# EARLY PRO-TECT Alport

## Introduction to Alport disease and motivation and rationale for the study

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# Introduction

Professor of Internal Medicine and attending nephrologist, UMG Goettingen

Adult nephrologist and Clinician

NOT at ALL an expert in any regulatory affairs or statistics

Alport research started 1995 (genetic testing), Alport mice research started 2000

founder of European Alport Registry, member of Executive Committee ASTOR

recognized as a leader in the field of hereditary type IV collagen diseases

main basic research topic potential therapies and type IV collagen receptors

main clinical research topic: registry and therapeutic trials in Alport patients

initiator and LKP (lead coord. physician) EARLY PRO-TECT Alport trial

# Agenda

1. The medical problem: Alport Syndrome
2. From bedside to bench: Alport animal model
   *nephroprotective therapy in mice*
3. … and back to bedside: Alport registry
   *therapy in man delays renal failure and improves life-expectancy*
4. Evidence based medicine in a rare disease??
   *randomised, placebo-controlled EARLY PRO-TECT Alport trial*
5. Future medical therapy
   *upcoming clinical trials*
6. Sum up for discussion and my questions for you

# Statistics of Alport Syndrome

1:5,000 to 1:10,000 X-chromosomal; 1:50,000 autosomal;
1:100 autosomal heterozygous carriers!

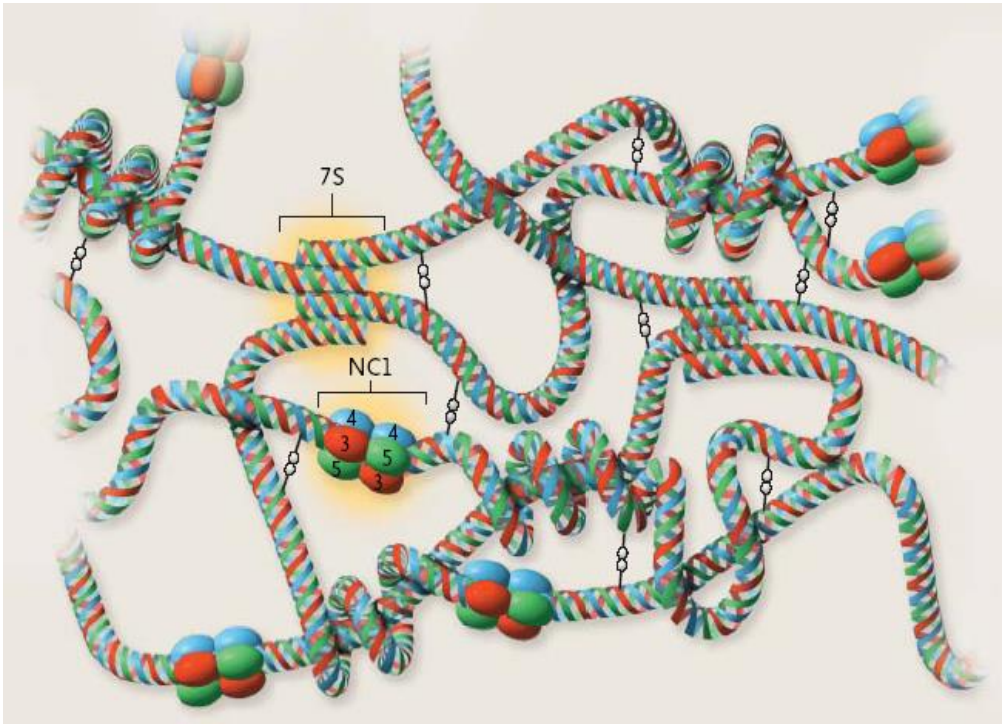
>20,000 patients in Europe
(data of more than 500 patients in Goettingen, last update 4/2014)

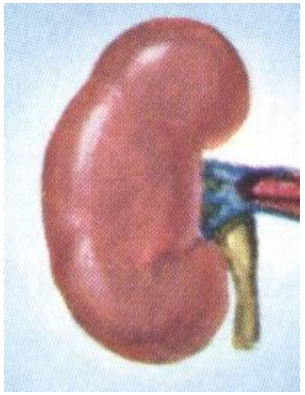
median age at end stage renal disease 22 years in Europe

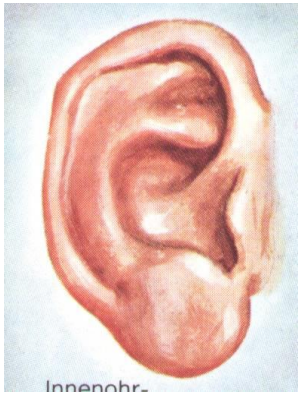
secondary diseases: 1000-fold cardiovascular risk; renal anemia, hypertension, osteopathy; infections; growth retardation
classified as **rare and awful disease** – special legal issues apply

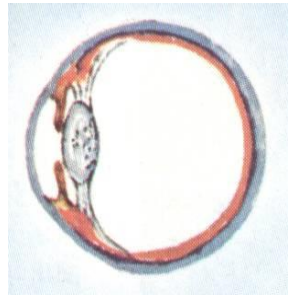
costs: ~40,000 € per patient per year on dialysis

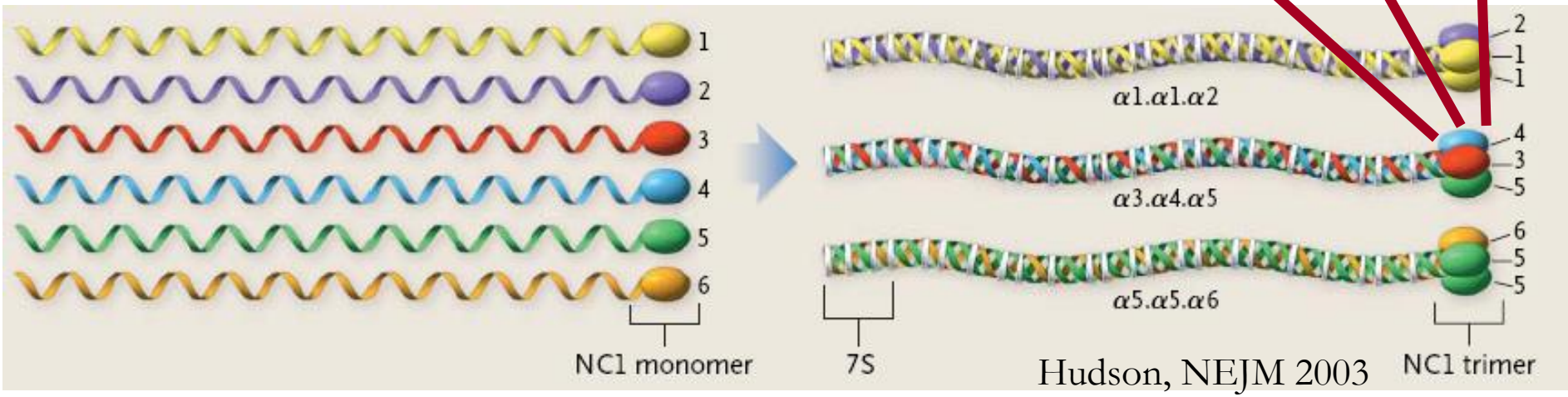
# Organ-specific distribution of type IV collagen chains



