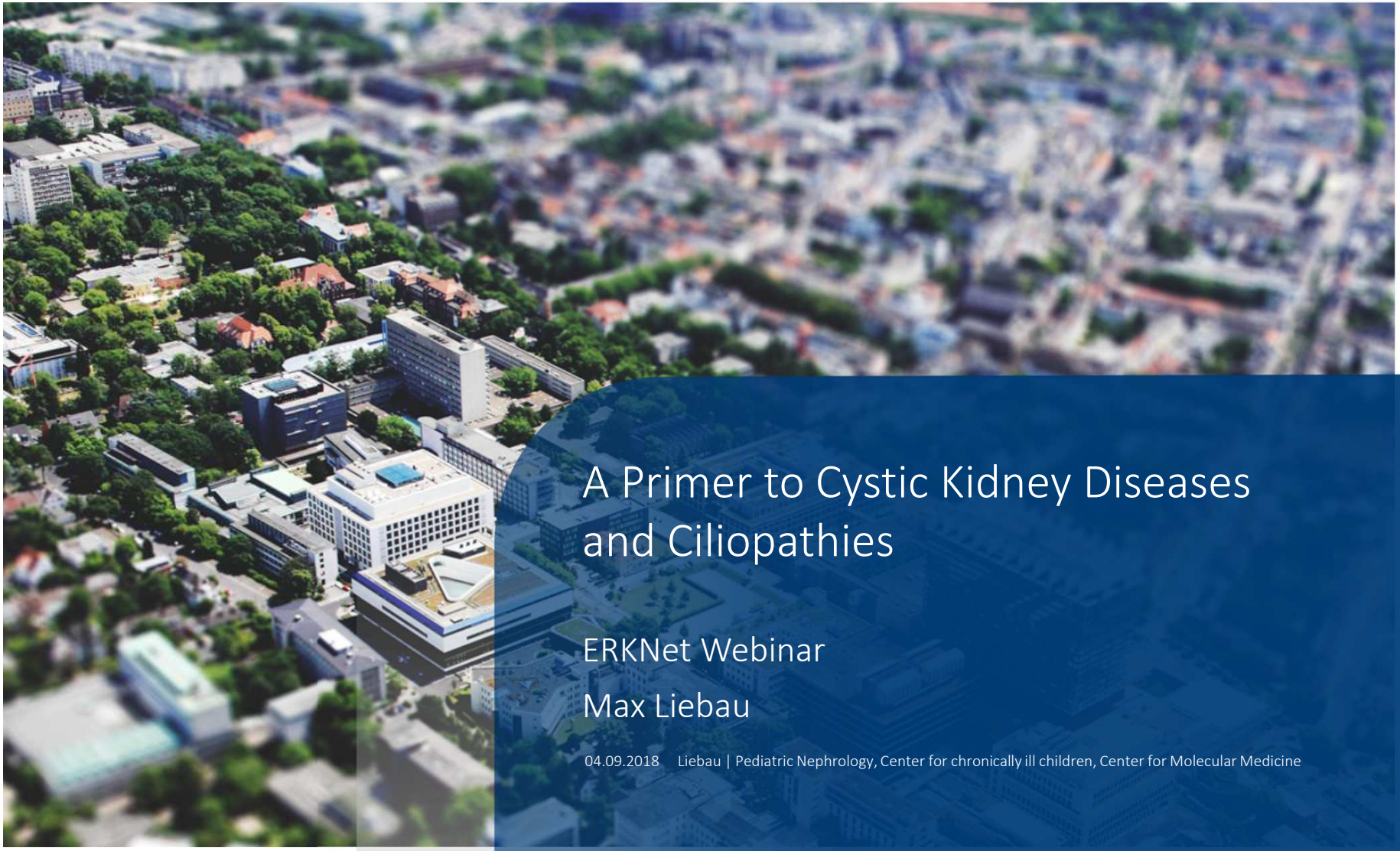
UNIKLINIK
KÖLN



A Primer to Cystic Kidney Diseases and Ciliopathies

ERKNet Webinar

Max Liebau

04.09.2018 Liebau | Pediatric Nephrology, Center for chronically ill children, Center for Molecular Medicine

ERKNet

The European
Rare Kidney Disease
Reference Network

WG CAKUT and Ciliopathies

Head of Experimental Pediatric Nephrology
Head of Interdisciplinary Center for Chronically Ill Children

Department of Pediatrics and
Center for Molecular Medicine,
University Hospital of Cologne, Germany

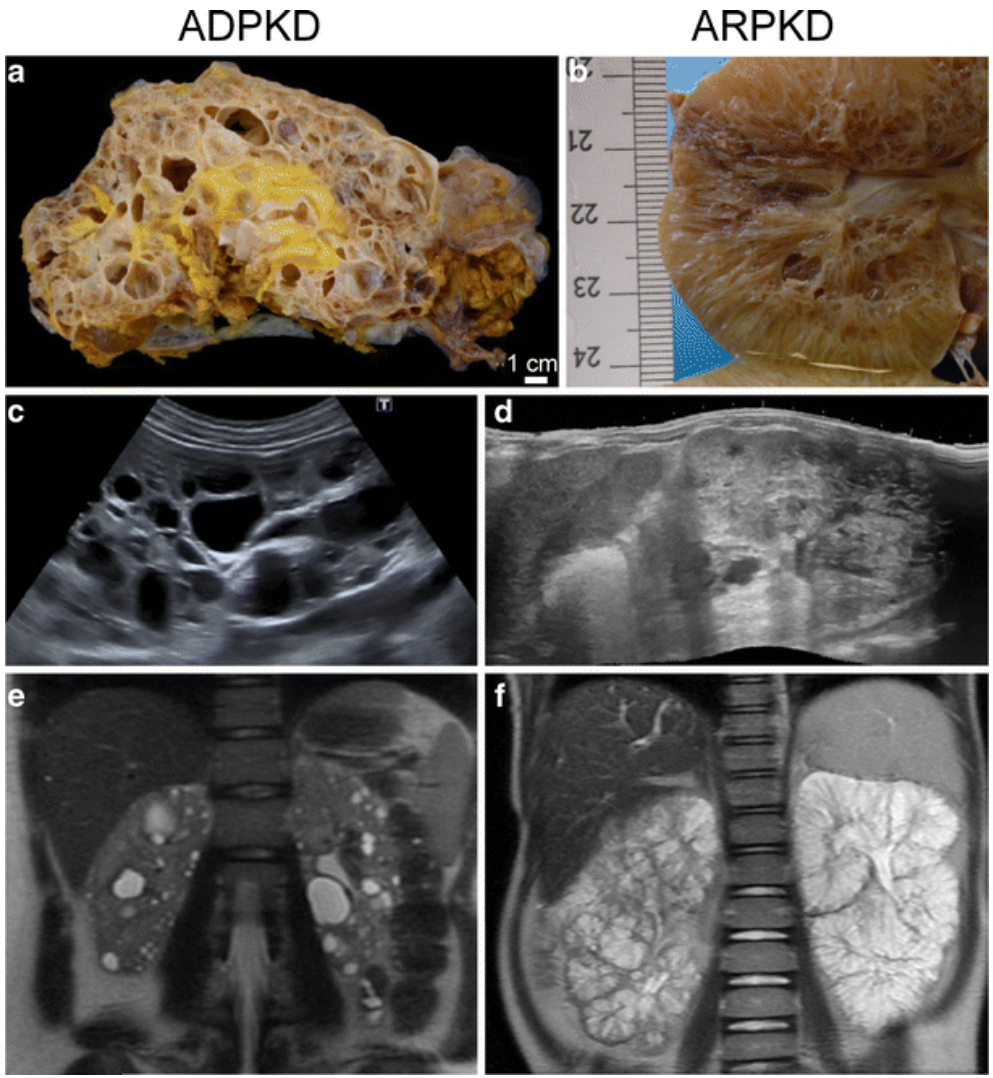
CMMC CENTER FOR MOLECULAR MEDICINE COLOGNE

UNIKLINIK KÖLN

A cyst in a kidney…

A cyst is a fluid-filled cavity lined with epithelium.

„Kidney cyst“ ⟷ „Cystic kidney“

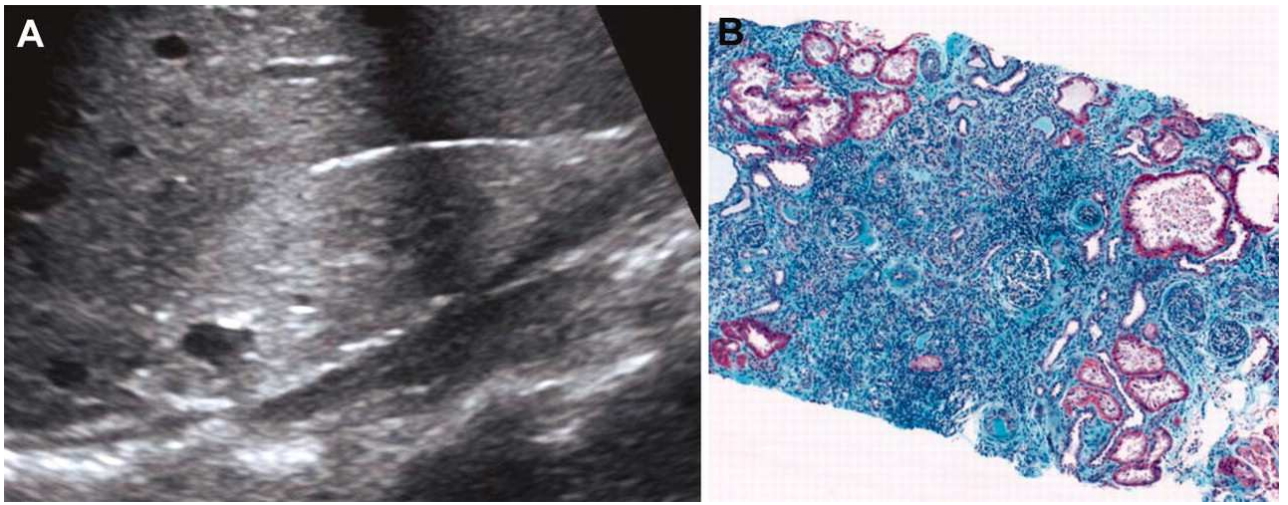


Liebau & Serra
Pediatr Nephrol, 2013

	ARPKD	ADPKD
Main genes	*PKHD1, DZIP1L*	*PKD1, PKD2, GANAB, DNAJB11*
Incidence	1:20.000	1:500-1:1000
Main clinical manifestations	CKD. Arterial hypertension. Hyponatremia. Neonatal respiratory distress/failure due to pulmonary hypoplasia. Congenital hepatic fibrosis and portal hypertension.	CKD. Arterial hypertension. Hematuria. UTIs. Pain. Polycystic liver disease. (…)
Risk for siblings	25%	50% (except in cases of spontaneous mutation with virtually no risk)
Risk for own children	<1% (unless unaffected parent is related to affected partner, or ARPKD is known in the unaffected partner's family)	50% (also for patients with spontaneous mutations)
Parental kidneys	No alterations	Usually one affected parent (unless parents are <30 yrs or in case of spontaneous mutation)
Prognosis	~50% ESRD in first two decades Substantial mortality in patients with neonatal respiratory distress. Severe complications due to portal hypertension.	Median age of ESRD: 58 yrs (PKD1) vs. 79 yrs (PKD2)

Nephronophthisis

- Most common genetic cause of ESRD in the first three decades of life
- Caused by mutations in more than 25 genes
- Classic clinical presentation with polyuria and/or loss of GFR in children



Hildebrandt et al., *JASN* 2009

	Disease entity	Phenotype: Renal manifestations	Phenotype: Extrarenal manifestations	Affected genes	
PKD complex	Autosomal Dominant Polycystic Kidney Disease (ADPKD)	enlarged kidneys with numerous ubiquitous macrocysts	- hepatic, splenic and pancreatic cysts - cardiac valve abnormalities - intracranial aneurysms	*PKD1* and *PKD2*	Phenotypic and genotypic overlap
PKD complex	Autosomal Recessive Polycystic Kidney Disease (ARPKD)	enlarged hyperechogenic kidneys with microcysts	- ductal plate malformation/congenital hepatic fibrosis - pulmonary hypoplasia	*PKHD1*	
NPH-MKS-complex	Isolated nephronophthisis	hyperechogenic kidneys with normal or reduced size and corticomedullar cysts	- none	*NPHP1-18, MKS 1-12, JBTS 1-22*	
NPH-MKS-complex	Senior-Løken Syndrome	nephronophthisis	- retinitis pigmentosa		
NPH-MKS-complex	Joubert Syndrome	nephronophthisis (renal symptoms may be absent)	- cerebellar vermis hypoplasia - ataxia, muscular hypotonia and psychomotor delay - retinal dystrophia - liver fibrosis		
NPH-MKS-complex	Meckel-Gruber-Syndrome	enlarged cystic kidneys	- progressive retinal degeneration - occipital encephalocele - severe psychomotor delay - liver fibrosis - hexadactyly		
BBS-complex	Bardet-Biedl-Syndrome	cystic kidney disease	- progressive retinal degeneration - postaxial polydactyly - obesity and hypogonadism - anosmia and ataxia	*BBS1-20*	

Figure 1 Clinical synopsis of the main disease entities and overview over the affected genes.

