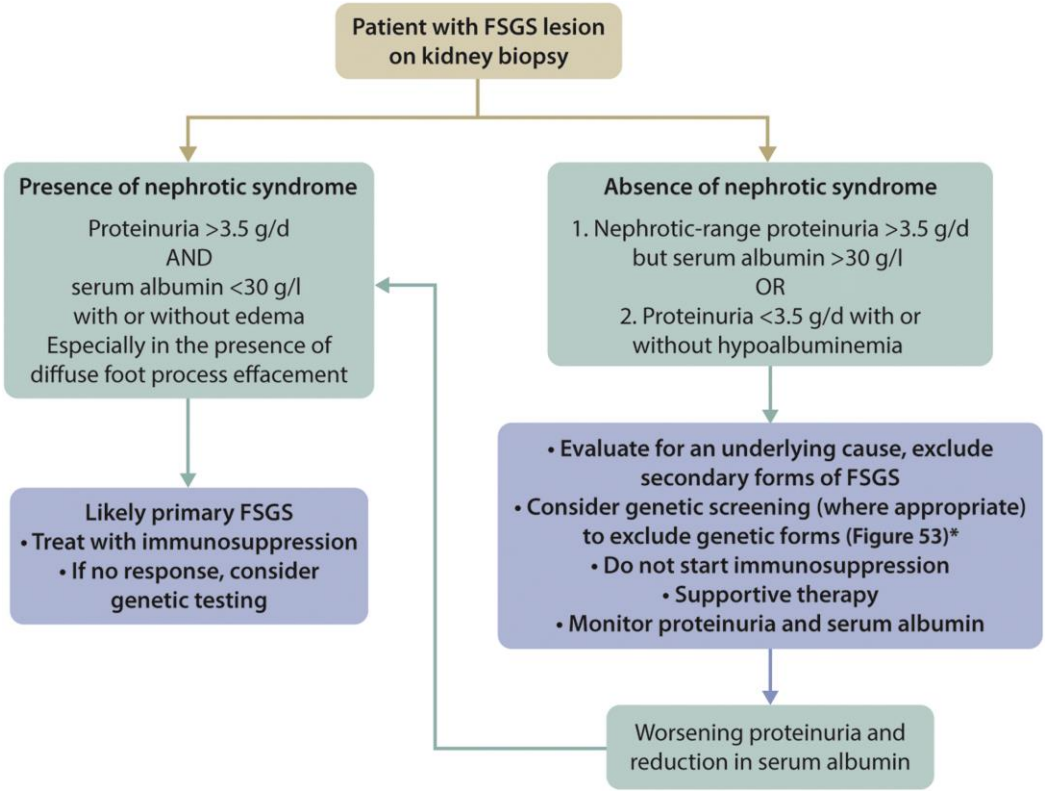
KDIGO 2021: nieuwe FSGS classificatie



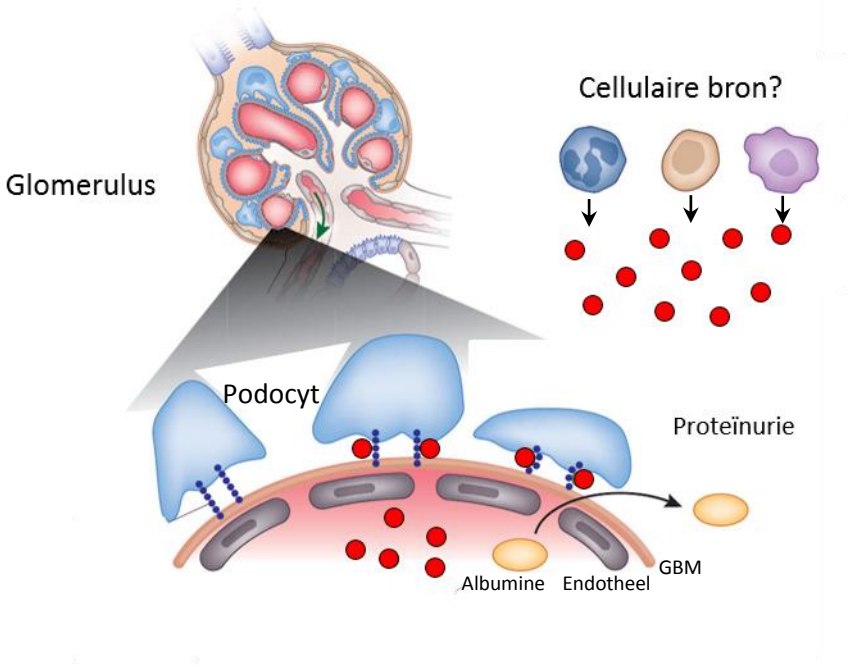
IMMUNO-SUPPRESSIE	**JA**	**NEE**	**NEE**	**NEE**

