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ESPN/ERKNet
Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: 5th of May 2020

Topic: Autosomal Recessive Polycystic Kidney Disease

Speaker: Max C. Liebau

Moderator: Francesco Emma

ERKNet
The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

IPNA International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS. EVERYWHERE

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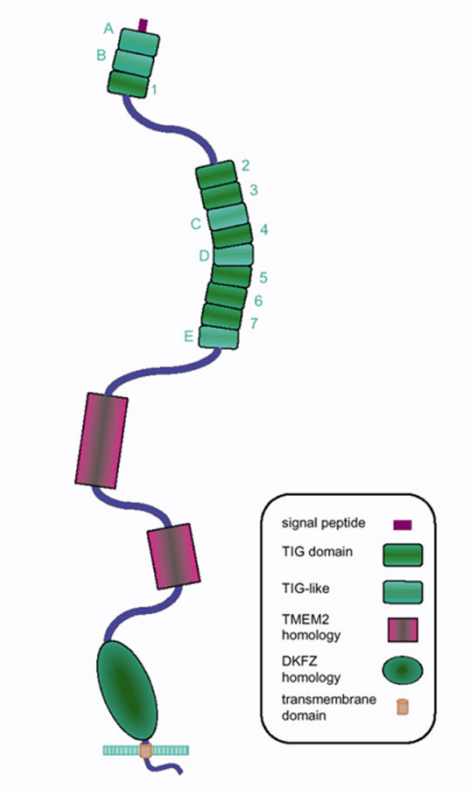
Disclosures

- Advisory Board Otsuka – representing the University Hospital of Cologne
- Honoraria for lectures: Pfizer

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

- 1:20.000, one main gene – *PKHD1, new: DZIP1L*



Ward et al.,
Nature Genetics, 2002

Autosomal Recessive Polycystic Kidney Disease

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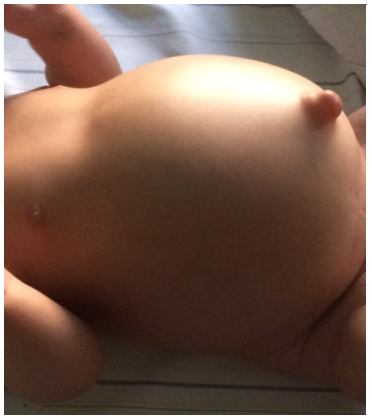
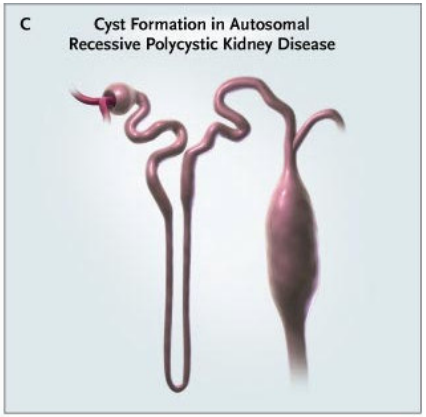
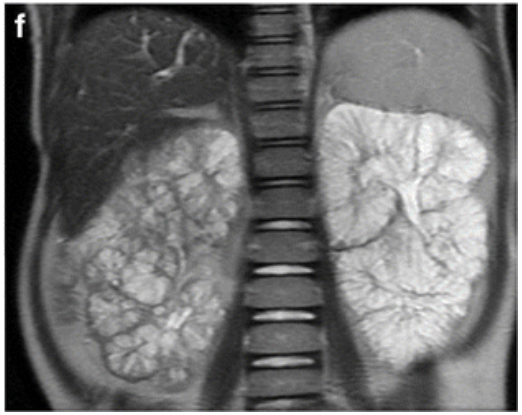
- Collecting duct dilatations, massively enlarged kidneys, variable kidney function