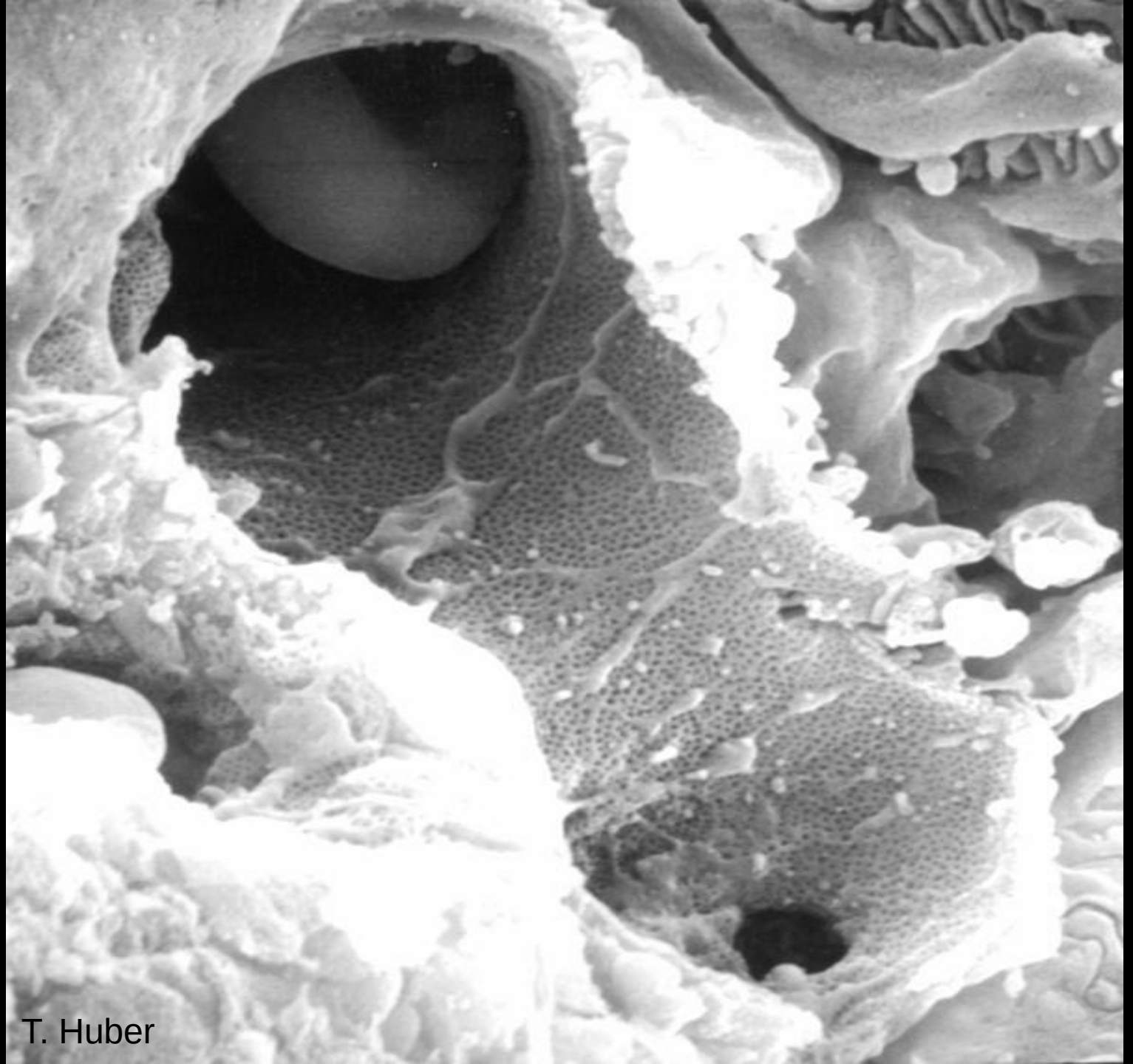







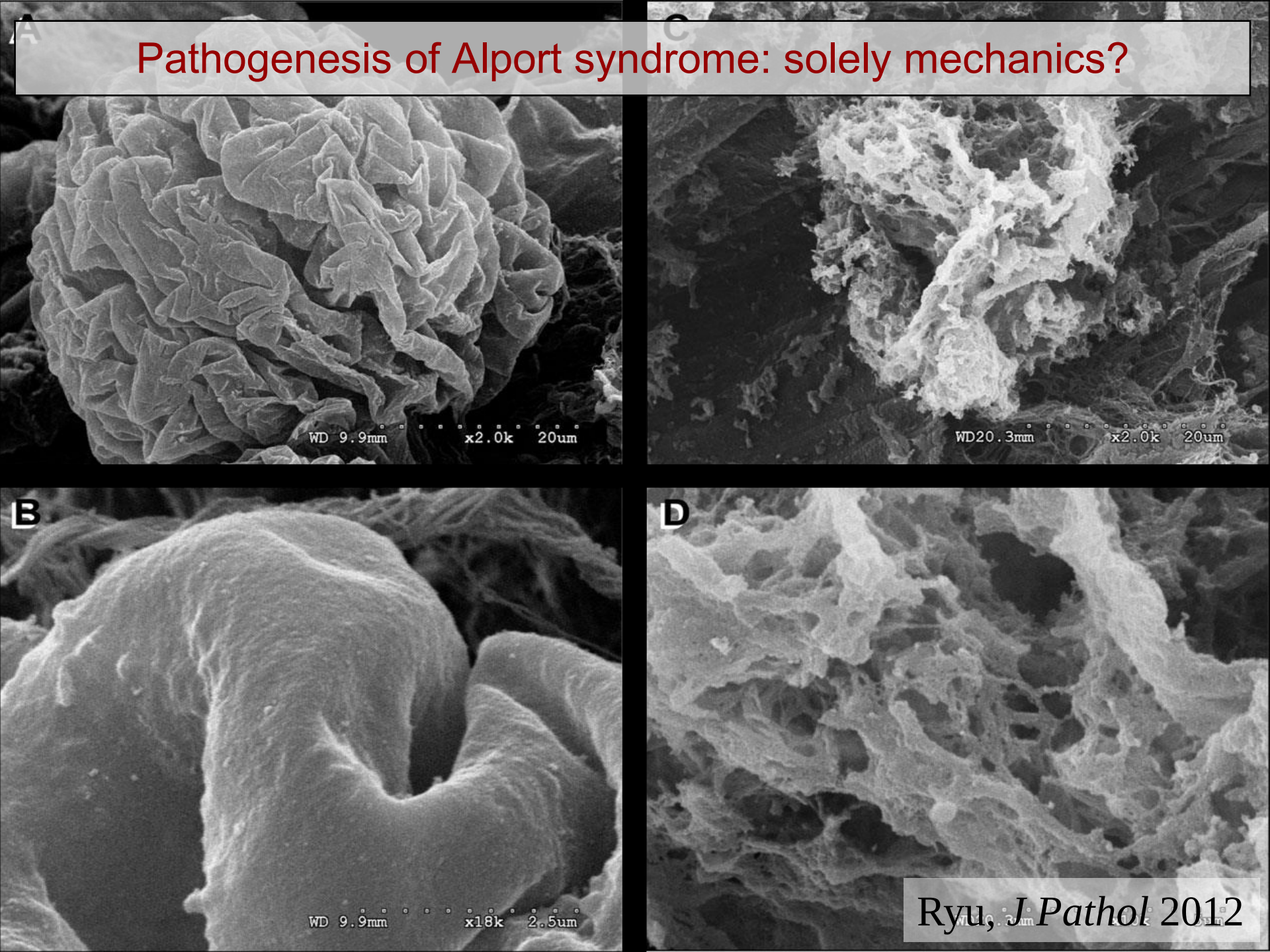



Hudson, NEJM 2003



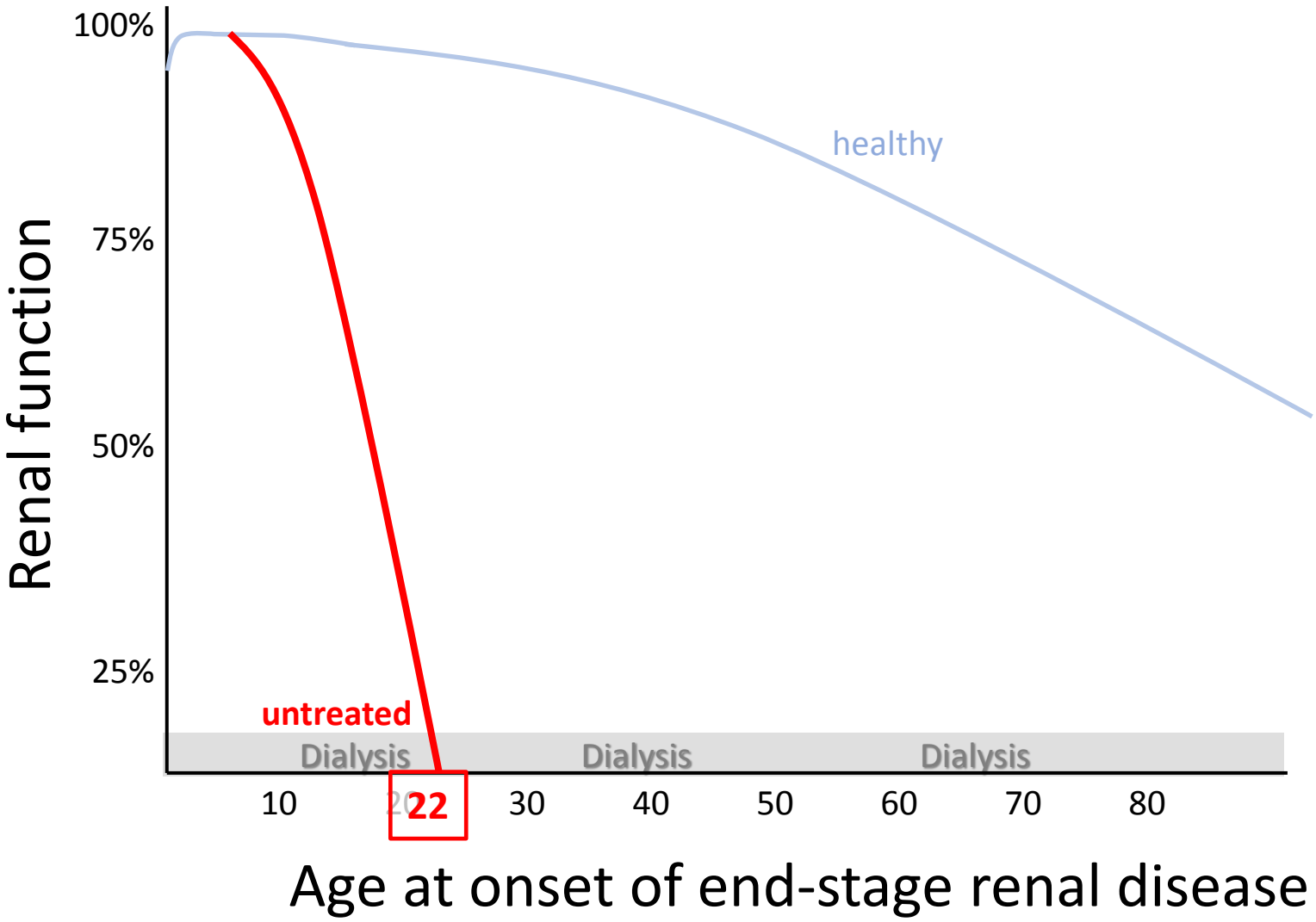
T. Huber

# Pathogenesis of Alport syndrome: solely mechanics?

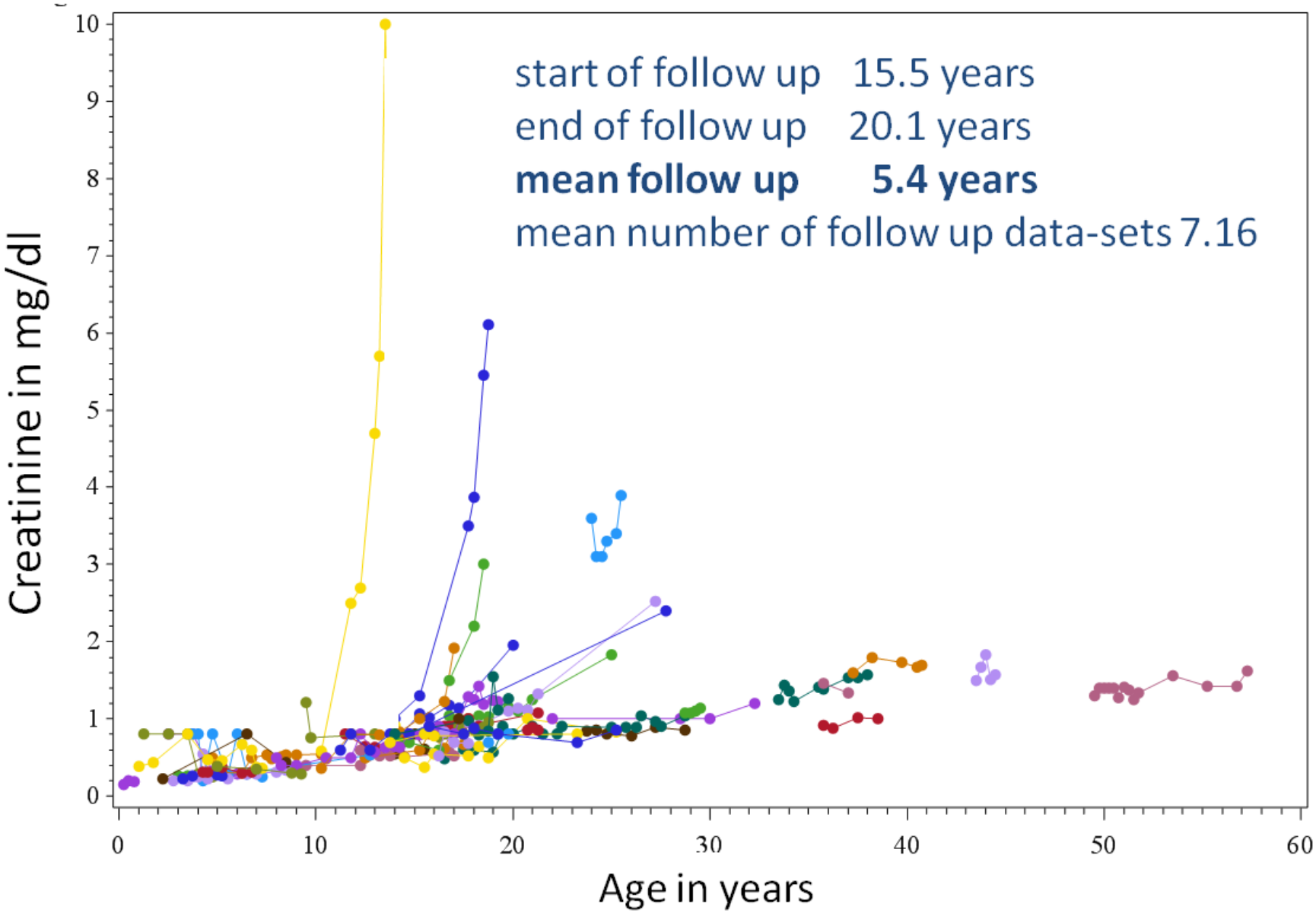



Ryu, *J Pathol* 2012