Criteria voor primaire FSGS

FSGS evaluatie en behandeling



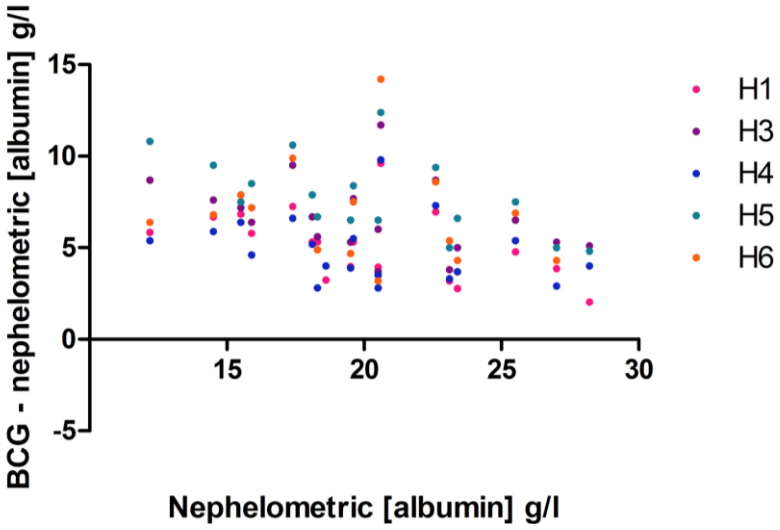
Presumed primary FSGS = permeability factor-related disease

