

Update on Polycystic Kidney Disease

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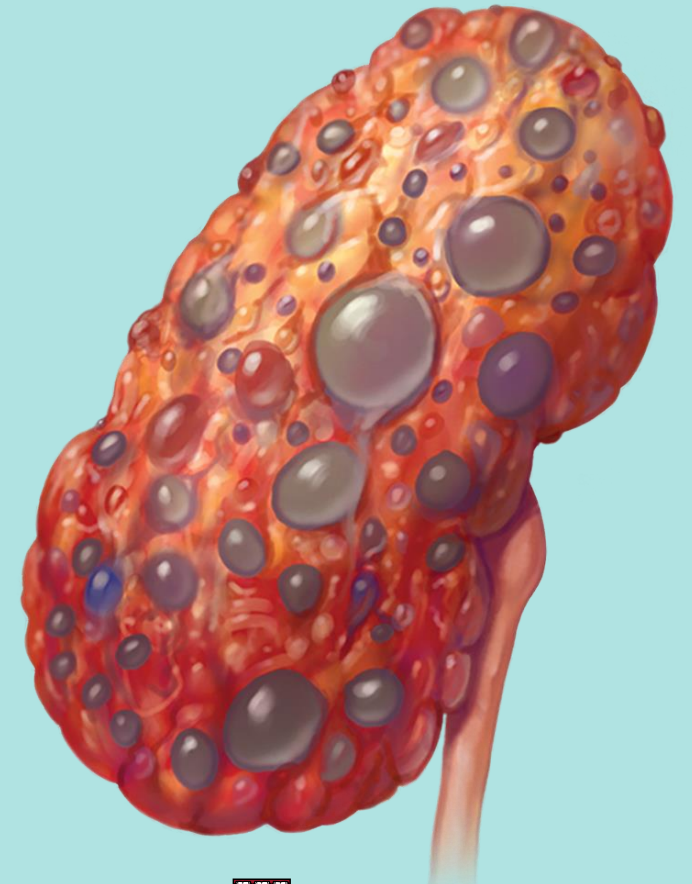
Research Chair, Division of Nephrology and Hypertension

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- Clinical focus: ADPKD and inherited kidney diseases
- Research focus: Novel therapeutics in ADPKD, Renal water handling, Biomarkers, AI, predictive modeling, Clinical trials

DISCLOSURES

- Research grants:
 - Natera: Site PI for RenaCare
 - Otsuka: Investigator-initiated clinical trial (Serendipity-PB1); educational grants
 - Regulus: Site PI
 - Vertex: Site-PI
- Advisory Boards: Vertex, Regulus, Traverso
- Board of Directors: PKD foundation, USA
- Consultant: Retex, AstraZeneca, Mezzion
- Issued patent: Probenecid as therapy for ADPKD

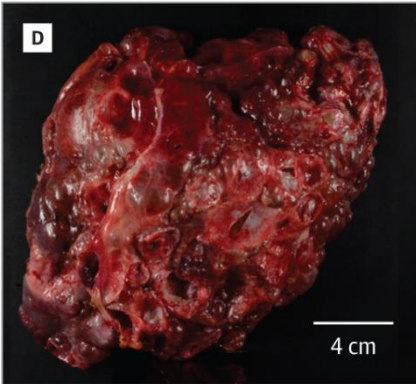
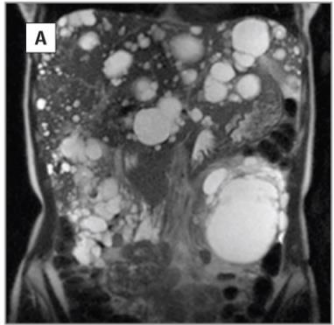


OBJECTIVES

1. Understanding the different methods of **diagnosing** ADPKD, including imaging and genetic testing, and their clinical utility.
2. Understanding various methods of **prognostication** of ADPKD, such as the Mayo classification, and their clinical applications.
3. Learning how to evaluate the risk of progression in ADPKD and identify patients at **high risk of progression**.
4. Understanding the current clinical management of ADPKD, including the management of **extrarenal manifestations** and the **slowing of disease progression**.



ADPKD, a multidimensional lifelong systemic disease



Most common inherited kidney disease

- 1:1000

4th cause of kidney failure

- 50% by age 60

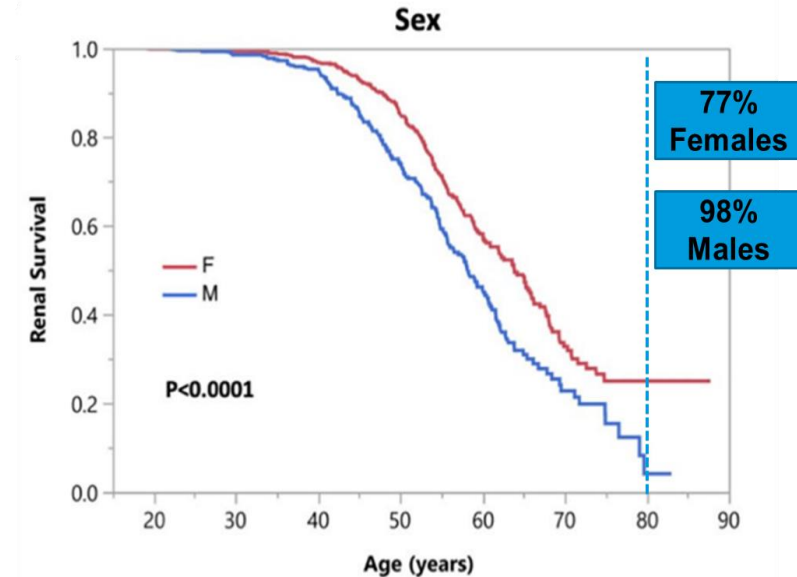
Systemic disease

- Kidney cysts
- Liver cysts
- Intracranial aneurysms

High phenotypic variability

Genetically heterogeneous:

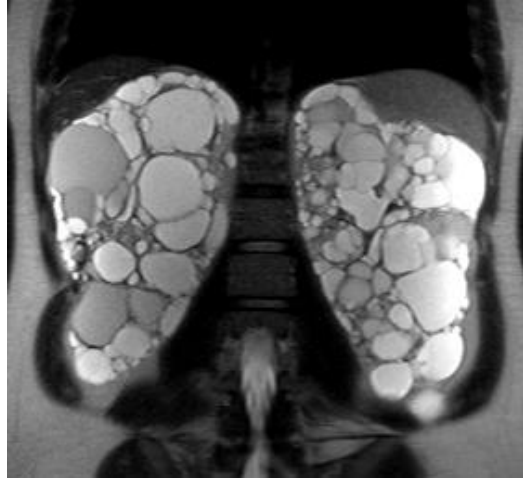
- *PKD1* (78%)
- *PKD2* (15%)
- Minor genes (7%): *IFT140*, *DNAJB11*, *GANAB*, *ALG5*, *ALG8*, *ALG9*, ...



Definite vs Likely vs Possible

Positive family history				
	Ultrasound-based	PPV %	CT/MRI based	PPV %
Age 15-29	≥ 3 cysts (total)	97.3	> 10 cysts (total)	100
Age 30-39	≥ 3 cysts (total)	94.7	> 10 cysts (total)	100
Age 40-59	≥ 2 cysts in each kidney	100	Not determined	
Age > 60	≥ 4 cysts in each kidney	100	Not determined	
Negative family history				
Any age	≥ 10 cysts in each kidney (bilateral kidney enlargement)	NA	Not determined	

Definite

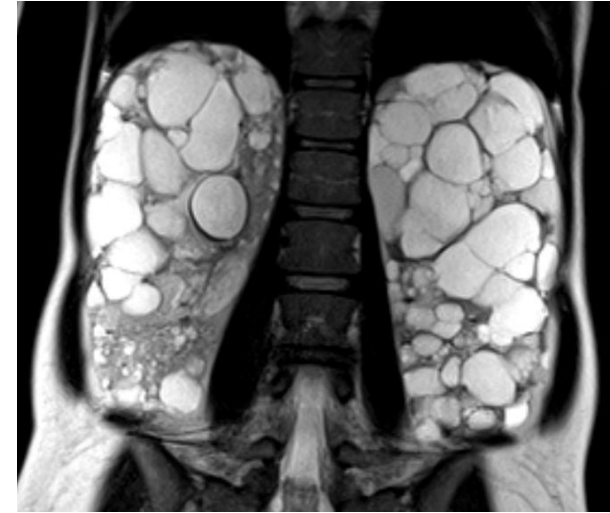


42 yo F,
definite ADPKD
PKD1 T, GFR 16,
HtTKV 2400, MIC1E
MRI w/o IV contrast

55 yo M,
definite ADPKD
PKD1 NT, GFR 38
HtTKV 1866, MIC1D
CT w/o IV contrast

21 yo F,
definite ADPKD
PKD1-T, GFR 129,
Kidney length 15.9 cm
Kidney ultrasound

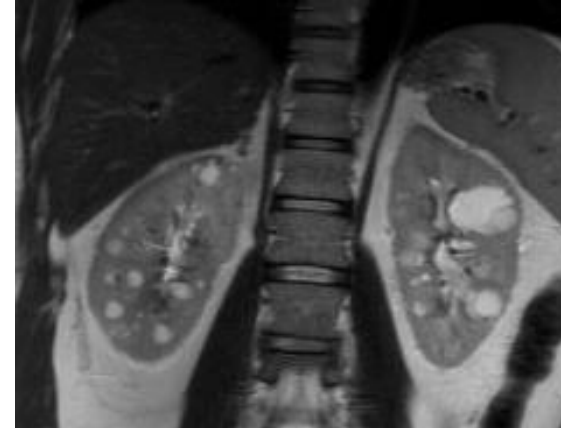
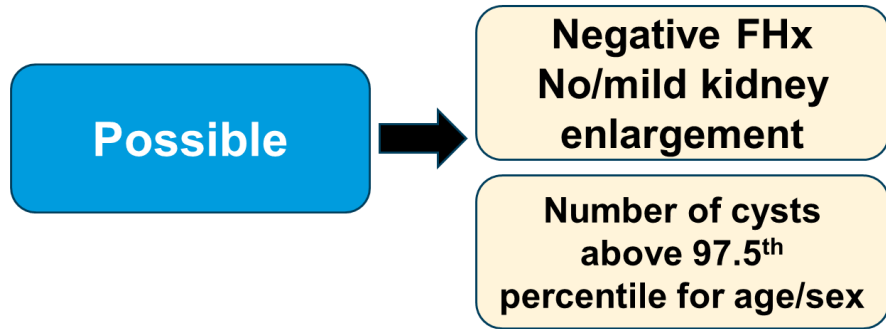
Likely



35 yo F,
likely ADPKD
No FHx, GFR 37,
HtTKV 1116, MIC1D
MRI w/o IV contrast

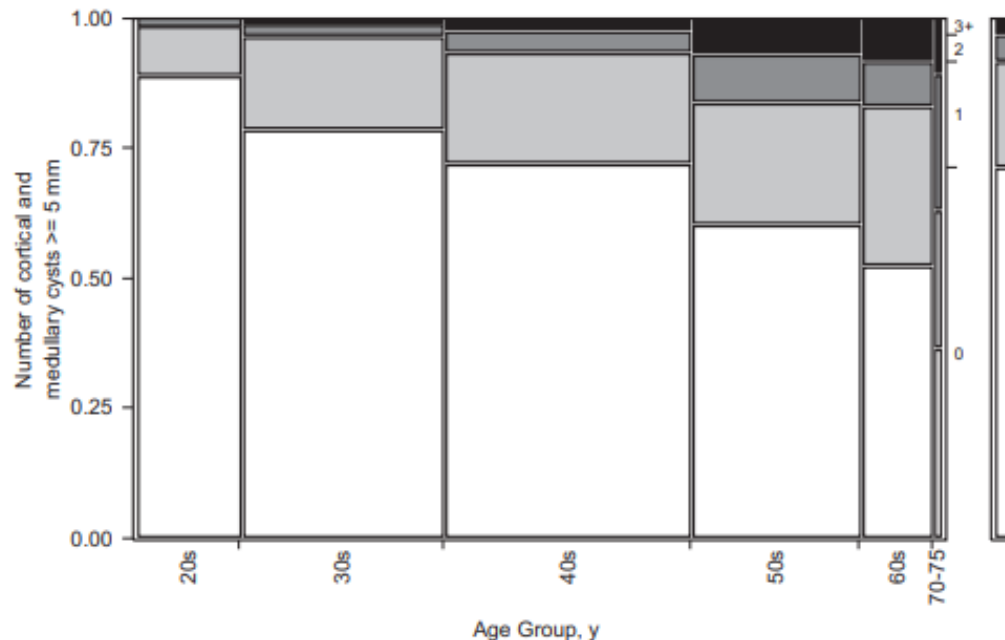


Possible ADPKD



43 yo M,
Possible ADPKD
No FHx, GFR 85,
HtTKV 288

Number of cysts (cortical/medullary) by age group
for 1948 potential kidney donors with CT w/ contrast

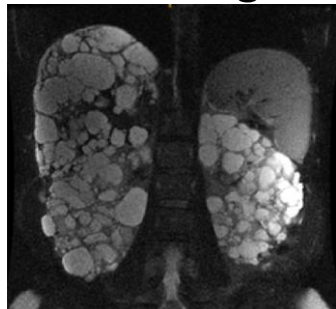


Age group	Number of cysts in both kidneys*	
	Men	Women
18-29 yr	≥2	≥2
30-39 yr	≥3	≥3
40-49 yr	≥4	≥3
50-59 yr	≥6	≥4
60-69 yr	≥11	≥5

* 97.5th percentile of cysts ≥5mm on enhanced CT abdomen

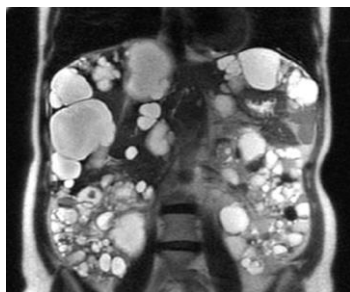
ADPKD-PKD1

Truncating



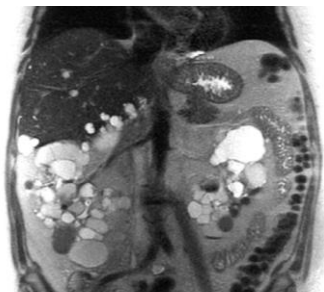
67 female
eGFR 31

Nontruncating1



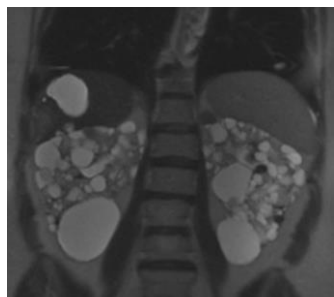
57 female
eGFR 42

Nontruncating 2

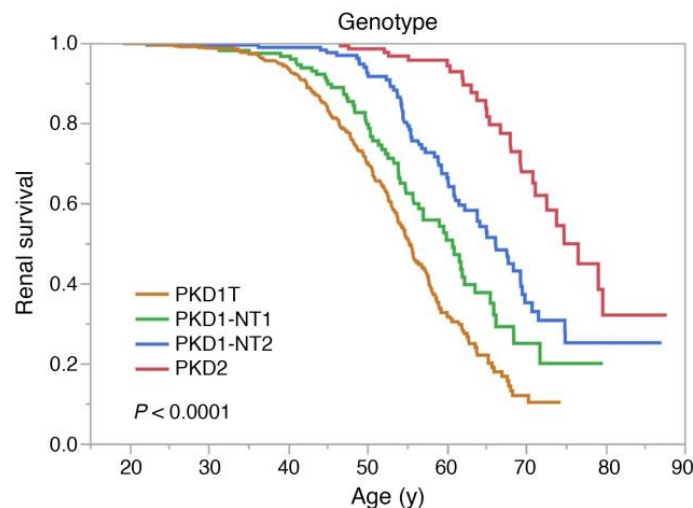


67 female
eGFR 42

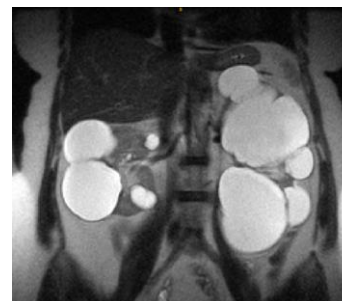
ADPKD-PKD2



65 female
eGFR 25

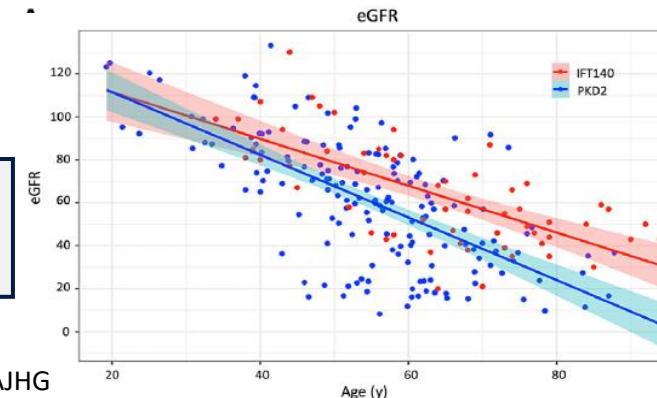


ADPKD-IFT140



59 female
eGFR 60

Senum et al 2022 AJHG

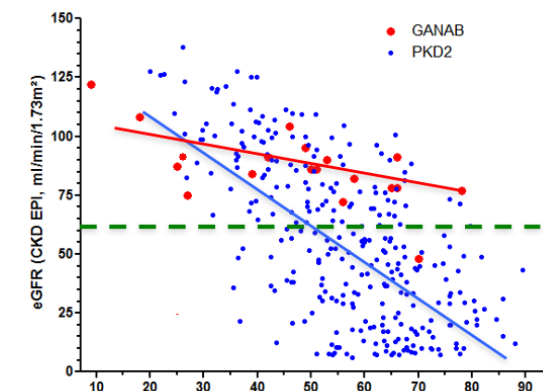


ADPKD-GANAB



68 female
eGFR 54

Porath B et al, AJHG 2016

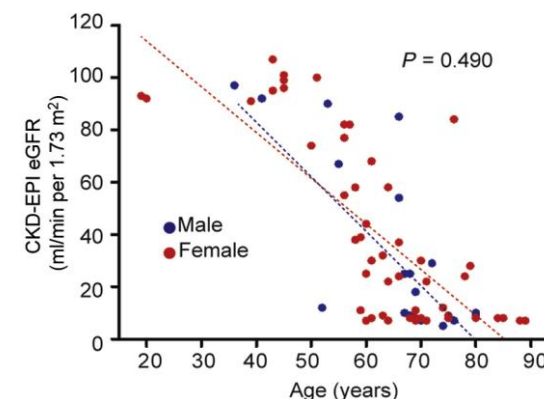


ADPKD-DNAJB11



62 female
eGFR 67

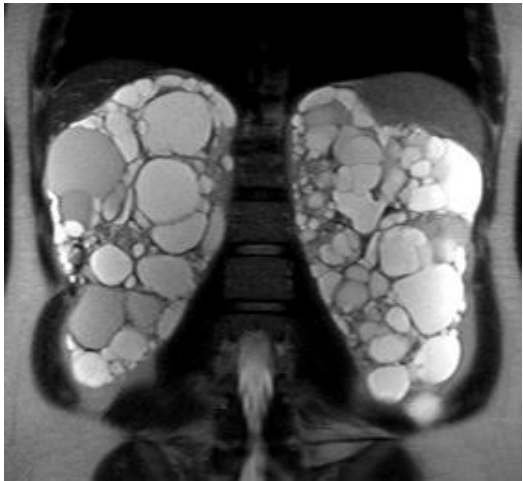
Huynh et.al. KI 2020



Lavu et al. (2020) JCI insight

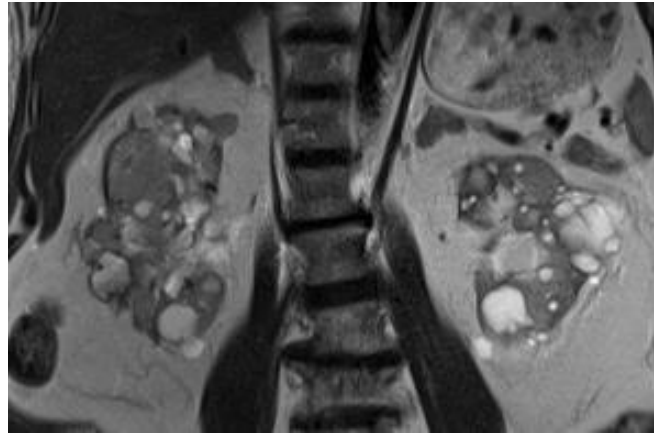
GFR and cystic burden

Congruent

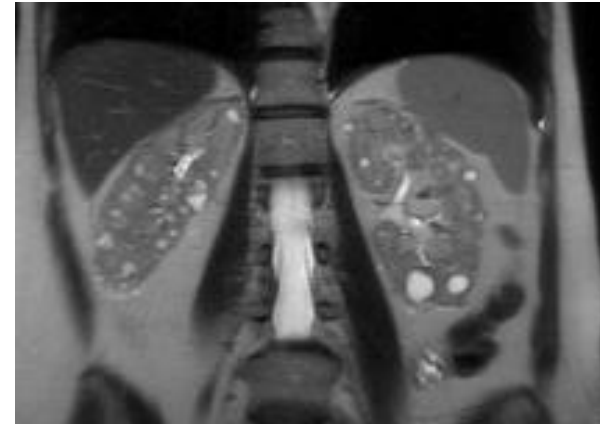


42 yo F,
definite ADPKD
PKD1 T, GFR 16,
HtTKV 2400, MIC1E

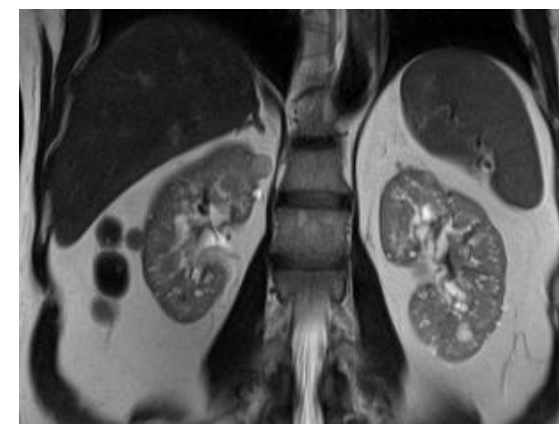
Non congruent



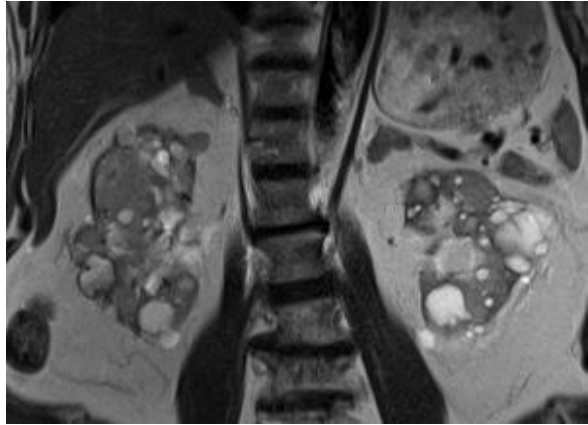
76 yo M,
Atypical ADPKD
ALG8, GFR 18,
HtTKV 456, MIC2B



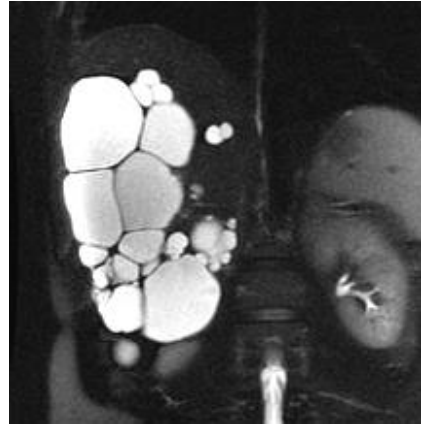
53 yo F,
Atypical ADPKD
DNAJB11, GFR 63,
HtTKV 295, MIC1A



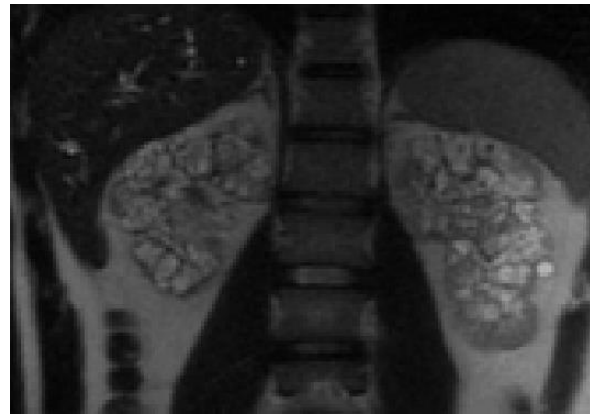
69 yo M, Lithium-
induced nephropathy
GFR 51