Wilson,
NEJM, 2004



Liebau and Serra,
Ped Neph, 2013

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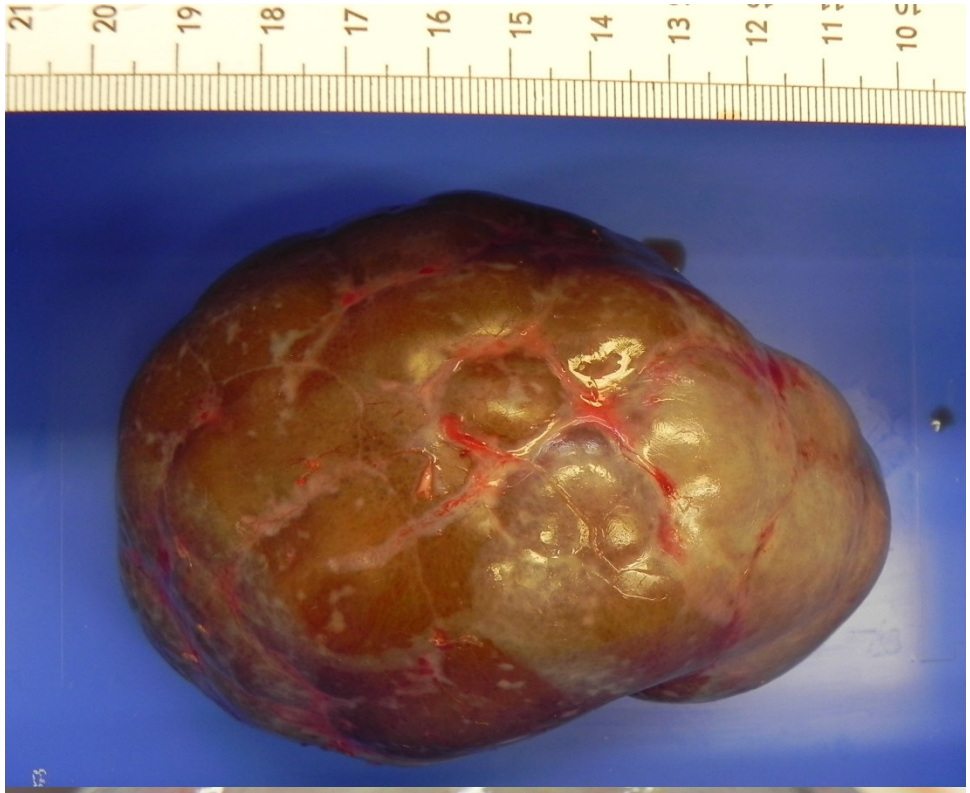
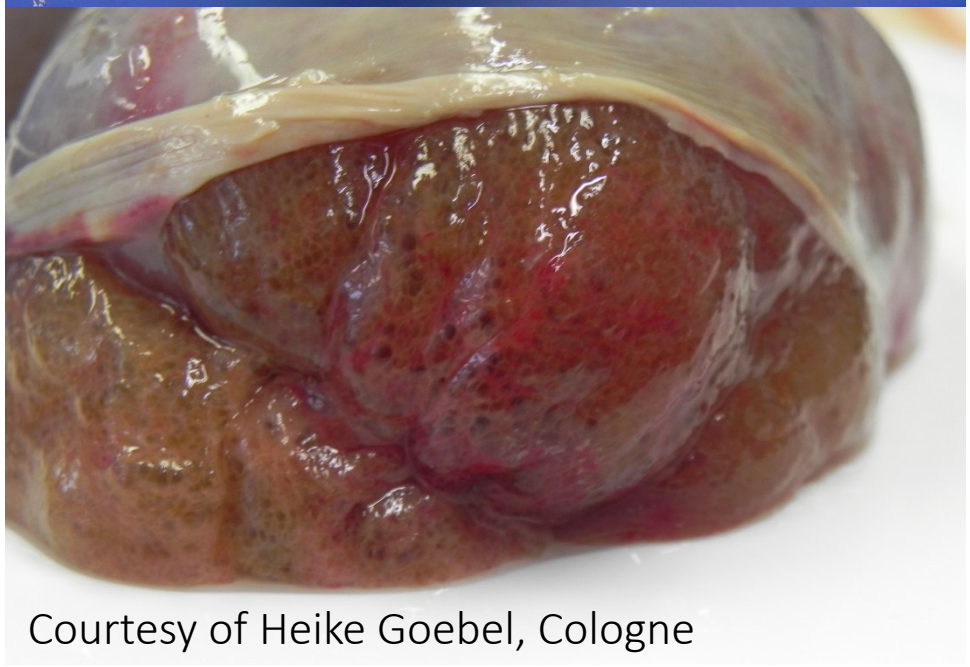
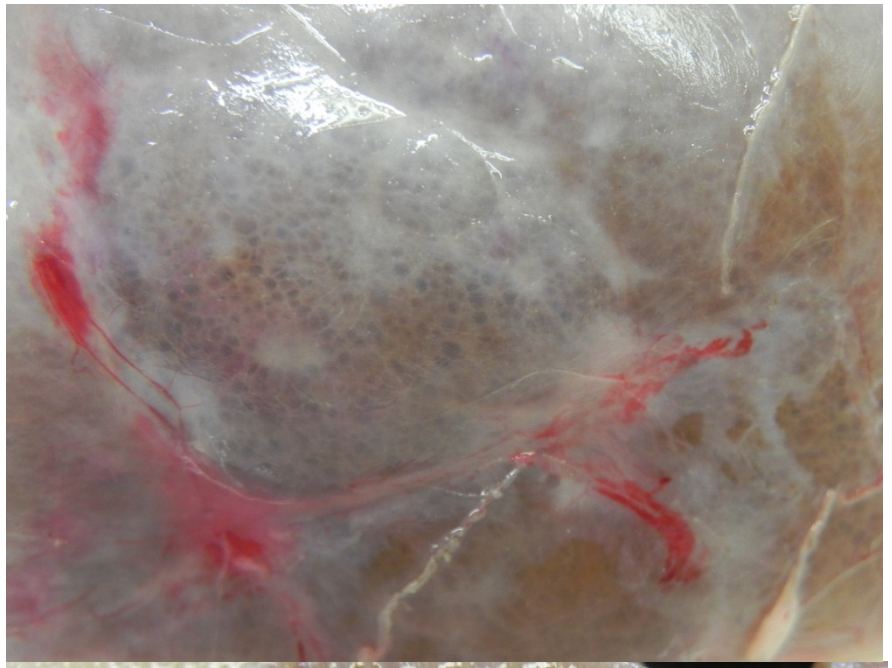
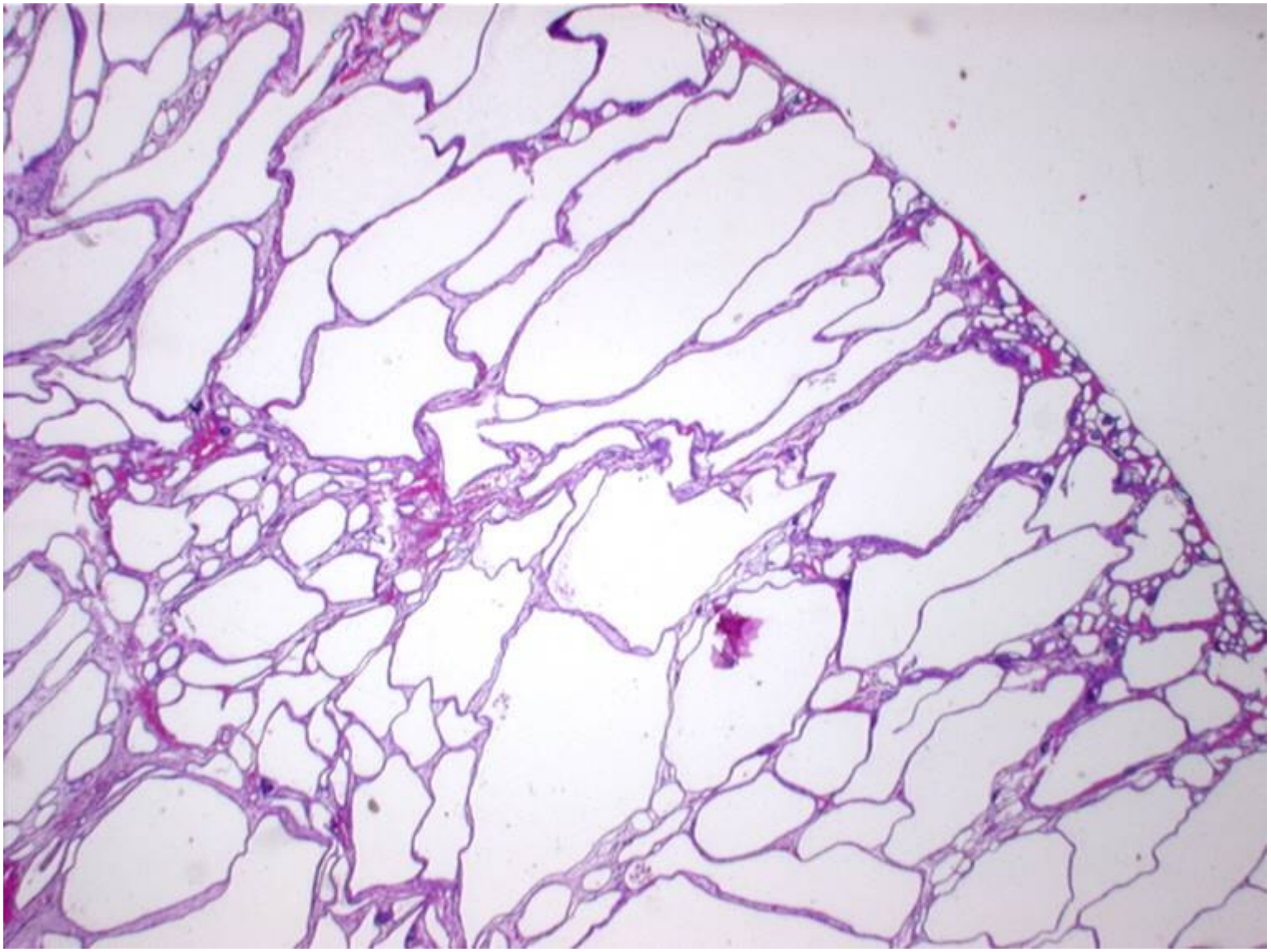




Courtesy of Heike Goebel, Cologne





Courtesy of Heike Goebel, Cologne

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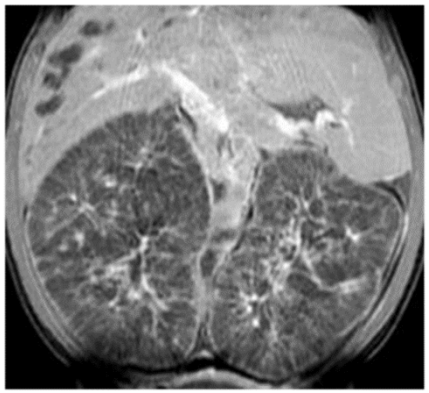
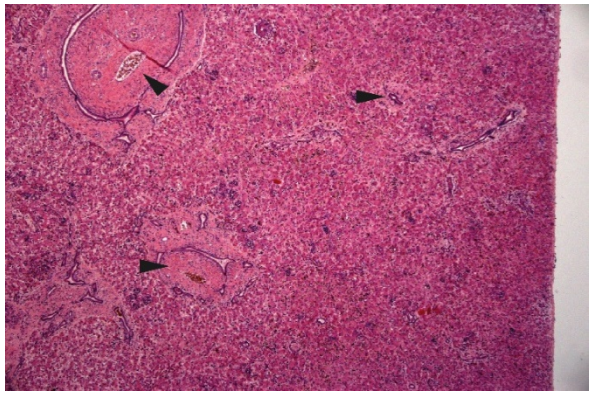
Autosomal Recessive Polycystic Kidney Disease

- 1:20.000, one main gene – *PKHD1, new: DZIP1L*
- Collecting duct dilatations, massively enlarged kidneys, variable kidney function
- Obligatory hepatic involvement – ductal plate malformation, CHF, Caroli‘s disease



Ebner et al.,
Pediatric Nephrology, 2017



Ebner and Liebau,
Der Nephologe 2014

Autosomal Recessive Polycystic Kidney Disease

- 1:20.000, one main gene – *PKHD1, new: DZIP1L*
- Collecting duct dilatations, massively enlarged kidneys, variable kidney function
- Obligatory hepatic involvement – ductal plate malformation, CHF, Caroli‘s disease
- Important clinical symptoms:
  - Severe hypertension
  - (transient) hyponatremia
  - Portal hypertension
  - Cholangitis/sepsis/UTI

Autosomal Recessive Polycystic Kidney Disease

- 1:20.000, one main gene – *PKHD1, new: DZIP1L*
- Collecting duct dilatations, massively enlarged kidneys, variable kidney function
- Obligatory hepatic involvement – ductal plate malformation, CHF, Caroli‘s disease
- *Variable clinical courses, difficult to predict clinical courses*