# Consequences



# 1. The medical problem: Alport syndrome



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1. The medical problem: Alport Syndrome
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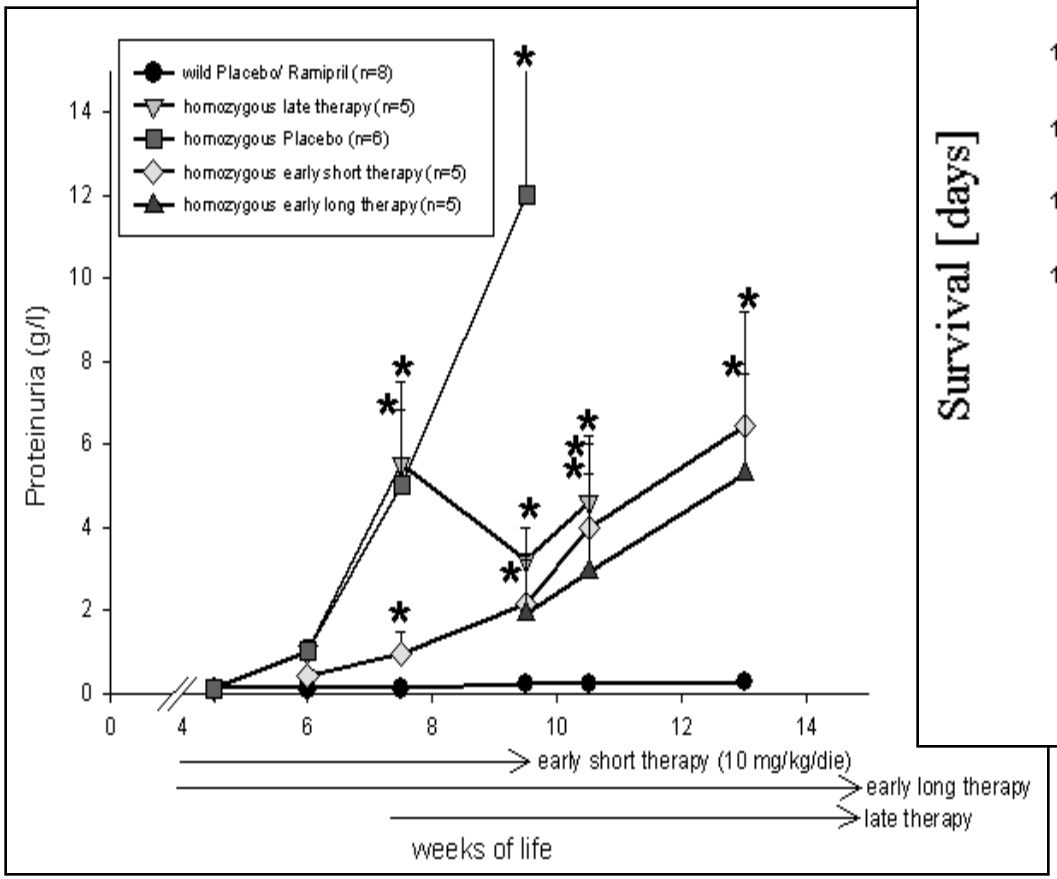
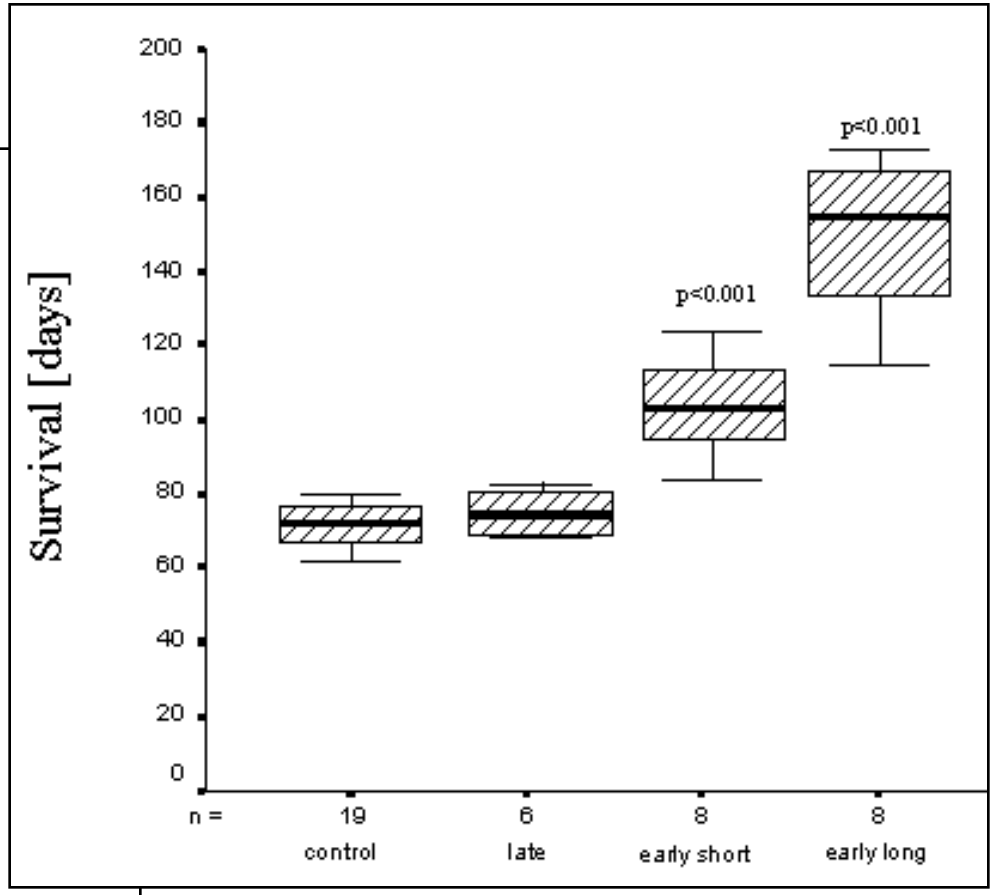
   *nephroprotective therapy in mice*

