Welcome to

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

WEBINAR

04/06/24

ADPKD in children

Speaker: Djalila Mekahli (Leuven, Belgium)

Moderator: Jens König (Münster, Germany)

KDIGO – Kidney Disease: Improving Global Outcomes

fwo Research Foundation Flanders – Opening new horizons

ERKNet – The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

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Disclosures

Paid to the institions UZ Leuven / KU Leuven

- Otsuka : Advisory board, research grant
- Galapagos : Advisory board, research grant

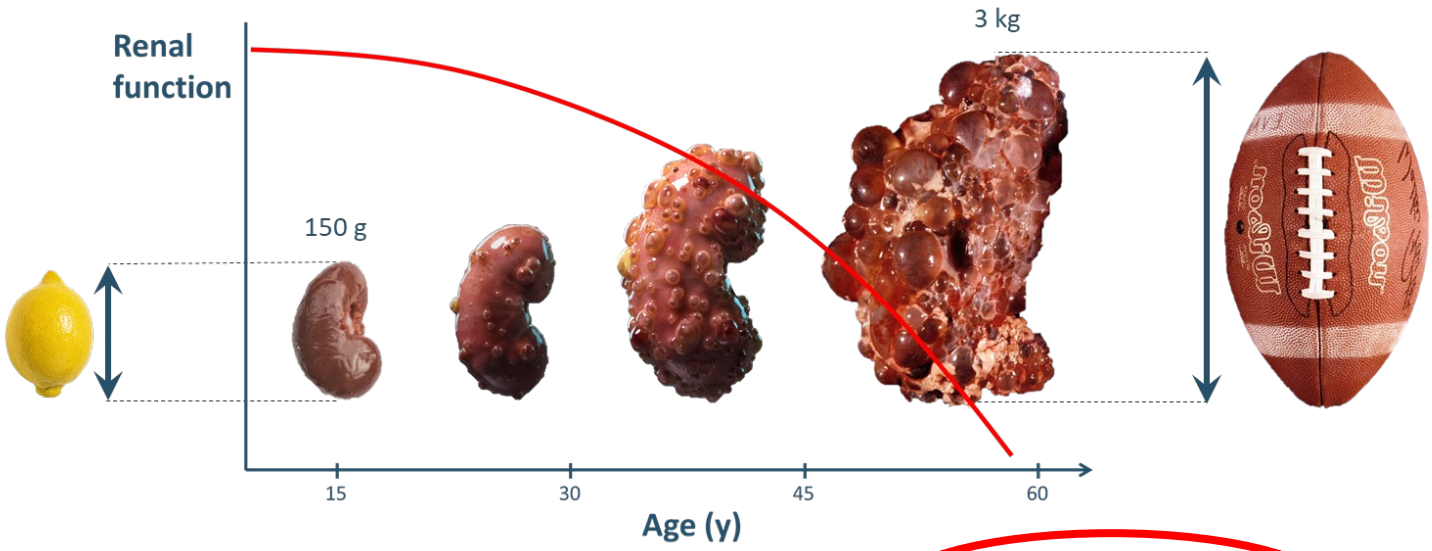
Introduction to ADPKD

Affects ~1/1.000 live births

12 millions patients worldwide

Most common hereditary kidney disease
4th common cause for kidney replacement therapy

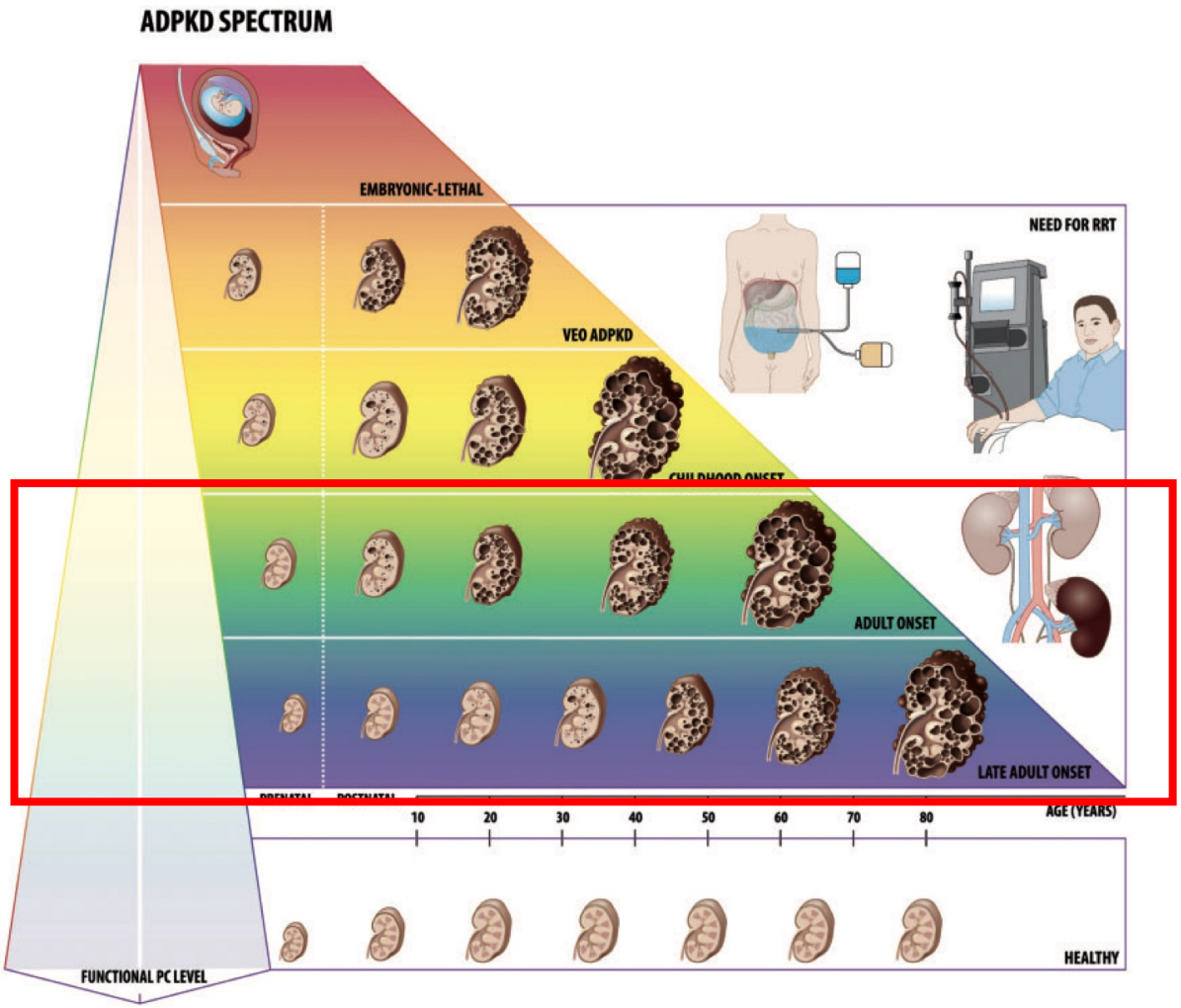
***PKD1* (80%) > polycystin 1**
***PKD2* (15%) > polycystin 2,**
***GANAB*, *DNAJB11*, *ALG9* (rare)**



Bilateral kidney cysts formation from all nephron segments - Kidney failure 50-70 years

Grantham *et al.* NEJM (2016)

ADPKD Spectrum



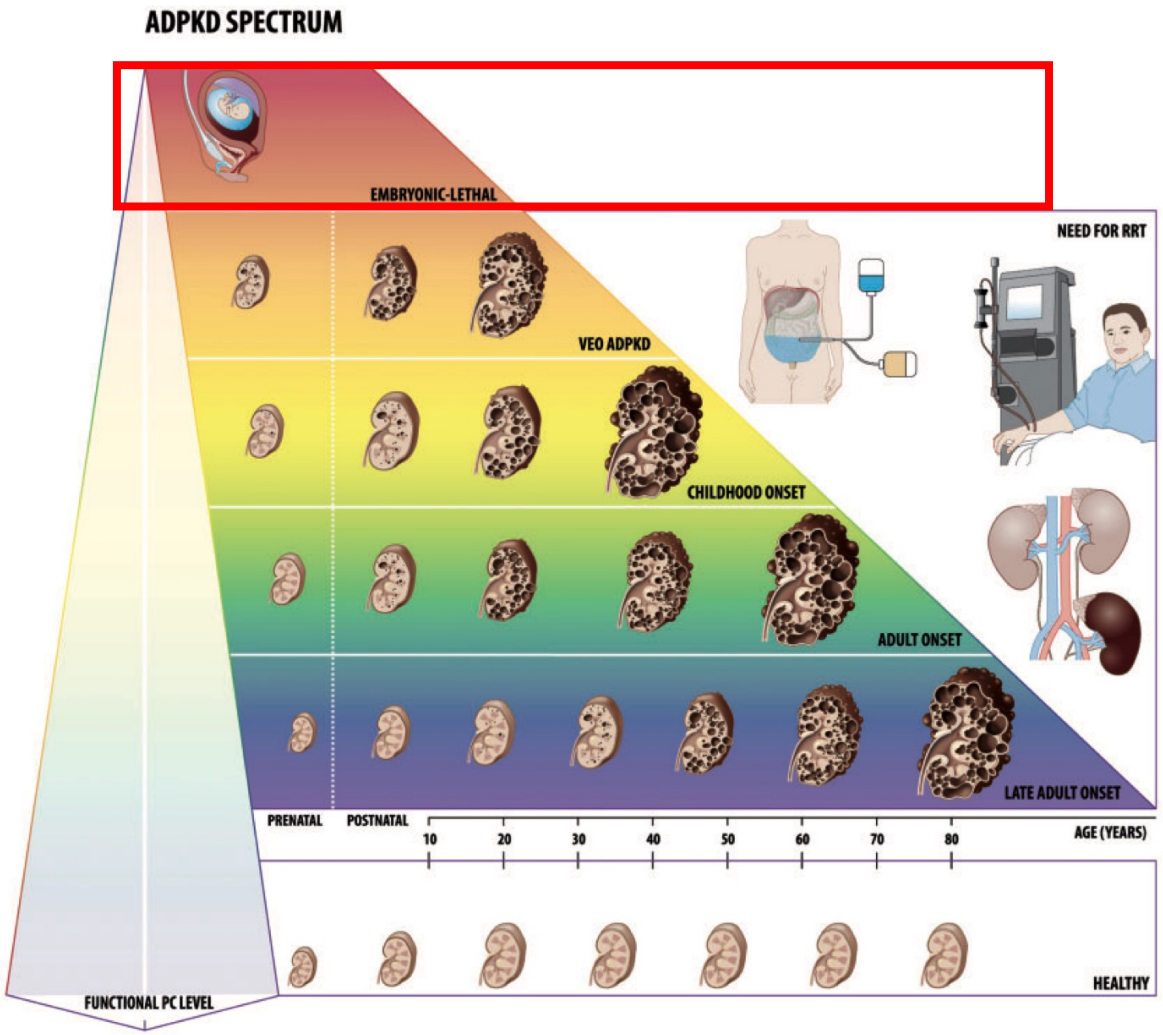
High phenotypic variability

PKD1
PKD2
GANAB
DNAJB11
ALG9
ALG5
....

