Modern Assessment and Management of Autosomal Dominant Polycystic Kidney Disease

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Outline

- Epidemiology of PKD
- Approach and differential diagnosis of bilateral renal cystic diseases
- Natural History of PKD
- Determining renal prognosis
- Delaying renal progression of renal progression
- Extra-renal manifestations of PKD

Disclosures

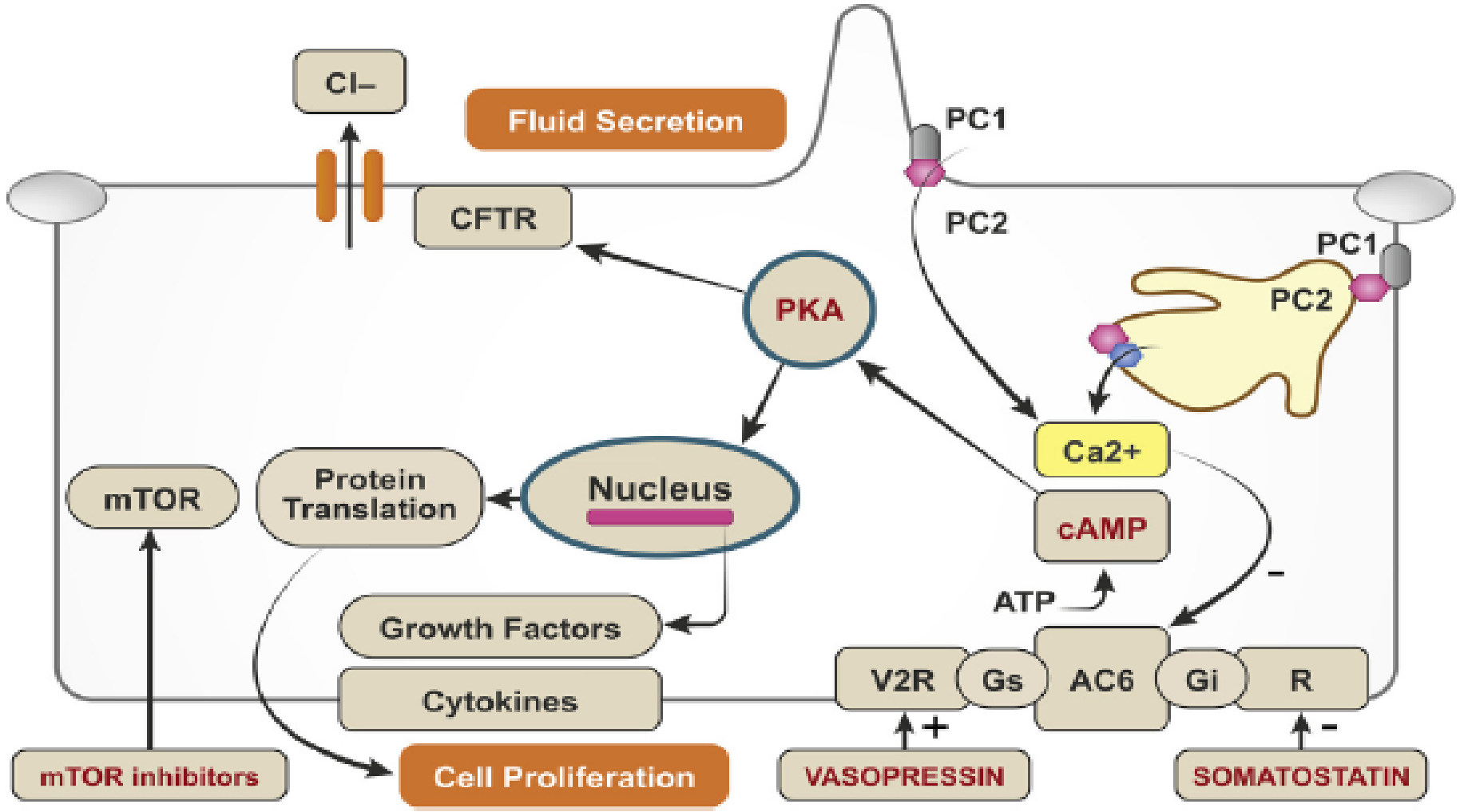
- Relevant to this topic, I disclose the following from Otsuka Canada Pharmaceuticals Inc:
  - An unrestricted grant to the BC Renal Agency to assist in creation of the BC PKD registry
  - Honoraria for scientific advisory work related to PKD imaging and treatment

Epidemiology and Natural History of PKD

Epidemiology

- Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder, affecting between 1-2.5/1000 live births
  - Although exact provincial numbers are lacking, this estimate would mean there are somewhere from 4600 to over 10000 British Columbians living with the disease.
- There is no racial predilection; it affects all groups equally
- Of patients with an identifiable etiology of ESRD, ADPKD is the 4th leading cause of ESRD in Canada

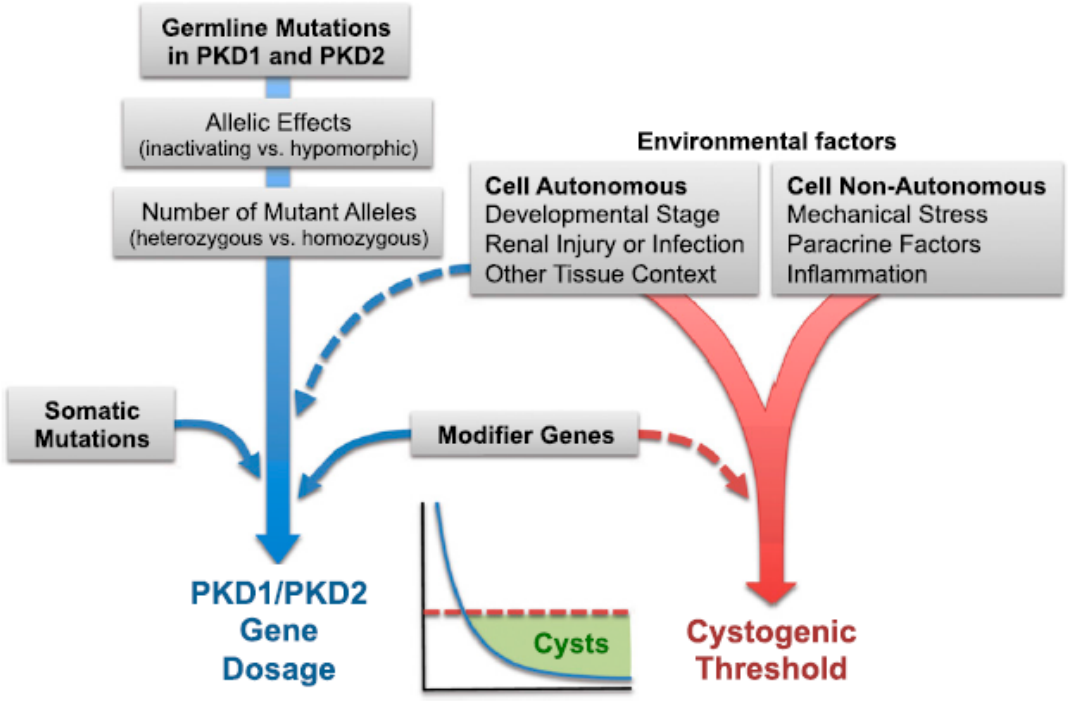
ADPKD pathophysiology



ADPKD pathophysiology

- Polycystin 1 and 2 localize to primary cilia. These are involved in tubulogenesis, maintenance of tubular structure and sensing of urinary flow to maintain normal orientation
- Abnormalities in these genes and the resultant loss of polarity can result in cyst formation
- What is clear in PKD is that intracellular cAMP levels are increased, and of its many effects, two that are relevant to the disease process occur:
  - Increase cell proliferation, including through the mTOR pathway
  - Activation of the CFTR chloride channel leading to calcium secretion at the apical membrane