# Early Ramipril therapy delays renal failure in mice

## Value of proteinuria and timing of therapy in Alport‘s



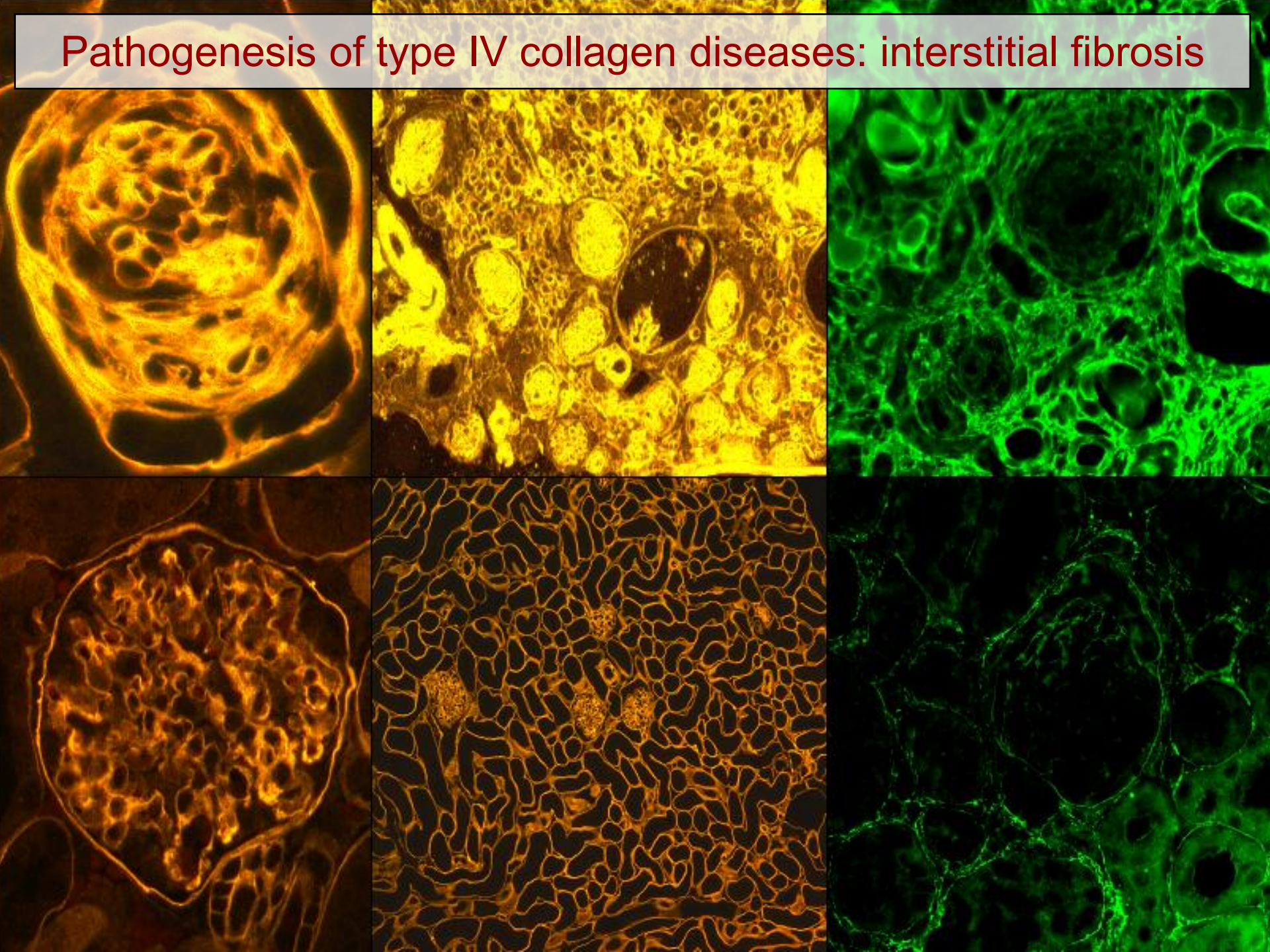

proteinuria is not a good end point in Alport‘s




timing of therapy in Alport‘s

Gross et al. *Kidney Int*, 2003

# Pathogenesis of type IV collagen diseases: interstitial fibrosis



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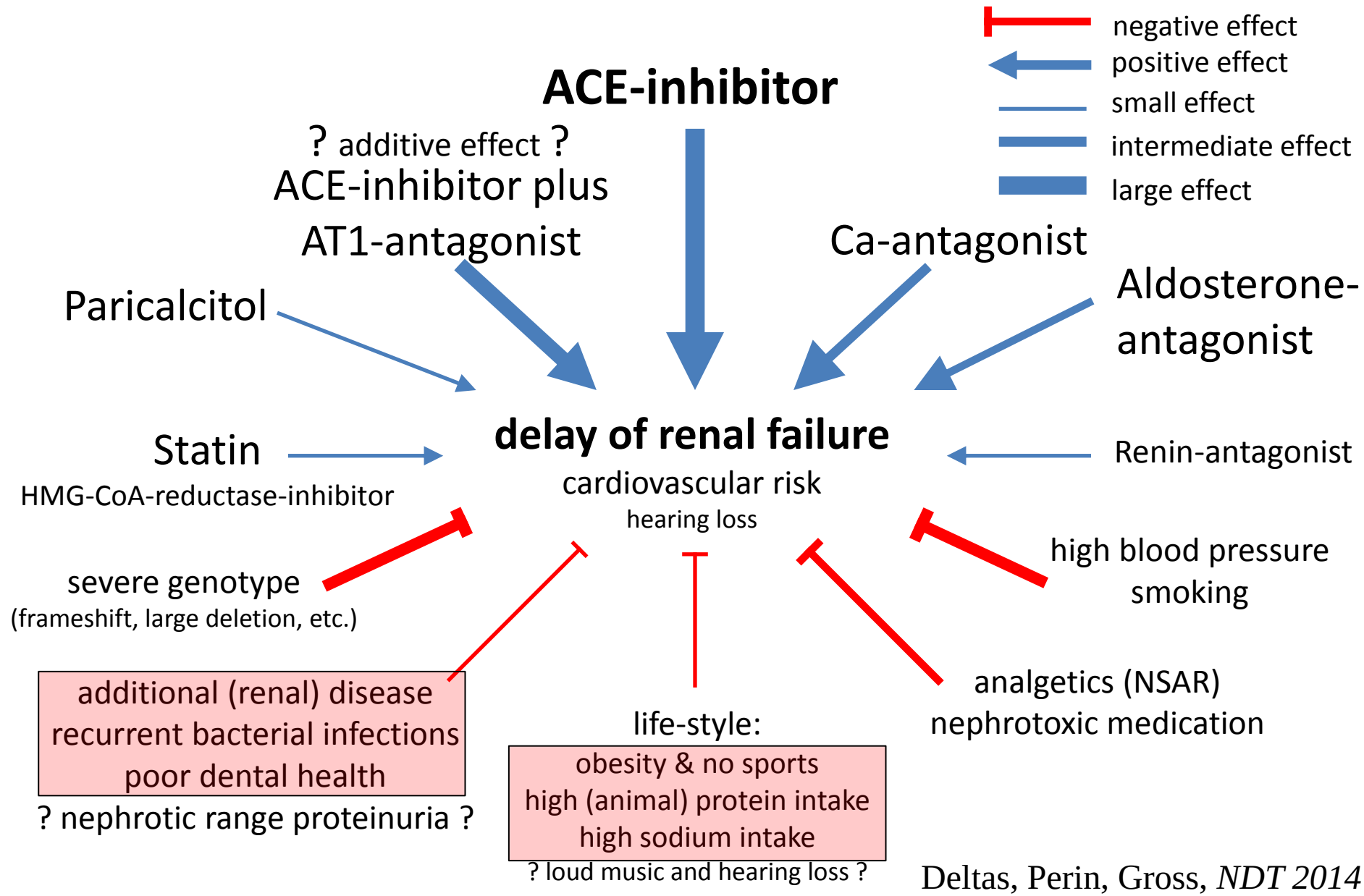
   *therapy in man delays renal failure and improves life-expectancy*

# Add on therapy currently used in Alport syndrome




Deltas, Perin, Gross, *NDT 2014*

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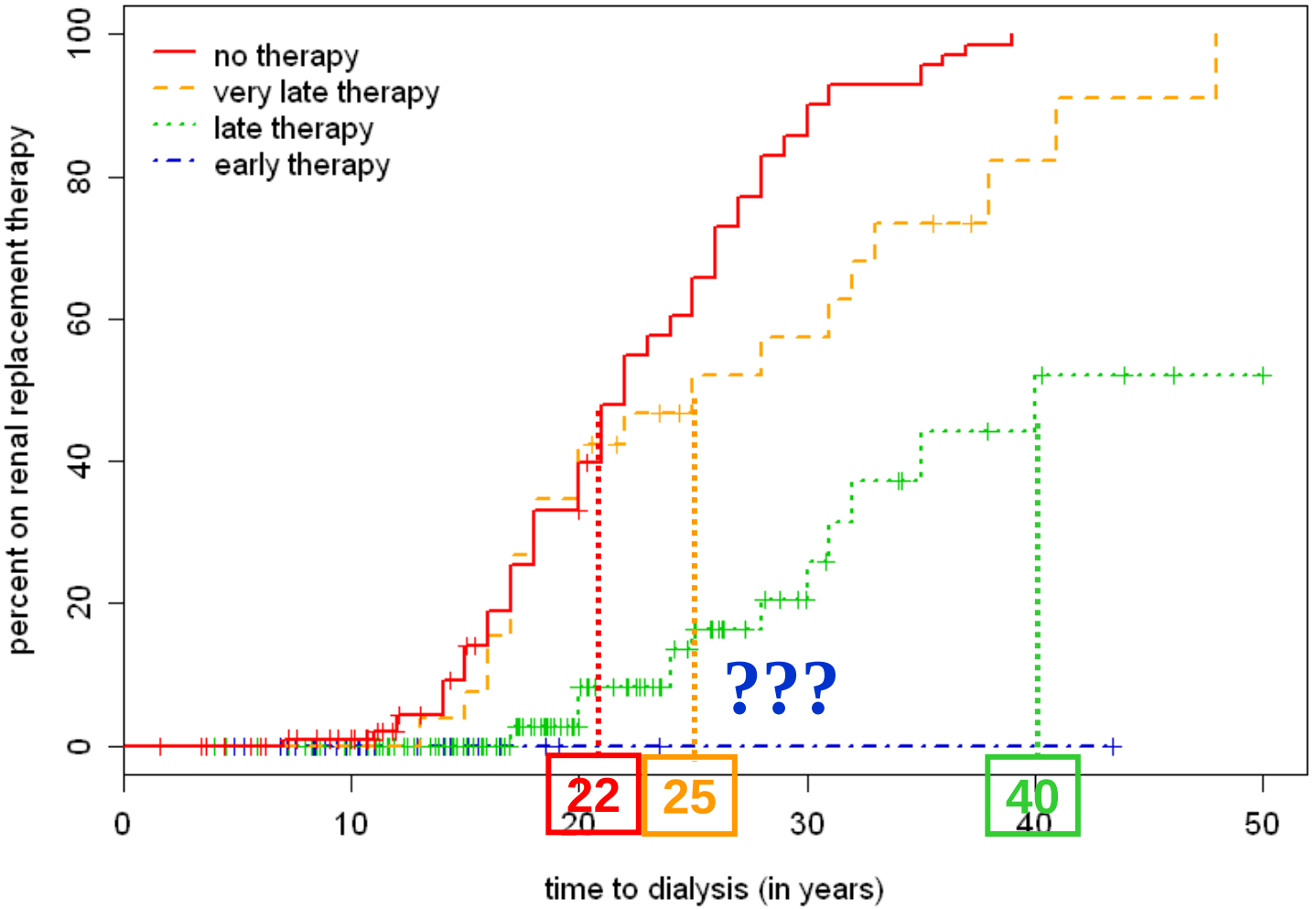
# Delay of renal failure: the earlier the better?