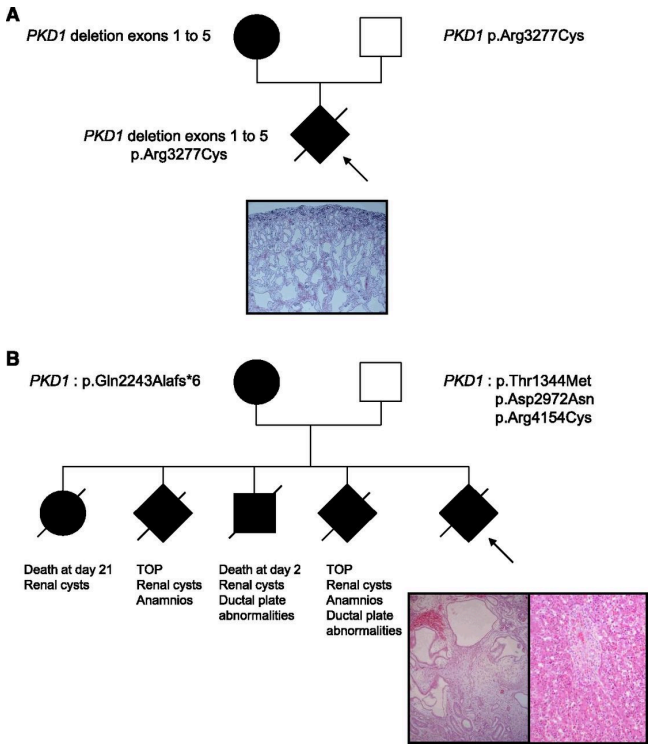
De Rechter et al. Clin Kidney J, 2018

Cornec-Le Gall E, JASN 2018
Cornec-Le Gall E, AJHG, 2022

ADPKD Spectrum

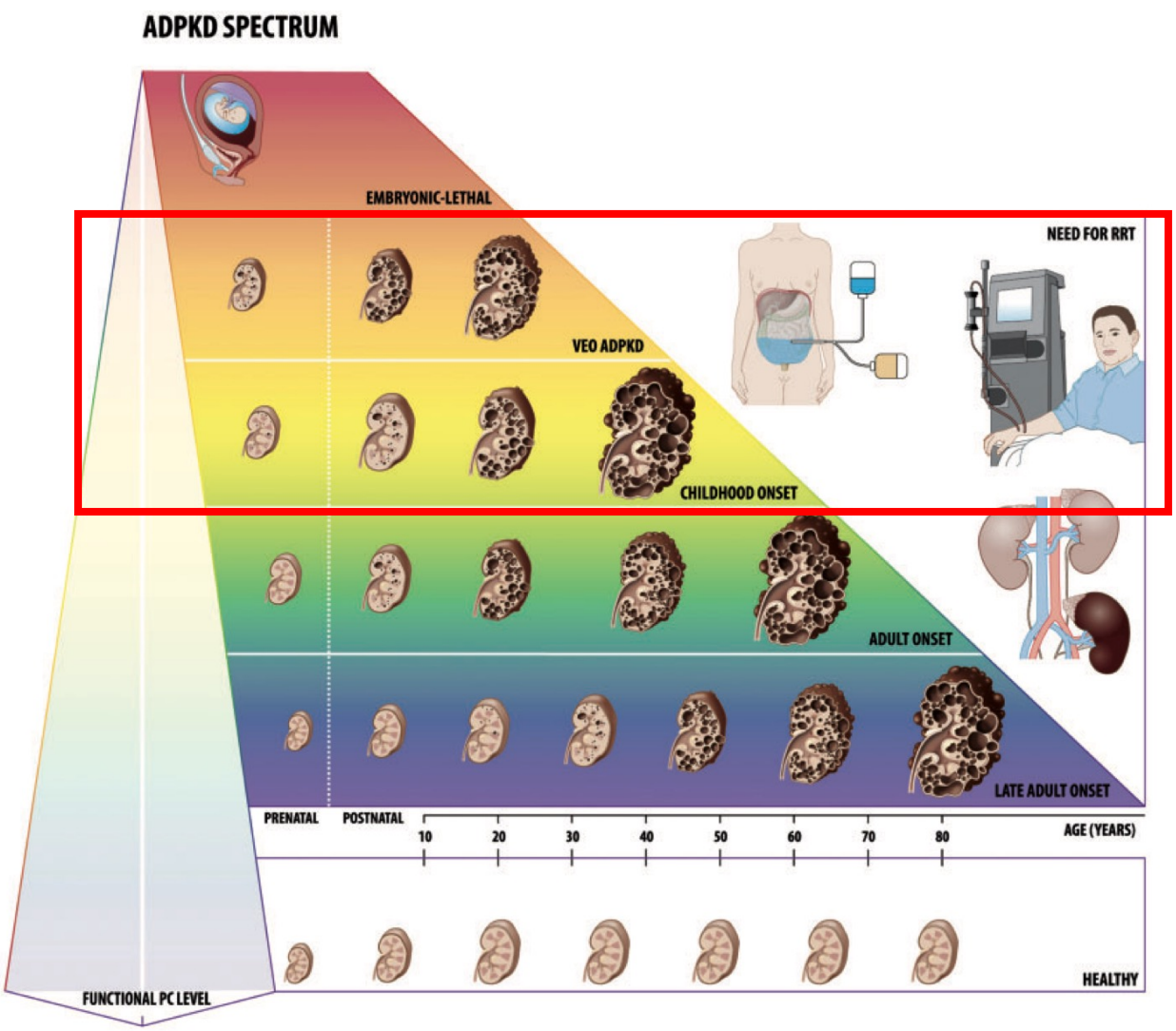


De Rechter et al. Clin Kidney J, 2018



Audrézet et al. JASN 2016

ADPKD Spectrum

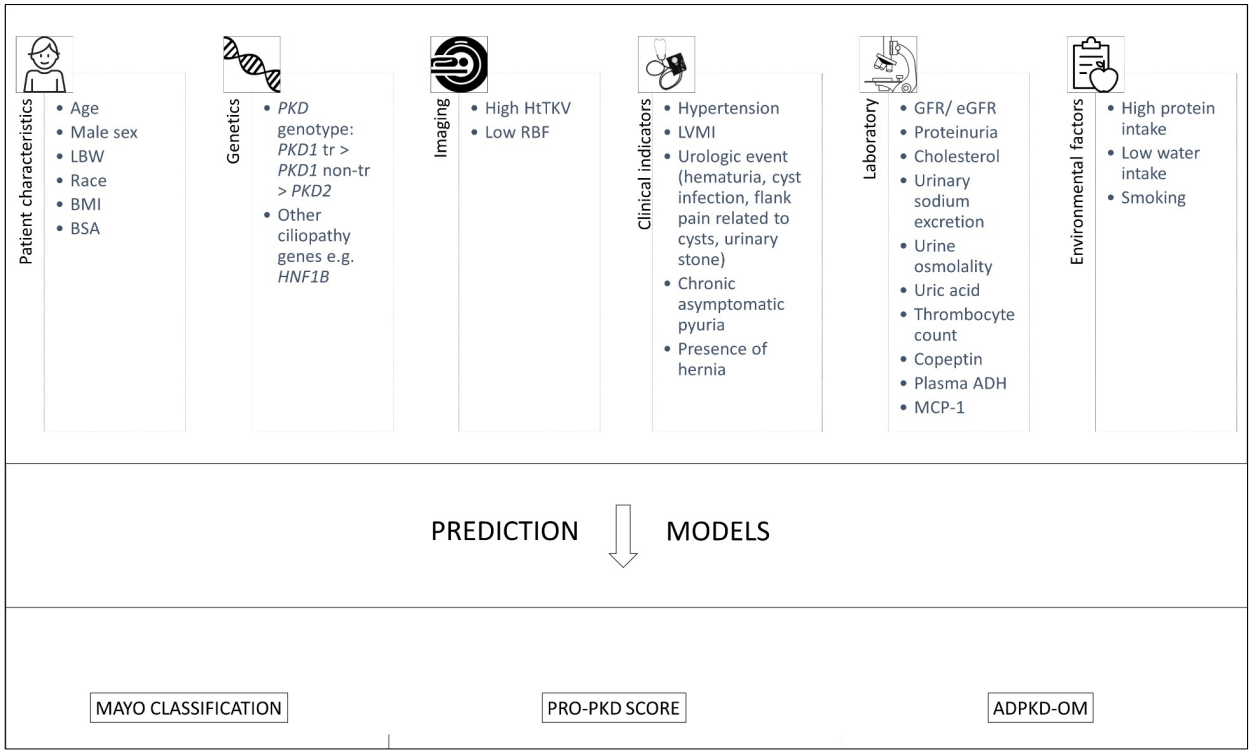


De Rechter et al. Clin Kidney J, 2018

De Rechter et al. Clin Kidney J, 2018

Disease severity and prediction models in ADPKD

Adults:

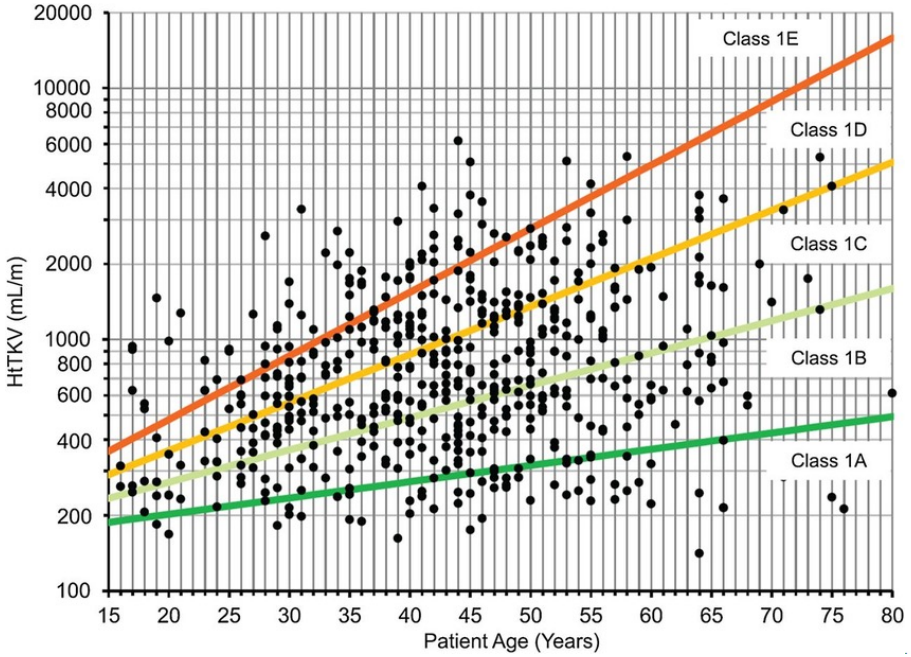


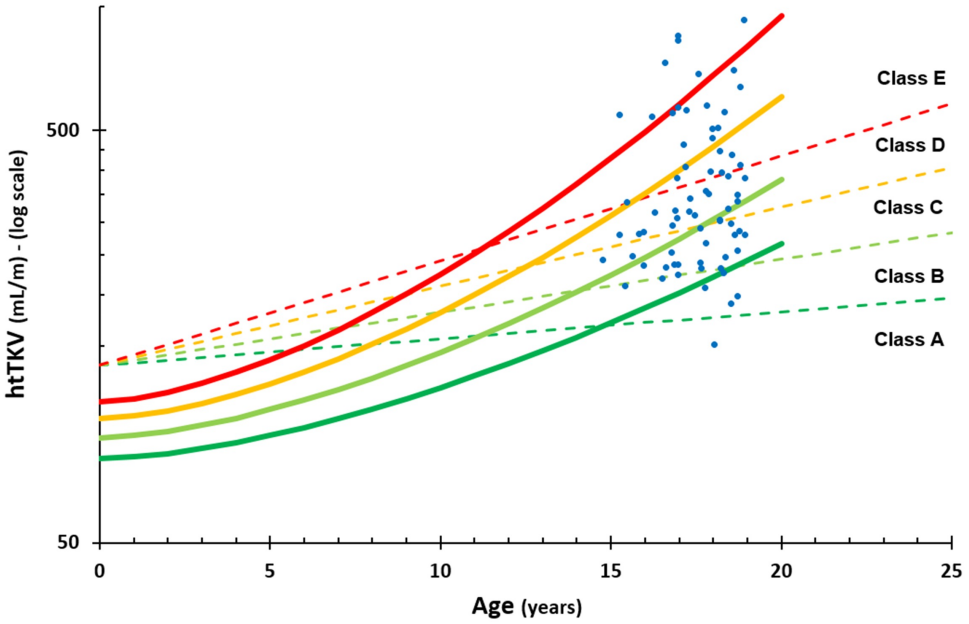
Children:

- No validated prediction factors
- Small cohorts
- No defined endpoints
- No long-term data

De Rechter et al. Clin Kidney J, 2018

Stratification TKV in patients with ADPKD





The Mayo Imaging Classification (MIC)

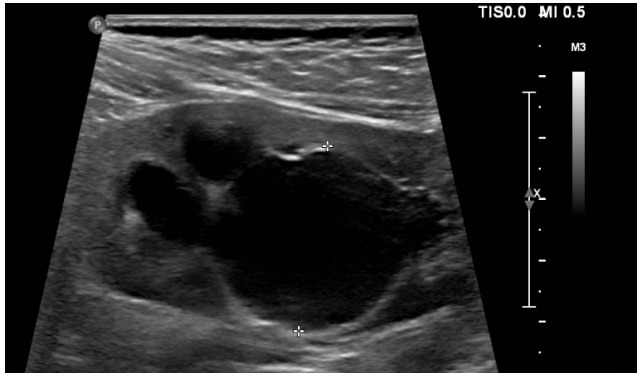
The Leuven Imaging Classification (LIC)

Breysem et al cJASN 2023

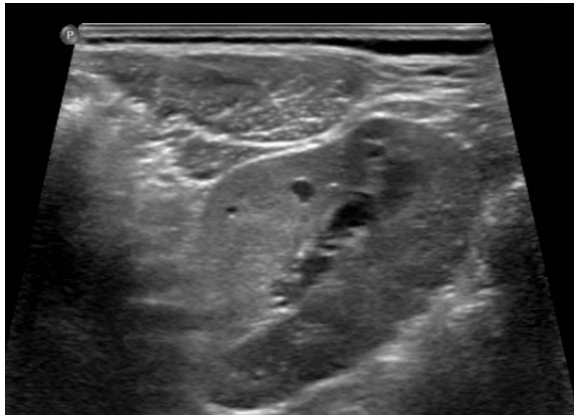
Case 1: Girl with incidental finding of kidney cysts /symptomatic

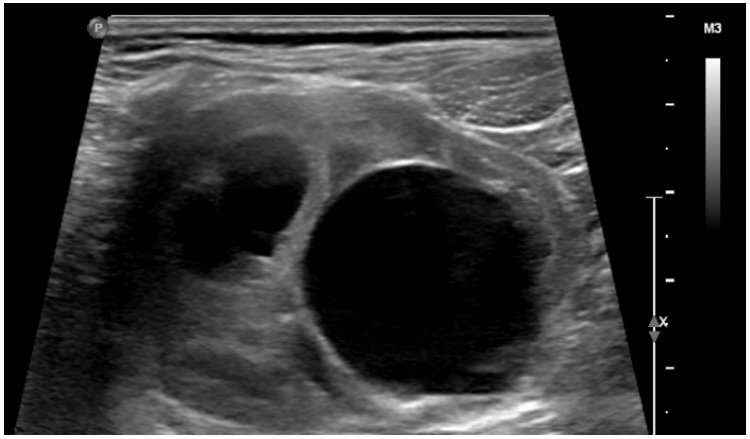
- At age 1 year: US because vomiting, few cortical cysts left kidney
- At age 2 years: US because of pain, suspicion of PUJ stenose left?
  Surgey planned
- Second opninion ADPKD clinic