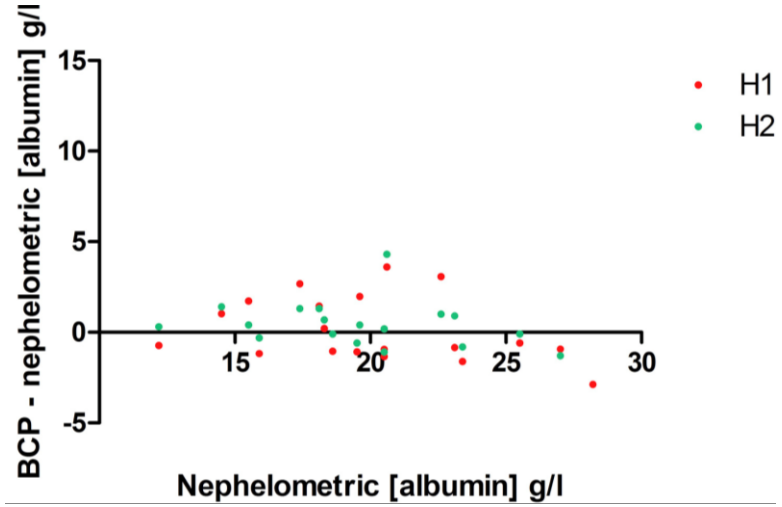


FSGS factor

Shankland, Nat Med 2011

Serum albumine: belang van de assay

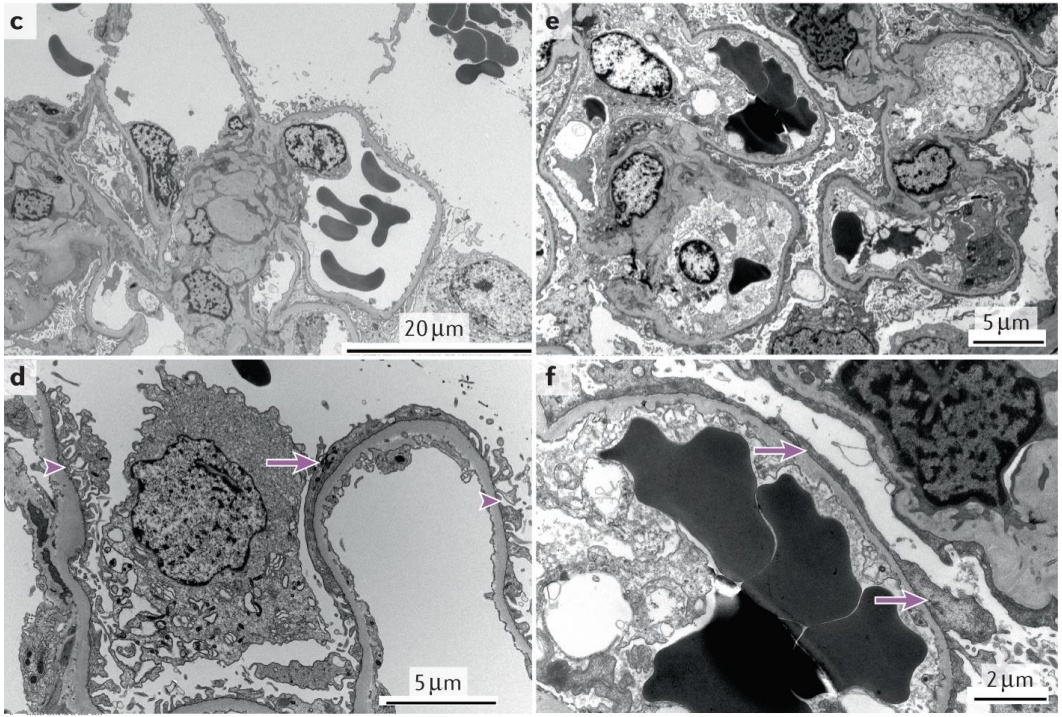




BCG assay: systematische overschatting

Van de Logt, KI 2019

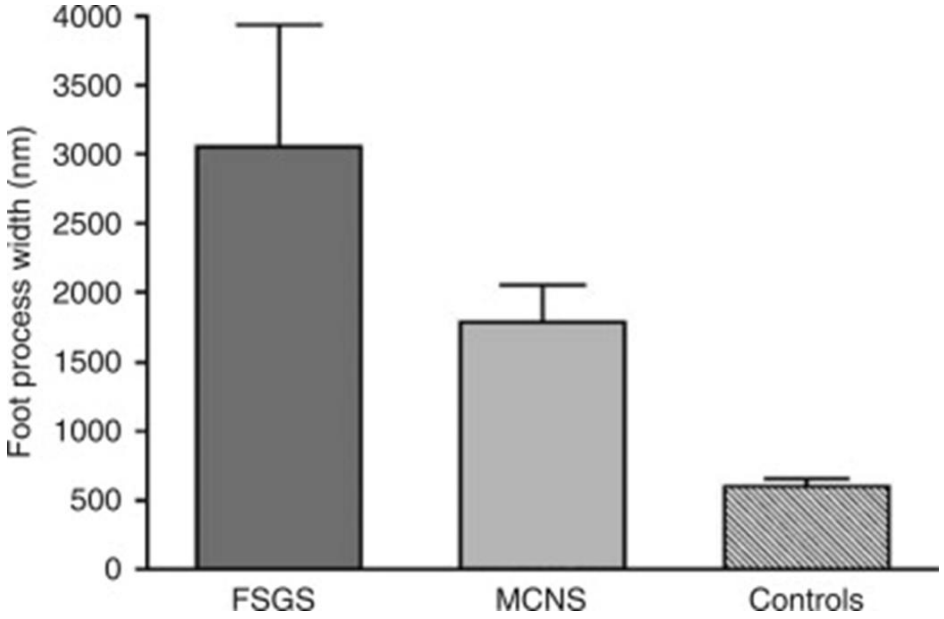
Podocyte foot process effacement

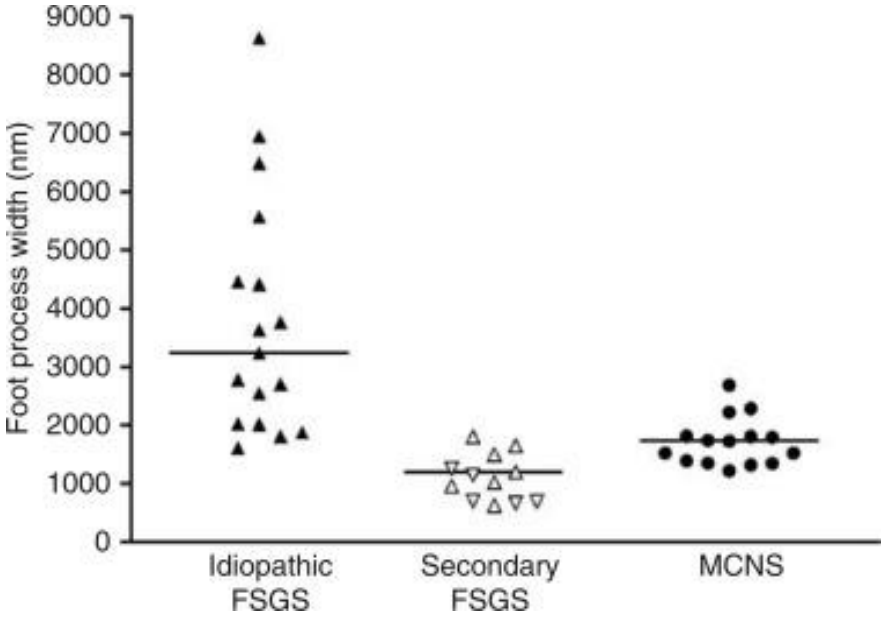


Secundaire FSGS: partieel **pFSGS: volledig**

De Vriese,
Nat Rev Nephrol 2021

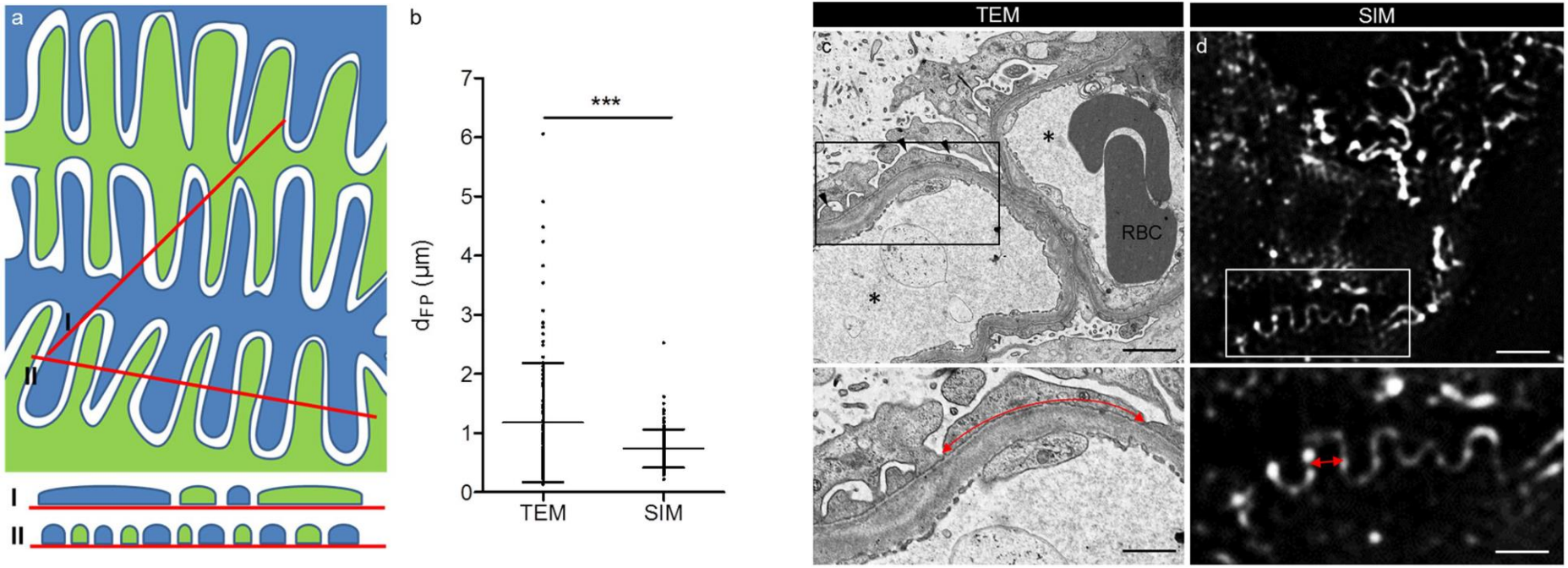
Kwantificatie podocyte FPW