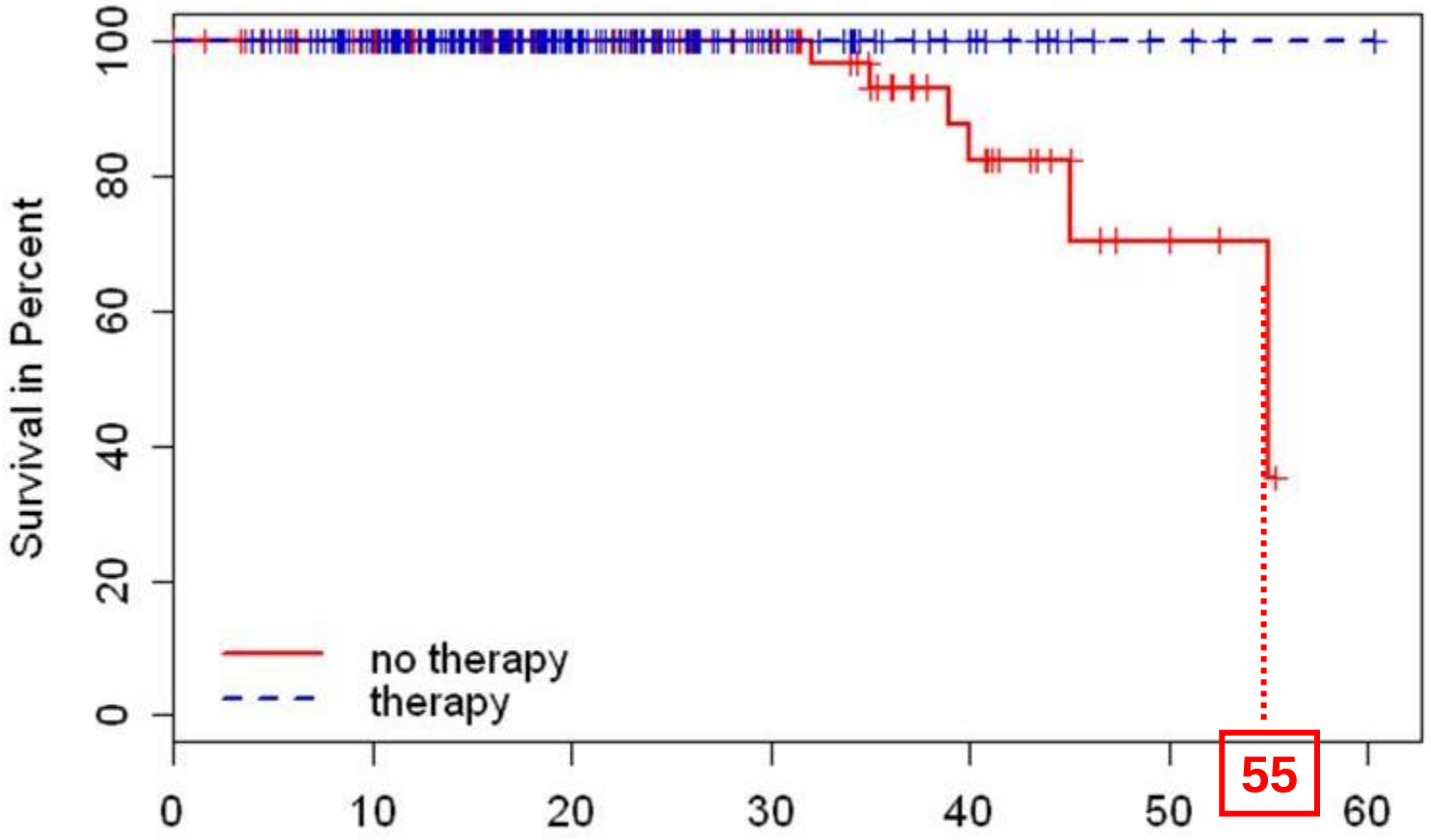



283 patients, 3 generations, mean duration of therapy >5 years

mean retrospective follow-up >20 years

Gross, *Kidney Int 2012*

# … and prolongs life-expectancy

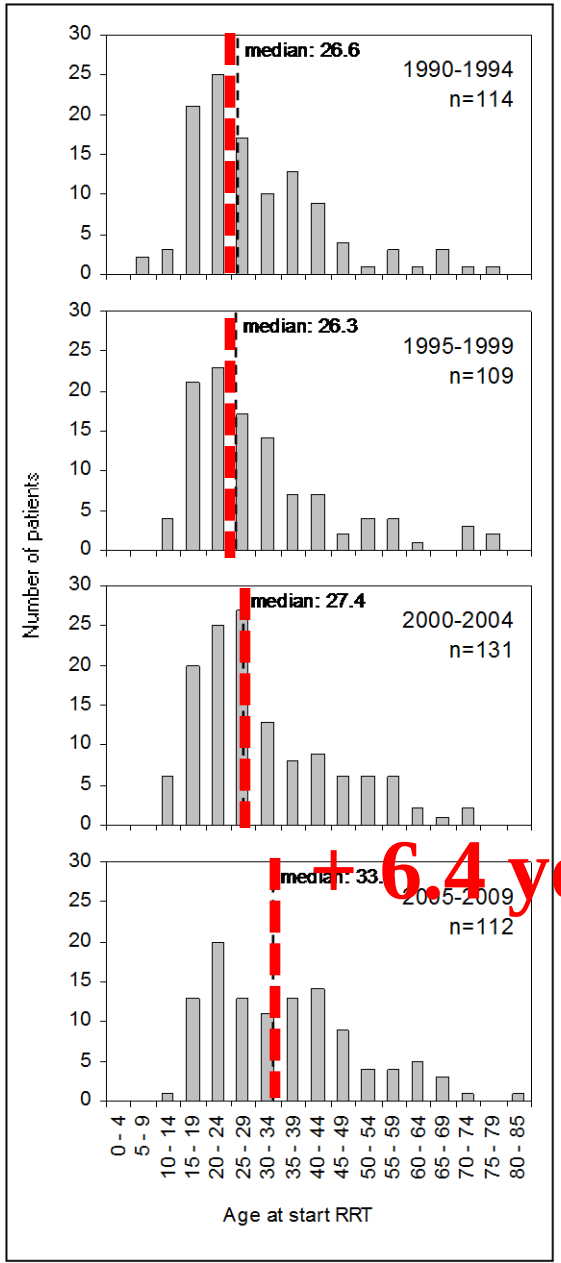



no. at risk

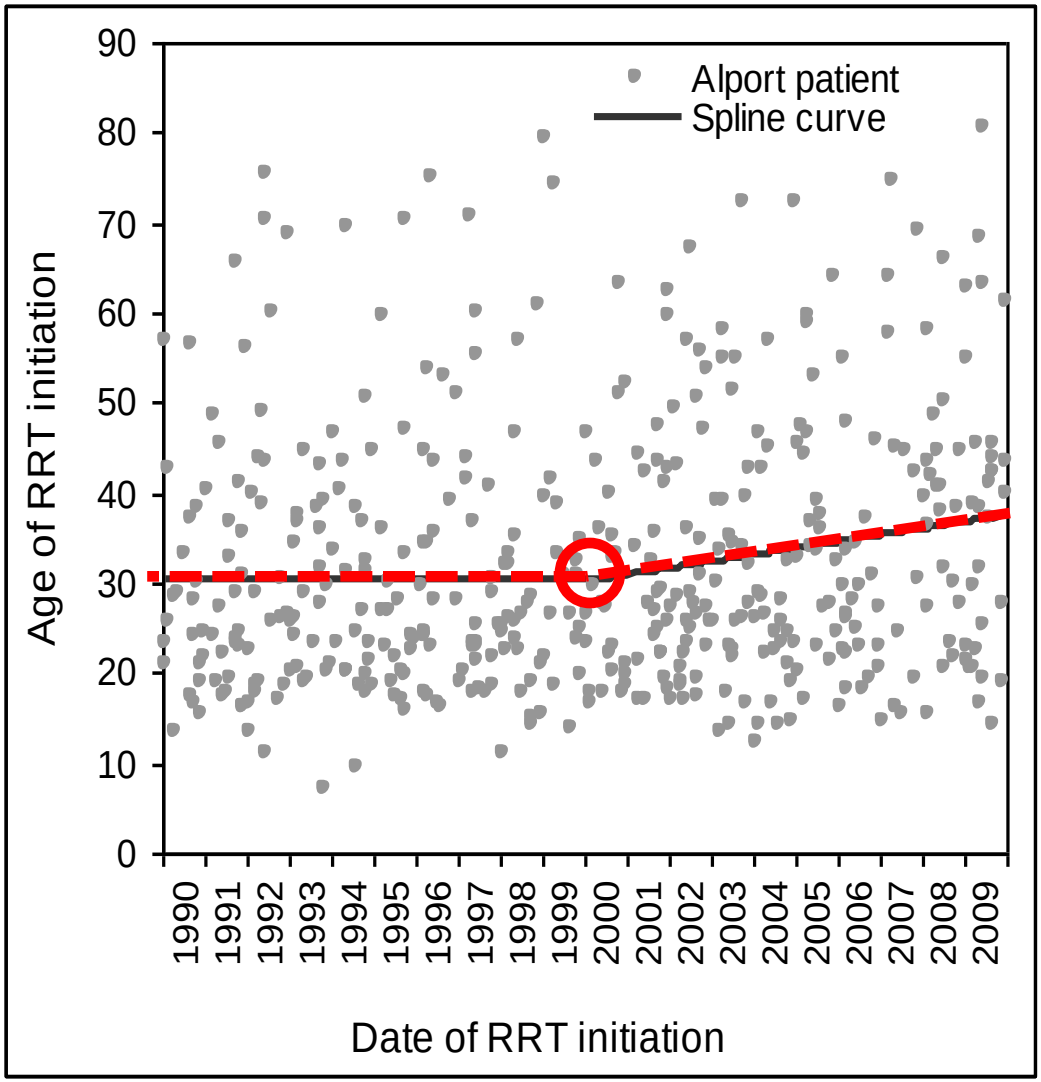
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| no therapy | 101 | 88 | 59 | 40 | 16 | 3 | 0 |
| therapy | 174 | 151 | 75 | 27 | 13 | 3 | 1 |