Habbig und Liebau,
Mol Cell Pediatrics, 2015

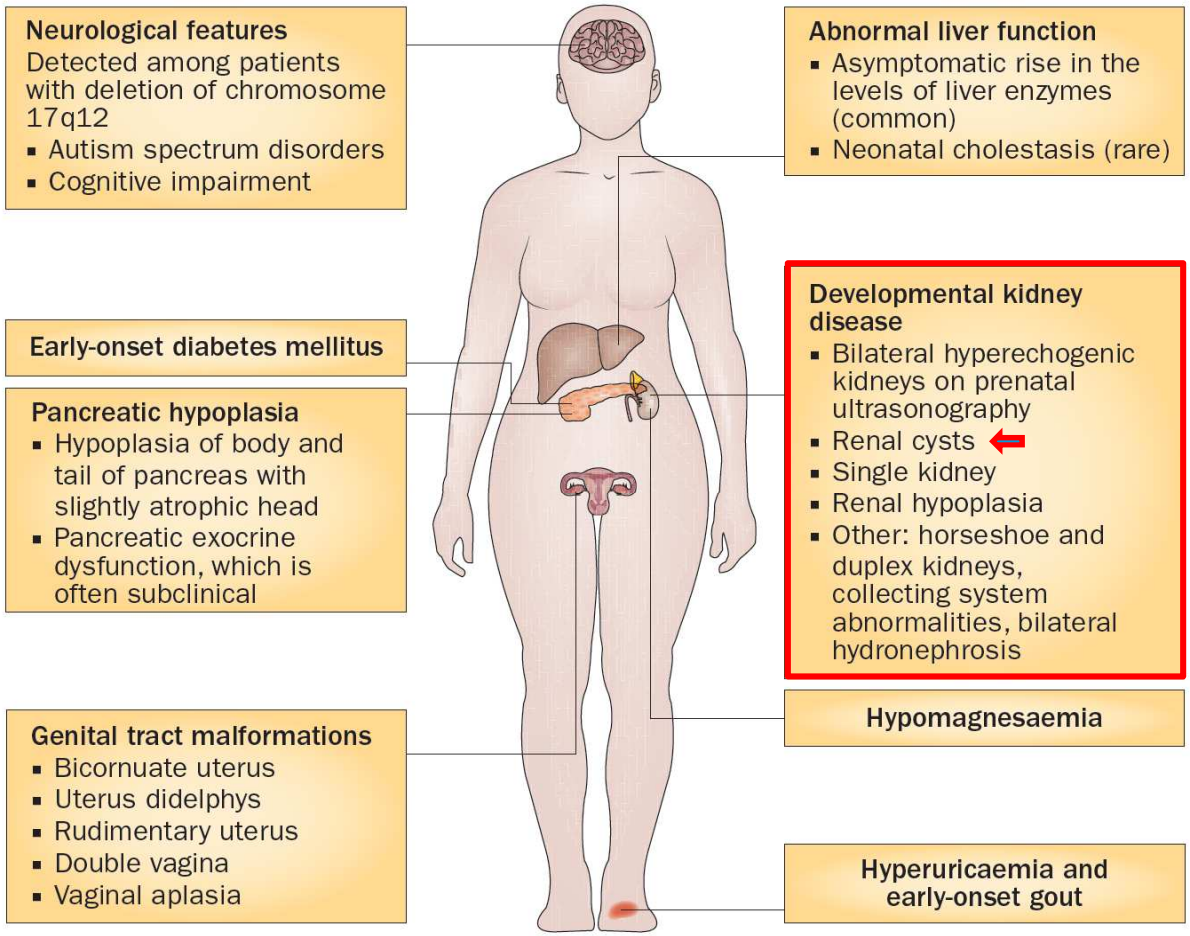
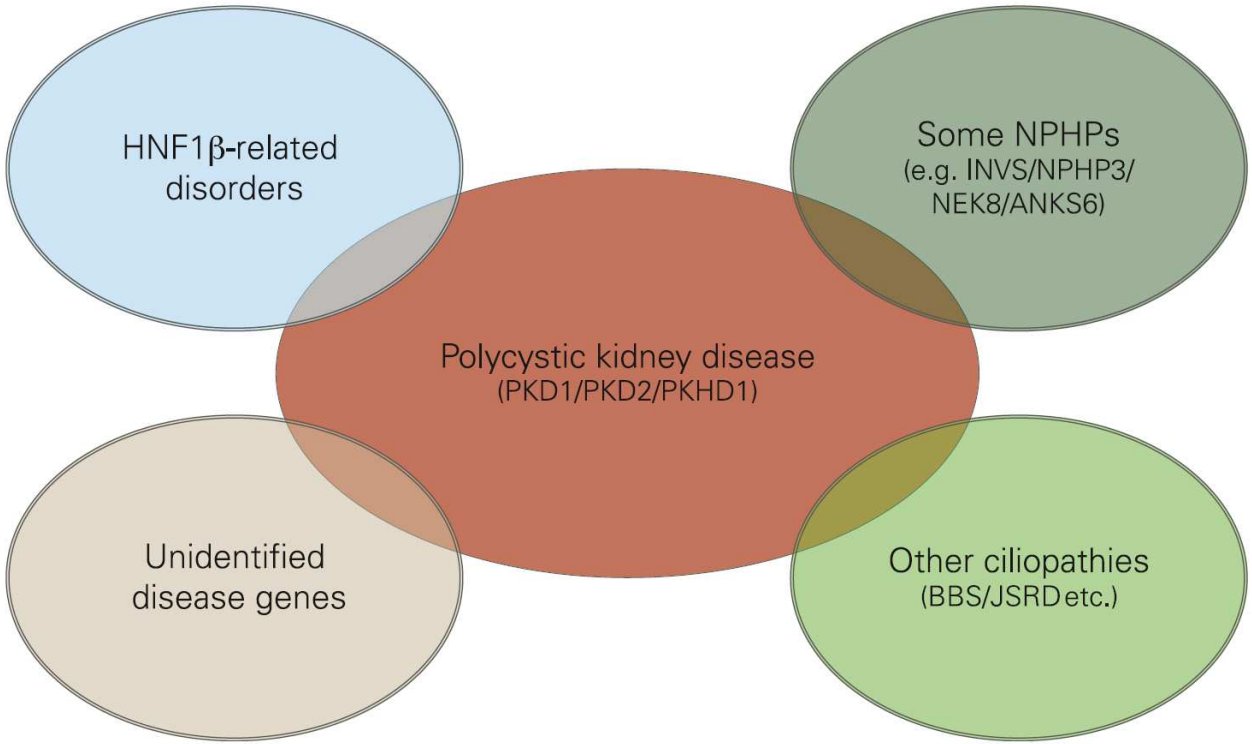


Figure 1 | Renal and extra-renal phenotypes frequently observed among patients with hepatocyte nuclear factor 1β-associated disease.

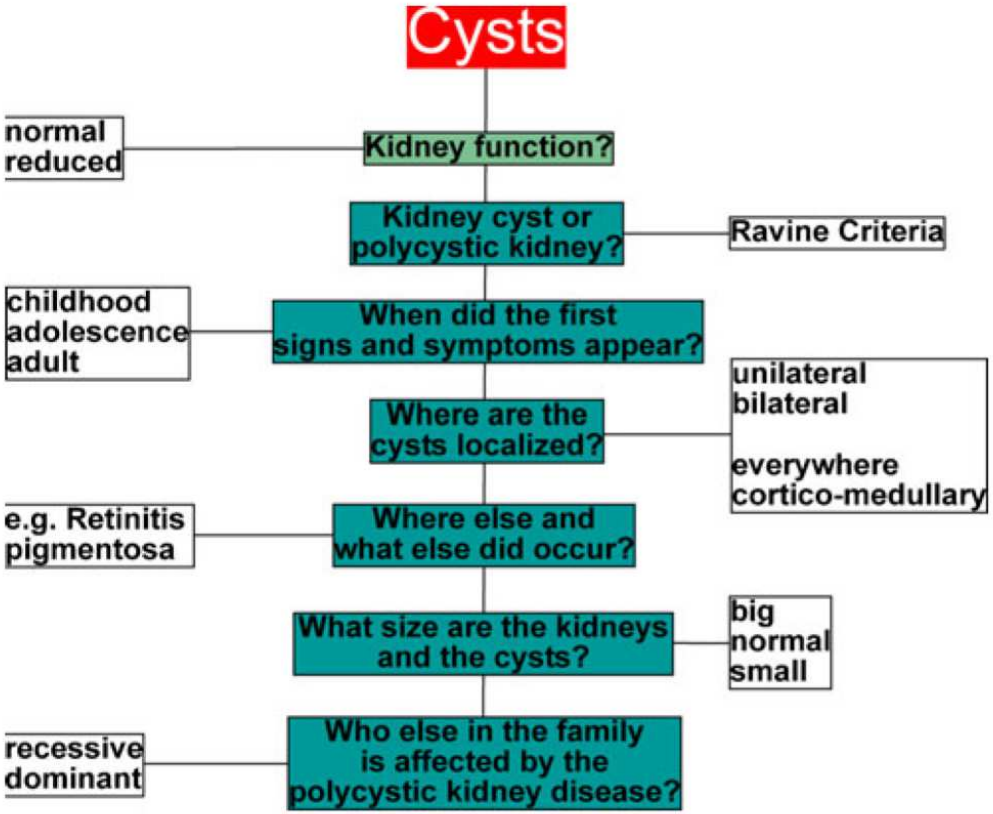
Clissold et al.,
Nat Rev Nephrology, 2015

Phenocopies



Bergmann,
Pediatric Nephrology, 2015

Helpful clinical criteria



Liebau & Serra
Pediatr Nephrol, 2013

1.) Family history

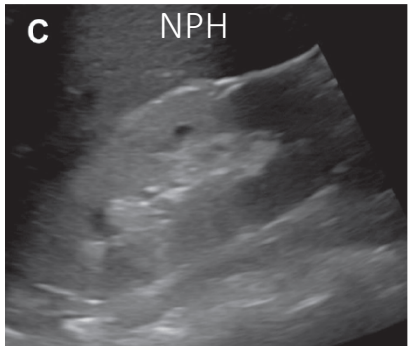
- Nephronophthisis, NPH-associated syndromes, BBS and ARPKD are recessive disorders – there is typically no prominent family history of cystic kidneys.
- Ask for consanguinity of parents
- ADPKD and *HNF1ß*-associated nephropathy show a dominant pattern of inheritance
- Spontaneous novel mutations can occur in about 10% of ADPKD cases and are even more common in *HNF1ß*-associated cases

2.) Age of presentation and kidney function

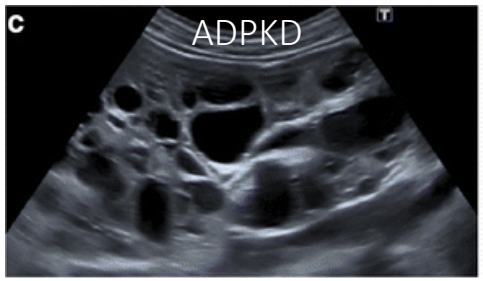
- ARPKD is typically found antenatally or in the first years of life
- NPH can present as an infantile form (very rare), a juvenile form (most common) or as adolescent NPH (rare) – depending on the underlying genetic defects
- In ADPKD first cysts can often be detected during childhood and adolescence. Children may be hypertensive or proteinuric. Kidney function typically starts to deteriorate later in life.

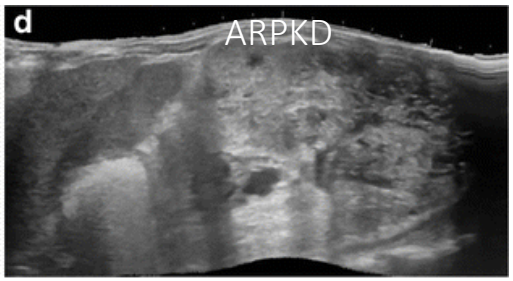
3.) Number of cysts

- For patients with a positive family history of ADPKD the Pei-Ravine criteria define age-dependent numbers of cysts to establish the diagnosis of ADPKD
- <30 years of age: 2 cysts (uni- or bilateral);
  30 to 59 years: ≥2 cysts per kidney;
  >60 years: ≥ 4 cysts per kidney (standard ultrasound)
- For other cystic disorder such criteria have not been established.