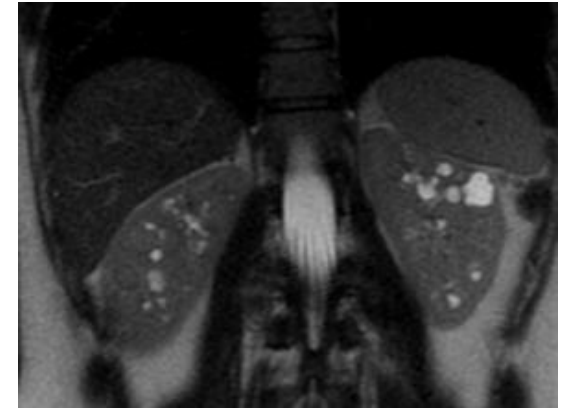
76 yo M,
Atypical ADPKD
ALG8, GFR 18,
HtTKV 455.8, MIC2B
MRI wo contrast



45 yo F, ADPLD
PRKCSH, GFR 106
MRI wo contrast



27 yo M, ARPKD
PKHD1, GFR 32
MRI without IV contrast



32 yo F, ADTKD
HNF1b, GFR 90
MRI wo contrast



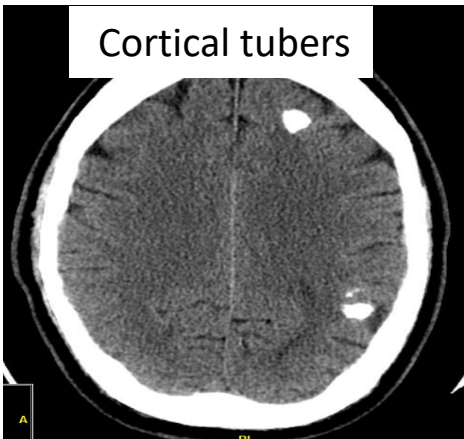
Not all cystic diseases= ADPKD

50M, GFR 23 ml/min
Bilateral renal cysts



Tuberous sclerosis

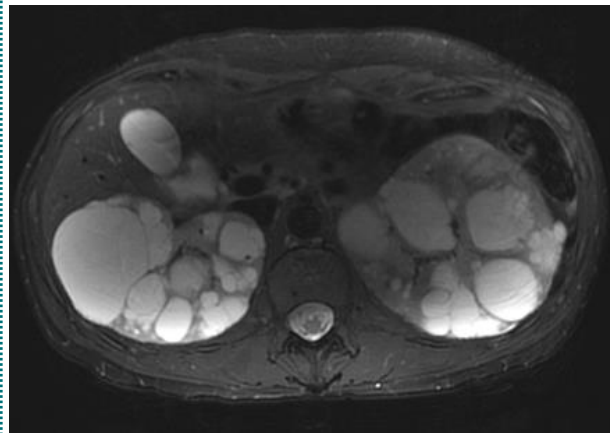
Cortical tubers



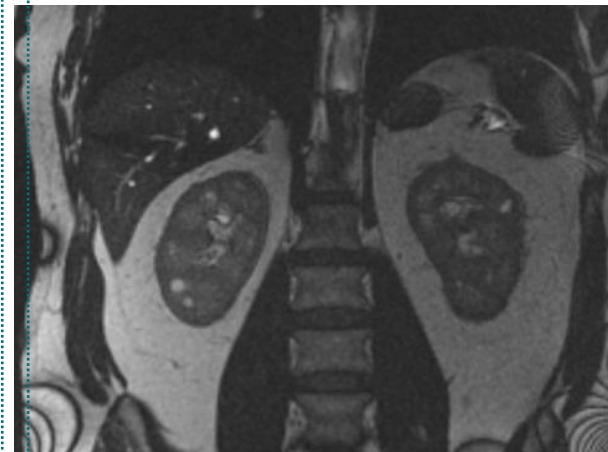
40F, GFR 45 ml/min
No FHx, cleft palate



**OFD1 mutation
(X-linked)**

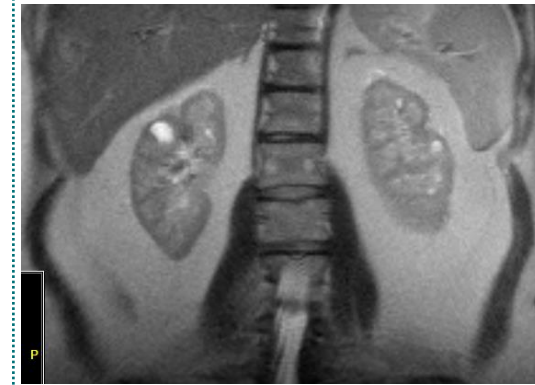


41 y.o male
htTKV 274 ml/m
eGFR 48 ml/min



ADTKD-MUC1

48 y.o female,
htTKV 179 ml/m
eGFR 66 ml/min



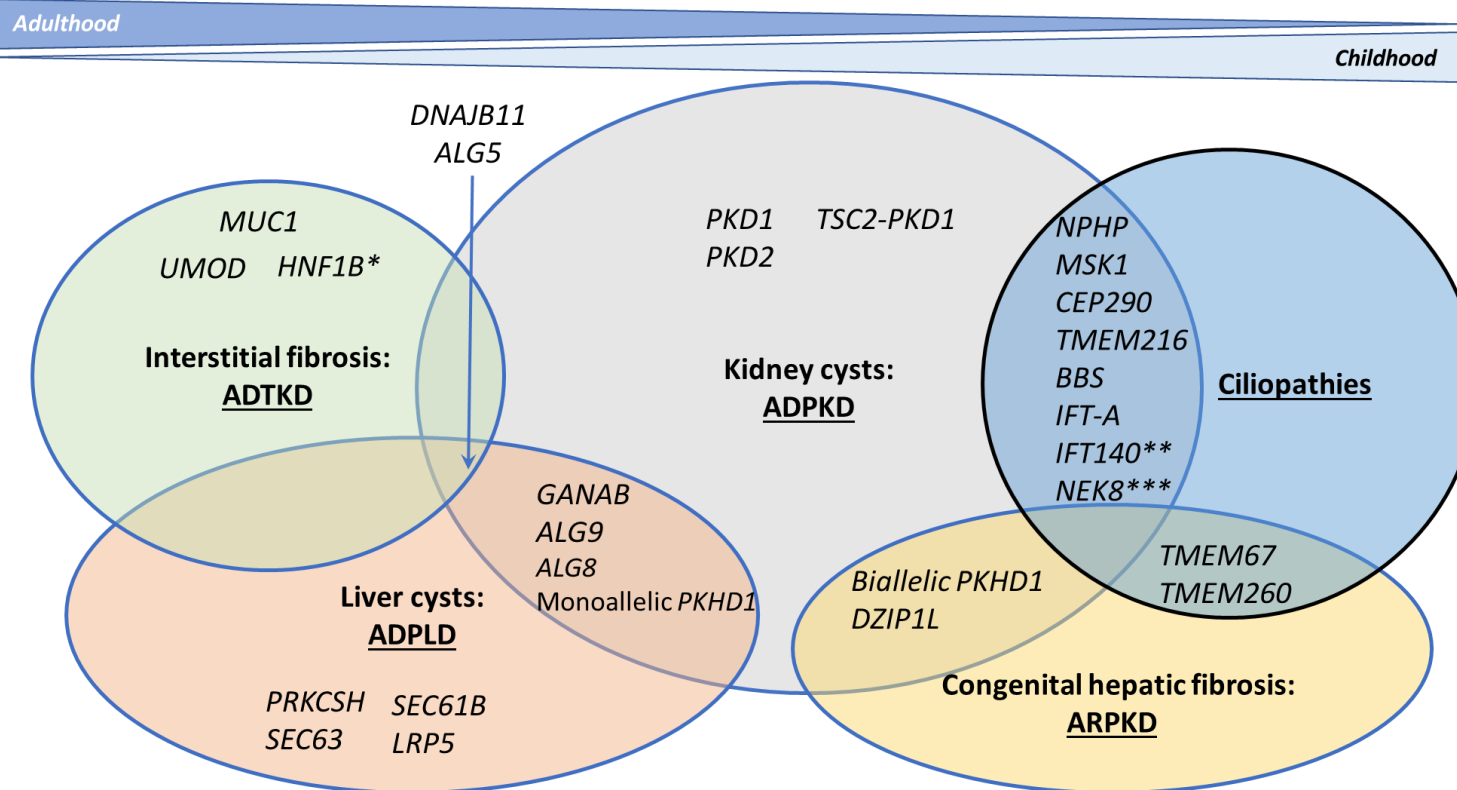
ADTKD-UMOD

ADPKD is a heterogenous disease

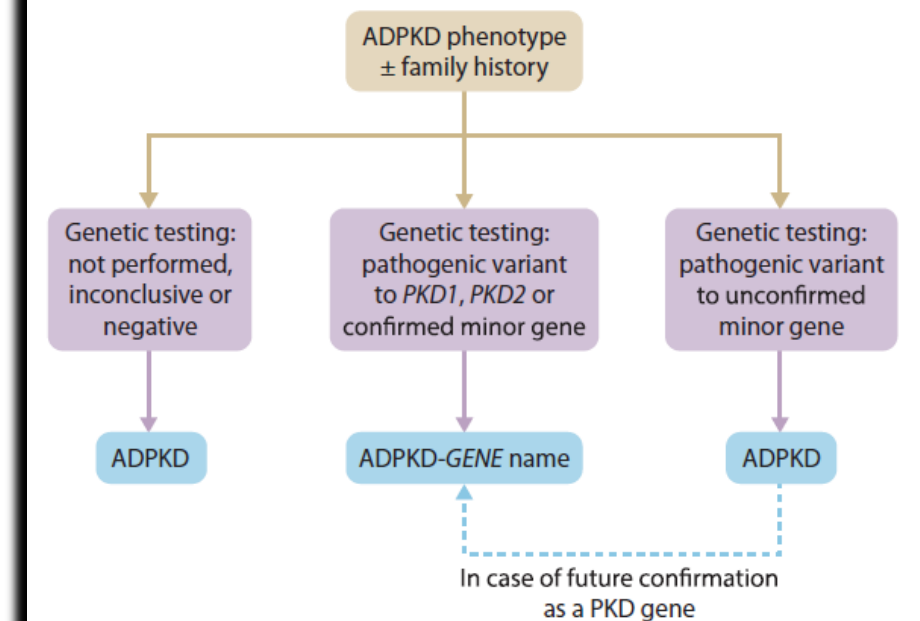
	IFT140	GANAB	DNAJB11	ALG5	ALG8	ALG9	PKHD1
Disease designation	ADPKD- <i>IFT140</i>	ADPKD- <i>GANAB</i>	ADPKD- <i>DNAJB11</i>	ADPKD- <i>ALG5</i>	ADPKD- <i>ALG8</i>	ADPKD- <i>ALG9</i>	<i>monoallelic PKHD1</i>
Proportion of ADPKD cases	1-2%	>0.5%	>0.5%	<0.5%	~1%	>0.5%	~1%
Kidney manifestations	Few, large bilateral cysts, Enlarged kidneys	Mild cystic burden	Bilateral small cysts , Mild enlargement	Mild-moderate cystic burden, mild enlargement	Mild cystic disease	Mild to moderate	Generally, very mild cystic disease
Renal outcome	Preserved GFR until old age	limited CKD, no ESKD	Limited early CKD <u>ESKD in 70s</u>	CKD, ESKD in older patients	Preserved GFR into old age	Significant CKD in older individuals	Preserved function into old age
Liver manifestations	Rare	Mild to severe	Mild	Few, rarely	Mild-severe PLD	Common	Common
Intracranial aneurysm risk	Unclear	unclear	Possible	Unclear	Unclear	Unclear	Unclear

Advances in the understanding of genetics of PKD

Genetic spectrum in cystic diseases



ADPKD nomenclature



Practice point: For people who are genetically tested, ADPKD will be employed as the name of the disease resulting from a pathogenic variant to the major ADPKD genes, *PKD1* or *PKD2*, and the minor genes when pathogenicity is well supported.

Patient with numerous bilateral kidney cysts on ultrasonography (US), computed tomography (CT), or magnetic resonance imaging (MRI)

Family history of renal cysts and/or cystic kidney disease (CKD)

Kidney length ≥ 13 cm

Age, y	No. of cysts on US
15-39	≥ 3 total
40-59	≥ 2 per kidney
≥ 60	≥ 4 per kidney

- or
- >10 cysts total on CT or MRI
 - Cystic burden congruent with progressive GFR decline

Autosomal dominant polycystic kidney disease (ADPKD)
(65%-70%)

- <5 cysts account for >50% total kidney volume
- Cysts >3 cm
- Higher GFR
- Mild or severe polycystic liver disease (PLD)

Atypical ADPKD
(5%-10%)

Kidney length <13 cm

≥ 20 cysts

- Cysts <1 cm
- Low GFR

<20 cysts

- Low cystic burden with low GFR
- Genitourinary malformation
- Gout
- Low magnesium
- Early diabetes

ADTKD
(<5%)

<20 cysts

- PLD
- GFR >60 mL/min/1.73 m²

ADPLD
(<2%)

No family history of renal cysts and/or CKD

Kidney length ≥ 13 cm

>16 cm
>10 cysts per kidney

Likely ADPKD
(15%-20%)

>16 cm
>10 cysts per kidney

- Female
- Oral, facial, or digital malformation

OFD1 syndrome
(<1%)

13-16 cm

- Congenital hepatic fibrosis

ARPKD
(1%)

Kidney length <13 cm

GFR >60 mL/min

- PLD
- No. of cysts >97.5th percentile of unaffected population^a

Possible ADPKD
(5%-10%)

Alternative diagnoses

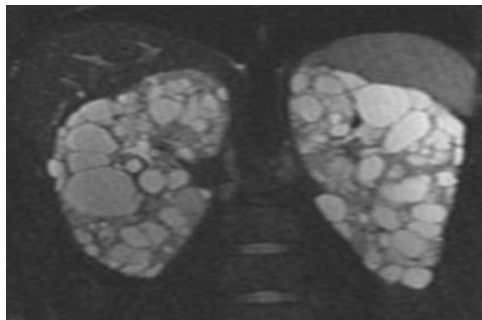
Acquired cystic kidney disease

Lithium-induced cystic disease

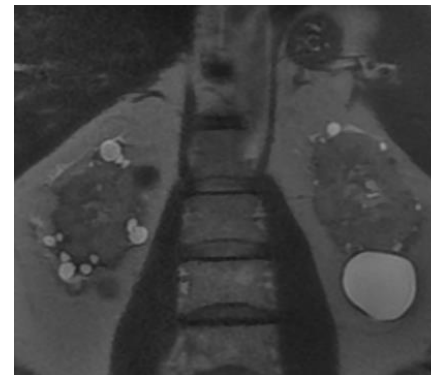
Tuberous sclerosis

Von Hippel-Lindau disease

Genetic testing positive for a pathogenic variant in one of the PKD genes

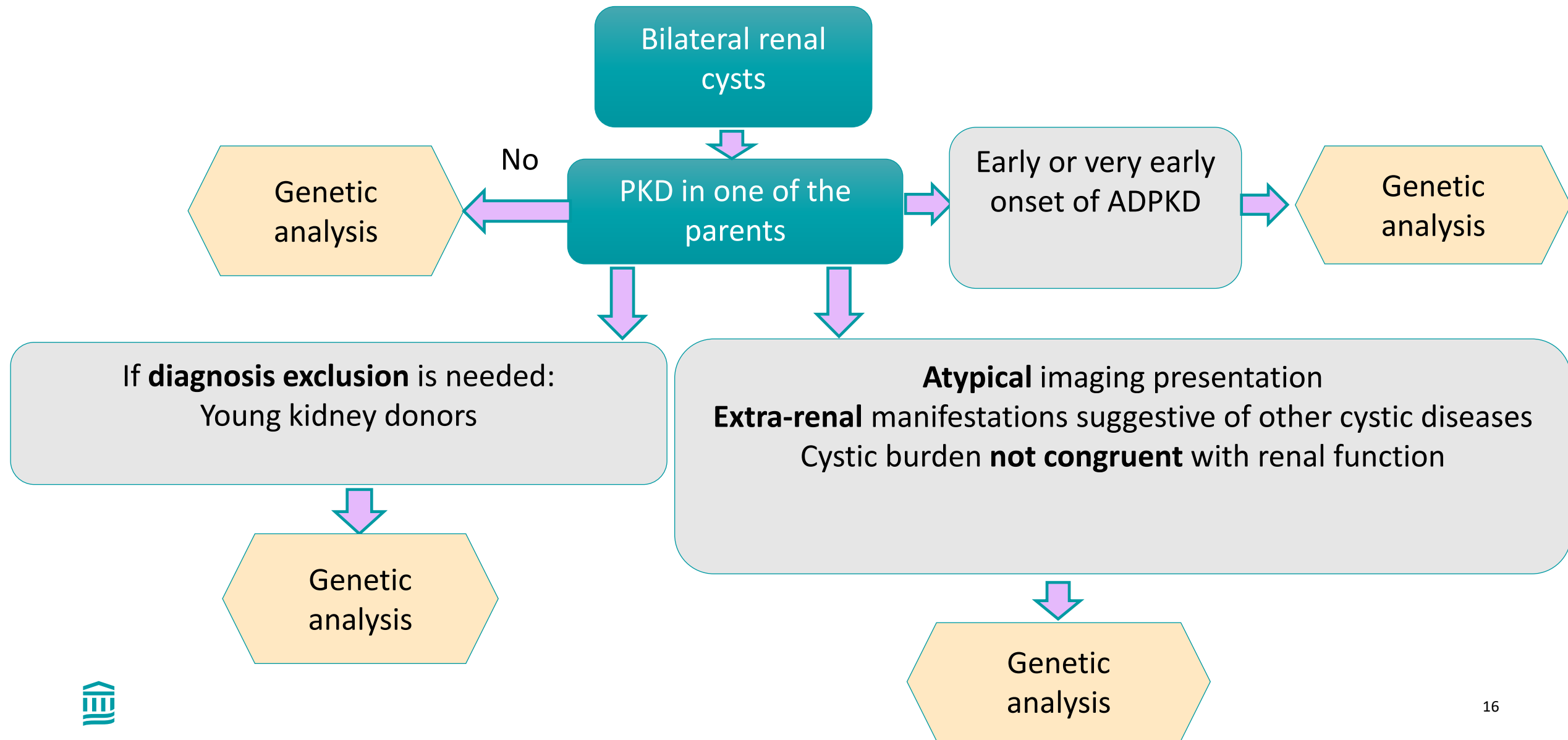


34 yo Female
Father and grandmother with ADPKD
eGFR 36 ml/min



50 yo Male
Neg. Fam. Hx
eGFR 23 ml/min
Facial angiofibroma,
cortical tubers

When would you need genetic testing?



High phenotypic and interfamilial variability

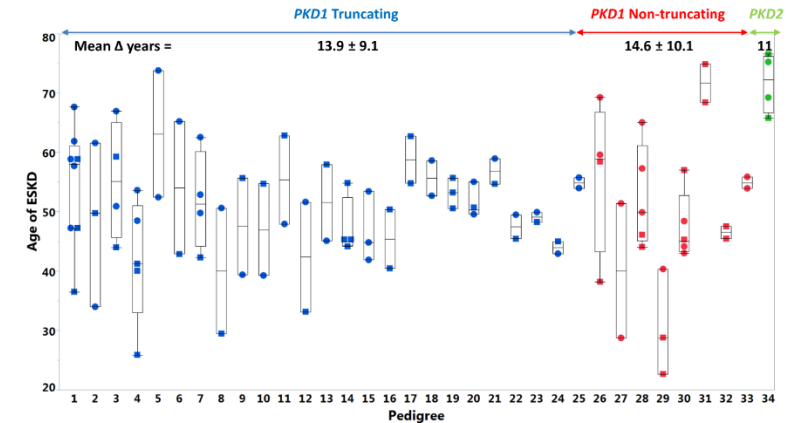
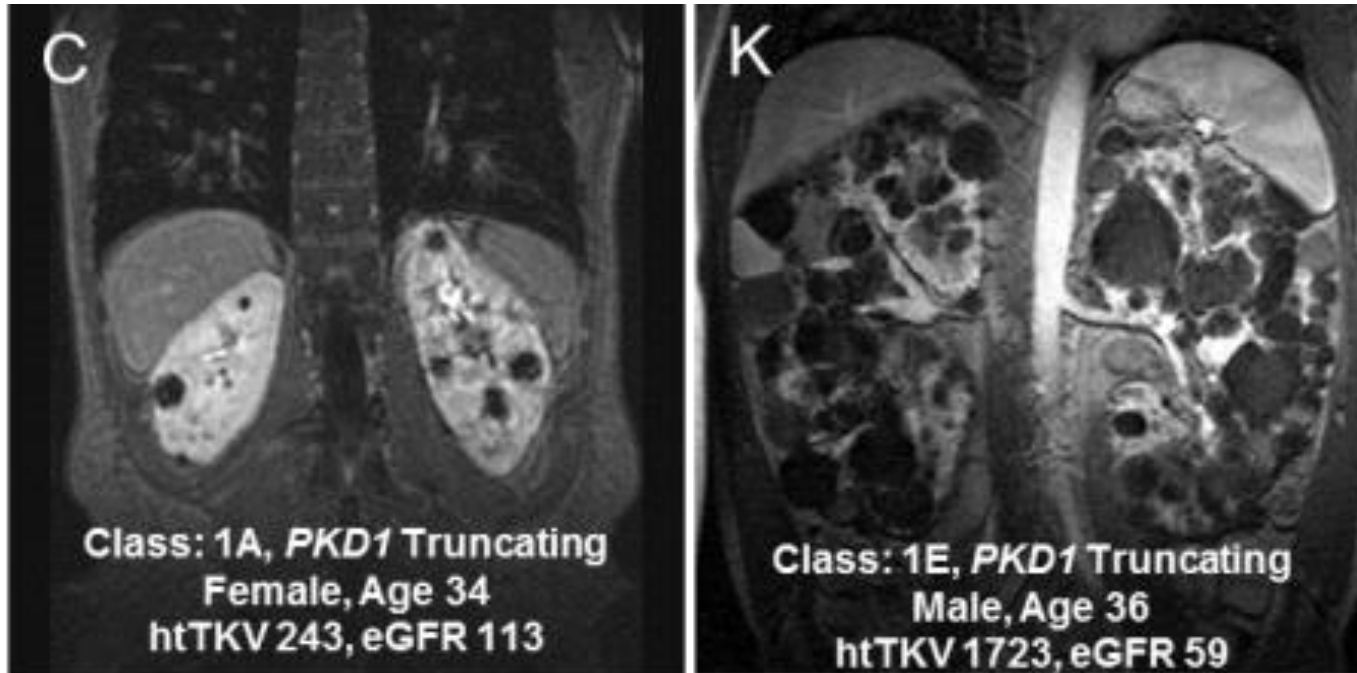
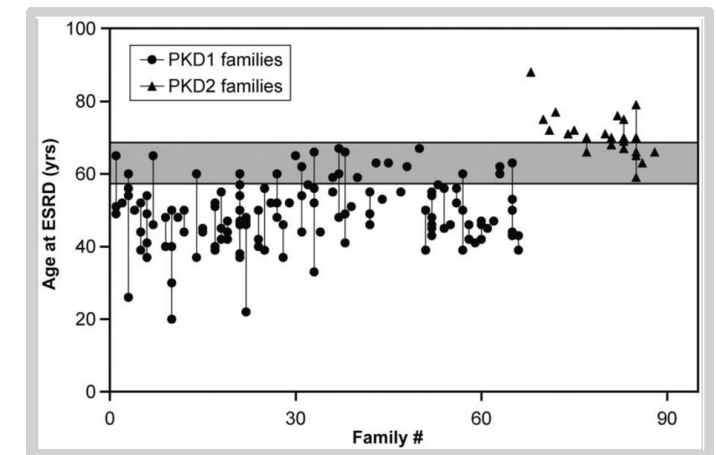