Gross, *Kidney Int 2012*

# … confirmed in ERA-EDTA registry




**+6.4 years**




Temme et Gross, *CJASN* 2012

# Do the retrospective data justify RAAS-blockade?

bias towards less severe mutations

loss of follow up

?

selection bias by reporting nephrologists

less data in patients, who do not like to go to nephrologists

# ALPORT SYNDROME
## - A CLINICIAN'S VIEW

CLIFFORD E. KASHTAN

WE HAVE A shared VISION...

WE NEED:

BRING BACK hope

TREATMENTS to PATIENTS

NEW GROUPED CLASSIFICATION

COLLAGEN IV & 345

ALPORT

XLAS + HETEROZYGOTE

ADAS

TBMN

ARAS

COL4A3/A4 heterozygote

ARAS CARRIER

IDENTIFY + VALIDATE biomarkers

+ OPEN ACCESS TO data

CONSIDER RISKS IN TESTING THERAPIES

PRICING MUST BE ~~£~~ ~~€~~ ~~$~~ AFFORDABLE

WE WANT YOU TO:

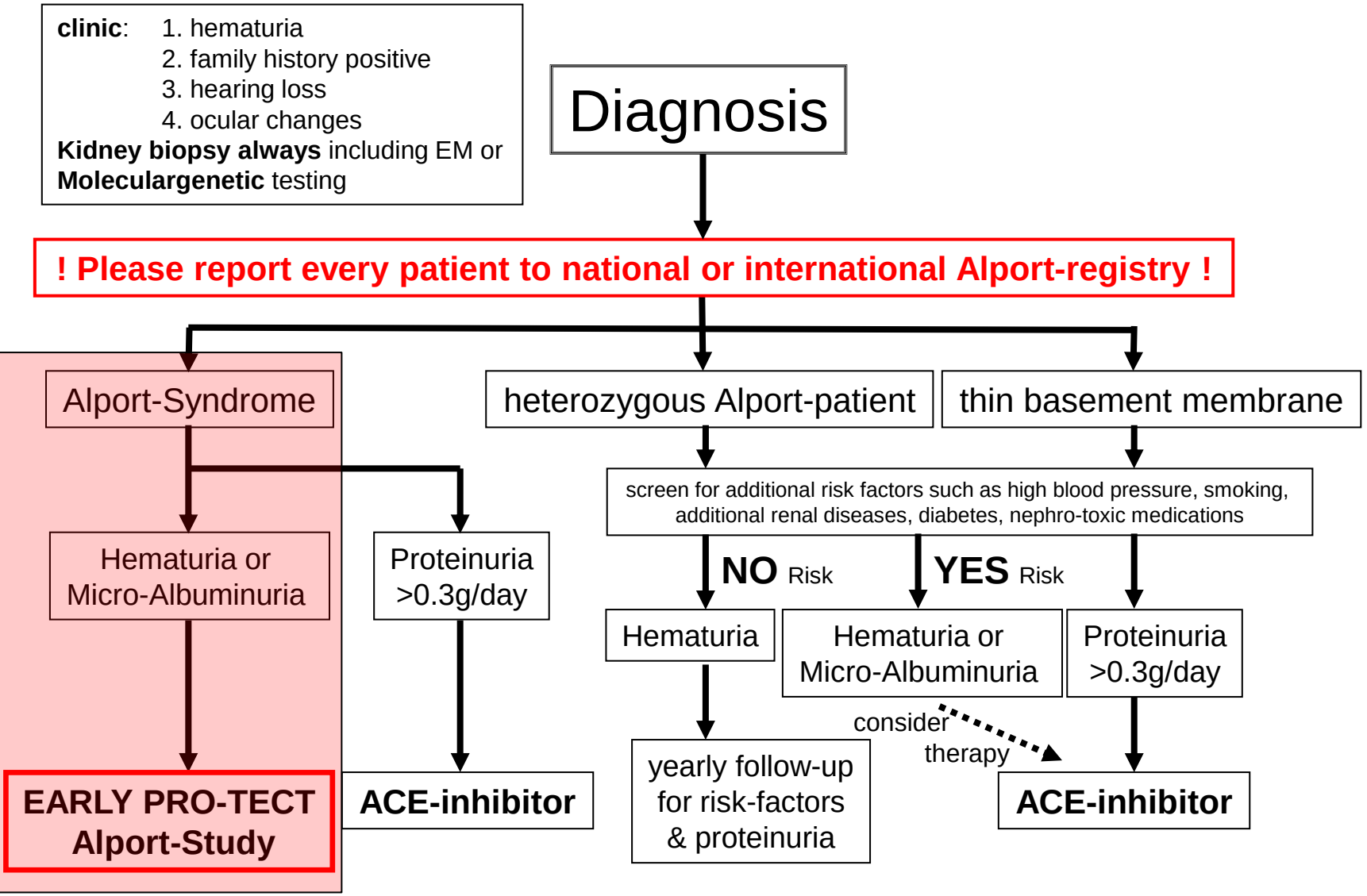
GET SPECIFIC

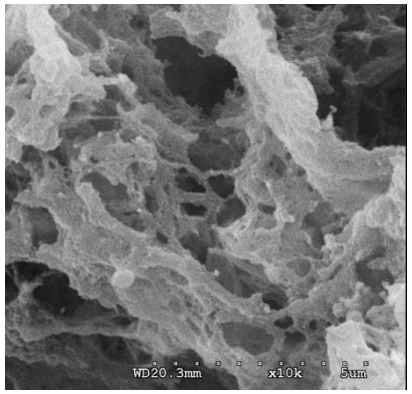
THINK STRATEGICALLY

what role CAN WE PLAY?

# ALPORT SYNDROME
## - A PATIENT'S VIEW

SHARON LAGAS


clinic: 1. hematuria
2. family history positive
3. hearing loss
4. ocular changes
Kidney biopsy always including EM or Moleculargenetic testing
Diagnosis
! Please report every patient to national or international Alport-registry !
Alport-Syndrome
heterozygous Alport-patient
thin basement membrane
screen for additional risk factors such as high blood pressure, smoking, additional renal diseases, diabetes, nephro-toxic medications
Hematuria or Micro-Albuminuria
Proteinuria >0.3g/day
NO Risk
YES Risk
Hematuria
Hematuria or Micro-Albuminuria
Proteinuria >0.3g/day
consider therapy
EARLY PRO-TECT Alport-Study
ACE-inhibitor
yearly follow-up for risk-factors & proteinuria
ACE-inhibitor




EARLY PRO-TECT

Alport

# Early prospective Therapy Trial to Delay Renal Failure in Children with Alport Syndrome

## Ramipril *versus* Placebo

Bundesministerium für Bildung und Forschung

**Coordinating Principal Investigator: Prof. Dr. Oliver Gross**

Sanofi-Aventis provides Ramipril&Placebo

**EudraCT Number:** **2010-024300-10**
**Protocol:** **Version 2.0, 28 February 2012**

**Trial Office** **O. Gross , J. Krügel , F. Weber**
UNIVERSITY MEDICAL CENTER GÖTTINGEN
Dept. of Nephrology and Rheumatology
Robert-Koch-Str. 40
37075 Göttingen, Germany
Tel: +49 (0)551 - 39-6910
Fax: +49 (0)551 - 39-6911
Email: studie@alport.de
Homepage: www.alport.de/EARLY_PRO-TECT_Alport