Liebau and Habbig,
DGfN-News 2015



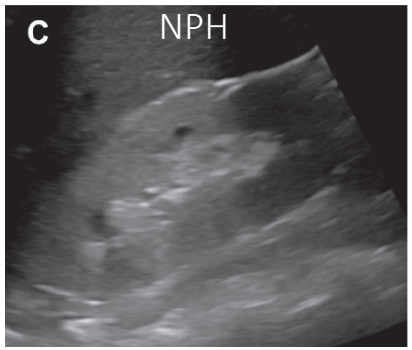


Liebau & Serra
Pediatr Nephrol, 2013

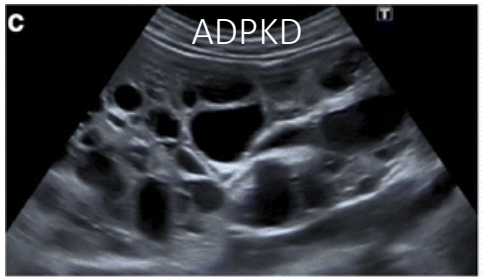
„In children with a renal cyst,
always consider an underlying cystic kidney disease
as a differential diagnosis.“

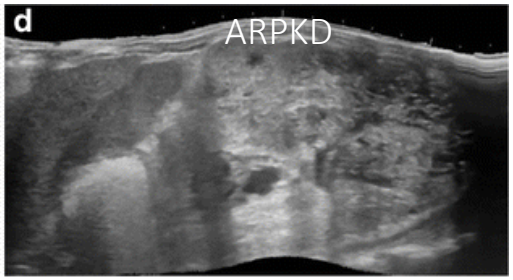
4.) Localization of cysts

- Unilateral – bilateral? Multicystic dysplastic kidney disease is a common unilateral differential diagnosis in young children.
- Medulla? Ubiquitous? Cortico-medullary border?



Liebau and Habbig,
DGfN-News 2015

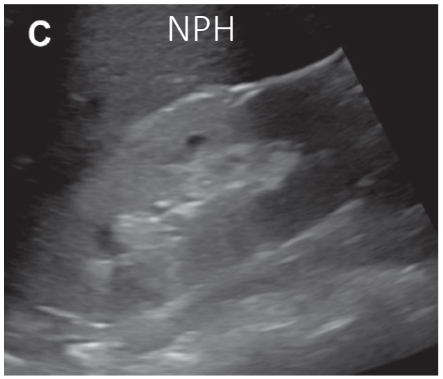




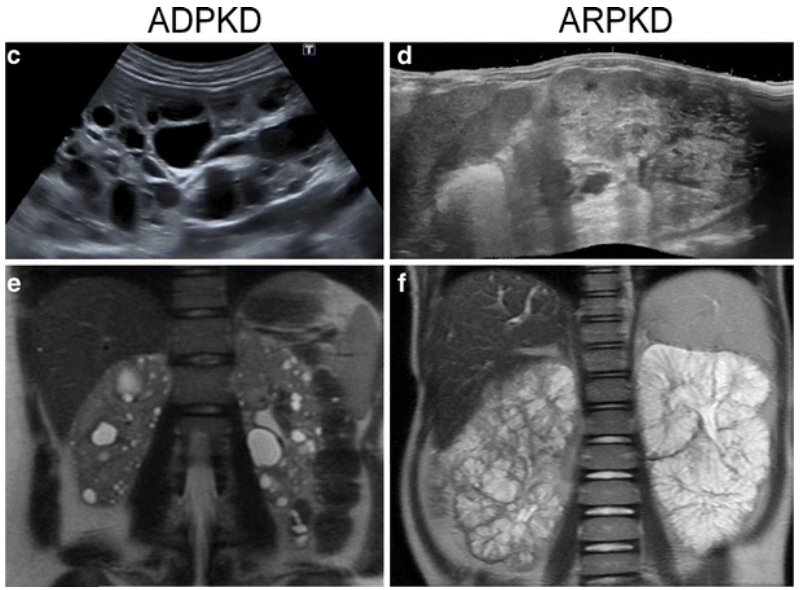
Liebau & Serra
Pediatr Nephrol, 2013

5.) Size of kidneys and of cysts

- In ARPKD and in ADPKD kidneys are enlarged.
- Kidneys in juvenile and adolescent NPH are normal-sized or small.
- ADPKD presents with macrocysts, while ARPKD primarily shows microcysts



Liebau and Habbig,
DGfN-News 2015



Liebau & Serra
Pediatr Nephrol, 2013

6.) Extrarenal symptoms

- Extrarenal can be crucial for establishing the clinical diagnosis
- Examples include:

  Polycystic liver disease in ADPKD,

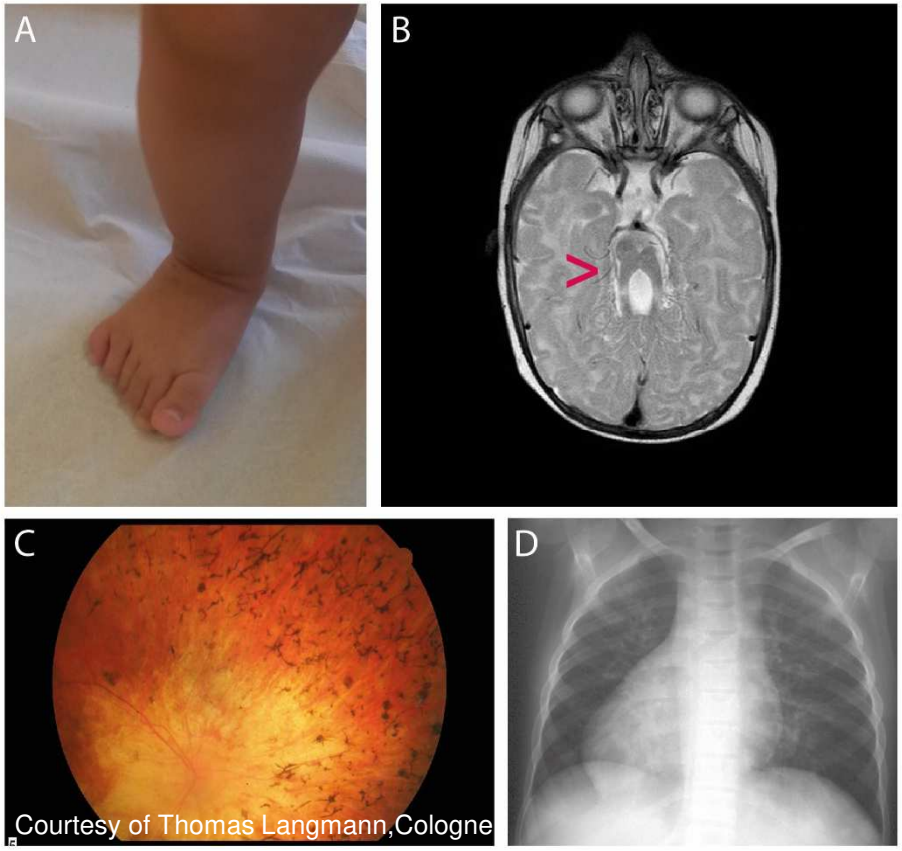
  Congenital hepatic fibrosis in ARPKD,

  Hexadactyly in BBS

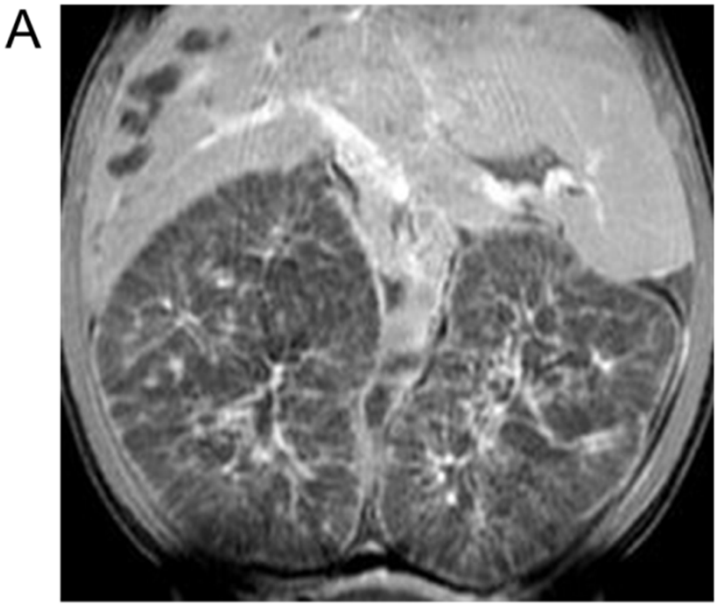
  Molar Tooth Sign in Joubert‘s syndrome

  Retinitis pigmentosa, Situs inversus in NPH-associated diseases

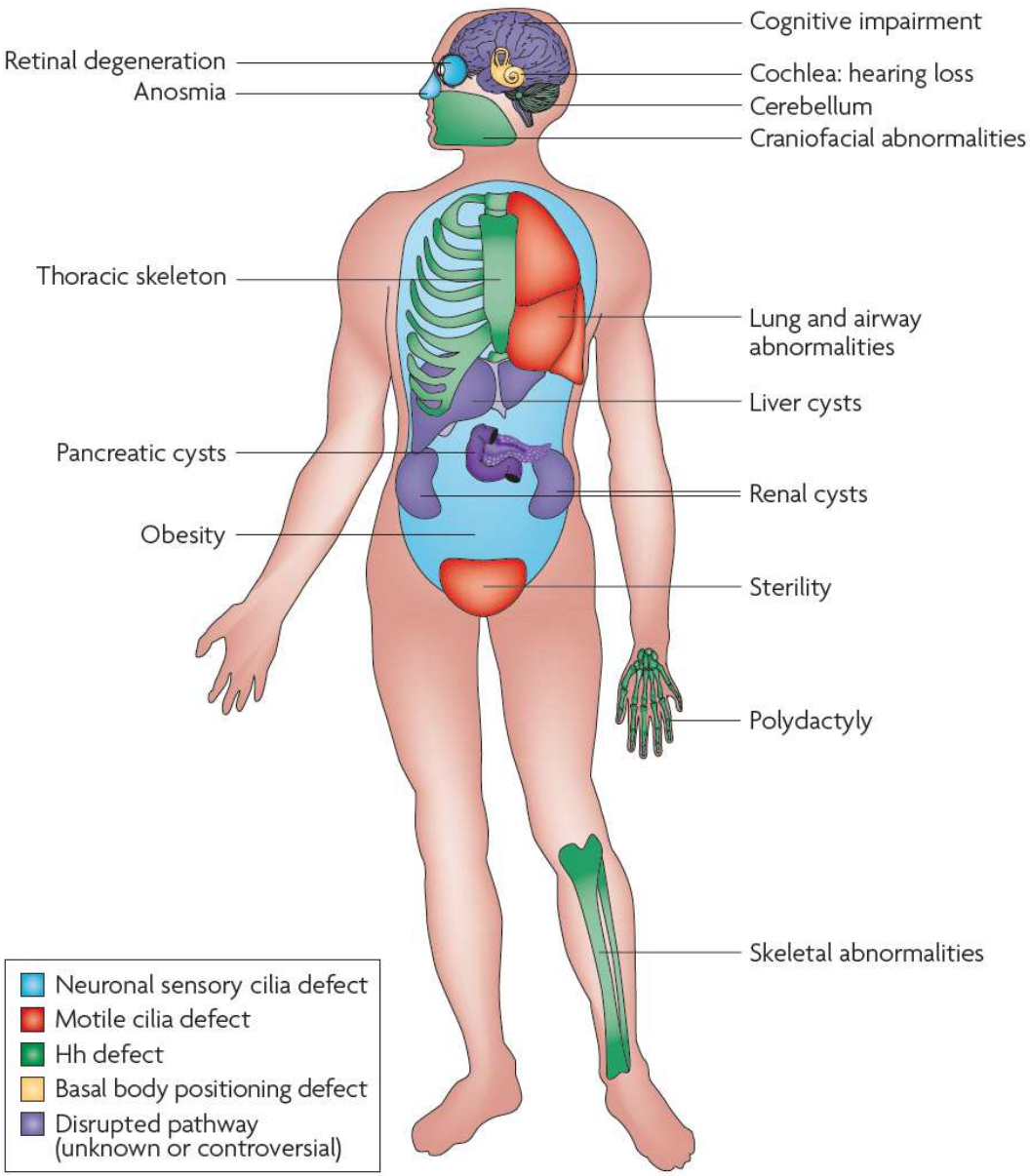
6.) Extrarenal symptoms



Müller and Liebau,
in „Nierenerkrankungen des Kindes- und Jugendalters“ (Dötsch/Weber Hrsg), 2017



Ebner et al.,
Pediatrics Nephrology, 2017



Cystic kidney diseases are systemic disorders – actively look for extrarenal symptoms!