Left Kidney

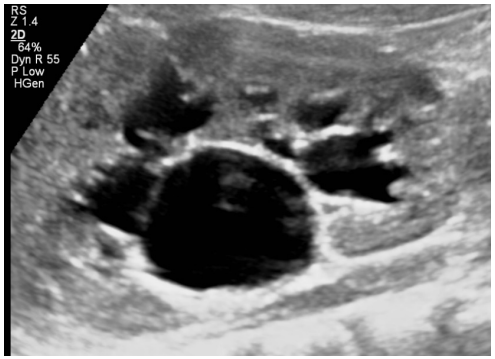


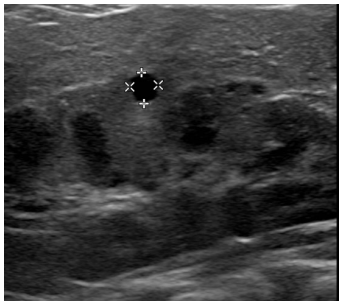
Right Kidney

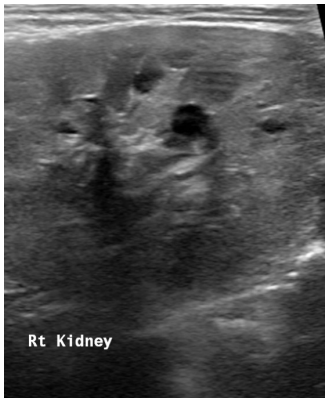


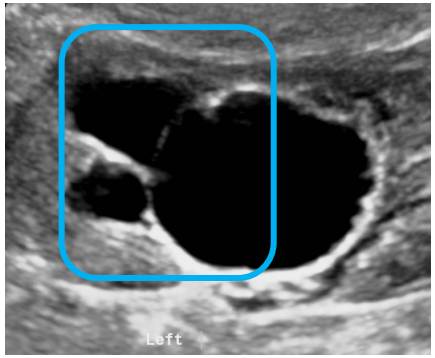


Case 1: Girl with incidental finding of kidney cysts /symptomatic

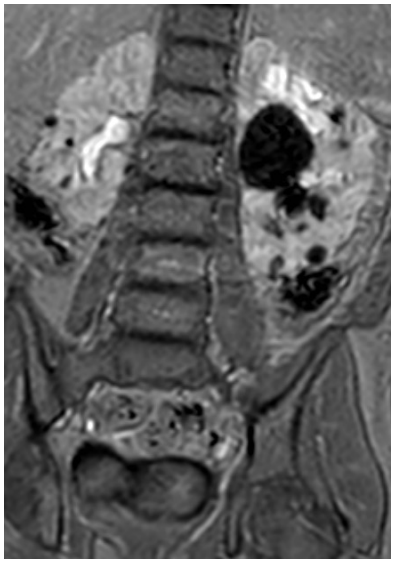


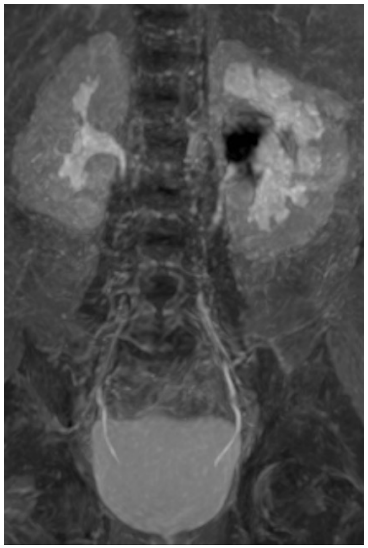


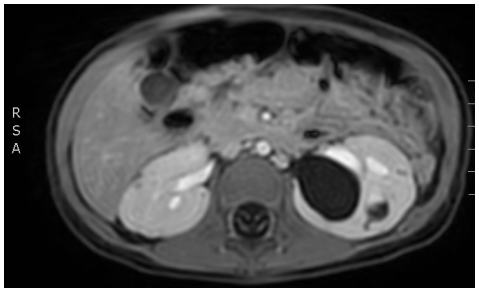


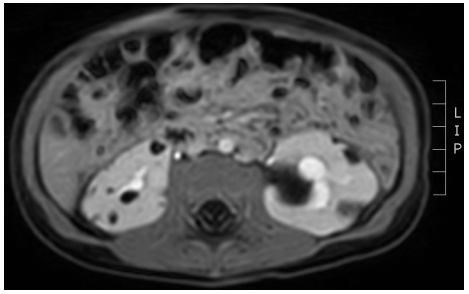


Kidney length R:7,37 cm
Kidney length L: 7,89 cm
TKV 2D: 115,1 ml
htTKV 2D: 121,67 ml







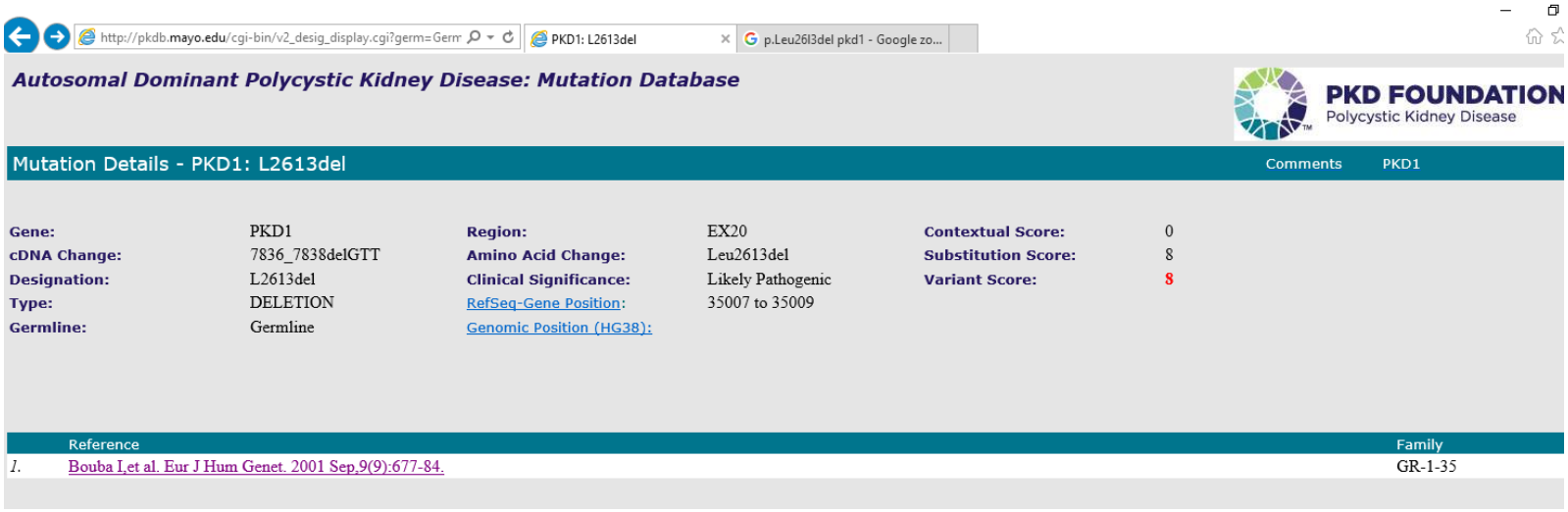


MRI with IV contrast

Case 1: Girl with incidental finding of kidney cysts

Familial history:

- Mother: At the age 15 y renal cysts, no follow-up
- No familial history: Grandparent: normal US
- Genetics in mother and daughter *PKD1* c.7837_7839delTTG;p.Leu26l3del mutatie



http://pkdb.mayo.edu/cgi-bin/v2_desig_display.cgi?germ=Germ

PKD1: L2613del

p.Leu26l3del pkd1 - Google zo...

Autosomal Dominant Polycystic Kidney Disease: Mutation Database

PKD FOUNDATION
Polycystic Kidney Disease

Mutation Details - PKD1: L2613del

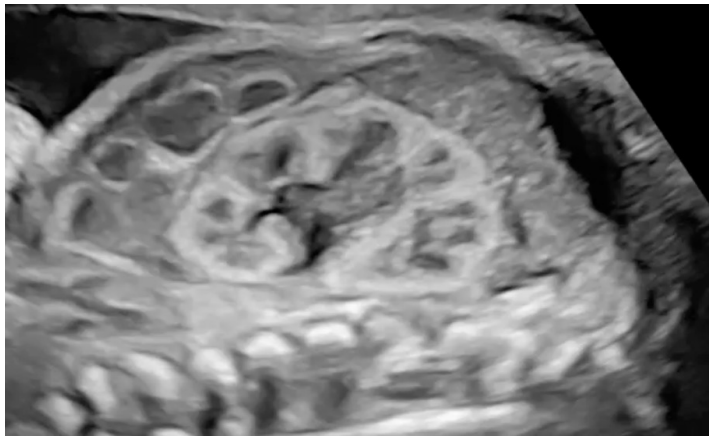
Comments PKD1

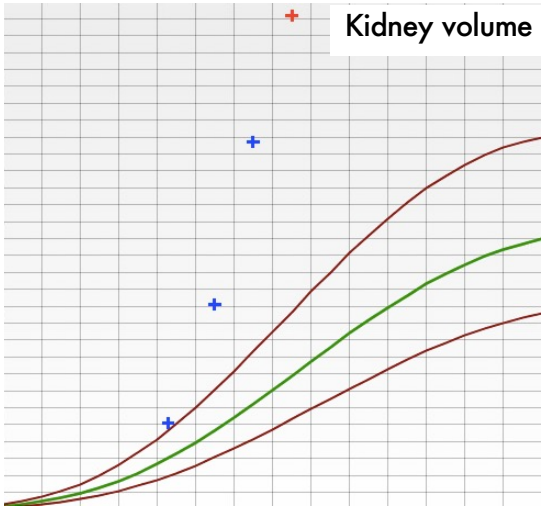
Gene:	PKD1	**Region:**	EX20	**Contextual Score:**	0
cDNA Change:	7836_7838delGTT	**Amino Acid Change:**	Leu2613del	**Substitution Score:**	8
Designation:	L2613del	**Clinical Significance:**	Likely Pathogenic	**Variant Score:**	8
Type:	DELETION	RefSeq-Gene Position:	35007 to 35009		
Germline:	Germline	Genomic Position (HG38):			

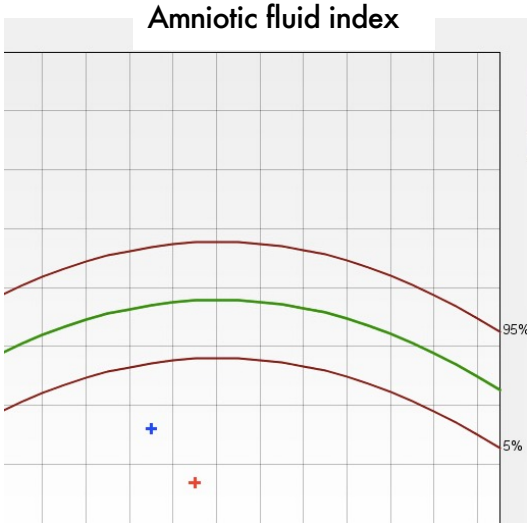
	Reference	Family
1.	Bouba I,et al. Eur J Hum Genet. 2001 Sep;9(9):677-84.	GR-1-35

Case 2: Prenatal large hyperechogenic kidneys

- Diagnosed prenatally in early pregnancy with ADPKD due to progressive nephromegaly and maternal familial ADPKD.
- 35wk: hydrops foetalis, ascites, pericardial effusion and subcutaneous oedema and bilateral large hyperechogenic kidneys of 10 cm.
- Birth PMA 35wk, Birth weight: 4000 g (> P90)



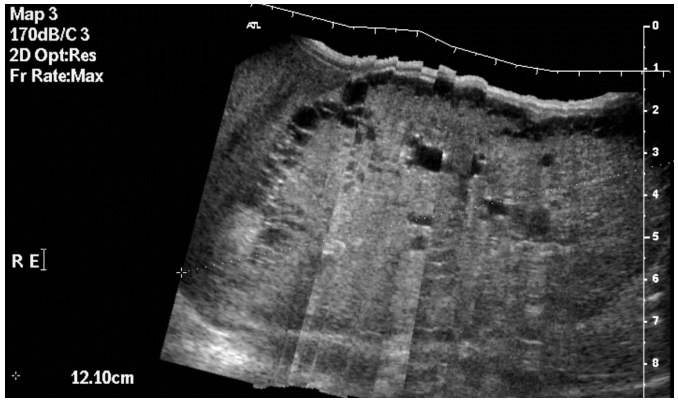


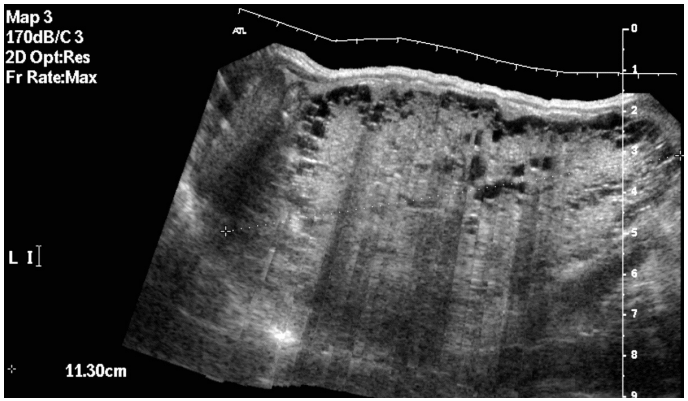


Case 2: Prenatal large hyperechogenic kidneys

Neonatal period

- Lung hypoplasia with need of ventilation and need of oxygenation
- Left and right ventricular hypertrophy and hypertension with need 2 antihypertensive drugs
- Progressive feeding problems caused by abdominal compression by the massively enlarged kidneys
- Neurological: normal
- Normal diuresis, D3: creatinine 1,52 mg/dl





2 weeks old
Kidney length R: 12,3 cm
Kidney length L: 10,8 cm
TKV 2D: 506,9 ml

Question 1: Which statement is WRONG regarding diagnosis of ADPKD in a child with kidney cyst?