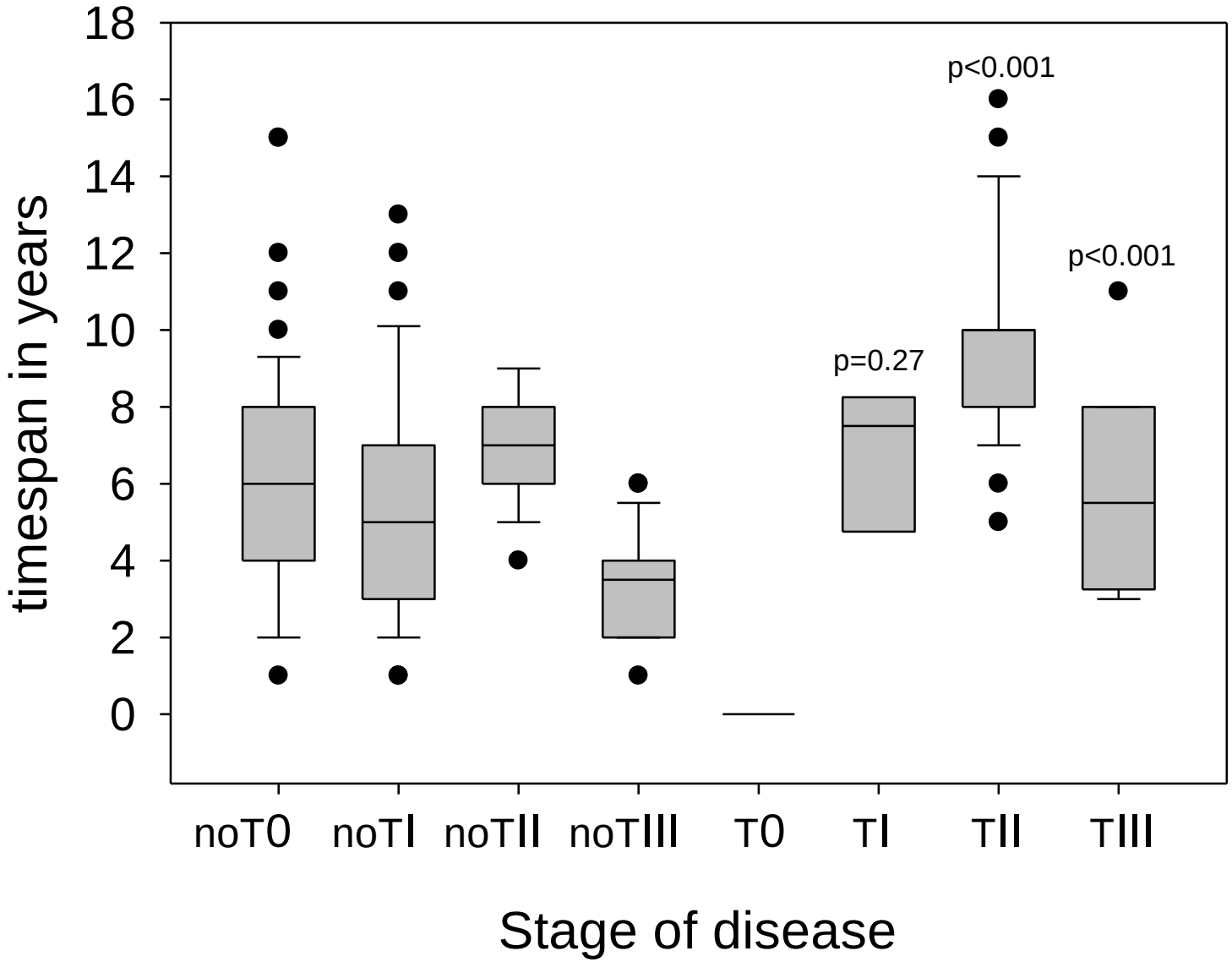
and Nick Kidney

GPN Gesellschaft für Pädiatrische Nephrologie

UNIVERSITÄTSMEDIZIN GÖTTINGEN : UMG

**GPN-supported trial**

# Power calculation for EARLY PRO-TECT Alport




Gross et al., confidential data

EARLY PRO-TECT


Recruitment-Phase (2 years)

3.5

Screening
n=160

Eligible and Inclusion
n=120

Pre-treated or withdrawal of consent to randomisation

Not pre-treated

Study-Phase (3 years)

6

Not Randomised
n=40 n=60

50

Randomisation
n=80 n=60

22

Ramipril Therapy
(open)

Ratio 1 : 1

2:1

Placebo Therapy
(double-blinded)

Ramipril Therapy
(double-blinded)

Unblinded upon Progress

**USA helps out with observational data**

# Endpoints

**Goal:**
Safety and Efficiancy of the ACE-inhibitor Ramipril in delaying the course of Alport syndrome in children with early stages of disease

**Randomisation of 80 children need** to achieve a reasonable power

**Overall-Time-On-Therapy** with Ramipril **~270 patient-years**

**Primary Efficiency End Point:**
Time to next level of disease within 3 years of Ramipril-therapy compared to Placebo, for all randomised patients.

Estimated: 50% in Placebo-Group
20% in Ramipril-Group

**Very strict criteria for „progress of disease“ to avoid disadvantages for the Placebo-Group**

**Treatment Phase up to 6 years (!) Results in spring 2019**

**EMA contributes by scientific advice and safety data**

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**clinic**: 1. hematuria
2. family history positive
3. hearing loss
4. ocular changes

**Kidney biopsy always** including EM or **Molecular genetic** testing

# Diagnosis

**! Please report every patient to national or international Alport-registry !**

## Alport-Syndrome

Hematuria or Micro-Albuminuria

**EARLY PRO-TECT Alport-Study**

Proteinuria >0.3g/day

**ACE-inhibitor**

## heterozygous Alport-patient

screen for additional risk factors such as high blood pressure, smoking, additional renal diseases, diabetes, nephro-toxic medications

**NO** Risk

Hematuria

yearly follow-up for risk-factors & proteinuria

**YES** Risk

Hematuria or Micro-Albuminuria

consider therapy

**ACE-inhibitor**

## thin basement membrane

Proteinuria >0.3g/day

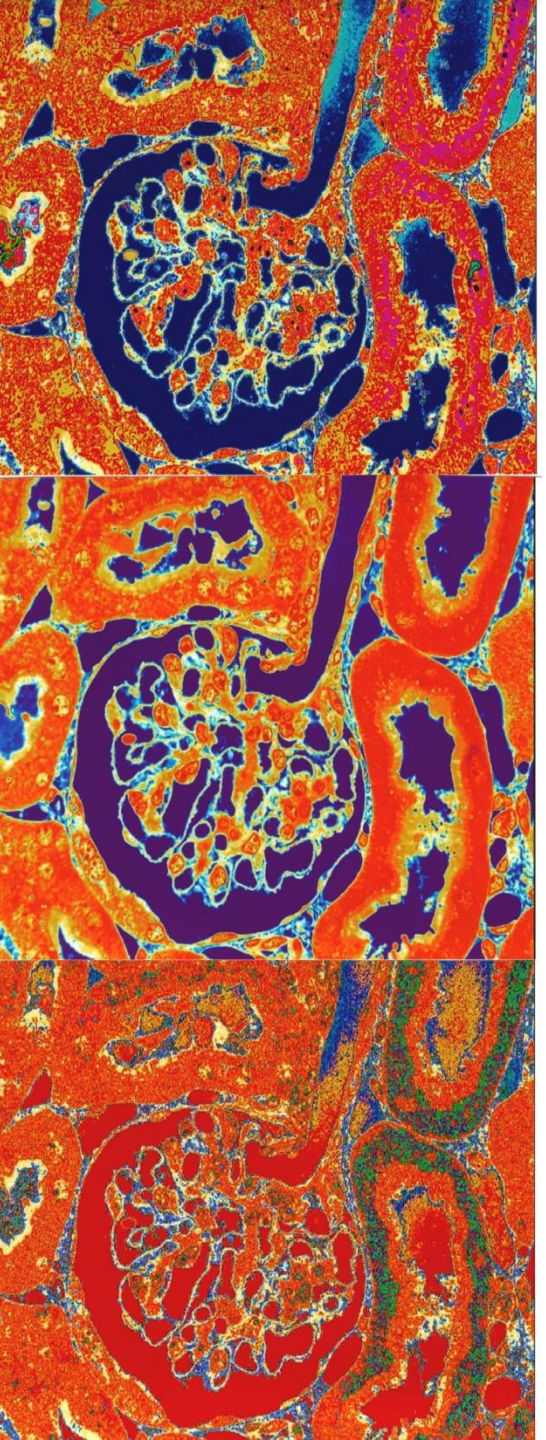
**ACE-inhibitor**

If progress use add-on therapy:

- AT1-Antagonist
- RR-target below 125/75 mmHg
- Statins
- Paricalcitol

**Studies with new Medications:**

- **HERA**
- **CARDINAL**



# INTERNATIONAL WORKSHOP ALPORT SYNDROME

**in cooperation with**

alport uk – a brighter future for people living with alport syndrome

AIRG France

FEDERG

ALPORT SYNDROME FOUNDATION – Hope | Action | Support

**the Alport Foundation of Australia and the Associations of Patients from Canada, Spain and Israel**

**supported by**

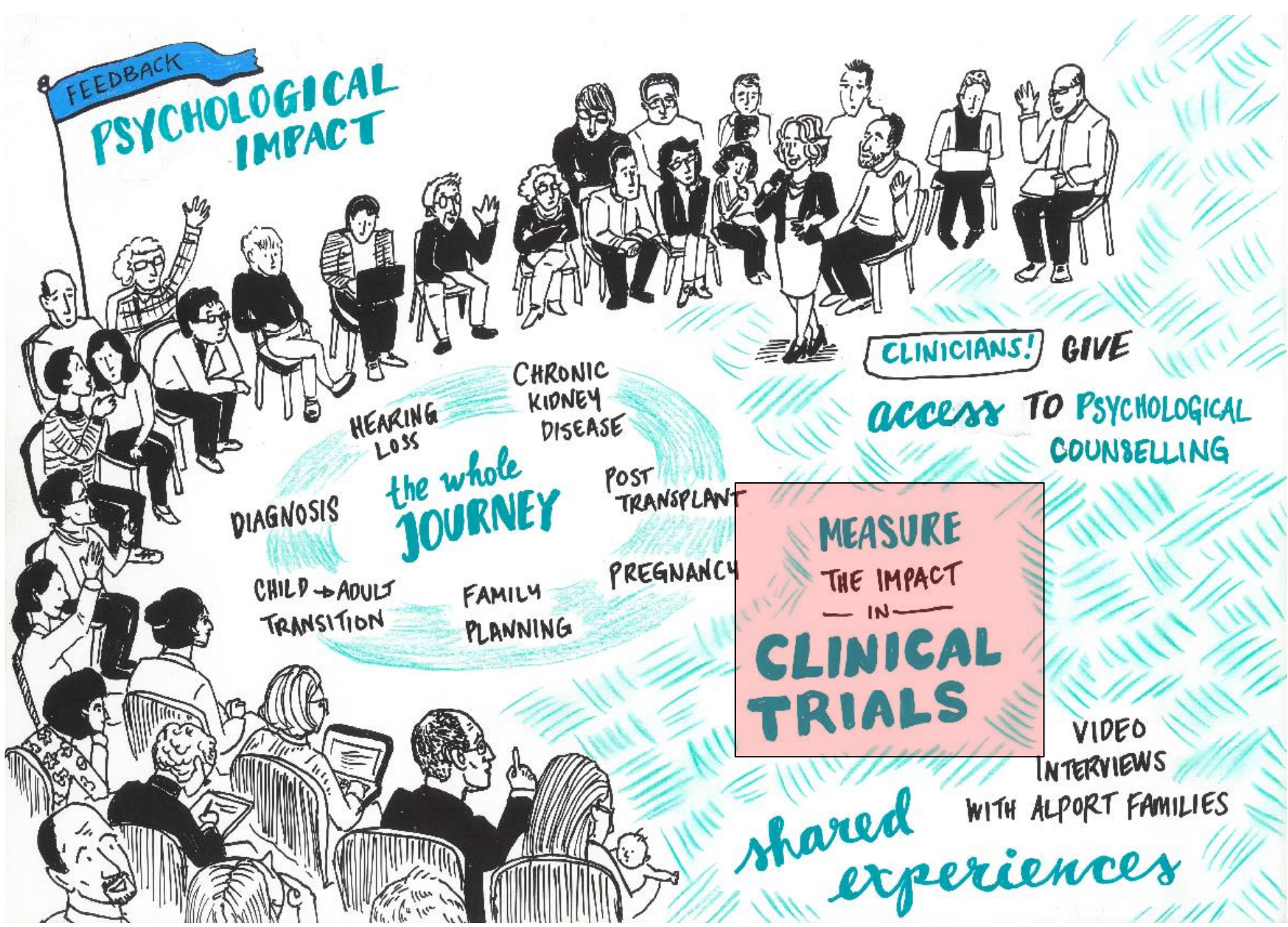
GPN – Gesellschaft für Pädiatrische Nephrologie

Deutsche Gesellschaft für Nephrologie

**SEPTEMBER, 25 - 27, 2015**

**GÖTTINGEN**

**CONFERENCE CENTER AT THE HISTORIC GAUSS OBSERVATORY**


FEEDBACK
PSYCHOLOGICAL IMPACT
CLINICIANS! GIVE
access TO PSYCHOLOGICAL COUNSELLING
HEARING LOSS
CHRONIC KIDNEY DISEASE
DIAGNOSIS
the whole JOURNEY
POST TRANSPLANT
PREGNANCY
CHILD → ADULT TRANSITION
FAMILY PLANNING
MEASURE THE IMPACT — IN — CLINICAL TRIALS
VIDEO INTERVIEWS WITH ALPORT FAMILIES
shared experiences

# Clinical Trials in Alport Syndrome in 2017

| | Type of study | Inclusion criteria | Recruitment | Expected end |
|---|---|---|---|---|
| **EARLY PRO-TECT Alport NCT01485978** | Phase 3, double-blinded Placebo controlled<br>Interventions:<br>- Ramipril vs. Placebo<br>End-points:<br>- Safety<br>- Progress of albuminuria | Age 2-17 years<br>Classical Alport only<br>Very early stages only<br>- Micro-Hematuria<br>- Micro-Albuminuria<br>- GFR>90ml/min/1,73m² | closed 9/2015 | Start 2/2012<br>End 8/2019 |
| **HERA NCT02855268** | Phase 2, double-blinded Placebo controlled<br>Interventions:<br>- anti-microRNA21 vs. Placebo<br>End-points:<br>- eGFR-loss | Age 16-60 years<br>GFR<90 | Expected start summer 2017 | ? 2019 |
| **CARDINAL NCT03019185** | Phase 2/3, double-blinded Placebo controlled<br>Interventions:<br>- Bradoxolone Methyl vs. Placebo<br>End-points:<br>- eGFR-loss | Age 12-60 years<br>GFR<90 | Expected start summer 2017 | ? 2019 |
| **ATHENA NCT02136862** | nicht-interventional observational study<br>End-points:<br>- eGFR-loss | Age 16-65 years<br>GFR<90 | Until 2017 | ? 2019 |
| **European Alport Registry NCT02378805**<br><br>**ASTOR NCT00481130** | nicht-interventional observational study<br>Interventions (observed):<br>- RAAS-blockade and Spironolacton<br>- Statins<br>- Paricalcitol<br>End-points:<br>- end stage renal failure<br>- death | Age 0-99 years<br>All stages including end-stage | Until 2038 | Start 2006<br>? End 2038 |

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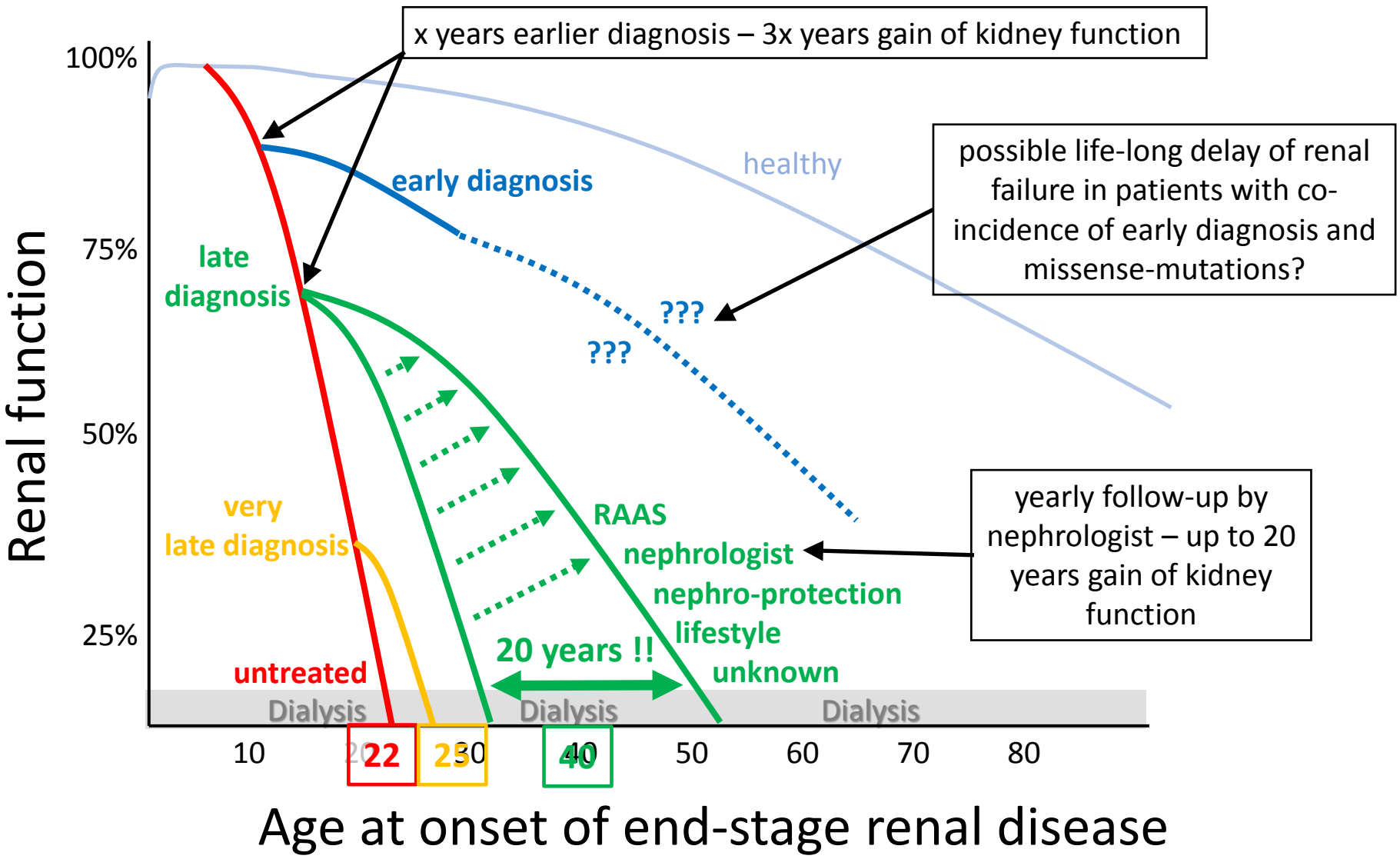
# Conclusions



# Hypothesis

- most serious Paediatric diseases can (better) be treated by repurposing/ „old-fashioned“ off-label therapy

- in everyday clinical practice repurposing or „old-fashioned“ therapy is more effective and safer than most new therapies

- expensive therapies trigger knowledge about the Paediatric disease – vice versa far too many „old“ therapies are not used in rare (boring?) Paediatric diseases, because of limited scientific/industrial interest

- IITs are needed, but far too complex for clinicians

- patients/parents (personal interest) and clinicians (legal and ethical interest) have the right to demand for better therapies by repurposing/ „old-fashioned“ off-label therapy

# My questions for **YOU**

Alport syndrome as example: why not invest in „old“ therapies? 10,000 treatable children, therapy delays dialysis by >20 years saves 10 billion €, social impact for families priceless

- How can we close the gap between evidence and real everyday off-label life in clinic?

- How can we improve the standard of care of off-label use of meds that work better than „new“ EMA-approved meds?

- How can we motivate patients, clinicians, regulatory AND biometrics/statisticians to contribute to evidence synthesis?

- Which mathematical processes can katalysate IITs? Ideas from whom? Who rates the ideas? How can we motivate industry and EMA to contribute?

# Thank you

**gross.oliver@med.uni-goettingen.de**

Bundesministerium für Bildung und Forschung

Deutsche Nierenstiftung
DFG GR 1852/4-1, 4-2, 6-2

**www.alport.de**

ARG France Association pour l'information et la recherche sur les maladies rénales génétiques

Fritz-Scheler Stipendium
GPN, BMBF, NIH

alport selbsthilfe