Goetz & Anderson,
Nature Reviews Genetics, 2010

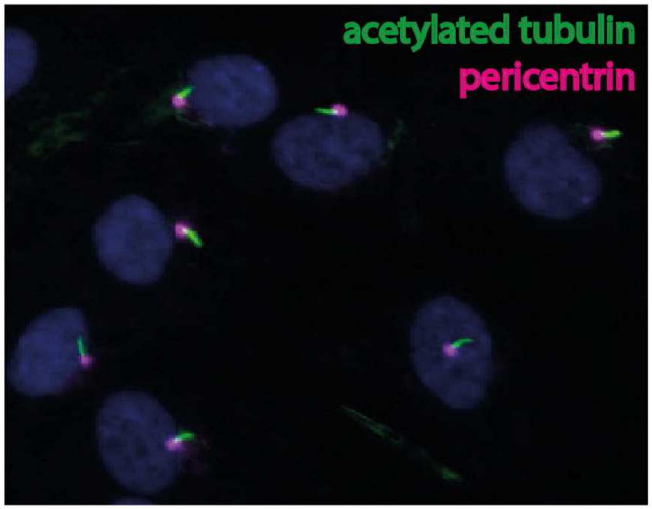
REVIEW

J Am Soc Nephrol 15: 2528–2536, 2004

Intraflagellar Transport and Cilia-Dependent Renal Disease: The Ciliary Hypothesis of Polycystic Kidney Disease

GREGORY J. PAZOUR
Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, Massachusetts

Cilia



Liebau;
Front Pediatr, 2014

Pazour et al.;
Trends Cell Biol, 2002

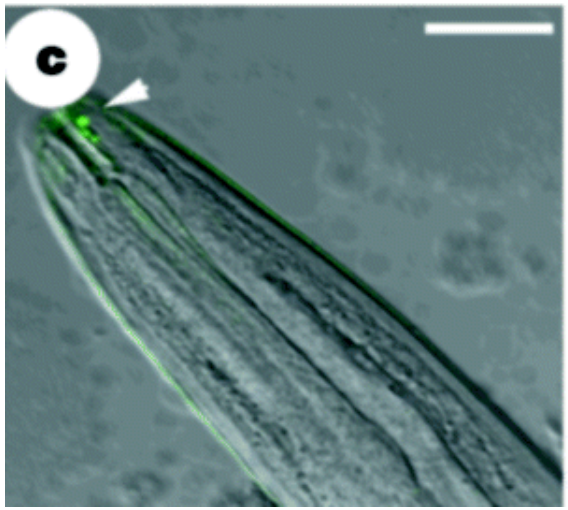
A polycystic kidney-disease gene homologue required for male mating behaviour in *C. elegans*

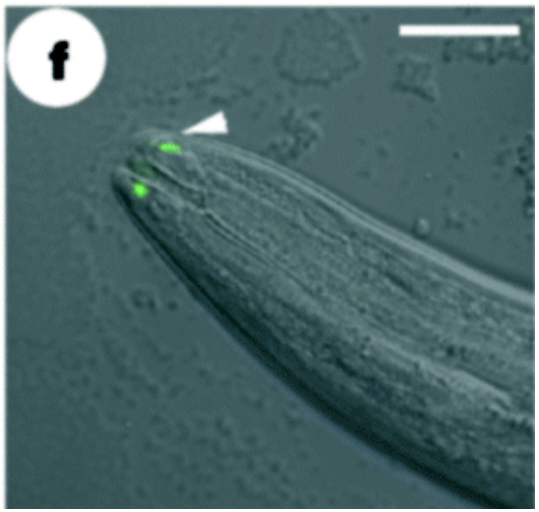
Maureen M. Barr & Paul W. Sternberg

Howard Hughes Medical Institute and Division of Biology, California Institute of Technology, Pasadena, California 91125, USA

Nature, 1999

www.easternct.edu



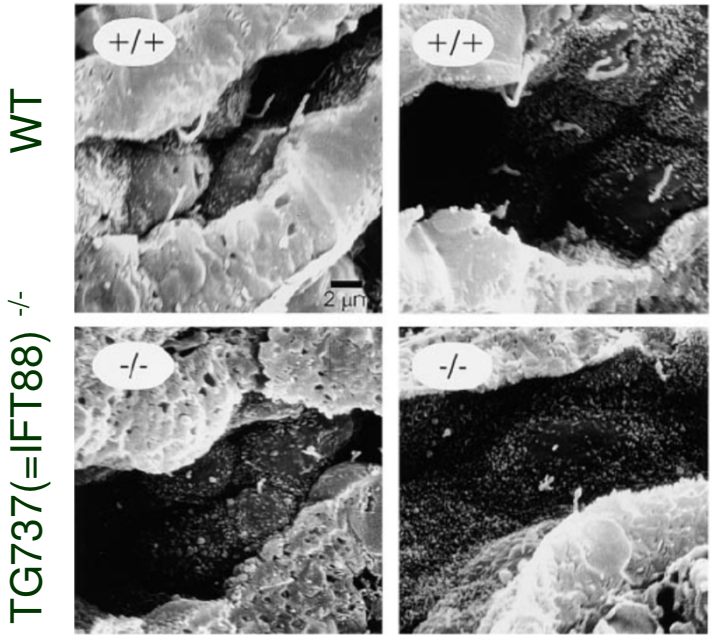


Published October 30, 2000

*Chlamydomonas IFT*88 and Its Mouse Homologue, Polycystic Kidney Disease Gene *Tg*737, Are Required for Assembly of Cilia and Flagella

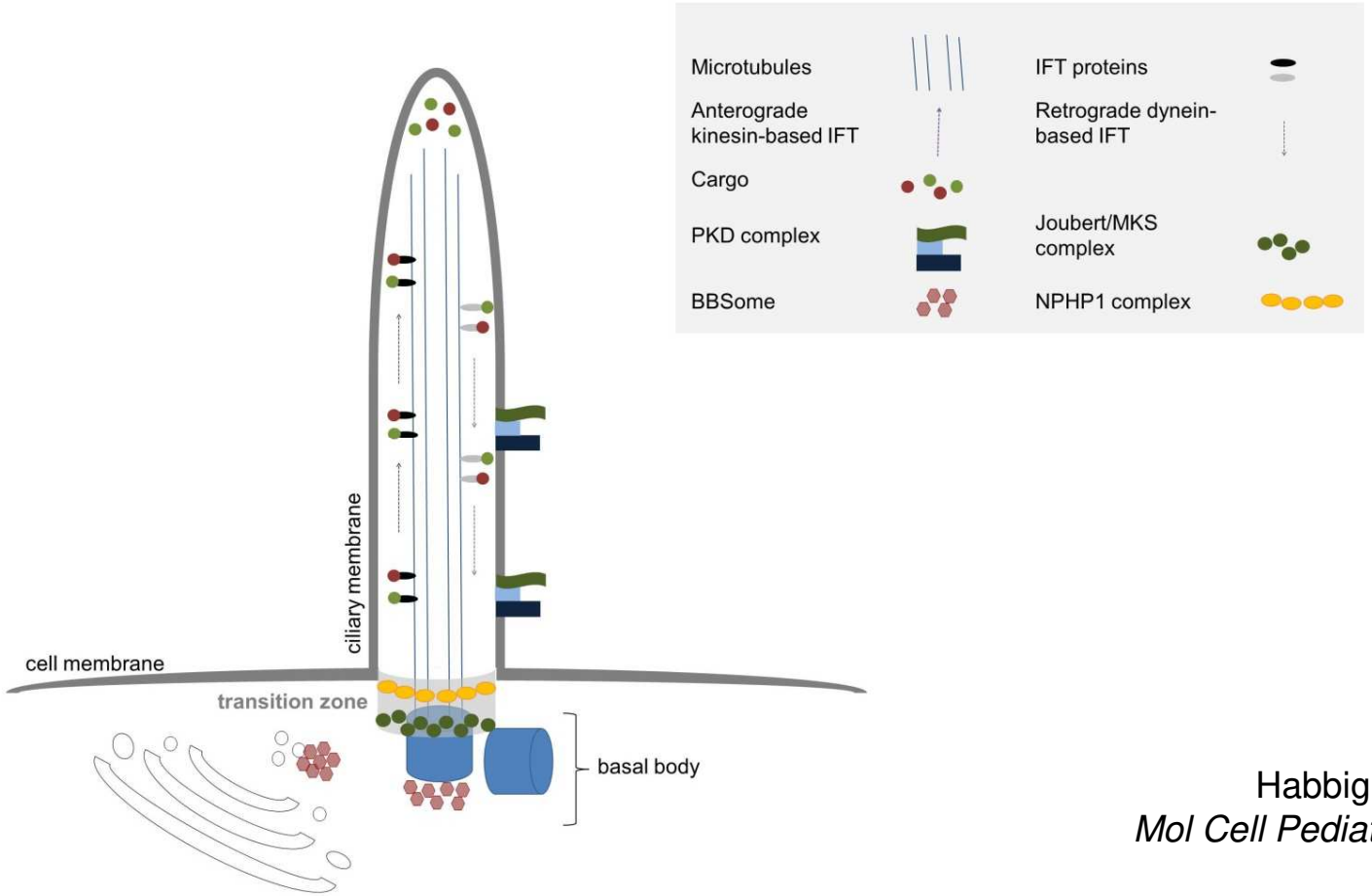
Gregory J. Pazour,* Bethany L. Dickert,* Yvonne Vucica,‡ E. Scott Seeley,‡ Joel L. Rosenbaum,‡ George B. Witman,* and Douglas G. Cole§

*Department of Cell Biology, University of Massachusetts Medical School, Worcester, Massachusetts 01655; ‡Department of Molecular, Cellular, and Developmental Biology, Yale University, New Haven, Connecticut 06520; and §Department of Microbiology, Molecular Biology, and Biochemistry, University of Idaho, Moscow, Idaho 83844