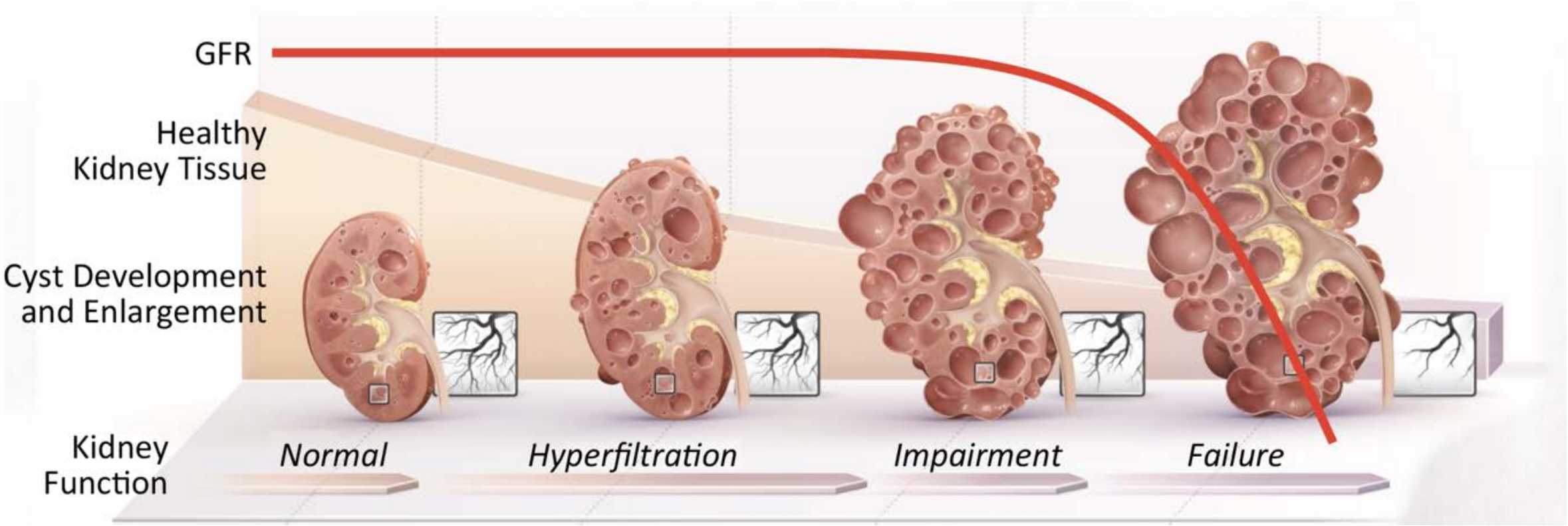
2nd (or 3rd, or 4th) hits



- Only a small minority of nephrons develop cysts
- There is much more than the PKD1/2 complex at play in the phenotypic presentation of ADPKD
- These other facilitating or attenuating factors account for much of the variability seen in ADPKD

J Am Soc Nephrol **26:** 2081–2095, 2015

Current understanding of progression of PKD



The disease course is a variable one, with the early portion of the disease marked by cyst proliferation and expansion with little renal dysfunction followed by a precipitous decline. The corollary here is that by the time there is a change in GFR, significant cyst expansion and proliferation has already occurred

Diagnosis of PKD

Table 2. Ultrasound Criteria for Diagnosis of ADPKD

Age, y	PKD1	PKD2	Unknown ADPKD Gene Type
15-30	≥3 cysts*		
	PPV, 100%	PPV, 100%	PPV, 100%
	SEN, 94.3%	SEN, 69.5%	SEN, 81.7%
30-39	≥3 cysts*		
	PPV, 100%	PPV, 100%	PPV, 100%
	SEN, 96.6%	SEN, 94.9%	SEN, 95.5%
40-59	≥2 cysts in each kidney	PPV, 100%	
	PPV, 100%	SEN, 88.8%	PPV, 100%
	SEN, 92.6%		SEN, 90%

Table 3. Ultrasound Criteria for Exclusion of ADPKD

Age, y	PKD1	PKD2	Unknown ADPKD Gene Type
15-30	≥1 cyst		
	NPV, 99.1%	NPV, 83.5%	NPV, 90.8%
	SPEC, 97.6%	SPEC, 96.6%	SPEC, 97.1%
30-39	≥1 cyst		
	NPV, 100%	NPV, 96.8%	NPV, 98.3%
	SPEC, 96%	SPEC, 93.8%	SPEC, 94.8%
40-59	≥1 cyst		
	NPV, 100%	NPV, 100%	NPV, 100%
	SPEC, 93.9%	SPEC, 93.7%	SPEC, 93.9%

Barua M, Pei Y. Diagnosis of Autosomal-Dominant Polycystic Kidney Disease: An Integrated Approach. Semin Nephrol. 2010 Jul;30(4):356–65.

Essentially two presentations:

- initial presentation with multiple renal cysts
- screening in a known family

Screening

- Our ability to detect cysts is quite good, so it is easier to confirm the diagnosis than it is to rule it out
- NPV is not adequate until later in life

These criteria apply to patients with known family history

New imaging findings of multiple cysts

- Need to consider ddx of multiple cysts

Differential diagnosis of multiple renal cysts

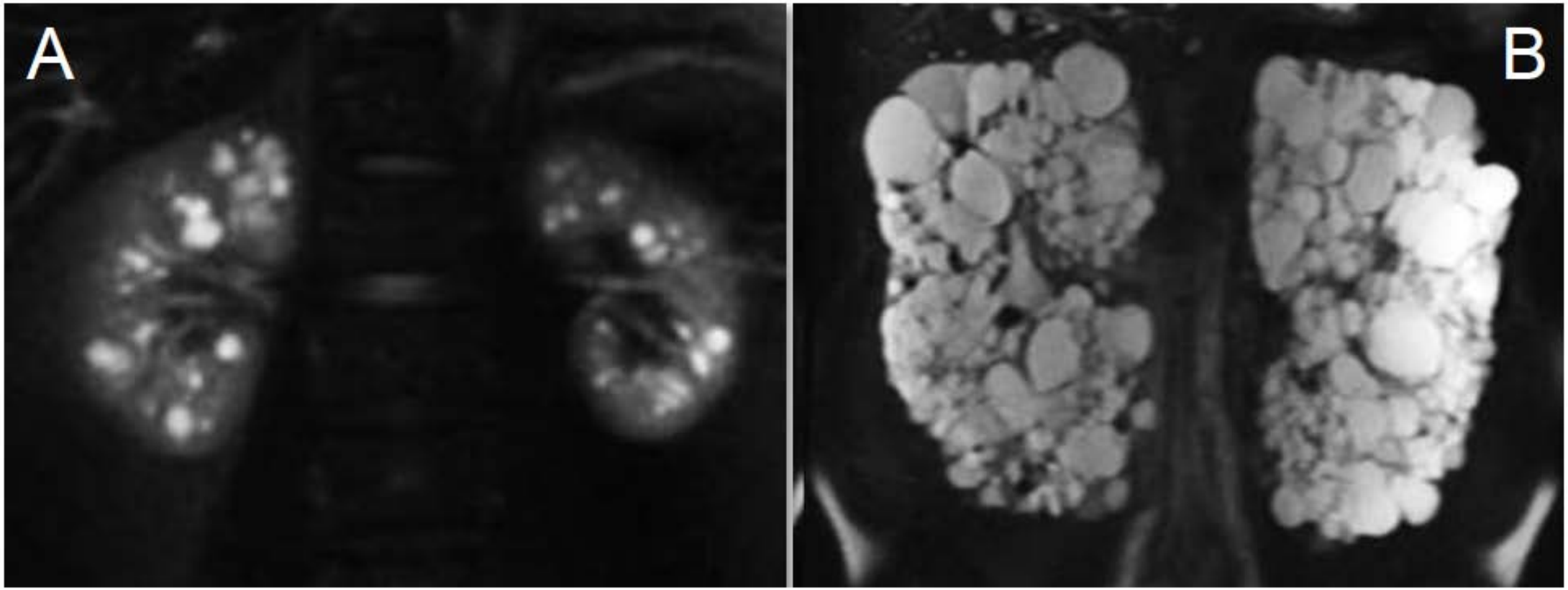
Table 2 | Differential diagnosis of other renal cystic diseases