Diagnostic criteria

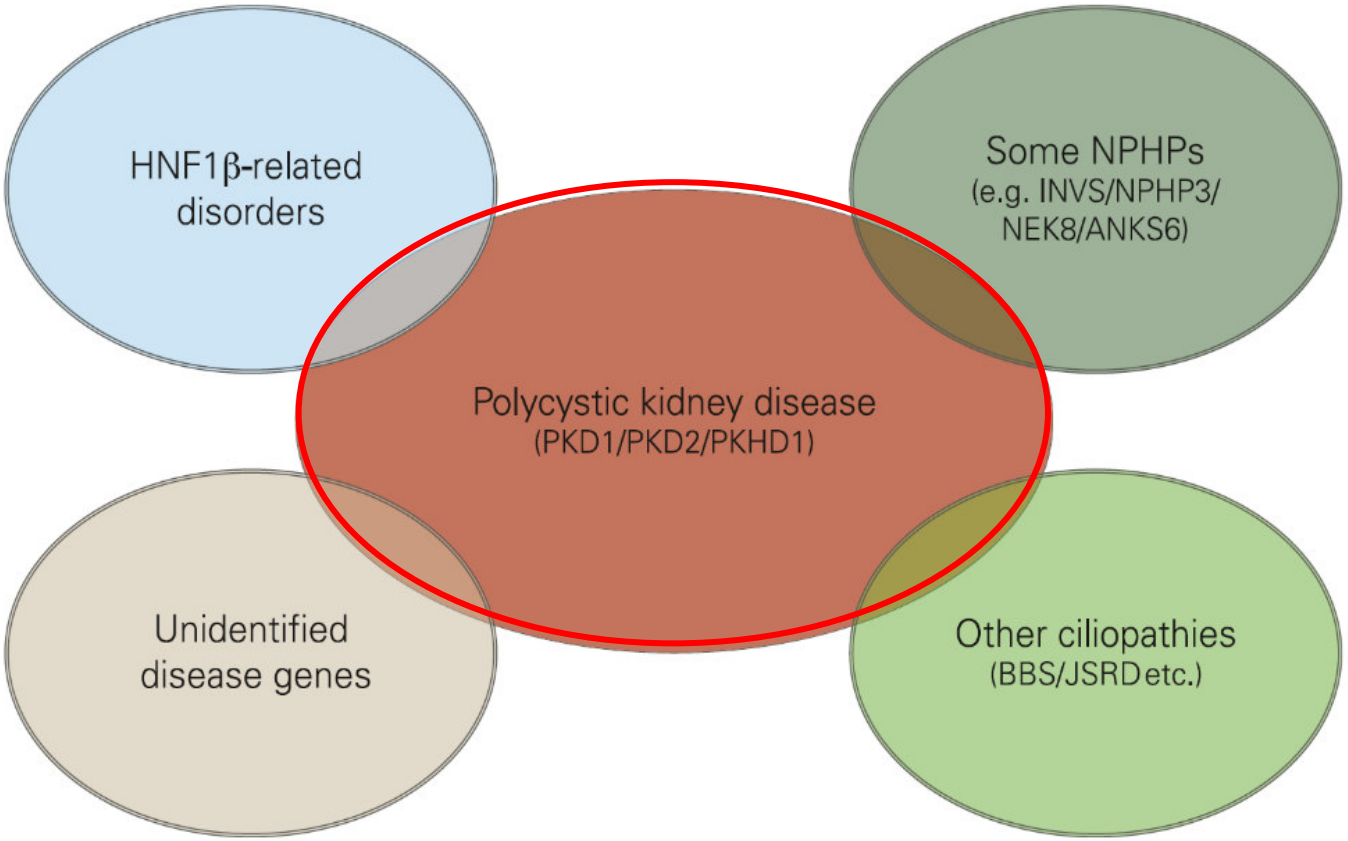
Zerres-criteria (Acta Paediatrica, 1996):

- Typical findings on renal imaging

AND one or more of the following:

- Imaging findings consistent with biliary ductal ectasia (e.g. sonography)
- Clinical/laboratory signs of CHF that leads to portal hypertension
- Hepatobiliary pathology finding demonstrating biliary ductal plate malformation
- Pathologic or genetic diagnosis of ARPKD in an affected sibling
- Absence of renal enlargement or typical imaging findings in both parents

Differential diagnoses of ARPKD - phenocopies



Bergmann,
Pediatric Nephrology, 2015

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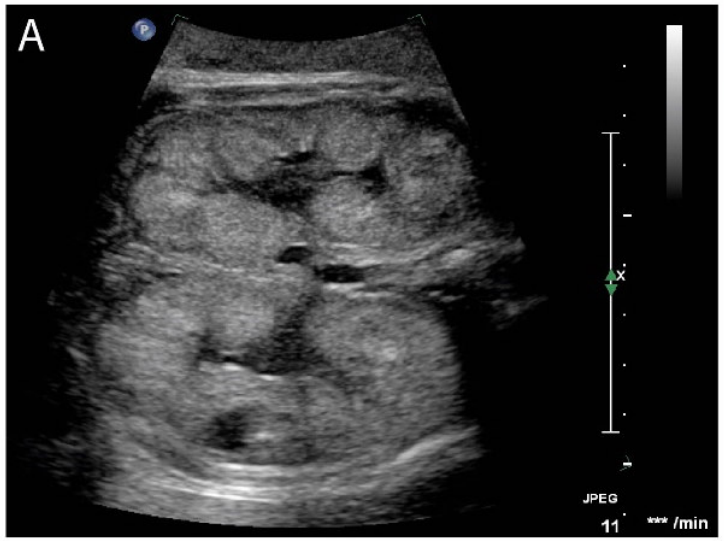
MC Question 1

Is genetic testing (GT) relevant in patients with a clinical diagnosis of ARPKD?

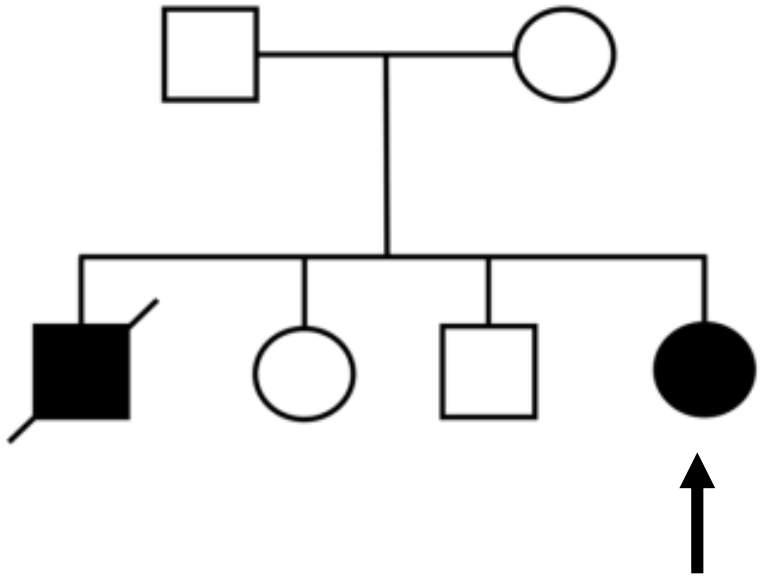
1.) No, as GT does not have clinical consequences.
2.) No, as just one gene is important for ARPKD.
3.) No, as GT does not give reliable results in ARPKD.
4.) GT is mandatory to clearly predict the disease course.
5.) GT is relevant to differentiate ARPKD from *phenocopies*.

Genetic confirmation of the clinical diagnosis
may be helpful for counseling families
and when looking for subtle extrarenal manifestations
in cystic kidney diseases, incl. ARPKD.

An ARPKD history….