1. Ultrasound of the parents (or grandparents if parents <40 years) should be considered when negative family history for ADPKD

2. The presence of a single kidney cyst/prenatal hyperechogenic kidneys in a child with a positive familial history is highly suspicious for the diagnosis of ADPKD

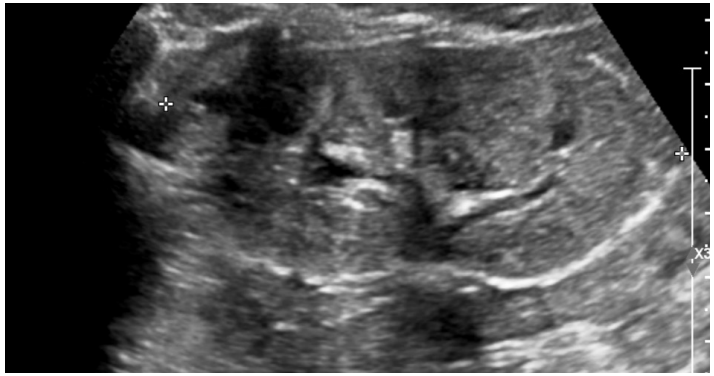
3. Consider observation in the presence of a single kidney cyst in a child with a negative familial history

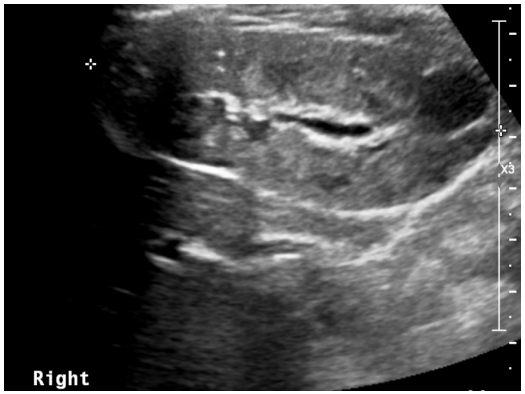
4. Genetic testing is mandatory for the diagnosis of ADPKD

Case 3: Familial screening

Presentation:

- Familial screening in a girl 2 years requested by the parents
- Known maternal familial ADPKD
- Mother ADPKD diagnosed incidentially with a very rapid progression with need RRT at 30 years





Kidney length R: 8,1 cm
Kidney length L: 8,1 cm
TKV 2D: 129,6 ml
htTKV 2D: 146,12 ml

Question 2: Which statement is CORRECT regarding counseling of an at-risk child for ADPKD?

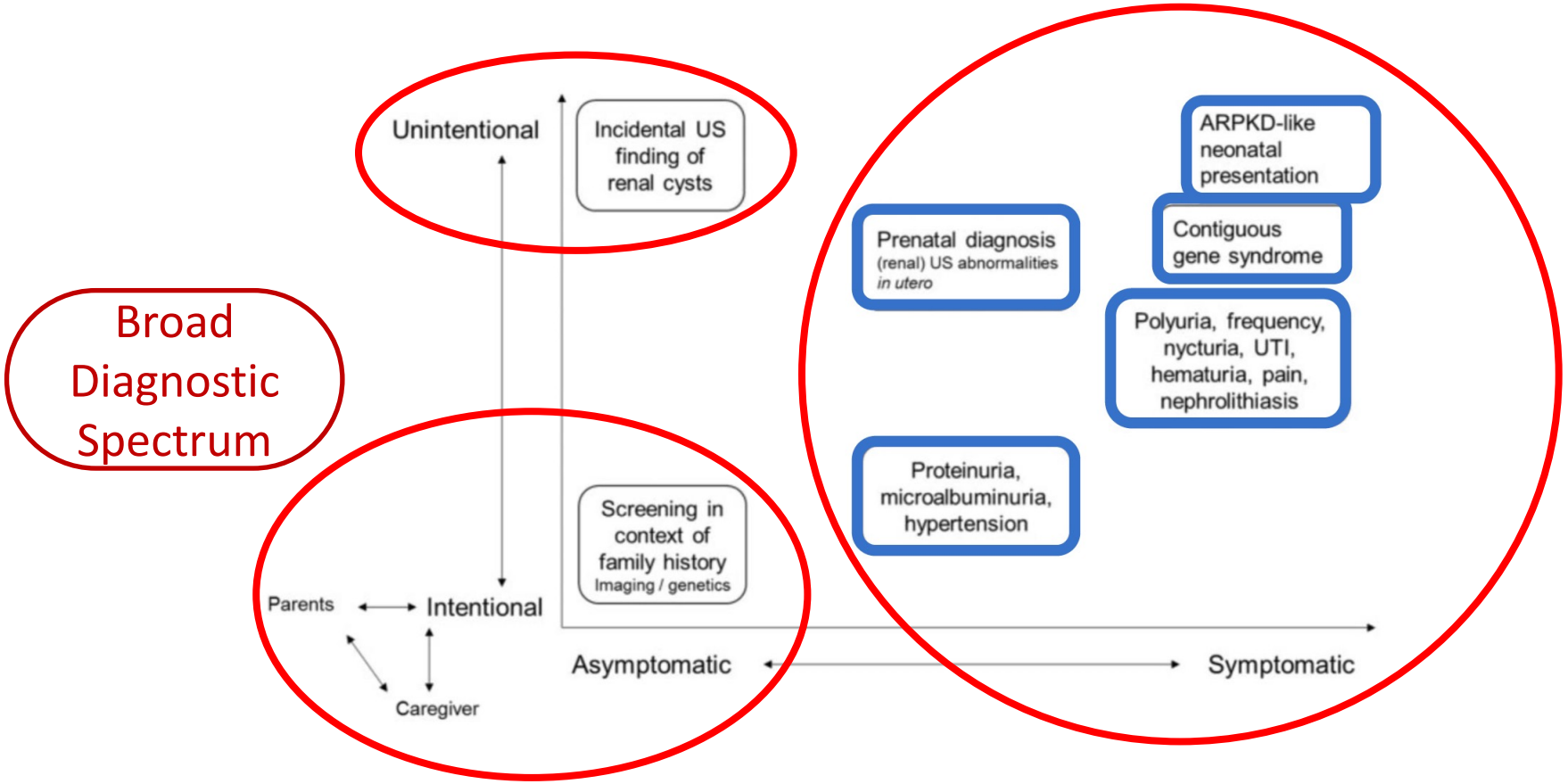
1. Shared decision-making related to screening/diagnosis (benefits and harms) with parents/legal guardians and the mature child

2. Screening of children at-risk for ADPKD is not recommended

3. Genetic testing of all the offspring's is recommended

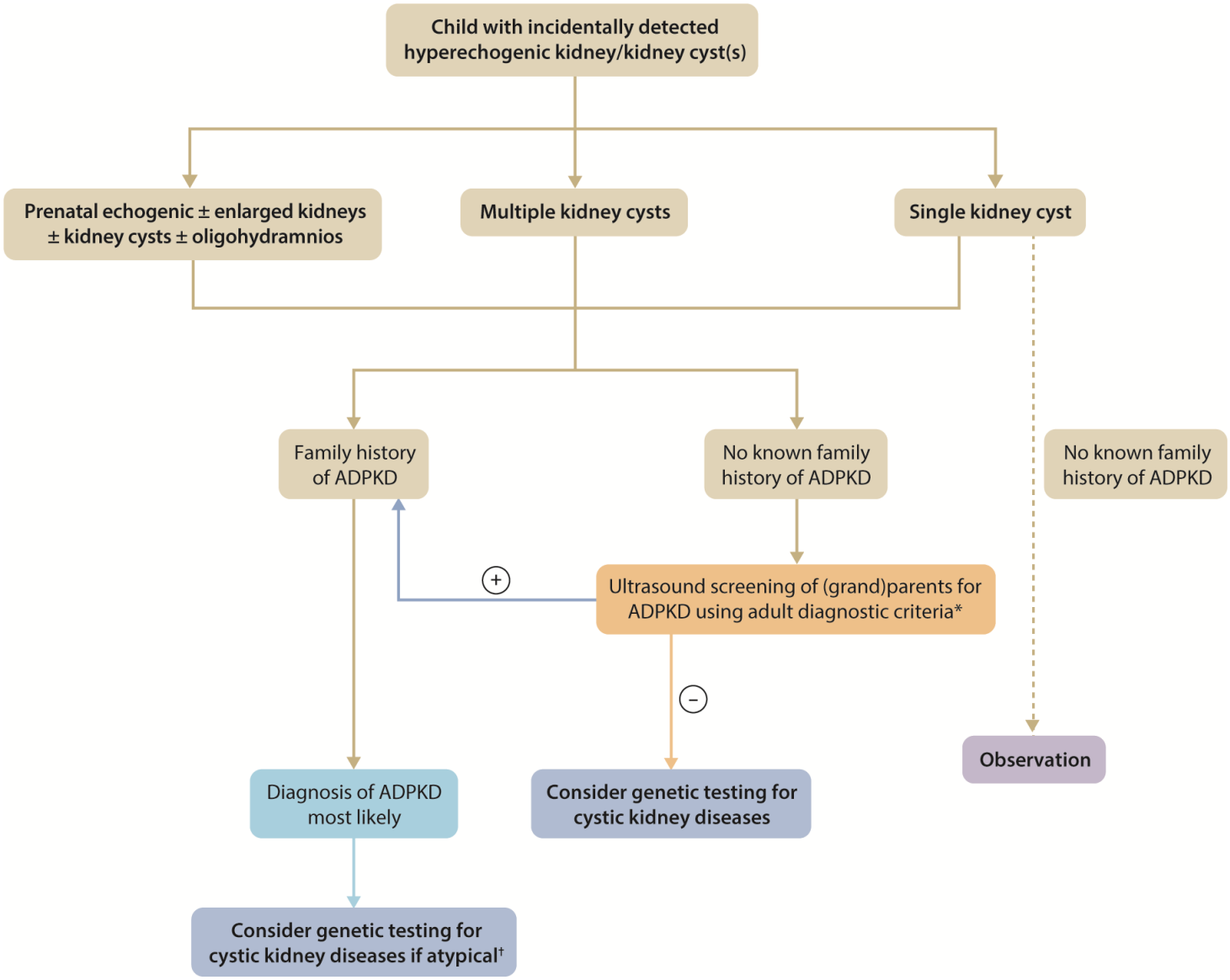
4. The absence of cysts on ultrasound could rule out ADPKD

Pediatric ADPKD Spectrum

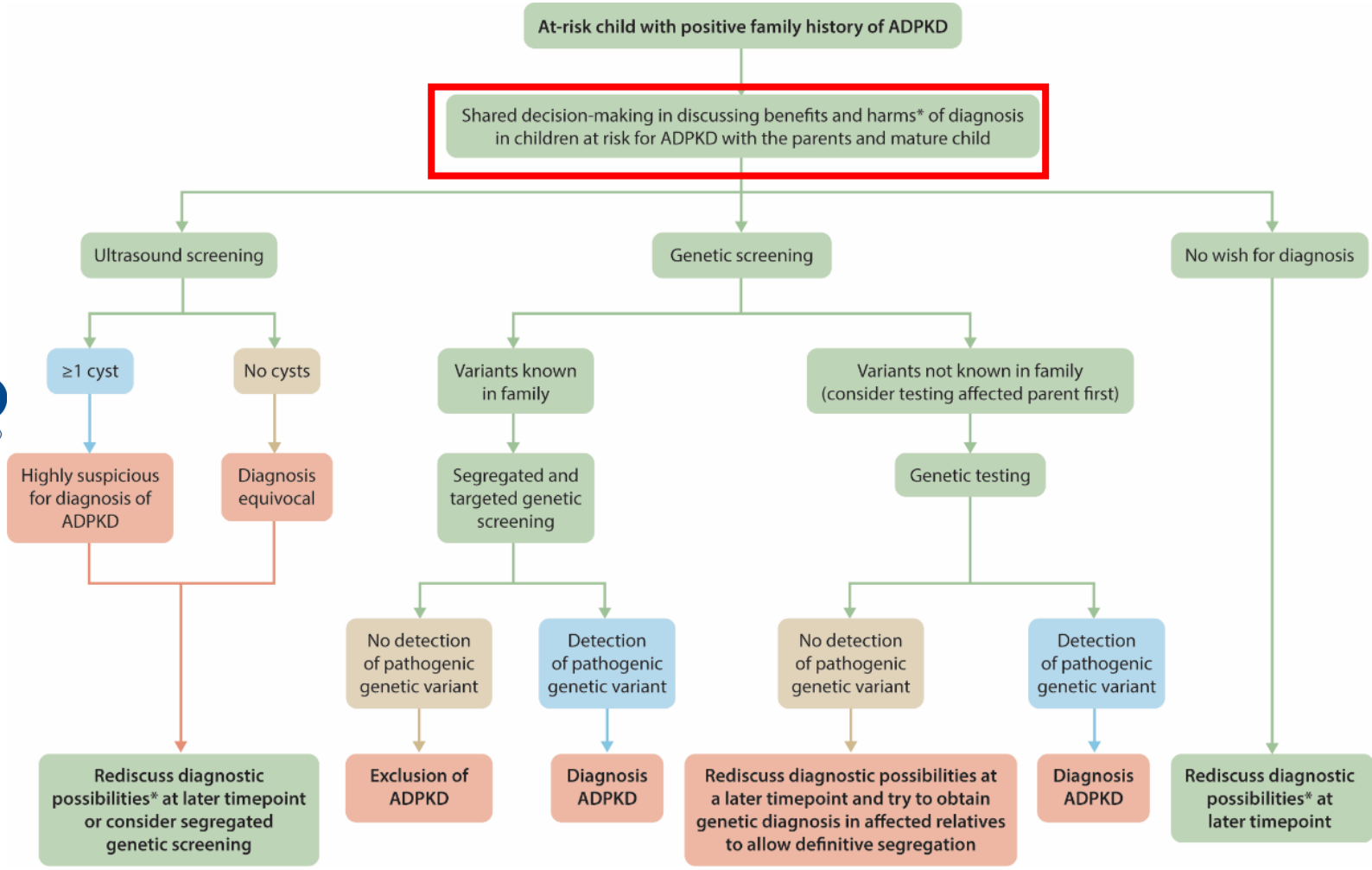


De Rechter et al. Clin Kidney J, 2018

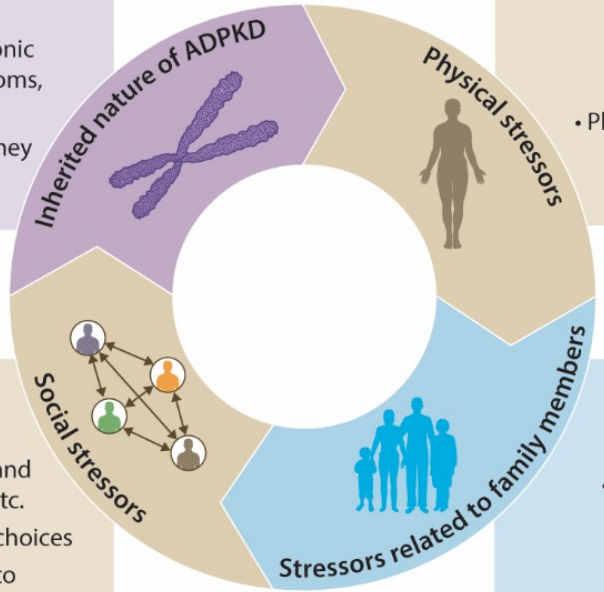
Diagnosis of children with clinical consideration of ADPKD