Disorder	Inheritance	Family history	Clinical features
Autosomal-recessive polycystic kidney disease	AR	Siblings (25%)	~1 in 20,000. Neonatal deaths in 30%; Potter's phenotype; biliary dysgenesis (congenital hepatic fibrosis, intrahepatic bile duct dilatation), resulting in portal hypertension and cholangitis.
Renal cysts and diabetes syndrome (RCAD/MODY5/ HNF-1B[a])	AD	*De novo* mutations (often deletions) in 50%	Renal cysts or malformation in 90%, diabetes mellitus in 45%, hypomagnesemia in 40%, genital tract abnormalities in 20%, hyperuricemia in 20%, elevated liver enzymes in 15%.
Tuberous sclerosis complex	AD	Absent in two thirds of families	~1 in 10,000 live births. Skin lesions (facial angiofibromas, periungual fibroma, hypomelanotic macules, shagreen patch), >90%; cerebral pathology (cortical tuber, subependymal giant cell astrocytoma), 90%; renal (polycystic kidneys, angiomyolipoma), 50–70%; retinal hamartomas, 50%; lymphangioleiomyomatosis.
PKD1-TSC contiguous gene syndrome	AD	Spontaneous presentation frequent	Presentation of severe ADPKD at an early age, with polycystic kidneys with renal angiomyolipomas frequently present after the first year of age.
von Hippel-Lindau disease	AD	*De novo* mutations in 20%	~1 in 36,000. Cerebellar and spinal hemangioblastoma; retinal angiomas; serous cystadenomas and neuroendocrine tumors of pancreas; pheochromocytoma; renal cell carcinoma.
Medullary cystic kidney disease[b]	AD	Rare	Slowly progressive kidney disease; medullary cysts (but uncommon in families with type 2 MCKD (now known as ADTKD-*UMOD*)); hyperuricemia and gout in type 2 MCKD (now known as ADTKD-*UMOD*); small- to normal-sized kidneys.
Medullary sponge kidney	Unclear	Familial clustering reported	~1 in 5000. Medullary nephrocalcinosis; kidney stones; 'brush' or linear striations on intravenous pyelogram.
Simple renal cysts	Acquired	None	Common; increase in number and size with age; normal renal function; normal-sized kidneys.
Acquired cystic kidney disease	Acquired	None	Common in patients with chronic renal failure or ESRD; multiple cysts associated with normal- or small-sized kidneys.

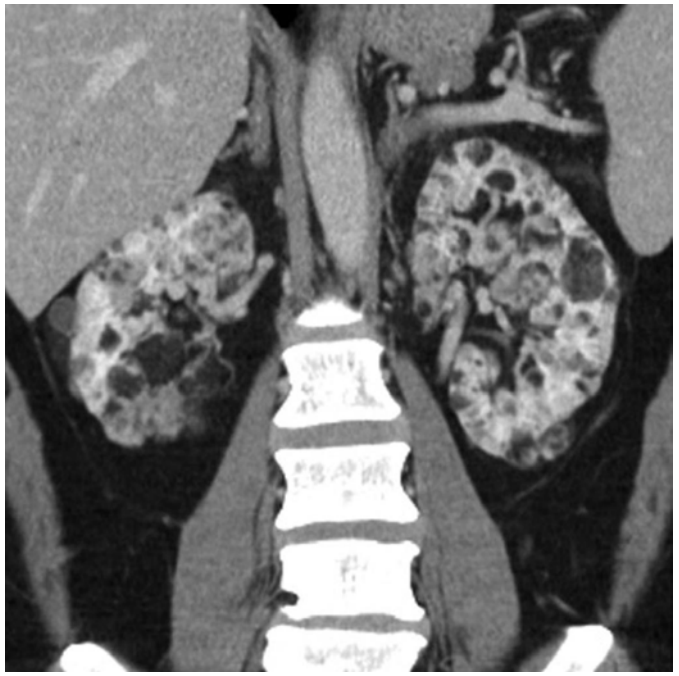
Abbreviations: AD, autosomal dominant; ADPKD, autosomal-dominant polycystic kidney disease; ADTKD, autosomal-dominant tubulointerstitial kidney disease; AR; autosomal recessive; ESRD, end-stage renal failure; MODY5, maturity-onset diabetes mellitus of the young type 5.
[a]Current designation is ADTKD-*HNF1B*.
[b]Use of the term MCKD is discouraged; formerly MCKD type 1 should now be referred as ADTKD-*MUC1* and formerly MCKD type 2 should now be referred as ADTKD-*UMOD*.

Chapman et al, 2015

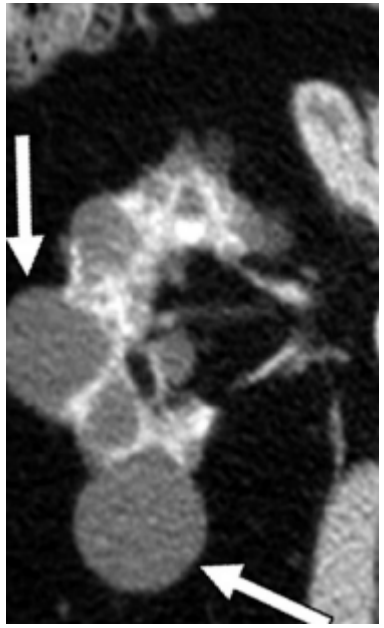
Typical radiographic morphology of ADPKD



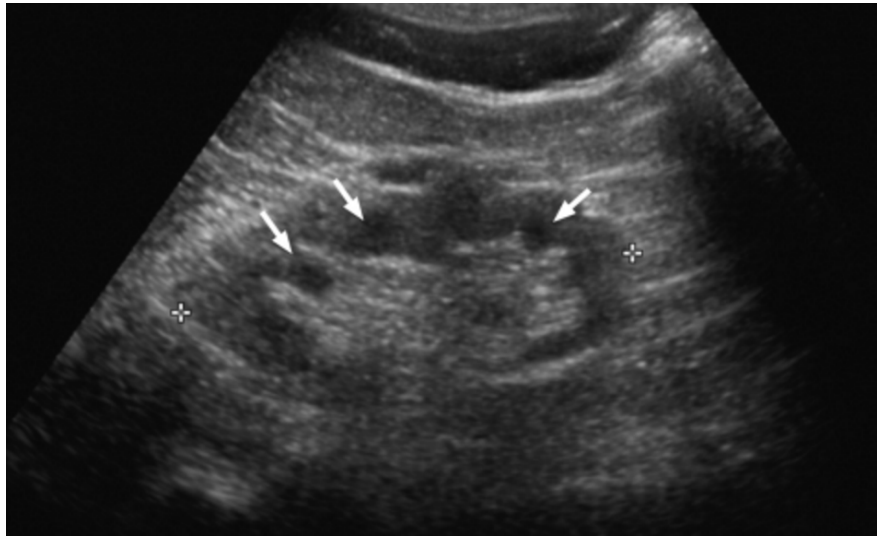
Diffuse, bilateral cystic involvement of both kidneys