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



Ebner et al.,
Pediatric Nephrology, 2017

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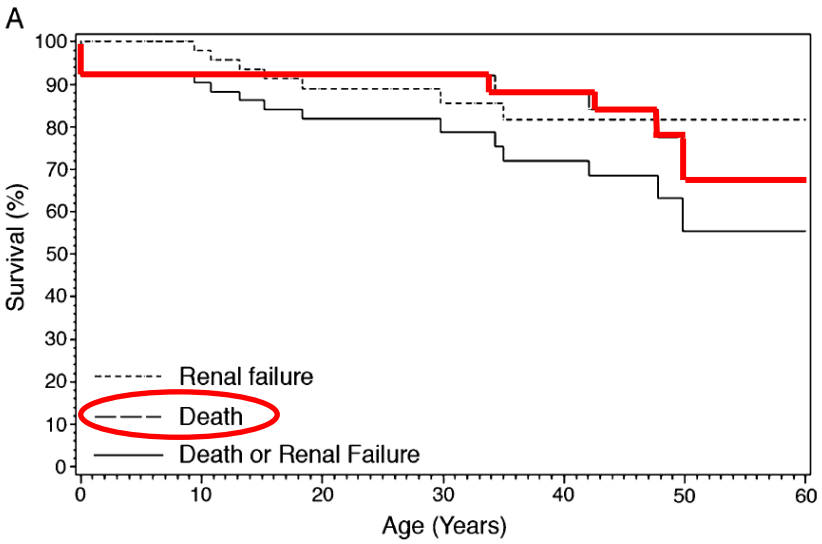
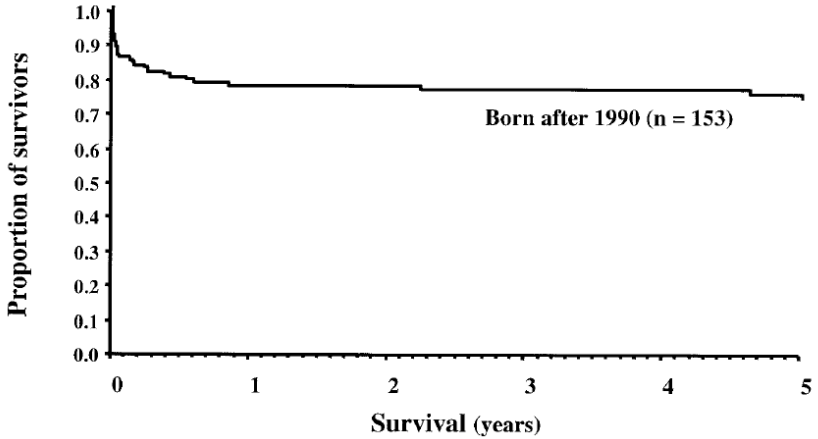
What can we tell the parents about ARPKD?

About survival?
About renal survival?
About treatment options?

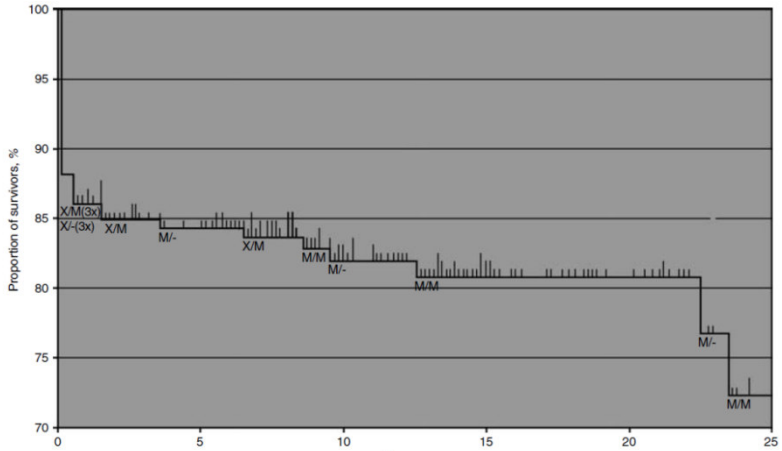
ARPKD - survival



Adeva et al., *Medicine*, 2006



Guay-Woodford and Desmond, *Pediatrics* 2003



Bergmann et al., *Kidney Int* 2006

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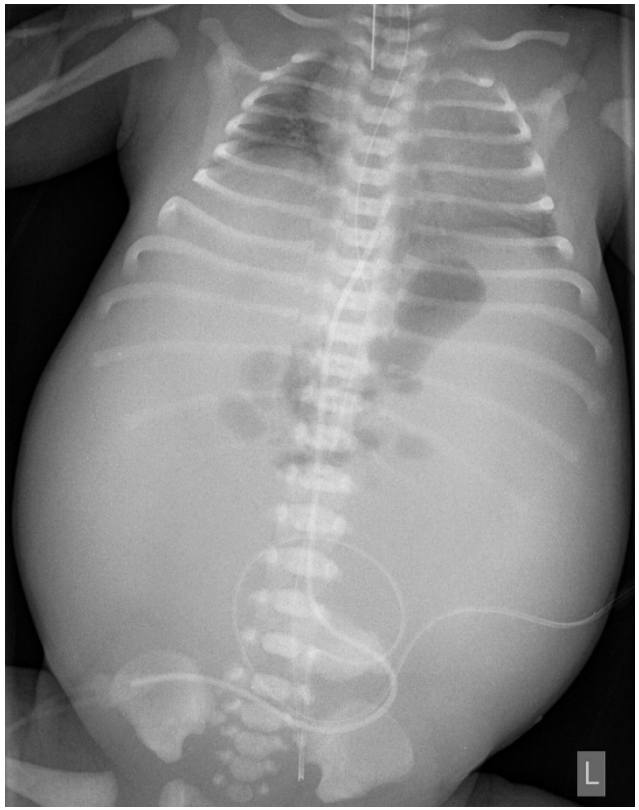
ARPKD - survival

No. of Studies	Quality Assessments: Study Design	Risk of Bias	Inconsis-tency	Indirect-ness	Impre-cision	Other Consider-ations	Effects: No. of Events/ Survivors	No. of Patients	Event Rate/ Survival Rate, % (Range)	Quality	Impor-tance
Prognosis of Neonatal ARPKD											
Neonatal survival											
4 Studies[57-60]	Cohort studies	Not serious	Not serious[b]	Not serious	Not serious	None	353	403	88 (82-96)	Medium	Medium
2 Studies[61,62]	Historical cohort studies	Not serious	Serious[c]	Not serious	Serious[c]	None	63	125	50 (25-87)	Low	Low
1-y Survival of neonatal survivors											
4 Studies[57-60]	Cohort studies	Not serious	Not serious[b]	Not serious	Not serious[b]	None	315	353	89 (85-92)	Medium	Medium
2 Studies[61,62]	Historical cohort studies	Not serious	Not serious	Not serious	Not serious	None	42	63	67 (62-78)	Medium	Low
Survival until end of observation											
4 Studies[57-60]	Cohort studies	Not serious	Not serious[b]	Not seriosu	Not serious[d]	None	323	416	78 (70-81)	Medium	Medium
3 Studies[61-63]	Historical cohort studies	Not serious	Serious[c]	Not serious	Serious[c]	None	139	235	59 (23-87)	Low	Low

Gimpel et al.,
JAMA Pediatrics, 2018

Causes of early death in ARPKD

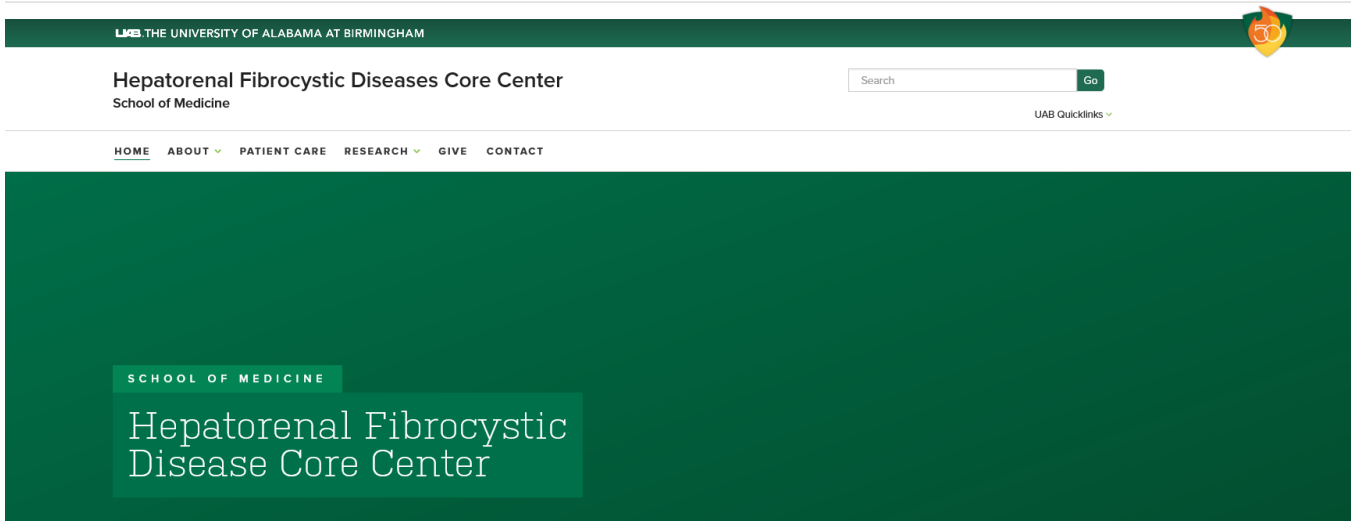
- Pulmonary hypoplasia
- Sepsis (in CKD/on KRT)
- KRT problems
- Parent's decision
- (…)



