From bench to bedside

Polycystic kidney diseases

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Outline

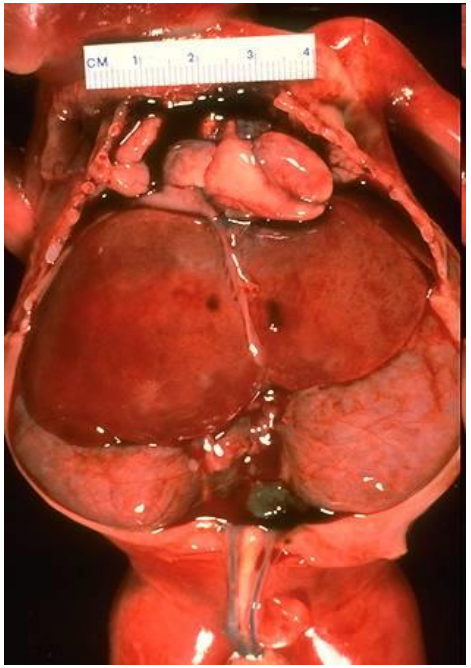
- Definitions, clinical presentation
- Pathophysiology of cyst formation
- Clinical implications, studies

Hereditary polycystic diseases

- **Polycystic Kidney disease**
  - **(AD, AR)**
- **Juvenile nephronophtisis**
- **Cysts associated with multiple malformations**
  - **Autosomal dominant**
    - **Tuberous sclerosis**
    - **von Hippel–Lindau disease**
  - **X linked dominant**
    - **Orofaciodigital syndrome, type I**
  - **Autosomal recessive:**
    - **Meckel syndrome, asphyxiating thorax dystrophy of Jeune type,**
    - **Zellweger cerebrohepatorenal syndrome,**
    - **Goldston syndrome, etc. (glomerulocystic disease in most of the cases)**
  - **Chromosomal abnormalities**
    - **21 trisomy, 13 trisomy, 18 trisomy**

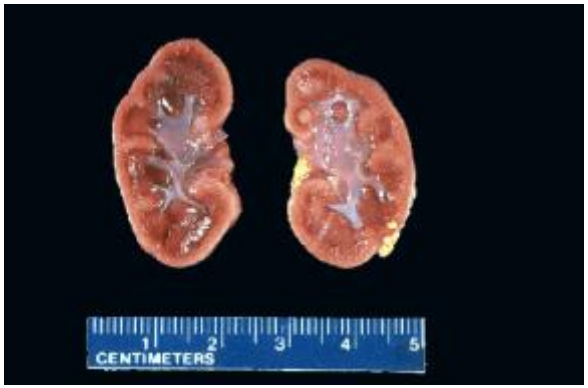
ARPKD

PKHD1
Carrier frequency 1:65
Incidence 1:15.000
ERDS in childhood

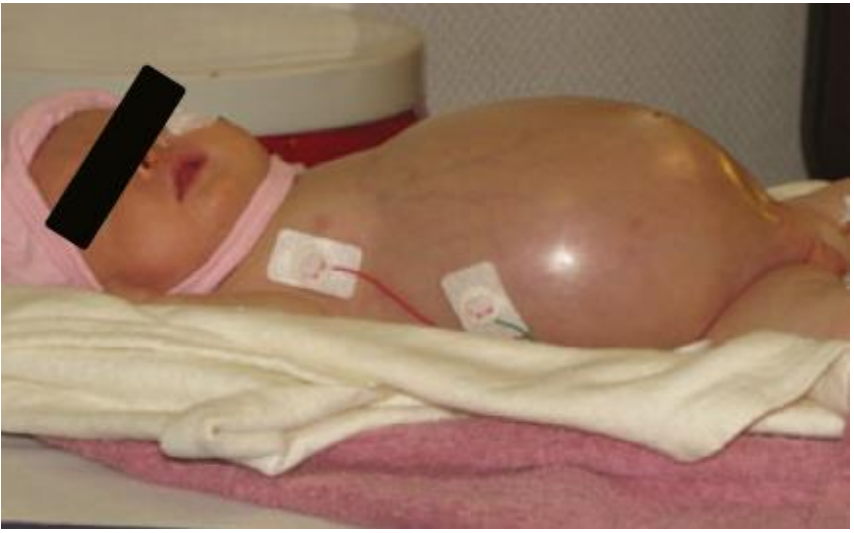


Enormous kidneys filling the abdomen
Preterm neonate (23. gestational week)
Respiratory distress, exitus lethalis

Normal kidney



ARPKD kidney

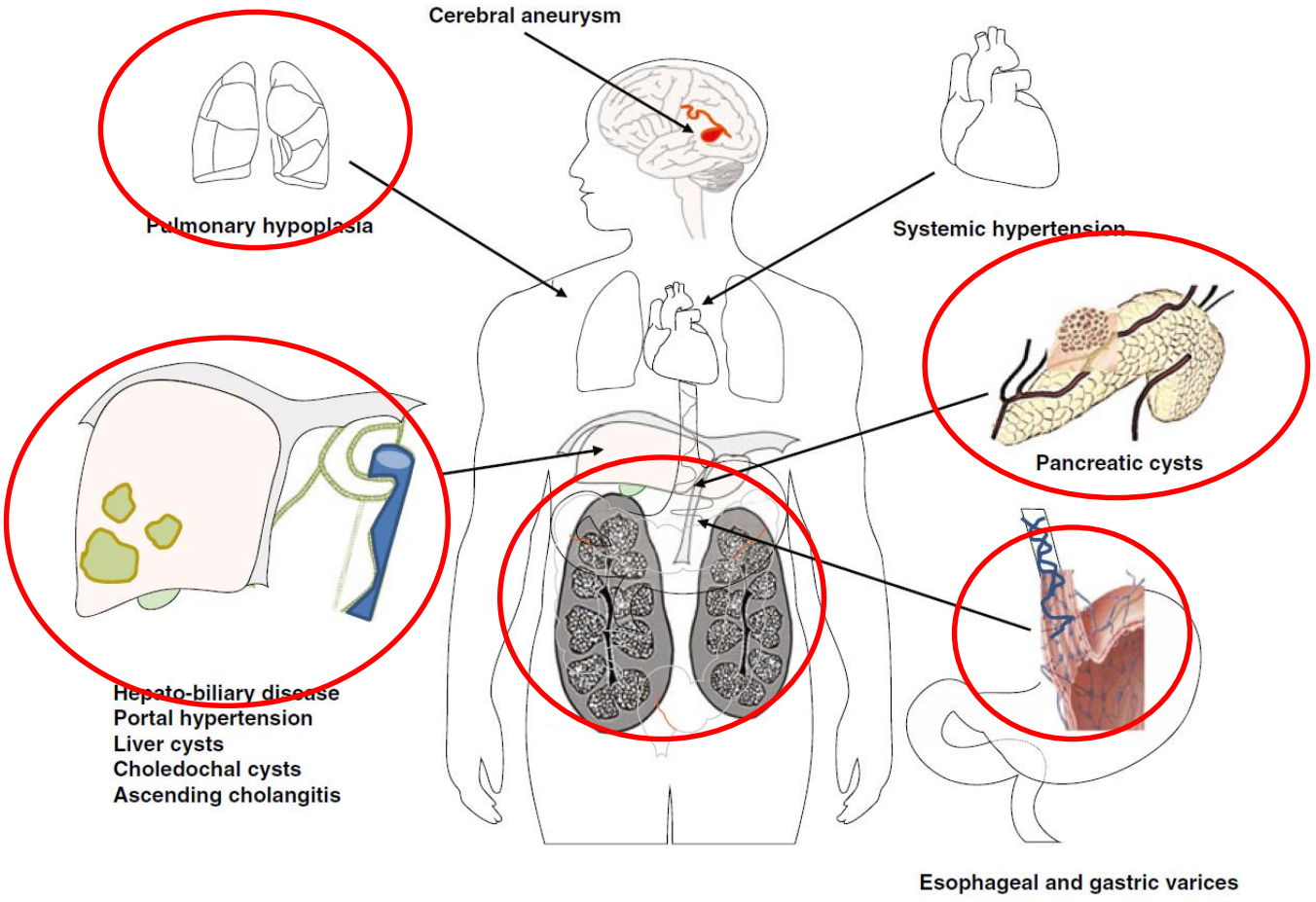


Ten-day-old preterm infant (34th week) with autosomal recessive polycystic kidney disease

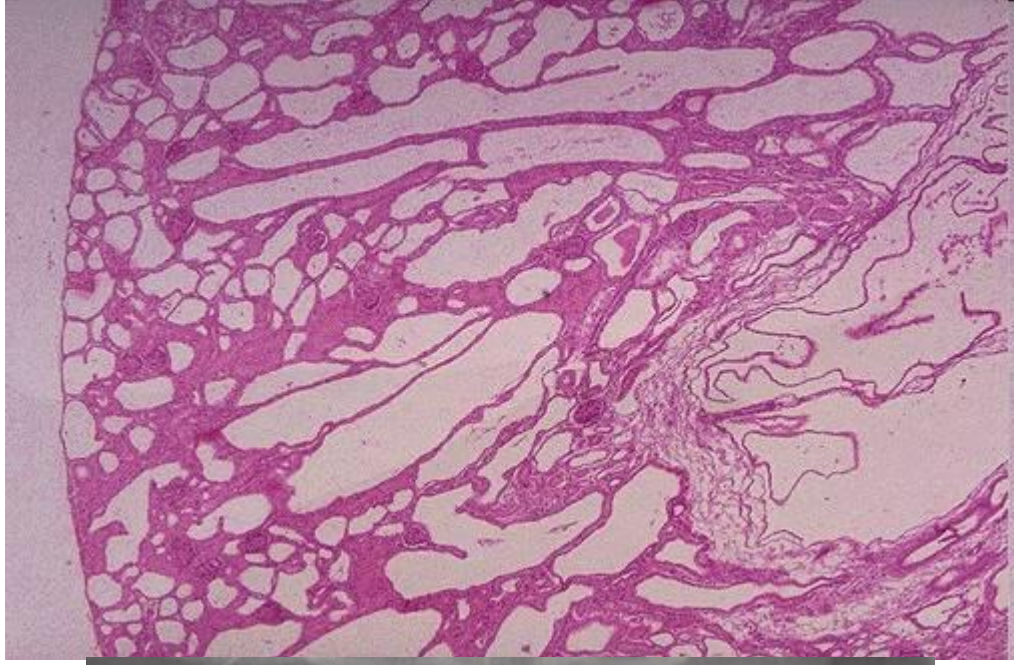
Enlarged kidney no corticomedullary difference

Büscher R et al; Pediatr Nephrol, 2013

ARPKD

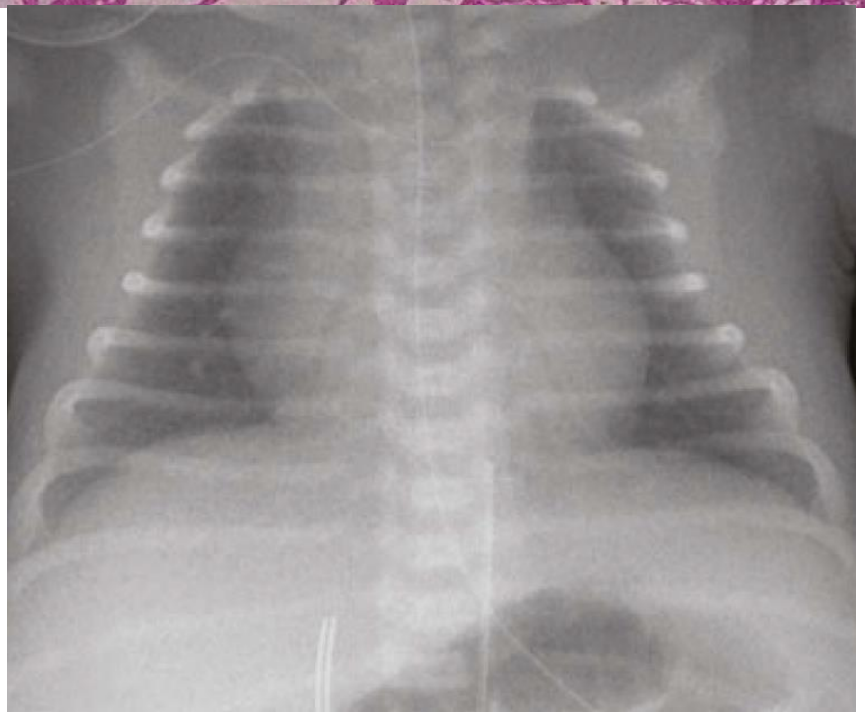


Büscher R et al; Pediatr Nephrol, 2013; DOI 10.1007/s00467-013-2634-1



ARPKD

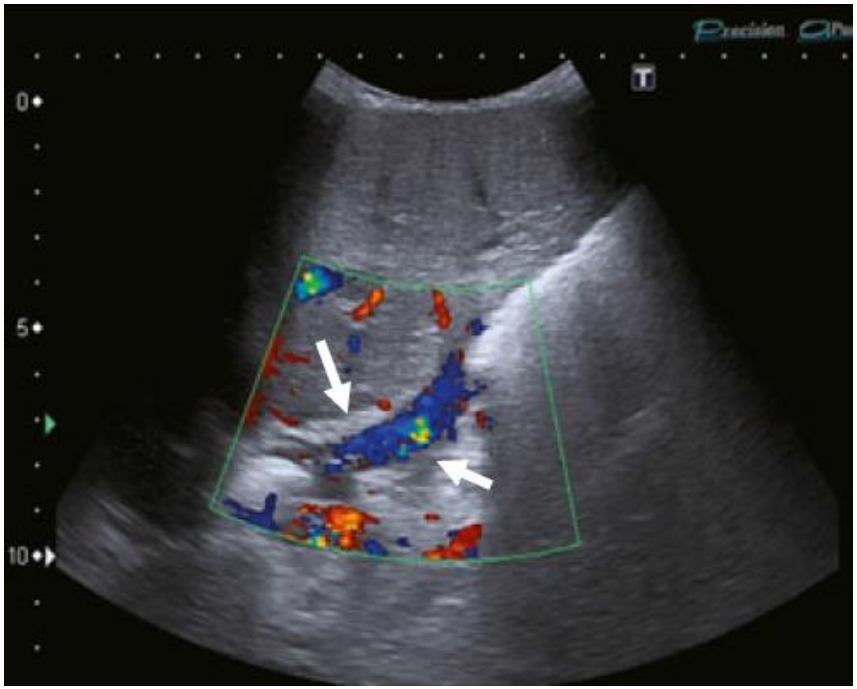
the kidney parenchyma is replaced by cysts

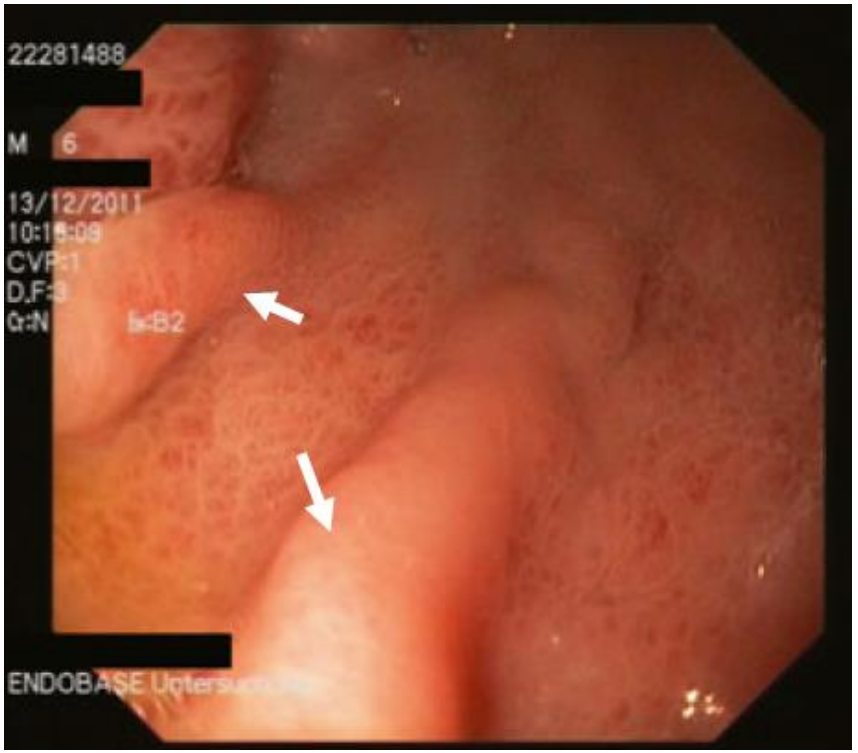


Pulmonary hypoplasia in ARPKD

Büscher R et al; Pediatr Nephrol, 2013; DOI 10.1007/s00467-013-2634-1

Color Doppler ultrasound image and endoscopy of a 8-year-old boy with autosomal recessive polycystic kidney disease (ARPKD) and esophageal and gastric varices





ARPKD: congenital liver fibrosis

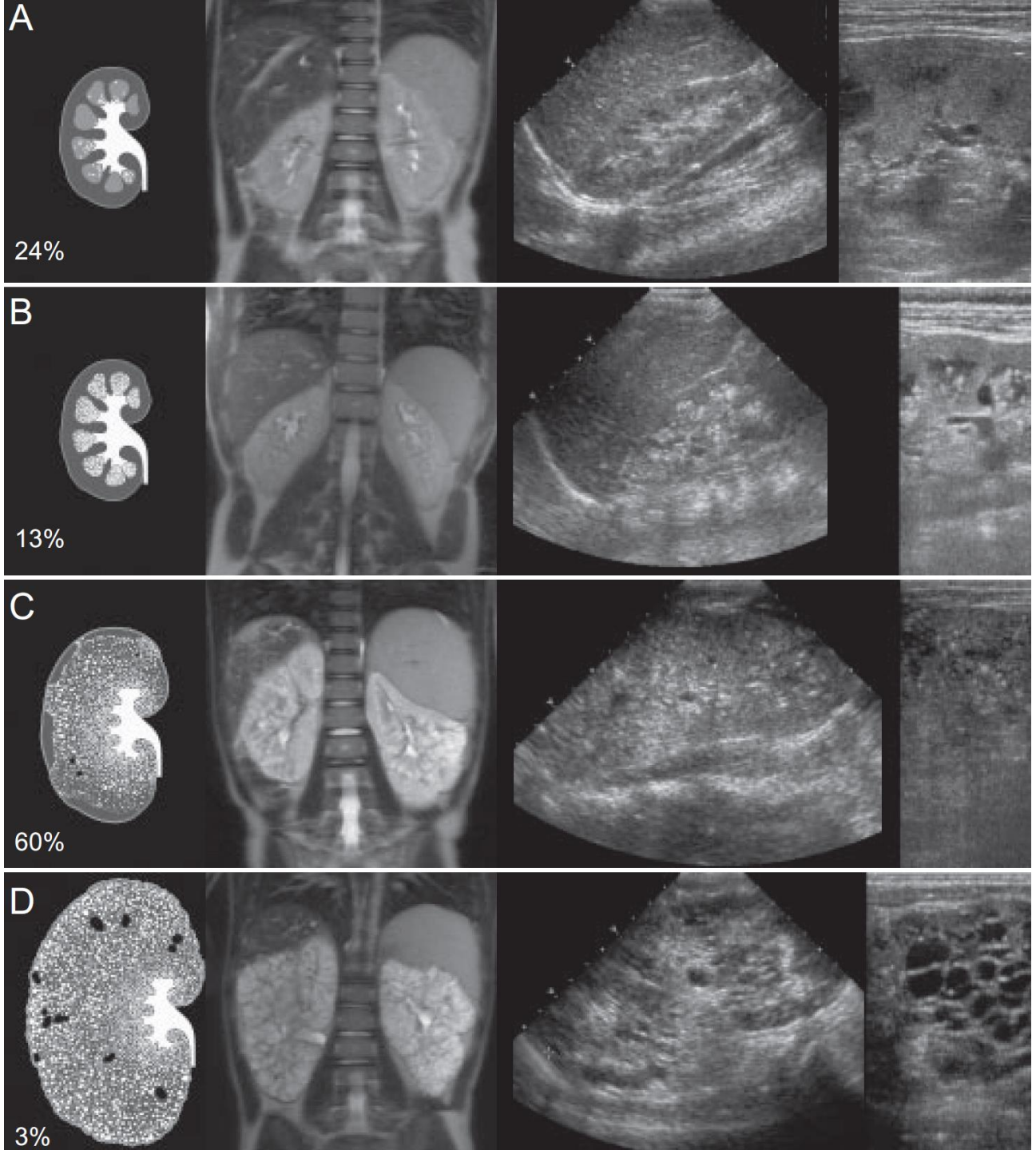
The defective fibrocystin (see later) is present in the kidney, the liver and the pancreas as well

Büscher R et al; Pediatr Nephrol, 2013; DOI 10.1007/s00467-013-2634-1

ARPKD

Principal consequences of renal manifestation

- Foetus (about 30% of the cases)
  - oligohydramnios, pulmonary hypoplasia, Potter sequence, IU death
- Newborn
  - **Severe CRF –** usually combined with respiratory distress
  - **Less severe CRF** - hypertension, electrolyte-, acid-base imbalance, failure to thrive
  - **Normal kidney function** and less severe manifestations
    - mild proteinuria, glucosuria, hyperphosphaturia, increased urinary excretion of magnesium)
  - Recurrent episodes of **UTI**
  - Kidney **function may recover with time**



Kidney ultrasound patterns in ARPKD

N=62

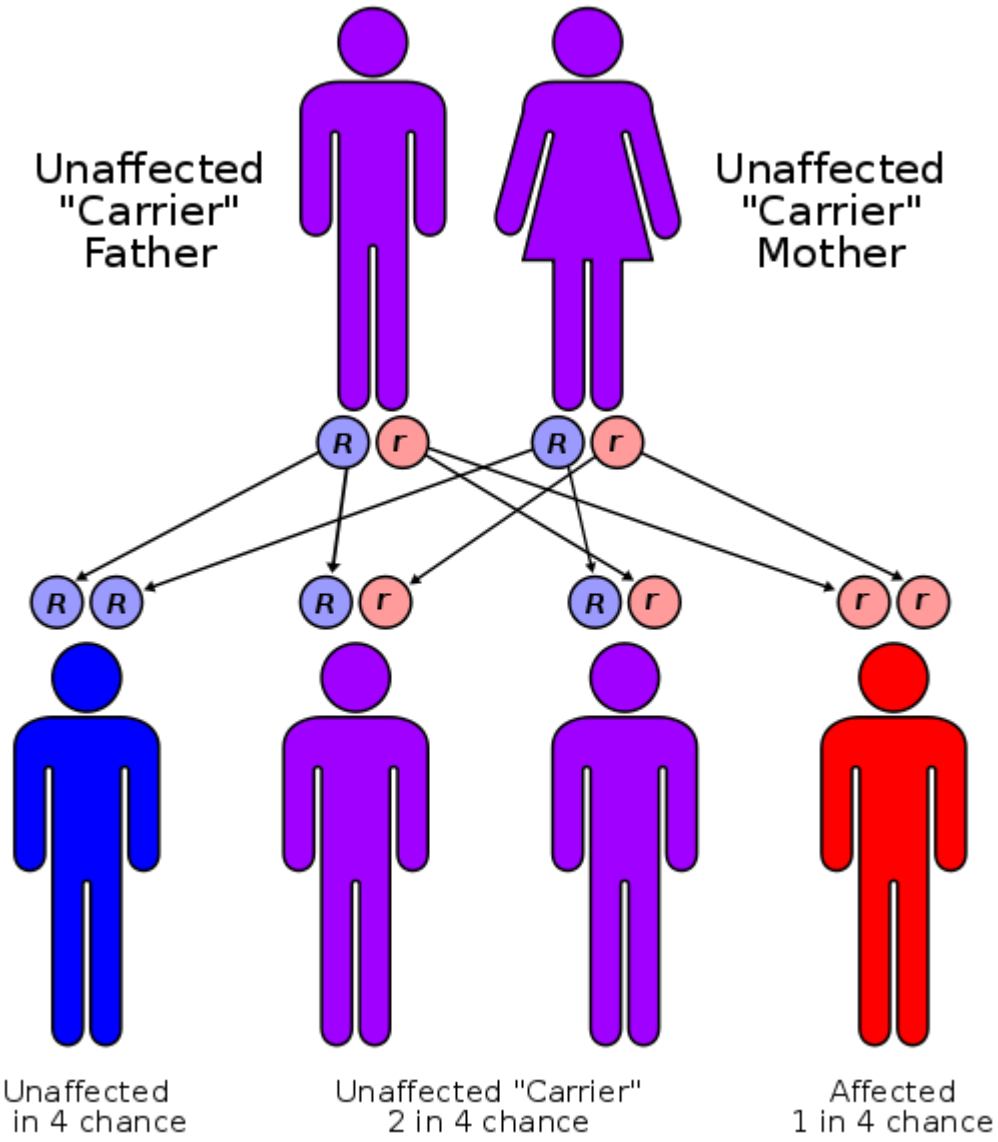
Clin J Am Soc Nephrol
5: 972–984, 2010

Principal extrarenal manifestations

- Hepatic fibrosis
  - May be present already at infancy
  - Dominantly vascular involvement (portal hypertension)
  - Parenchymal insufficiency later during the course
  - Severe adverse events
    - Bleeding from esophageal varices
    - Encephalopathy
  - Finally may need hepatic transplantation