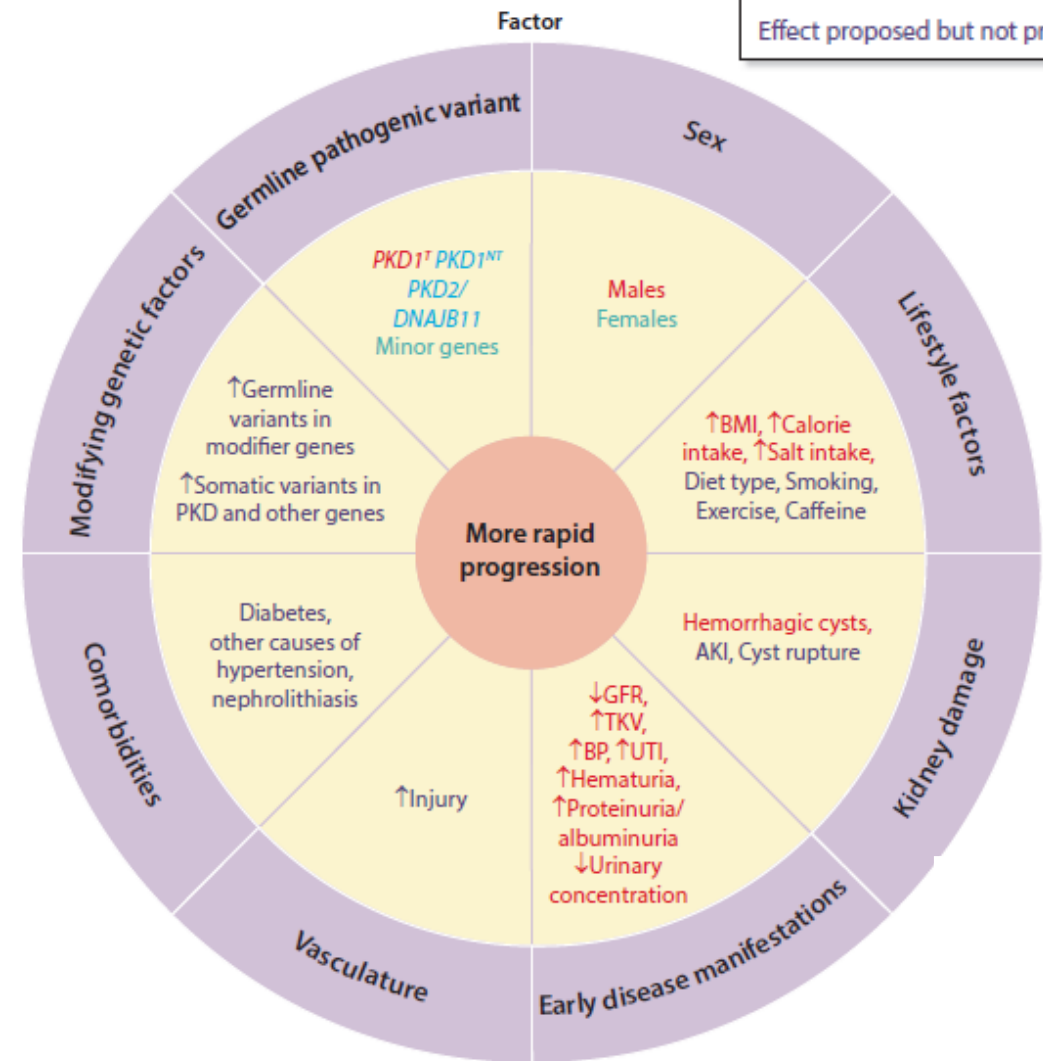
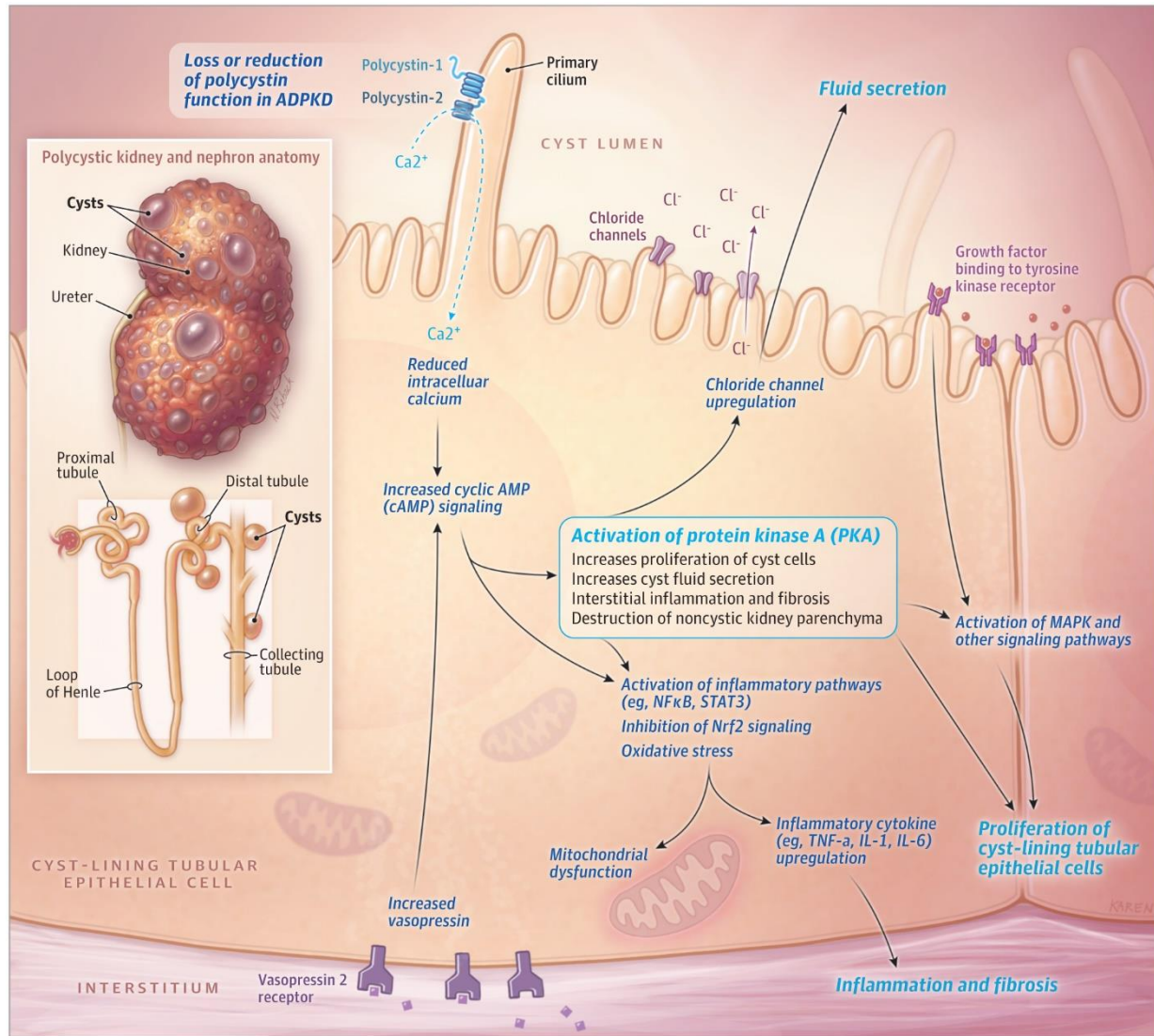
Figure 4A- Age of ESKD is plotted for each pedigree based on their familial PKD mutation. The difference in ESKD age onset between the youngest and oldest family member was calculated. The mean and SD of the age differences is noted.



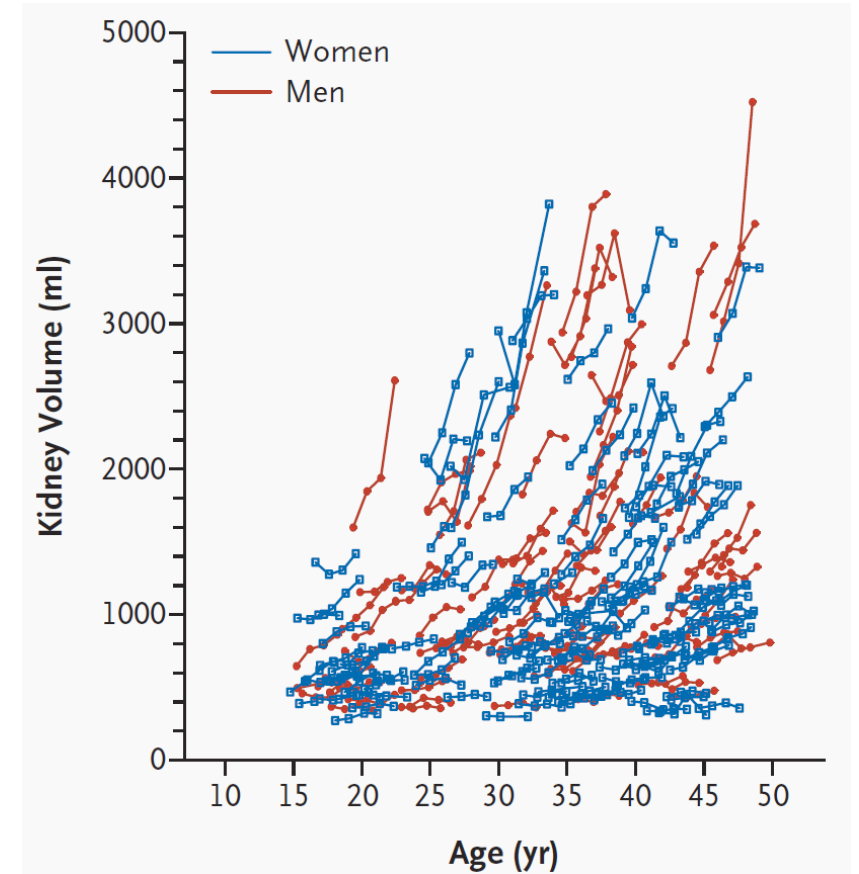
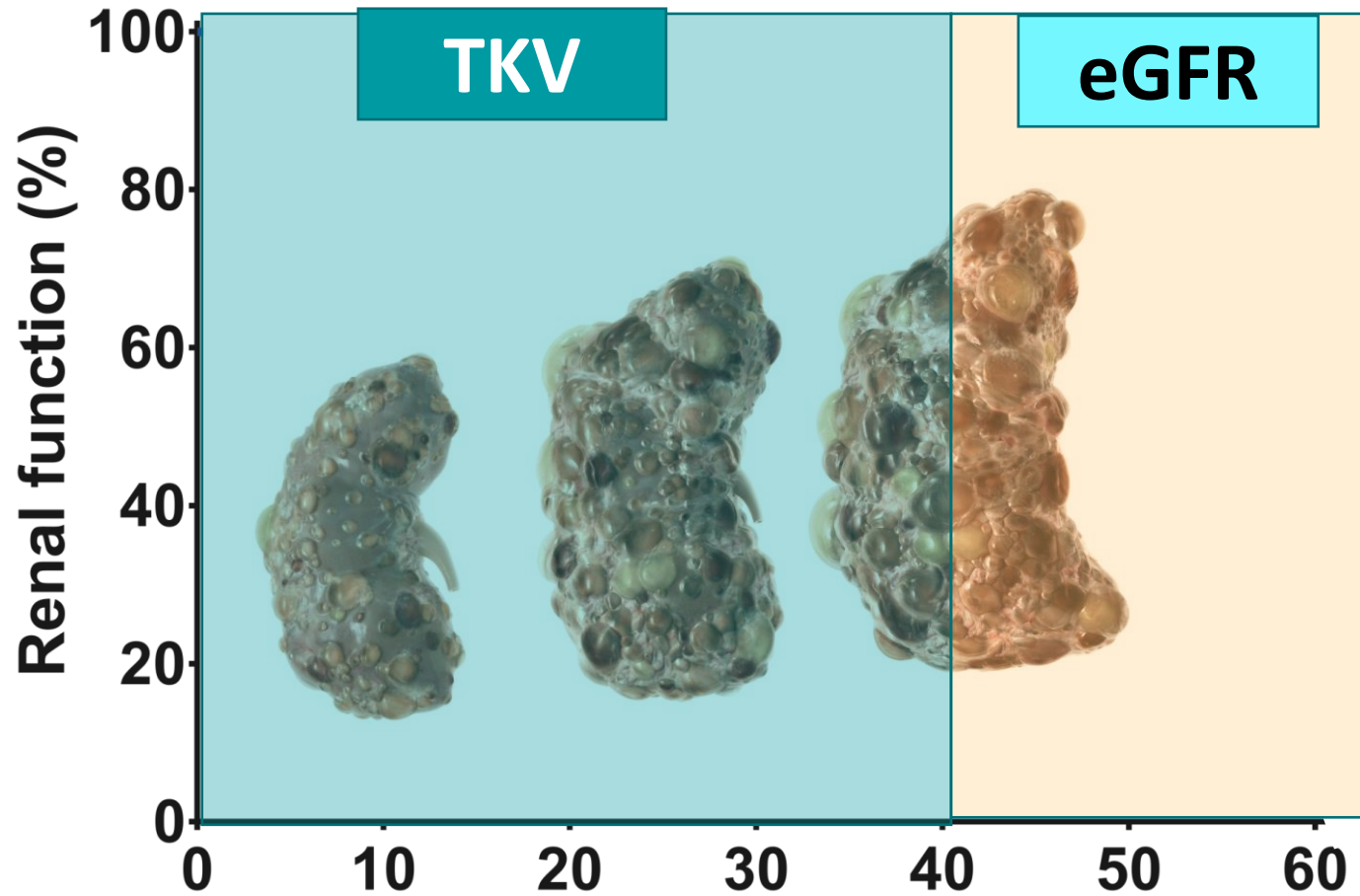
ESRD ≤ 55 : PKD1 mutation (PPV 100%, sensitivity 72%)
ESRD ≥ 70 : PKD2 mutation (PPV 100%, sensitivity 74%)

Factors contributing to rapid progression

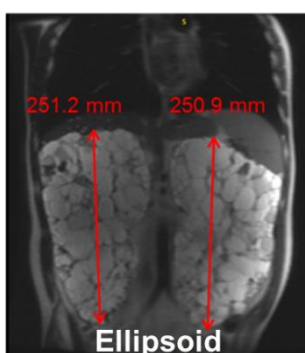
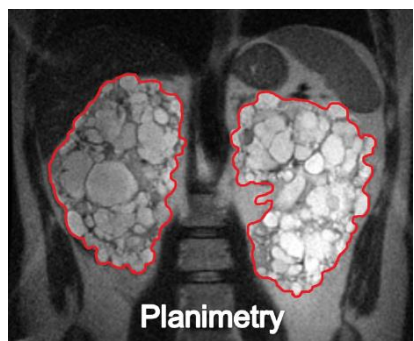
Associated with more severe disease
Associated with less severe disease
Intermediate effect
Effect proposed but not proven



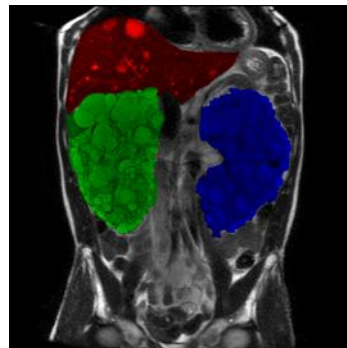
Clinical natural history of ADPKD: Prognostic biomarker in early ADPKD



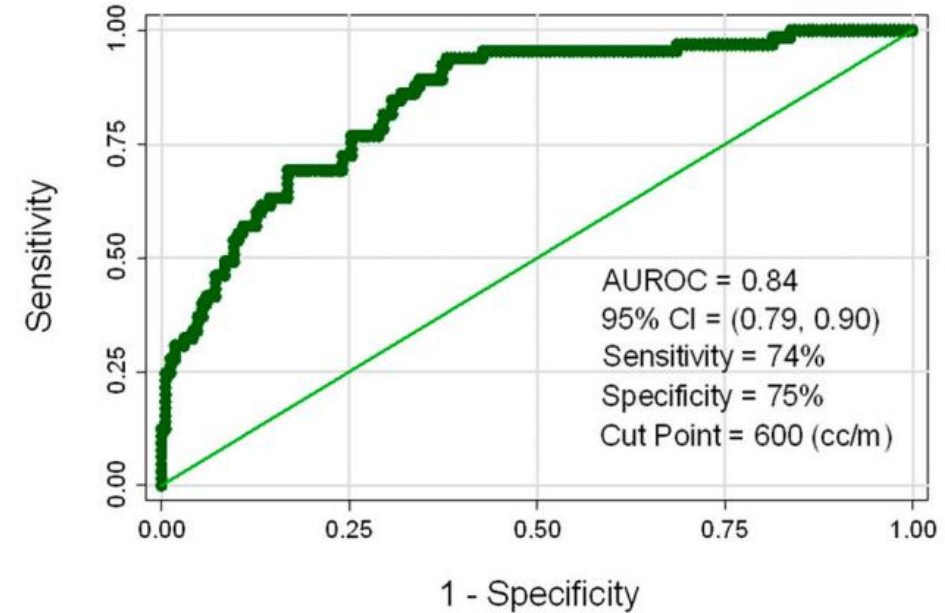
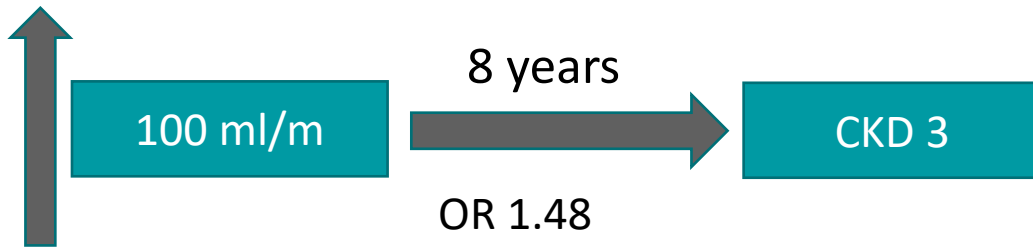
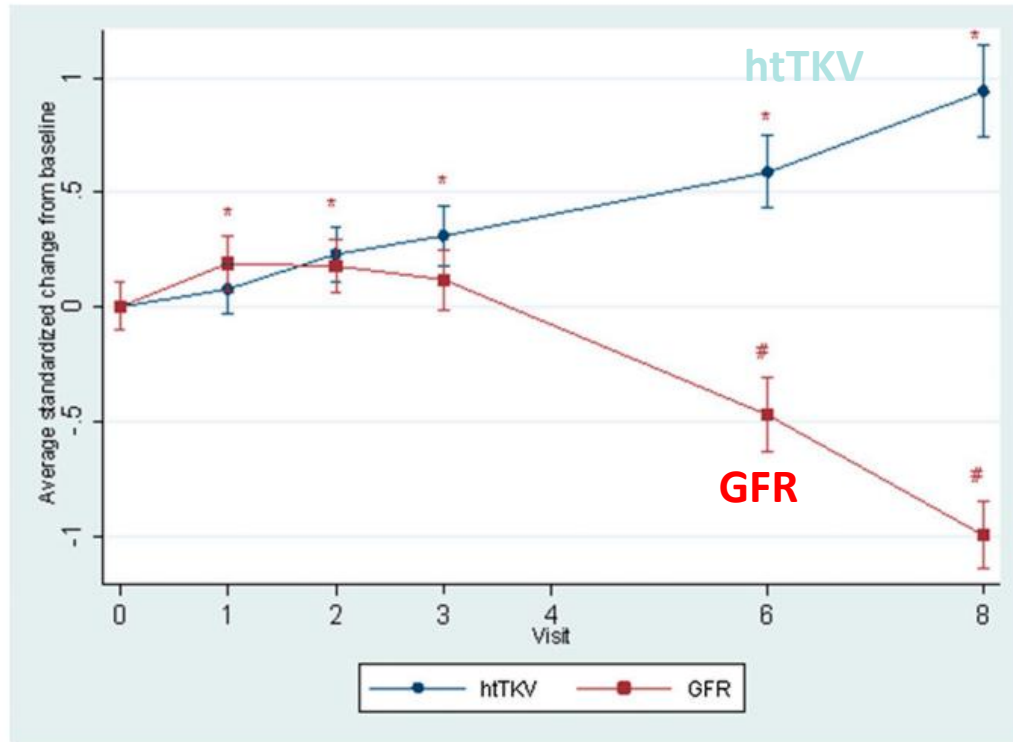
N= 214; 4 centers; 3 years
Higher **TKV** growth rate
→ faster **GFR** decline



Age



CRISP II: Kidney Volume and Functional Outcomes in ADPKD



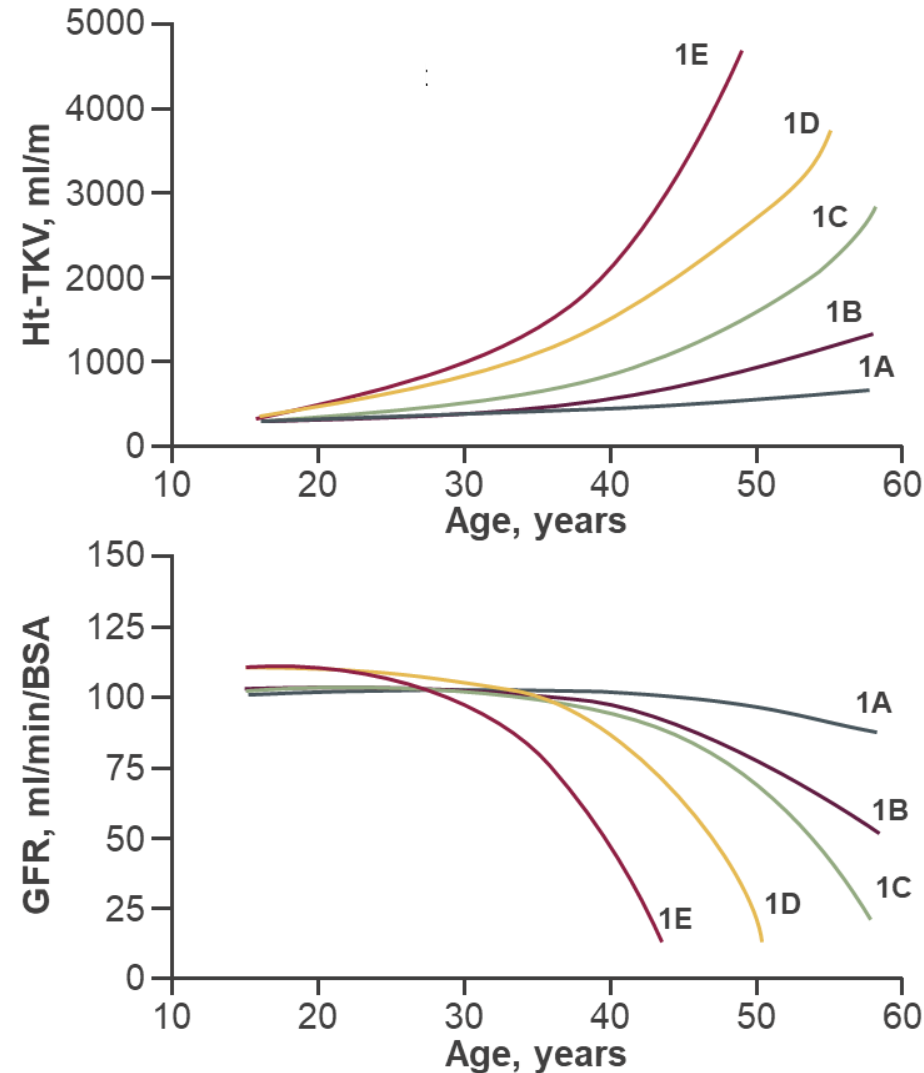
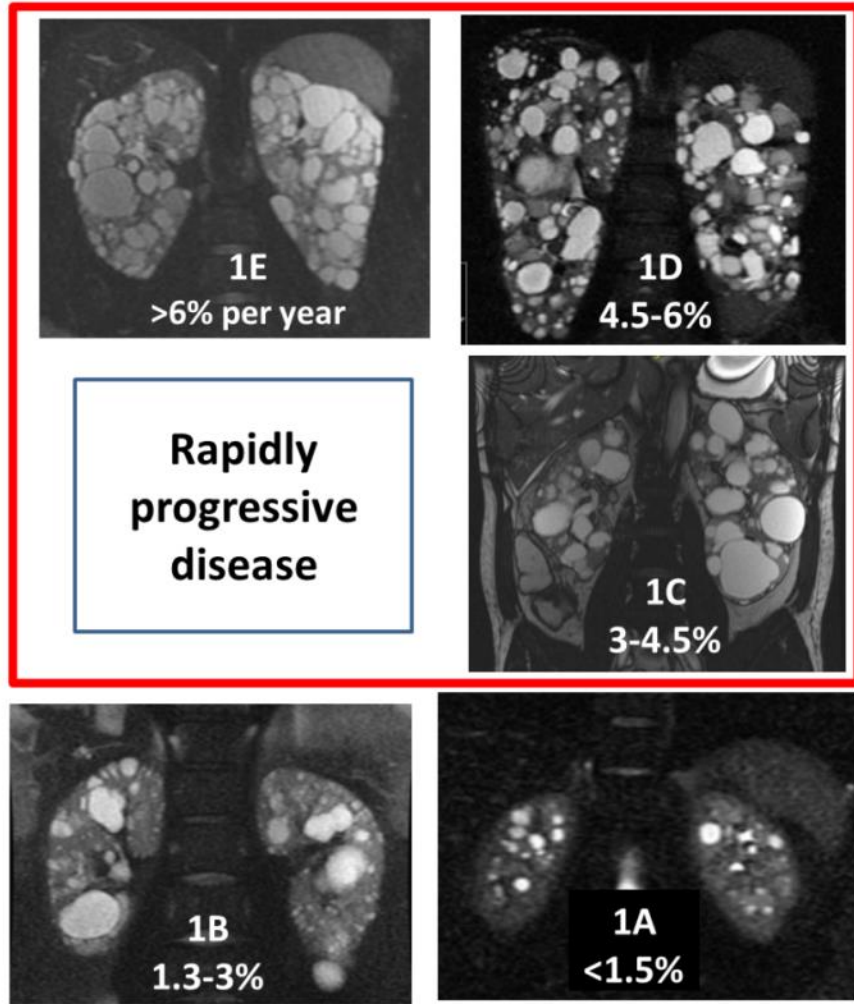
htTKV was a better predictor ($p < 0.05$) than:

- baseline age
- serum creatinine, BUN
- urinary albumin
- monocyte chemotactic protein-1 excretion

Chapman et al. (2012) CJASN



Risk stratification: Not all ADPKD are created equally

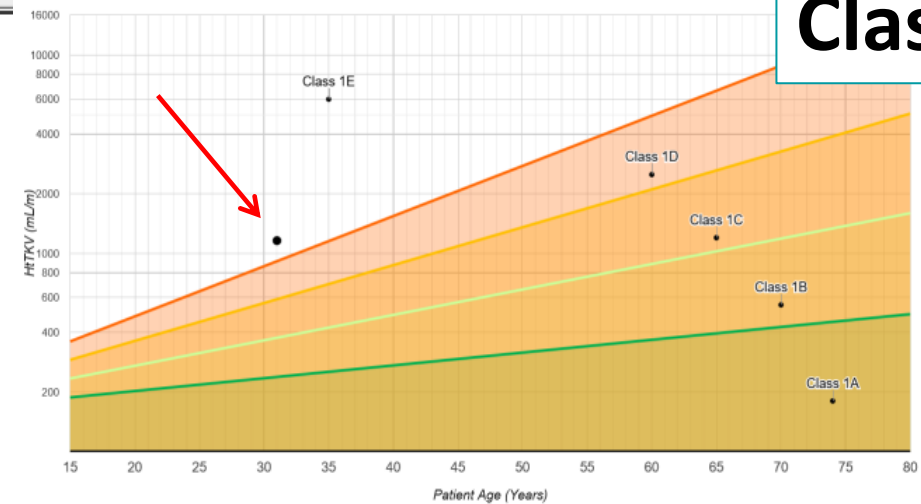


MIC	Mean age at KF, yrs
1E	43.4 ± 7
1D	53.5 ± 8.6
1C	58.4 ± 7.9
1B	65 ± 6.8



3 ADPKD Classification if Kidney Volume previously calculated by Stereology	
Required Data Entry	
Kidney Volume (mL)	2018.1
Patient Height (m)	1.74
Patient Age (years)	31
<input type="button" value="Clear All"/>	
Calculated Results	
Height Adjusted TKV (mL/m)	1159.8
ADPKD Classification	1E

Class 1E



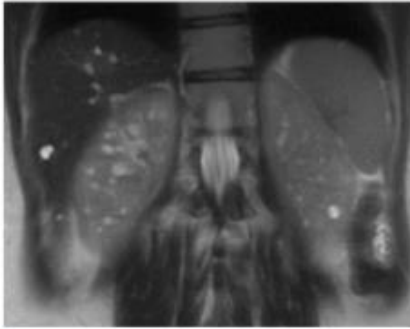
Estimate future GFR

31 yo, GFR 85 ml/min

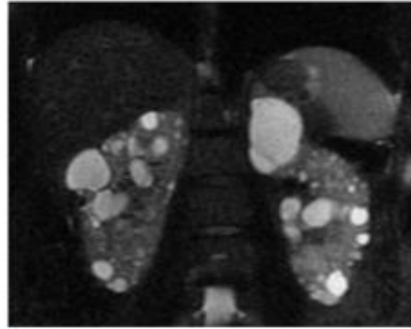
4 Prediction of Future eGFR based on Classification	
Required Data Entry	
Serum Creatinine (mg/dL)†	0.9
Age (years)	31
Race (AA/O)‡	o
Gender (M/F)	f
ADPKD Classification	1E
Future time (years)	14
<input type="button" value="Clear All"/>	
Calculated Results	
Current eGFR (mL/min/1.73m ²)	85.2
Future eGFR (mL/min/1.73m²)	7.3
<input type="button" value="Calculate Current and Future eGFR"/>	

ESKD in 14 years
At age 45

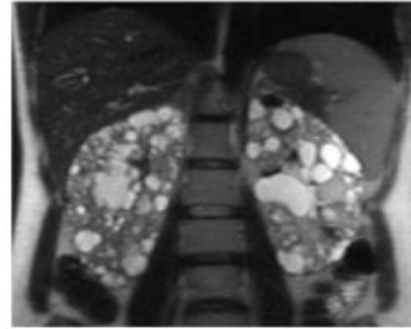
Typical
ADPKD



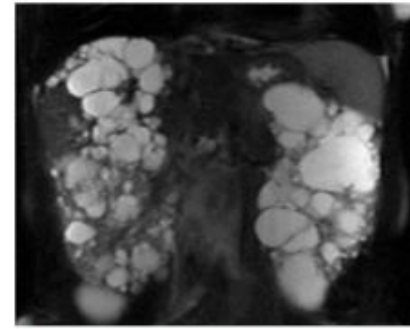
Female, 48 y.o.
MIC-1A



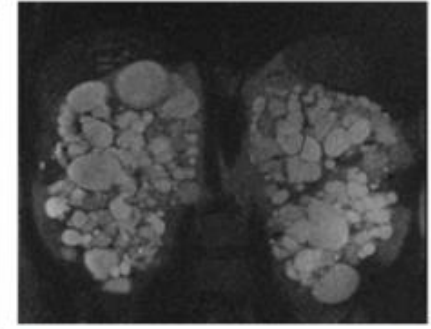
Female, 45 y.o.
MIC-1b



Female, 36 y.o.
MIC-1C

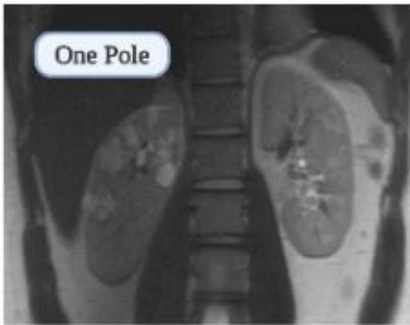


Female, 47 y.o.
MIC-1D

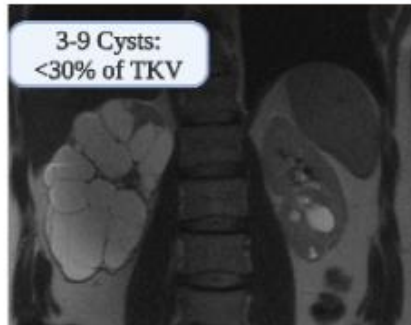


Male, 48 y.o.
MIC-1E

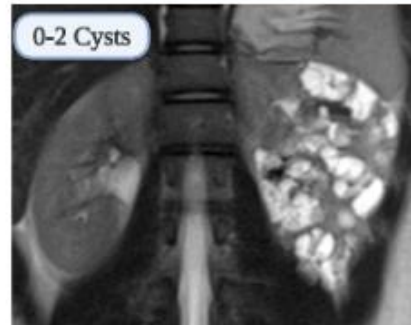
Atypical
ADPKD



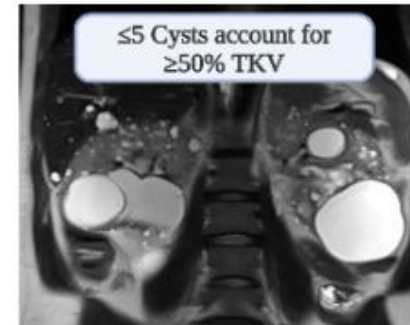
Male, 32 y.o.
MIC-2A
(Segmental)



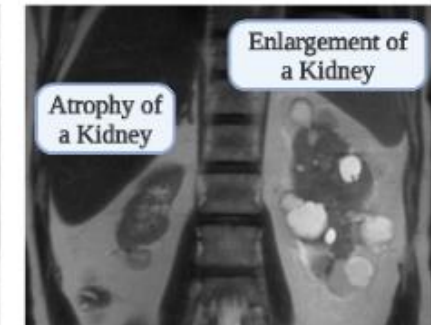
Male, 56 y.o.
MIC-2A
(Asymmetric)



Female, 19 y.o.
MIC-2A
(Unilateral)



Female, 45 y.o.
MIC-2A
(Lopsided)

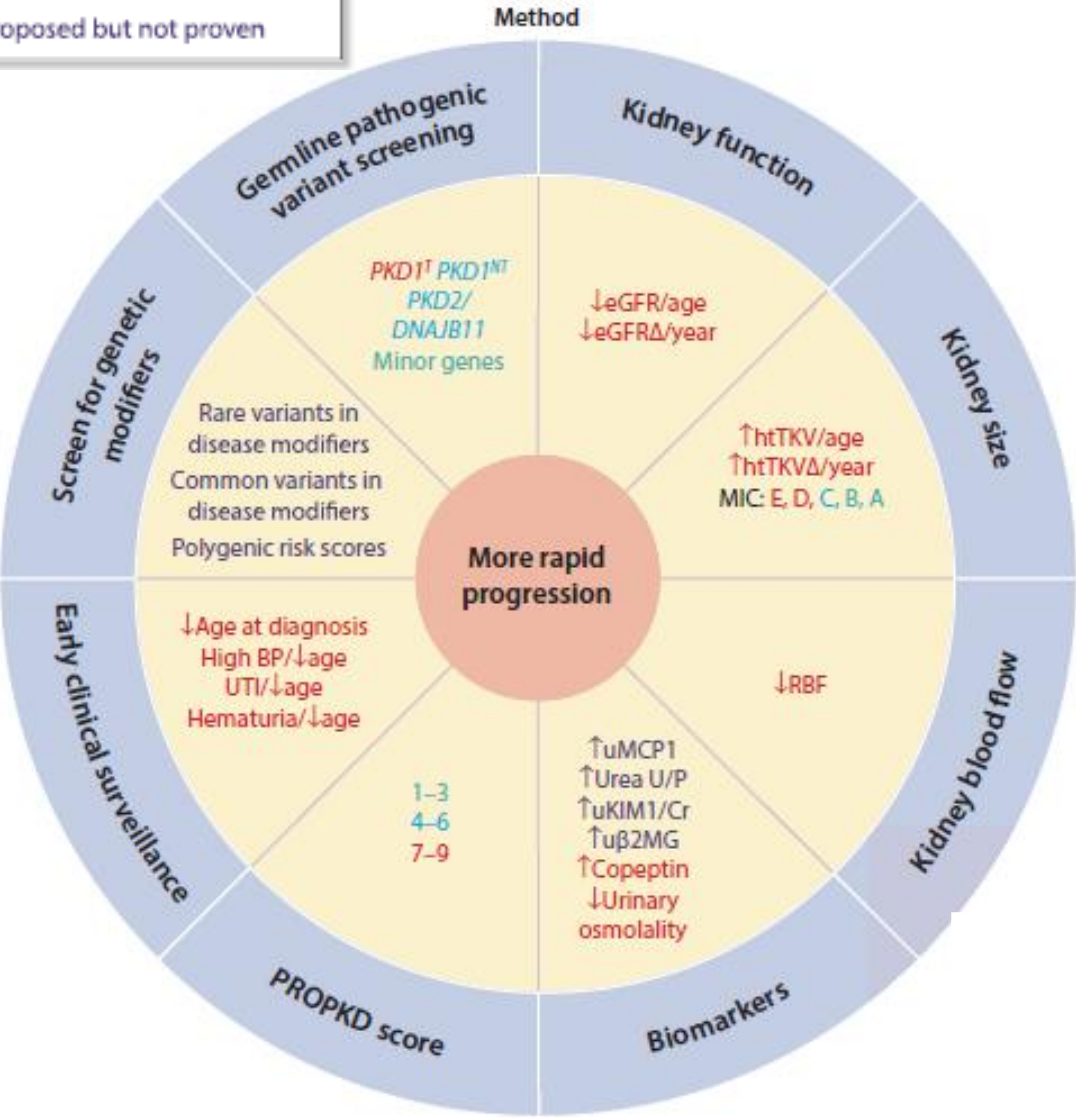


Male, 69 y.o.
MIC-2B



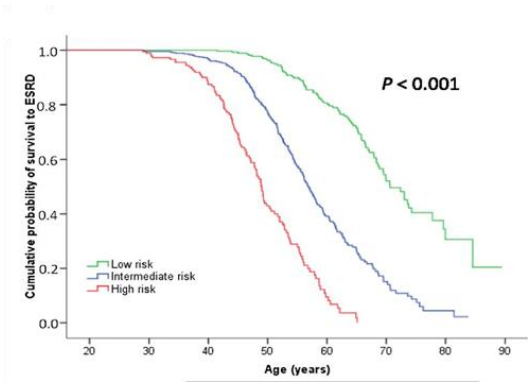
Methods to assess risk of disease progression

Associated with more severe disease
Associated with less severe disease
Intermediate effect
Effect proposed but not proven

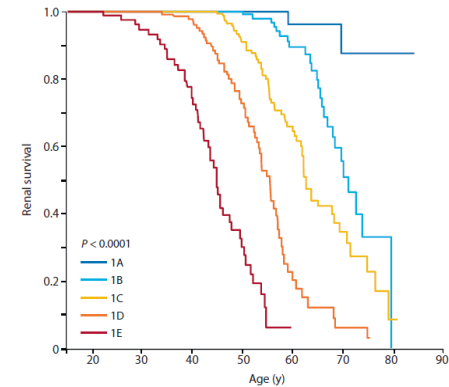
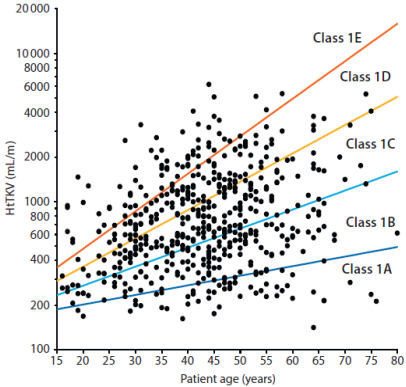


PROPKD score

	Point
Male	1
HTN < 35 years	2
Urological event < 35 years	2
PKD2 mutation	0
PKD1 non-truncating mutation	2
PKD1 truncating	4

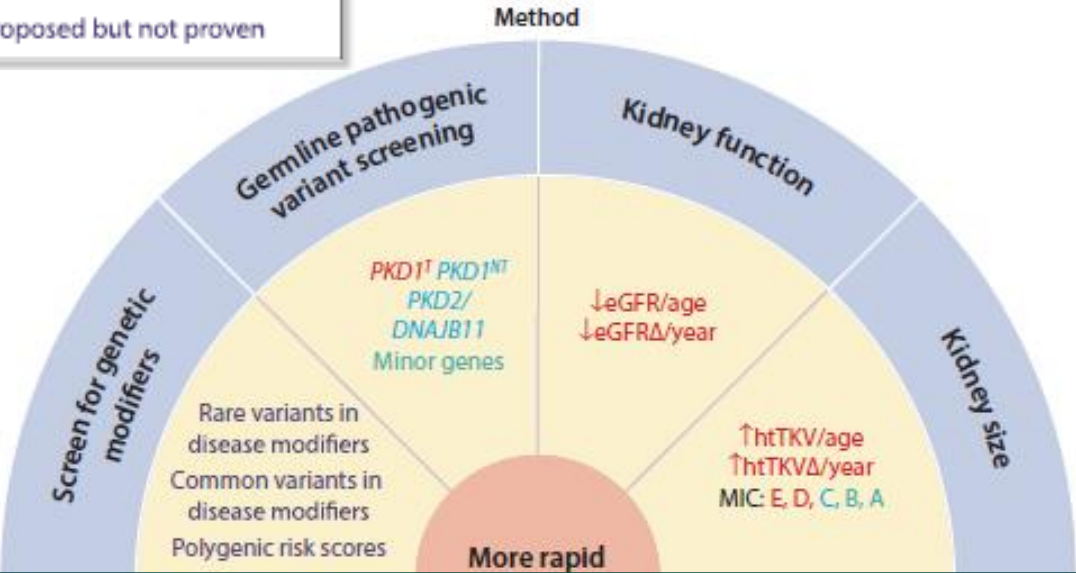


MIC



Methods to assess risk of disease progression

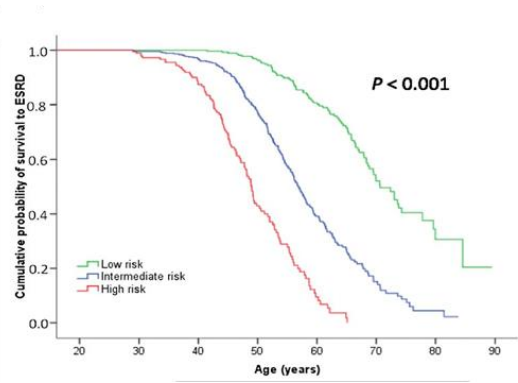
Associated with more severe disease
Associated with less severe disease
Intermediate effect
Effect proposed but not proven



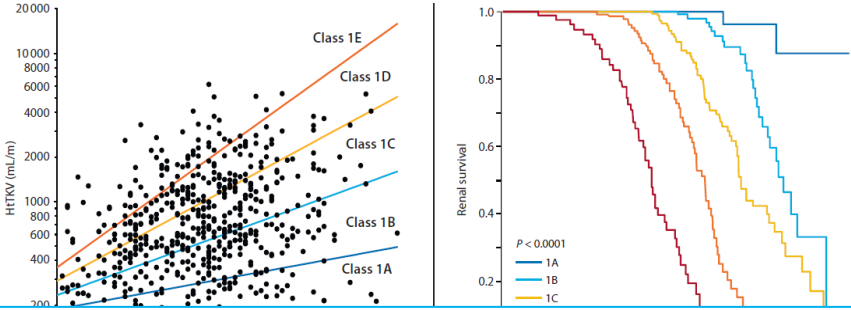
We recommend employing the Mayo Imaging Classification (MIC) to predict future decline in kidney function and the timing of kidney failure (1B).

PROPKD score

	Point
Male	1
HTN < 35 years	2
Urological event < 35 years	2
PKD2 mutation	0
PKD1 non-truncating mutation	2
PKD1 truncating	4



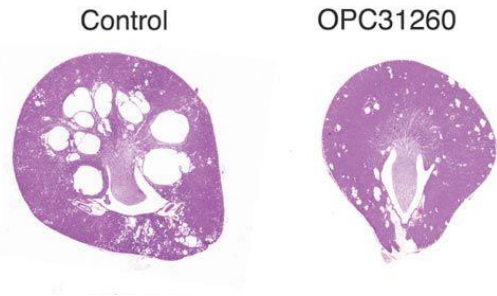
MIC



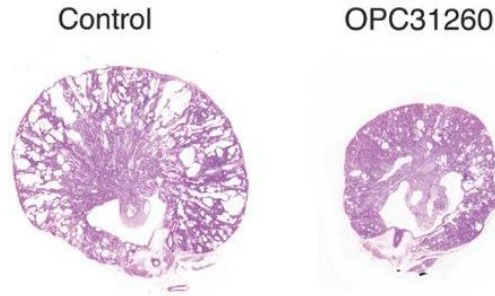
Practice Point: When using the MIC for prognostics, **exclude** people who have pathogenic variants in genes other than *PKD1* or *PKD2* (if genetic information is available), as the predictions are likely unreliable in these people.

Rationale for Vasopressin receptor (V2) antagonists in ADPKD

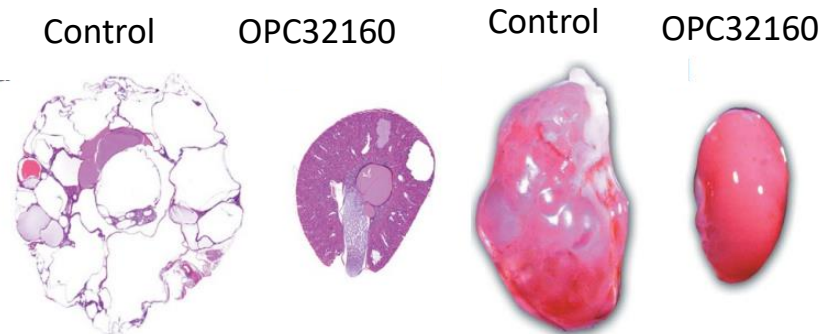
PCK rats



pcy mice



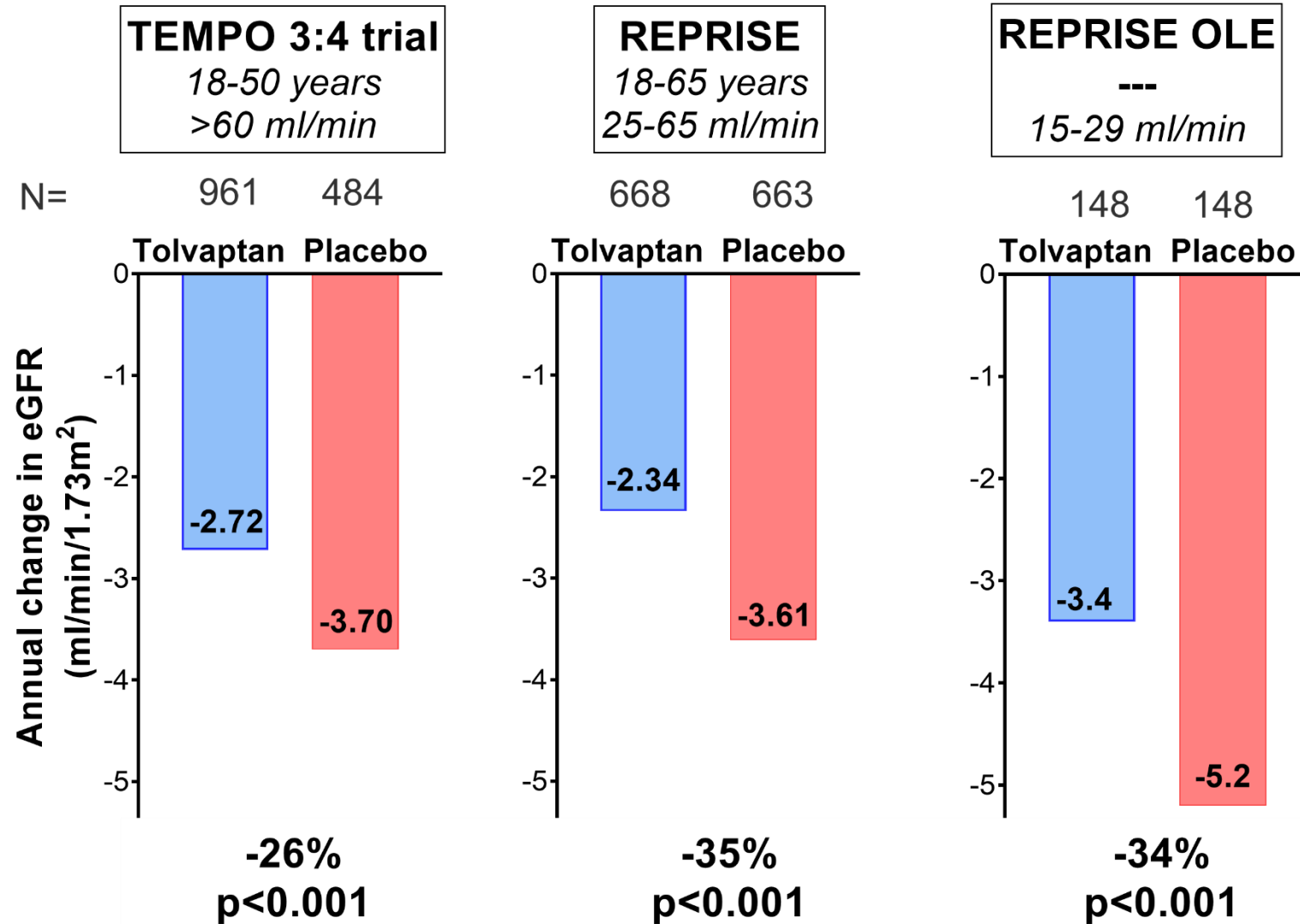
Pkd2^{-tm1Som} mice



No Vasopressin → No Cysts

<i>pck</i> rat <i>AVP</i> ^{+/+}	<i>pck/Brattleboro</i> <i>AVP</i> ^{-/-}	<i>pck/Brattleboro</i> <i>AVP</i> ^{-/-} + DDAVP
 Male	 Male	 Male
 Female	 Female	 Female

Treatment effect of Tolvaptan on annual rate of eGFR decline



TEMPO 4:4 (OLE)