Diagnosis of children at risk of ADPKD by a pediatrician with expertise in ADPKD



Stressors associated with psychosocial problems in poeple with ADPKD



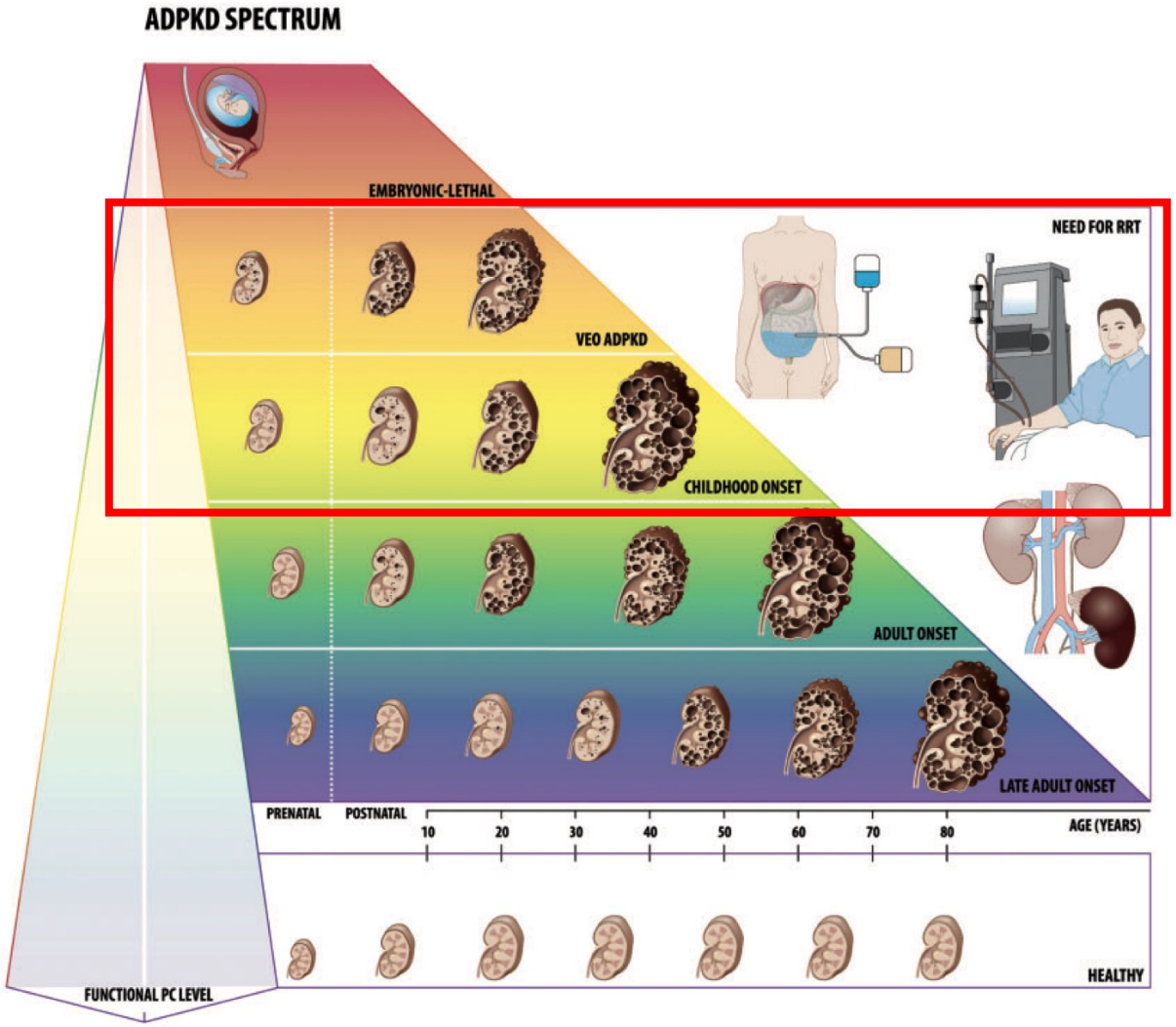
- Genetic guilt: self-blame, constant burden of guilt
- Decision on genetic testing and disclosure
- Pregnancy and family planning
- Disempowerment in self-management
- Sense of helplessness
- Health anxiety from living with a chronic incurable condition, its various symptoms, and treatment modalities
- Fear of the future: progression to kidney failure and low life expectation

- Chronic pain
- Functional limitations of participation in recreational, sport and social activities
- Body image/dysmorphia
- Sexual dysfunction
- Dietary constraints
- Sleep disturbances
- Physical conditions related to chronic kidney disease progression

- Inability to plan ahead
- Social isolation from missing school and social activities, dietary limitations, etc.
- Employment barriers and limited career choices
- Financial burden: concerns related to insurance, healthcare costs
- Other emotional responses to social challenges

- Fear of inheritance
- Caregiver burden
- "Chosen" to be the kidney donor
- Loss of family member
- Distress in family relationship: blaming parents or partners
- Disturbed family communications on issues related to having a child, marriage, etc.
- Financial burden

ADPKD Spectrum



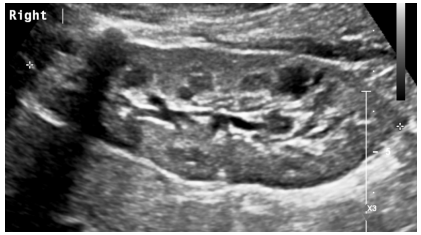
De Rechter et al. Clin Kidney J, 2018

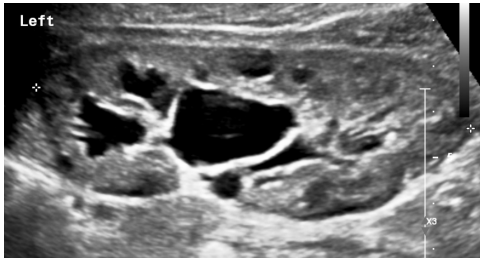
Definitions of phenotypical entities in children with ADPKD

Subentity	Definition
VEO-ADPKD	Symptoms or clinical evidence of severe ADPKD **under 18 months of age** defined by: • antenatal diagnosis of hyperechogenic enlarged kidneys (>2 SD for gestational age) with oligohydramnios, OR • enlarged cystic kidneys (>2 SD for age, sex, height) between birth and 18 months of age with hypertension (BP ≥95th percentile for age, sex, and height) and/or decreased eGFR
EO-ADPKD	Symptoms or clinical evidence of severe ADPKD **between 18 months and 15 years of age** determined by: • presence of enlarged cystic kidneys (>2 SD for age, sex, and height) between 18 months and 15 years of age with hypertension (BP ≥95th percentile for age, sex, and height) and/or decreased eGFR
Child with ADPKD	A child with diagnosis of **ADPKD not fulfilling VEO-ADPKD or EO-ADPKD criteria**
Child at risk of ADPKD	A child **with potential for heritability of ADPKD in the setting of a relative known to have ADPKD**

Case 1: Girl with incidental finding of kidney cysts /symptomatic

Update at age of 8 years

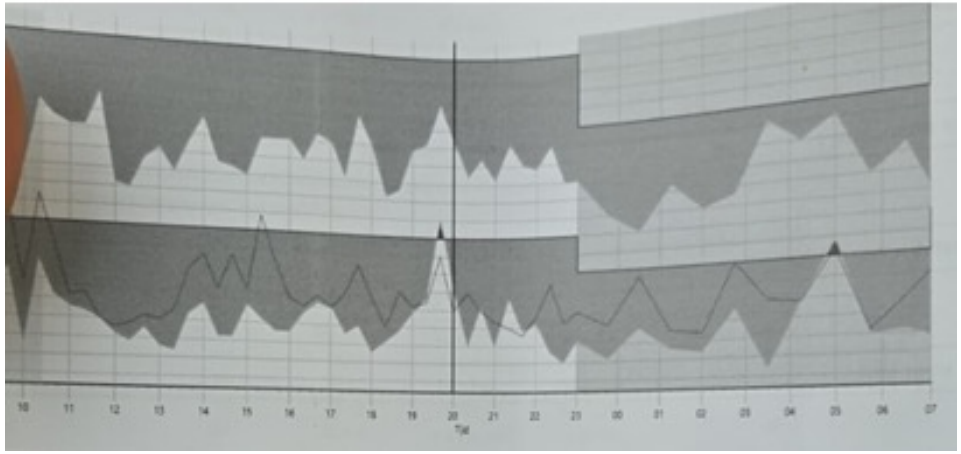


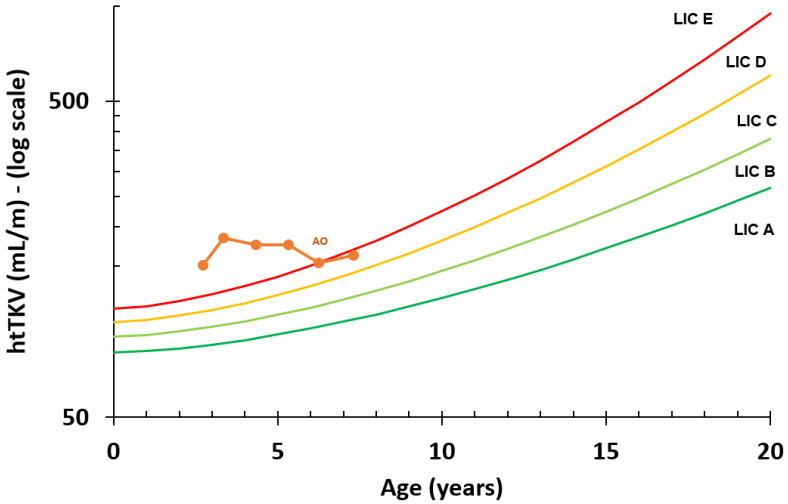


ABPM :

	Patient	P50	P95
• 24 u	110/65	105/66	117/75
• Day	111/66	112/72	124/84
• Night	97/55	109/66	103/63

- dipping: **syst 7.4% , Dia 5.2%**

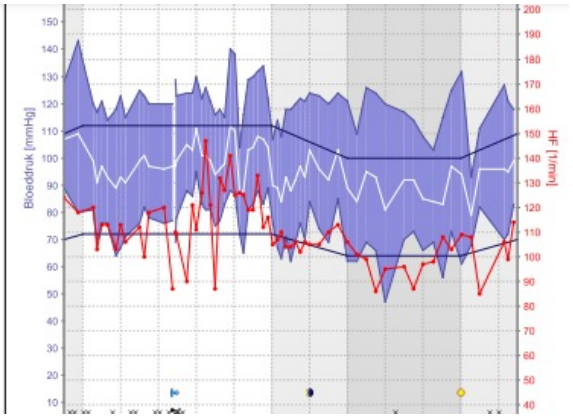




Kidney length R:9,3 cm
Kidney length L: 9,4 cm
TKV 2D: 178,26 ml
htTKV: 140,14 ml

Case 3: Familial screening

Update at age of 8 years

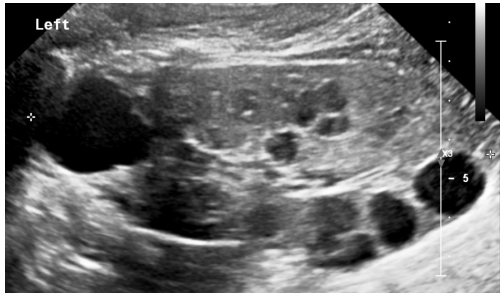


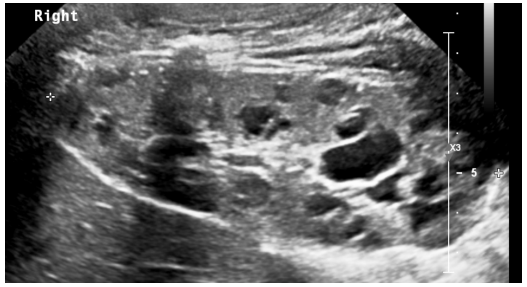
- Dysfunctional voiding
- Hypertension at the age of 6 years

ABPM at age of 6 years:

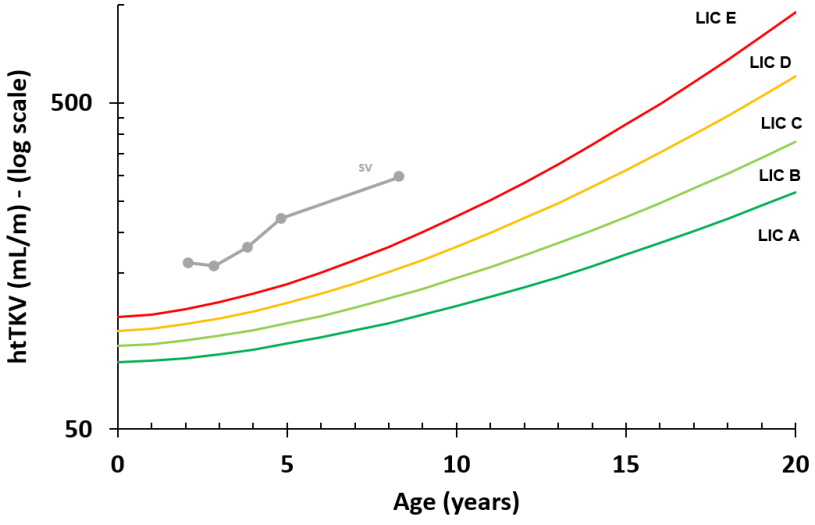
	Patient	P50	P95
• 24 u	120/73	104/66	114/72
• Day	122/78	110/73	120/82
• Night	117/64	95/55	106/65

- dipping: **syst 3.3% , Dia 16.9%**





Kidney length R: 11,4 cm
Kidney length L: 11,8 cm
TKV 2D: 346,19 ml
htTKV 2D: 260,29 ml



Question 3: Which statement is WRONG regarding the management of hypertension in a child with or at-risk for ADPKD?