Deegens, KI 2008

Structured illumination microscopy



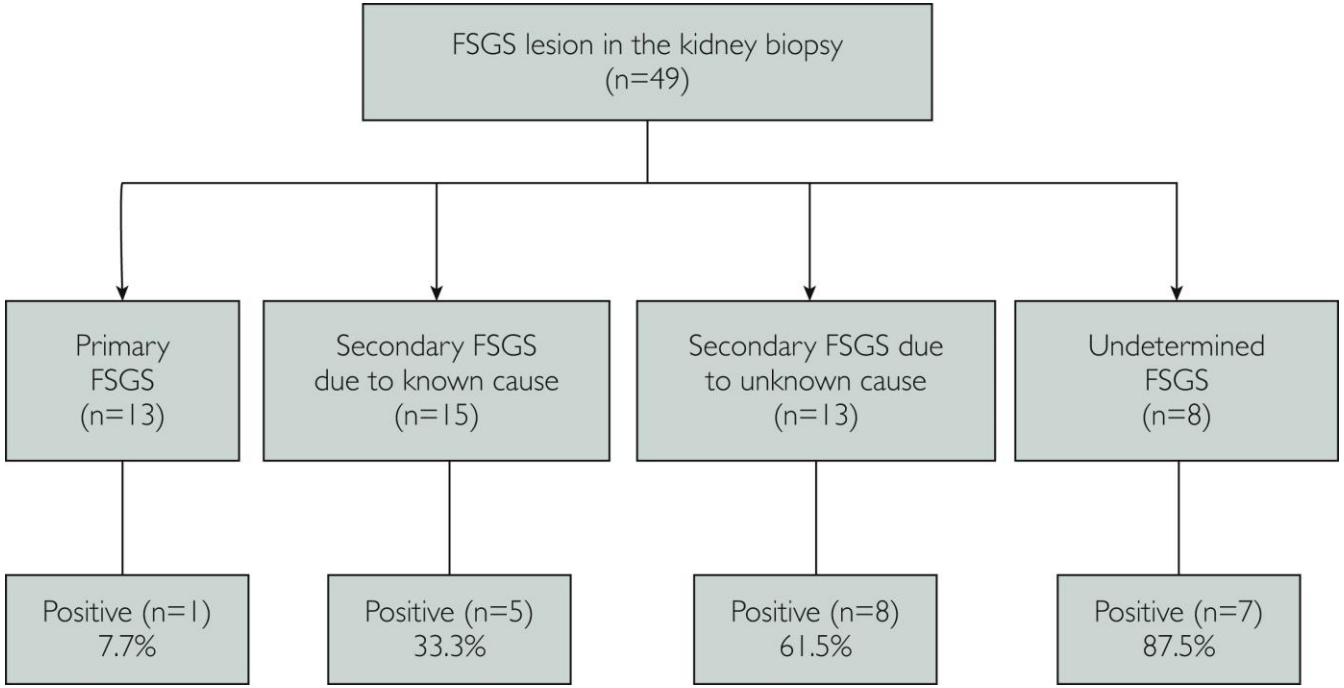
Siegerist, Sci Rep 2017

Wanneer genetische diagnostiek?

Genetische FSGS binnen nieuwe classificatie

- Retrospectief onderzoek Mayo Clinic, 1999-2019
- 49 volwassenen met FSGS in het nierbiopt
- Klinisch-pathologische classificatie (ongeveer) conform KDIGO
- Undetermined FSGS: discrepantie klinische presentatie vs histologie
- Vervolgens exoom analyse nier genen-panel bij alle patiënten