Family counseling - genetic testing

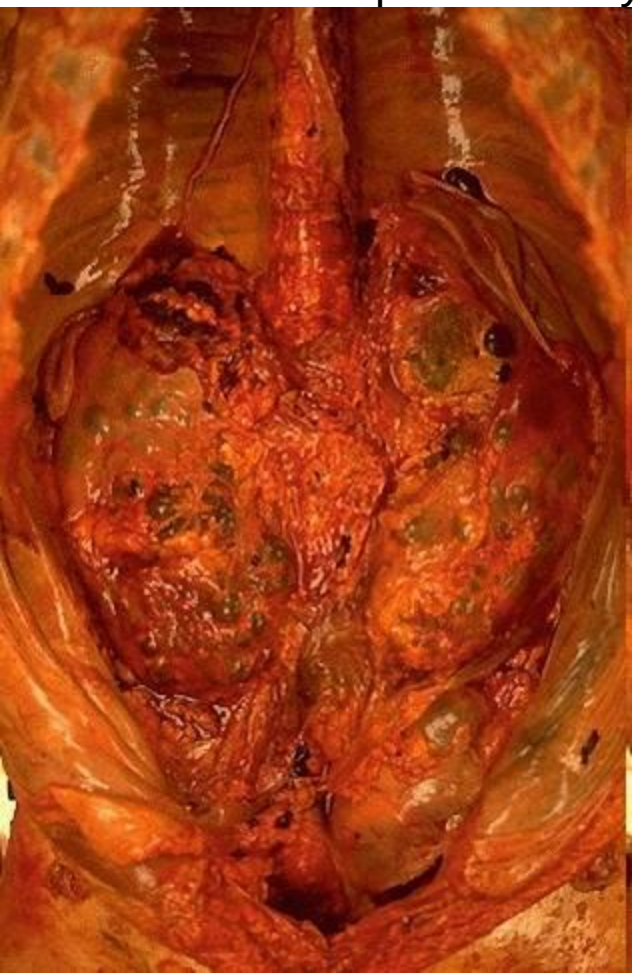
- AR patte
- Preimpla laborator

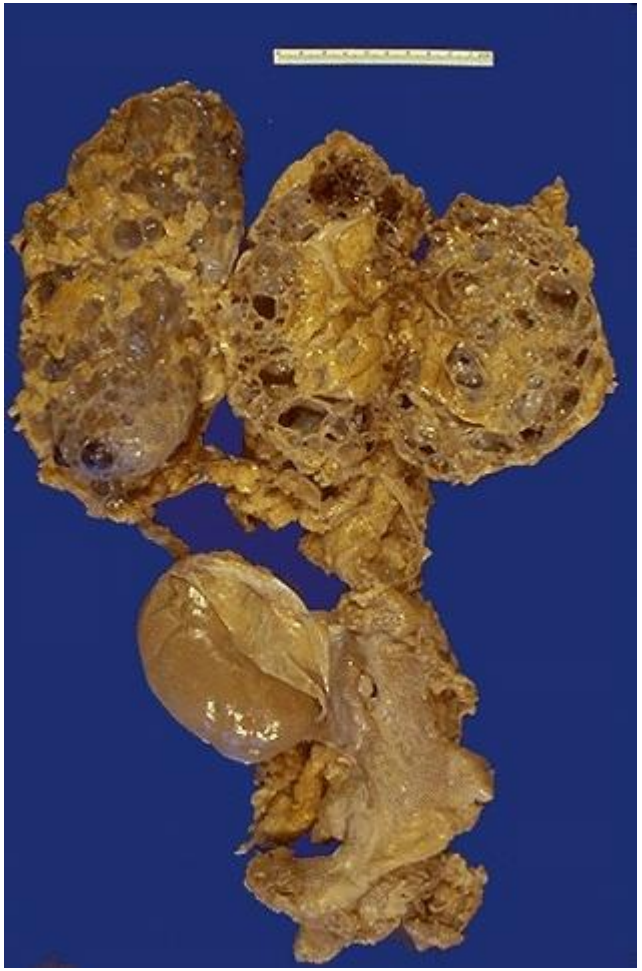


e in some

ADPKD

PKD1>PKD2
Incidence 1:500-1.000 (5% sporadic)
Fourth cause of ESRD
PKD1: ESRD at 54 y - PKD2 at 74 y
Collecting duct, distal nephron
Liver and pancreatic cysts





Enlarged kidneys filling the retroperitoneum and the abdominal cavity

The parenchyma is replaced by cysts

Principal consequences of renal manifestation

Hypertension

May be the first sign of disease

Hematuria

May be due to kidney stone formation or macro/micro trauma affecting one or multiple cysts

UTI

Infection of the cystic parenchyma may lead to abscess formation

Cyst rupture

Cysts subject to trauma may ruprute

Principal extrarenal manifestations

Hepatic and pancreatic cysts

Asymptomatic in many patients, but can expand and cause pain and infection; rarely massive PLD

Cardiac valvular abnormalities

Mitral, tricuspid and aortic valve prolapse and regurgitation

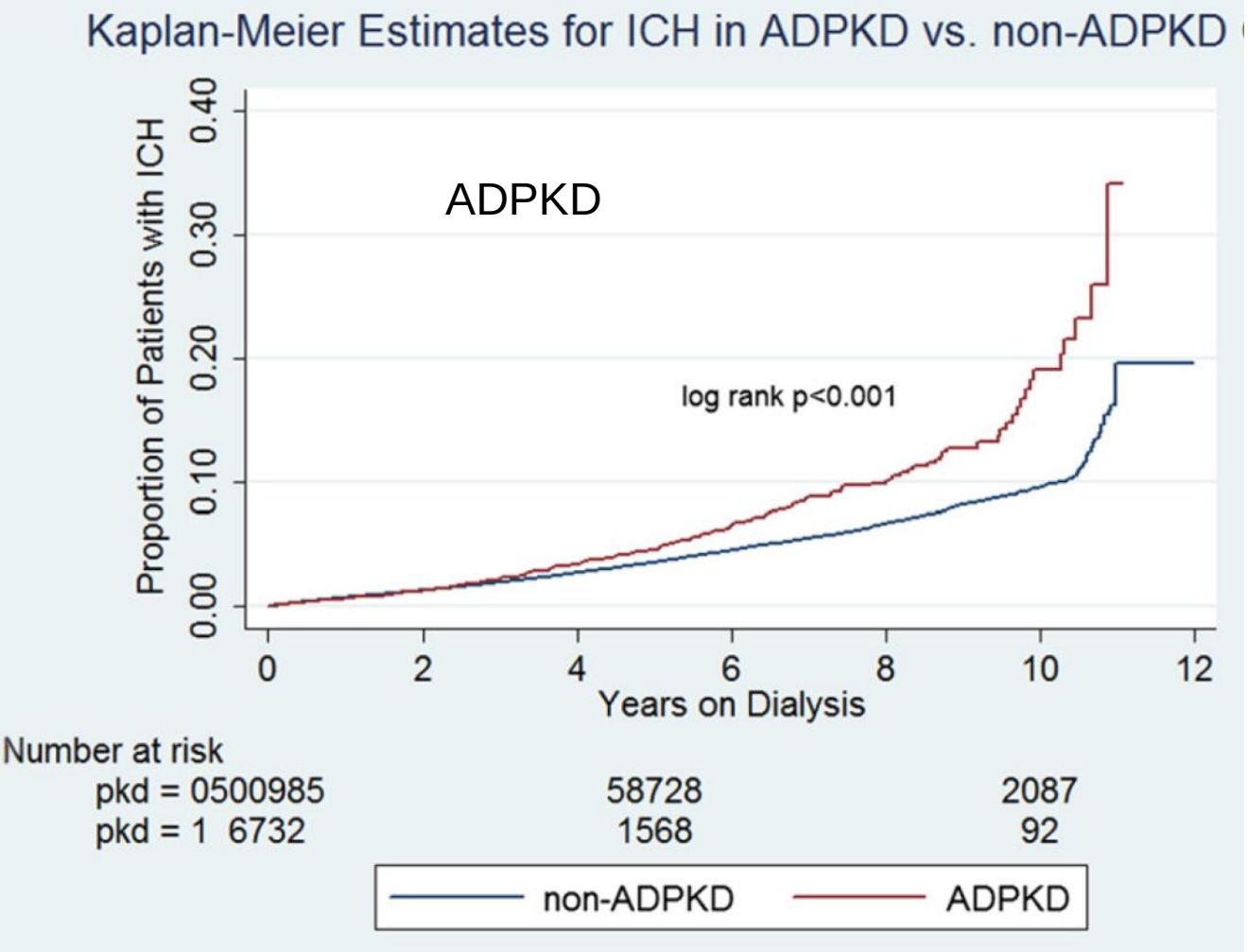
Intracranial aneurysms

Risk of rupture; size predictive. Found in approximately 5% of patients with no family history and about 22% of patients with family history of ICA or SAH

Seminal vesicle cysts

Found in 39-60% of men; undefined risk of infertility

ADPKD is a significant risk factor for ICH among patients on maintenance dialysis



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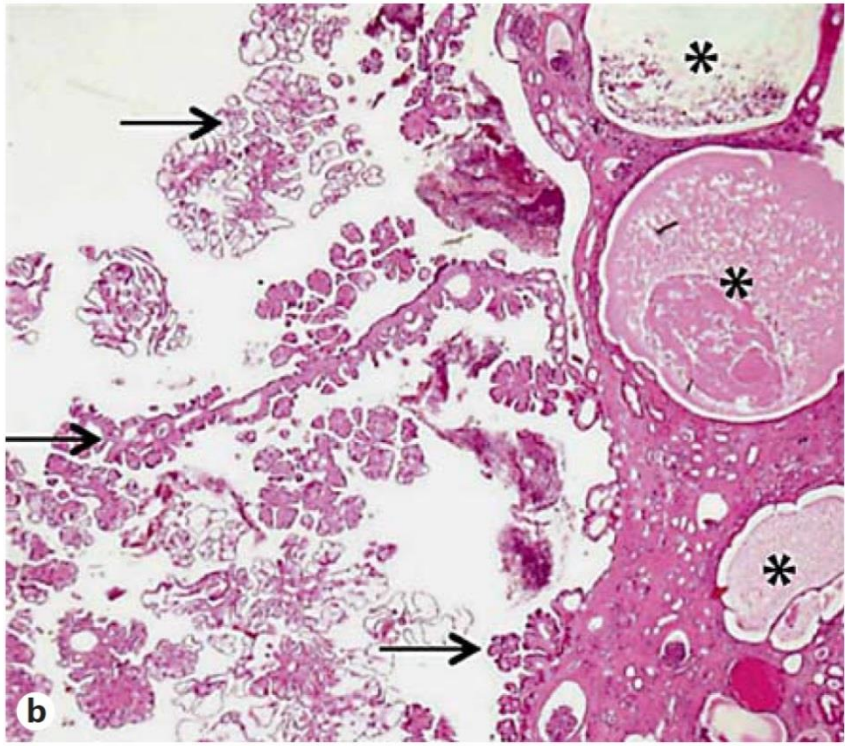
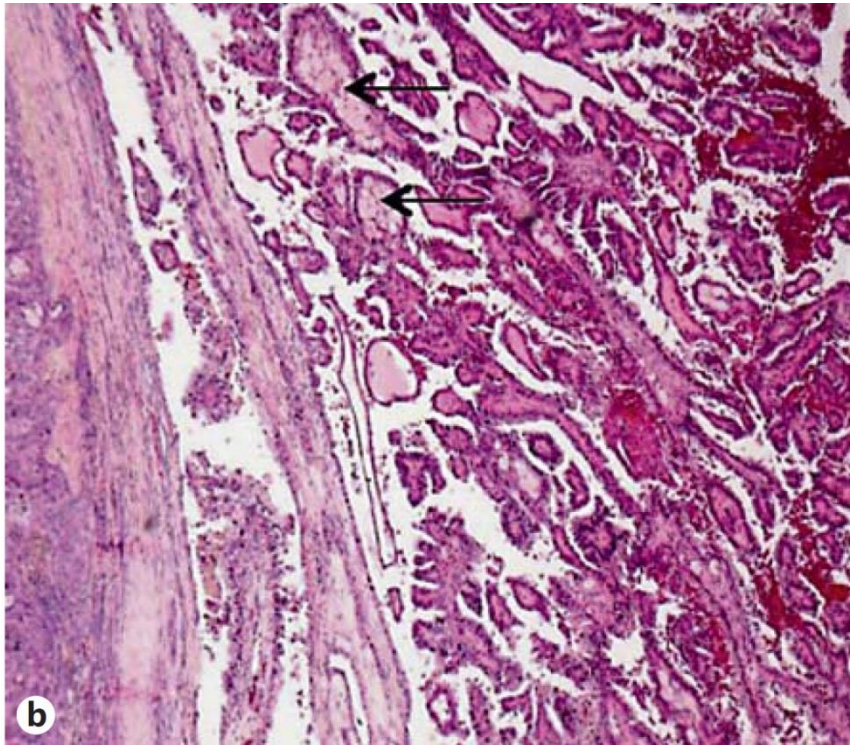
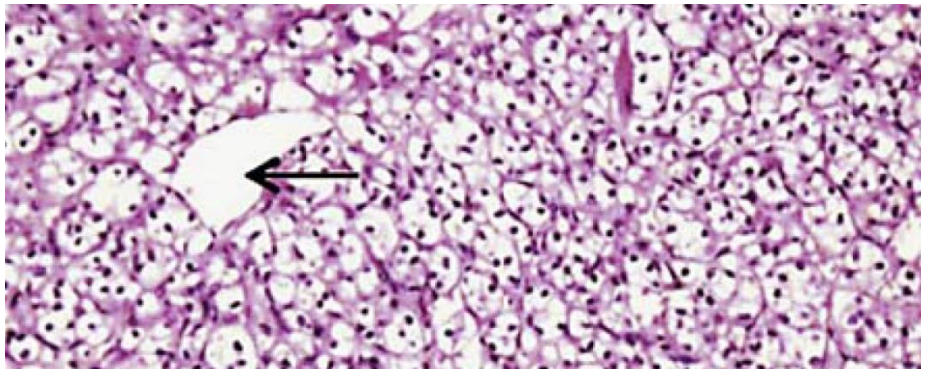
Yoo et al. BMC Nephrology 2014, 15:39

ADPKD: Renal Neoplasias in Surgical Kidney Specimens







N=240
Malignancy: 12/240 =5% (8/12 on dialysis)
63% papillary 31% clear cell RCC
6% urothelial CC

Jilg CA et al: Nephron Clin Pract 2013;123:13–21

Presymptomatic diagnosis of ADKPD

- AD inheritence
- Selection of transplant donor within an ADPKD family
- Benefits
  - Earlier clinical intervention, i.e., for hypertension
- Potential adverse impact on insurability and employment
  - Indicated if there is specific therapy available for ADPKD

- ?Prenatal diagnosis
- ?Preimplantation Genetic Diagnosis

US criteria for ADPKD in a PKD family

age	Number of cysts
< 30	At least 2 cysts in one or both kidneys
30-59	At least 2 cysts/kidney
>60	At least 4 cysts/kidney

At least one family member ESRD ≤ 55 years

JASN 20:205, 2009, JASN 20:1833, 2009

US criteria
or in a family with unknown genotype

age	cysts
15-39	At least 3 cysts in one or both kidneys
40-59	At least 2 cysts/kidney
>60	At least 4 cysts/kidney
No ADPKD if:	
≥40	< 2 cysts

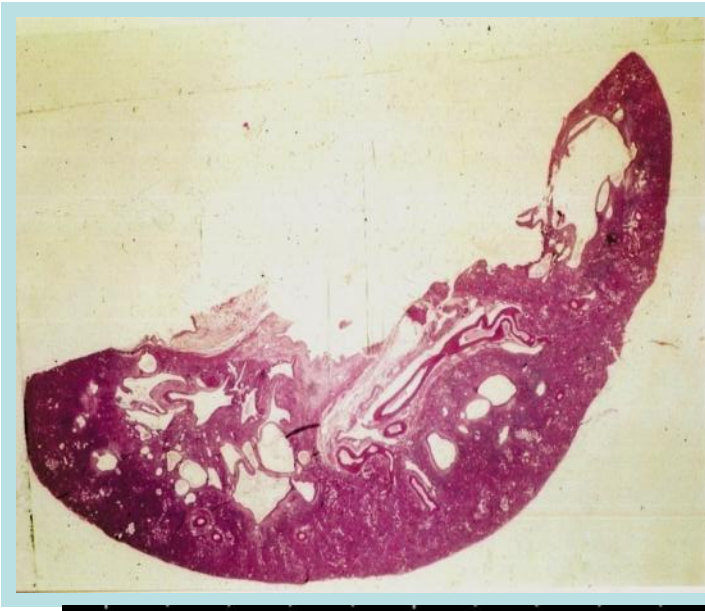
JASN 20:205, 2009, JASN 20:1833, 2009

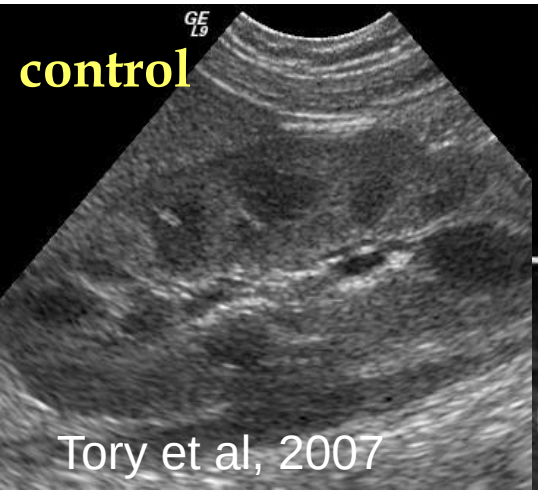
Nephronophthisis – macroscopic morphology

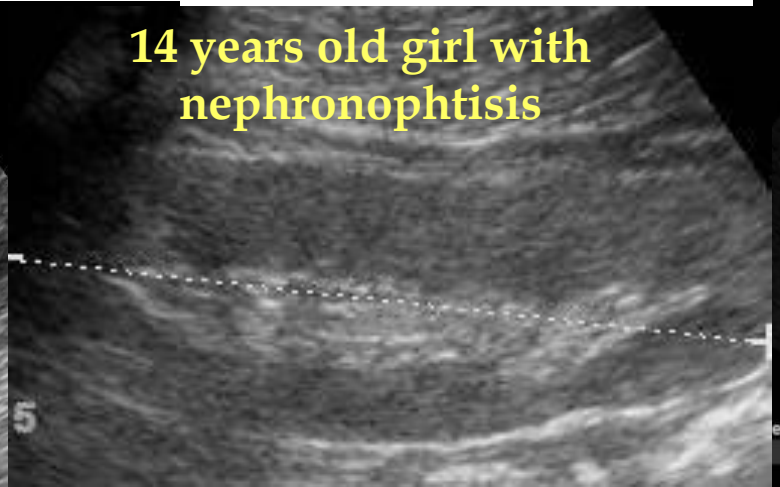
1. Dimension: in juvenile NPH the kindey is usually small, in the infantile type it may be enlarged (+2-3 SD)

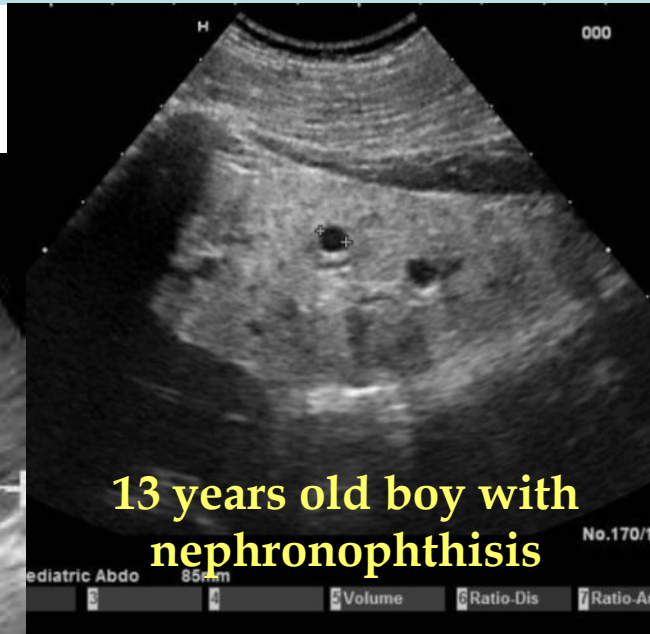
2. Cysts: several cysts at the cortico-medullary boundary. Not a real „cystic” disease

3. **Hyperechogenic**, the cortico-medullary boundary is blurred









Outline

- Definitions, clinical presentation
- Pathophysiology of cyst formation
- Clinical implications, studies

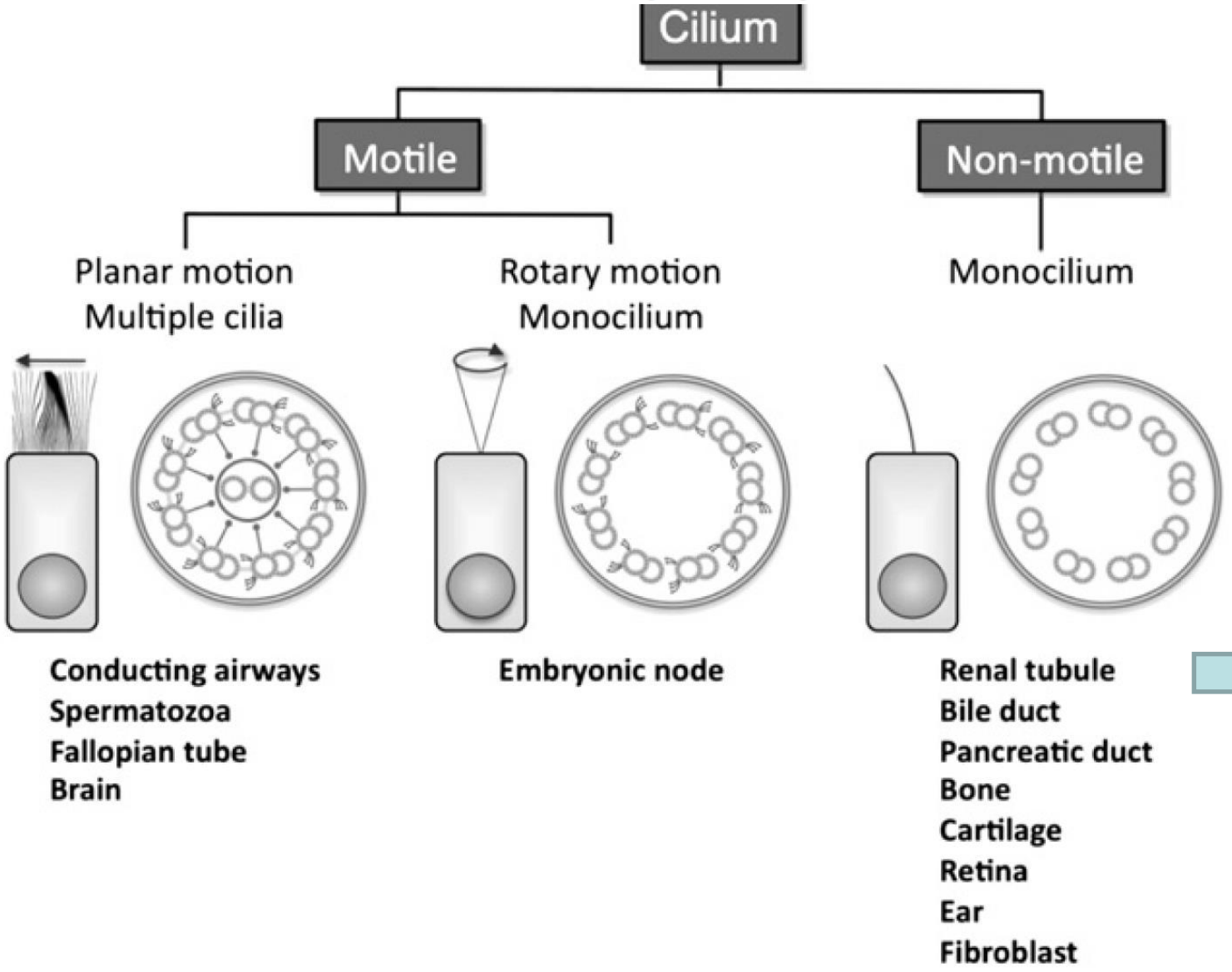
The Cilia Saga

Genes involved in hereditary cystic diseases:

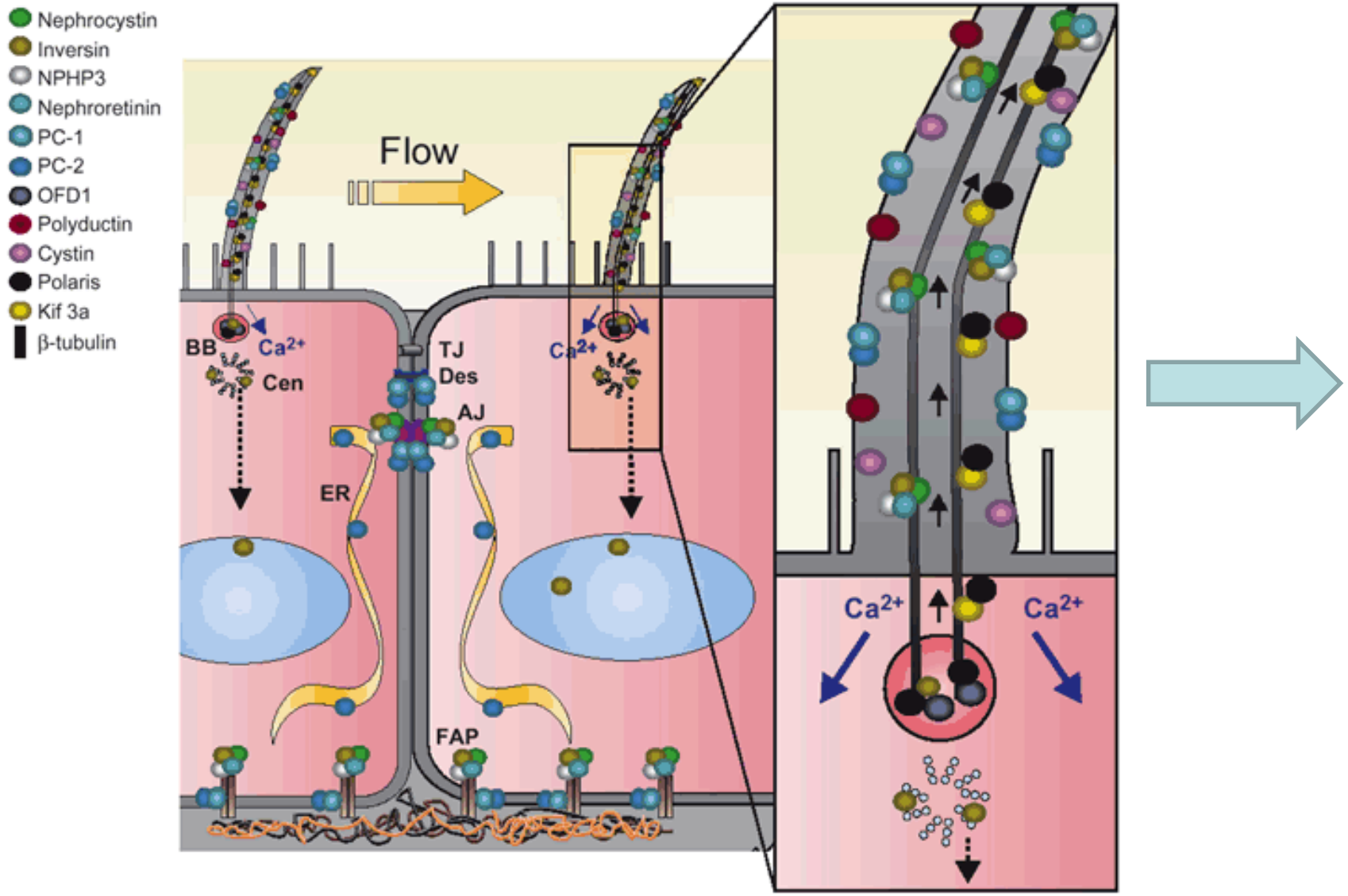
cystic deseases are caused by mutations in genes encoding for proteins involved in the function or structure of the cilia and/or the basal bodies

Ciliopathies: The Central Role of Cilia in a Spectrum of Pediatric Disorders

Thomas W. Ferkol, MD[1], and Margaret W. Leigh, MD[2]



Ferkol TW and Leigh MW: The Journal of Pediatrics, 2012, 160: 366-371



Watnick T & Germino G: **From cilia to cyst***Nature Genetics* **34**, 355 - 356 (2003)

Unifying concept: the example of nephronophtisis

- Tubulointerstitial nephropathy
- Polyuria, polydipsia
- Anemia
- Normal blood pressure
- ESRD

- Further caracteristics
  - Multiple syndromes and type of inheritance
    - Joubert, Bardet Biedl
    - Associated anomalies
      - Liver,
      - CNS
      - Retina
      - Olfactory
      - (Hearing)
      - Situs inversus
      - Kartagener syndrome

Nephronophtysis

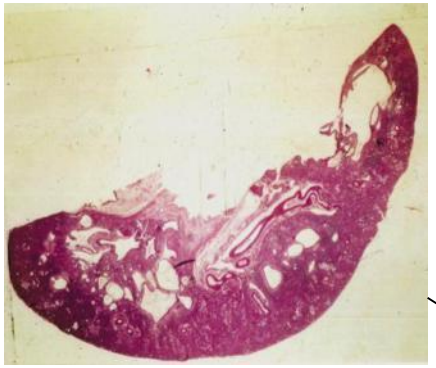
- diversity

Table 1 Genetic heterogeneity and overlap of nephronophthisis (NPH), Senior-Løken, Joubert, and Meckel-Gruber syndromes

Locus	Chromosome	Gene*	Clinical manifestations
NPHP1/SLSN1	2q13	*NPHP1* (nephrocystin-1)	Juvenile nph (mild JBTS, mild RP, Cogan)
NPHP2	9q31	*NPHP2/INVS* (Inversin)	Infantile nph (RP, liver fibrosis, HT)
NPHP3/SLSN3	3q22	*NPHP3* (nephrocystin-3)	Juvenile nph (liver fibrosis, RP)
NPHP4/SLSN4	1p36	*NPHP4* (nephrocystin-4 or nephroretinin)	Juvenile nph (Cogan, RP)
NPHP5/SLSN5	3q21	*NPHP5/IQCB1*	Juvenile nph + severe RP
NPHP6/SLSN6/JBTS5/ MKS4	12q21	*NPHP6/CEP290*	Juvenile nph + JBTS + severe RP, isolated RP, (MKS)
NPHP7	16p	*NPHP7/GLIS2*	Juvenile nph
NPHP8/JBTS7/MKS5	16q	*NPHP8/RPGRIP1L*	Juvenile nph + JBTS (MKS)
NPHP9	17q11	*NPHP9/NEK8*	Juvenile and infantile nph

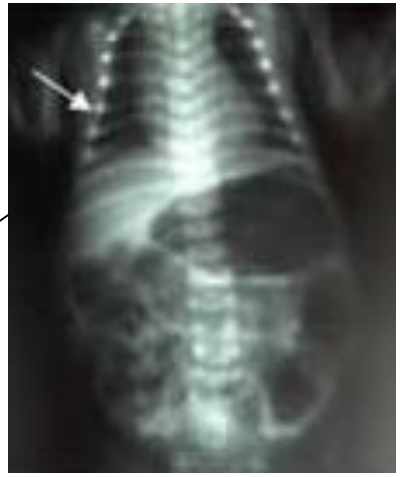
- … and ciliae

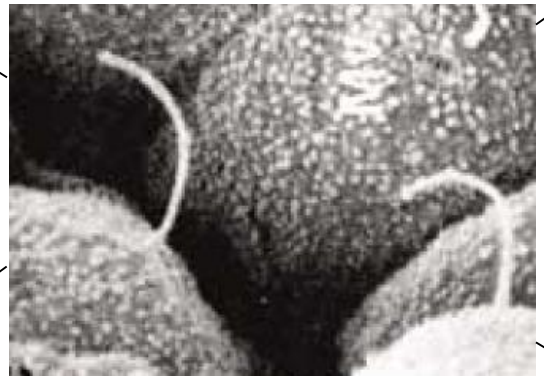
Ciliary proteins – the nephrocystins

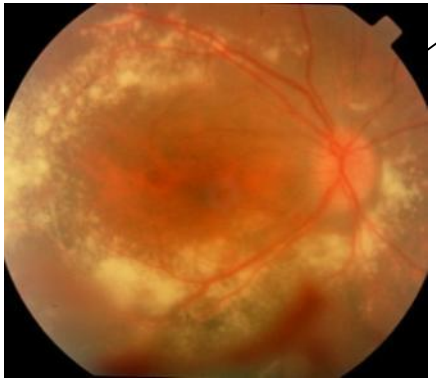


Nephrocystin 1-10

IFT-80



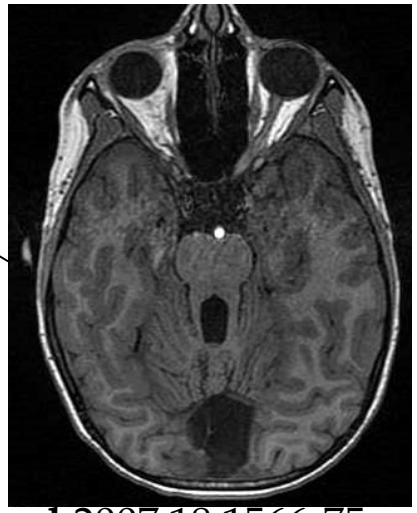




Nephrocystin 1,3,4,5,6,

RPGR, RPGRIP1

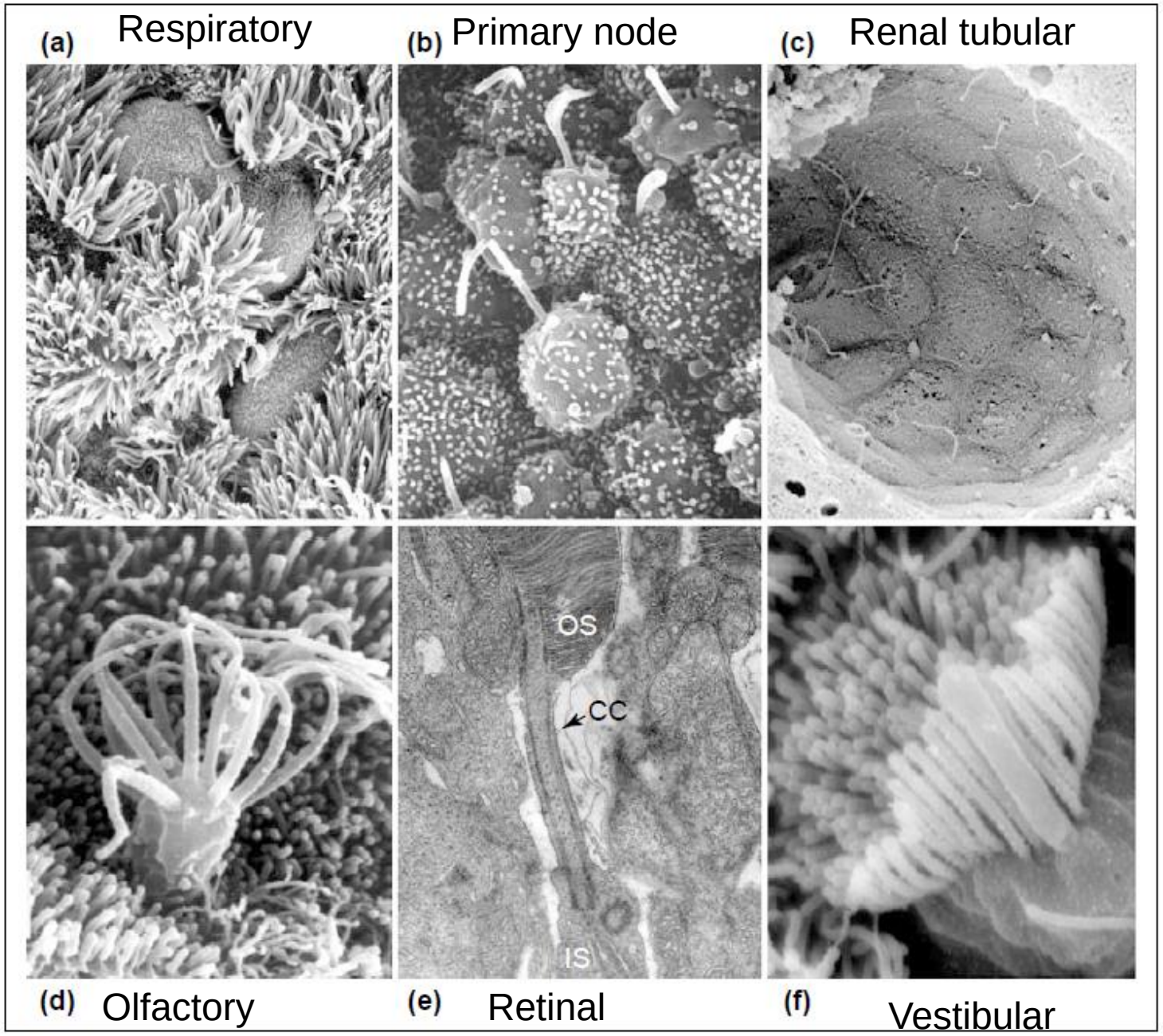
Nephrocystin 1,6,8, meckelin



Tory K et al. **J Am Soc Nephrol** 2007;18:1566-75.

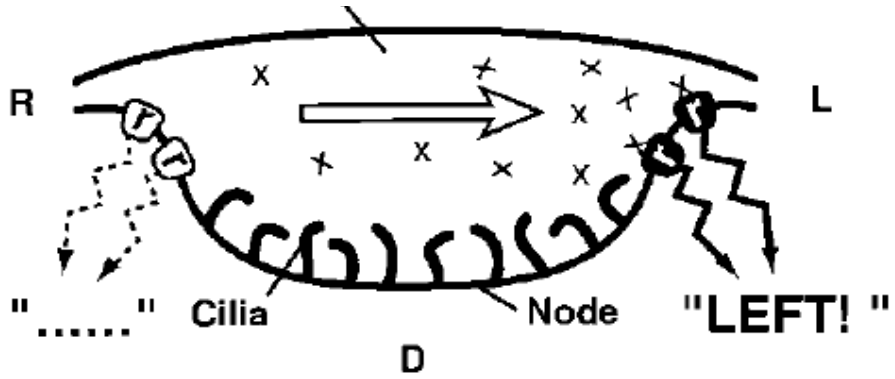
The concept

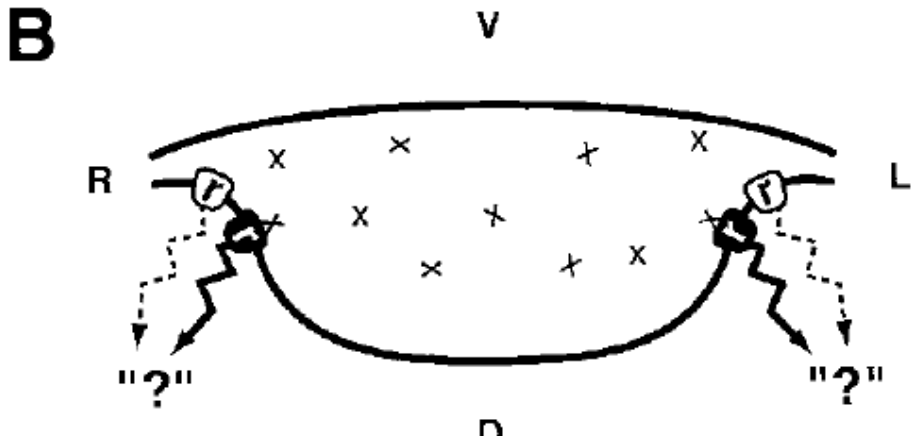
- Inherited cystic diseases are caused by:
  - a defect of proteins involved in the structure and/or the function of the ciliae
- Clinical signs and symptoms: depend on the distribution of the expression of the given protein in the different types of ciliae



Current Opinion in Genetics & Development 2005, 15:308–314

Randomization of Left–Right Asymmetry due to Loss of Nodal Cilia Generating Leftward Flow of Extraembryonic Fluid in Mice Lacking KIF3B Motor Protein

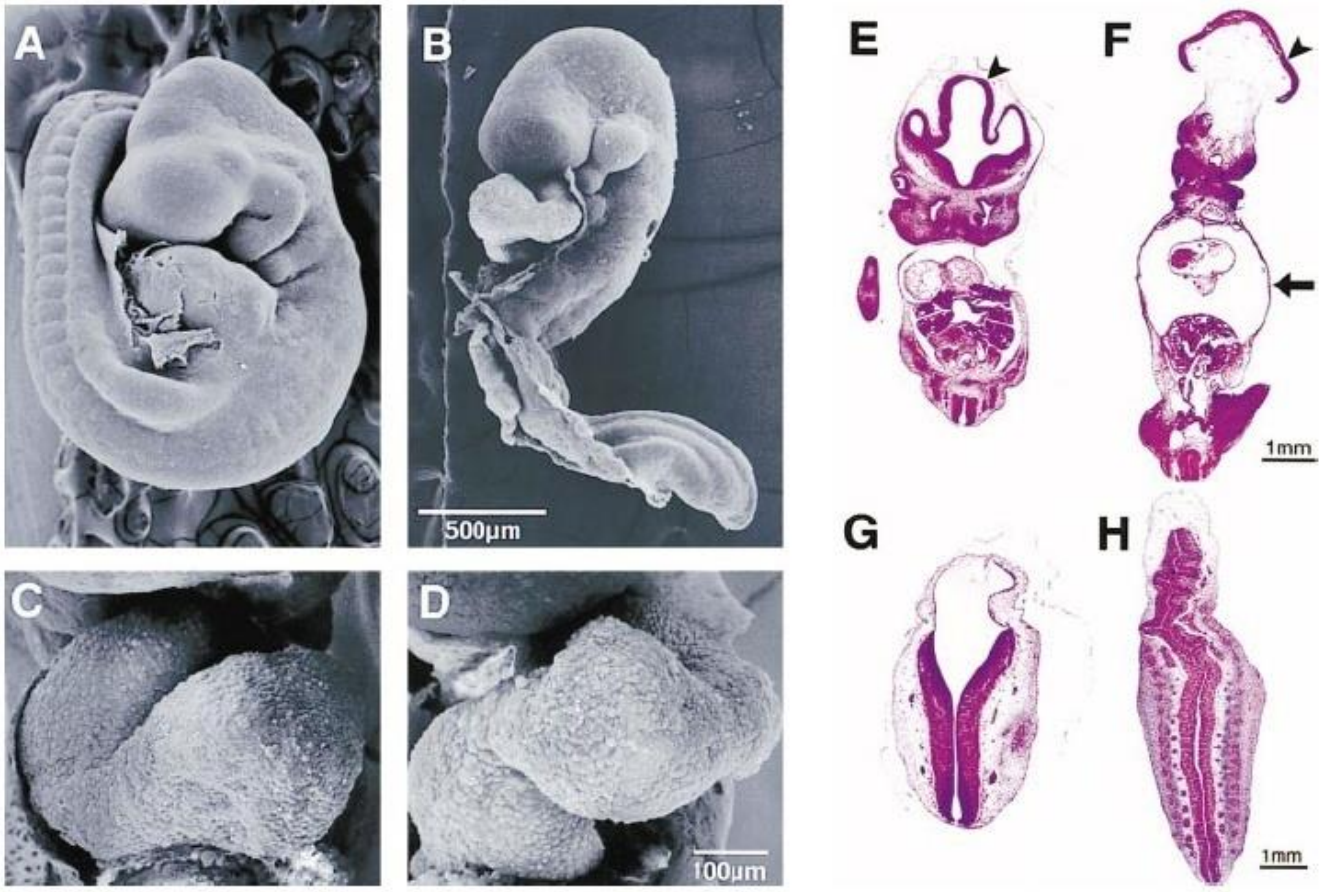




Shigenori Nonaka,

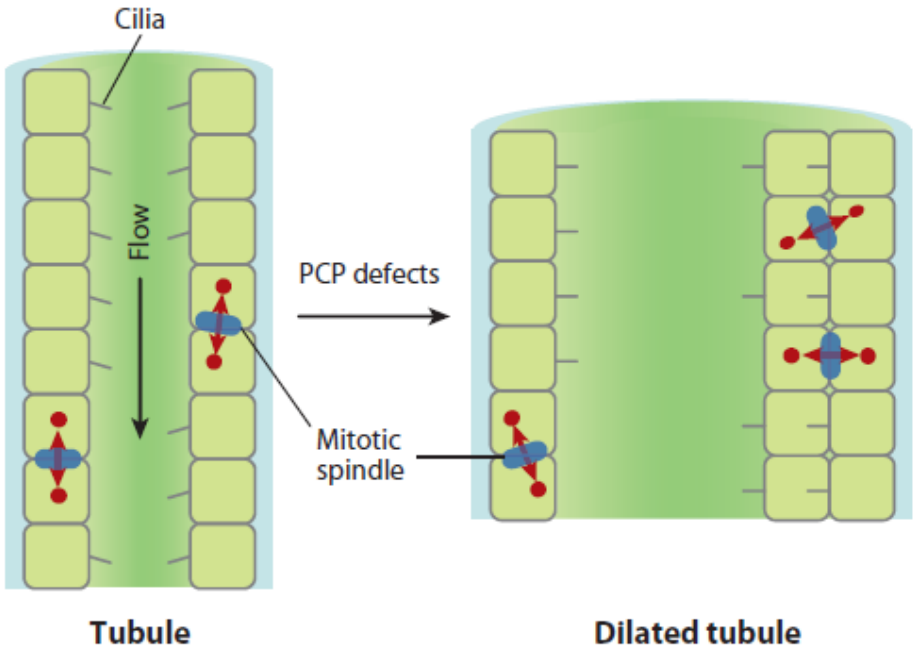
Cell, Vol. 95, 829–837, December 11, 1998, Copyright ©1998 by Cell Press

Randomization of Left–Right Asymmetry due to Loss of Nodal Cilia Generating Leftward Flow of Extraembryonic Fluid in Mice Lacking KIF3B Motor Protein