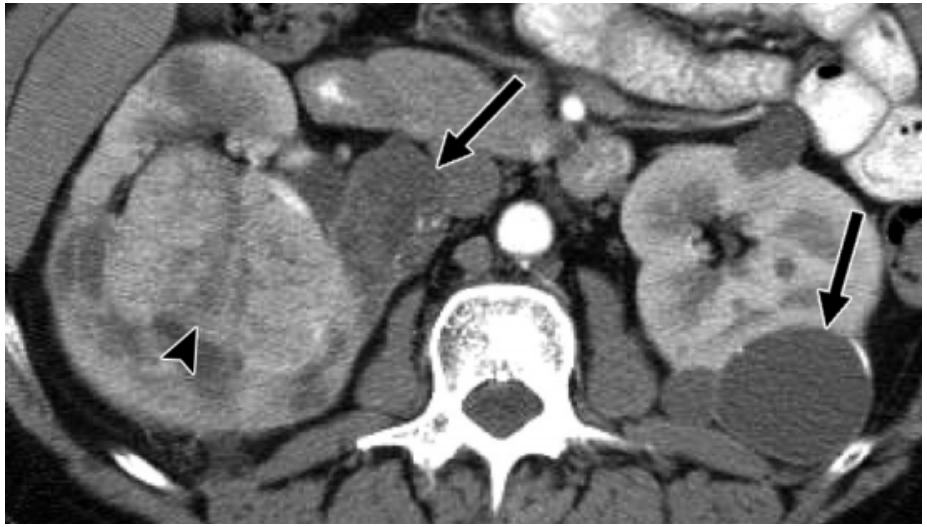
TSC: cysts + AMLs



Acquired multicystic disease



Medullary cystic dz's



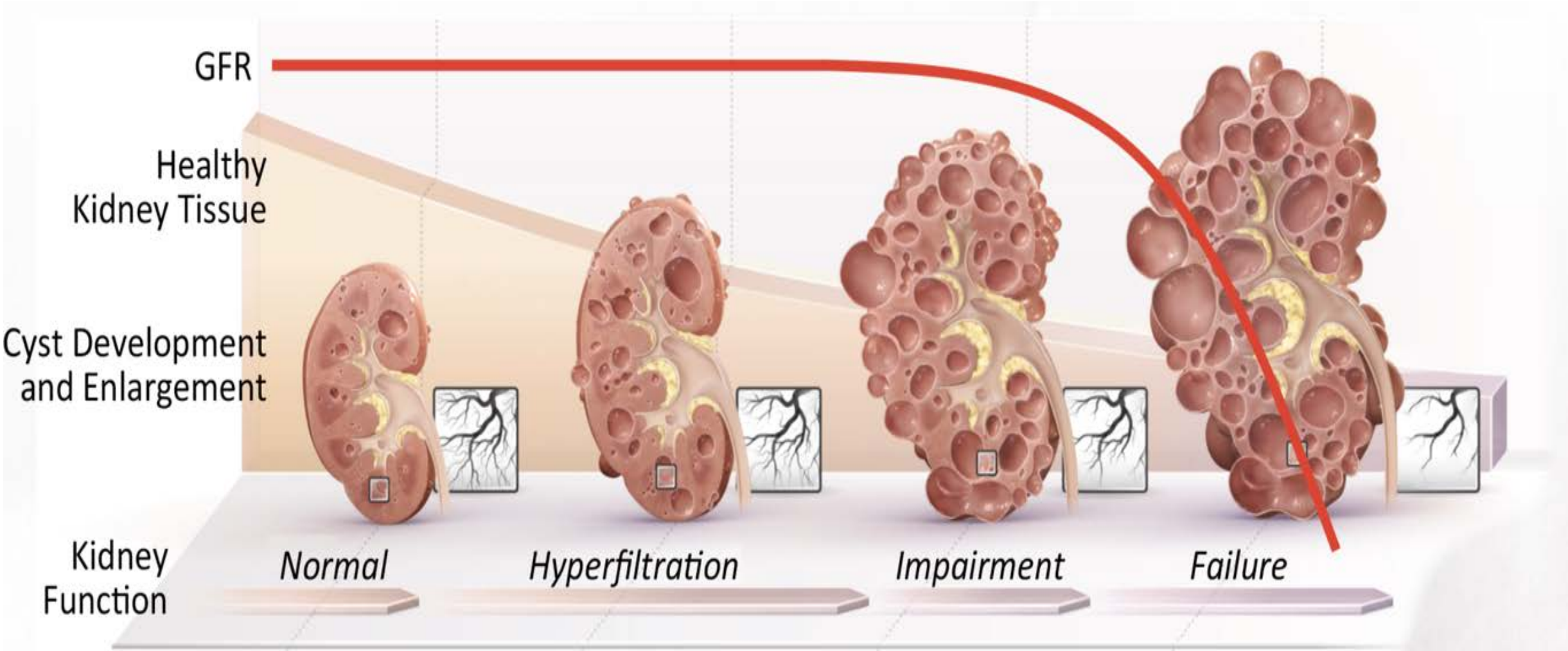
VHL: cyst +RCC

In most cases these can be differentiated radiographically by two key radiographic features of ADPKD:

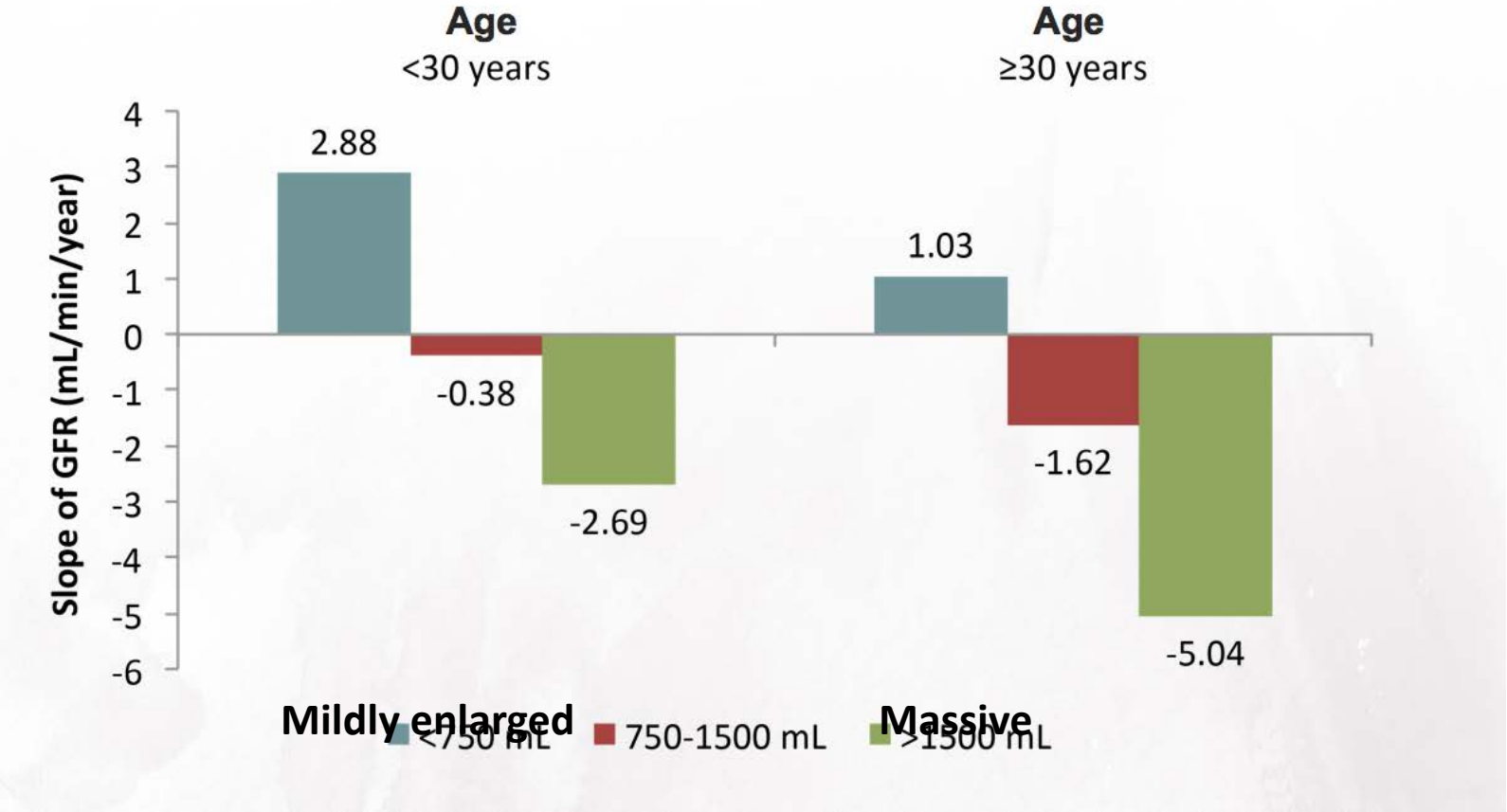
- Multiple simple cysts throughout the kidneys
- Renal enlargement

Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 8772

Katabathina VS, Kota G, Dasyam AK, Shanbhogue AKP, Prasad SR. Adult Renal Cystic Disease: A Genetic, Biological, and Developmental Primer. RadioGraphics. 2010 Oct;30(6):1509–23.