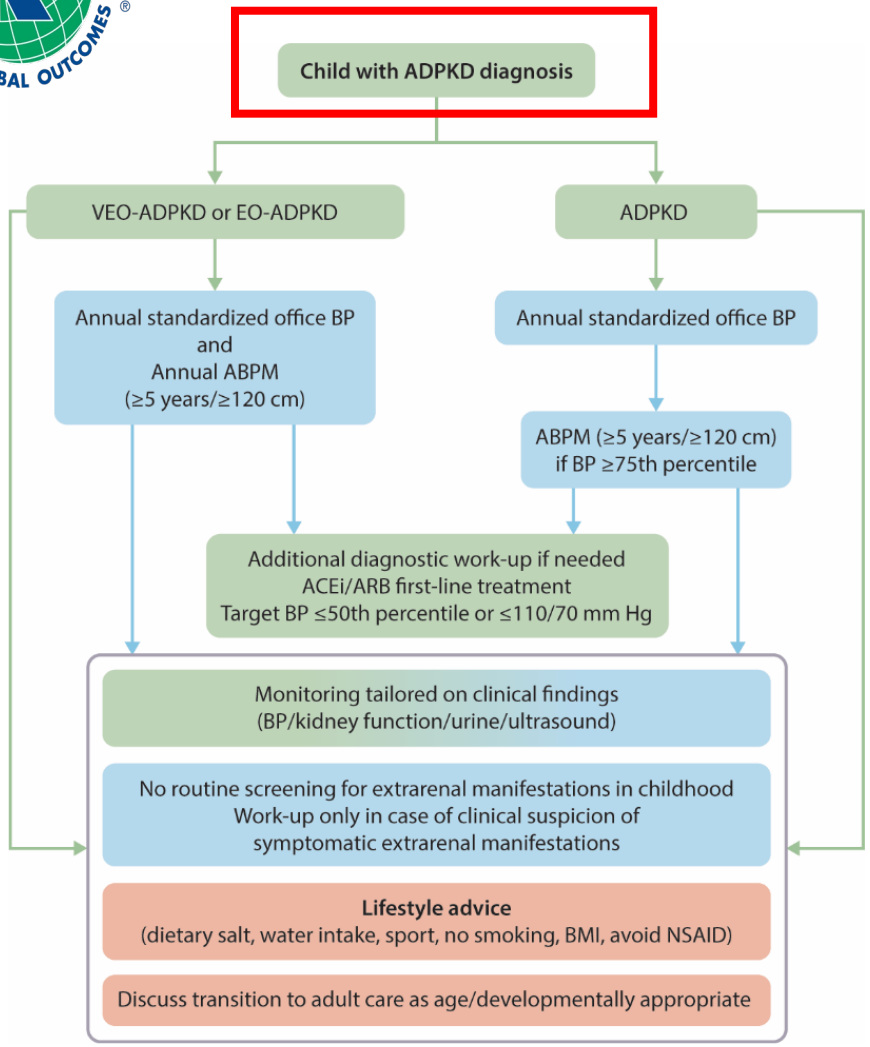
1. Standardized office BP should be assessed annually in children (≥5 years) and adolescents with or at risk for ADPKD

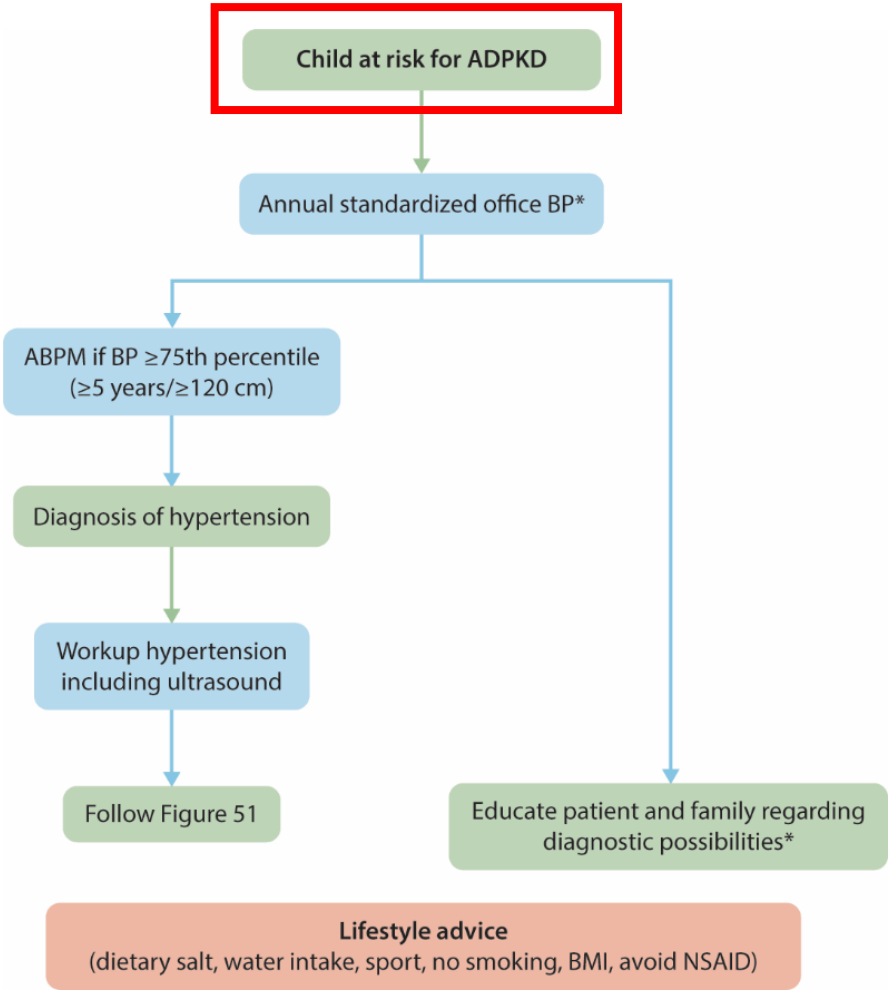
2. Annual 24-hour ABPM should be performed in children and adolescents (≥5 years and height ≥120 cm) with VEO-ADPKD or EO-ADPKD

3. We recommend targeting BP to ≤97th percentile for age, sex, and height or ≤130/80 mm Hg in adolescents in the setting of ADPKD and high BP

4. RASi (i.e., ACEi or ARBs) are the first-line therapy for high BP in children and adolescents with ADPKD

Management of children with and at-risk for ADPKD

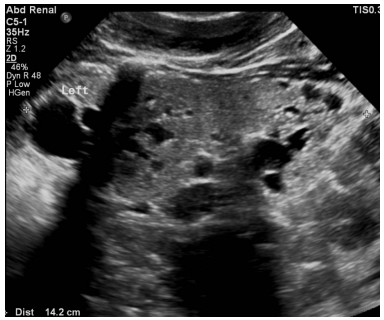


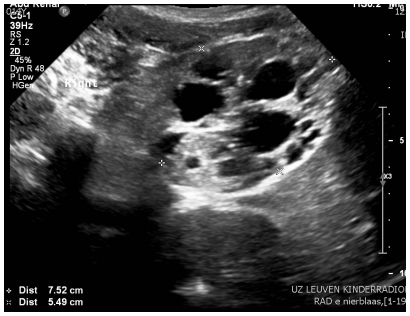


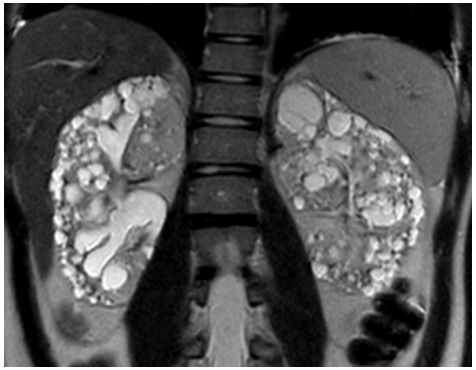
Case 2: Prenatal large hyperechogenic kidneys

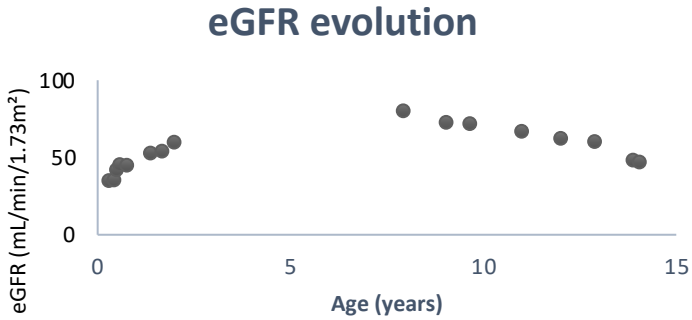
At the age of 16 years
Hypertension : ACEi + Ca blok

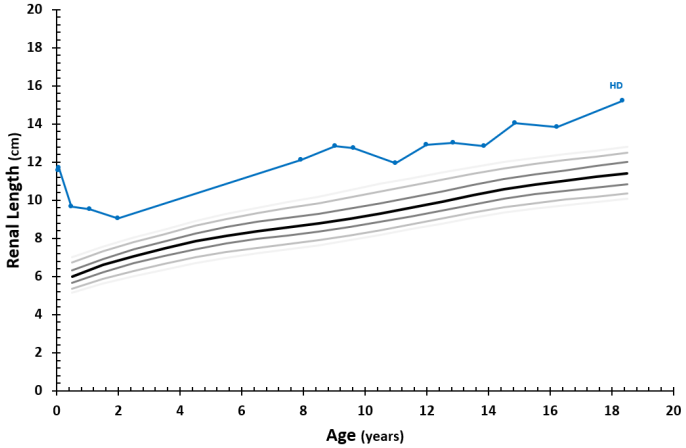
Kidney length R: 14,9 cm
Kidney length L: 12,8 cm
TKV 2D: 576,2 ml
htTKV 2D:321,9 ml











Metformin?
Tolvaptan?
(Pre-emptive) Tx

Question 4: Which statement is WRONG regarding the management of a child with ADPKD?

1. Children with ADPKD should follow general recommendations for a healthy diet, consistent with WHO guidelines and should maintain a healthy body weight and physical activity

2. We recommend targeting BP to ≤50th percentile for age, sex, and height or ≤110/70 mm Hg in adolescents in the setting of ADPKD and high BP

1. There is currently no sufficient evidence to support the use of Statins for ADPKD in children

2. There is currently sufficient evidence to support the use of Tolvaptan for ADPKD in children

Tolvaptan for children and adolescents with autosomal dominant polycystic kidney disease

CJASN
Clinical Journal of the American Society of Nephrology

20 academic pediatric nephrology centers

ADPKD eGFR≥60 mL/min/1.73m^2

Study population Age 4-17 N=91

Randomized Trial

1 year

	Mean reduction in spot urine osmolality (Week 1)	Height-adjusted total kidney volume (htTKV) (12 month)	Change in eGFR mL/min/1.73m^2 (Week 1–Month 12)	Aquaretic adverse events
Tolvaptan	-390 mOsm/kg	2.6%	1.9	65%
Placebo	-90 mOsm/kg	5.8%	-1.8	16%

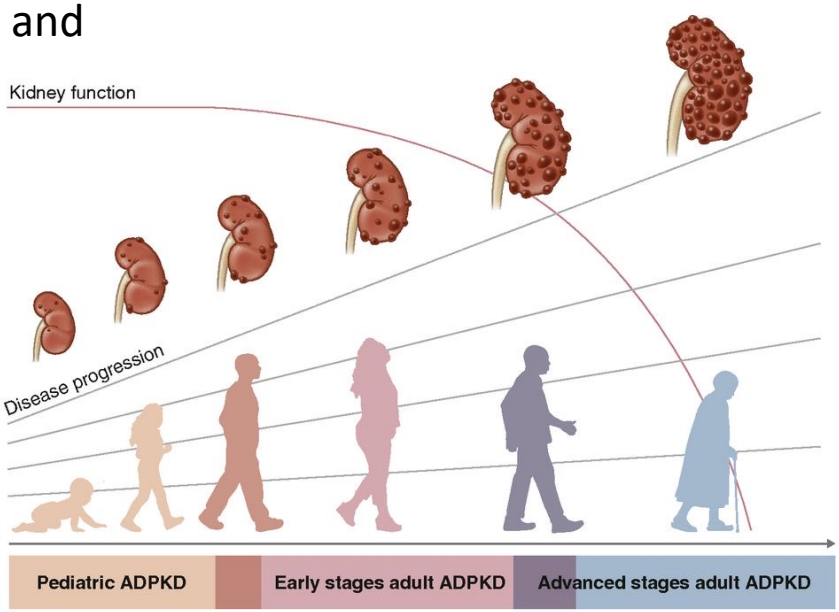
There were no elevated transaminases or drug induced liver injuries

Conclusions: Tolvaptan exhibited pharmacodynamic activity in pediatric ADPKD. Tolvaptan increased urine output, but few patients (n=1 in each treatment arm) discontinued the study due to adverse events.