Cell, Vol. 95, 829–837, December 11, 1998, Copyright ©1998 by Cell Press

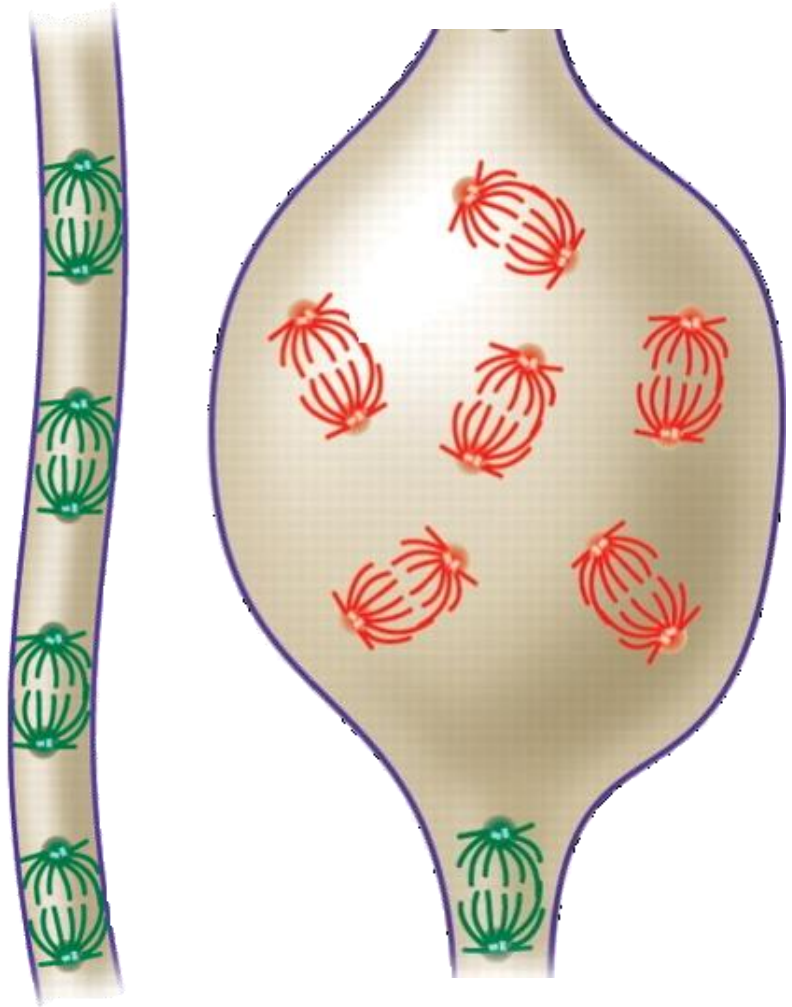
Ciliary disease and the kidney: „loss of orientation”



Annu. Rev. Physiol. 2009. 71:83–113

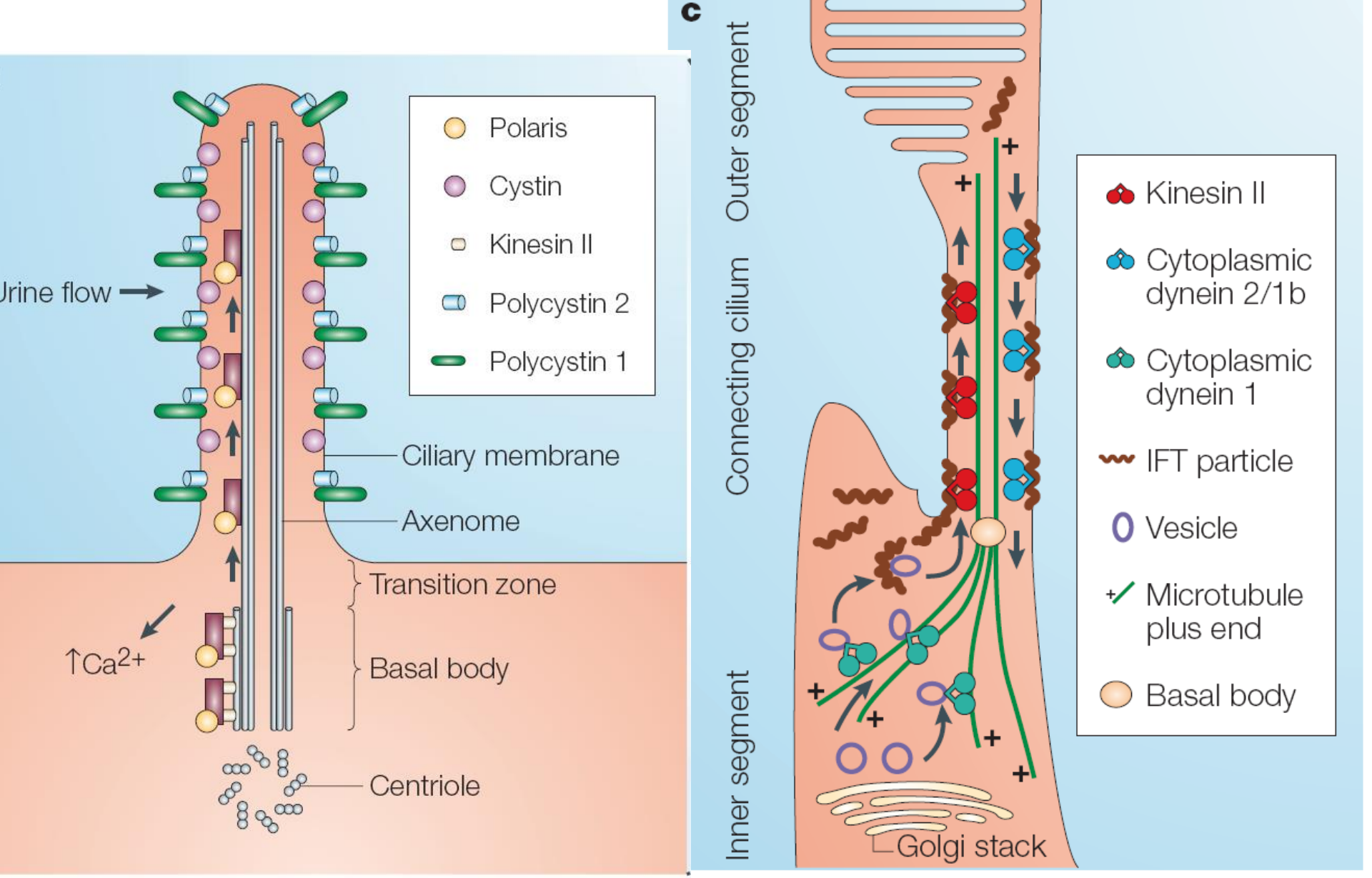
Loss of Planar Polarity: Cyst Initiation

Normal

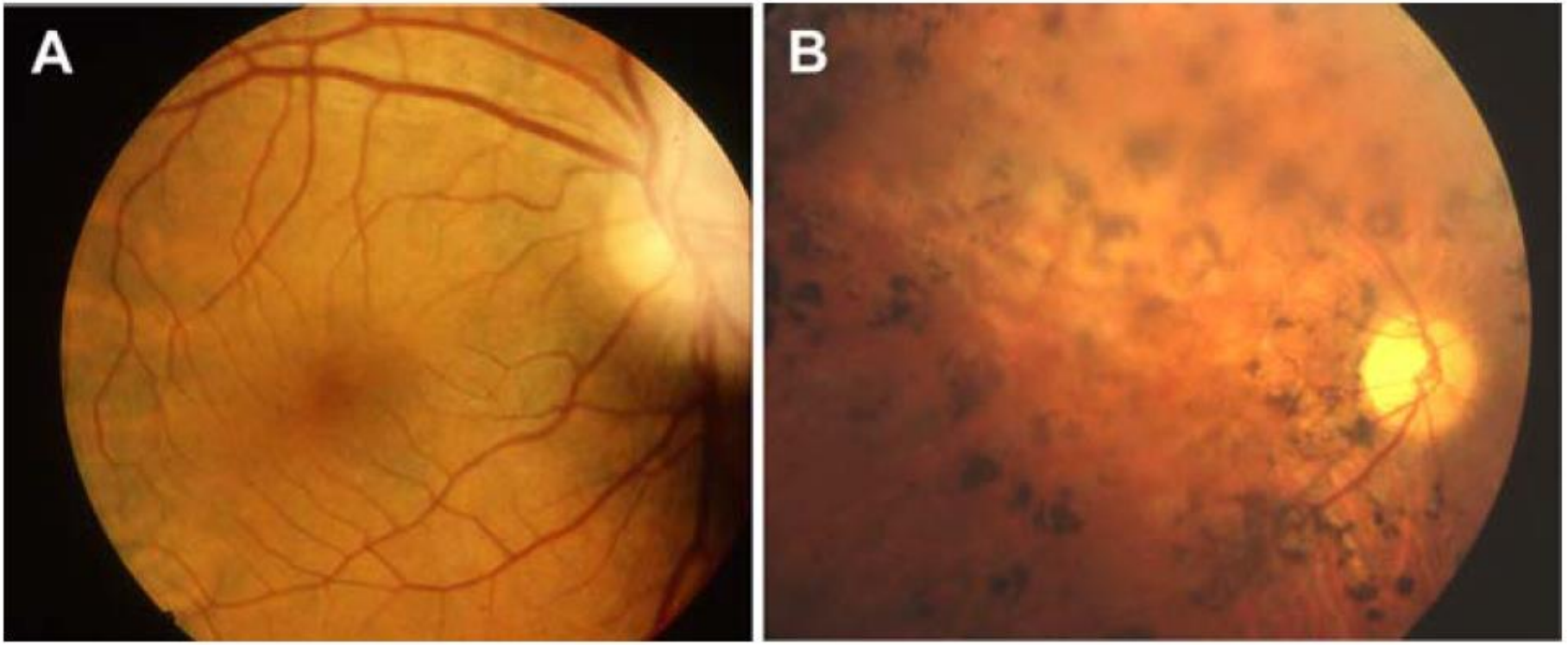


PKD

Fischer, Nature Genetics, 38:21, 2006
Singla Science 313:629, 2006


Polaris
Cystin
Kinesin II
Polycystin 2
Polycystin 1
Urine flow
Ciliary membrane
Axenome
Transition zone
↑Ca2+
Basal body
Centriole
c
Outer segment
Connecting cilium
Inner segment
Kinesin II
Cytoplasmic dynein 2/1b
Cytoplasmic dynein 1
IFT particle
Vesicle
Microtubule plus end
Basal body
Golgi stack

Ciliary disease and the retina: transport defect



Nephronophthisis

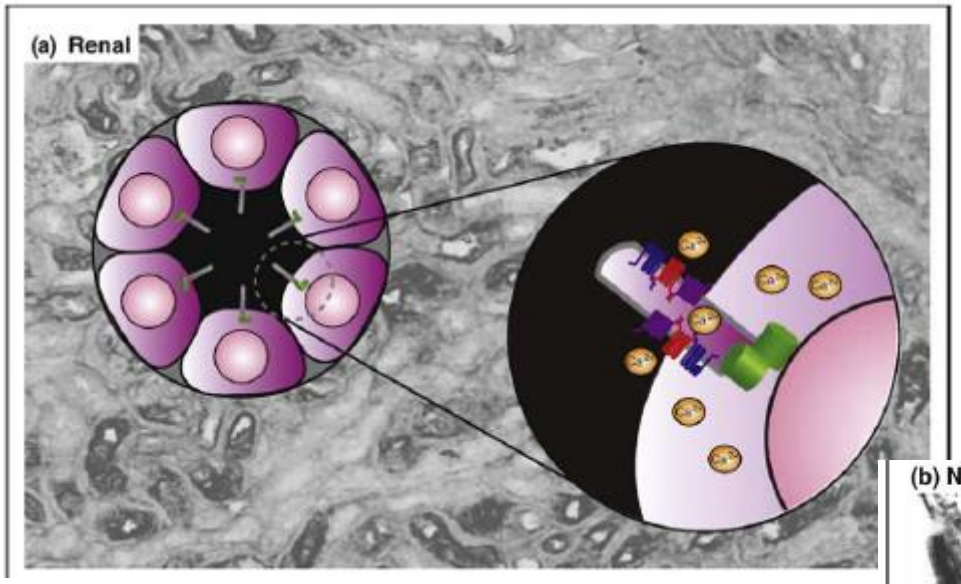
Rémi Salomon · Sophie Saunier · Patrick Niaudet

Pediatr Nephrol (2009) 24:2333–2344

Ophtalmoscopic examinations of a control subject (a) and an affected individual (b) showing typical retinitis pigmentosa fundus characterized by very thin retinal vessels, retinal pigment epithelium atrophy, abnormal pigmentary migrations, and pallor of the optic disk

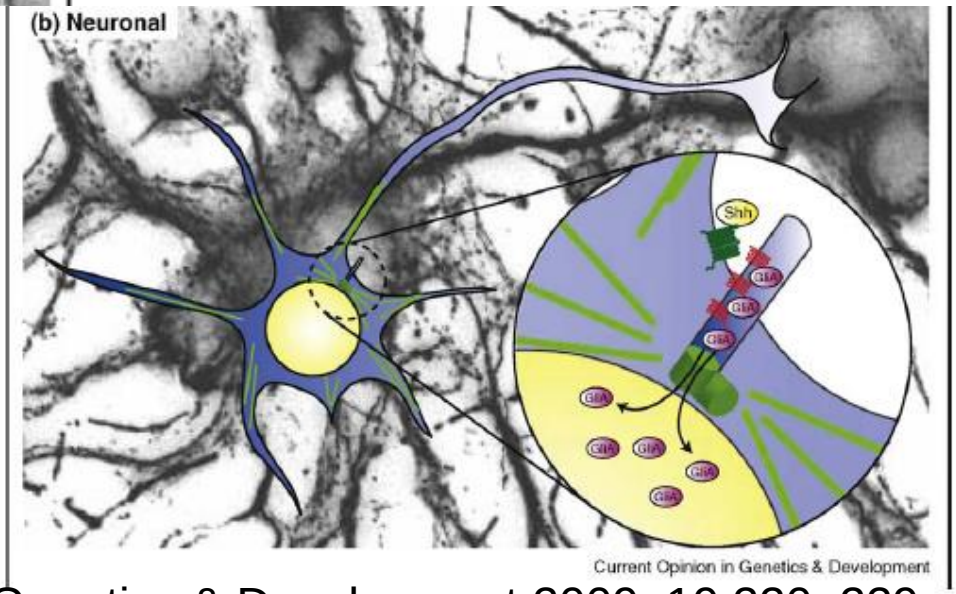
Retinitis pigmentosa

Ciliary disease and the central nervous system: defect of migration & orientation



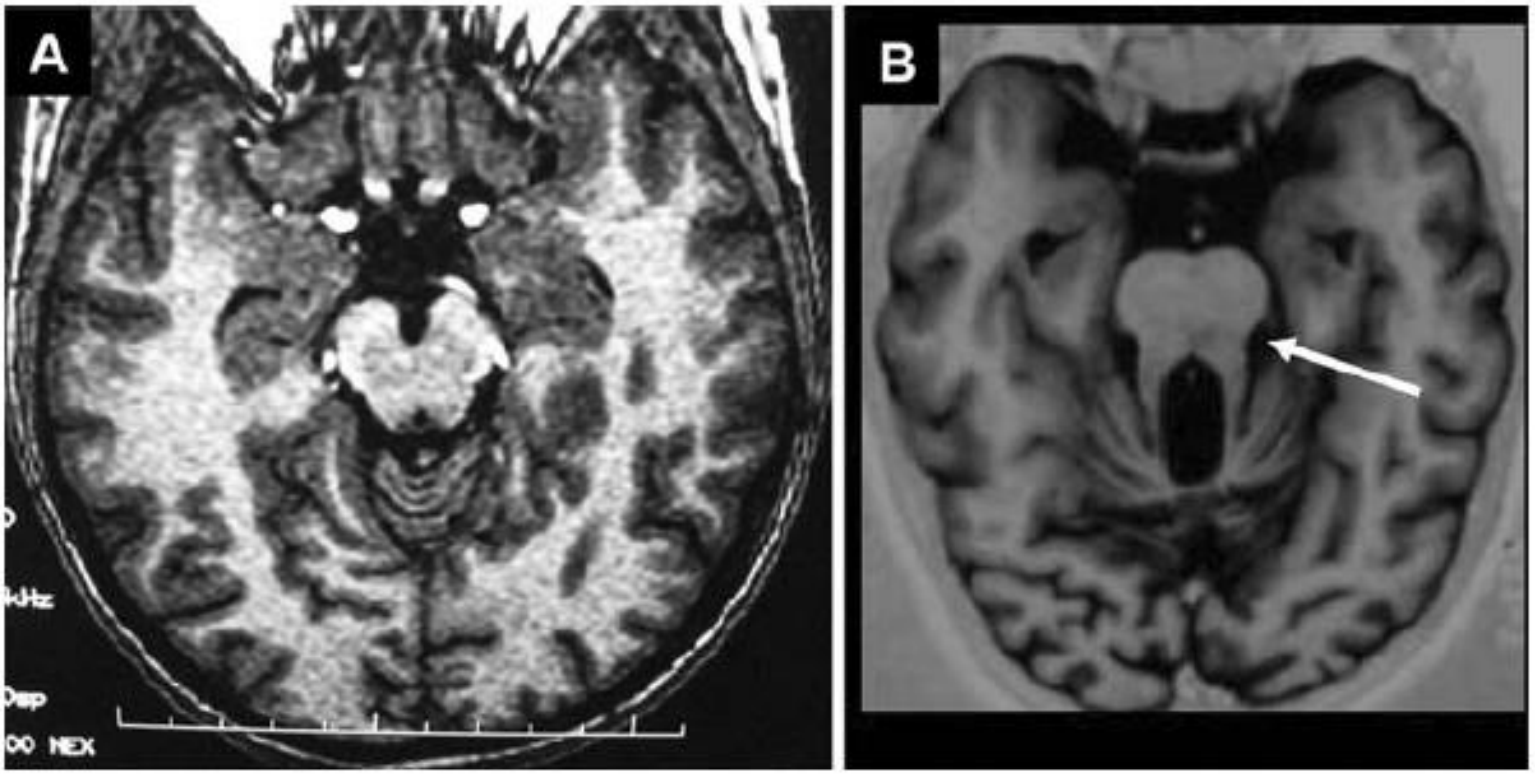
Tubular cell

Hyppocampic neurons in cell culture

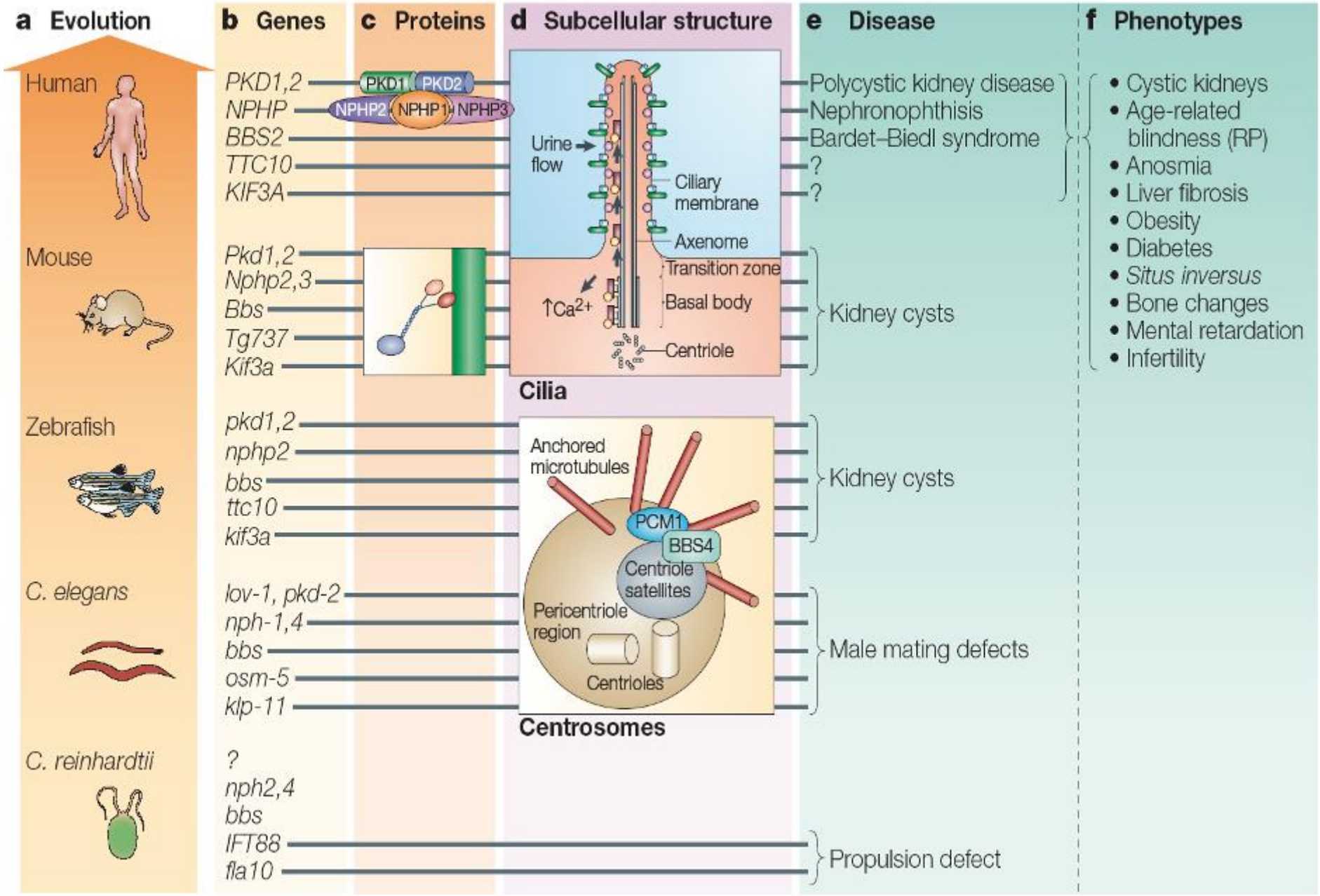


Madeline A Lancaster: Current Opinion in Genetics & Development 2009, 19:220–229

Ciliary disease and the central nervous system: defect of migration & orientation



Pediatr Nephrol (2009) 24:2333–2344


a Evolution
b Genes
c Proteins
d Subcellular structure
e Disease
f Phenotypes
Human
Mouse
Zebrafish
C. elegans
C. reinhardtii
PKD1,2
NPHP
BBS2
TTC10
KIF3A
Pkd1,2
Nphp2,3
Bbs
Tg737
Kif3a
pkd1,2
nphp2
bbs
ttc10
kif3a
lov-1, pkd-2
nph-1,4
bbs
osm-5
klp-11
?
nph2,4
bbs
IFT88
fla10
PKD1
PKD2
NPHP2
NPHP1
NPHP3
Urine flow
Ciliary membrane
Axenome
Transition zone
Basal body
Centriole
↑Ca2+
Cilia
Anchored microtubules
PCM1
BBS4
Centriole satellites
Pericentriole region
Centrioles
Centrosomes
Polycystic kidney disease
Nephronophthisis
Bardet–Biedl syndrome
?
?
Kidney cysts
Kidney cysts
Male mating defects
Propulsion defect
• Cystic kidneys
• Age-related blindness (RP)
• Anosmia
• Liver fibrosis
• Obesity
• Diabetes
• Situs inversus
• Bone changes
• Mental retardation
• Infertility

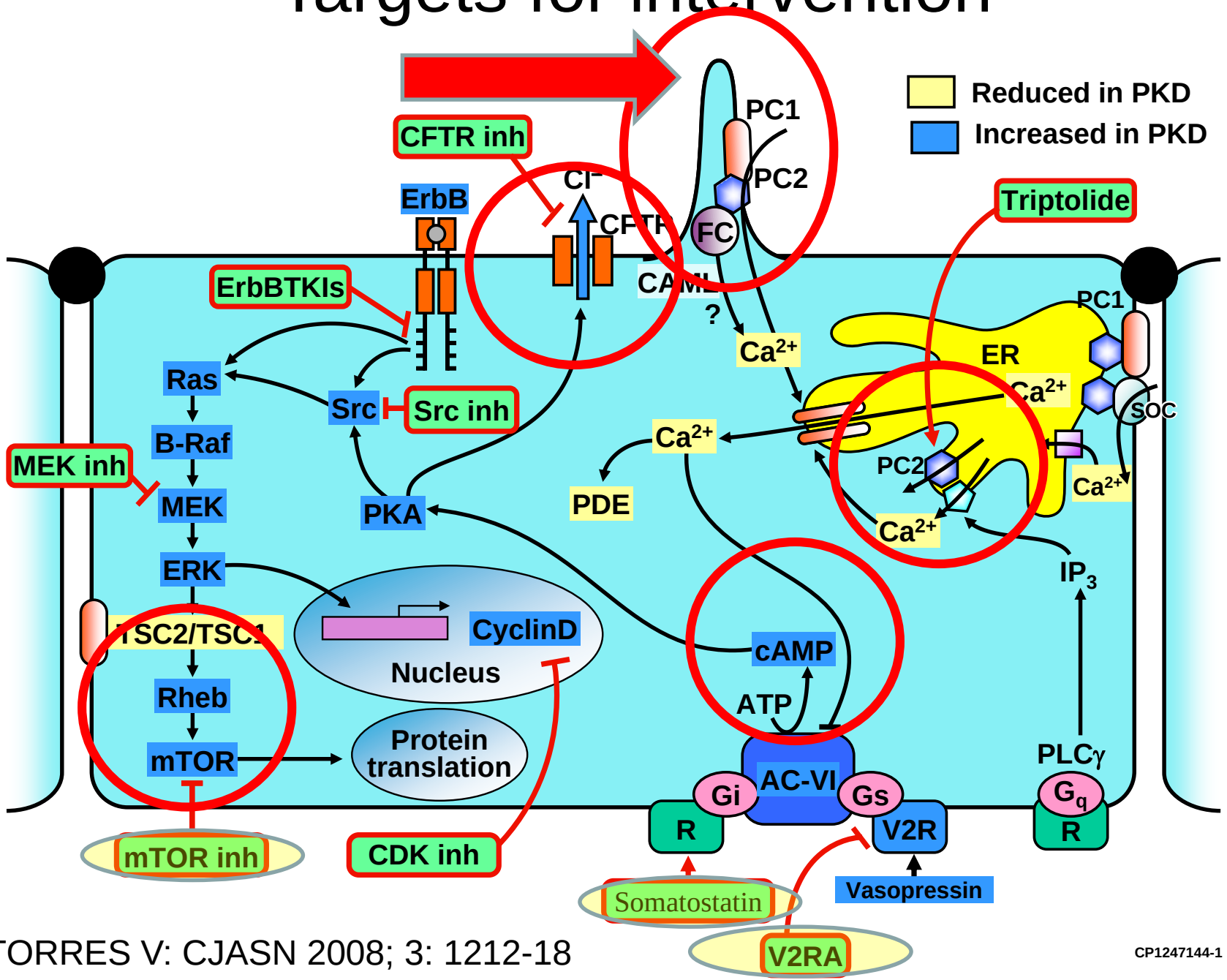
Outline

- Definitions, clinical presentation
- Pathophysiology of cyst formation
- Clinical implications, studies