GFR
Healthy Kidney Tissue
Cyst Development and Enlargement
Kidney Function
Normal
Hyperfiltration
Impairment
Failure

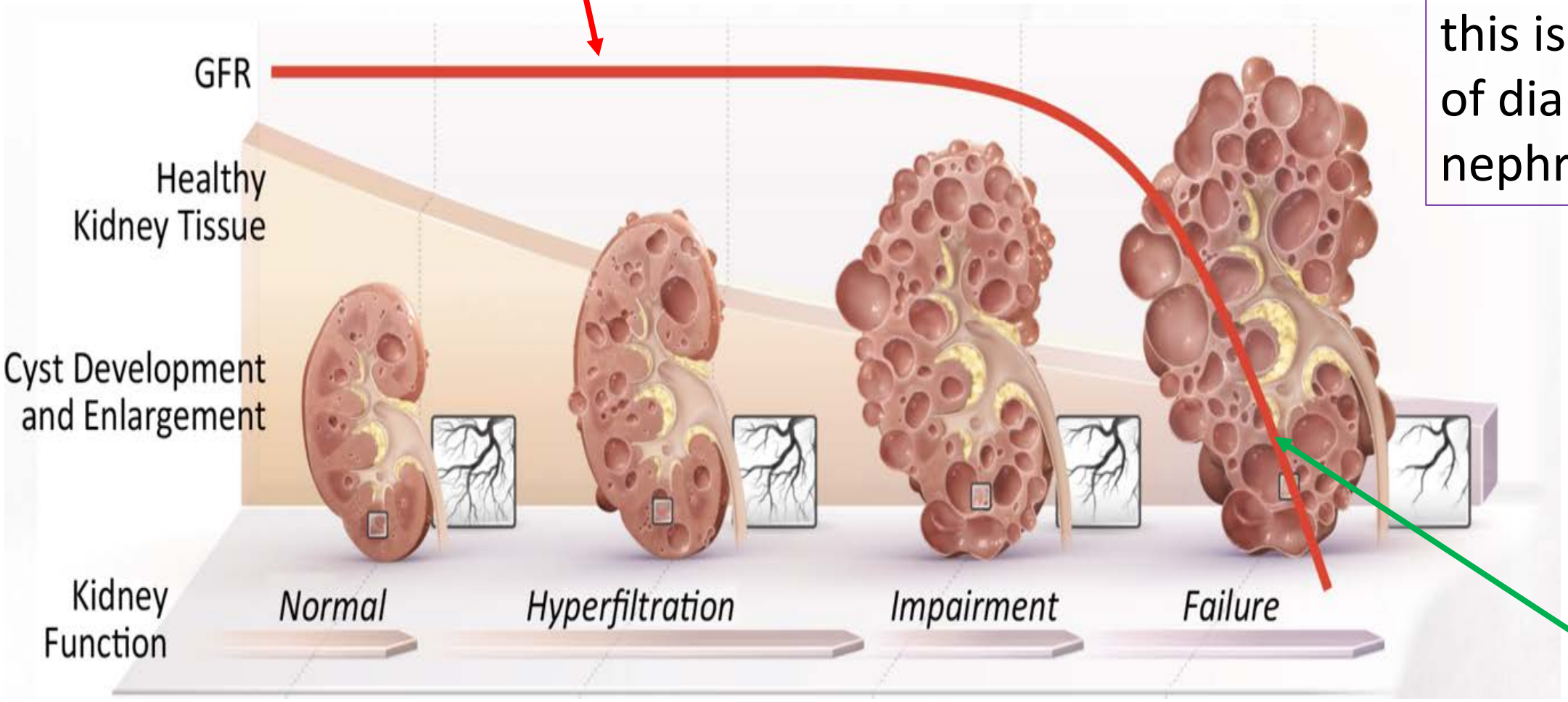
A key new understanding of PKD: Hyperfiltration



Grantham JJ, Torres VE, Chapman AB, Guay-Woodford LM, Bae KT, King Jr BF, et al. Volume progression in polycystic kidney disease. New England Journal of Medicine. 2006;354(20):2122–30.

Maintained GFR in the setting of renal parenchymal loss = hyperfiltration

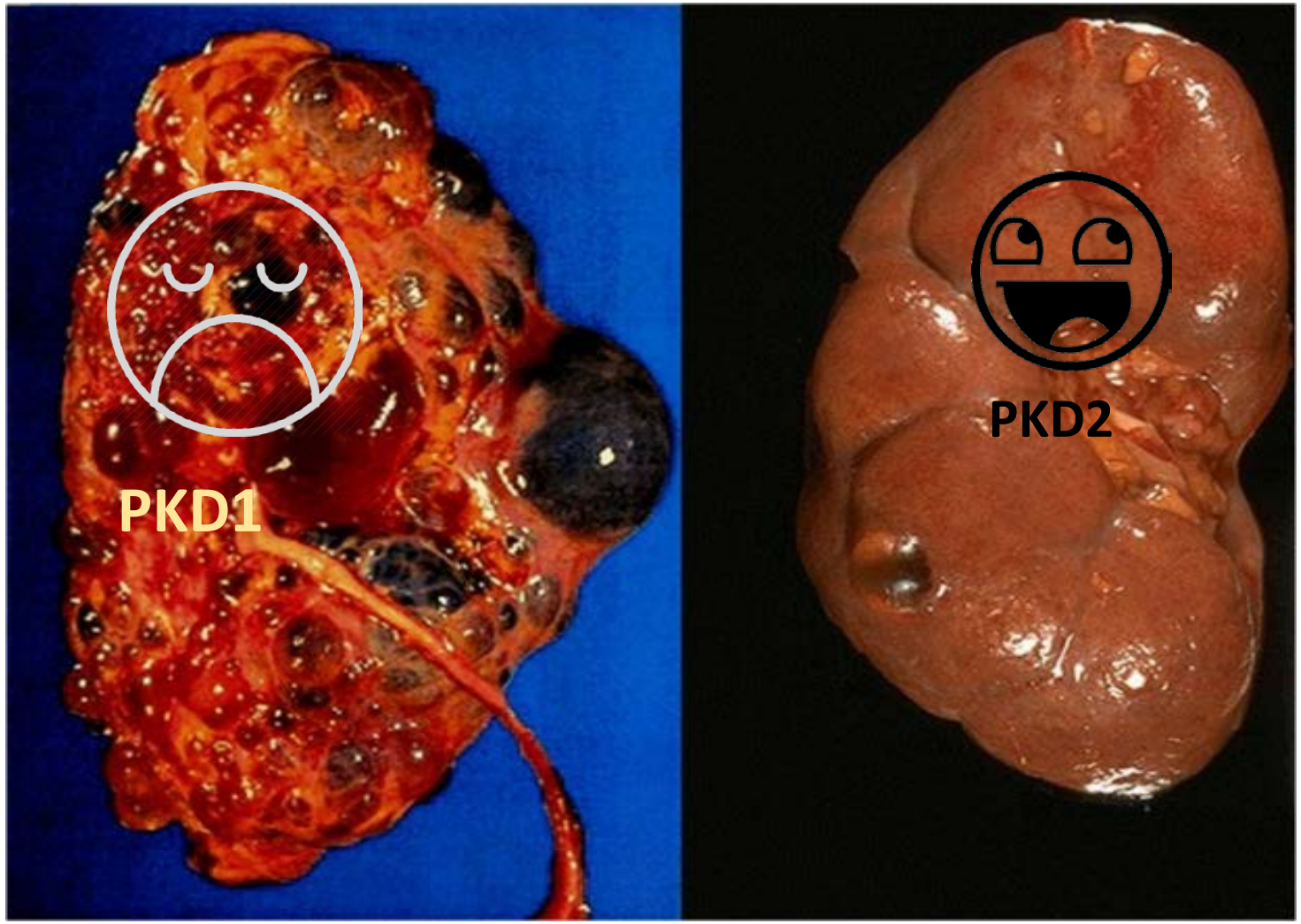
A good way to conceptualize this is to think of diabetic nephropathy