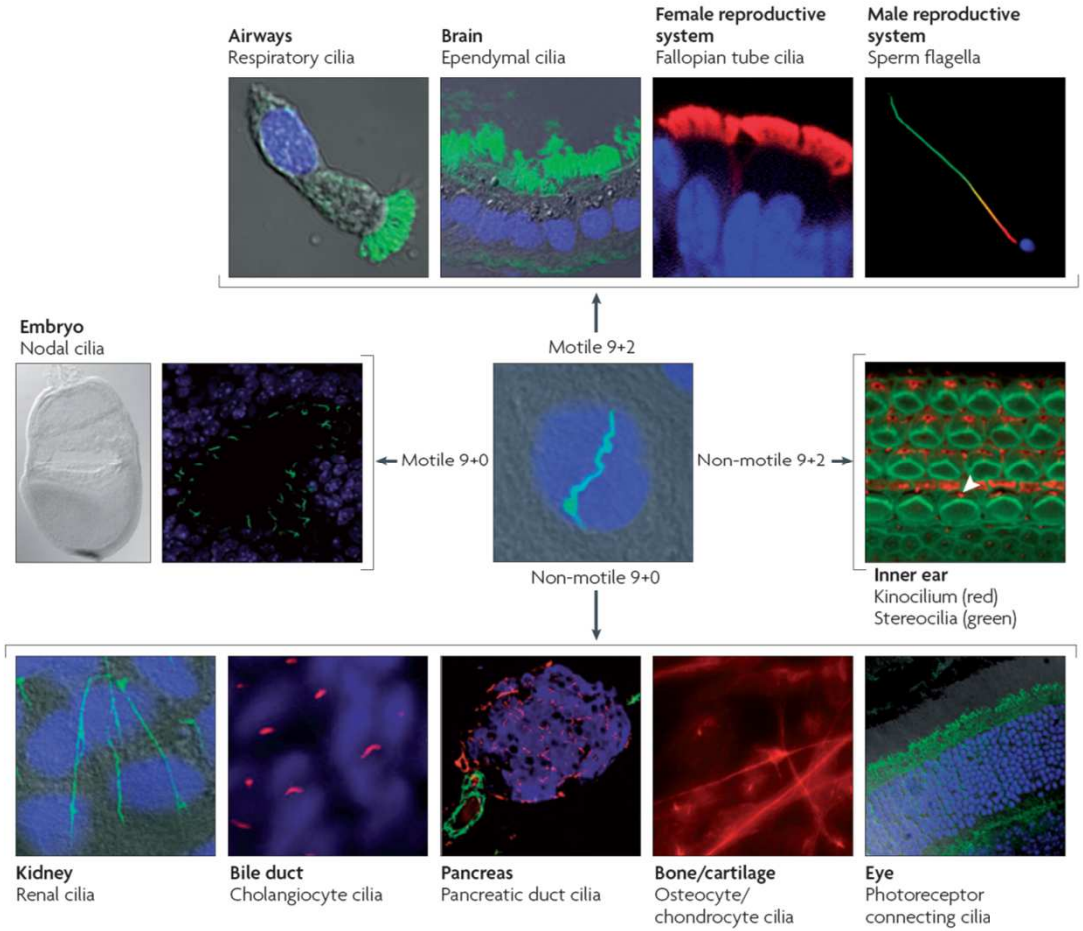
J Cell Biol, 2000

PKD proteins form complexes at the cilium

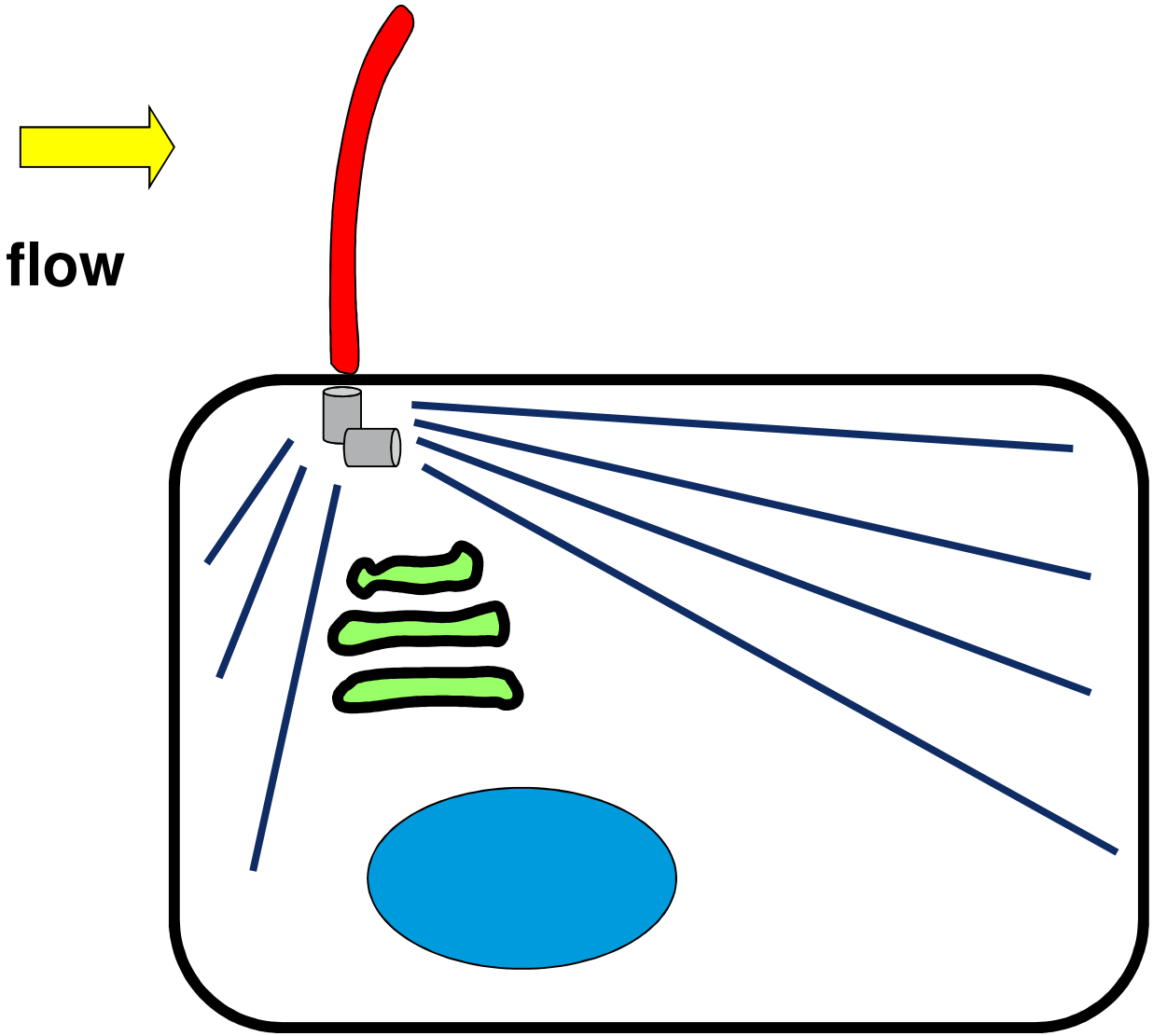


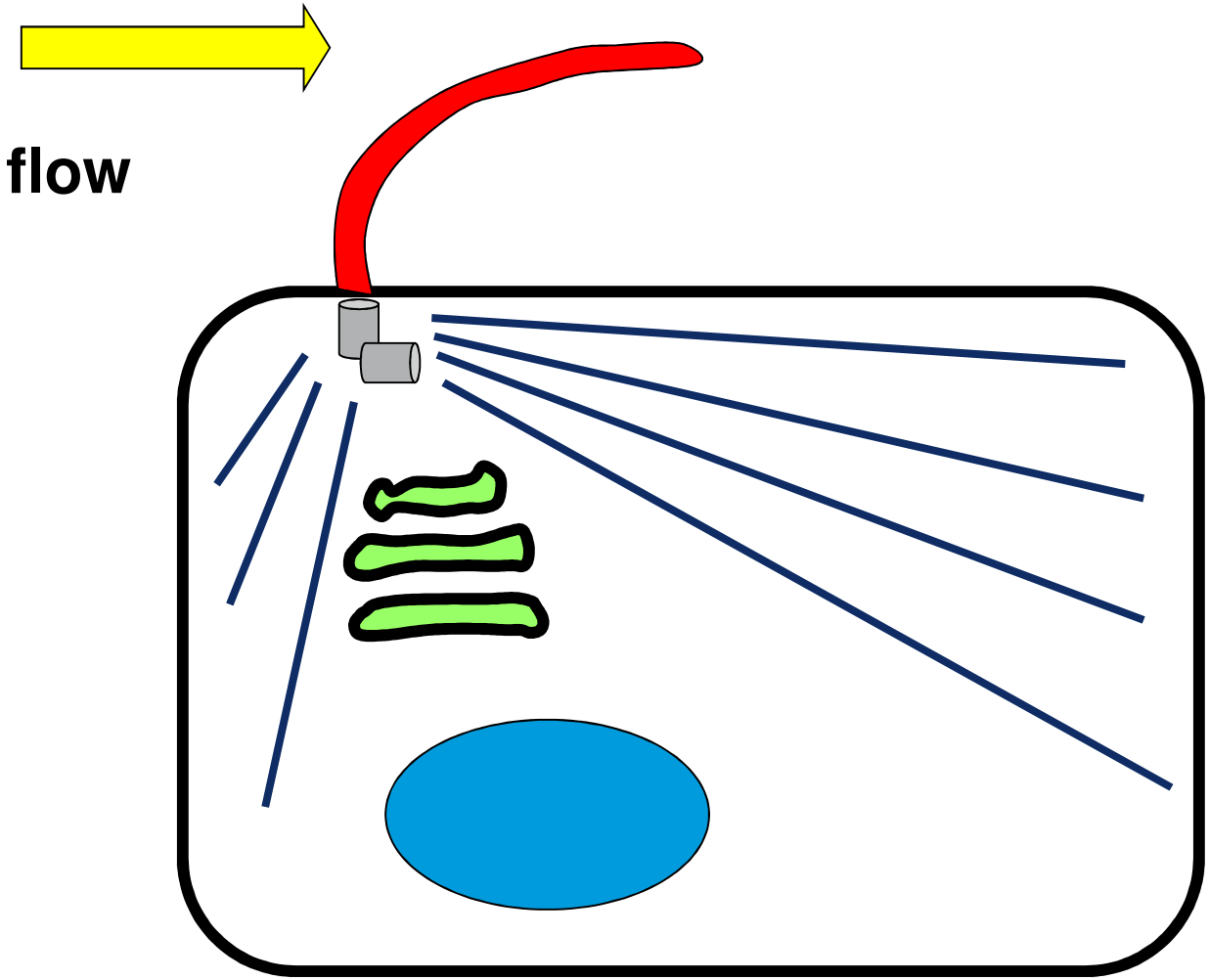
Habbig & Liebau,
Mol Cell Pediatrics, 2015

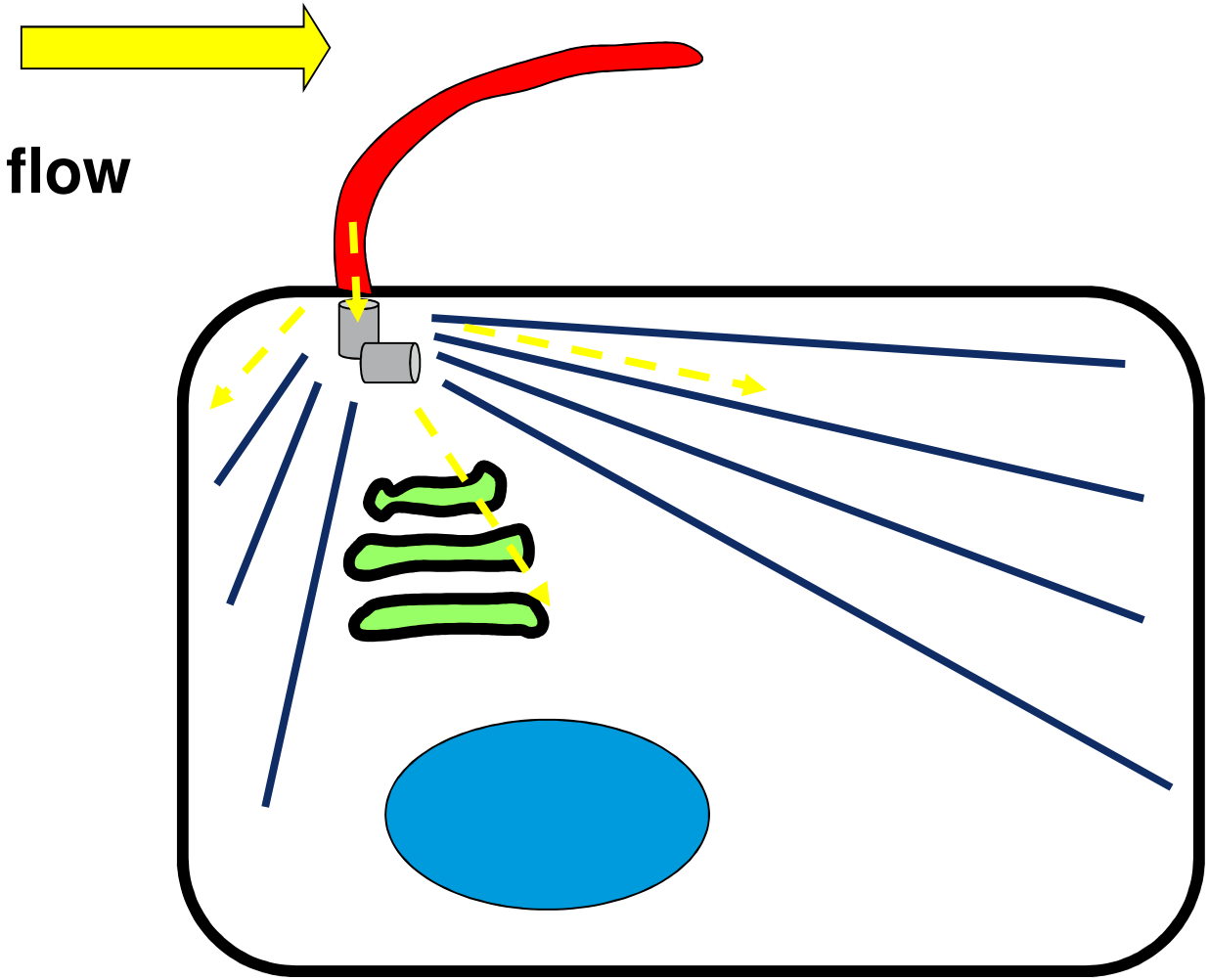
Cilia can be found on multiple cell types