Therapeutic perspective

Signalling pathways

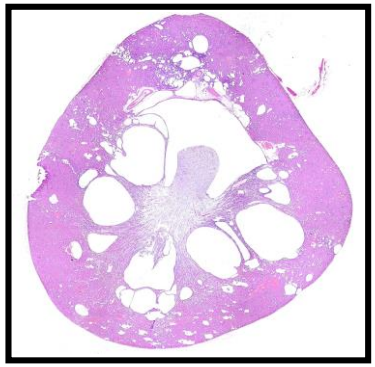
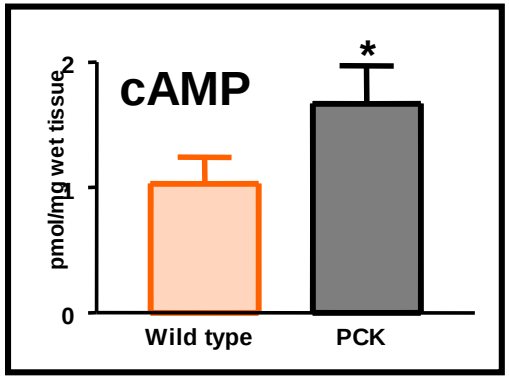
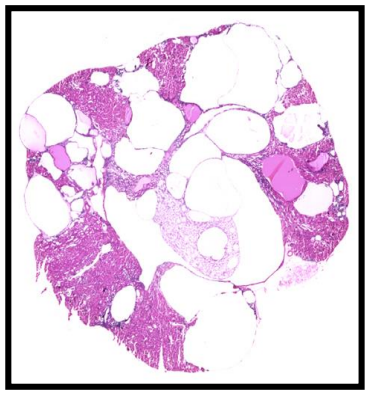
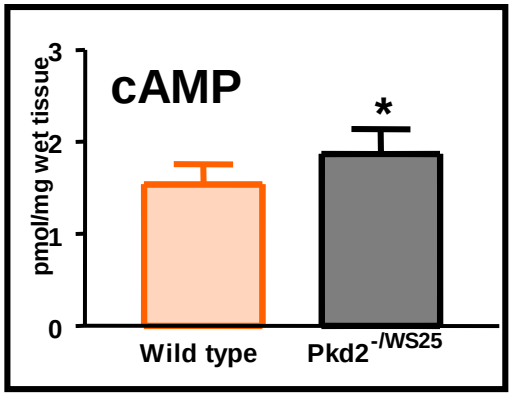
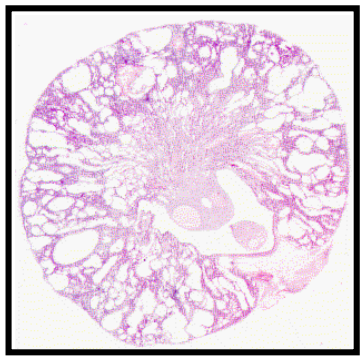
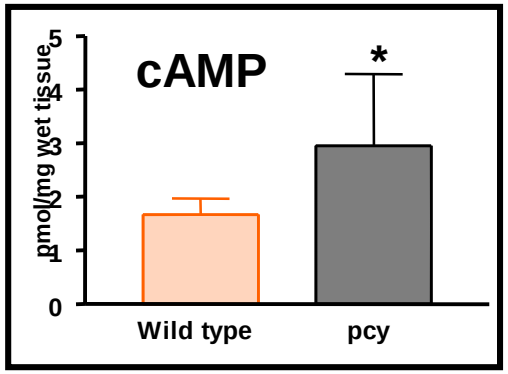
Targets for intervention



TORRES V: CJASN 2008; 3: 1212-18

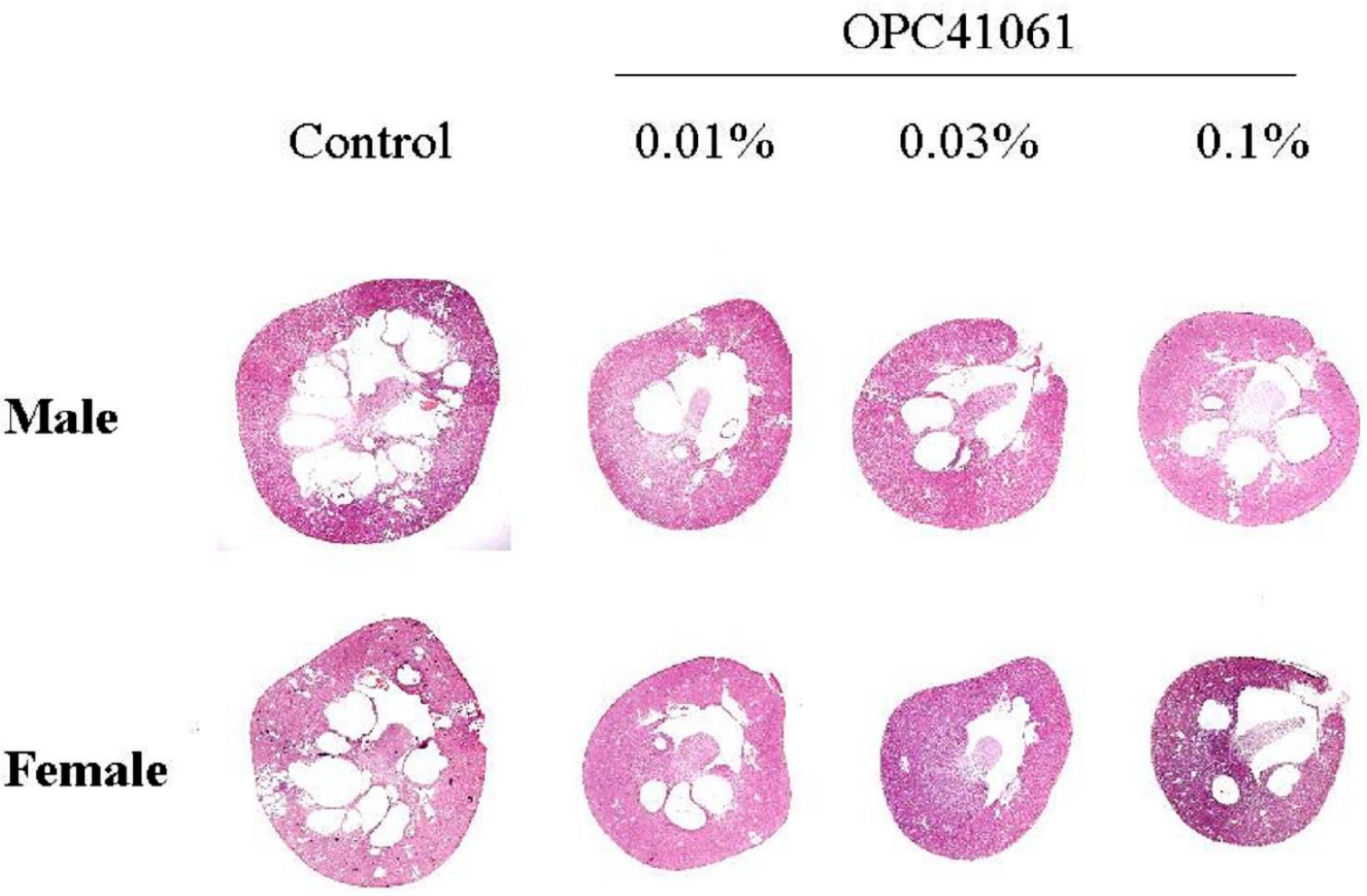
CP1247144-1

Human disease and animal homologues

Model			Human
PCK rat			**ARPKD**
Pkd2$^{WS25/-}$ mouse			**ADPKD**
***pcy* mouse**			**NPHP3**

Torres V: 2007

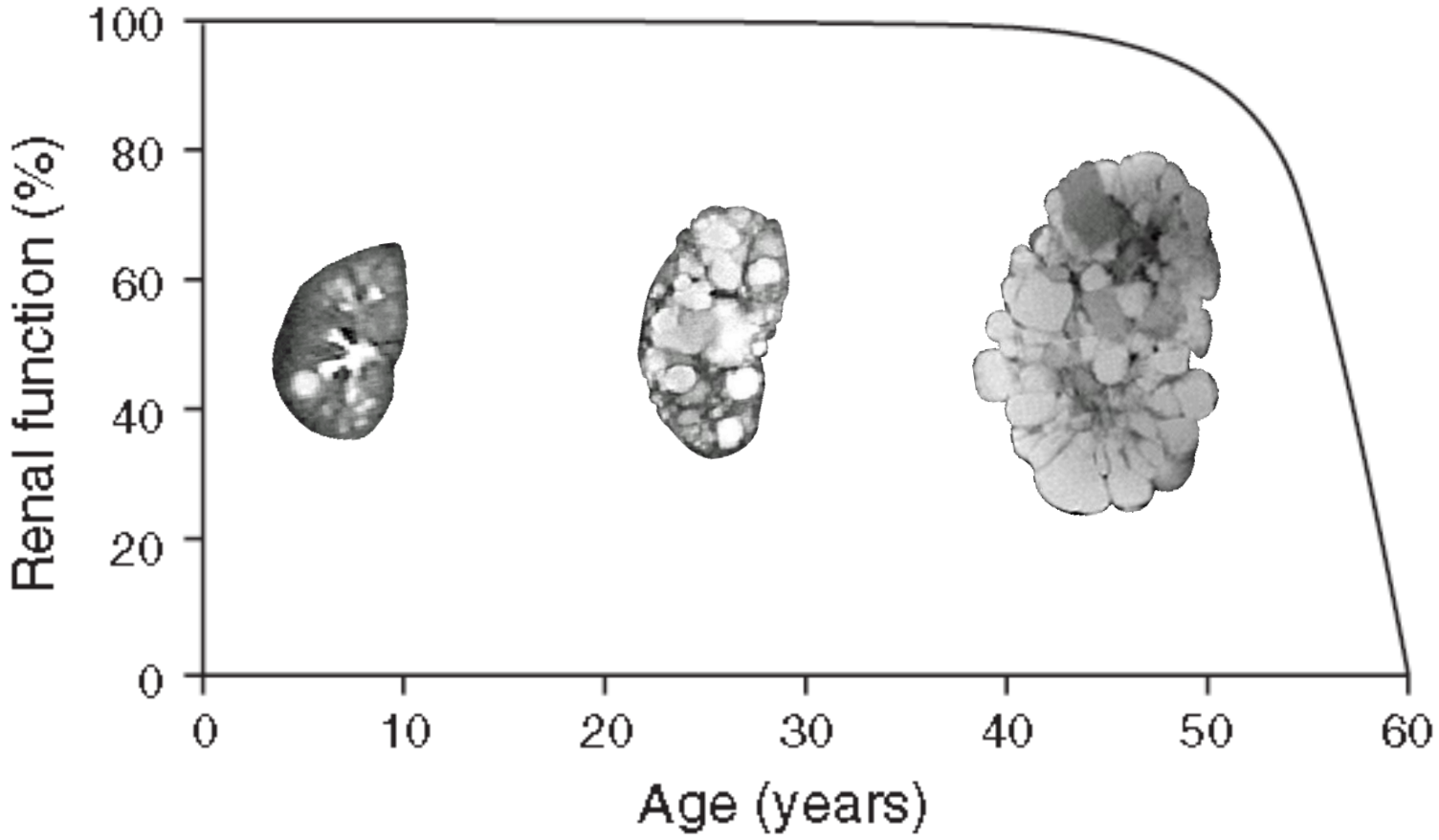
Vasopressin antagonists



Wang JASN 16:846, 2005

Renal survival curve in ADPKD

long duration of intact renal function before loss of renal function or entry into ESRD



Chapman et al: Clin J Am Soc Nephrol 3: 1197–1204, 2008.

ADPKD: Clinical studies

- CRISP – morphology and function
- V2 receptor antagonists: tolvaptan
- Somatostatin analogues: octreotide, lanreotide
- mTOR inhibitors: sirolimus, everolimus
- ACEI & ACEI+ARB: lisinopril - telmisartan

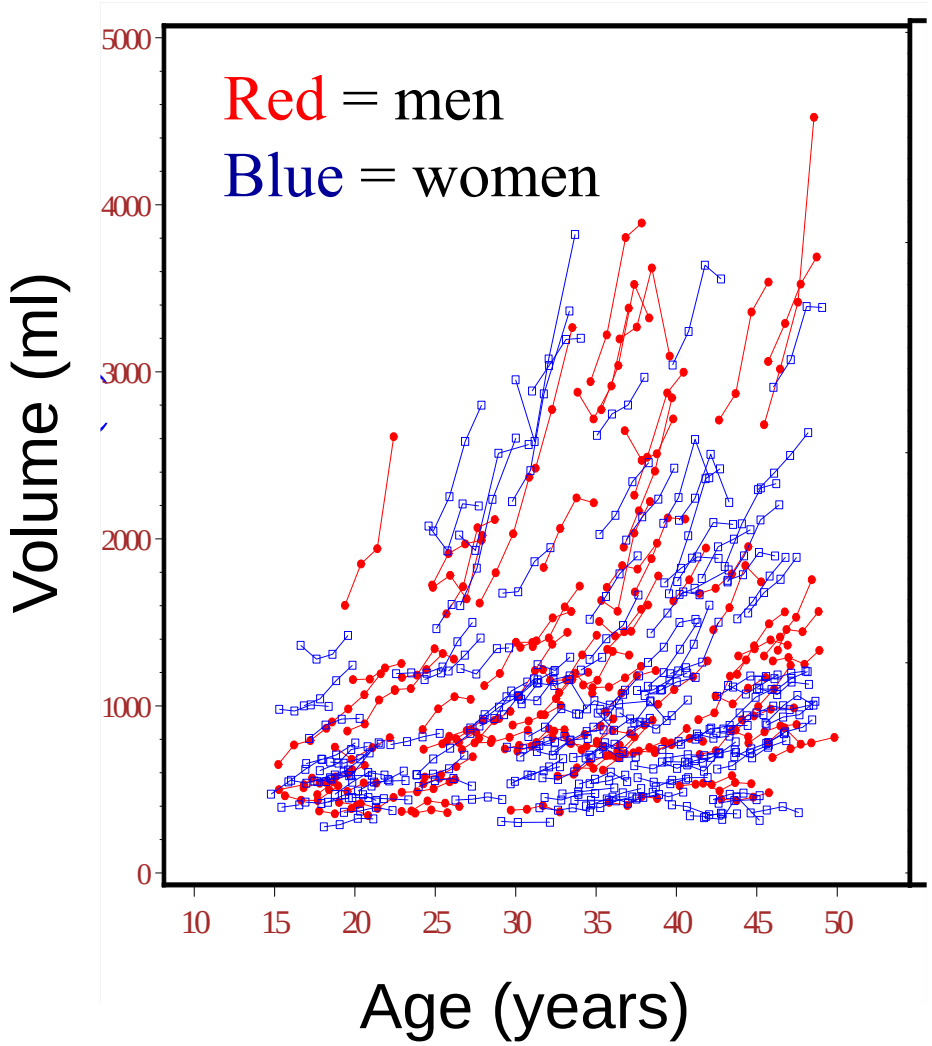
CRISP

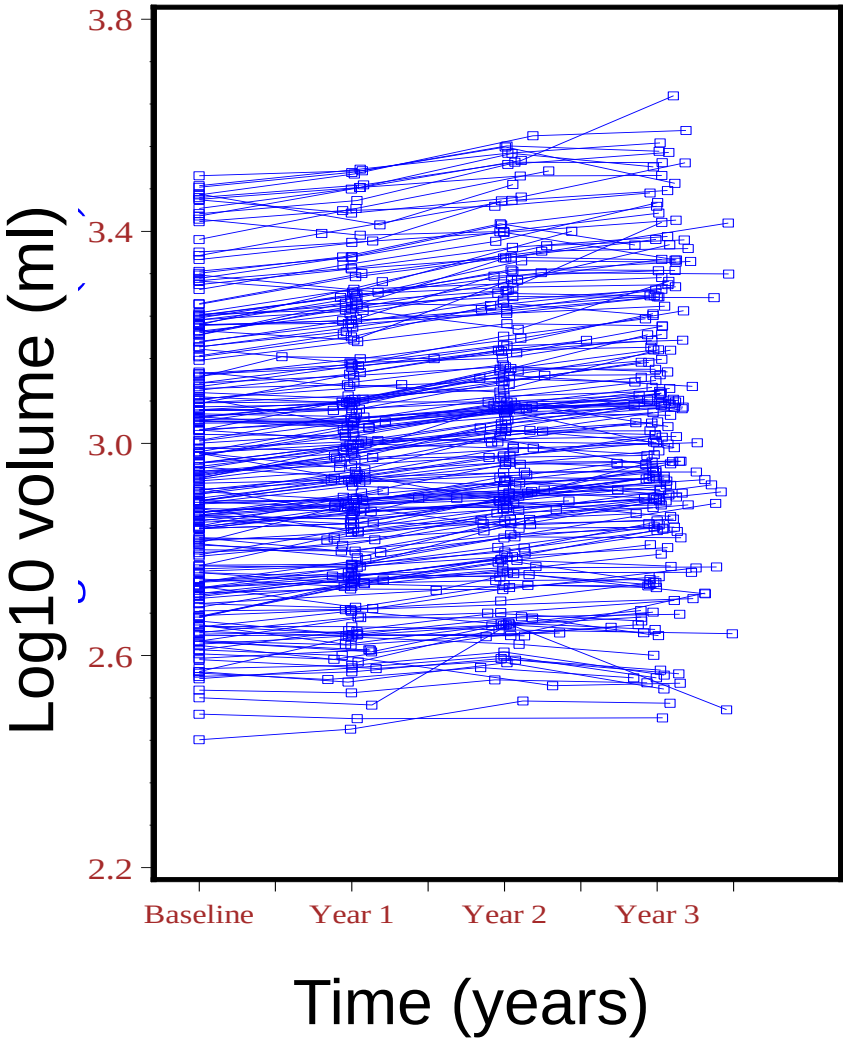
Consortium for Radiological Imaging in Studies of Polycystic Kidney Disease

- Need for a more sensitive tool than GFR to assess progression of ADPKD

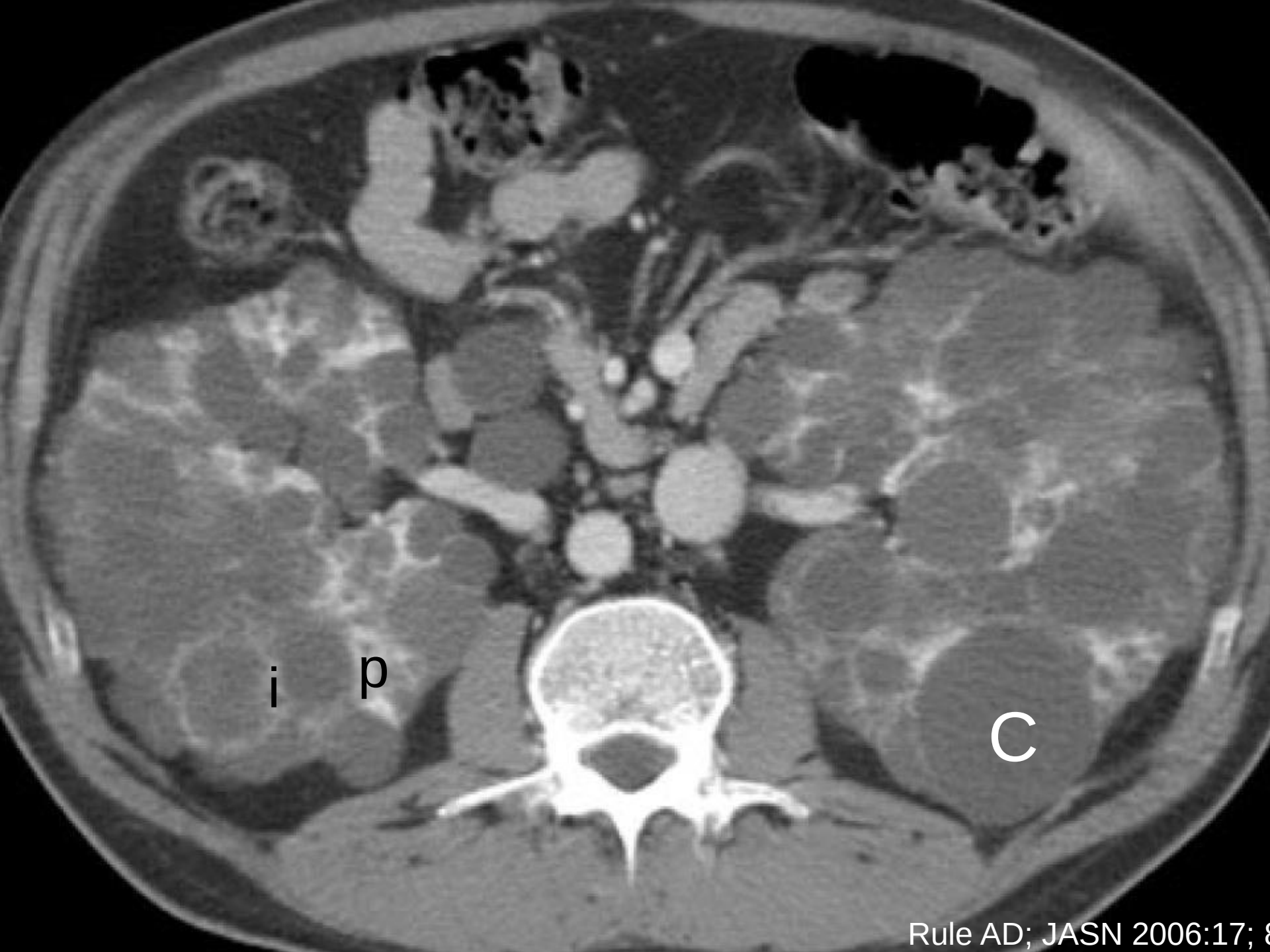
- CRISP
  - Whether kidney/cyst volume changes
    - can be detected over a short period of time
    - and are associated with loss of renal function
  - Prospective observational study
  - Patients with eGFR >70 ml/min

Kidney enlargement is detectable over a short period of time, it is continuous and relatively constant