Miao, Mayo Clin Proc 2021



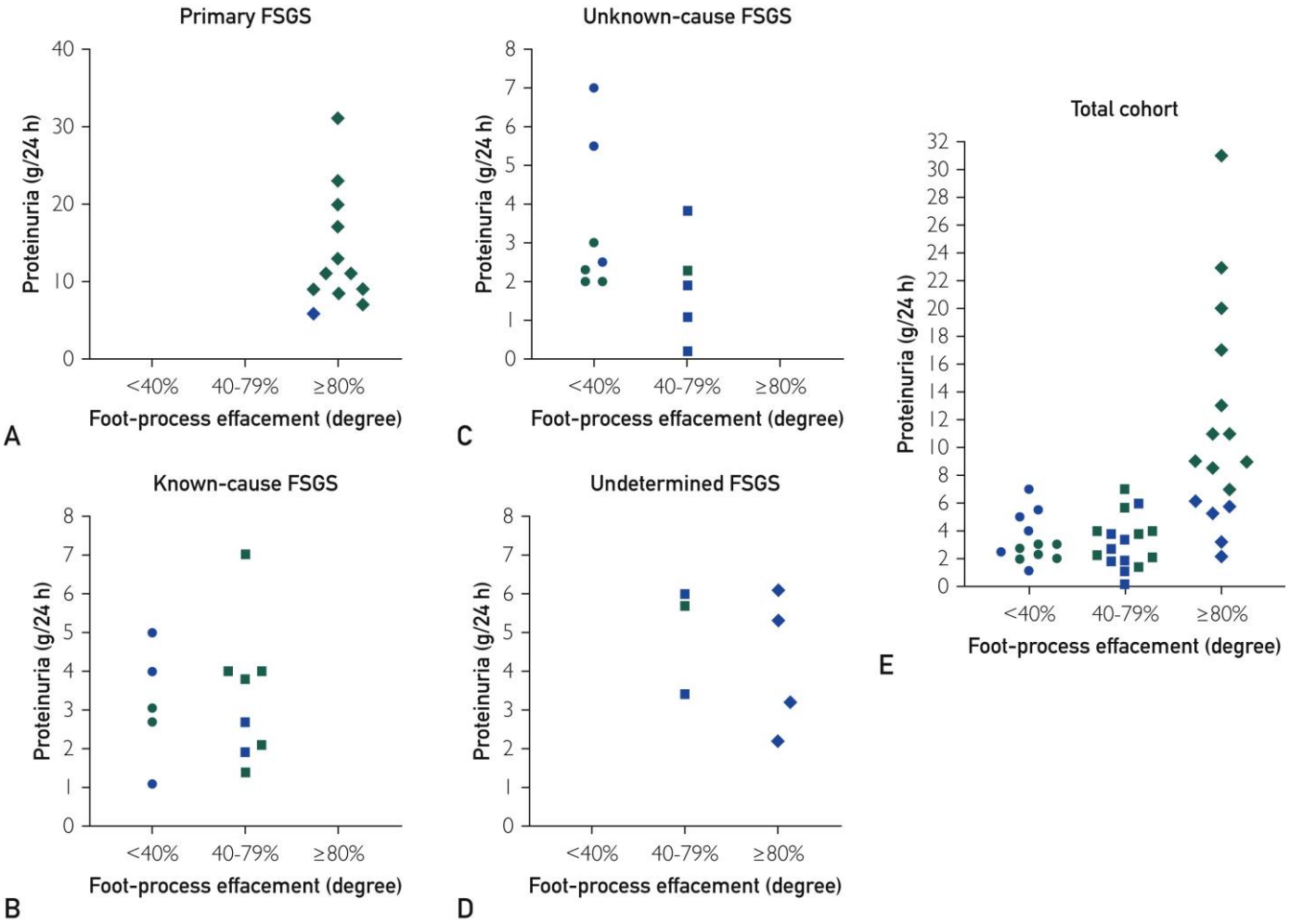
NPHS2

COL4A3
COL4A4
NPHS1
TRPC6

COL4A3
COL4A4
COL4A5
INF2
UMOD

COL4A3
NPHS2
INF2
SMARCAL1

2/21 nefrotisch
15/21 familie-anamnese pos


Primary FSGS
Proteinuria (g/24 h)
40
30
20
10
0
<40%
40-79%
≥80%
Foot-process effacement (degree)
A
Unknown-cause FSGS
Proteinuria (g/24 h)
8
7
6
5
4
3
2
1
0
<40%
40-79%
≥80%
Foot-process effacement (degree)
C
Total cohort
Proteinuria (g/24 h)
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
<40%
40-79%
≥80%
Foot-process effacement (degree)
E
Known-cause FSGS
Proteinuria (g/24 h)
8
7
6
5
4
3
2
1
0
<40%
40-79%
≥80%
Foot-process effacement (degree)
B
Undetermined FSGS
Proteinuria (g/24 h)
8
7
6
5
4
3
2
1
0
<40%
40-79%
≥80%
Foot-process effacement (degree)
D