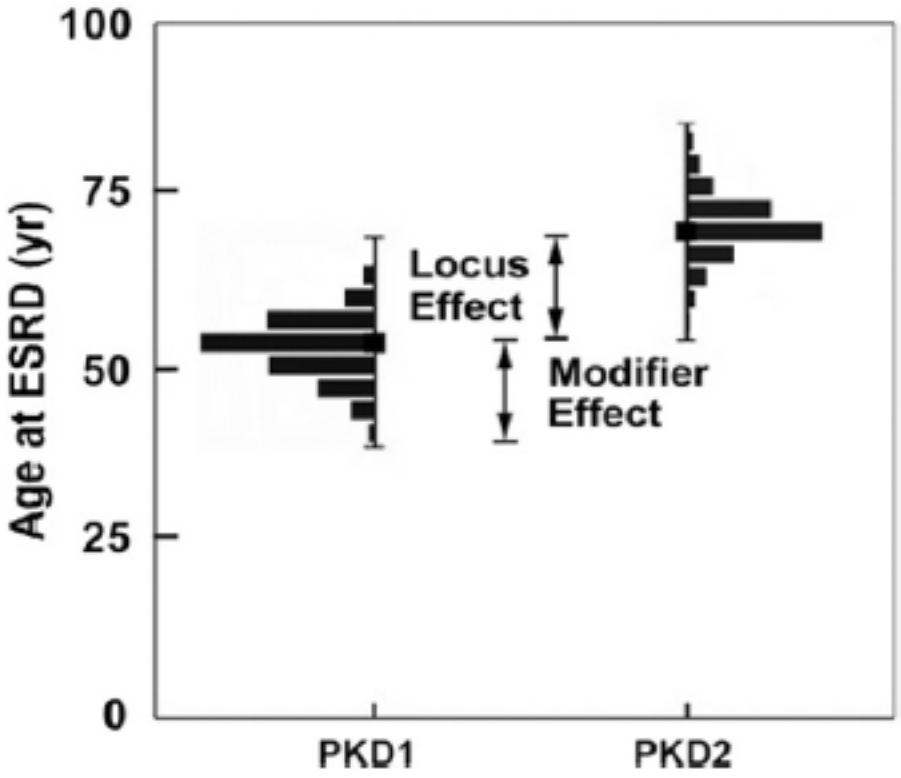
Upwards of 4-5ml/year decline

The disease course is variable one, with the early disease marked by cyst proliferation and expansion with little renal dysfunction followed by a precipitous decline. The corollary here is that by the time there is a change in GFR, significant cyst expansion and proliferation has already occurred

Genetics in PKD



Genetics are only part of the story…



While PKD1 on average portends a worse prognosis than PKD2 there is substantial variation and overlap

Family history can suggest genotype in the extremes:

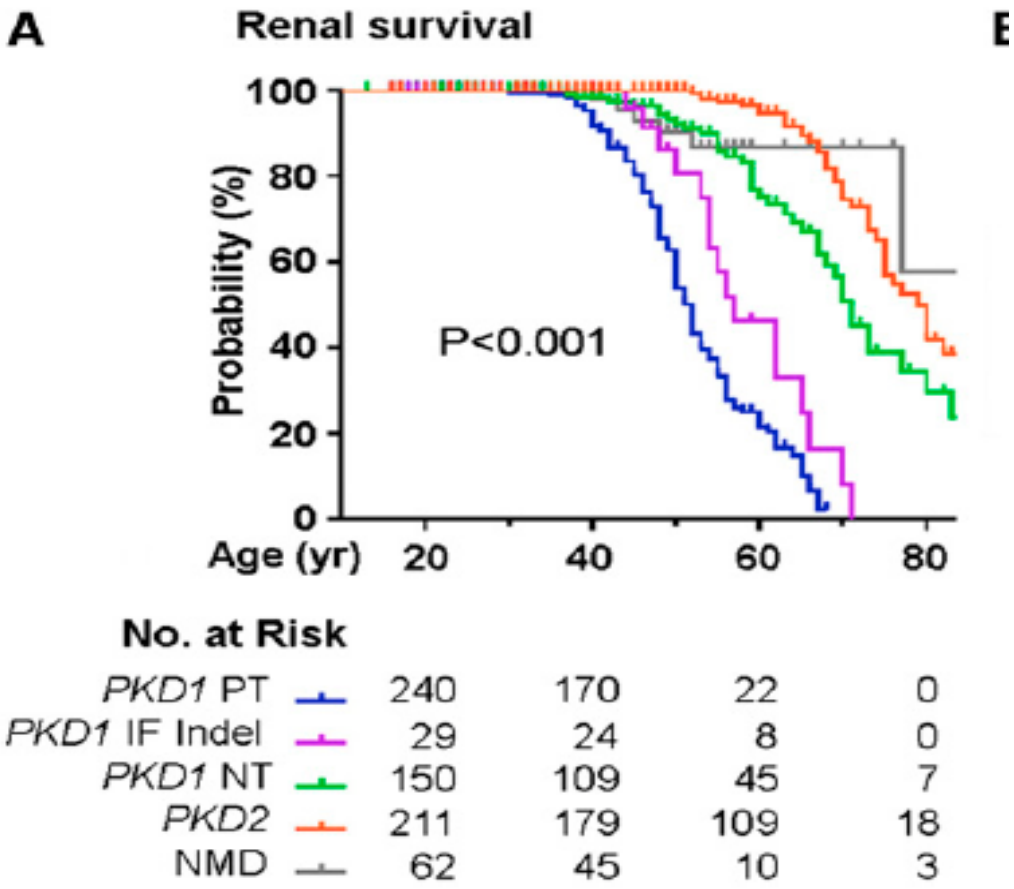
- Affected family member with ESRD <55 years, 100% PPV for PKD1

- Affected kin without ESRD >70 – 100%PPV PKD2

For everything else there is substantial overlap

Barua M, Pei Y. Diagnosis of Autosomal-Dominant Polycystic Kidney Disease: An Integrated Approach. Seminars in Nephrology. 2010 Jul;30(4):356–65.

It is more complicated than 1 vs 2…



Hwang Y-H, Conklin J, Chan W, Roslin NM, Liu J, He N, et al. Refining Genotype-Phenotype Correlation in Autosomal Dominant Polycystic Kidney Disease. Journal of the American Society of Nephrology. 2016 Jun 1;27(6):1861–8.