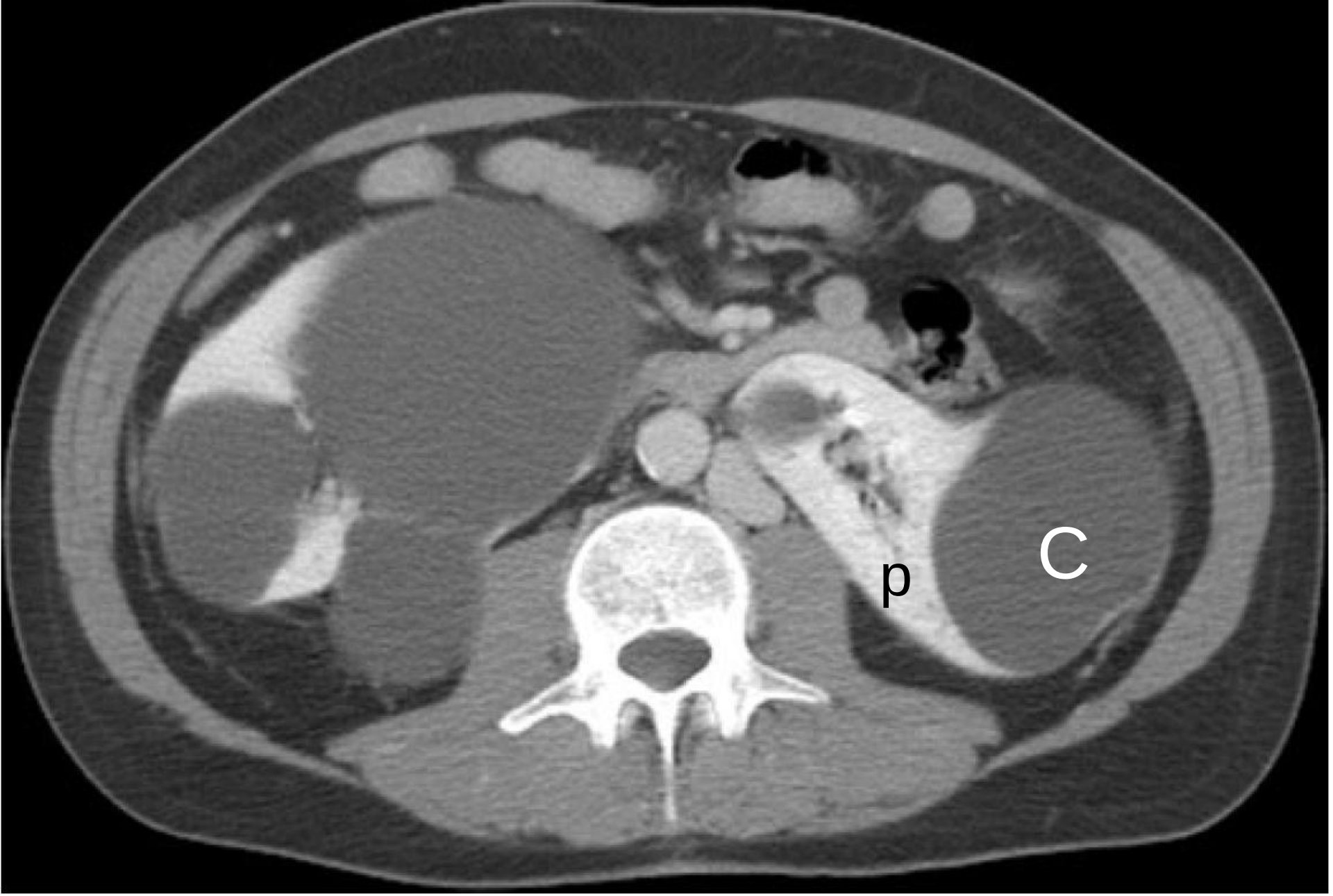




Grantham NEJM 354:2122-2130, 2006



Rule AD; JASN 2006:17; 8

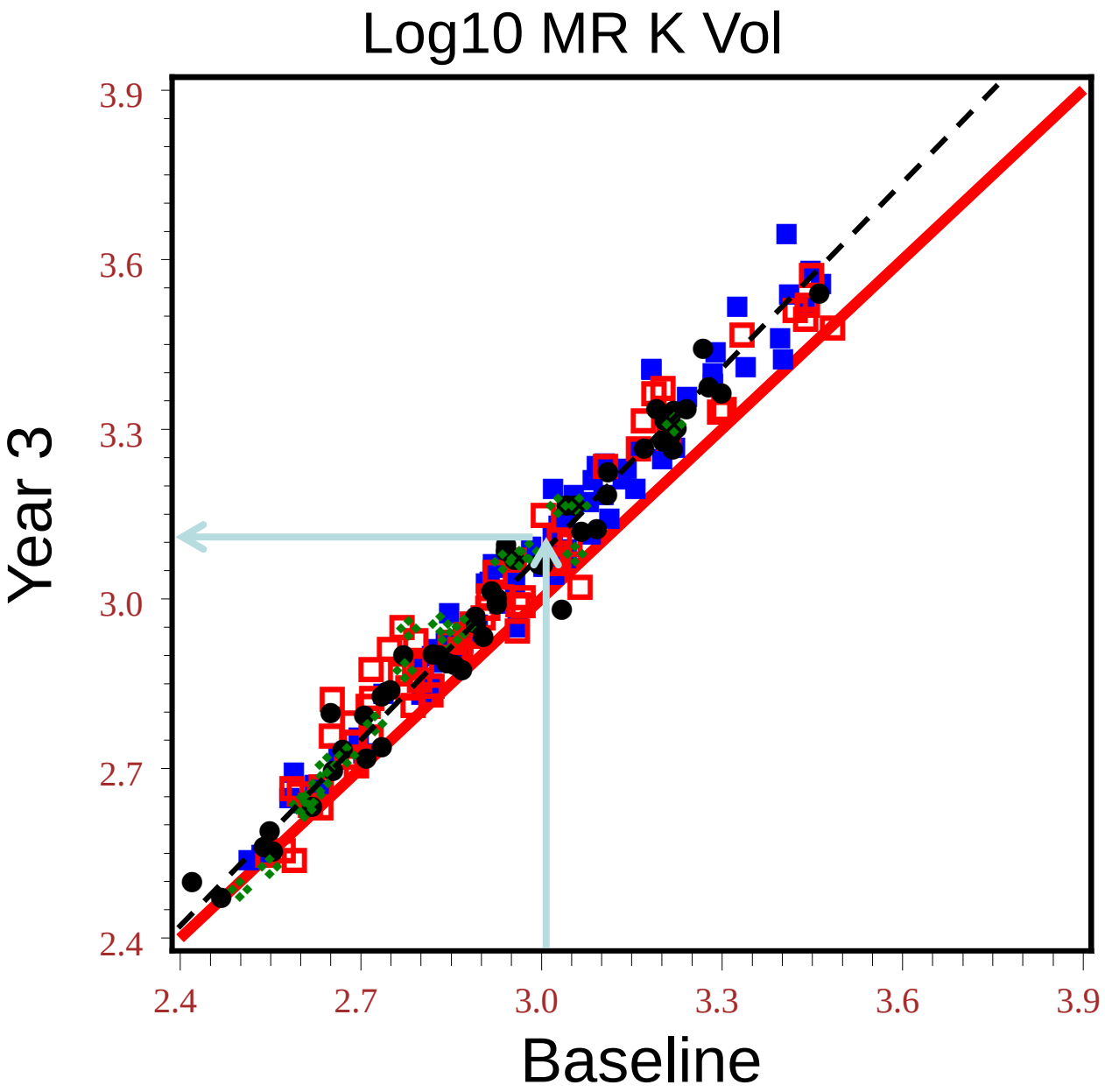


C=cyst P=parenchyma

CT

Rule AD; JASN 2006:17; 854-862

Renal volume predicts rate of enlargement



5.3 % average yearly increase in renal size

Grantham NEJM 354:2122-2130, 2006

CRISP Conclusions

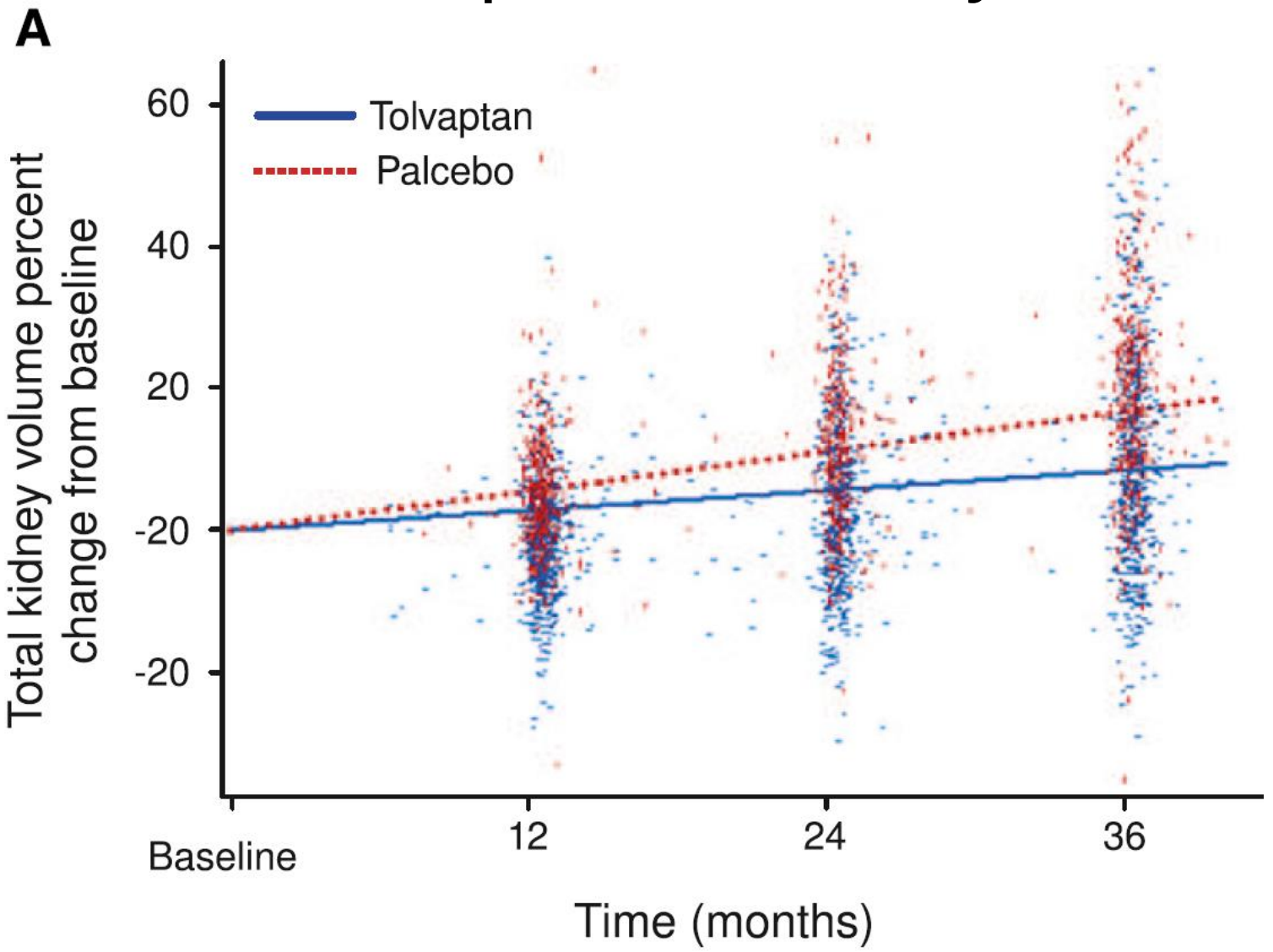
Kidney enlargement is

- Detectable over a short period of time
- A strong predictor of functional progression
- A surrogate endpoint “reasonably likely” to predict clinical benefit in clinical trials

Interventional studies

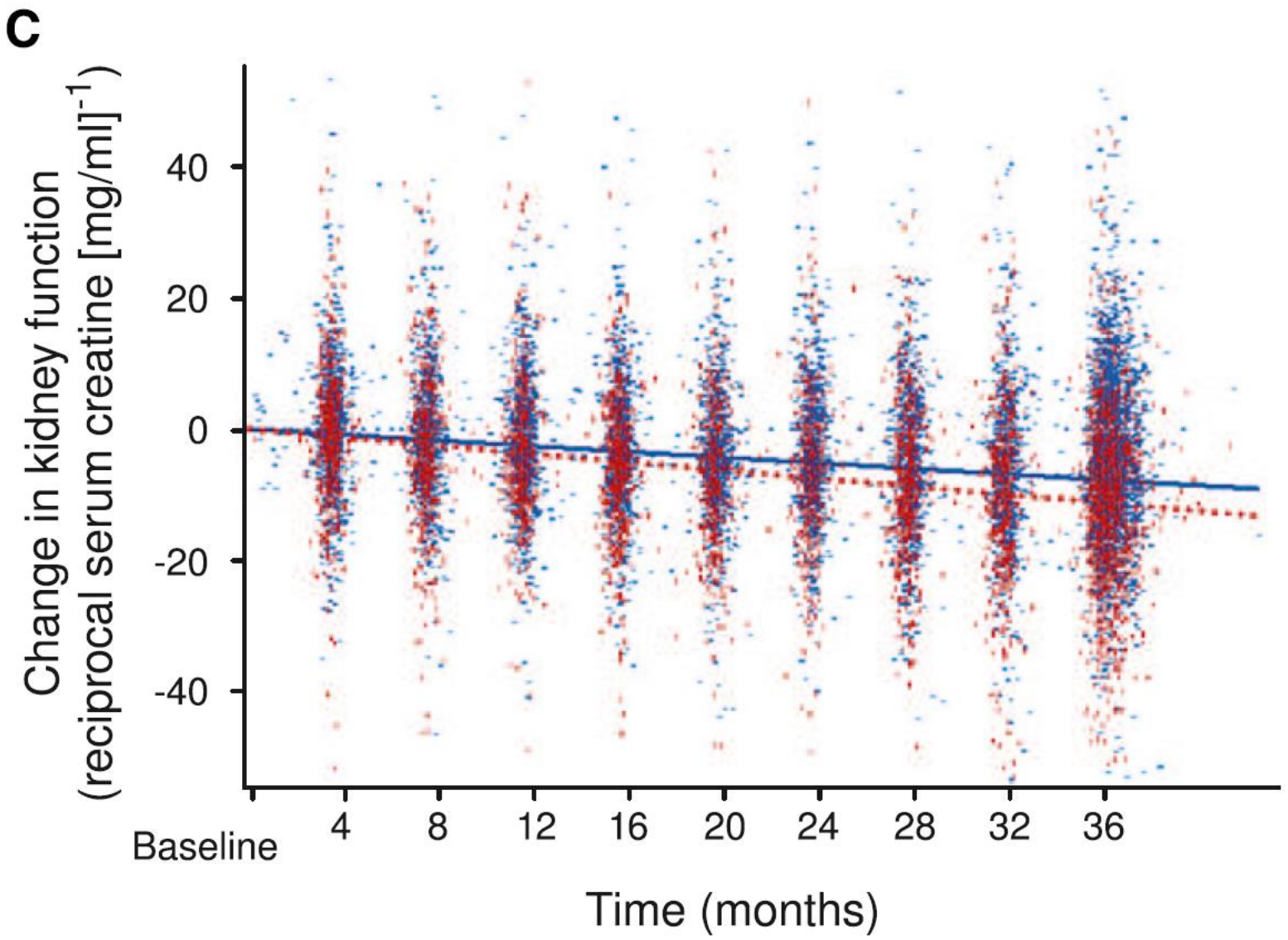
V2 receptor antagonist

Effect of tolvaptan on kidney volume



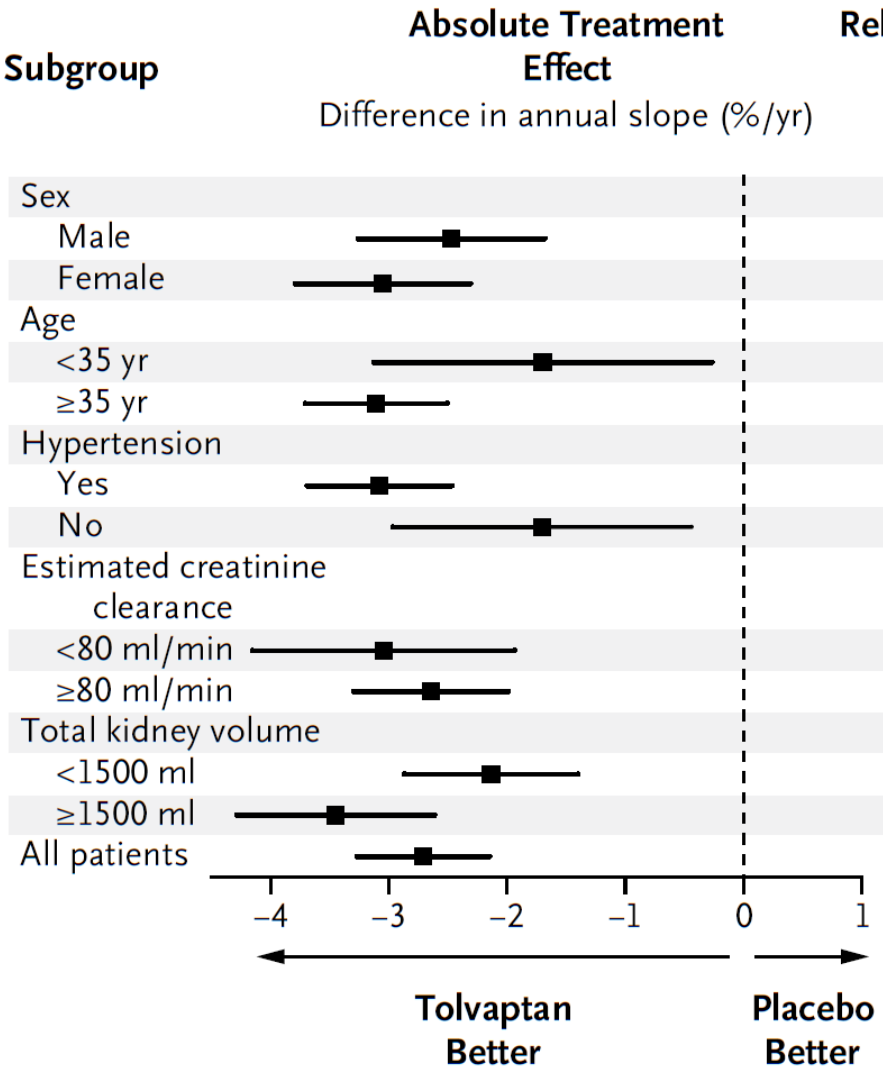
Torres VE et al. N Engl J Med 2012; 367: 2407–2418,

Effect of Tolvaptan on kidney function



Torres VE et al. N Engl J Med 2012; 367: 2407–2418,

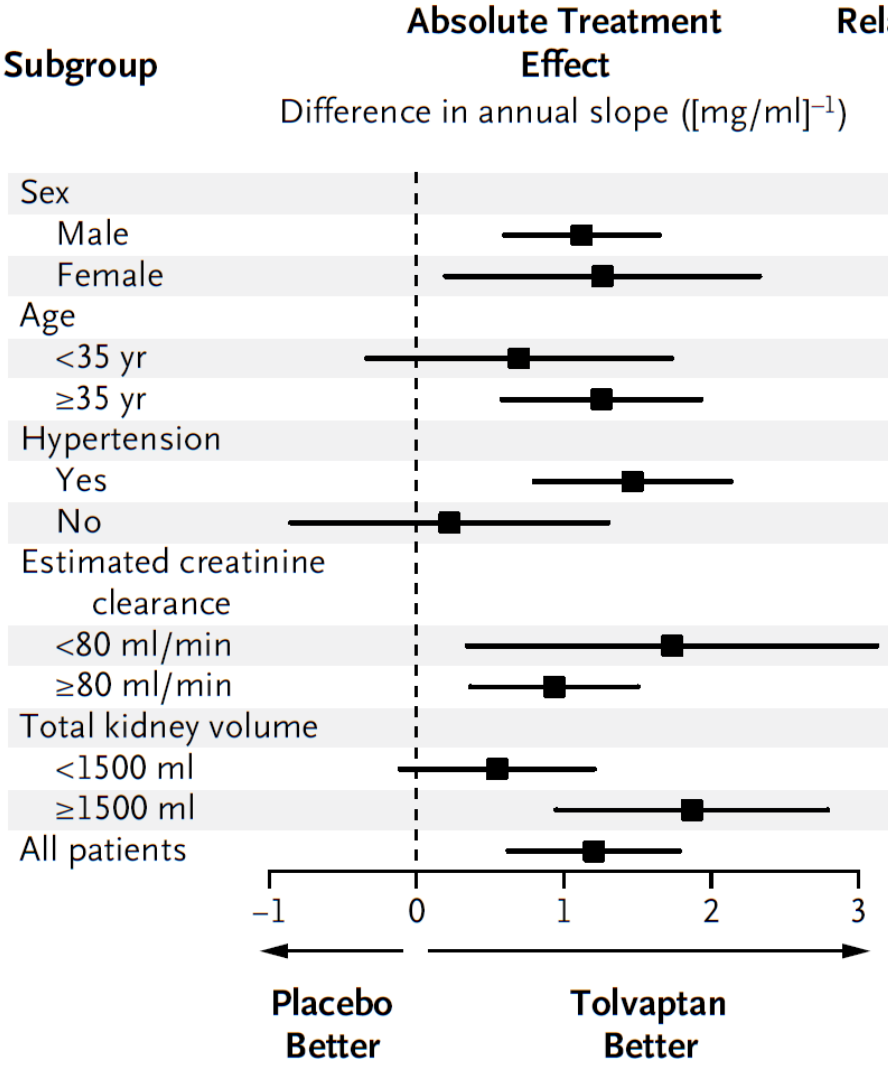
B Treatment Effect for Total Kidney Volume



Subgroup	Relative Treatment Effect	Annual Slope		P Value
	%	Tolvaptan %/yr	Placebo	
Sex				
Male	37.3	4.15	6.62	<0.001
Female	71.1	1.24	4.29	<0.001
Age				
<35 yr	28.0	4.37	6.06	0.02
≥35 yr	58.2	2.23	5.34	<0.001
Hypertension				
Yes	50.5	3.01	6.09	<0.001
No	51.2	1.62	3.32	0.008
Estimated creatinine clearance				
<80 ml/min	57.2	2.27	5.32	<0.001
≥80 ml/min	47.5	2.92	5.56	<0.001
Total kidney volume				
<1500 ml	48.8	2.24	4.37	<0.001
≥1500 ml	51.1	3.29	6.74	<0.001
All patients	49.2	2.80	5.51	<0.001

Torres VE et al. N Engl J Med 2012; 367: 2407–2418,

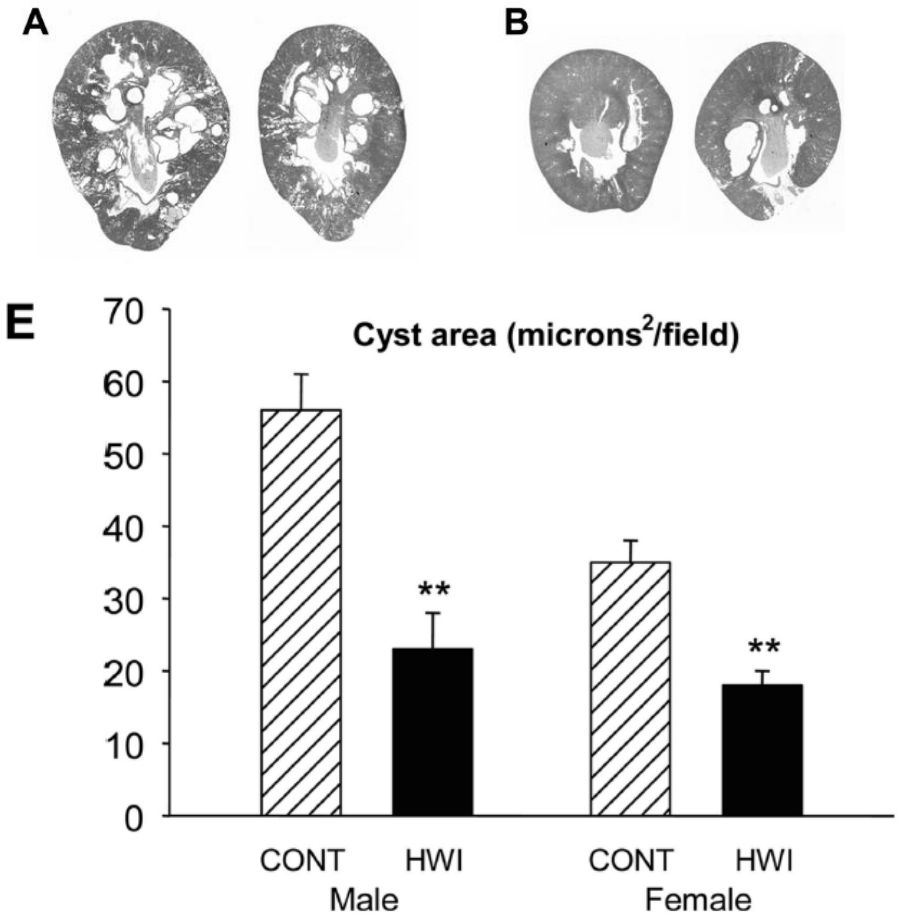
D **Treatment Effect for Kidney Function**