N= 871

2 years

Mayo Clinic

N= 97

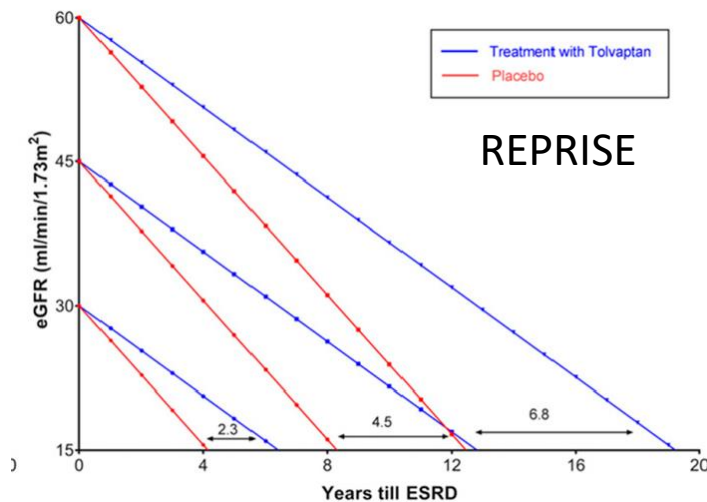
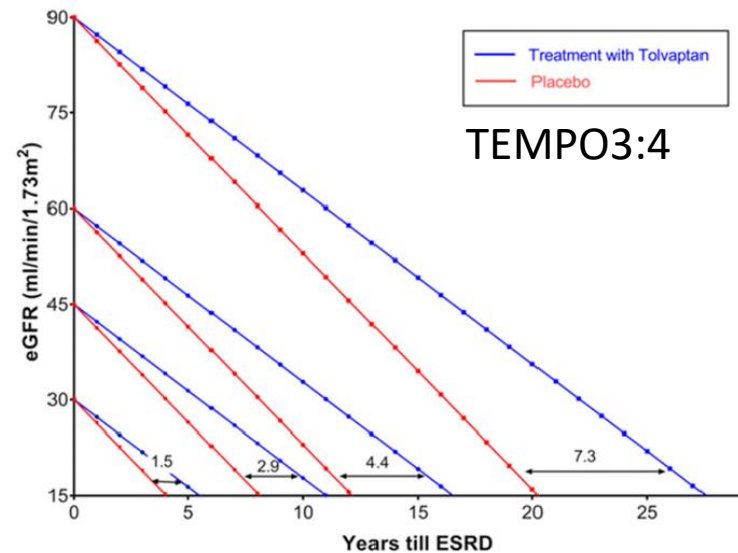
Up to 11 years

Effect on eGFR = sustained and cumulative

Torres et al (2012) NEJM ; Torres et. al (2017) NEJM ; Torres et al. (2021) KI reports;

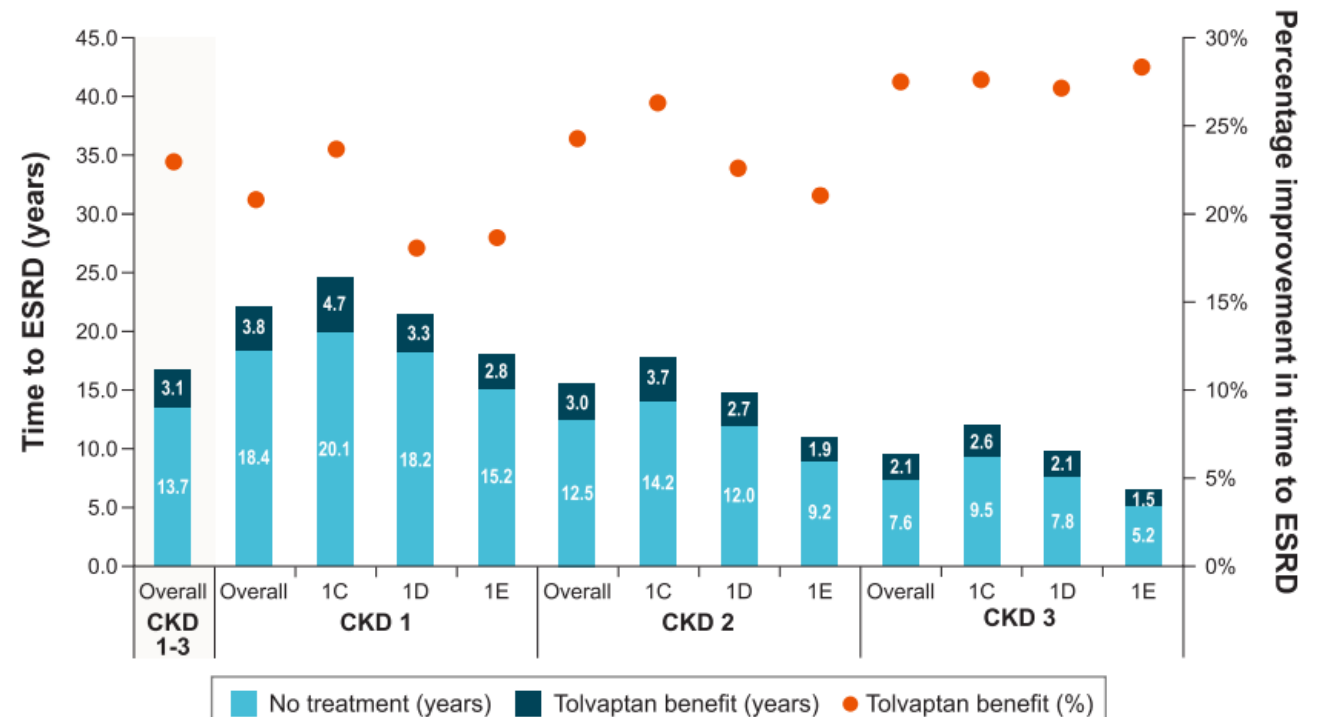
Torres (2017) NDT; Edwards (2018) CJASN

Estimation of kidney protection from tolvaptan treatment



Total gain = **1.3 ml/min** x years of treatment

Every 4 yrs of treatment → 1 yr delay in reaching ESRD



Predicted 3.1-year delay of ESRD
23% improvement over ~13.7 yrs

Indications for tolvaptan in ADPKD

Recommendation 4.1.1.1: We recommend initiating tolvaptan treatment in adults with ADPKD with an estimated glomerular filtration rate (eGFR) ≥ 25 ml/min per 1.73 m^2 who are at risk for rapidly progressive disease (Figure 25) (1B).

Initiation of tolvaptan should be offered to adults with ADPKD and:
eGFR ≥ 25 ml/min per 1.73 m^2

AND

Risk of rapid disease progression* as indicated by either:
Mayo class 1C⁺ to 1E

OR

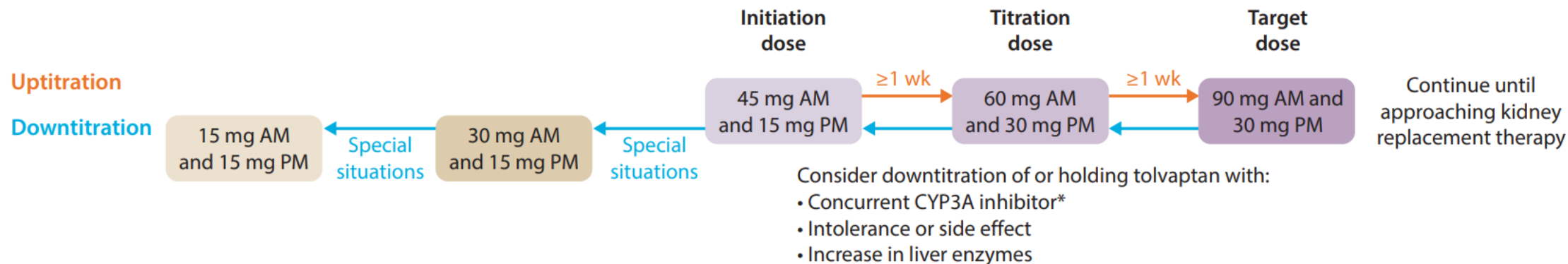
Historical rate of eGFR decline[†] (≥ 3 ml/min per 1.73 m^2 per year)

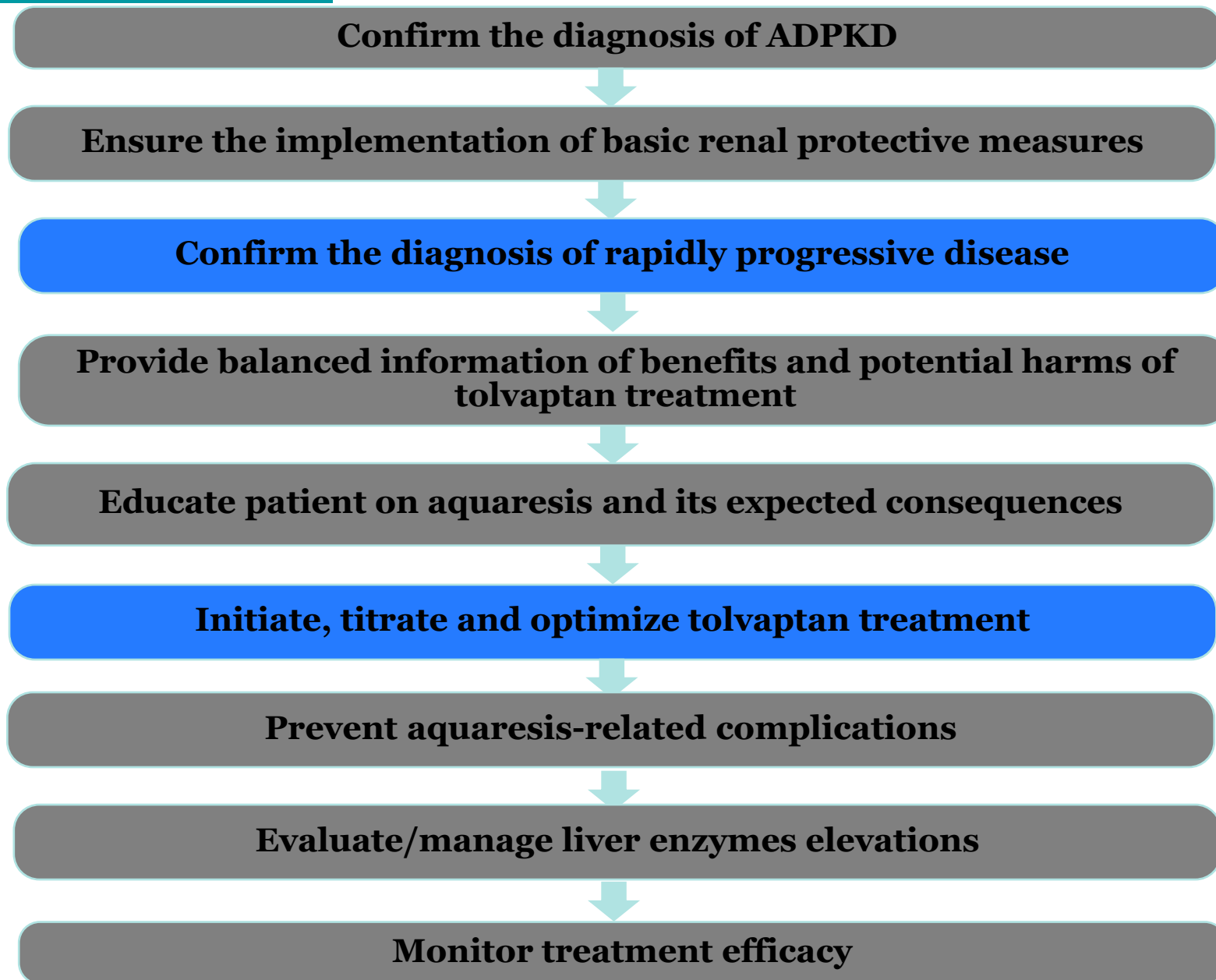
Rapid disease = reaching ESKF by age 60
MIC 1C:

- Some patients might be slow progressors (borderline with 1B)
- PROPKD score (>6)
- Family members reaching ESKD <60
- Reduced age-calibrated eGFR
- GFR rate of decline >3 ml/yr

GFR rate of decline:

- No other explanation such as vascular disease, uncontrolled HTN, DM2, proteinuria $> 1\text{g/d}$, AKI

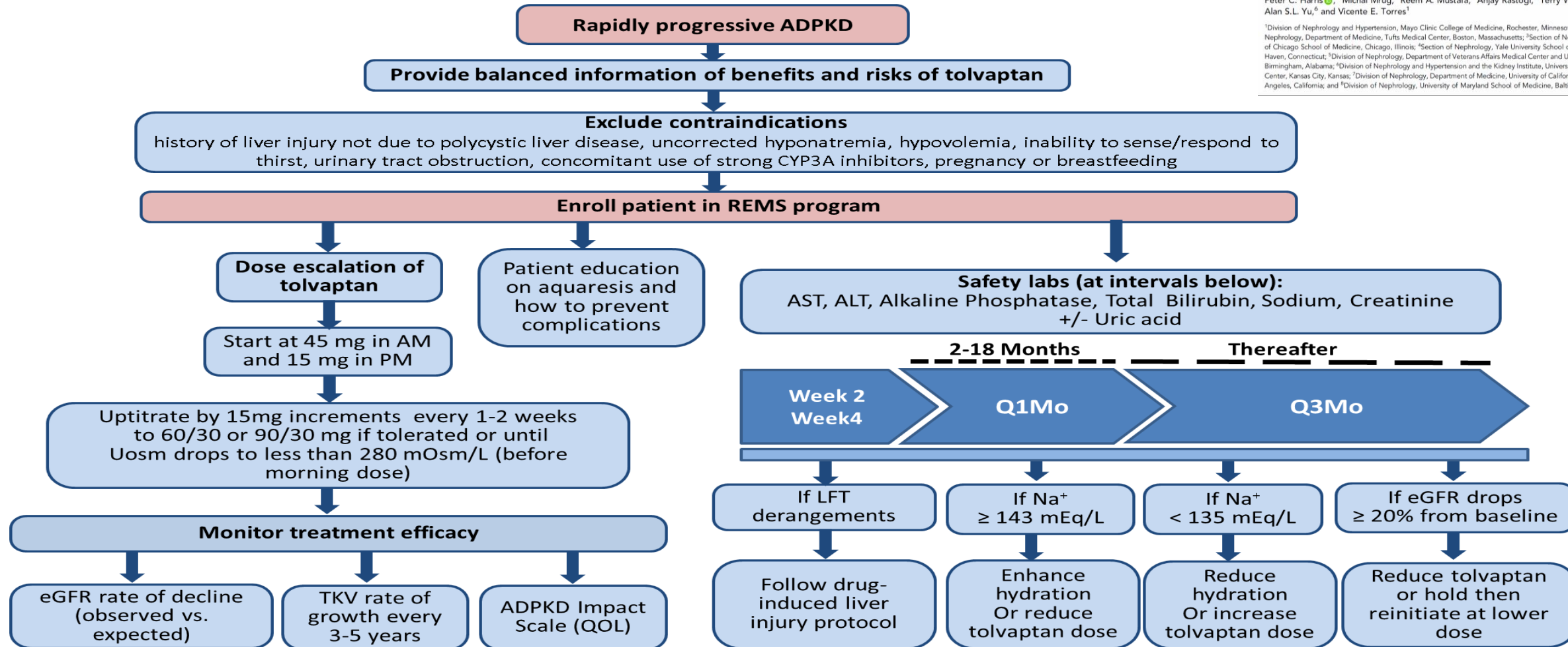




A Practical Guide for Treatment of Rapidly Progressive ADPKD with Tolvaptan

Fouad T. Chebib,¹ Ronald D. Perrone,² Arlene B. Chapman,³ Neera K. Dahl,⁴ Peter C. Harris,⁵ Michal Mrug,⁶ Reem A. Mustafa,⁶ Anjay Rastogi,⁷ Terry Watnick,⁸ Alan S.L. Yu,⁹ and Vicente E. Torres¹

¹Division of Nephrology and Hypertension, Mayo Clinic College of Medicine, Rochester, Minnesota; ²Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, Massachusetts; ³Section of Nephrology, University of Chicago School of Medicine, Chicago, Illinois; ⁴Section of Nephrology, Yale University School of Medicine, New Haven, Connecticut; ⁵Division of Nephrology, Department of Veterans Affairs Medical Center and University of Alabama, Birmingham, Alabama; ⁶Division of Nephrology and Hypertension and the Kidney Institute, University of Kansas Medical Center, Kansas City, Kansas; ⁷Division of Nephrology, Department of Medicine, University of California, Los Angeles, Los Angeles, California; and ⁸Division of Nephrology, University of Maryland School of Medicine, Baltimore, Maryland

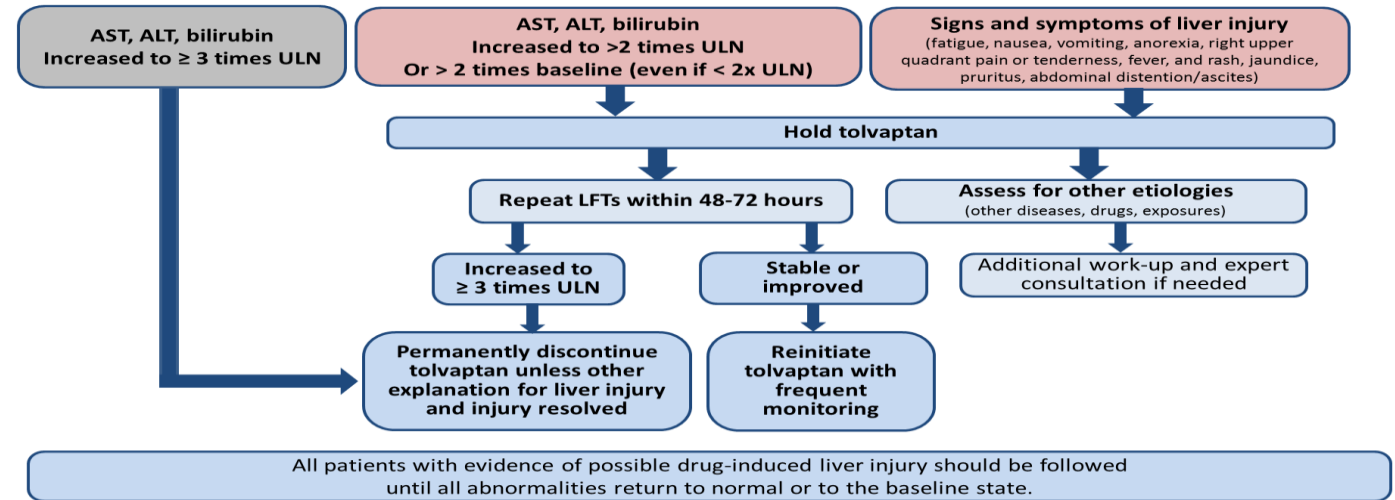
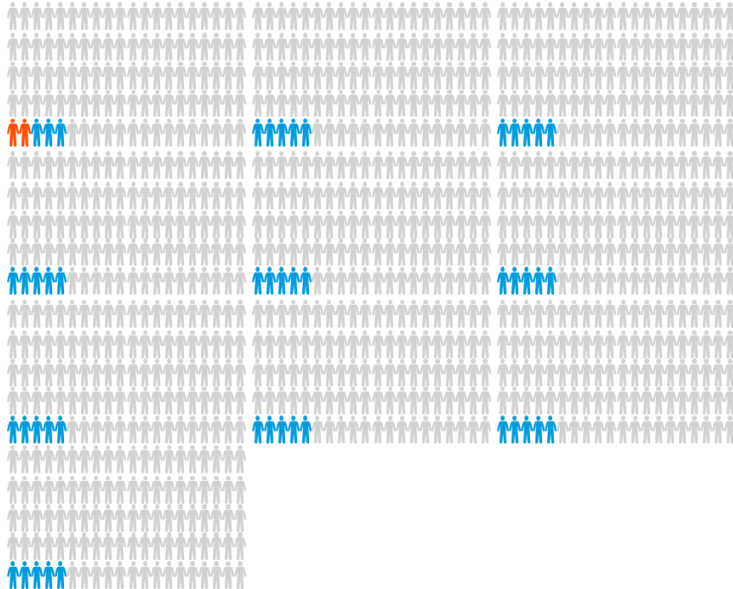


5% risk of increase in LFTs

0.2% risk of severe hepatotoxicity

Risk of hepatotoxicity mitigated by REMS

5% risk of increase in LFTs
0.2% risk of severe hepatotoxicity



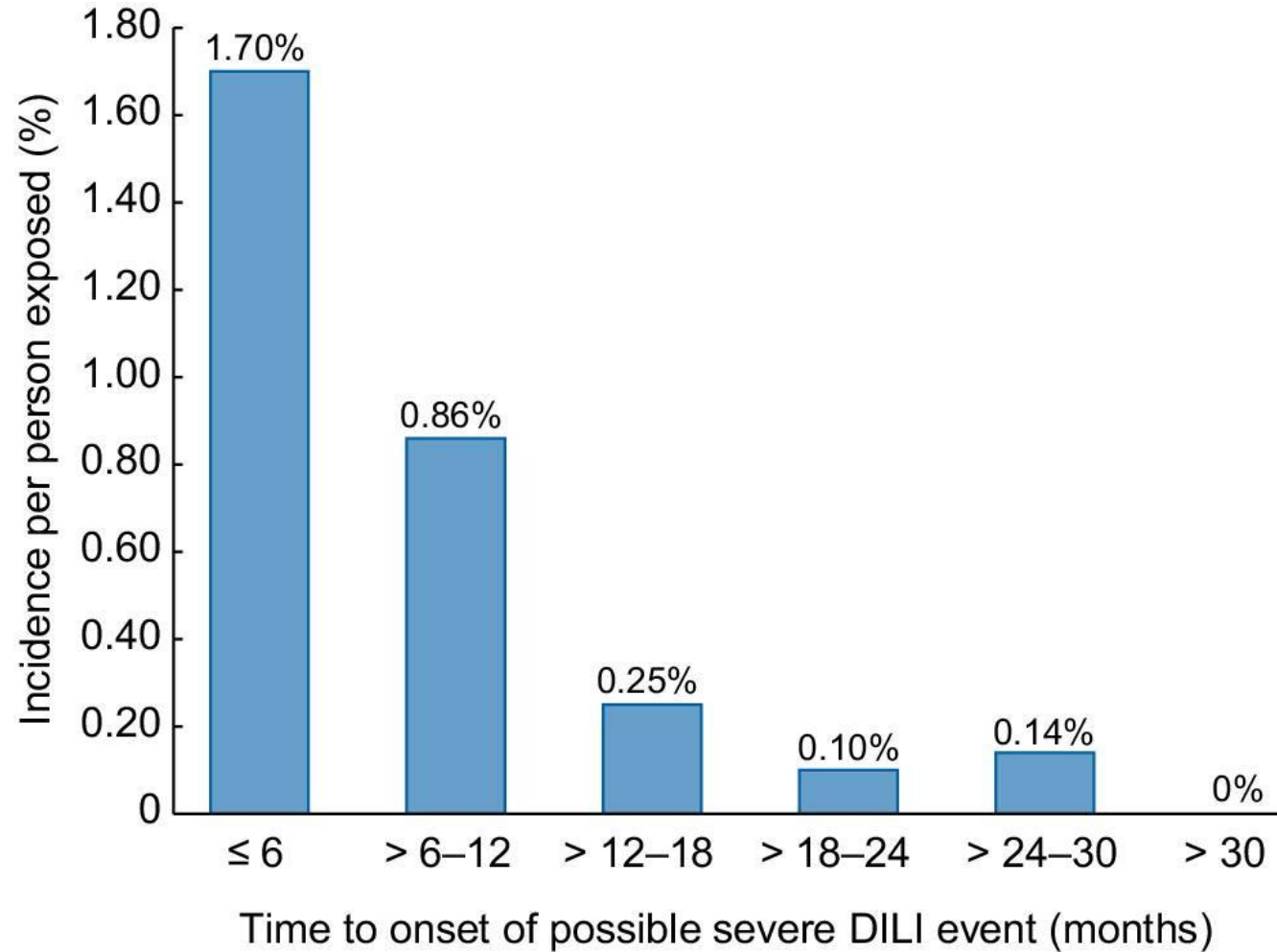
PLD is not a contraindication to start tolcapant

Clinical signature of tolcapant hepatotoxicity:

- Within the first 18 months of treatment
- Transaminases may continue to increase after discontinuation
- Resolve within 1-3 months after discontinuation
- ? Dose dependent
- Likely due to a tolcapant oxybutyric acid metabolite (DM-4103)



REMS 2018-2021



**6711 REMS
patient**



**60 (0.9%) with possible
severe DILI**

**4/60 had serious/potentially
fatal**

1/4 met Hy's law

**4/4 had LFTs normalized
after stopping tolvaptan**

Tolvaptan in patients 56-65 year old

- Practice Point 4.1.1.1:
Shared and individualized decision-making should be undertaken when determining whether to initiate tolvaptan in people aged >55 years with rapid progression.