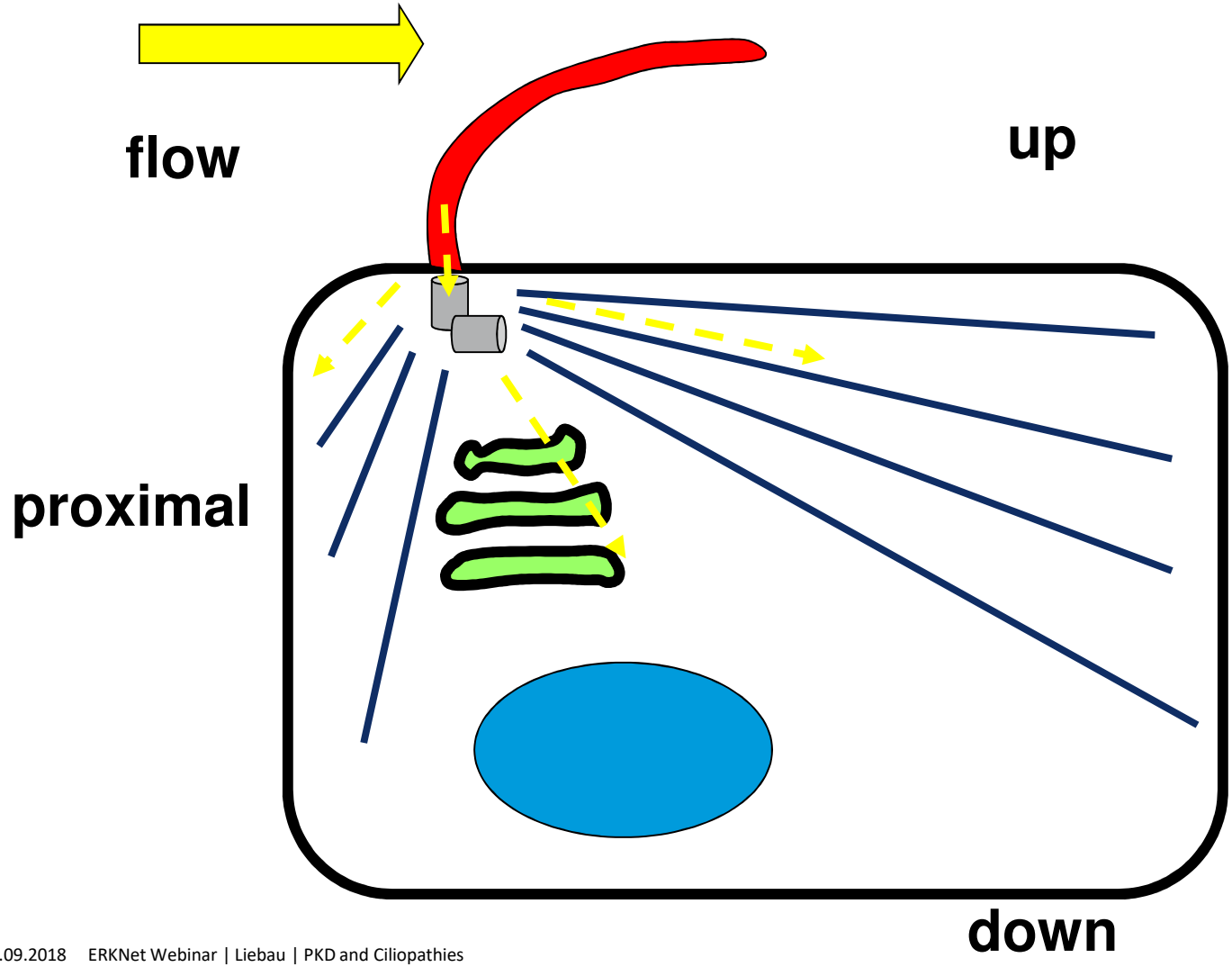


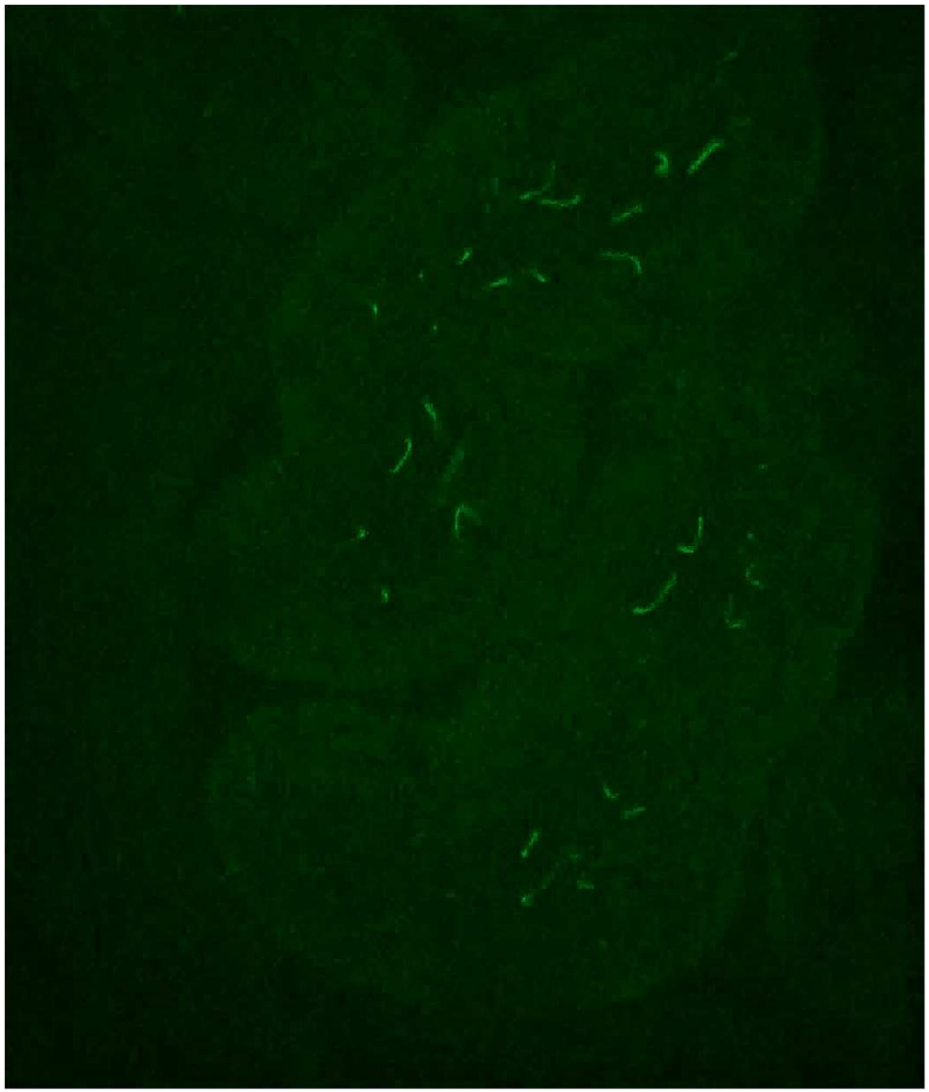
Fliegauf, Benzing, Omran,
Nat Rev Mol Cell Biol, 2007