Subgroup	Relative Treatment Effect	Annual Slope		P Value
	%	Tolvaptan (mg/ml)$^{-1}$	Placebo (mg/ml)$^{-1}$	
Sex				
Male	32.1	−2.37	−3.49	<0.001
Female	30.7	−2.85	−4.11	0.02
Age				
<35 yr	26.5	−1.93	−2.62	0.19
≥35 yr	30.6	−2.84	−4.09	<0.001
Hypertension				
Yes	35.0	−2.72	−4.19	<0.001
No	9.6	−2.09	−2.31	0.69
Estimated creatinine clearance				
<80 ml/min	32.0	−3.69	−5.43	0.01
≥80 ml/min	29.7	−2.21	−3.14	0.001
Total kidney volume				
<1500 ml	21.7	−1.97	−2.52	0.10
≥1500 ml	36.6	−3.24	−5.11	<0.001
All patients	31.6	−2.61	−3.81	<0.001

Torres VE et al. N Engl J Med 2012; 367: 2407–2418,

Increased Water Intake Decreases Progression of PKD the Rat

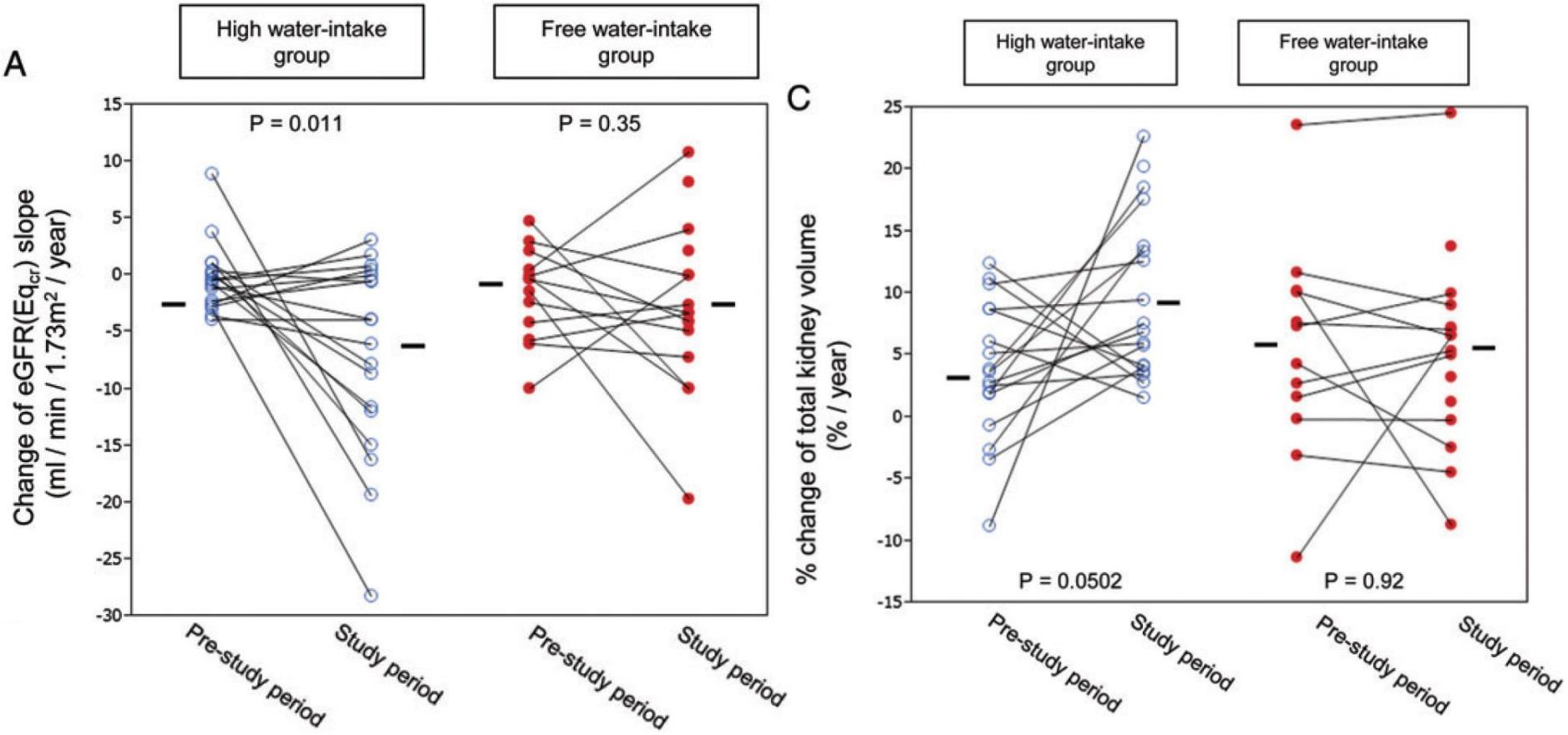


Nagao S et al: J Am Soc Nephrol 17: 2220–2227, 2006.

Does increased water intake prevent disease progression in autosomal dominant polycystic kidney disease?

ndt
Nephrology Dialysis Transplantation

Eiji Higashihara[1,2], Kikuo Nutahara[2], Mitsuhiro Tanbo[2], Hidehiko Hara[2], Isao Miyazaki[3], Kuninori Kobayashi[4] and Toshiaki Nitatori[3]



high water intake enhanced disease progression

Higashihara E et al: Nephrol Dial Transplant (2014) 0: 1–10

Nephrol Dial Transplant (2016) 0: 1–12
doi: 10.1093/ndt/gfv456

ndt
Nephrology Dialysis Transplantation

NDT Perspectives

Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice

Ron T. Gansevoort[1], Mustafa Arici[2], Thomas Benzing[3], Henrik Birn[4,5], Giovambattista Capasso[6], Adrian Covic[7], Olivier Devuyst[8,9], Christiane Drechsler[10], Kai-Uwe Eckardt[11], Francesco Emma[12], Bertrand Knebelmann[13], Yannick Le Meur[14], Ziad A. Massy[15,16,17], Albert C.M. Ong[18], Alberto Ortiz[19], Franz Schaefer[20], Roser Torra[21,22], Raymond Vanholder[23], Andrzej Więcek[24], Carmine Zoccali[25] and Wim Van Biesen[23]

Pillars of decision making

- European Medicines Agency EMA approved the use of the tolvaptan in ADPKD
  - with chronic kidney disease stages 1–3 at initiation of treatment
  - to slow the progression of cyst development and renal insufficiency
- with evidence of rapidly progressing disease

Pillars of decision making
ERA-EDTA recommendations

- series of recommendations
  - hierarchical decision algorithm
  - a sequence of risk-factor assessments in a descending order of reliability
- to select patients who are most likely to benefit from tolvaptan
  - improving the benefit-to-risk ratio and
  - cost-effectiveness of this treatment

Pillars of decision making

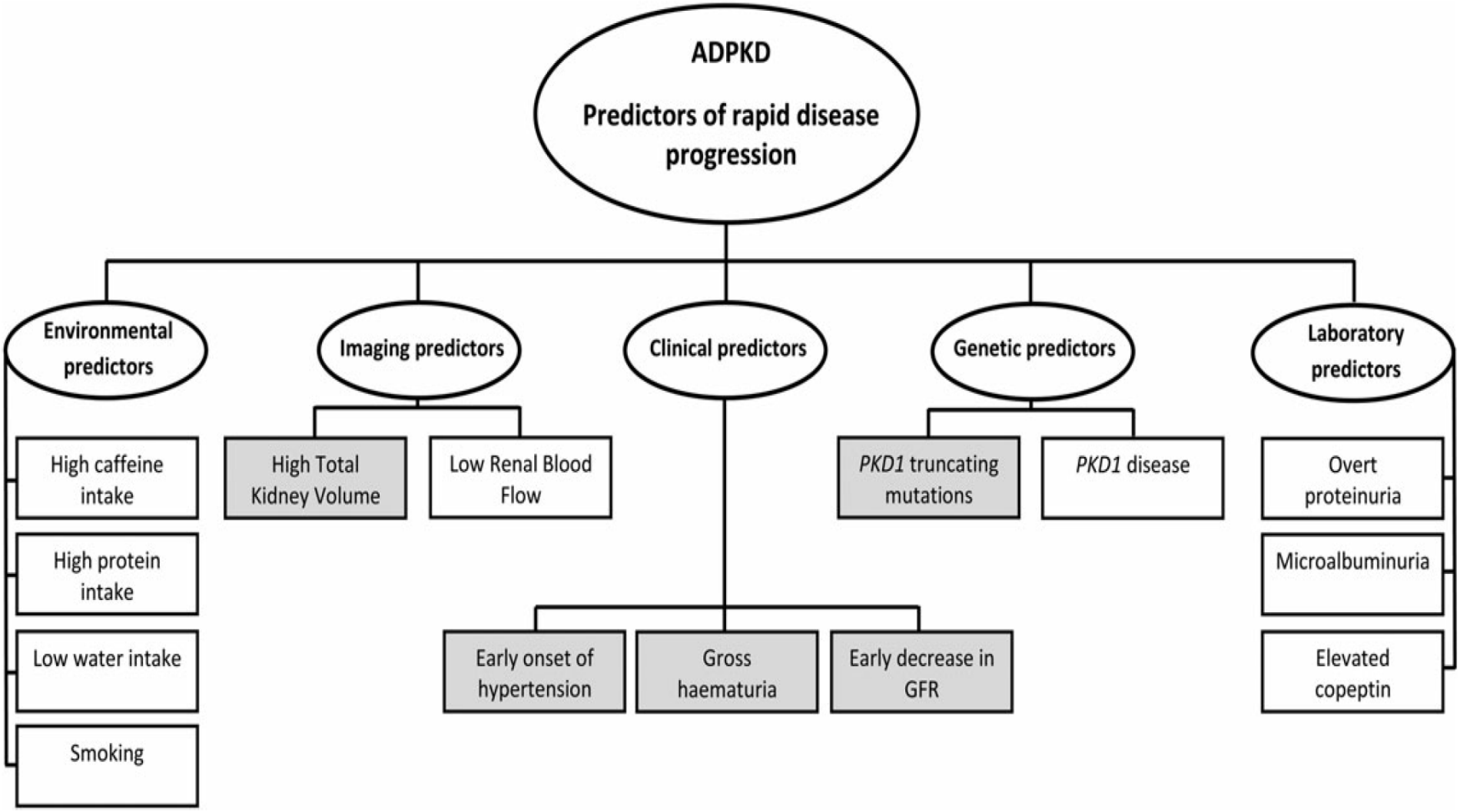
DOCUMENTED/Predicted progression of kidney function

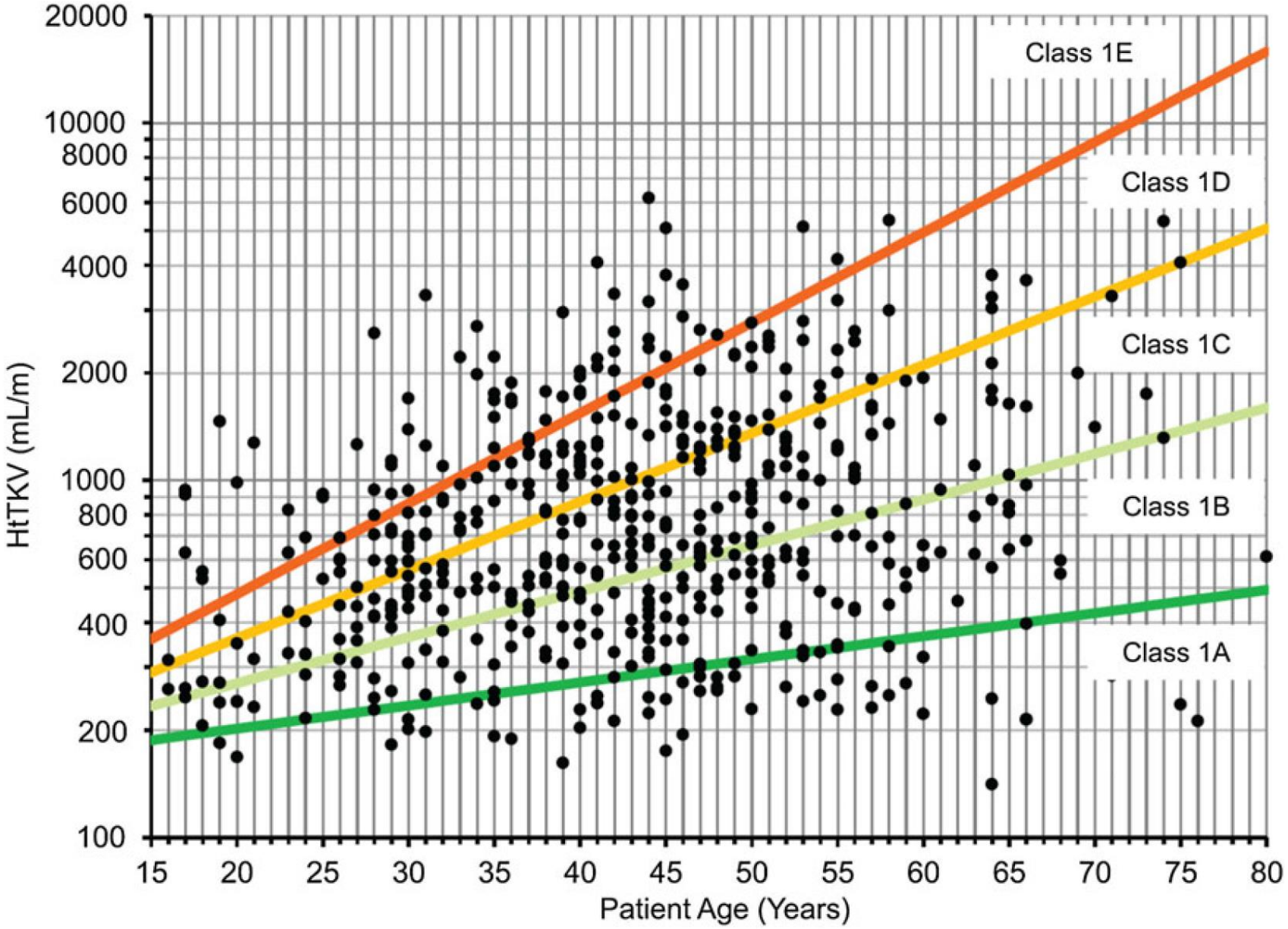
- Serial creatinine and eGFR determinations
- Prediction based on age and GFR based tables

DOCUMENTED/Predicted progression of kidney volume

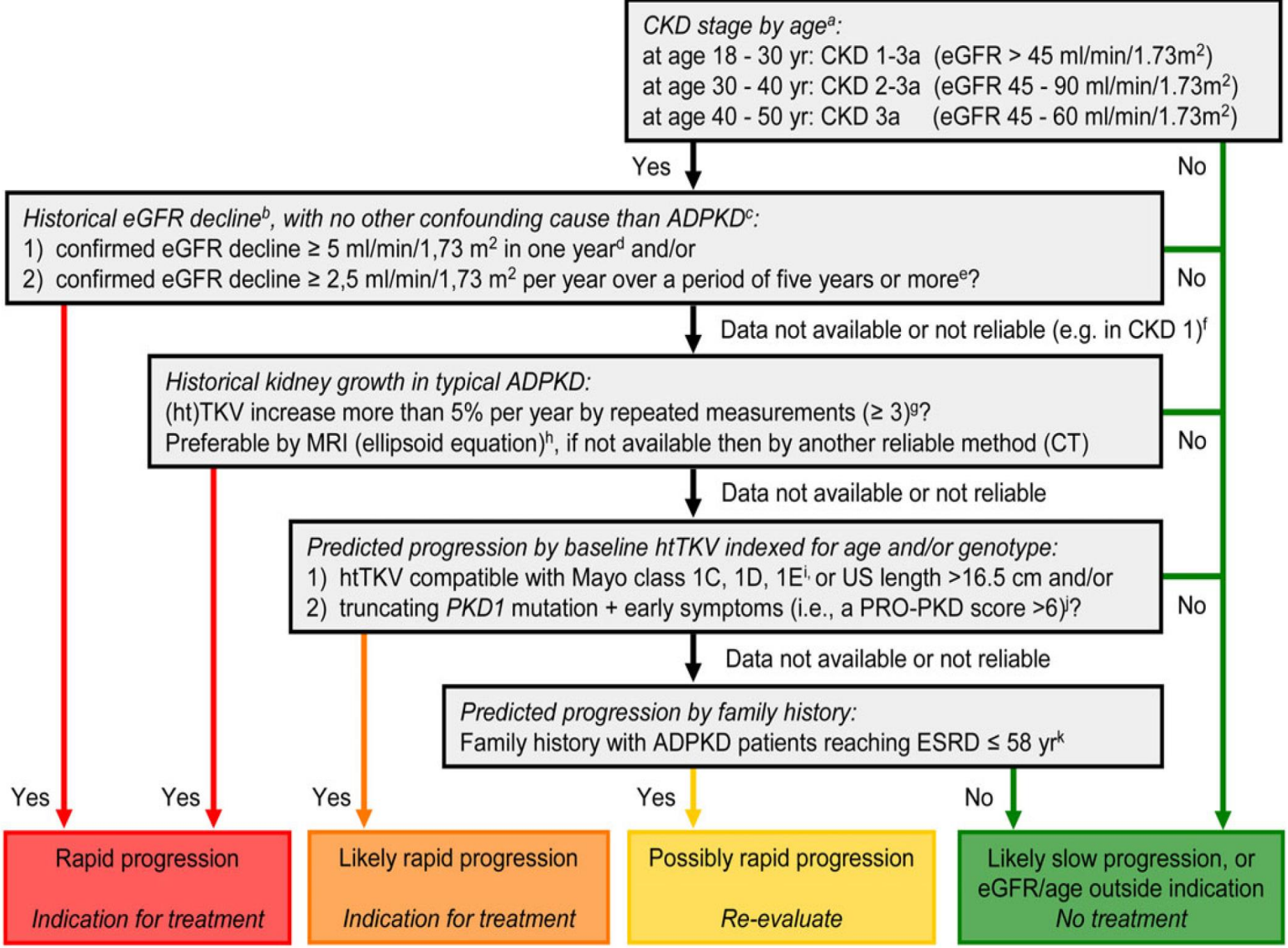
- Serial TKV/h measurements
- Prediction based on age and TKV/h based tables
- <45 years and a kidney length of >16.5 cm as assessed by ultrasound, rapid disease progression is likely.

- Further risk factors of progression


ADPKD
Predictors of rapid disease progression
Environmental predictors
Imaging predictors
Clinical predictors
Genetic predictors
Laboratory predictors
High caffeine intake
High protein intake
Low water intake
Smoking
High Total Kidney Volume
Low Renal Blood Flow
Early onset of hypertension
Gross haematuria
Early decrease in GFR
PKD1 truncating mutations
PKD1 disease
Overt proteinuria
Microalbuminuria
Elevated copeptin



The Mayo classification. (J Am Soc Nephrol 2015; 26: 160–172)


CKD stage by age[a]:
at age 18 - 30 yr: CKD 1-3a (eGFR > 45 ml/min/1.73m²)
at age 30 - 40 yr: CKD 2-3a (eGFR 45 - 90 ml/min/1.73m²)
at age 40 - 50 yr: CKD 3a (eGFR 45 - 60 ml/min/1.73m²)
Yes
No
Historical eGFR decline[b], with no other confounding cause than ADPKD[c]:
1) confirmed eGFR decline ≥ 5 ml/min/1,73 m² in one year[d] and/or
2) confirmed eGFR decline ≥ 2,5 ml/min/1,73 m² per year over a period of five years or more[e]?
No
Data not available or not reliable (e.g. in CKD 1)[f]
Historical kidney growth in typical ADPKD:
(ht)TKV increase more than 5% per year by repeated measurements (≥ 3)[g]?
Preferable by MRI (ellipsoid equation)[h], if not available then by another reliable method (CT)
No
Data not available or not reliable
Predicted progression by baseline htTKV indexed for age and/or genotype:
1) htTKV compatible with Mayo class 1C, 1D, 1E[i], or US length >16.5 cm and/or
2) truncating PKD1 mutation + early symptoms (i.e., a PRO-PKD score >6)[j]?
No
Data not available or not reliable
Predicted progression by family history:
Family history with ADPKD patients reaching ESRD ≤ 58 yr[k]
Yes
Yes
Yes
Yes
No
Rapid progression
Indication for treatment
Likely rapid progression
Indication for treatment
Possibly rapid progression
Re-evaluate
Likely slow progression, or eGFR/age outside indication
No treatment

Recommendations 1

Recommendation 1.1:

We suggest that tolvaptan can be prescribed to adult ADPKD patients aged <50 years with CKD stages 1–3a (eGFR >45 mL/min/1.73 m2) who have demonstrated or who are likely to have rapidly progressing disease, but that CKD stage must be interpreted in conjunction with age.

Recommendation 1.2:

We recommend not starting tolvaptan in patients aged 30–40 years with CKD stage 1 (eGFR >90 mL/min/1.73 m¸).

Recommendation 1.3:

We recommend not starting tolvaptan

in patients aged 40–50 years with CKD stages 1 or 2

(eGFR >60 mL/min/1.73 m2).

Recommendation 2-3

Recommendation 2:

- A confirmed annual eGFR decline ≥5 mL/min/1.73 m2 in 1 year, and/or
- ≥2.5 mL/min/1.73m2 per year over a period of 5 years, defines rapid progression

Recommendation 3:

A TKV increase of >5% per year by repeated measurements (preferably three or more, each at least 6 months apart and by MRI), defines rapid progression progression

Recommendation 4

Recommendation 4.1:

We recommend the use of the Mayo classification of ADPKD […] for age and height to define five classes of patients according to prognosis (1A–1E).

Recommendation 4.2:

We suggest that in ADPKD patients with Mayo classes 1C–1E disease (corresponding to a predicted eGFR decrease ≥2.5 mL/min/1.73 m˛ per year),

rapid disease progression is likely.

[…]

Recommendation 4.4:

We suggest that in a patient with age <45 years and a kidney length of >16.5 cm as assessed by ultrasound, rapid disease progression is likely.