● genetisch

Behandeling primaire FSGS

KDIGO: therapie primaire FSGS

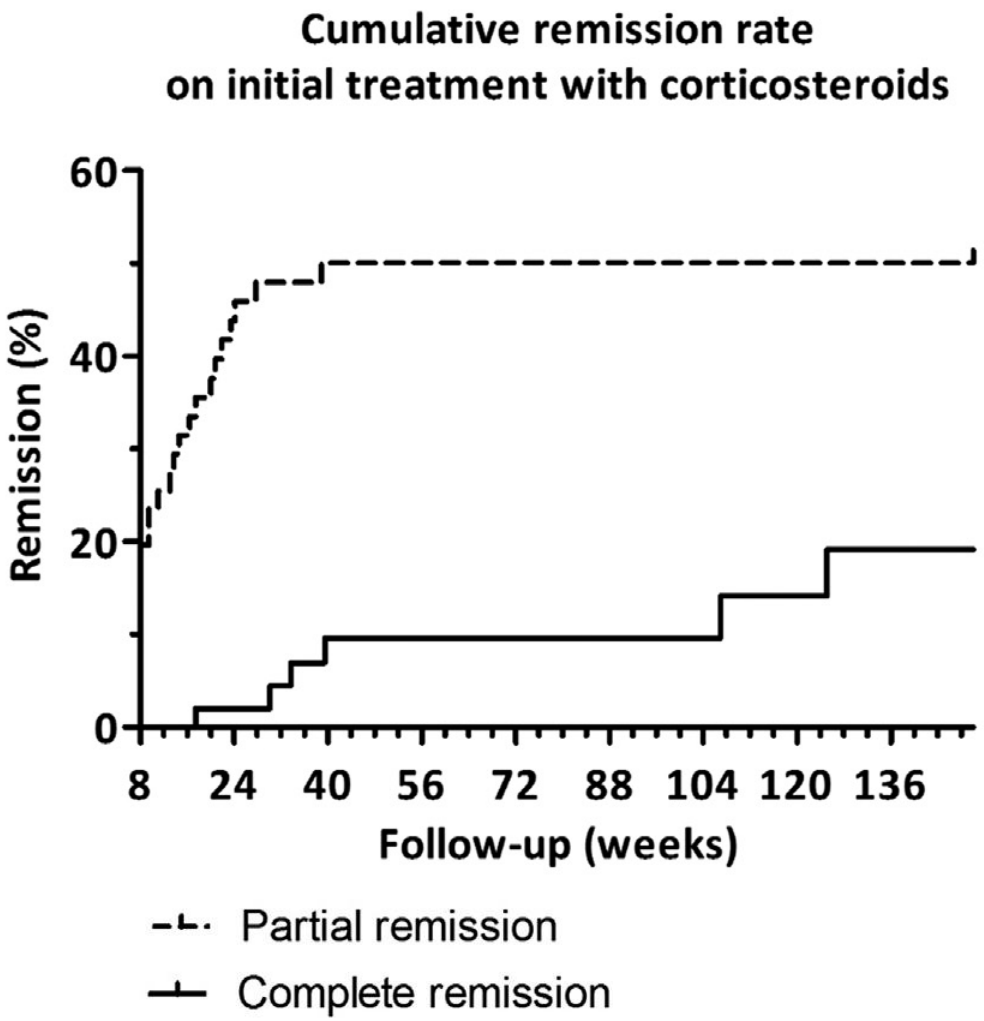
- Hoge dosis prednisolon 1mg/kg per dag
  - Behandelen tot CR
  - Minimaal 4 weken
  - Maximaal 16 weken

- Steroïd-resistente FSGS
  - PU >3,5g en <50% reductie (geen PR) na 16 wkn prednisolon
  - Behandeling met calcineurineremmers tenminste 4-6 mnd

Resultaten bij primaire FSGS

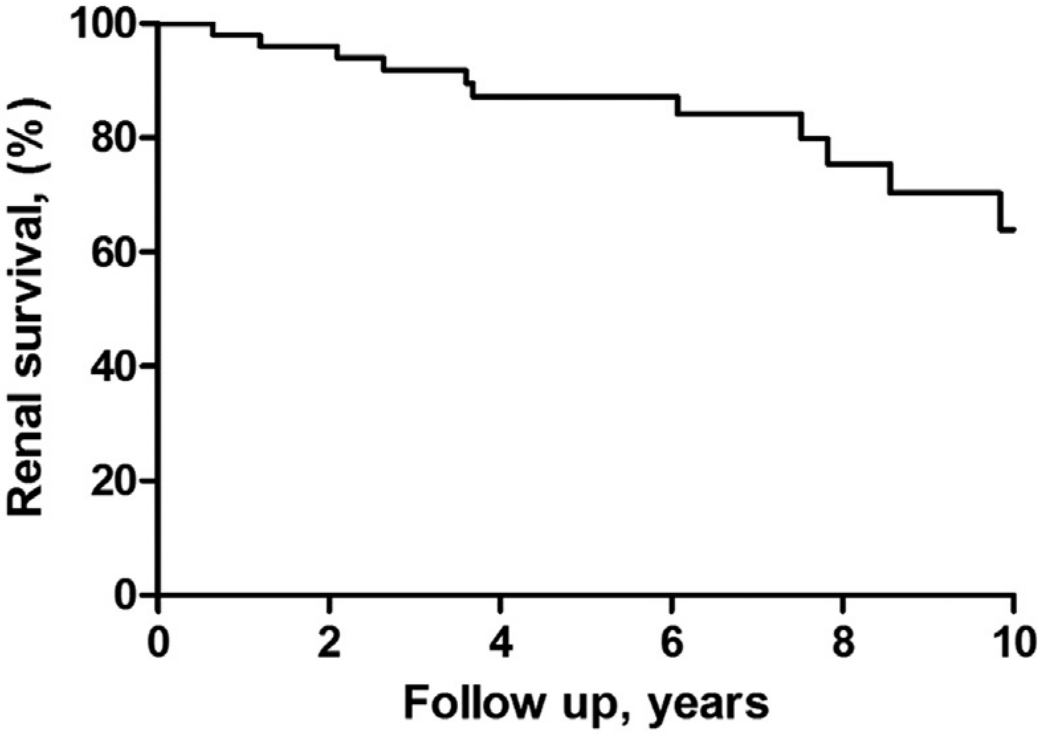
- Retrospectieve studie Radboudumc en regio (1995-2014)
- 51 volwassen patiënten met FSGS bij biopsie
- Presentatie met nefrotisch syndroom (*presumed* pFSGS)
- Complete voetprocesversmelting podocyten bij 27/29
- Genetisch onderzoek: 2 mutaties (*NPHS2*, MELAS)

Rood, KI Rep 2021



	NR (n)	PR/CR (n)
< 20%	7	3
>20%	1	**23**

Proteïnurierespons na 8 weken Pred voorspelt therapierespons



10 yr renal survival 64%

Nierfunctieverlies >15 ml/min bij 15/41 responders

Rol van CNI toxiciteit?