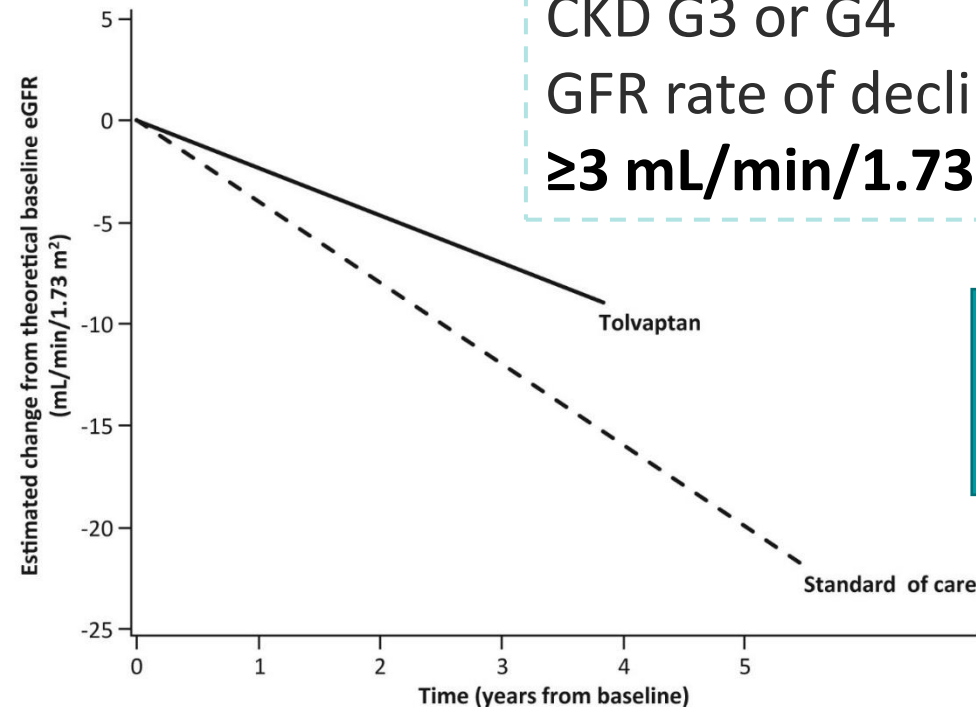
Matched participants age 55+ from 8 clinical trials

Tolvaptan
95 patients
60 years-old

SOC
SOC - Standard of Care
95 patients
60 years-old

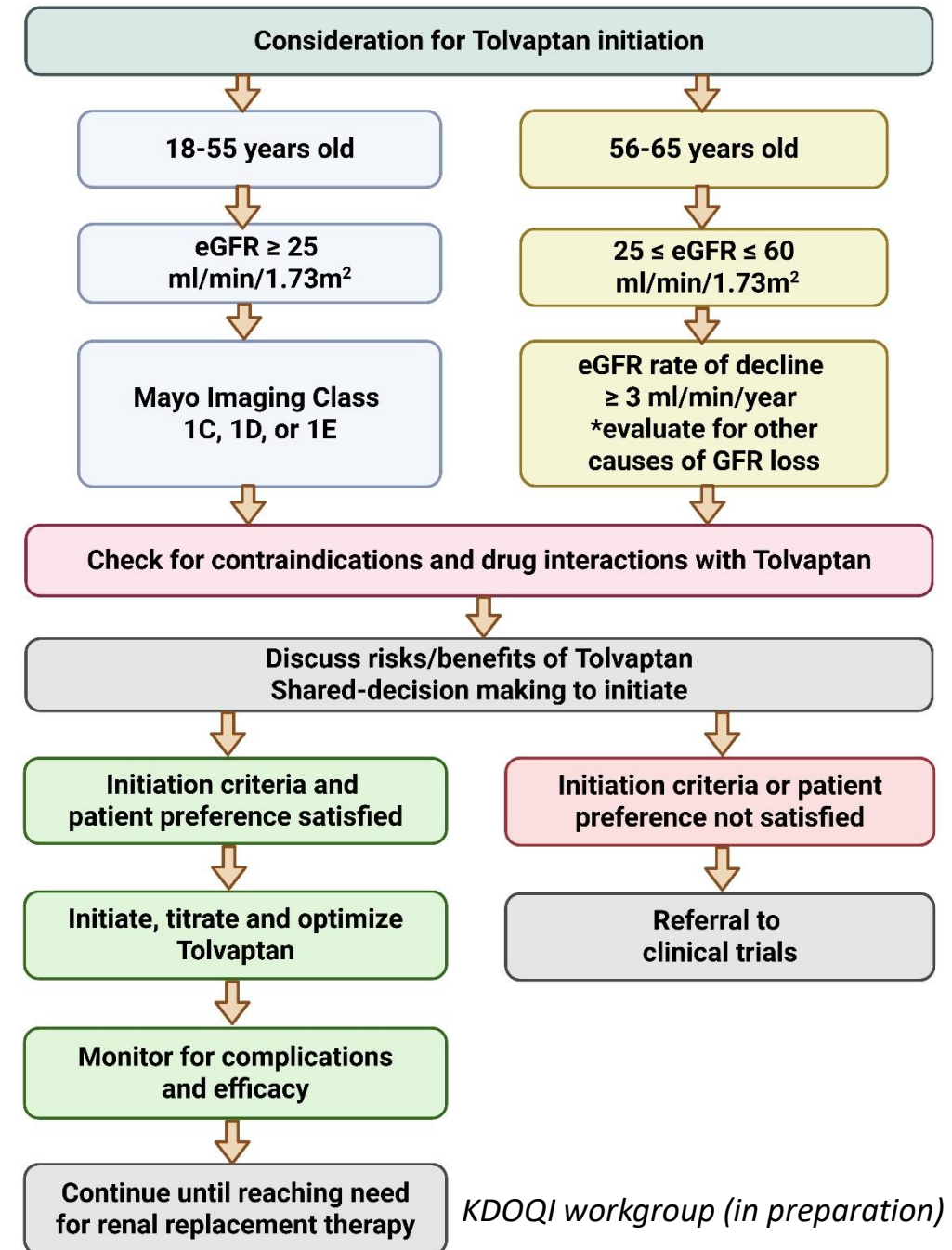
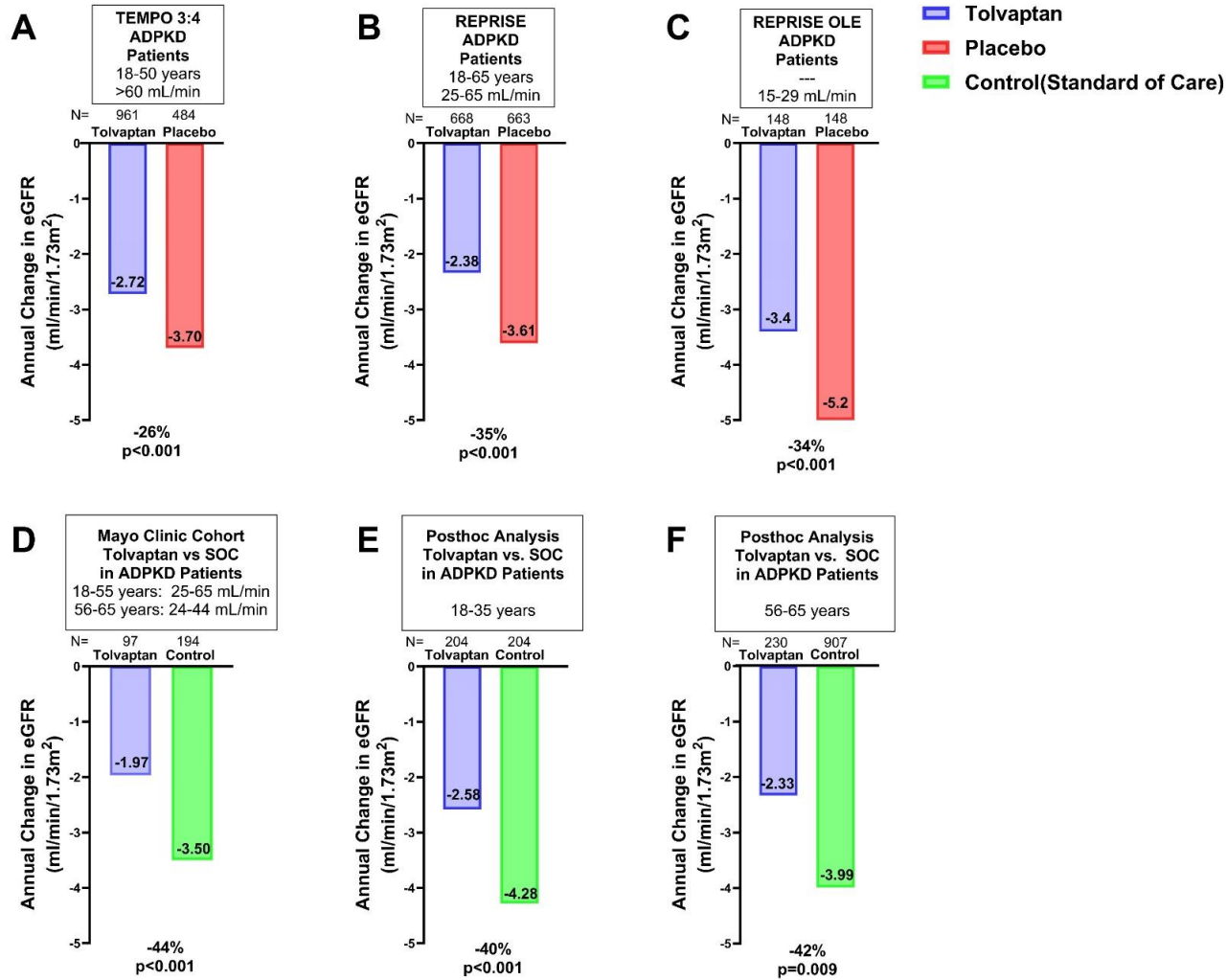
CKD G3 - G4

Outcome/Time	Estimate (95% CI)			P Value
	Tolvaptan (n = 95)	Standard of Care (n = 95)	Difference (Tolvaptan – Standard of Care)	
eGFR				
Year 1	29.66 (28.84, 30.47)	30.23 (29.38, 31.09)	-0.58 (-1.76, 0.61)	0.34
Year 3	25.00 (23.39, 26.62)	22.25 (20.53, 23.97)	2.75 (0.39, 5.11)	0.02
Change from theoretical baseline eGFR				
Year 1	-2.33 (-3.16, -1.49)	-3.99 (-4.90, -3.08)	1.66 (0.43, 2.90)	0.009
Year 3	-6.98 (-9.49, -4.47)	-11.97 (-14.70, -9.25)	4.99 (1.29, 8.70)	0.009
Annual Rate of Change	-2.33 (-3.16, -1.49)	-3.99 (-4.90, -3.08)	1.66 (0.43, 2.90)	0.009



56-65 years
CKD G3 or G4
GFR rate of decline
≥3 mL/min/1.73 m²/year

Difference in annual rate of change:
1.66 ml/min



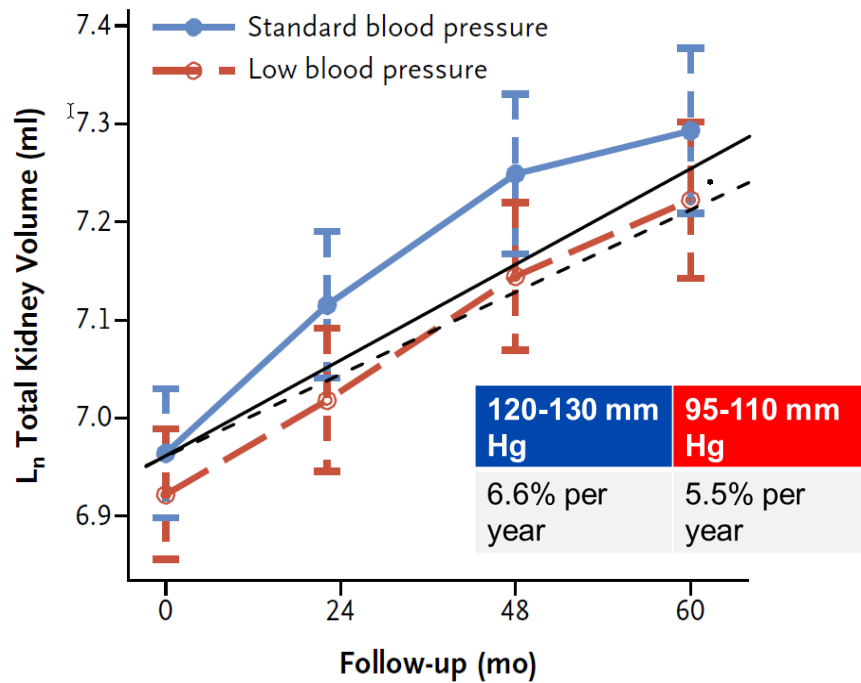
KDOQI workgroup (in preparation)

Blood pressure control in ADPKD

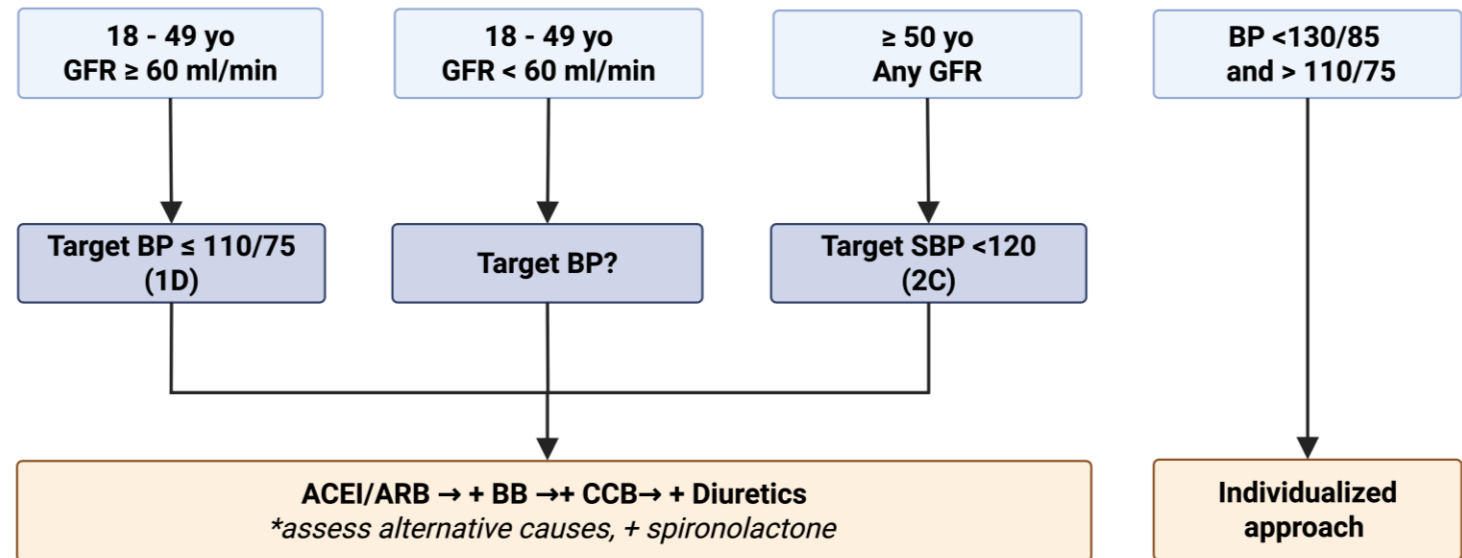
HALT A study (n= 558, CKD 1-2)

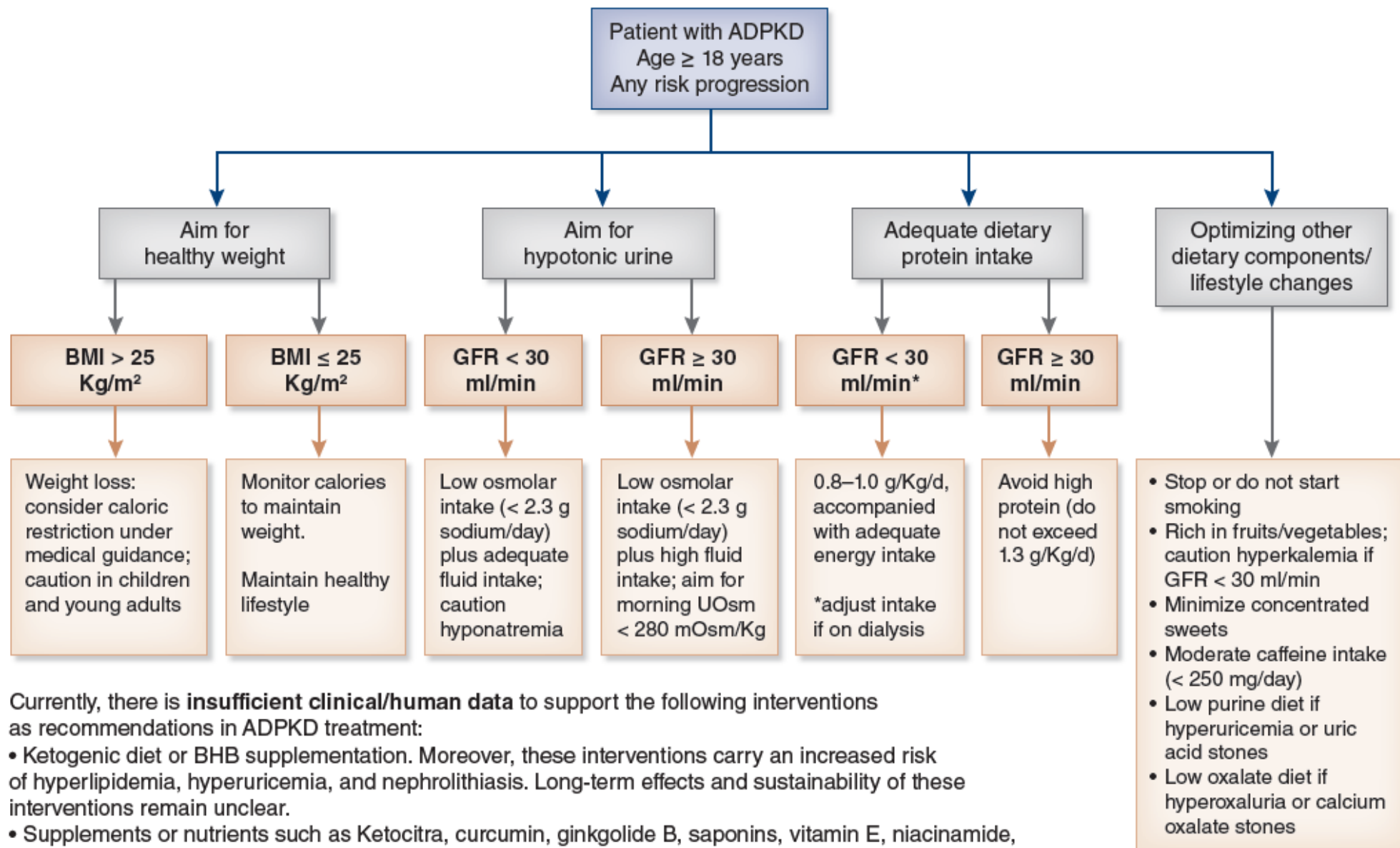
ACE, ACE+ARB

Changes in Total Kidney Volume over Time



Blood Pressure Control





Confirmed autosomal dominant polycystic kidney disease diagnosis by imaging or genotyping

Risk stratification based on abdominal imaging and clinical parameters

Mayo Imaging Classification (MIC) ^a	MIC 1A	MIC 1B	MIC 1C, MIC 1D, or MIC 1E
PROPKD score ^b	Score 0-3	Score 4-6	Score 7-9
Polycystic kidney disease genotype	<i>GANAB/IFT140</i>	<i>PKD2</i>	<i>PKD1</i>
Glomerular filtration rate (GFR) rate of decline	<2 mL/min/ 1.73 m ² per y	2-3 mL/min/ 1.73 m ² per y	>3 mL/min/ 1.73 m ² per y

Slow progressors

Chronic kidney disease (CKD) or no kidney failure

► Reassure patient

Intermediate progressors

Kidney failure after age 65 y

► Confirm rate of progression in 2-3 y

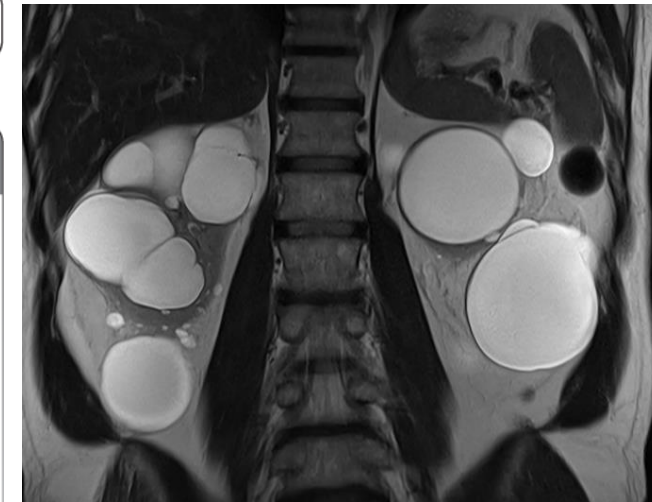
Rapid progressors

Estimated onset of kidney failure before age 65 y

► Discuss candidacy for tolvaptan
► Refer to clinical trial

Basic optimized management for all patients with ADPKD

- Control blood pressure to <120 mm Hg
- Engage in regular physical activity
- Restrict salt intake to <2000 mg/d
- Maintain serum bicarbonate ≥ 22 mEq/L
- Avoid smoking cigarettes
- Increase hydration to >2.5 L/d
- Implement dietary restrictions
- Control cholesterol
- Maintain healthy BMI of 18.5-24.9
- Other CKD care (eg, electrolytes, anemia, and CKD mineral and bone disorder management)



54 yo M
eGFR 72 ml/min
No FHx
TKV 1603 ml
MIC 1C

ADPKD-IFT140

Kidney cyst infection

Patient with suspected kidney cyst infection

- Fever ($>38^{\circ}\text{C}/100.4^{\circ}\text{F}$)
- Acute abdominal pain
- Serum C-reactive protein ≥ 50 mg/l or white blood cell count $>11 \times 10^9/\text{l}$

2 in 2

Other source of infection or inflammation?
(imaging using ultrasound, CT or MRI required)

Yes

No

Kidney cyst infection unlikely

No

Positive for diagnostic features?

Yes

Likely kidney cyst infection

Confirmation of infected cyst required?

No

Yes

No additional imaging

^{18}F FDG PET-CT scan

Diagnostic features

Diagnostic features considered positive in the presence of at least two items from at least 2 categories:

Clinical factors

1. Acute pain or tenderness in kidney area
2. Symptoms of urinary tract infection
3. Recent instrumentation of urinary tract
4. Immune compromised patient (including patients on dialysis)

Microbiology

5. Positive urine and/or blood culture
6. Positive cyst fluid culture

Imaging

7. Imaging (ultrasound, CT, or MRI) before and after onset of symptoms demonstrating a new complex cyst
8. Intracystic gas (ultrasound, CT, or MRI)
9. Pericystic inflammation (CT or MRI)
10. Fluid-fluid levels in a cyst (MRI)
11. Thickened cyst wall (CT or MRI)
12. Contrast enhancement in the lining of cyst walls (CT or MRI)
13. Diffusion weighted imaging showing increased cyst density compared to normal cysts
14. Single-photon emission CT with Ga-67 abnormal uptake by a cyst
15. ^{111}In Indium-white blood cell scan showing accumulation in a cyst

Treatment

16. Clinical response to antibiotic treatment

In people with ADPKD and kidney cyst infection, we suggest treatment with 4–6 weeks of antibiotic therapy rather than a shorter course (2D).