<u>Mayo PKD mutation database</u>

- PKD1 – 2323 known mutations, 868 clear pathogenic significance
- PKD2 – 278 mutations, 168 clear pathogenic significance

In any case, genetics only tells you about average disease course, not your individual patient

It is very difficult to get detailed genetic analysis in BC

Genetic analysis methods

	DNA linkage analysis		Gene-based mutation screening		NGS	
	PKD1	PKD2	PKD1	PKD2	PKD1	PKD2
Cost	n/a	—	n/a	~$1000	$1155-$2290	$1155-$2290
Availability (# of sites worldwide)	1	0	16	24	18	29
Interpretation	Should be interpreted with caution given the possibility of de novo mutations, mosaicisms, and hypomorphic alleles (Torra-Balcells and Ars-Criach, 2011)		May be difficult to differentiate missense mutations from benign variants; mutations detected in approximately 65%-75% of subjects; approximately 8% of patients have no confirmed pathogenic mutation (Heyer et al., 2016)		Offers sensitivity of 99.2% and specificity of 99.9% in identifying mutations in PKD1 and PKD2 (Tan et al., 2014)	

Role of genetics

- Due to the difficulty obtaining genetics, the accuracy of image-based diagnosis of PKD and the limited prognostic information provided by genetics (more later) this plays a minor role in clinical PKD management
  - Potential donors
  - Uncertain imaging
  - New presentations with unusual manifestations
  - Family planning

In BC, this is only covered if approved by a medical geneticist

Take home points: Natural history

- Imaging based diagnosis of PKD is age dependent
- Decline in GFR is a late finding in PKD – by the time that happens there has been substantial disease progression
- PKD is a hyperfiltering and fibrotic disease
- Genetics have some prognostic value but there is substantial variation in the disease course of individual patients

Symptom burden in PKD

Abdominal symptoms

Over ¼ of people with GFR >60 have abdominal symptoms related to their PKD

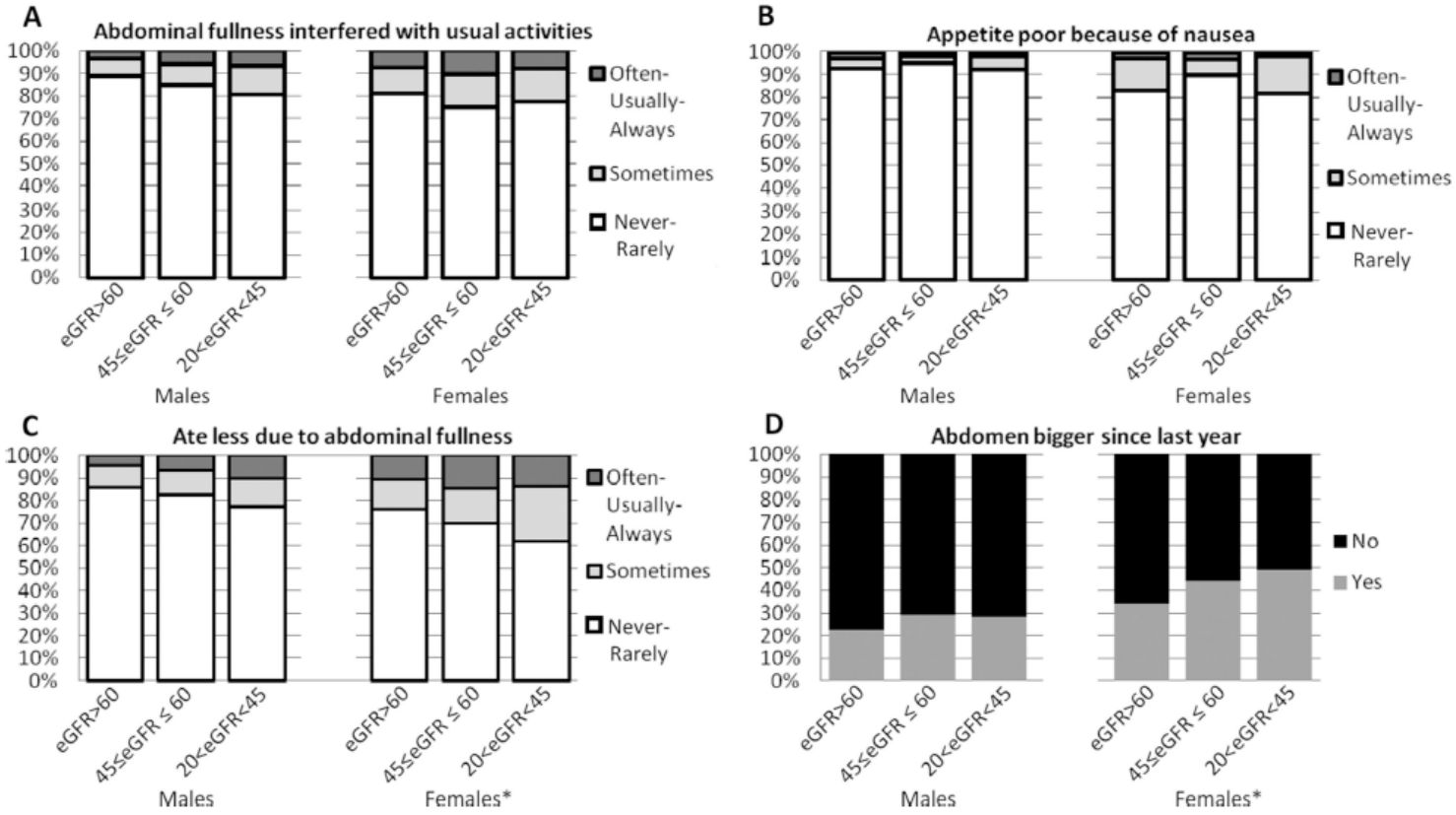
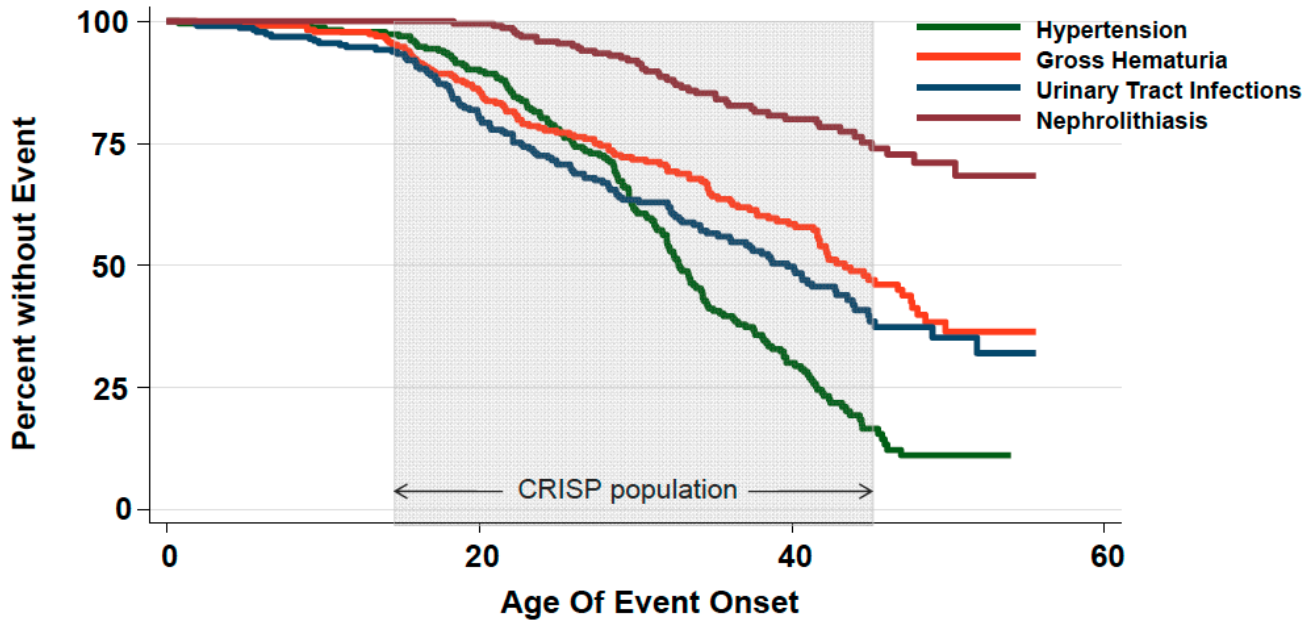


Figure 1. ADPKD patients' reports of frequency of abdominal symptoms

Miskulin DC, Abebe KZ, Chapman AB, Perrone RD, Steinman TI, Torres VE, et al. Health-Related Quality of Life in Patients With Autosomal Dominant Polycystic Kidney Disease and CKD Stages 1-4: A Cross-sectional Study. American Journal of Kidney Diseases. 2014 Feb;63(2):214–26.

Other complications of PKD



By age 30, over 50% have at least one complications

NIH CRISP Studies; Chapman *J. Amer. Soc. Neph*, 21:384A, 2010.