Djalila Mekahli, Lisa M. Guay-Woodford, Melissa A. Cadnapaphornchai, et al. ***Tolvaptan for Children and Adolescents with Autosomal Dominant Polycystic Kidney Disease***. CJASN doi: 10.2215/CJN.01590222. **Visual Abstract by Nayan Arora, MD**

Perspectives on Drug Development in Early ADPKD

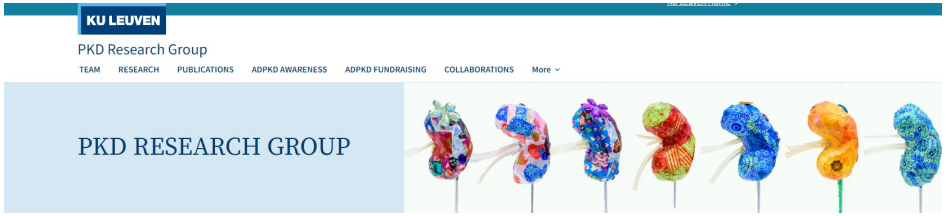
Pediatric and young ADPKD patients represent a novel and crucial target for clinical trials



Patient stratification	• Very early onset, genetics, hypertension • No available stratification scores	• Age, genetics, urological events, hypertension • Stratification according to Mayo classification/PRO-PKD score	
Current primary end points	• Urine osmolarity	• Ht-TKV • eGFR	• eGFR • Ht-TKV
Current secondary end points	• Ht-TKV • eGFR	• Urine osmolarity • Number of cysts • Copeptin	• Copeptin • Liver cysts
Potential end points	• Texture/segmentation imaging • Number of cysts • Hypertension • uMCP1 • PRO	• Texture/segmentation imaging/ liver cysts • uMCP1/uEGF/suPAR/Kim-1/ β2 microglobulin/NGAL/ FGF23 • Urine-to-plasma urea ratio • PRO/pain	• PRO/pain/QoL • Liver cysts
Future directions	• "Bridging biomarkers": proteomic PKD score, microRNAs, and proteins in urinary extracellular vesicles		• Prediction modeling

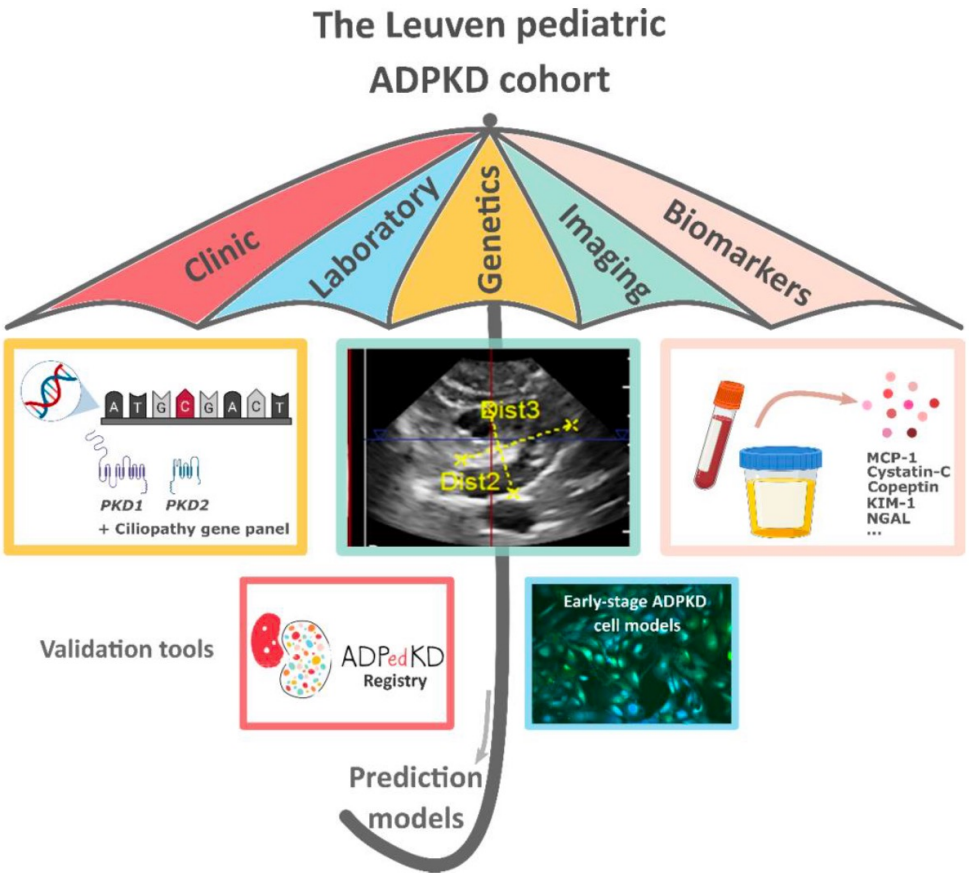
Mekahli D *et al*. CJASN 2022

Leuven Translational Research in ADPKD



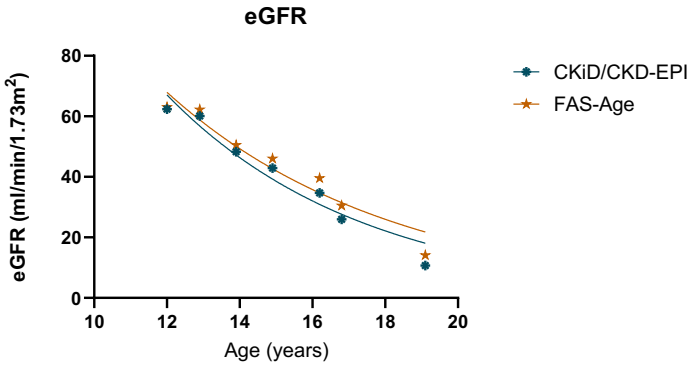
Mission

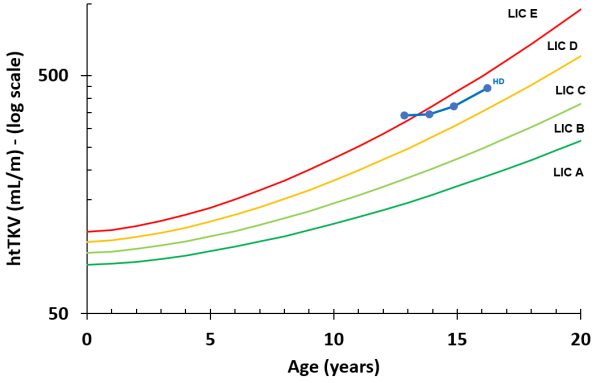
The PKD Research Group of the Laboratory of Ion Channel Research performs translational research on autosomal dominant polycystic kidney disease (ADPKD). This is the most common genetic nephropathy (1 in 1000) with more than 12 million patients worldwide (according to PKD international). It is characterized by the progressive formation of renal cysts and increased kidney volume leading to renal failure by the median age of 50 years. Patients then undergo dialysis, nephrectomy and are placed on the kidney transplantation waiting list. Unfortunately, ADPKD cannot be cured and the current treatments only delay kidney failure by suppressing kidney damage and cyst growth. Mutations causing ADPKD are found

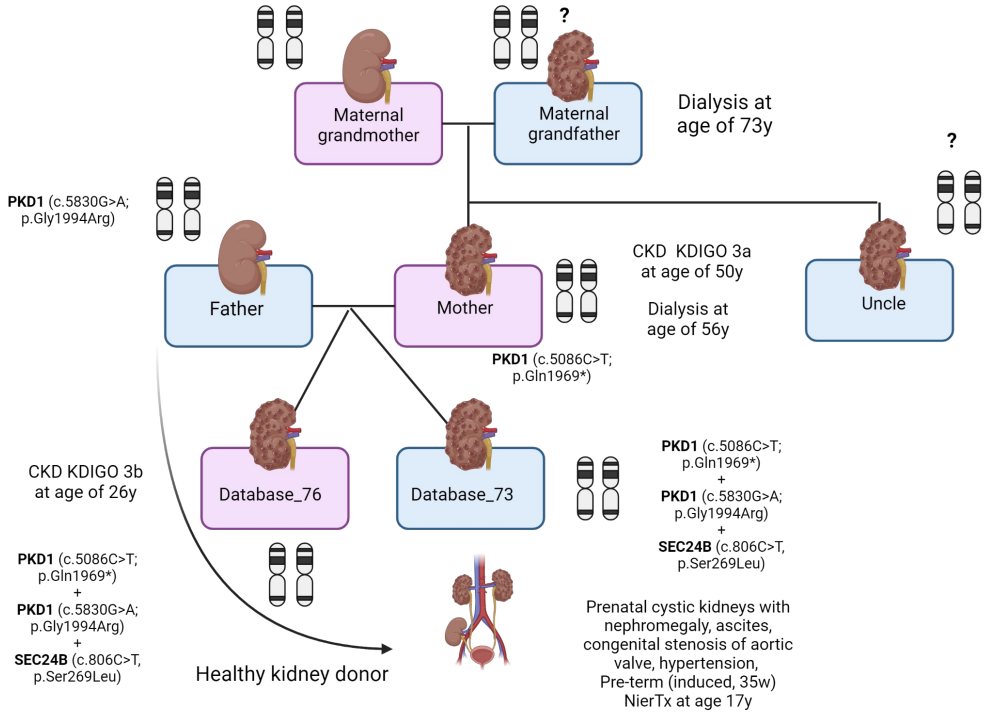


Case 2: Prenatal large hyperechogenic kidneys

At age of 17 years , GFR 14
Living donor Tx from the father







ADPedKD registry: www.ADPedKD.org

Lisa M. Guay Woodford

Daniel Gale

Detlef Bockenhauer

Djalila Mekahli

Max Liebau

Franz Schaefer

41 NIH Hepato-Renal Fibrocystic Disease database

269RaDaR

ADPedKD North-America

ADPedKD UK

ADPedKD Europe

ADPedKD Asia

ADPedKD Africa

ADPedKD South-America

Andrew Mallet

ADPedKD Australia

17 KiDGen

91 centres

33 countries

1819 patients

SCAN TO OPEN ADPedKD

Data 2024

ADPedKD registry: www.ADPedKD.org

Charlotte Gimpel

Aim

- Describe mode of **presentation of ADPKD** in children and young persons <19 years
- Analyze **geographical and temporal trends**

Registries

ADPedKD

Including NIH and KidGen registries (USA and Australia)

17 high income countries

8 middle income countries

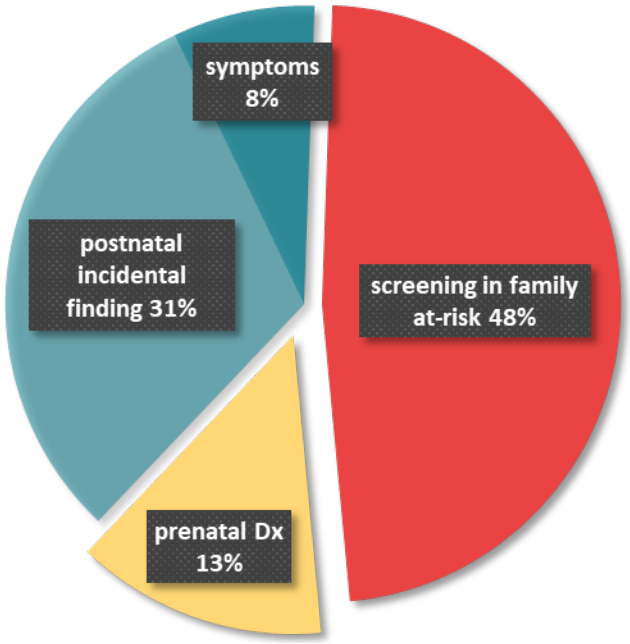
ERKReg
The European Rare Kidney Disease Registry

16 high income countries

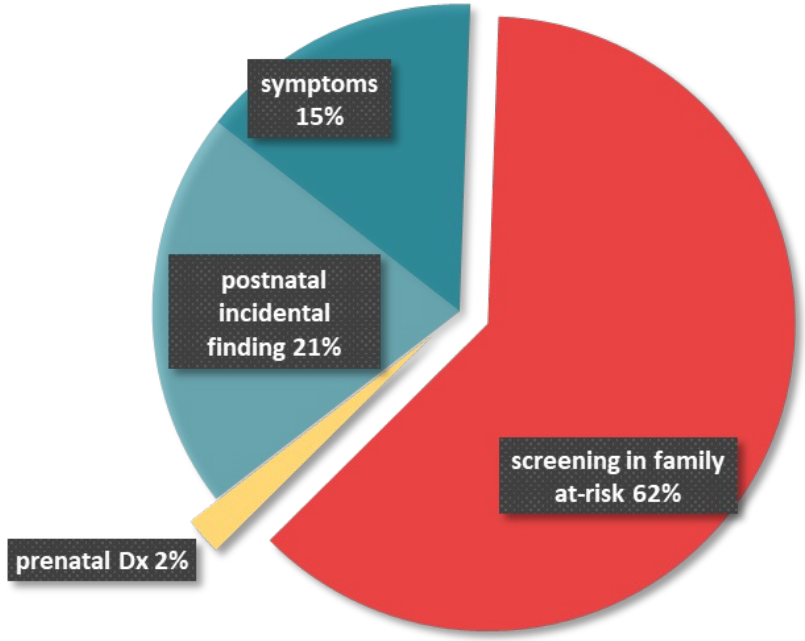
1 middle income country

Mode of presentation

ADPedKD (n=950)



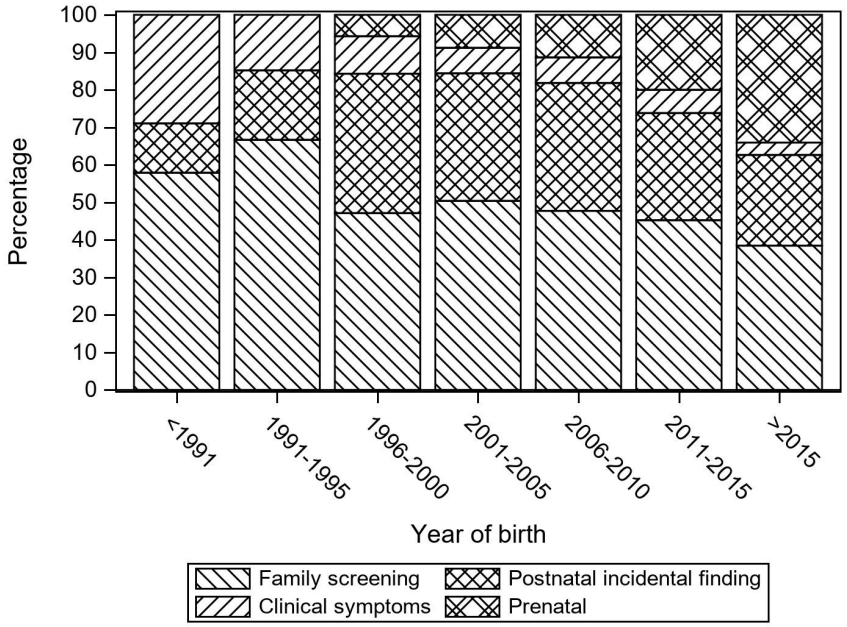
ERKReg (n=596)