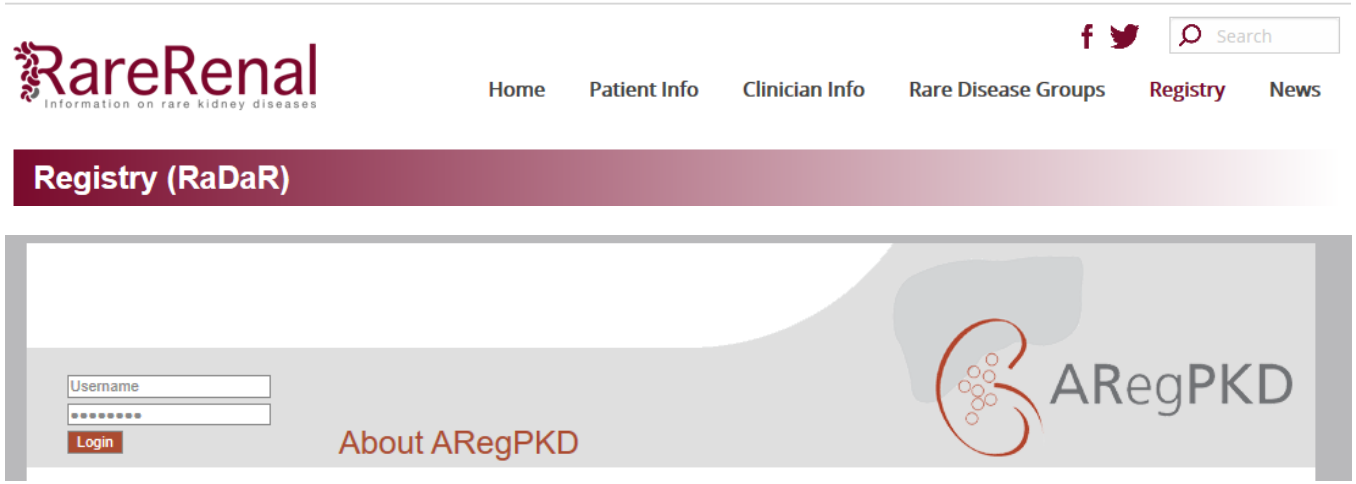
What can we tell the parents?

About survival?
About renal survival?
About treatment options?

Observational studies on ARPKD



L. Guay-Woodford



L. Kerecuk

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ARegPKD

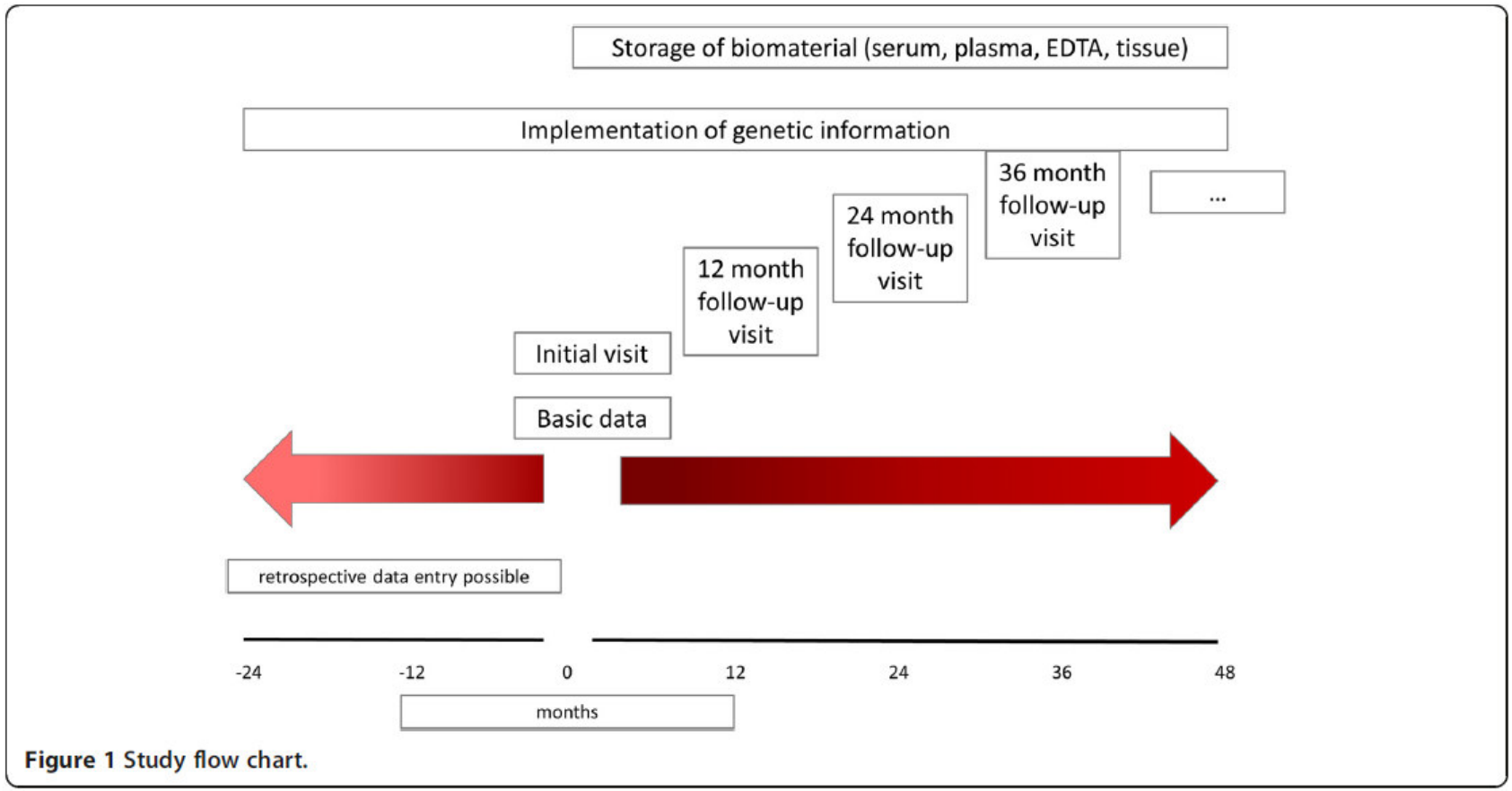
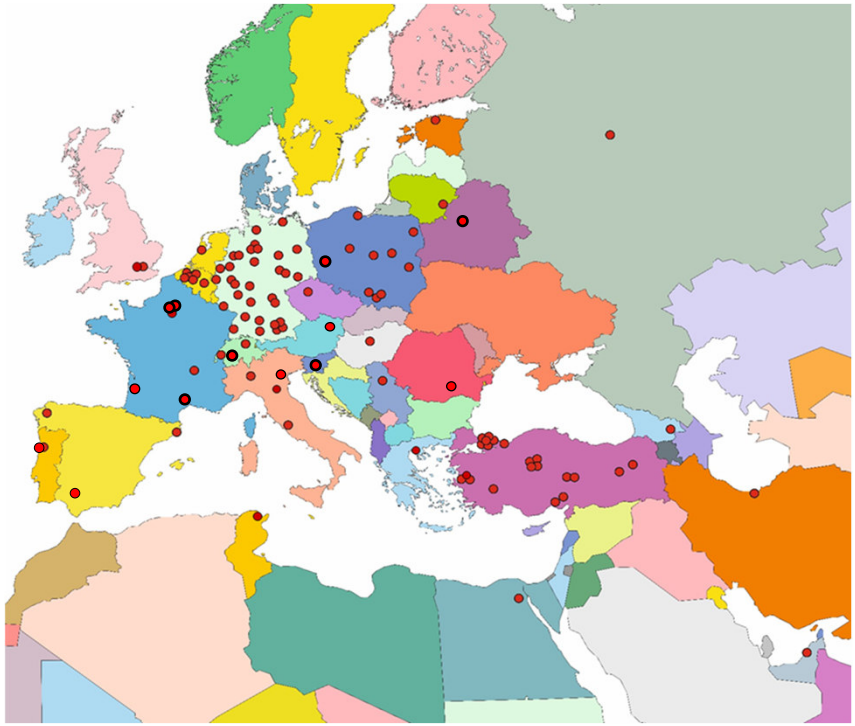