Extracorporele therapie

- 19 Franse centra
- Prednisolon + ≥ 1 ander middel
- Diverse modaliteiten
  - Plasmaferese
  - DFPP
  - Immuun-absorptie
  - LDL aferese

Moret, KI Reports 2021

Resultaten

At 12 months follow-up:

33% Complete or partial remission

Factors associated with remission:

- Need for dialysis before apheresis
- Decrease in proteinuria between diagnosis & apheresis initiation
- Age ≥ 50 years
- < 12 months between diagnosis & apheresis

Therapie
12 sessies (4-39)
47 dagen (17-172)

Partieel steroïd-gevoelig
(afname 5,5 g/24u)

Relatief vroeg in
ziektebeloop

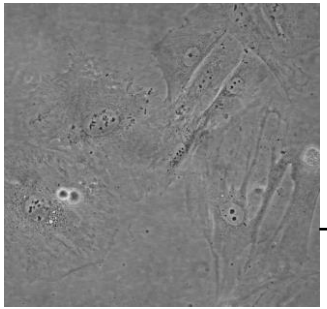
De FSGS permeability factor

Effecten FSGS plasma op podocyten in kweek

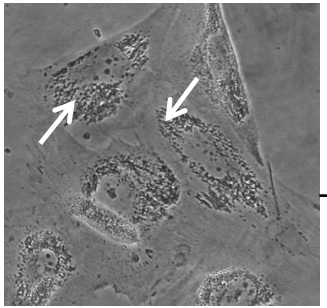
Podocyten kweek (microscopie)

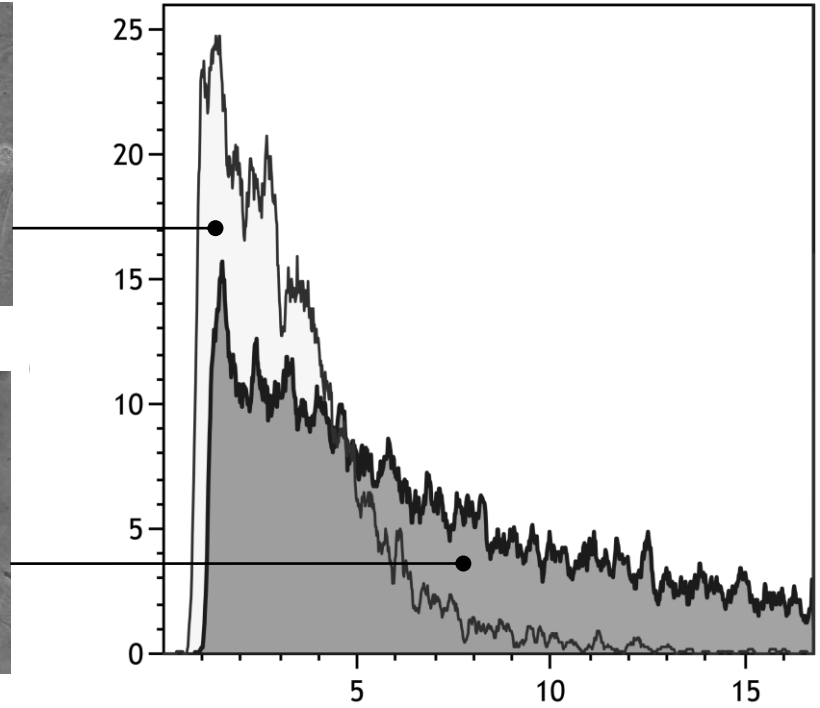
Flowcytometrie van podocyten (side scatter plot)