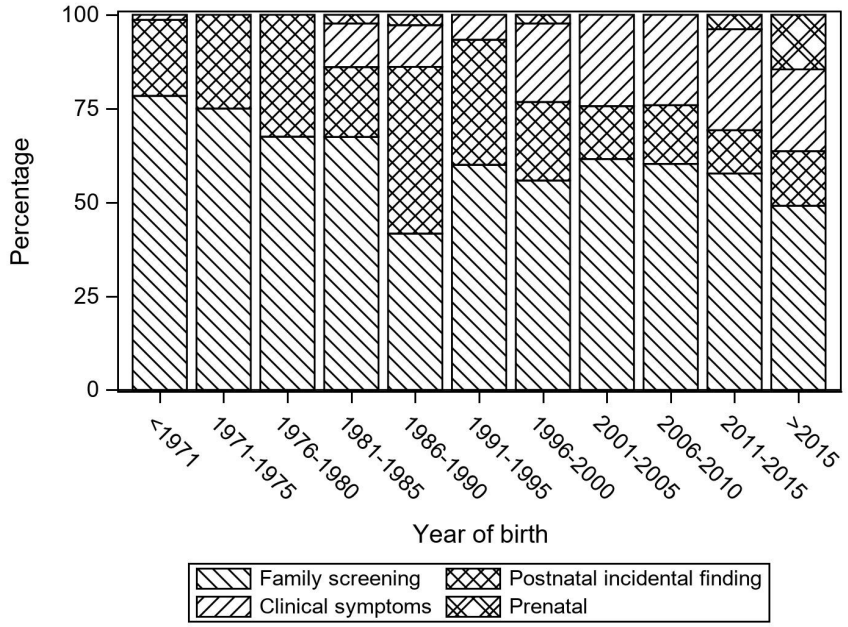
ADPedKD registry: www.ADPedKD.org

Temporal changes – prenatal diagnosis

ADPedKD



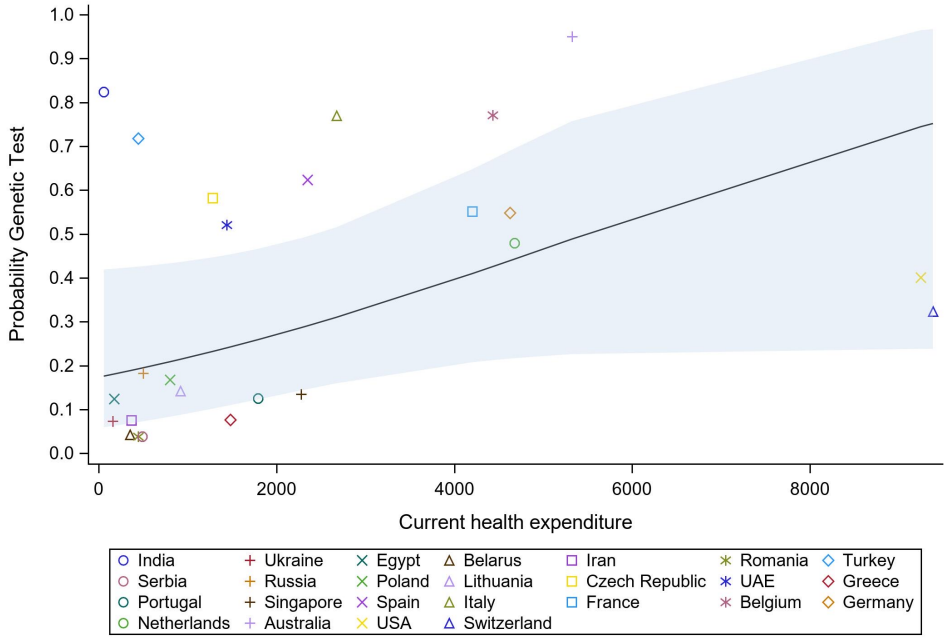
ERKReg



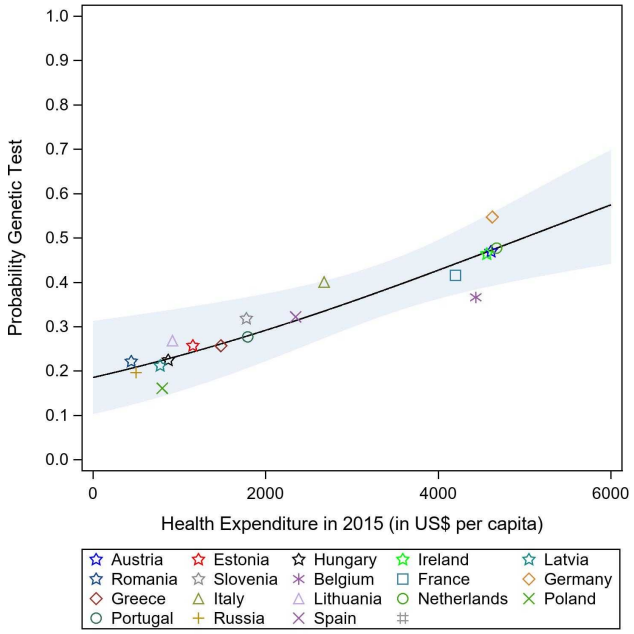
Geographical variations in screening indicate influence of local healthcare systems, local legal and ethical frameworks

Geographical influence – healthcare spendings & genetic testing rate

ADPedKD



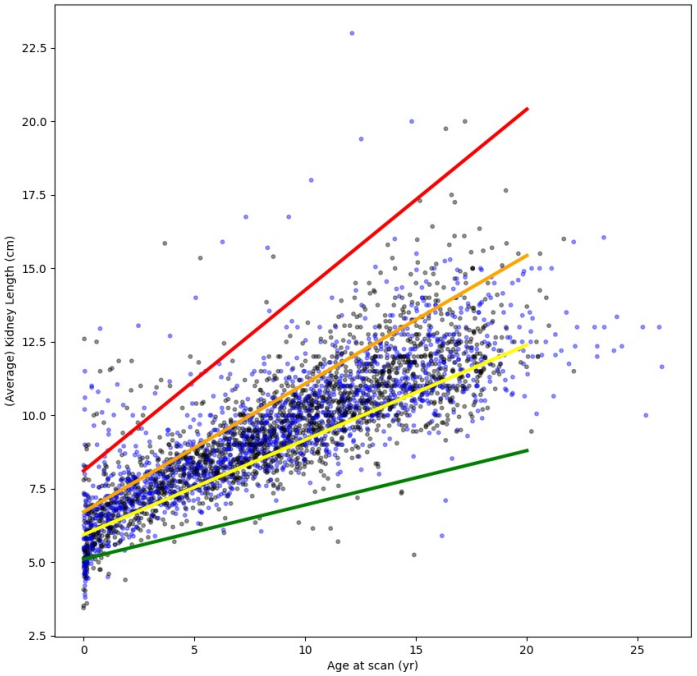
ERKReg

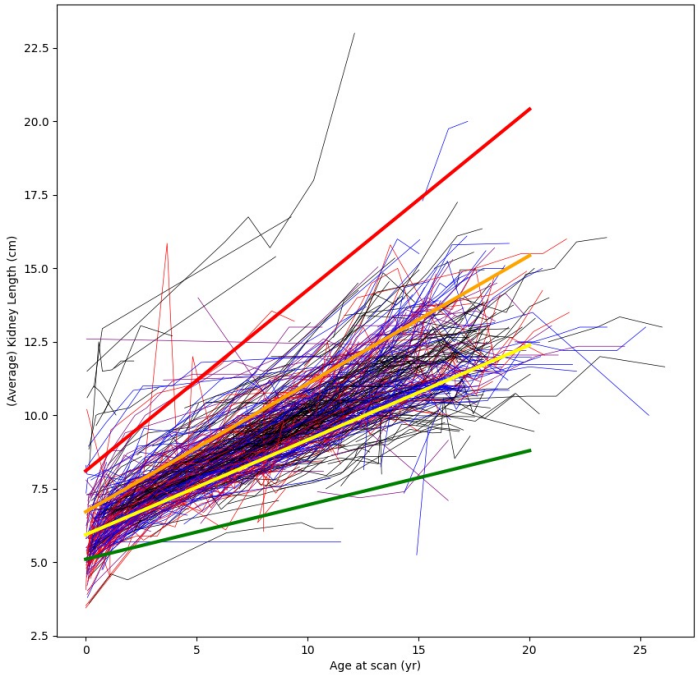


Geographical variation of genetic testing correlated to healthcare spendings, indicating unequal access

ADPedKD registry: www.ADPedKD.org

1103 patients children with ADPKD, **3544** evaluations
'PKD1', 429 pats, 1551 evaluations

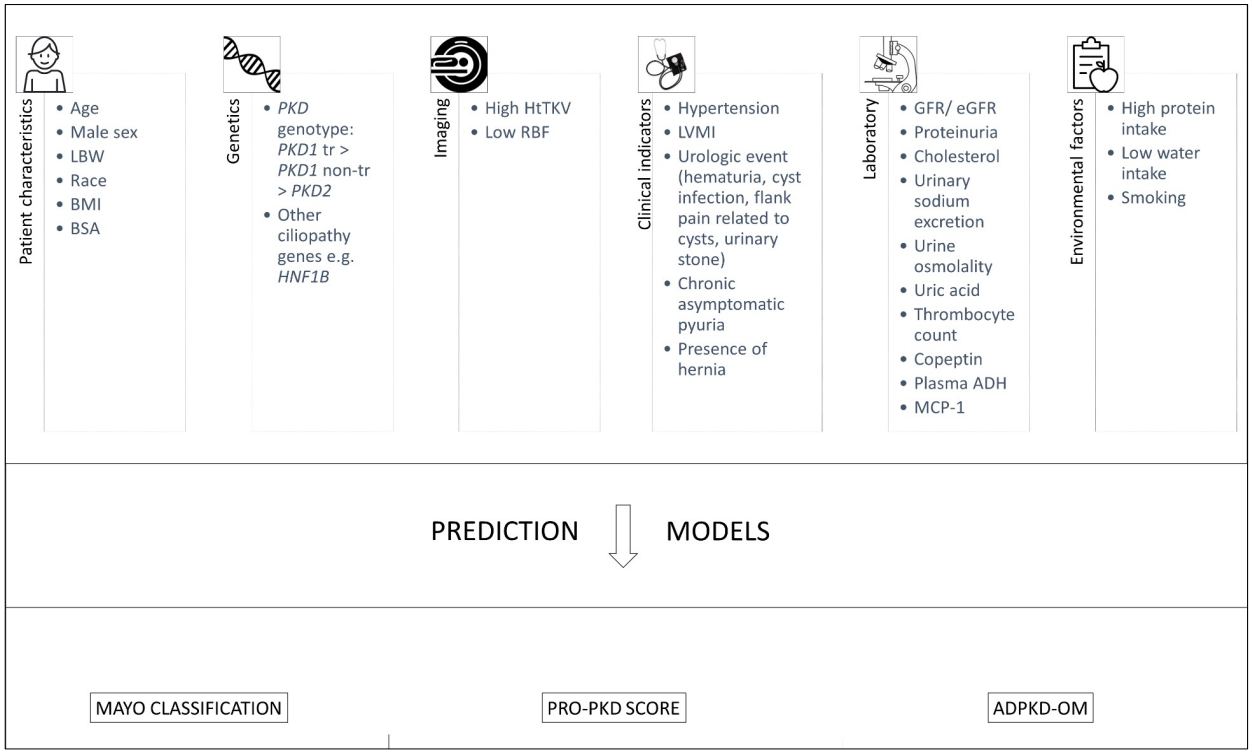




SCAN TO OPEN
ADPedKD

Disease severity and prediction models in ADPKD

Adults:



Children:

- ADPedKD registry
- Leuven imaging classification
- Biomarkers

General conclusions

- Huge progress on understanding ADPKD in children
- Structural kidney disease and vascular dysfunction are evident in ADPKD childhood
- Screening for modifiable disease manifestations and implementation of lifestyle recommendations are important
- ADPKD families need counselling to make informed decisions regarding diagnostic testing
  - High proportion of active screening diagnoses in children with ADPKD
  - Prenatal diagnoses increasingly important after ~ 2000
- Children with ADPKD represent a novel and crucial target for disease understanding and management before a point of no return
- It is critical to establish a reliable measures to identify children at highest risk for rapid progression

LEUVEN TRANSLATIONAL PKD CONSORTIUM

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Thanks to the ADPKD children

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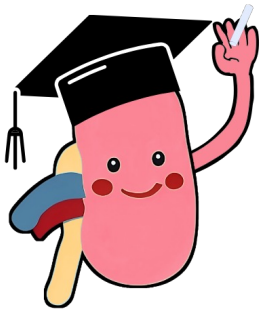
https://gbiomed.kuleuven.be/pkdresearchgroup/

NEXT WEBINARS



18/06/24	<u>Renal Tubular Acidosis</u> Detlef Böckenhauer (Leuven, Belgium)
02/07/24	<u>Familial Hypomagnesemia</u> Karl Peter Schlingmann (Münster, Germany)
10/09/24	<u>MGRS</u> Roberta Fenoglio (Turin, Italy)

ERKNet The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

IPNA

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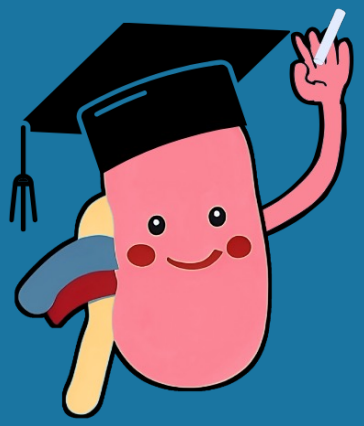

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