Nephrectomy

Indications	<ul style="list-style-type: none"> • Recurrent and/or severe kidney infection • Symptomatic nephrolithiasis • Recurrent and/or severe kidney cyst bleeding • Intractable pain • Suspicion of kidney cancer • Insufficient space for insertion for a kidney graft • Ventral hernia in the setting of massively enlarged kidneys • Severe symptoms related to massively enlarged kidneys
Surgical Approach	<ul style="list-style-type: none"> • Unilateral nephrectomy is preferred when appropriate 2D • Bilateral Nephrectomy is rare and reserved for select cases • Laparoscopic nephrectomy is preferred over open nephrectomy (less blood loss, quicker recovery, and lower pain burden) 2D • Open nephrectomy may be needed in patients with extremely large kidneys
Potential Complications	<ul style="list-style-type: none"> • Operative Risks (hemorrhage, infections, bowel perforation, rarely death) • Loss of residual kidney function, loss of EPO function • Hemodynamic instability • Fluid retention due to anuria • Sensitization risk from transfusions • Inadvertent adrenalectomy
Evidence	<ul style="list-style-type: none"> • No clear improvement in graft survival or mortality in post-transplant nephrectomy cohorts • Relatively low surgical complication rates, but the benefit is often uncertain • Recommendation is against routine nephrectomy unless specific indications are met


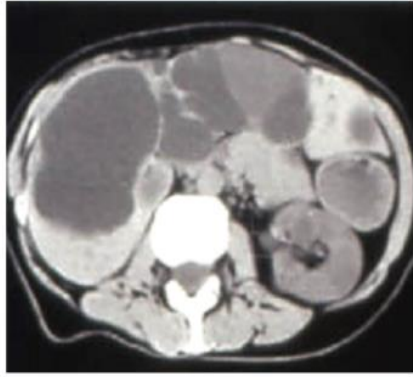
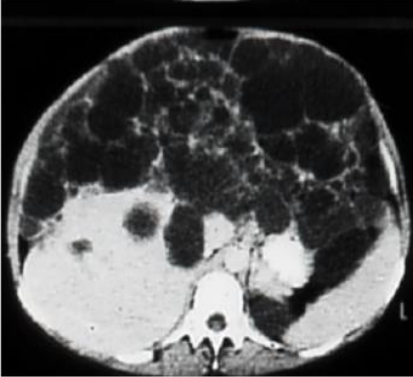
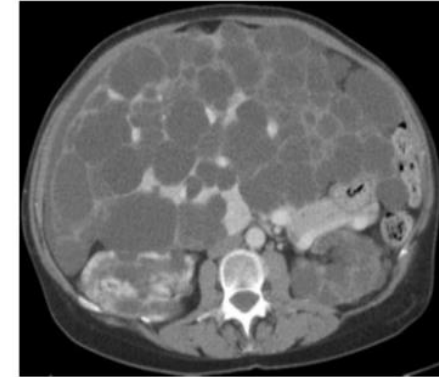
We suggest that native nephrectomy in people with ADPKD receiving a kidney transplant should be performed only for specific indications **when the benefit outweighs the risk** (2C).

We suggest that kidney transplant candidates with ADPKD who require native nephrectomy undergo the procedure **at the time of or after, but not before,** transplantation, whenever possible (2C).

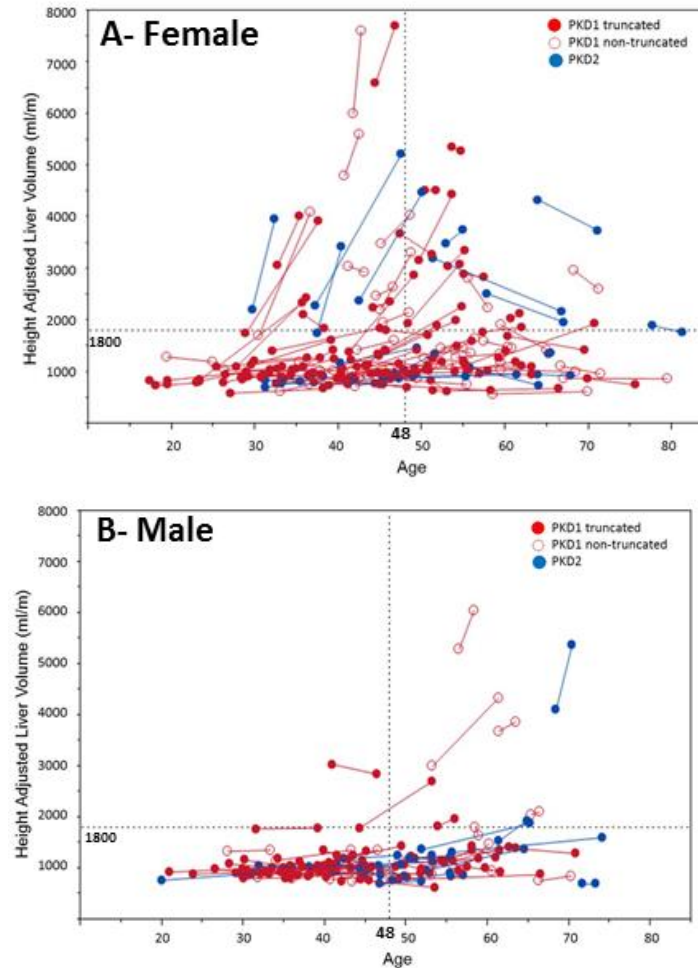
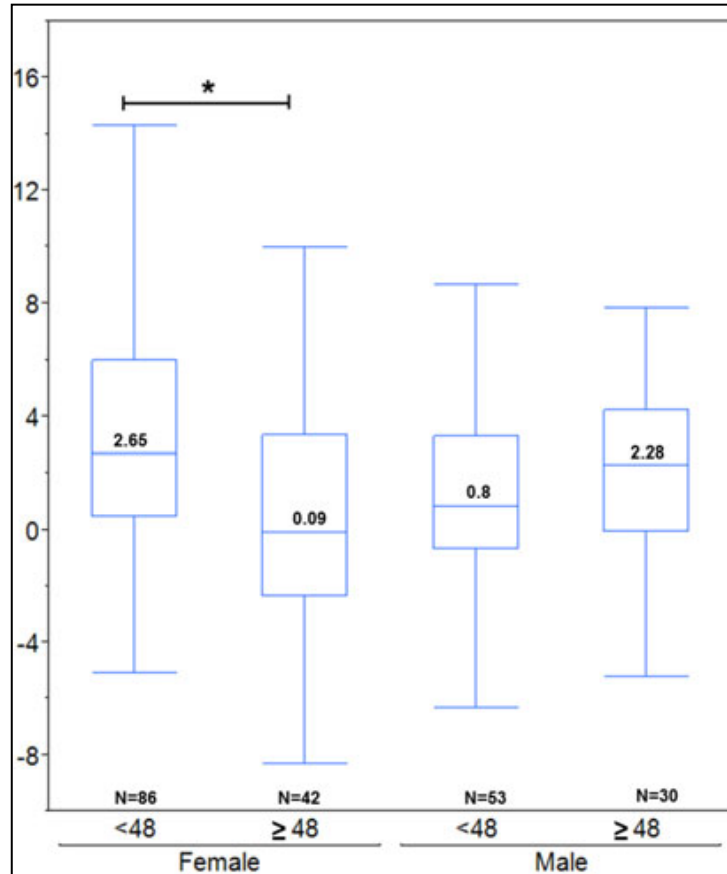


Severe PLD can lead to poor quality of life



Type A	Type B	Type C	Type D
			
Type A	Type B	Type C	Type D
Absent/mild Sx	Mod/severe Sx	Severe Sx	Severe Sx
Focal cysts	Focal cysts	Diffuse cysts	Diffuse cysts
≥ 3 normal segments	≥ 2	≥ 1	< 1
No portal vein/hepatic V. occlusion	No	No	Yes

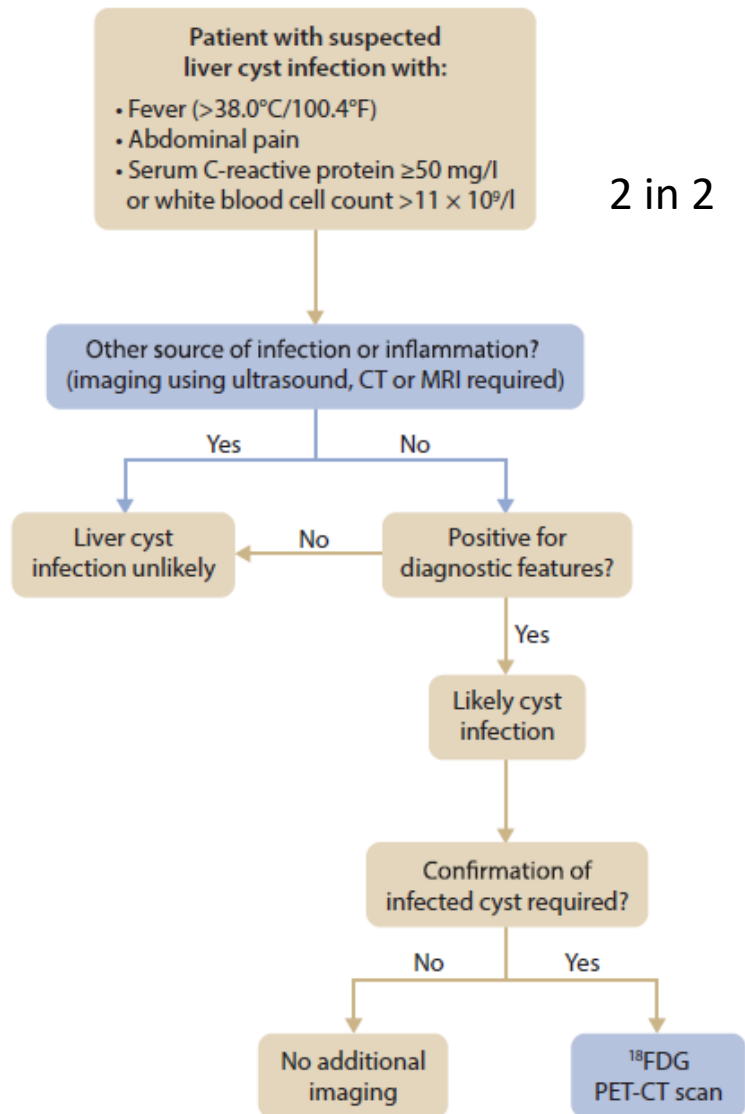
Liver Cyst Growth, Age and Estrogen



- Being female, multiple pregnancies, and exogenous estrogen exposure increase risk
- Cyst burden usually higher in women than men
- >80% of liver transplants are done in women

KDIGO suggests **an individualized discussion of estrogen-containing birth control or post-menopausal estrogen supplementation** for women depending on their risk of PLD or hepatomegaly, and counsel limiting use for patients with hepatomegaly or high cyst burden.

Liver Cyst Infections



Diagnostic features

Diagnostic features considered positive in the presence of at least two items from at least 2 categories:

Clinical factors

1. Pain presenting as acute pain or tenderness in liver area
2. History of cyst infection
3. Recent instrumentation of biliary tract
4. Immune compromised patient (including patients on dialysis)

Microbiology

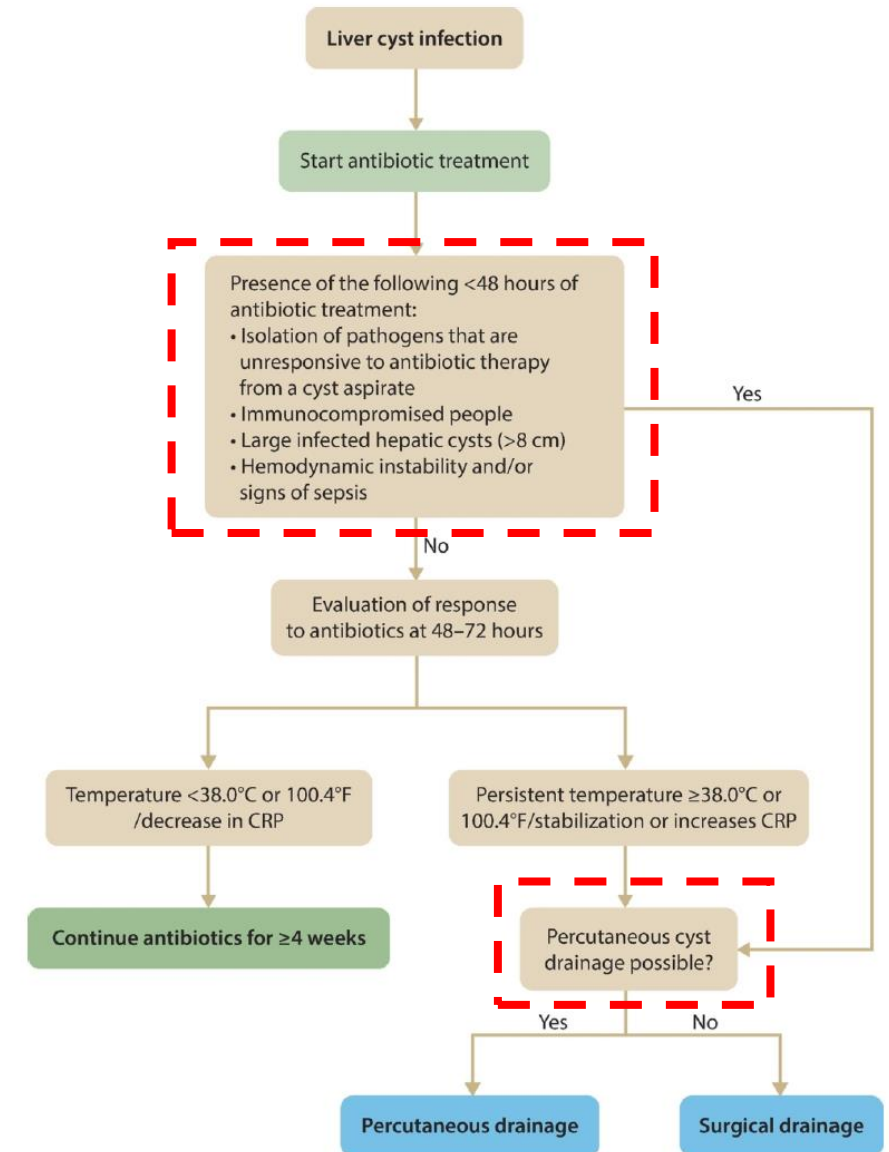
5. Positive blood culture
6. Positive cyst fluid culture

Imaging

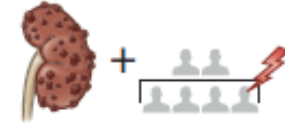
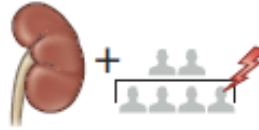
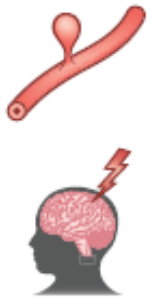
7. Imaging showing changes before and after onset of symptoms (ultrasound, CT or MRI)
8. Intracystic gas (ultrasound, CT or MRI)
9. Pericystic inflammation (CT or MRI)
10. Fluid-fluid levels in a cyst (MRI)
11. Thickened cyst wall (CT or MRI)
12. Contrast enhancement in the lining of cyst walls (CT or MRI)
13. Diffusion weighted imaging showing increased cyst density compared to normal cysts
14. Single-photon emission CT with Ga-67 abnormal uptake by a cyst
15. ^{111}In -white blood cell scan showing accumulation in a cyst

Treatment

16. Clinical response to antibiotic treatment



CNS findings and Intracranial aneurysms in ADPKD



	General population	General population with family history of ICA or SAH	ADPKD population	ADPKD population with family history of ICA or SAH
Prevalence of ICA (95% CI)	2.9% (1.9–4.5)	3.4 (1.9–5.9) higher risk ^a	12.9% (10.4–15.4) (Figure 36)	17.1% (13.4–21.1) ^b
Incidence rates of SAH (per 1000 person-years, 95% CI)	0.079 (0.069–0.09) ^c	3–7 higher risk	0.57 (0.19–1.14) (Figure 37)	Likely higher (based on data from general population)

Thunderclap headache

Definition:

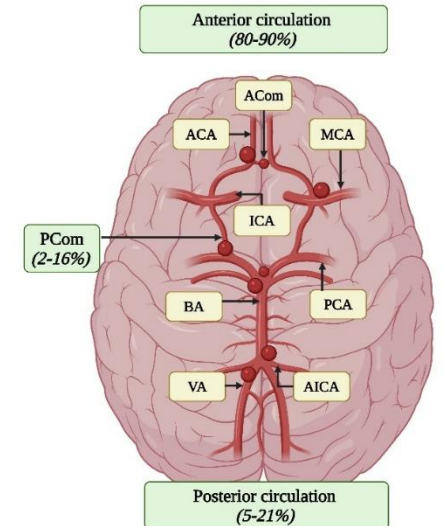
- Strikes suddenly
- Intense pain: “worst headache in my life”
- Reaches maximal intensity within 60 seconds

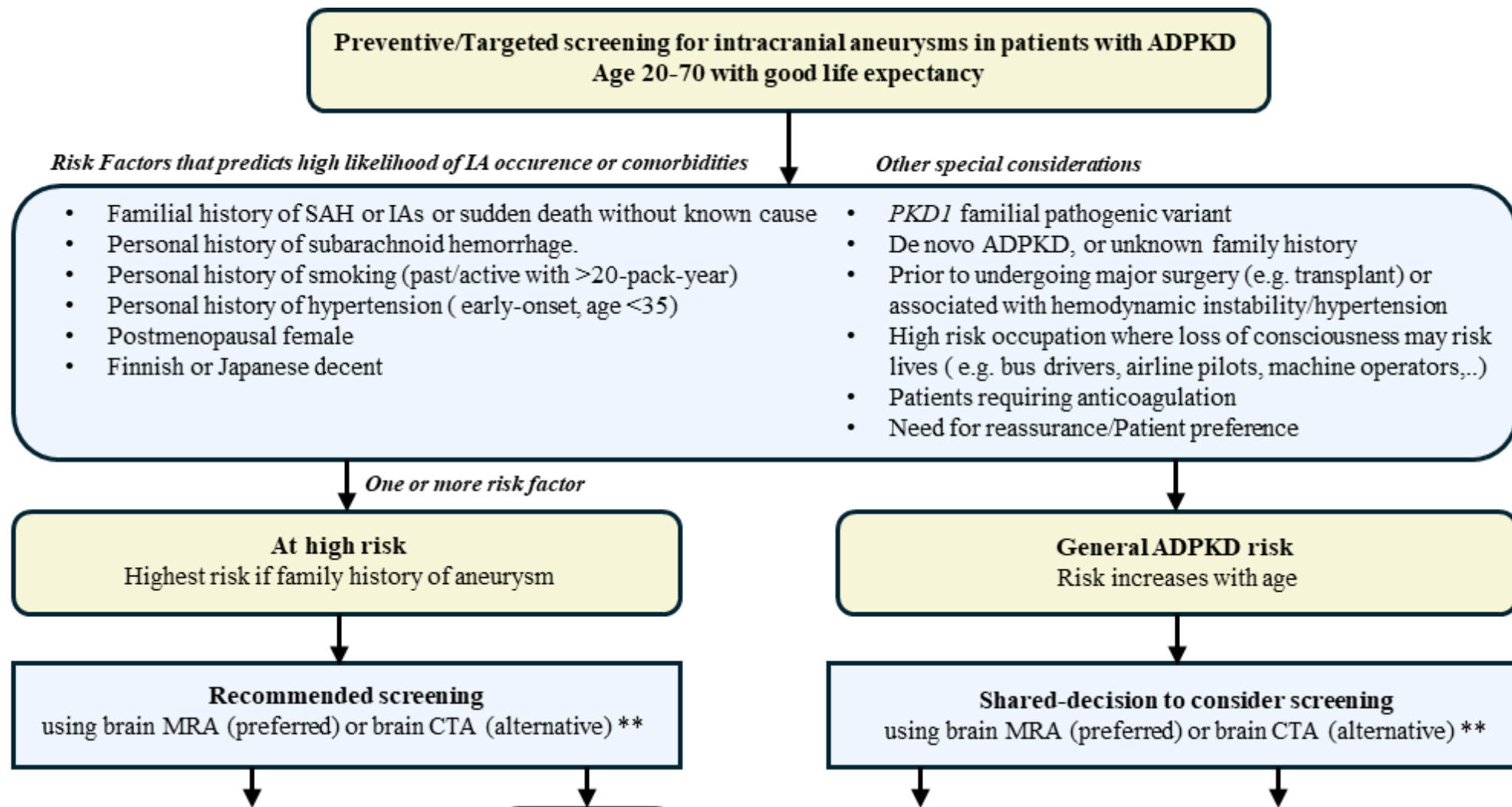
May be associated with or followed by:

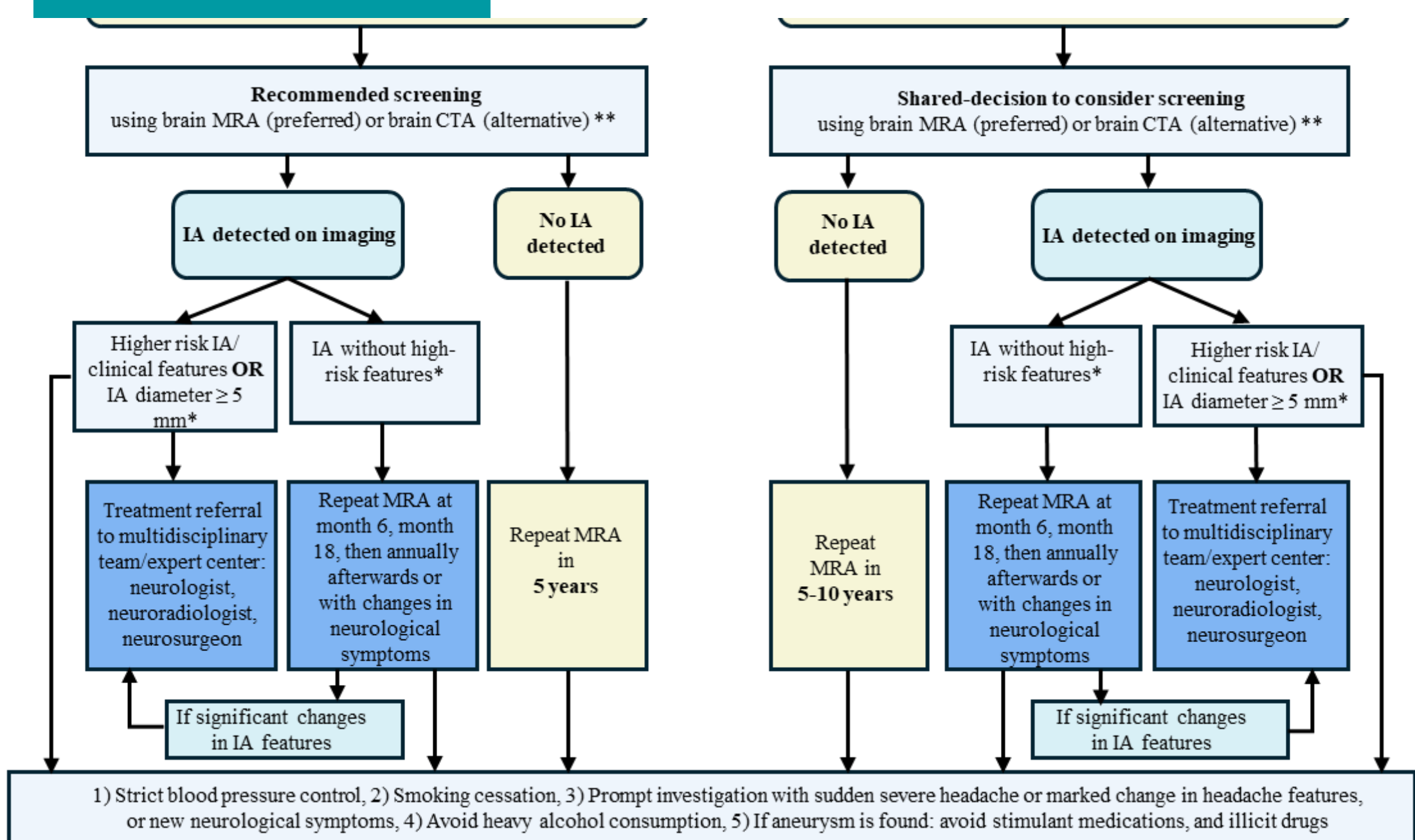
- Nausea or vomiting
- Seizures
- Altered mental state/loss of consciousness

What to do:

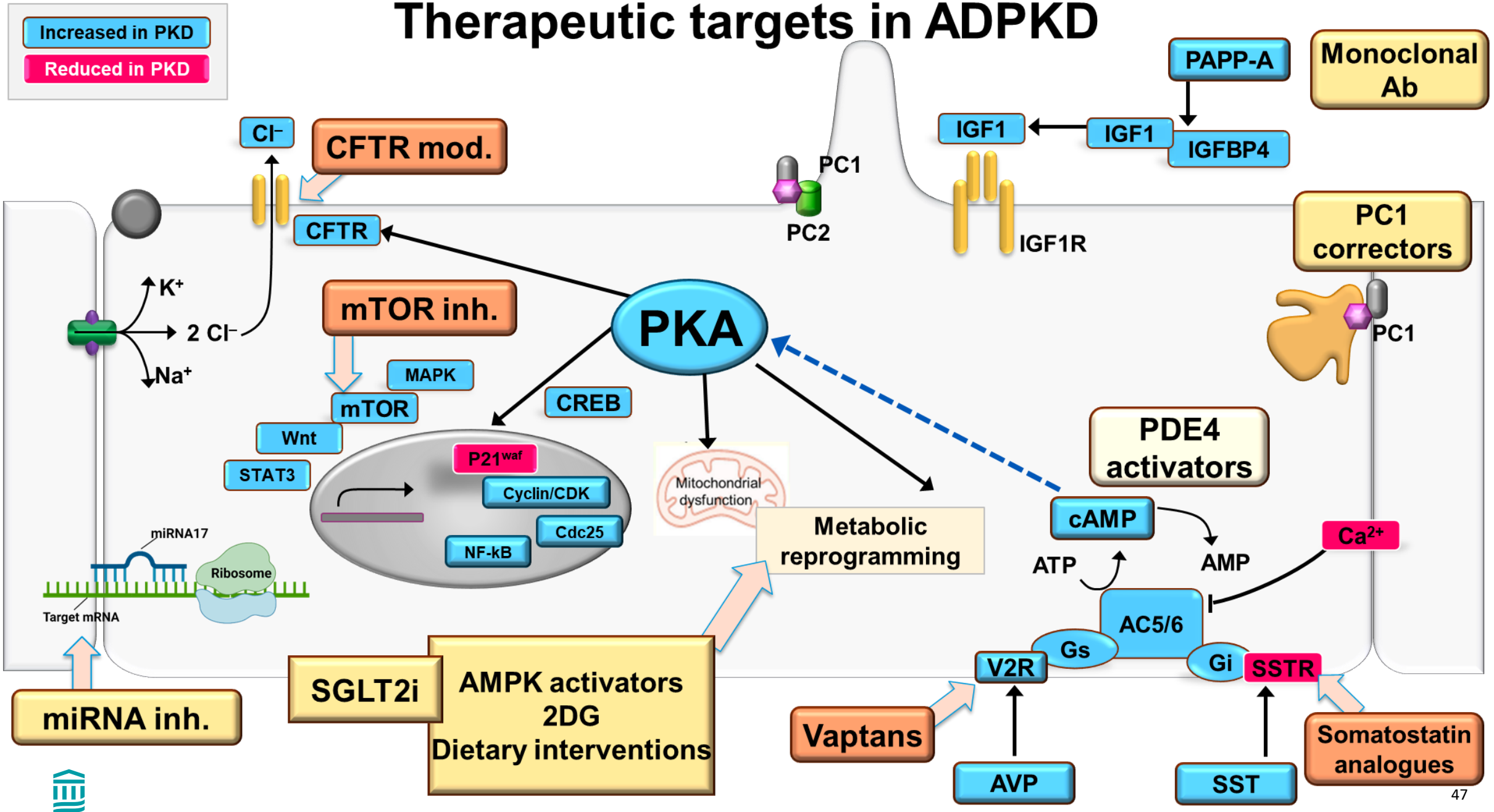
- Seek immediate medical attention
- Have evaluation in an emergency department equipped with CT scan
- Inform caregivers about the increased risk for subarachnoid hemorrhage associated with ADPKD



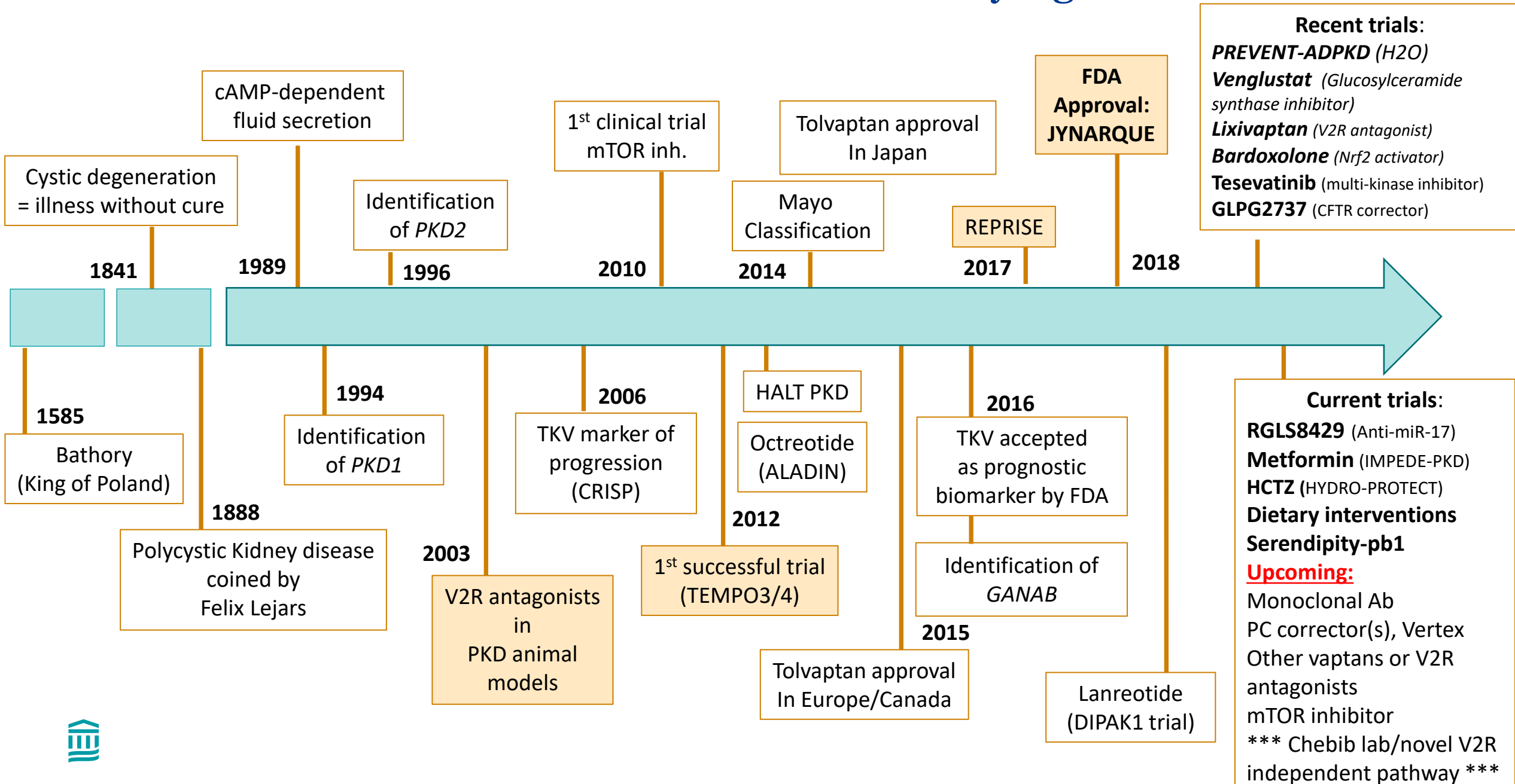




Therapeutic targets in ADPKD



Milestones in ADPKD: Disease-modifying treatment




TAKE HOME MESSAGES

- ADPKD is a heterogeneous disease
- ADPKD has a high phenotypic variability
- Indications for genetic testing might not be as controversial in the future
- Predicting risk of rapid progression is feasible through imaging (TKV or MIC) or clinical and genetic tools (PROPKD score)
- Tolvaptan is approved to slow disease progression, with aquaresis and DILI as two major considerations
- Multiple novel therapies are being considered in clinical trials (Anti-miR17, PAPPa mAb, PC1 corrector)
- Avoid Estrogen-based therapies if severe polycystic liver disease
- Review intracranial aneurysm screening strategy with all your patients



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Visit Mayo Clinic
PKD Resource
Center

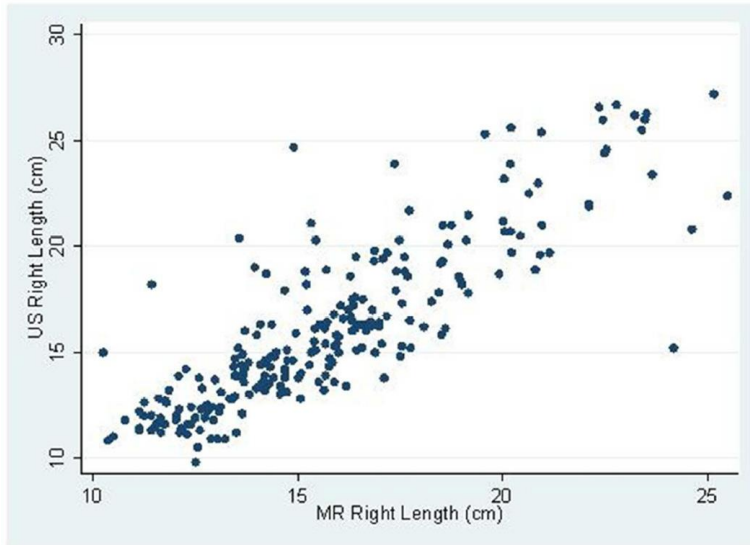


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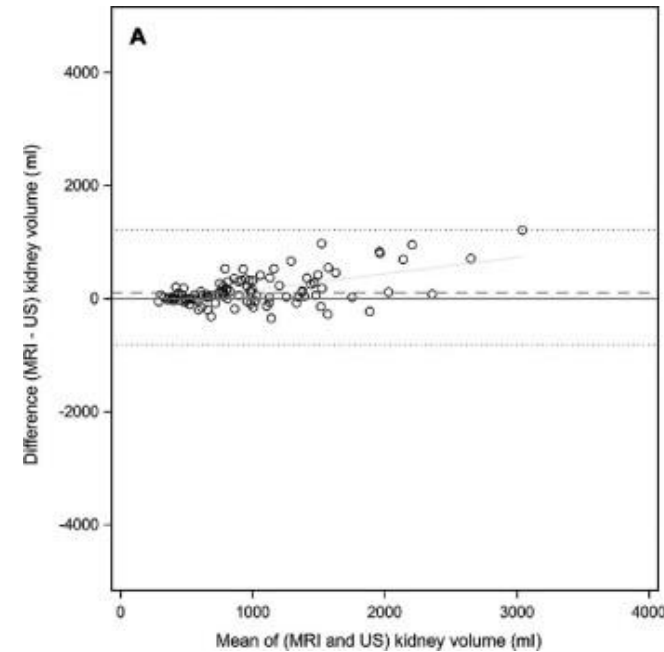
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Kidney length 16.5 cm predicts CKD3 in 8 years

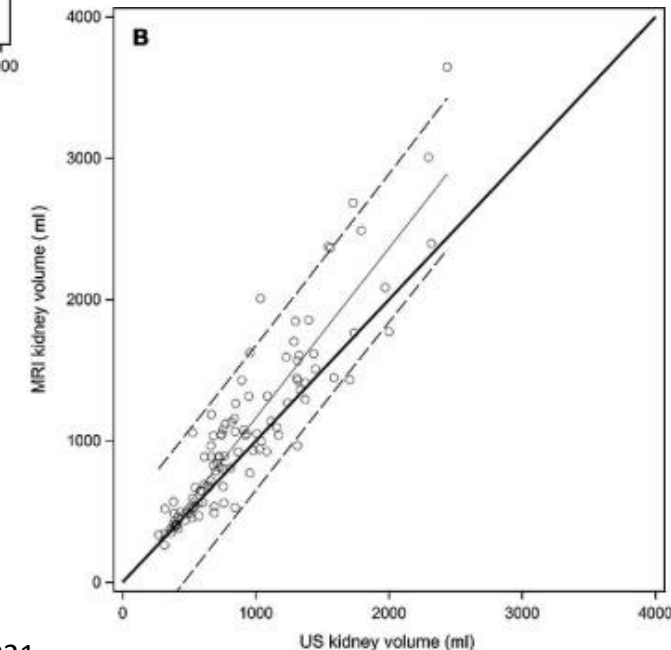


TKV by Kidney US



Predicting CKD within 8 years in CRISP

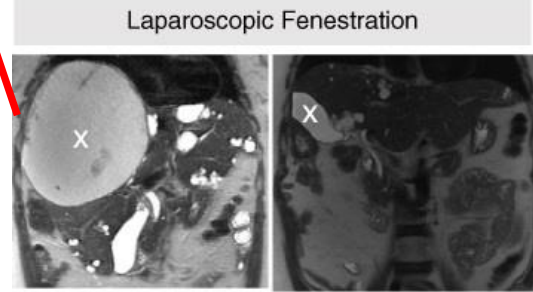
Method	AUC ROC	sensitivity	specificity	Optimal cut point
htTKV (MR) ml/m (ref 7)	0.84	74.0%	75.0%	600 ml
htTKV (US) ml/m	0.87	79.5%	73.2%	630 ml
KL (MR) cm	0.87	85.4%	92.3%	16.7 cm
KL (US) cm	0.86	82.9%	80.8%	16.8 cm



Cyst Burden Determines Treatment

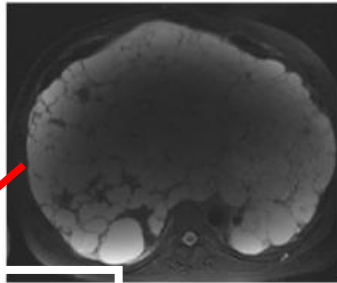
Recurrence 34%

Severe Complications 7.2%,
Mortality 2.3%

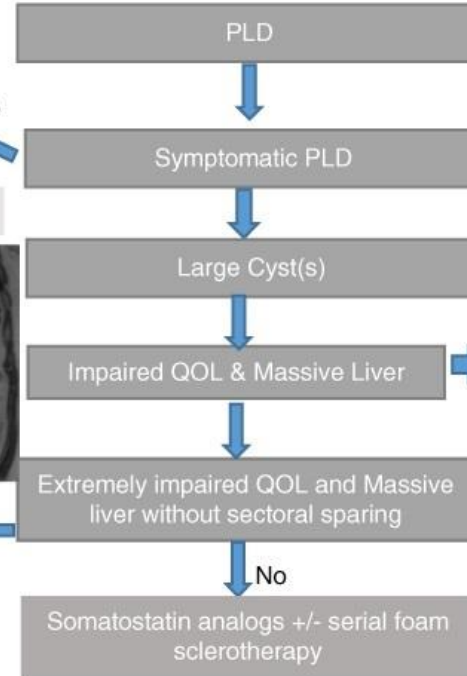


Laparoscopic Fenestration

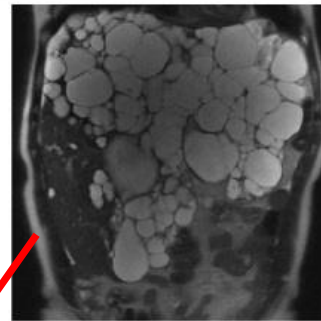
Liver transplant



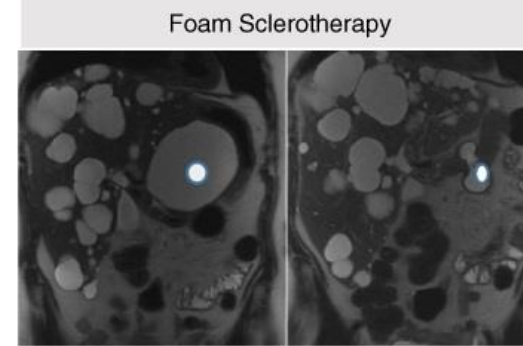
Severe complications
46%,
Mortality 9%



Reduction in annual liver growth
rate of 6%-15%
after 1-3 yr of follow-up

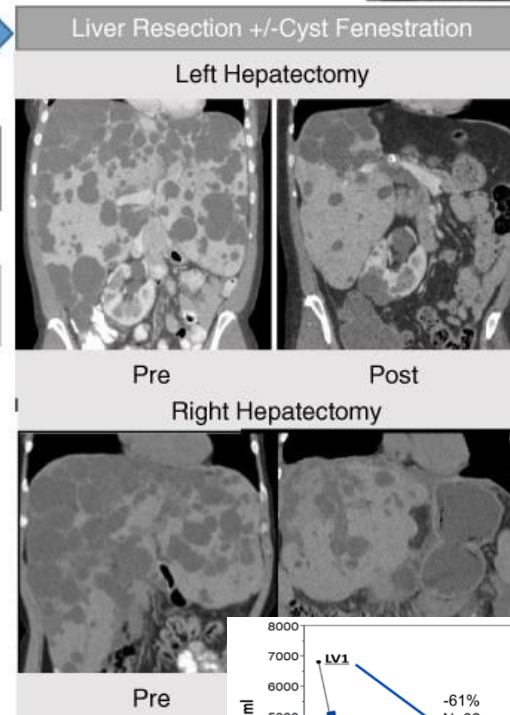


Foam Sclerotherapy
Or Laparoscopic
Fenestration

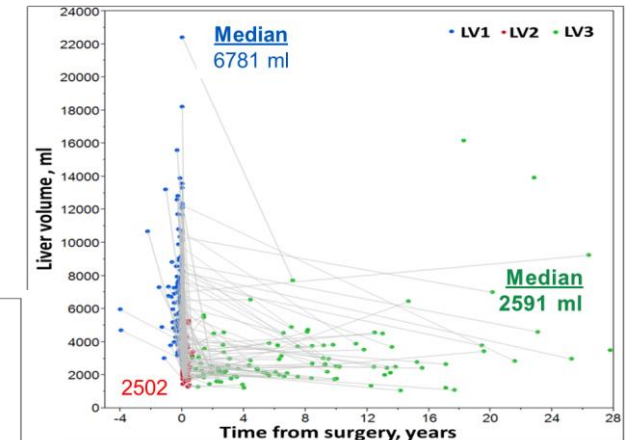
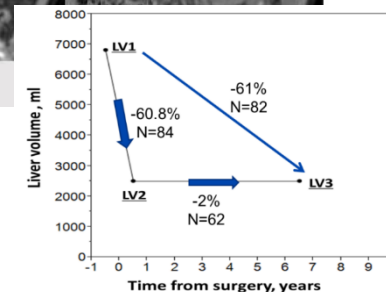


Foam Sclerotherapy

Improvement
72-100%, Minor
complications 5%-
90%,
mortality <1.0%



Reduction in TLV 61%,
perioperative
complications 21%,
mortality 2.7%

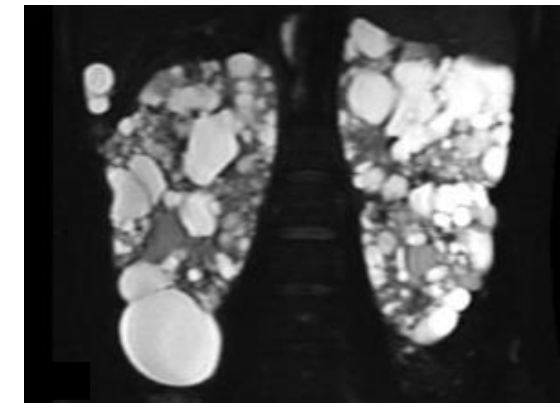
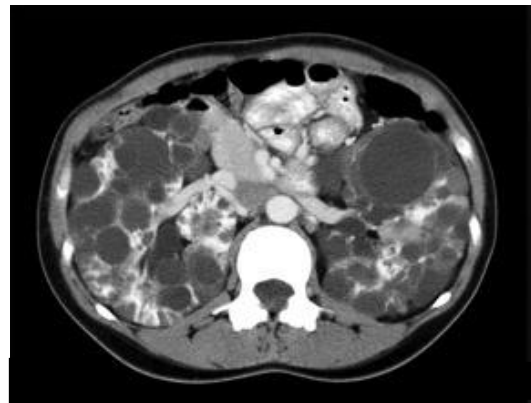
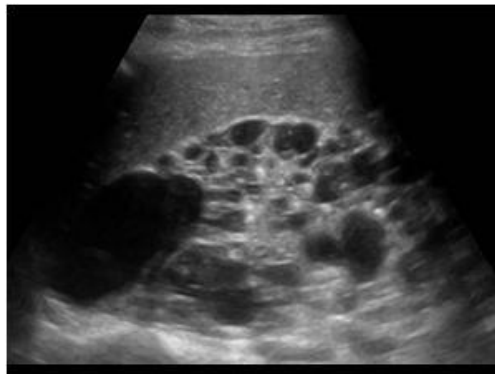


Chebib et al. (2016) J Am Coll Surg.



Imaging modalities in ADPKD

Ultrasound	CT scan	MRI
Cyst size detection 7-10 mm	Cyst size detection 2 mm	Cyst size detection 2 mm
Cost-effective	Radiation/ needs contrast	No radiation/ No contrast
Screening	Prognostication Follow up	Prognostication Follow up

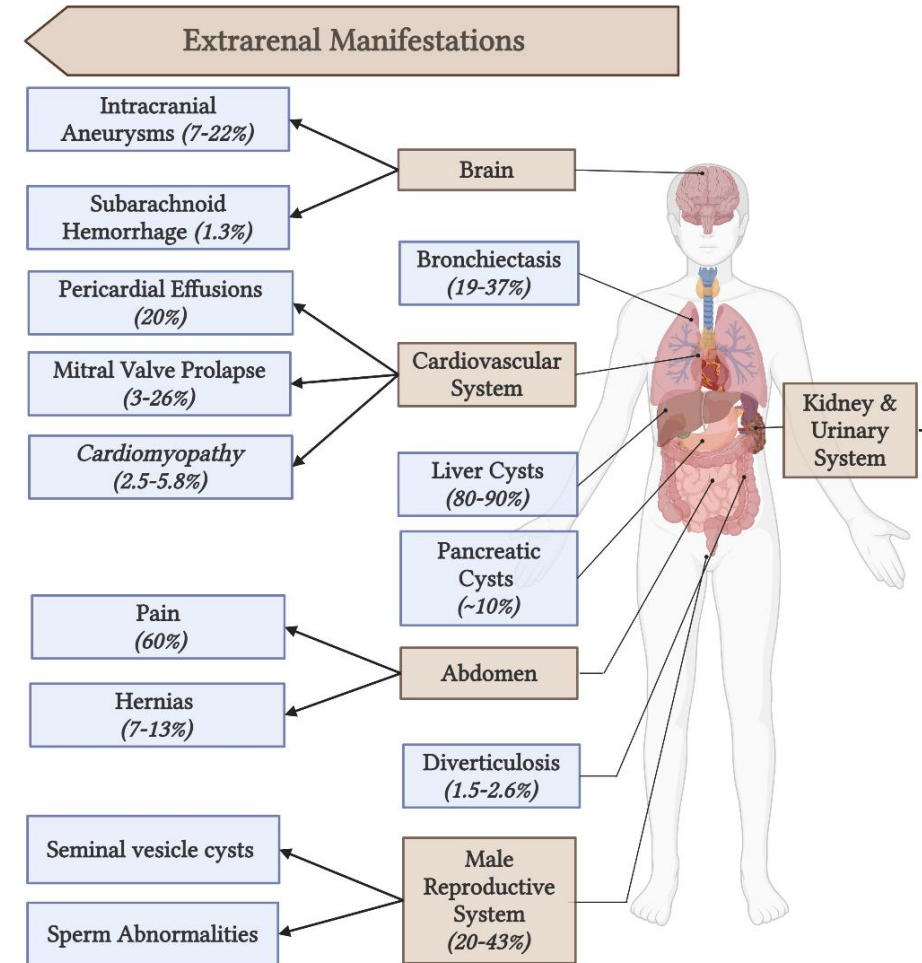


Beyond the kidneys: ADPKD as a systemic disease

Estimation of the % affected

Hepatic and gastrointestinal manifestations

Symptomatic polycystic liver disease	<5% (> in females)	Liver cysts are present in >80% by age 30yr
Congenital hepatic fibrosis	Very rare case reports	More common in ARPKD
Pancreatic cysts and IPMN	Pancreatic cyst ~10%	Any complex pancreatic cyst or in case of multiple cysts should be followed and evaluated to exclude malignancy
Splenic cysts	~7%	Like general population. Usually asymptomatic, incidental diagnosis
Abdominal wall hernia	Common	Very common clinical findings
Dilated extrahepatic bile duct	~40%	Small-cohort single study
Colonic diverticulosis	1.5% (vs. 0.8% gen. pop) adjusted OR: 1.88 2.6% kidney transplant and ADPKD (vs. 0.8% without)	Single, large national database
Duodenal or small-bowel diverticula	Rare case reports	Rare, associated with obstructive jaundice or ascending cholangitis. Small-bowel diverticula may be associated with bacterial growth



Factors associated with increased risk of aneurysm

Risk Factor	Fold increased Risk
Female Sex	1.47
Age (40 vs 70 yrs)	1.3% vs 8.1%
Family History of ICA/SAH	<u>4 folds</u>
Higher TKV or Mayo Imaging Class	2.81 for TKV \geq 1000 ml 2.52 for MIC 1C,1D,1E
Advanced CKD (stages G3-G5)	2.31

Predictors for prevalent ICA or rupture of ICA and strength of the association

- Family history of SAH or ICA (stronger when first-degree relative)—*Strong*
- Personal history of SAH or ICA—*Strong*
- Tobacco smoking (especially >20 pack-years)—*Strong*
- Female sex—*Moderate*
- PKD1 genotype—*Moderate*
- Uncontrolled hypertension—*Moderate*
- Early-onset hypertension (age <35 yr)—*Moderate*
- Severity of ADPKD—*Weak*

In general population:
Japanese or Finnish ancestry
Alcohol in large quantity (risk for ICA rupture)