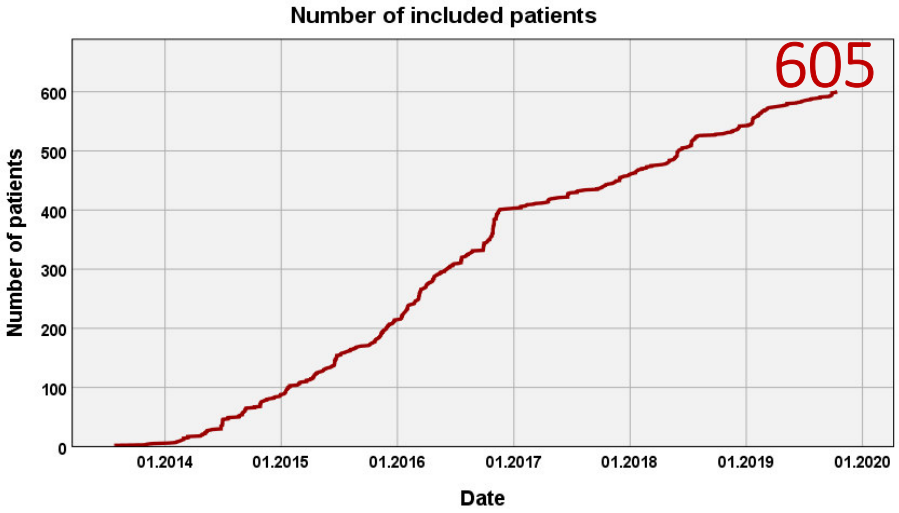
Figure 1 Study flow chart.