Summary 1

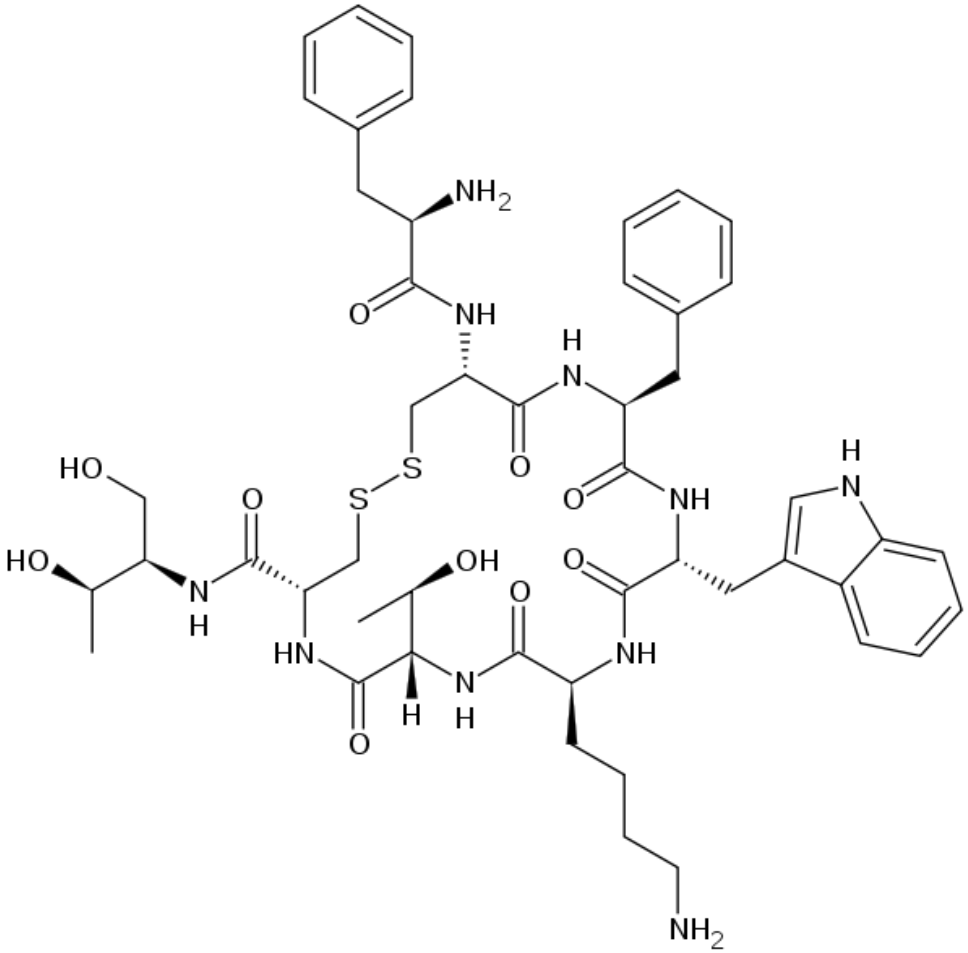
- Tolvaptan is the first pharmaceutical treatment approved to
- slow disease progression in ADPKD.
  - Given the side effect profile and for cost reasons, it is necessary to identify patients most likely to benefit from this drug.
  - A hierarchical decision algorithm should be adopted to assess whether treatment is warranted

Interventional studies

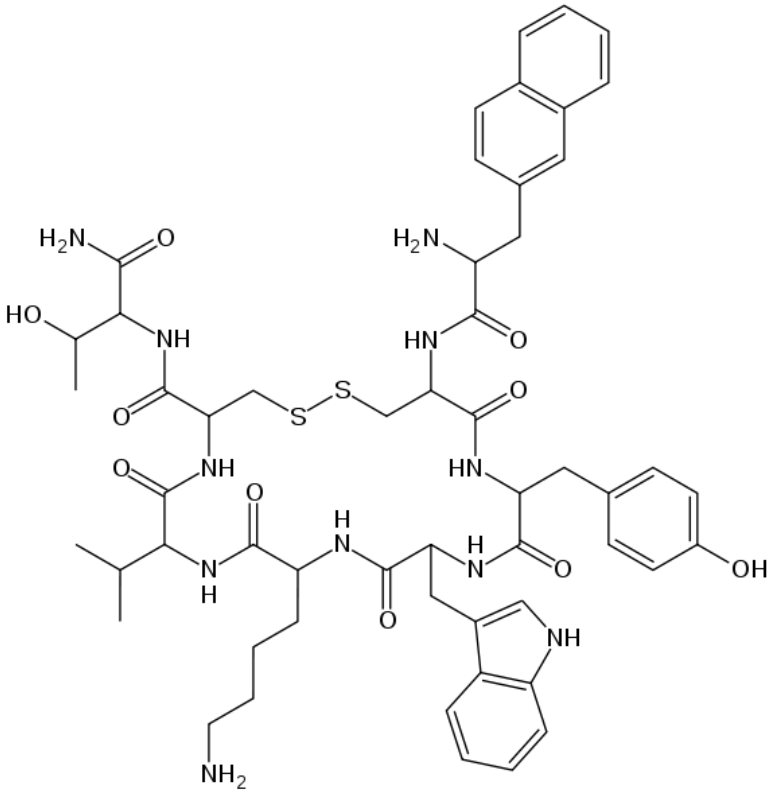
- Somatostatin analogues
- mTOR inhibitors
- ACEI-ARB

Somatostatin analogues

Octreotide (Sandostatin)



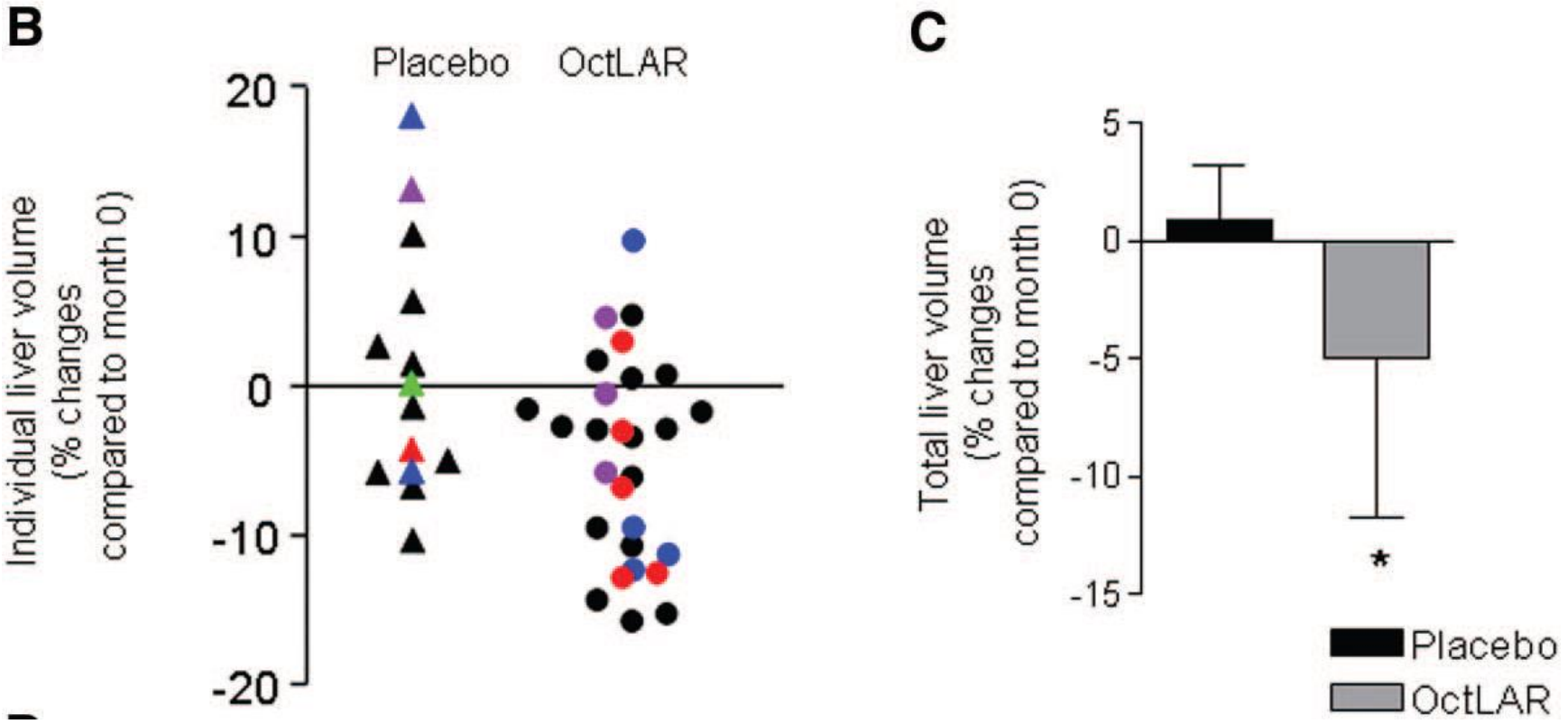
Lanreotide (Somatuline LA and Depot)



Randomized Clinical Trial of Long-Acting Somatostatin for Autosomal Dominant Polycystic Kidney and Liver Disease

LAR 40 mg IM every 4 weeks for 2 years

LIVER



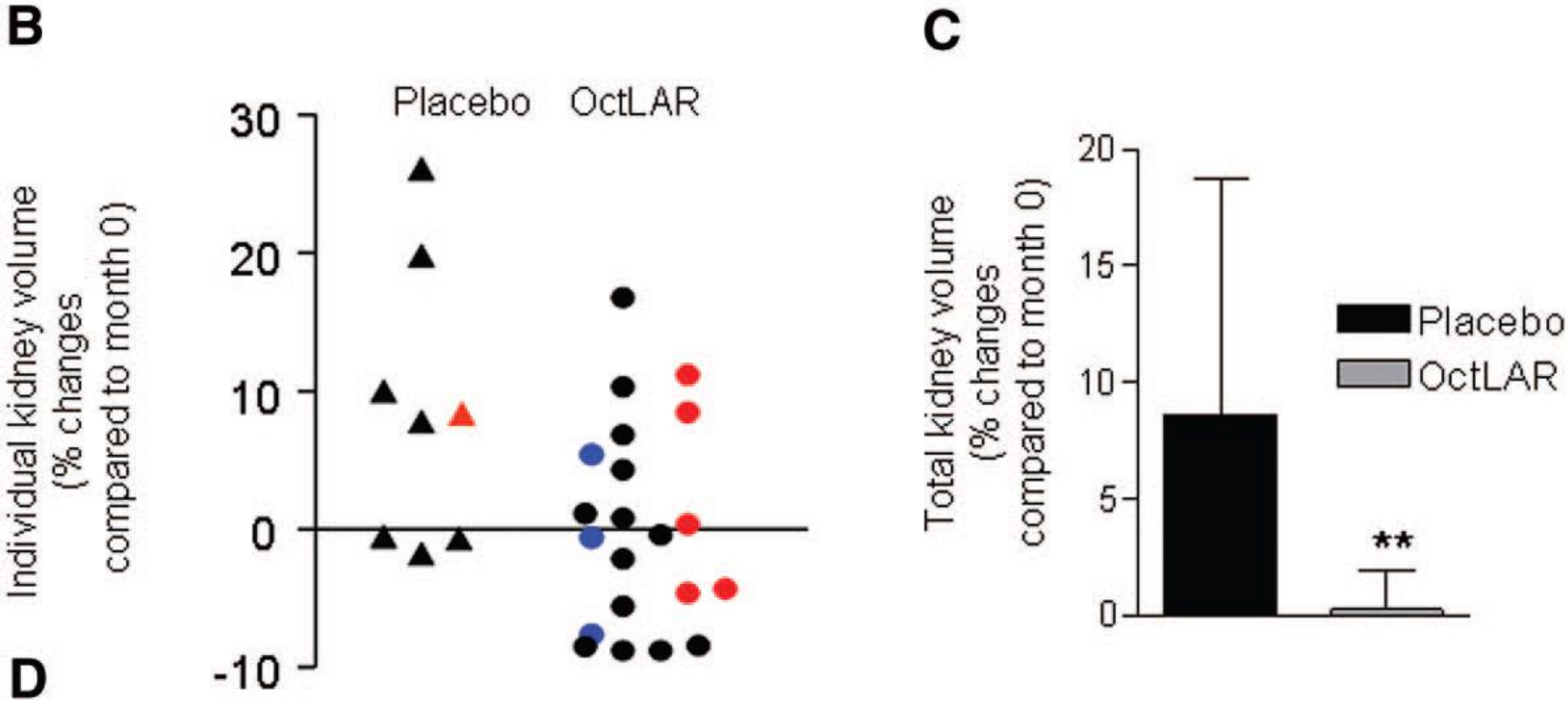
N=42
Liver volume >4000 mL

J Am Soc Nephrol 21: 1052–1061, 2010.

Randomized Clinical Trial of Long-Acting Somatostatin for Autosomal Dominant Polycystic Kidney and Liver Disease

LAR 40 mg IM every 4 weeks for 2 years

KIDNEY



N=42
Liver volume >4000 mL

J Am Soc Nephrol 21: 1052–1061, 2010.

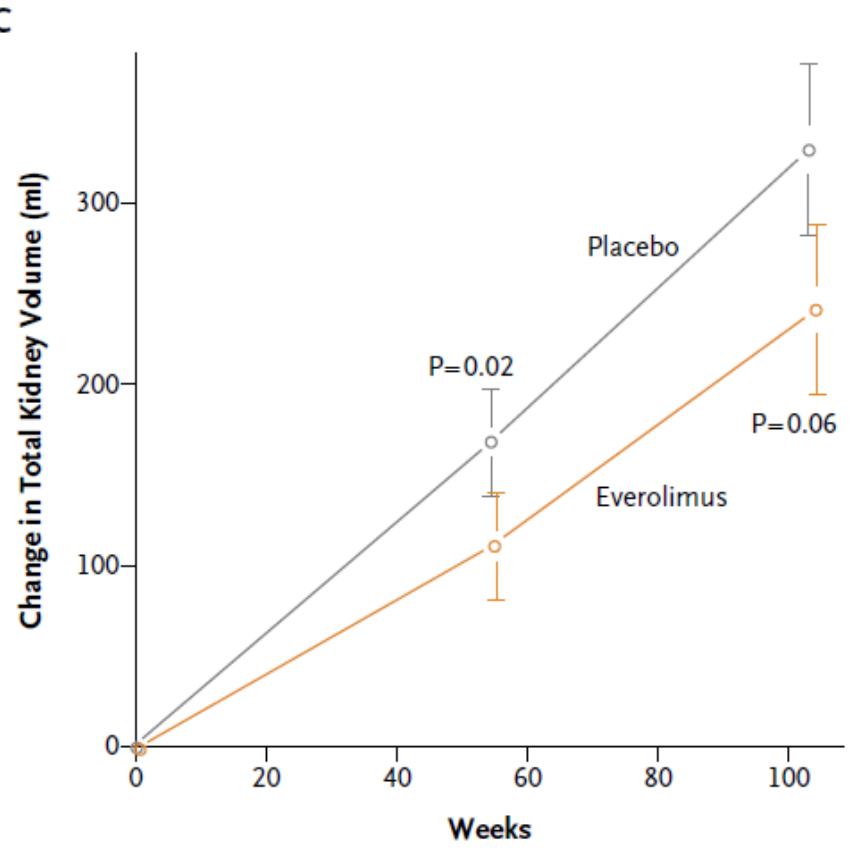
Interventional studies

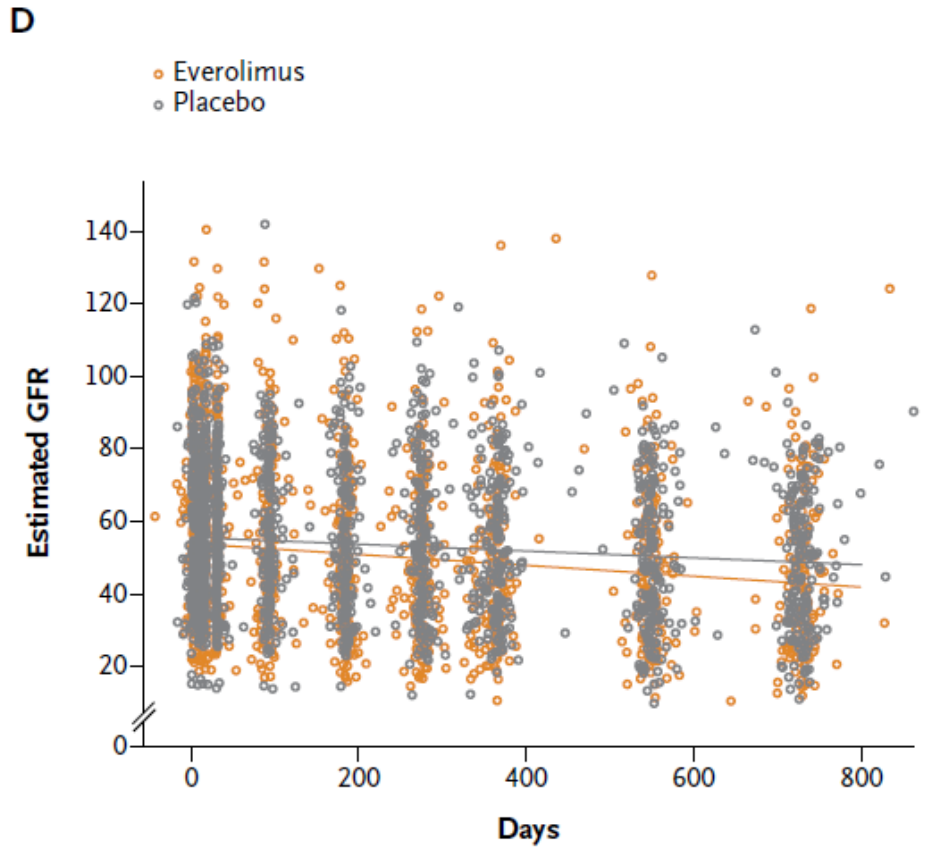
mTOR inhibitors

Sirolimus

Everolimus

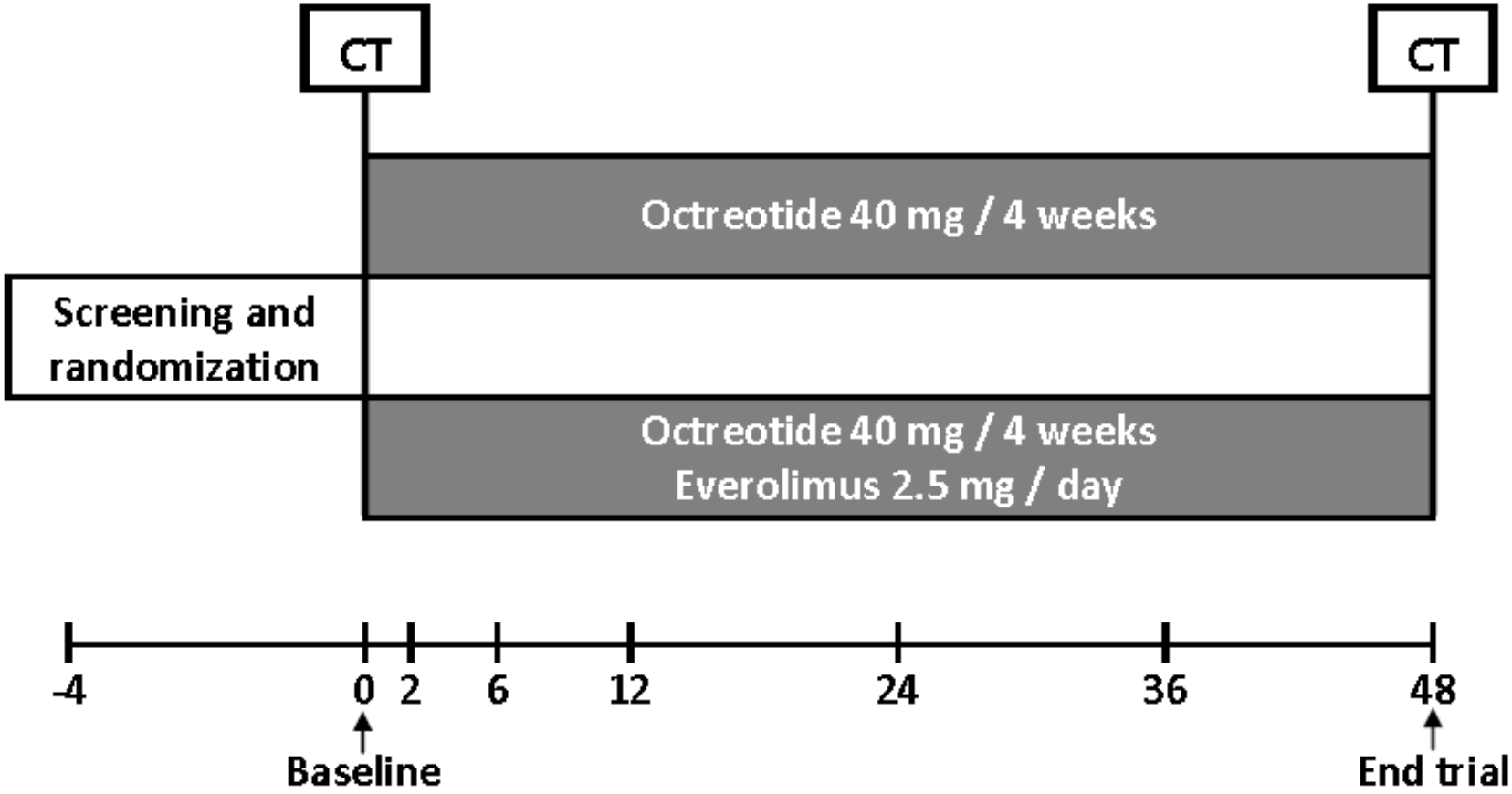
Everolimus in Patients with Autosomal Dominant Polycystic Kidney Disease





N Engl J Med 2010;363:830-40.

Everolimus and long acting octreotide as a volume reducing treatment of polycystic livers (ELATE): study protocol for a randomized controlled trial

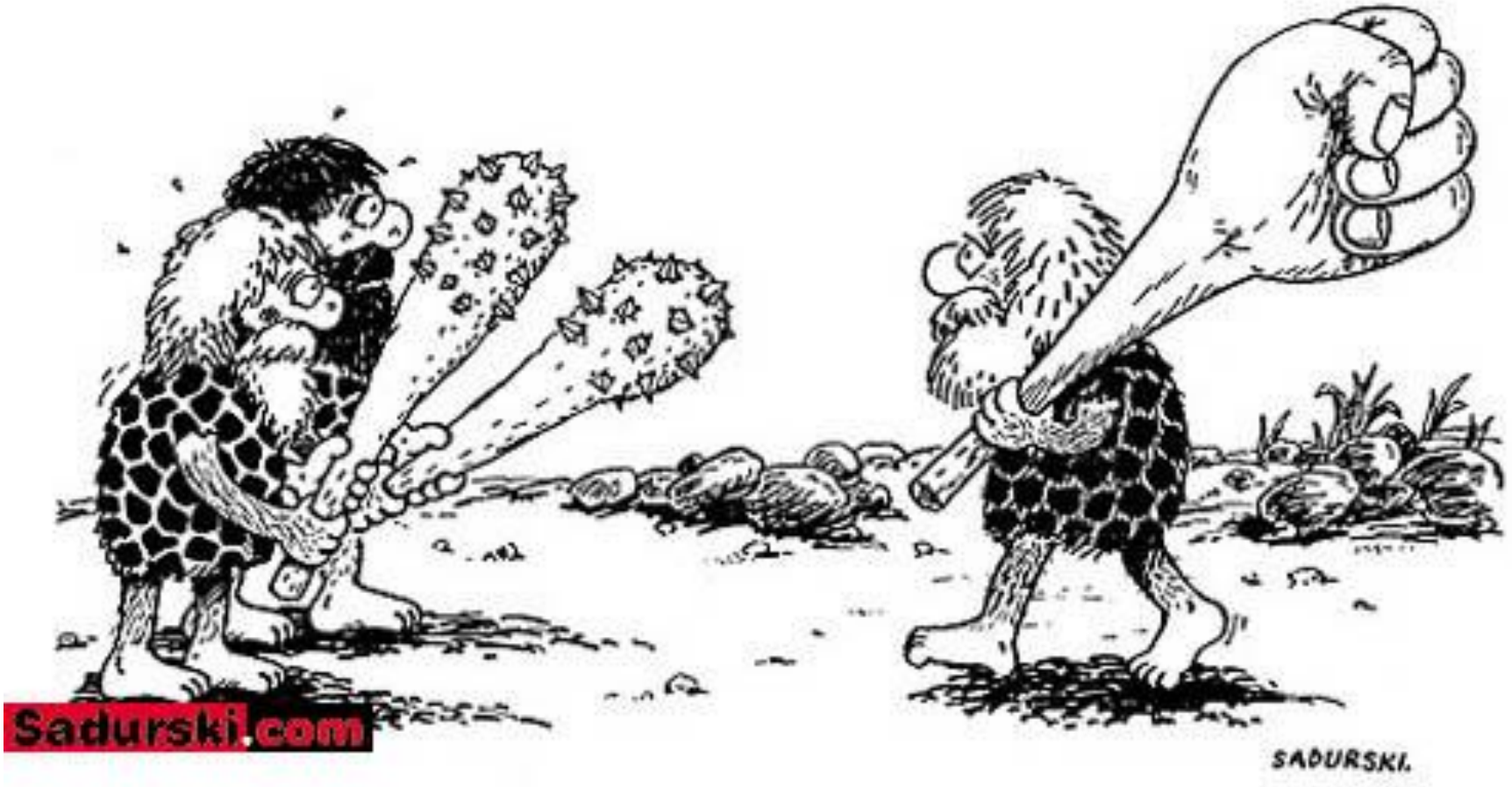


ClinicalTrials.gov: NCT01157858

Chrispijn and Drenth Trials 2011, 12:246

Conclusions

- Promising results of interventional studies
- Still to be answered:
  - When should we intervene?
  - Potential side effects of life-long treatment
    - Mutagenic, cancerogenic immunosuppressive
- Known complications
  - Hypertension, LVH, nephrolithiasis, bleeding, UTI, cerebral aneurisms
  - should be monitored closely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