flow

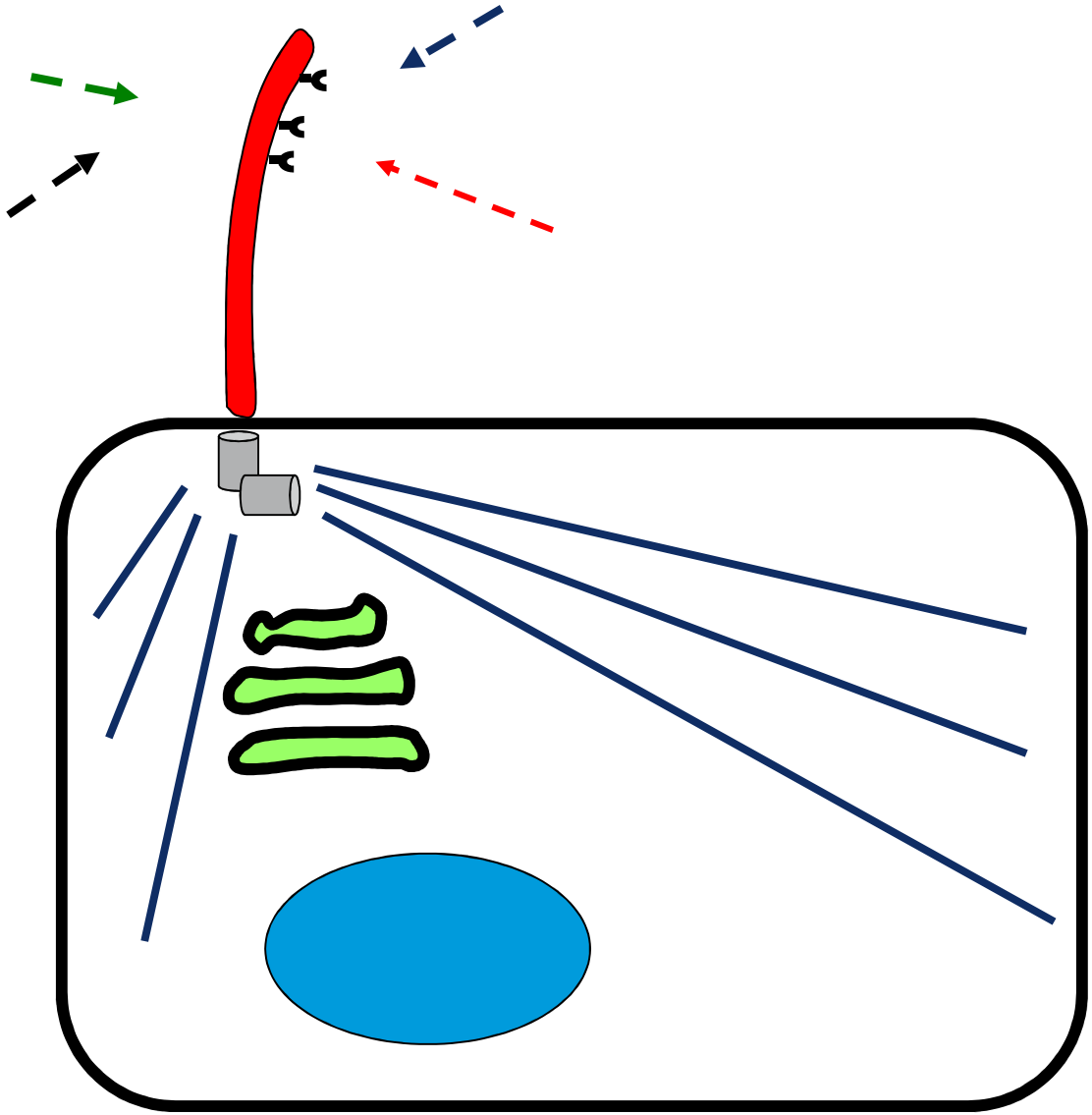

flow

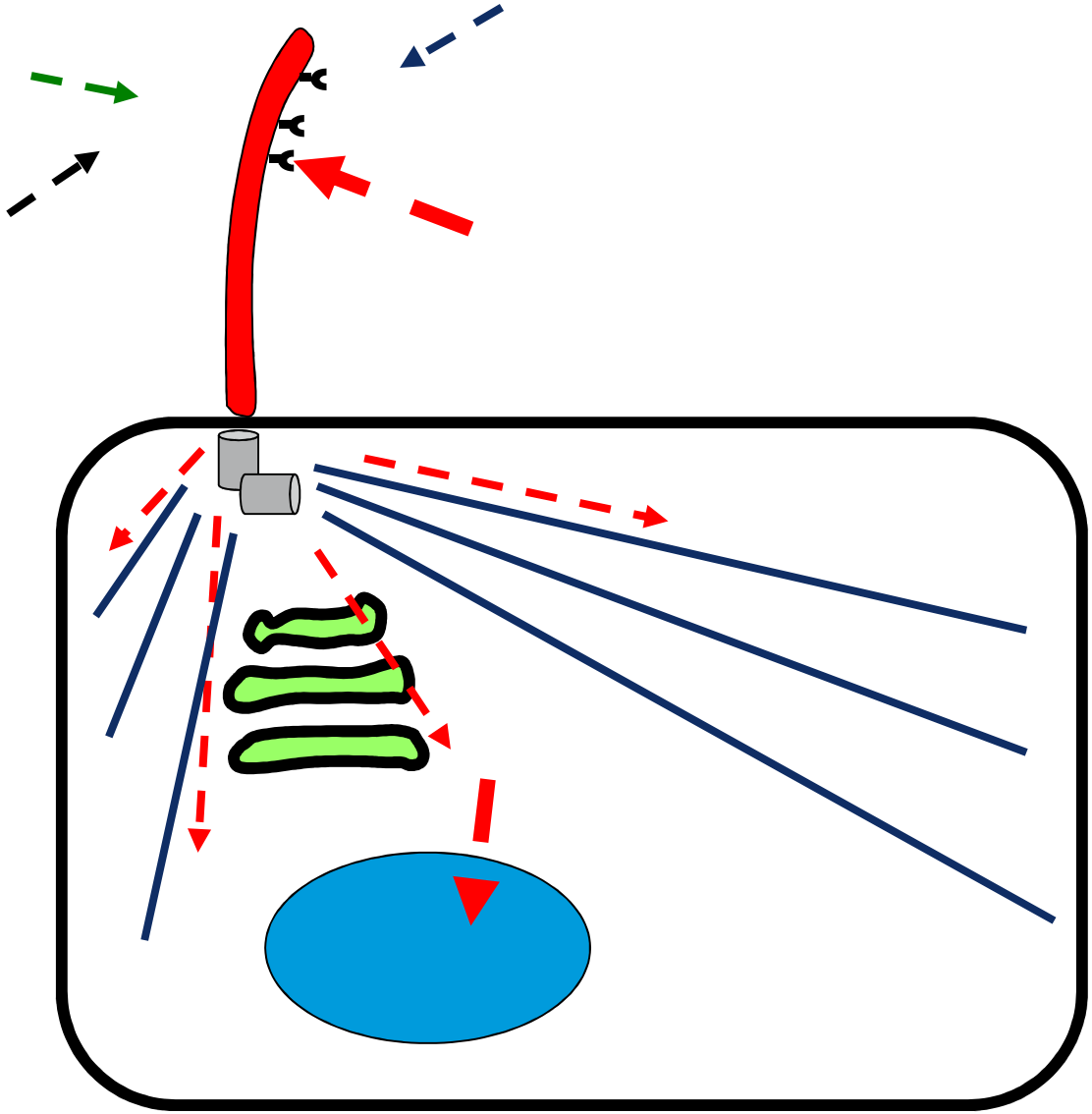

flow

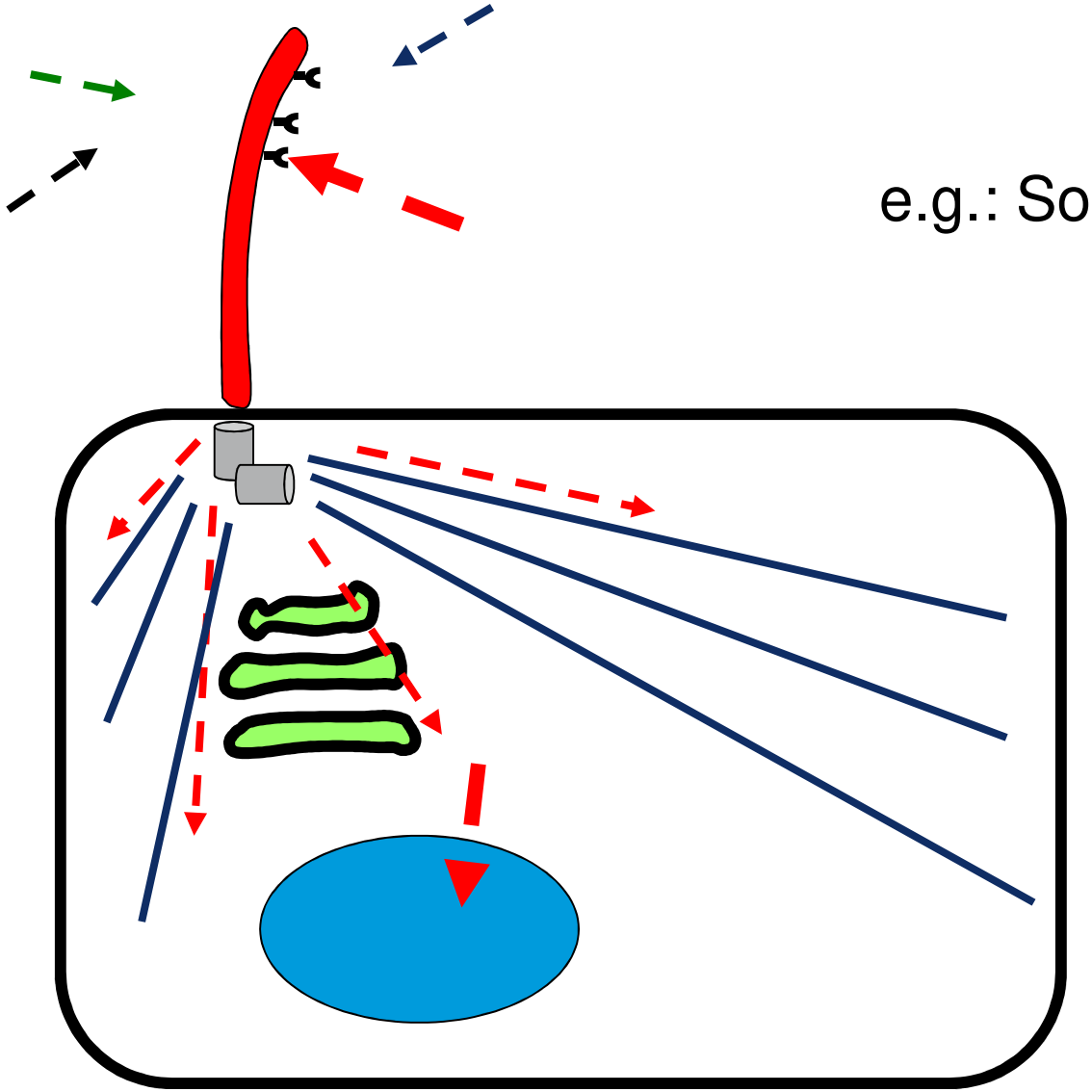

flow
up
proximal
distal
down



O‘Connor et al., *Cilia,* 2013

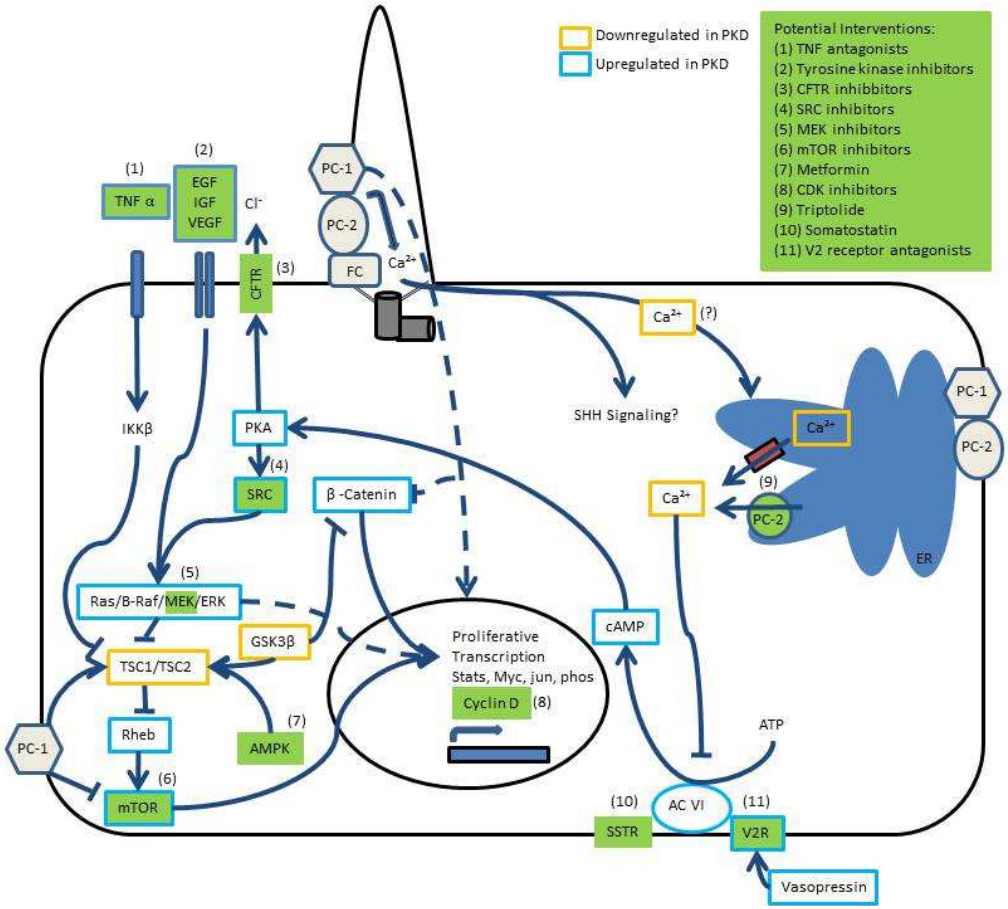






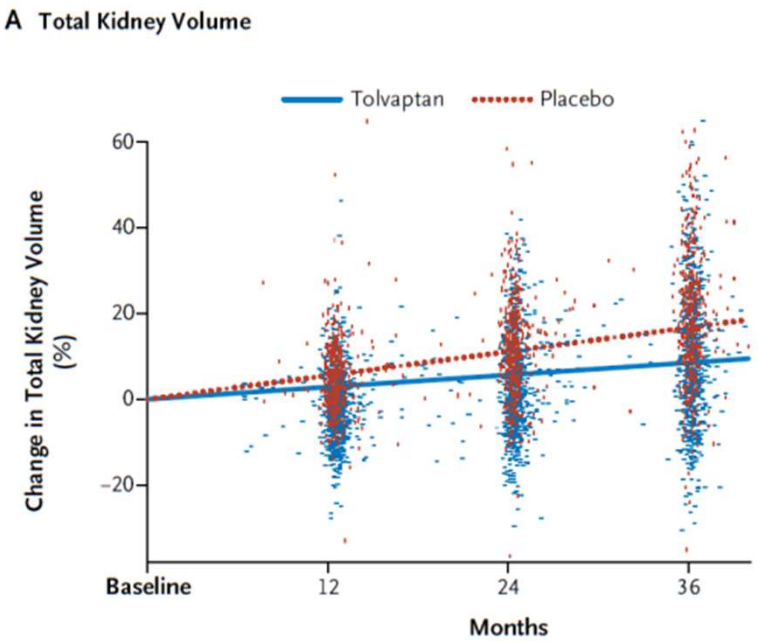
e.g.: Sonic Hedgehog

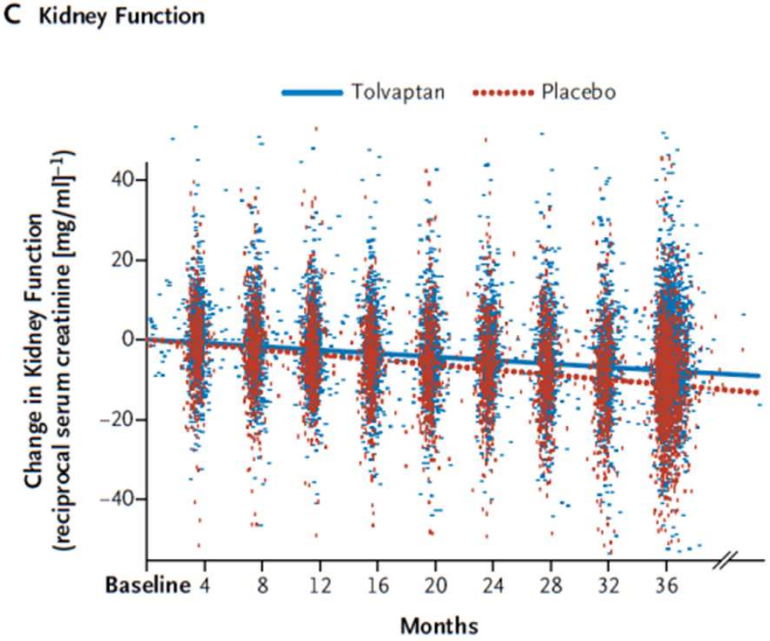
PKD-associated signaling



Liebau and Bergmann, 2016
In Schaefer/Geary *Pediatric Kidney Disease* 2nd edition