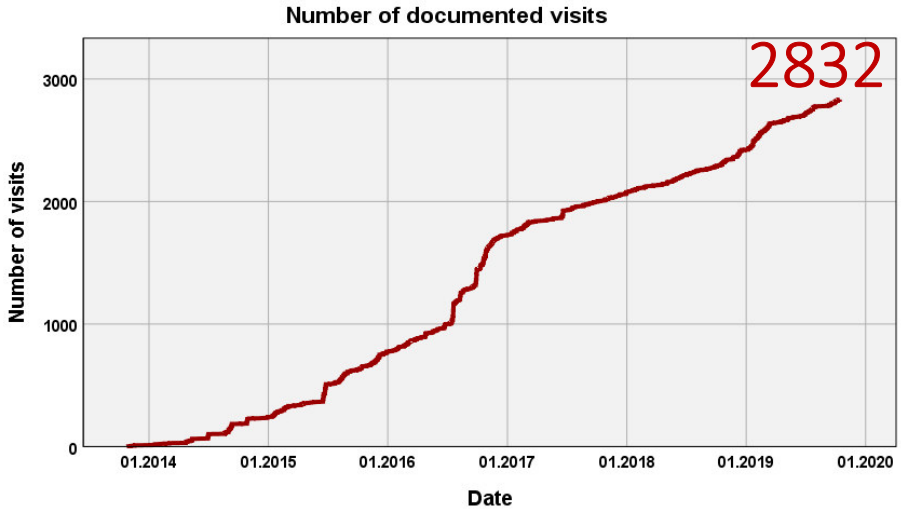
Ebner et al.,
BMC Nephrology, 2015

ARegPKD – 118 centers in 30 countries



ARegPKD – 118 centers in 30 countries

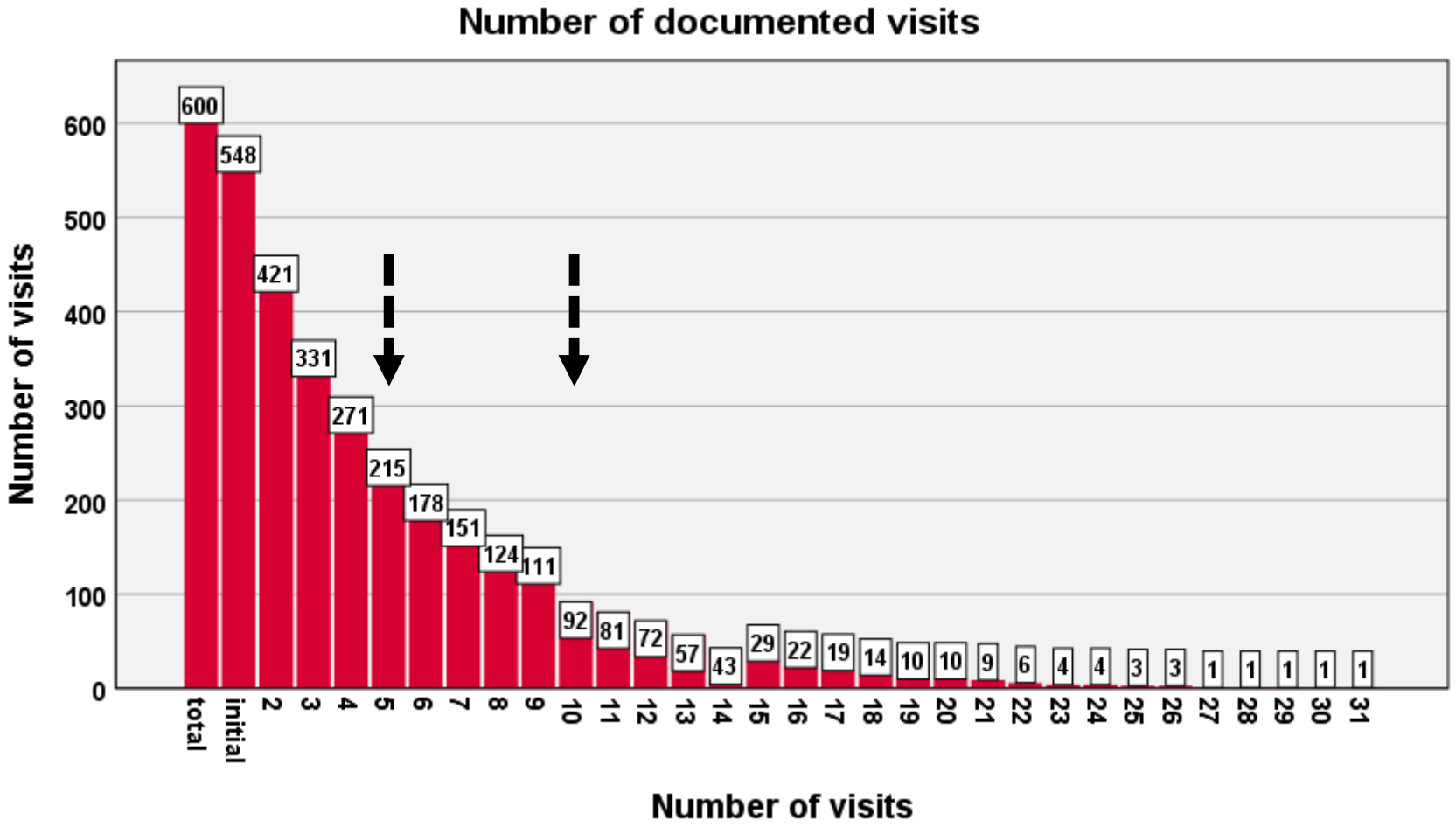




11/2019

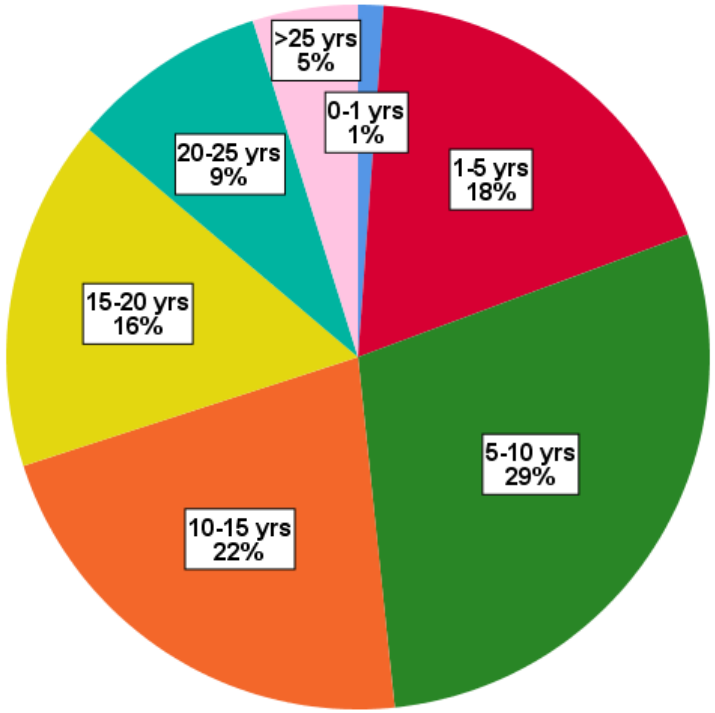
ARegPKD – number of visits

n=600



Cohort description – current age

n=600



Unpublished

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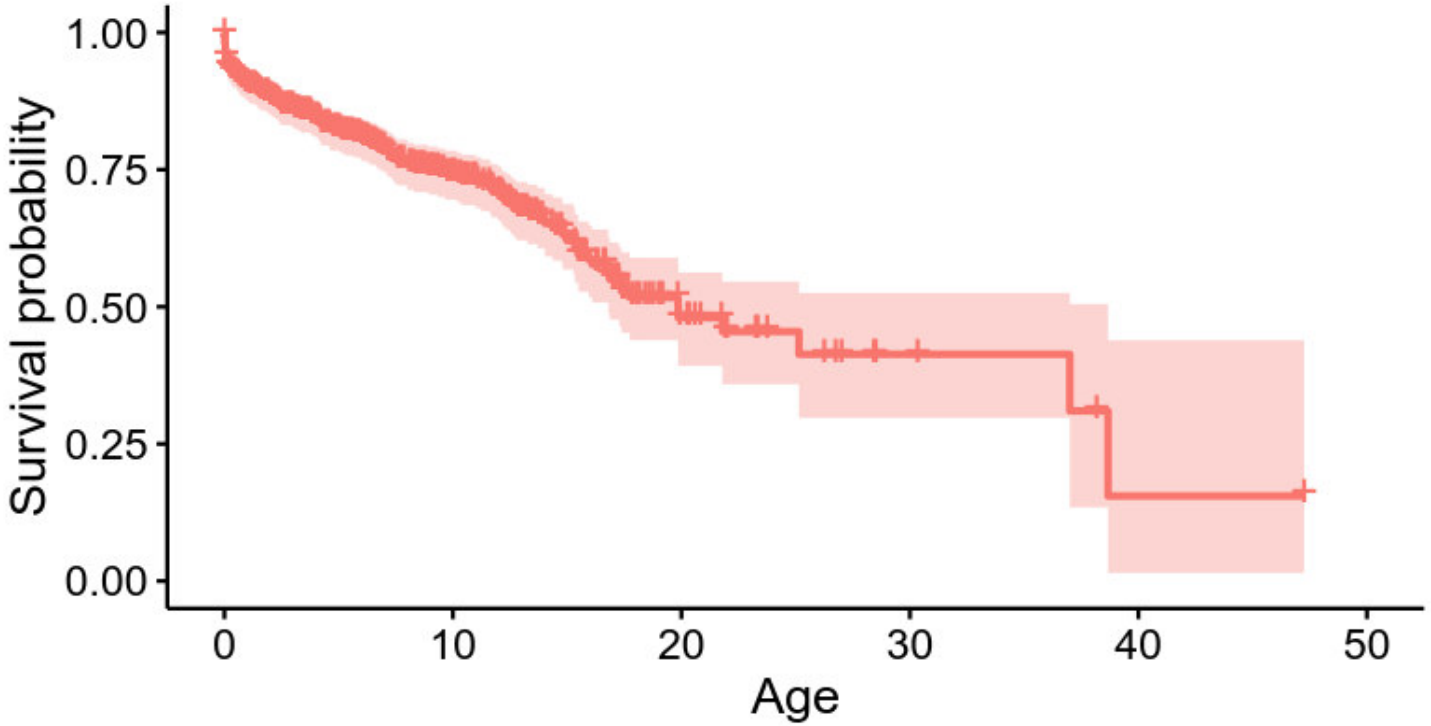
Renal survival



N=573

Unpublished

Risk factors for early dialysis dependency?

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

Antenatal risk factors for early dialysis dependency?

Table IV. Model-based predicted probabilities for dialysis or renal replacement therapy within 12 and 36 months after birth

Prenatal symptoms	No. of dialysis cases within 12 mo after birth/ no. of observations	Probability of dialysis within 12 mo after birth (95% CI)	No. of cases with RRT within 36 mo after birth/ no. of observations	Probability of RRT within 36 mo after birth (95% CI)
No prenatal abnormalities	1.2/186.5	0.015 (0.005-0.041)	1.2/166.9	0.017 (0.006-0.047)
Enlarged kidneys	1.1/7.1	0.033 (0.006-0.155)	1.1/6.0	0.035 (0.006-0.170)
Renal cysts	0.2/18.6	0.034 (0.008-0.135)	0.2/16.5	0.039 (0.009-0.154)
Enlarged kidneys and renal cysts	2.6/17.2	0.071 (0.021-0.215)	2.6/15.2	0.076 (0.022-0.233)
OAH	4.2/32.6	0.087 (0.032-0.214)	4.2/26.6	0.103 (0.037-0.254)
OAH and enlarged kidneys	2.2/15.4	0.174 (0.055-0.431)	2.2/14.3	0.189 (0.059-0.463)
OAH and renal cysts	2.3/8.2	0.178 (0.047-0.486)	2.3/7.0	0.207 (0.054-0.546)
OAH and enlarged kidneys and renal cysts	22.3/74.4	0.323 (0.222-0.445)	22.3/69.5	0.348 (0.239-0.475)

Observation numbers are not integers due to averaging of the imputed dataset.
OAH, oligohydramnios/anhydramnios; RRT, renal replacement therapy.

Burgmaier et al., *J Peds*, 2018

Antenatal sonographic detection of kidney enlargement, renal cysts and oligo-/anhydramnios may help to estimate the risk for early dialysis dependency in ARPKD.

MC Question 2

What is the course of kidney function in ARPKD?

1.) All children will require KRT within the first weeks of life.
2.) Only children with severe liver affection will require KRT.
3.) KRT is generally not needed until 20 years of age.
4.) KRT may be required in the first weeks of life.
5.) The kidney phenotype is only variable in terms of kidney size.

What can we tell the parents?

About survival?
About renal survival?
About treatment options?

THE JOURNAL OF PEDIATRICS • www.jpeds.com WORKSHOP/SYMPOSIUM SUMMARY

Consensus Expert Recommendations for the Diagnosis and Management of Autosomal Recessive Polycystic Kidney Disease: Report of an International Conference

Lisa M. Guay-Woodford, MD[1], John J. Bissler, MD[2], Michael C. Braun, MD[3], Detlef Bockenhauer, MD[4], Melissa A. Cadnapaphornchai, MD[5], Katherine M. Dell, MD[6], Larissa Kerecuk, MD[7], Max C. Liebau, MD[8], Maria H. Alonso-Peclet, MD[9], Benjamin Shneider, MD[10], Sukru Emre, MD[11], Theo Heller, MD[12], Binita M. Kamath, MD[13], Karen F. Murray, MD[14], Kenneth Moise, MD[15], Eric E. Eichenwald, MD[16], Jacquelyn Evans, MD[17], Roberta L. Keller, MD[18], Louise Wilkins-Haug, MD[19], Carsten Bergmann, MD[20,21], Meral Gunay-Aygun, MD[22,23], Stephen R. Hooper, PhD[24], Kristina K. Hardy, PhD[25], Erum A. Hartung, MD[26], Randi Streisand, PhD[1], Ronald Perrone, MD[27], and Marva Moxey-Mims, MD[28]

Guay-Woodford et al.,
J Peds 2014

JAMA Pediatrics | Special Communication

Perinatal Diagnosis, Management, and Follow-up of Cystic Renal Diseases
A Clinical Practice Recommendation With Systematic Literature Reviews

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Gimpel et al.,
JAMA Peds 2018

Treatment of ARPKD in neonates

- Symptomatic treatment under best possible conditions (NICU, multidisiciplinary pre- and postnatal consultation and treatment etc.)

- As for other renal disorders PD is the preferred dialysis modality for neonates

- Treatment of hypertension may require multiple antihypertensive agents, lower sodium levels may need to be tolerated.

- The rationale for unilateral nephrectomy is based on few small nutrition studies. There is no evidence that nephrectomy results in respiratory improvement. There is no evidence to support nephrectomy for severe HTN in early ARPKD.