+ Gezond plasma



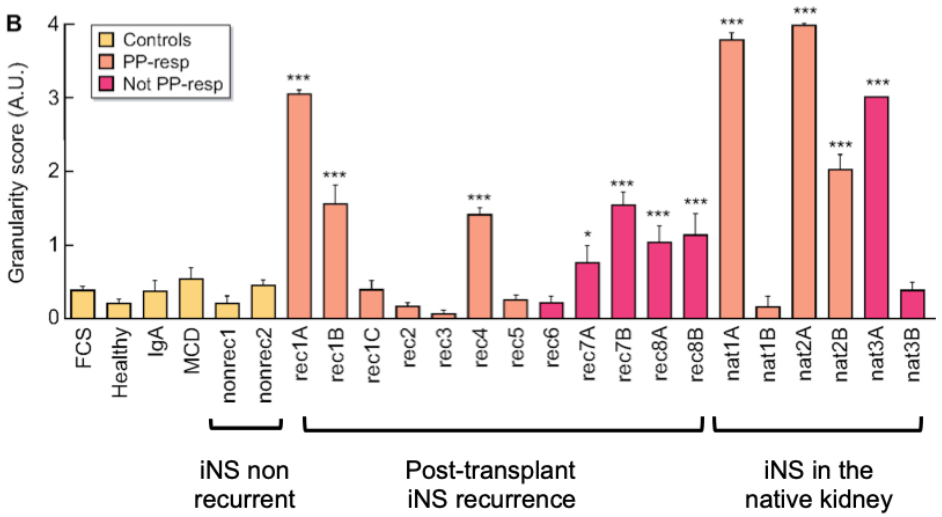
+ FSGS PF plasma
actieve ziekte



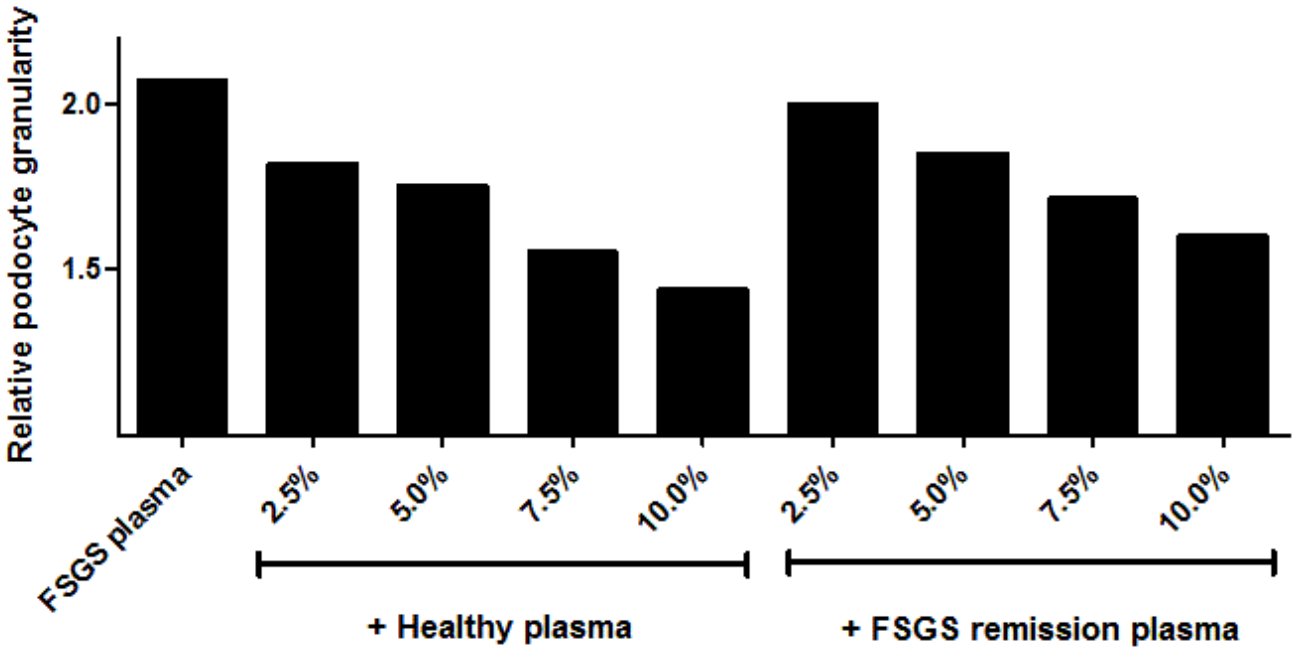


Den Braanker, NDT 2021

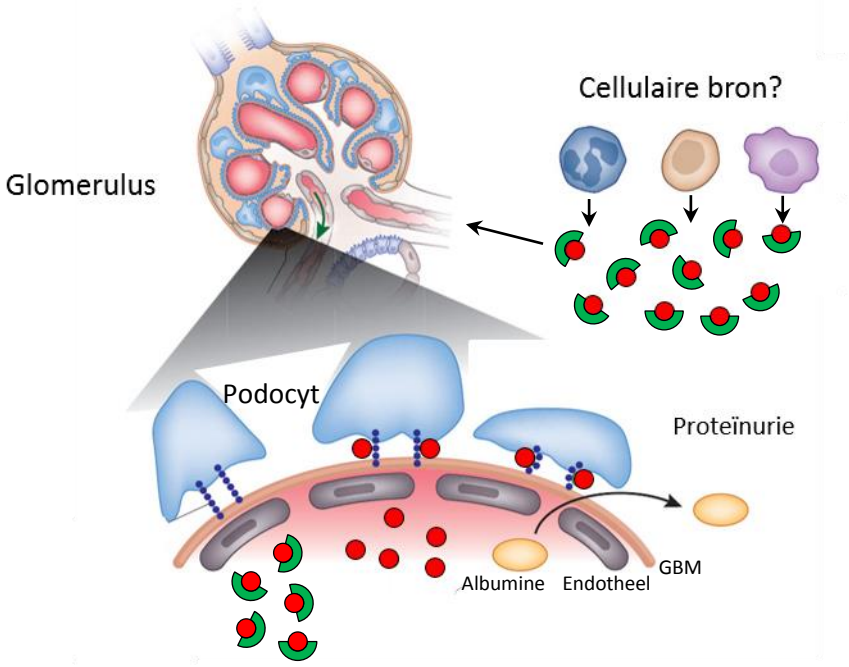
Podocyten assay bij plasmaferese cohort



FSGS remmer in gezond plasma en remissie plasma



Hypothese: FSGS permeability factor en remmer



- FSGS factor
- Remmer van FSGS factor
- Complex van FSGS factor en remmer

NIERSTICHTING

Kolff+ Creativity Project
R. Maas/T. Nijenhuis/J. van der Vlag

Conclusies

GENETISCHE FSGS BIJ VOLWASSENEN

Familie-anamnese

Meestal niet nefrotisch

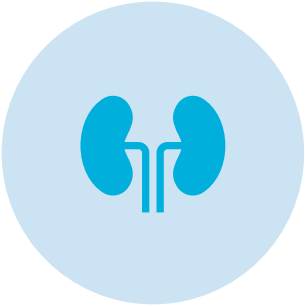
<20% PU reductie na 8wkn Pred?

PRIMAIRE FSGS

Vertraagde respons op steroïden

Behandeling is (nefro)toxisch

Plasmaferese: rescue-therapie?



PERMEABILITY FACTOR

(Nog) niet geïdentificeerd

Model bevestigt podocyt-toxiciteit

Rol van remmers?