Emerging therapeutic approaches

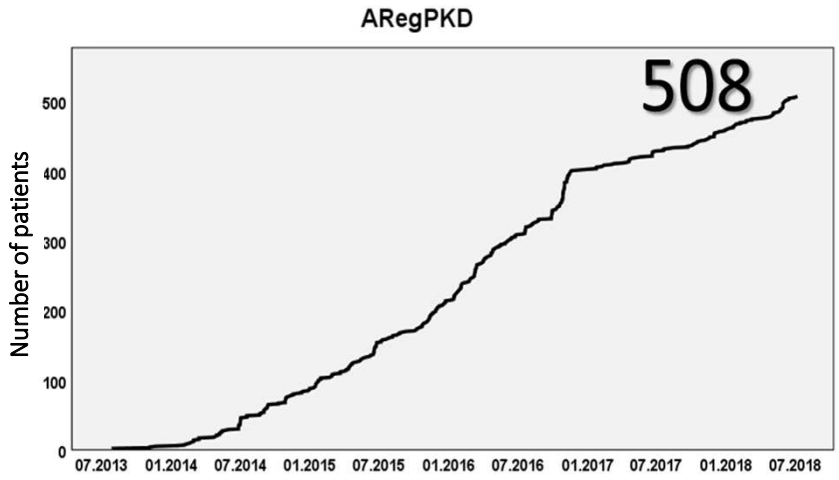


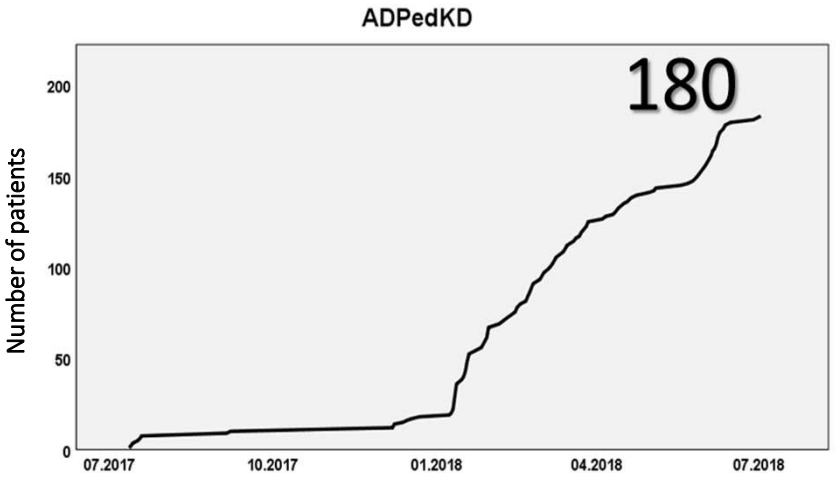


Torres et al., *NEJM* 2012

Defining pediatric end points for RCTs

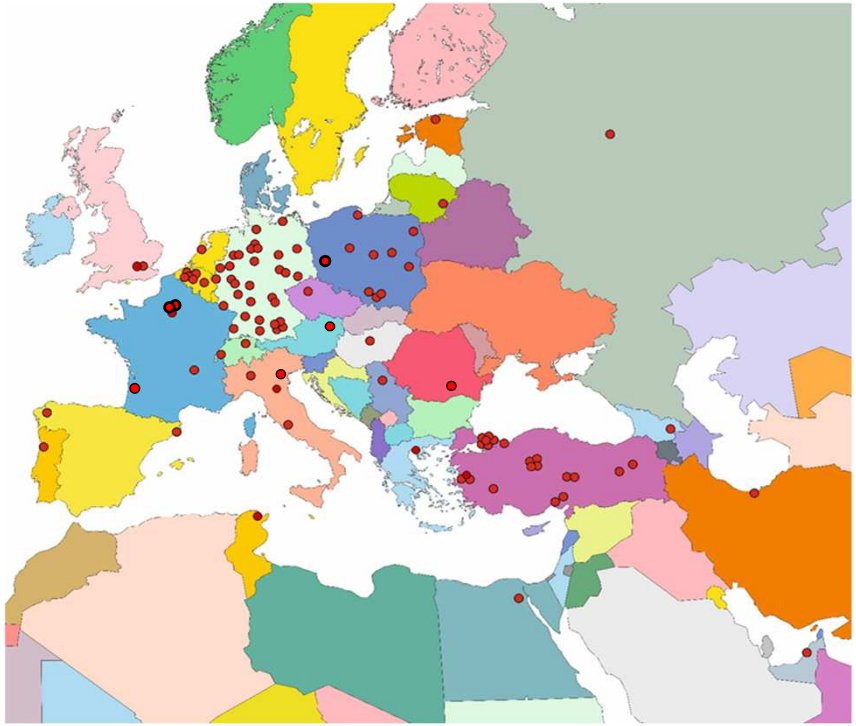
- International registry studies: ARegPKD and ADPedKD





UNIKLINIK KÖLN

ARegPKD – 111 centers in 27 countries



PKD Familiäre Zystennieren e.V.

KÖLN FORTUNE

Marga und Walter Boll - Stiftung

PKD International

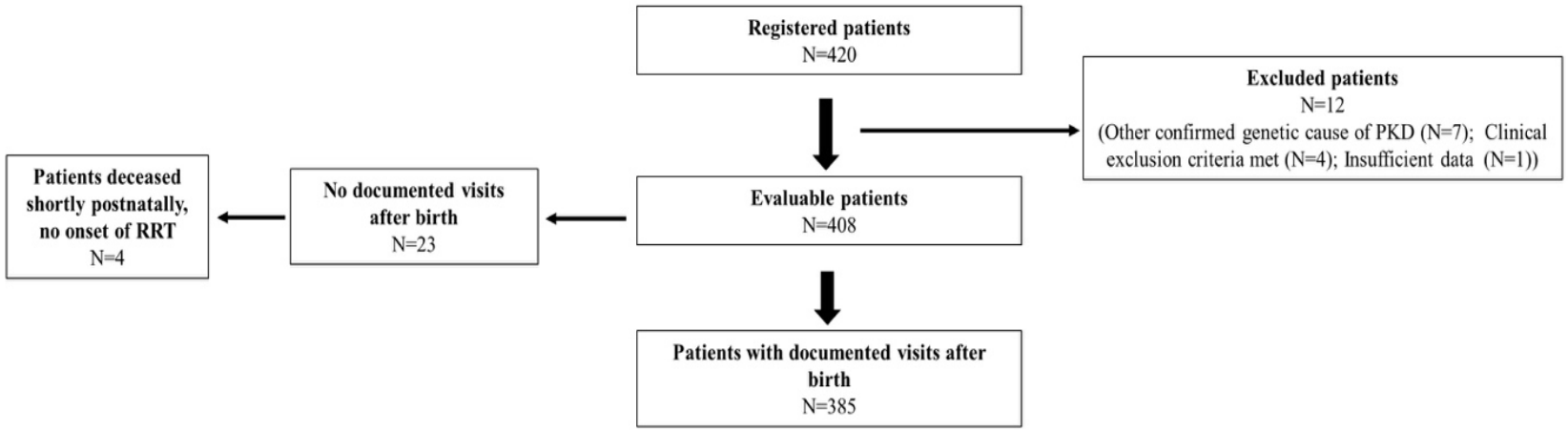
NEOCYST

GEFÖRDERT VOM Bundesministerium für Bildung und Forschung

european society for paediatric nephrology

GPN Gesellschaft für Pädiatrische Nephrologie

Risk factors for early dialysis dependency?



Burgmaier et al., *J Peds,* 2018

Table I. Patient characteristics and univariate analysis of prenatal, perinatal, and postnatal predictors of dialysis dependency within the first year of life

Characteristics	All cases (n = 385)	No dialysis in first year of life (n = 349)	Dialysis in first year of life (n = 36)	*P* Value
Prenatal information				
Oligohydramnios or anhydramnios, n/N (%)	107/318 (33.6)	77/284 (27.1)	30/34 (88)	<.001
Gestational age at diagnosis, wk (n = 96), mean (SD)	29.9 (5.1)	30.2 (5.3)	29.1 (4.6)	.20
Increased echogenicity, n/N (%)	78/291 (26.8)	60/267 (22.5)	18/24 (75.0)	<.001
Gestational age at diagnosis, wk (n = 72), mean (SD)	28.9 (5.0)	28.6 (5.3)	29.7 (4.1)	.55
Enlarged kidneys, n/N (%)	70/301 (23.3)	47/272 (17.3)	23/29 (79.3)	<.001
Renal cysts, n/N (%)	82/312 (26.3)	59/282 (20.9)	23/30 (76.7)	<.001
Amnioninfusion performed, n/N (%)	8/322 (2.5)	4/288 (1.4)	4/34 (11.8)	<.001
Perinatal information				
Vaginal delivery, n/N (%)	182/315 (57.8)	164/279 (58.8)	18/36 (50.0%)	.007
Gestational age at birth, wk (n = 285), mean (SD)	37.5 (2.7)	37.7 (2.7)	36.1 (2.4)	<.001
Birth weight (n = 277), kg, mean (SD)	3.058 (0.657)	3.065 (0.644)	3.001 (0.757)	.92
(n = 250) (SDS)	−0.1 (1.4)	−0.1 (1.5)	0.4 (1.3)	.003
Birth length (n = 203), cm, mean (SD)	49.9 (4.4)	50.0 (4.4)	48.8 (4.0)	.15
(n = 190) (SDS)	−0.1 (1.3)	−0.1 (1.4)	−0.1 (1.1)	.87
Apgar 1 min (n = 176), mean (SD)	7.5 (2.4)	7.9 (2.1)	5.0 (2.5)	<.001
Apgar 5 min (n = 172), mean (SD)	8.4 (1.9)	8.7 (1.5)	6.3 (2.4)	<.001
Apgar 10 min (n = 157), mean (SD)	8.9 (1.4)	9.1 (1.3)	7.7 (1.6)	<.001
Admission to NICU, n/N (%)	83/336 (24.7)	60/300 (20.0)	23/36 (63.9)	<.001
Days on NICU (n = 73), mean (SD)	39 (68)	27 (32)	69 (113)	.003
Assisted breathing/ventilation, n/N (%)	78/333 (23.4)	54/297 (18.2)	24/36 (66.7)	<.001
Pharmacologic pulmonary maturation, n/N (%)	18/325 (5.5)	11/290 (3.8)	7/35 (20.0)	<.001
Postnatal information				
Poor adaptation, n/N (%)	75/338 (22.2)	54/302 (17.9)	21/36 (58.3)	<.001
Pulmonary hypertension, n/N (%)	23/323 (7.1)	13/291 (4.5)	10/32 (31.3)	<.001
Potter facies, n/N (%)	13/329 (4.0)	6/297 (2.0)	7/32 (21.9)	<.001
Genetic information				
Documentation of *PKHD1* testing, n/N (%)	169/385 (43.9)	150/349 (43.0)	19/36 (52.8)	
Truncating/truncating	10/169 (5.9)	6/150 (4.0)	4/19 (21.1)	
Truncating/missense	38/169 (22.5)	34/150 (22.7)	4/19 (21.1)	
Missense/missense	68/169 (40.2)	65/150 (43.3)	3/19 (15.8)	
One single mutation	16/169 (9.5)	13/150 (8.7)	3/19 (15.8)	
No mutation detection in case of *PKHD1* testing (n = 22) or insufficient data (n = 15)	37/169 (21.9)	32/150 (21.3)	5/19 (26.3)	
No documentation of *PKHD1* testing, n/N (%)	216/385 (56.1)	199/349 (57.0)	17/36 (47.2)	

NICU, neonatal intensive care unit.

Burgmaier et al., *J Peds,* 2018

Risk factors for early dialysis dependency?

Table II. Multivariate Cox model of prenatal, perinatal, and postnatal predictors of the need for renal replacement therapy within the first year of life

Parameter	HR	95% CI	*P* value
Sex	0.925	0.462-1.850	.825
Oligohydramnios/anhydramnios	4.473	1.295-15.449	.018
Prenatal enlarged kidneys	3.177	1.087-9.282	.035
Vaginal delivery	1.271	0.584-2.765	.545
Gestational age at birth, wk	1.121	0.917-1.371	.265
Gestational age at birth * time	0.666	0.426-1.040	.074
Birth weight SDS	1.291	1.031-1.618	.026
Birth weight SDS * time	0.451	0.158-1.288	.137
Apgar 10-min	0.748	0.564-0.991	.043
Apgar 10-min * time	1.548	0.485-4.945	.460
Assisted breathing and/or ventilation	6.994	1.536-31.845	.012
Assisted breathing and/or ventilation * time	0.008	0.000-0.320	.010

Time interaction terms are denoted with "* time".

Burgmaier et al., *J Peds,* 2018

Summary

- Cystic kidney diseases are important causes of ESRD in children and adults.
- Various important subtypes of cystic kidney diseases exist. Genetic testing may be required to confirm a specific diagnosis but widely available markers can help to rapidly establish a clinical diagnosis. Extrarenal manifestations should actively be sought.
- Cystic kidney diseases are currently considered to be ciliopathies and, as such, are systemic disorders.
- For pediatric patients the definition of primary end points for clinical trials is challenging as there is ample phenotypic variability. International registry studies aim to characterize large pediatric ARPKD and ADPKD cohorts.