Guay-Woodford et al., *J Peds 2014*
Gimpel et al., *JAMA Peds 2018*

ARPKD – very early bilateral nephrectomies

- ARegPKD analysis: four groups
  - *Very early bilateral nephrectomies (VEBNE): bilateral nephrectomies within first 3 months of life*
  - *Early bilateral nephrectomies (EBNE): bilateral nephrectomies: 4-15 months*
  - *Very early dialysis: dialysis within first 3 months but w/o bilateral nephrectomies*
  - *Total kidney volume control: same sized kidneys but w/o nephrectomies or dialysis*

- Few differences in pre- or perinatal aspects over all four groups

Under review

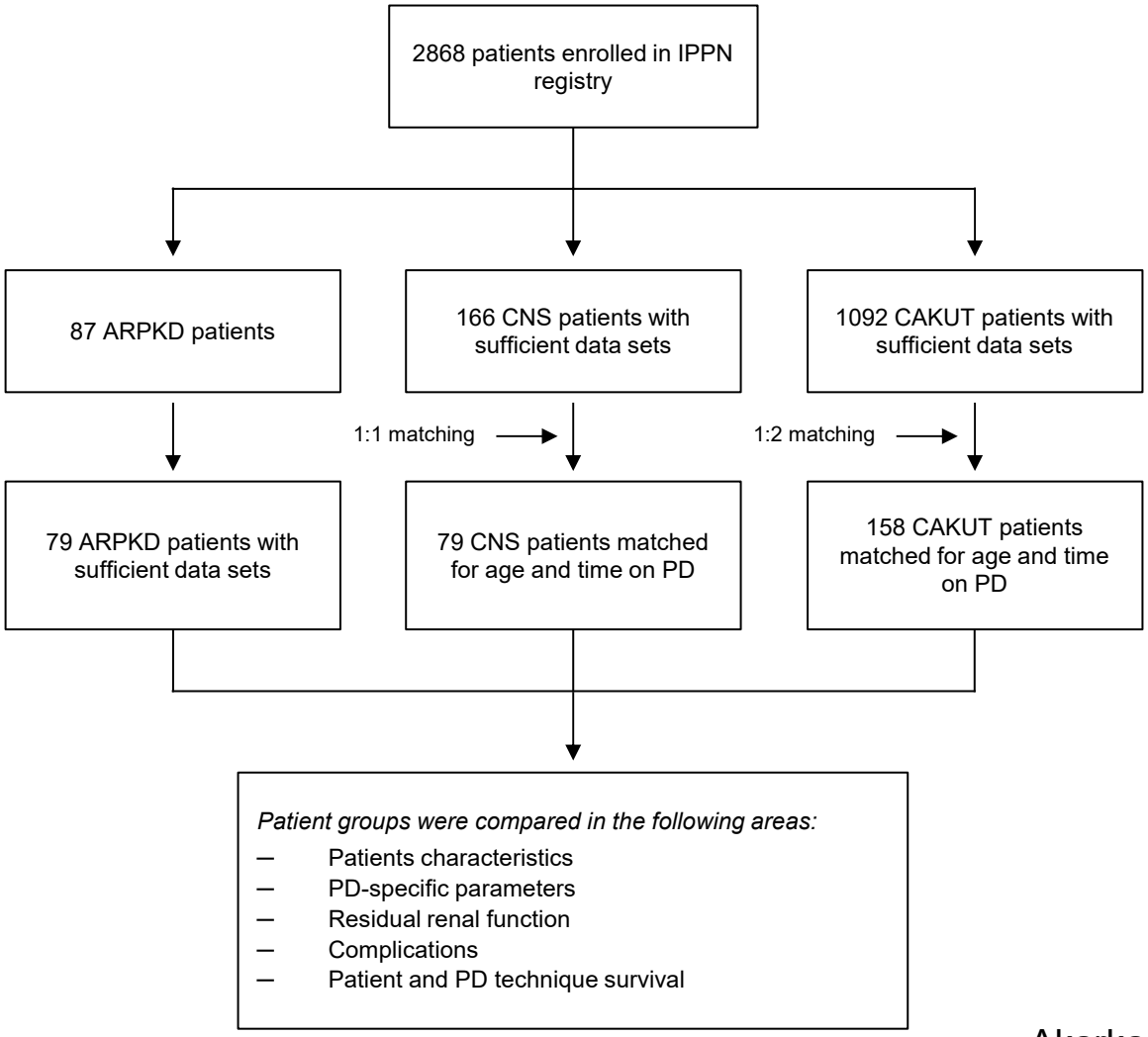
ARPKD – very early bilateral nephrectomies

- Severe neurological complications (ischemia, infarction, parenchymal defect, hypoxic encephalopathy, atrophy of optical nerve with loss of vision…) in
  - 12/19 VEBNE (63%)
  - 2/9 EBNE (22%)
  - 2/12 VED (17%)
  - 0/11 TKV controls patients (0%)

Under review

Very early bilateral nephrectomies in children with ARPKD may be associated with more neurological complications.

Course on peritoneal dialysis?



Akarkach et al., AJKD, 2020

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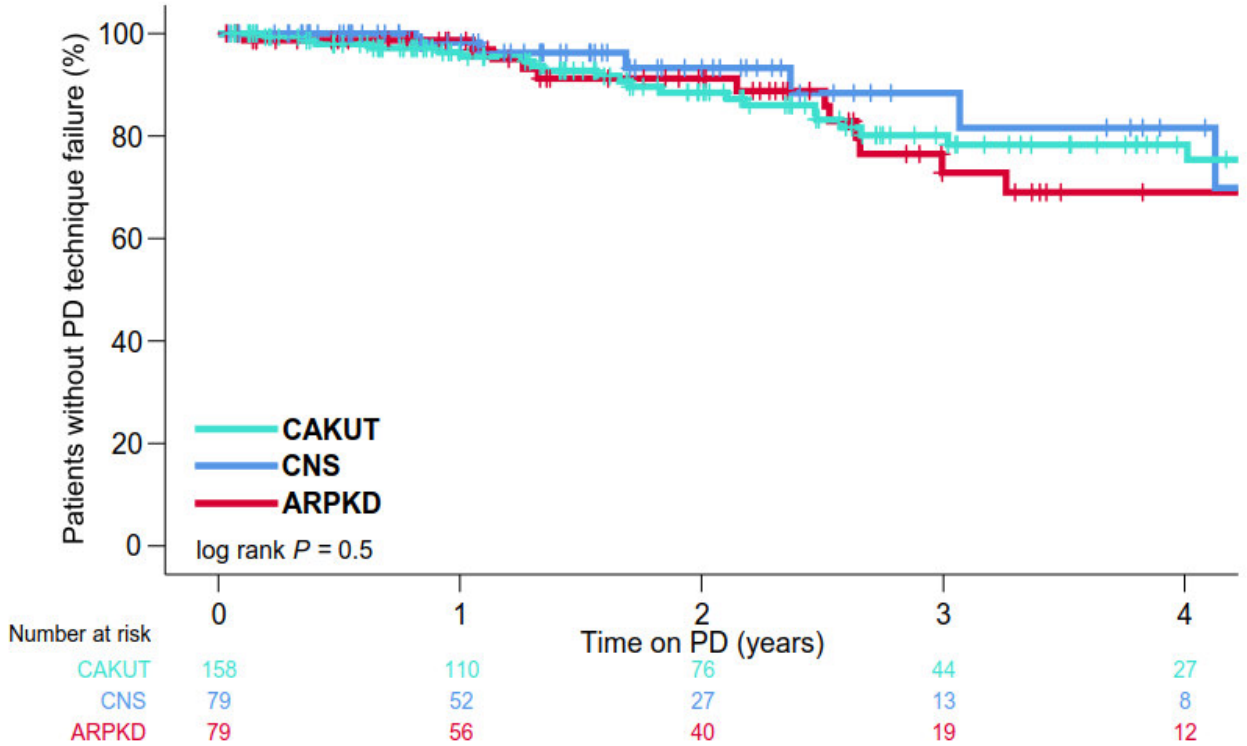
PD technique survival – data from the IPPN registry



Akarkach et al., AJKD, 2020

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PD can be used in children with ARPKD
as in children with other early-onset renal diseases
and requires only minor adaptations.

MC Question 3

What are treatment approaches in ARPKD?

1.) Gene therapy for ARPKD is established and is curative.
2.) Targeted and disease-modifying treatment is available.
3.) Treatment remains symptomatic.
4.) PD is not possible in ARPKD as kidneys are too large.
5.) ARPKD patients must undergo bilateral NE as soon as possible.

Limitations

- Observational studies – „real world“ clinical data is used
- Partially missing genotypes/datapoints
- Selection bias
- (…)

Summary

- ARPKD in newborns remains a clinical challenge. Genetics may help to establish the correct diagnosis.

- Treatment for ARPKD currently remains largely symptomatic and opinion-based, but first observational evidence is emerging:
  - Very early bilateral nephrectomies may be associated with neurological complications.
  - PD in young children shows good results and requires minor adaptions

- Further translational international research approaches will be crucial to progress towards evidence-based targeted therapies for pediatric PKD.

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