Pain, hematuria, infection and stones can occur early in the disease course

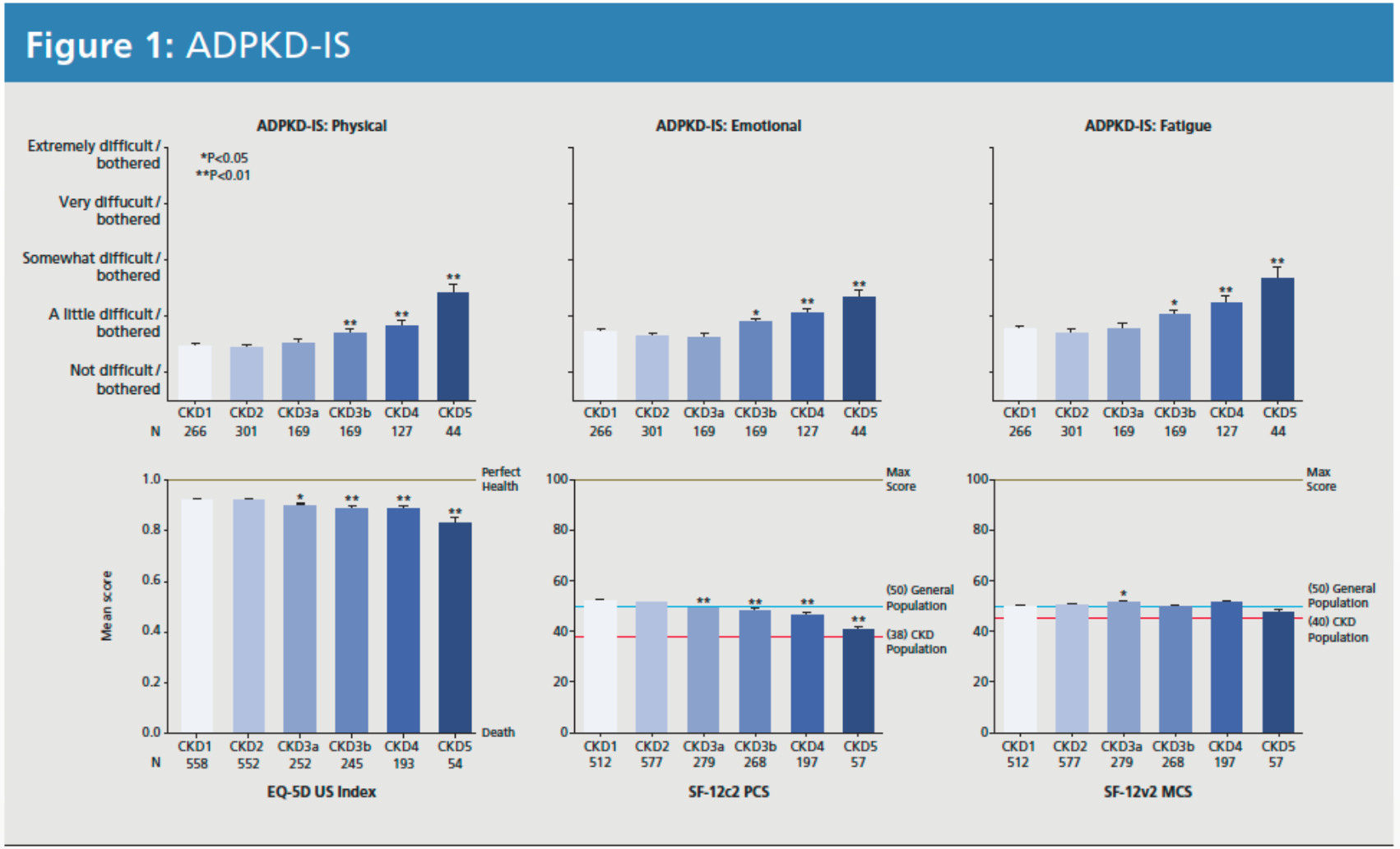
- Up to 25% of PKD patients present with these symptoms in the setting of preserved renal function

- The occurrence of these symptoms does not completely coincide with their renal disease course

Gabow PA, Duley I, Johnson AM. Clinical profiles of gross hematuria in autosomal dominant polycystic kidney disease. Am J Kidney Dis. 1992 Aug;20(2):140–3.

Bajwa ZH, Sial KA, Malik AB, Steinman TI. Pain patterns in patients with polycystic kidney disease. Kidney international. 2004;66(4):1561–9.

Health related quality of life in PKD

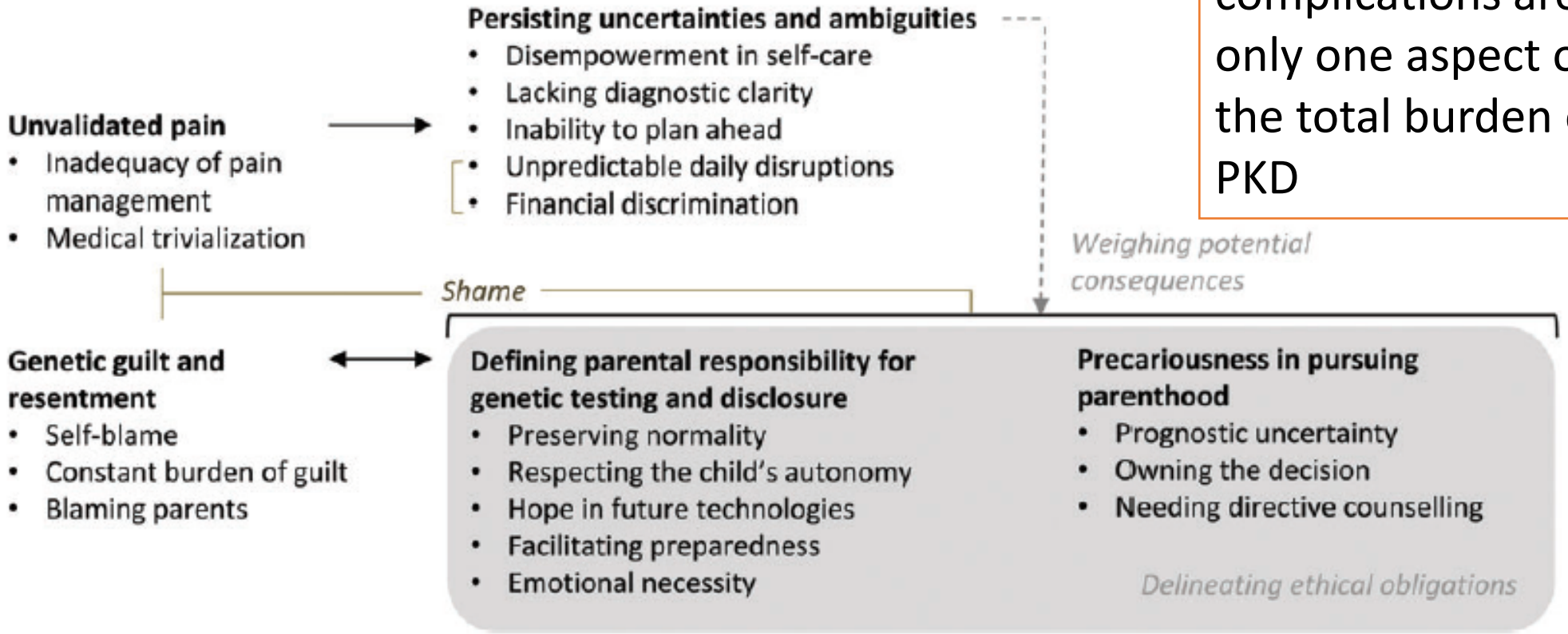


- Even early stage (CKD1) PKD patients show impacts of PKD on their life
- In other studies, PKD patients score lower on HR-QoL scores than CKD peers at similar GFRs

Oberdhan; ASN 2015

Patient perspectives of PKD

The physical symptoms and complications are only one aspect of the total burden of PKD



Tong A, Rangan GK, Ruospo M, Saglimbene V, Strippoli GFM, Palmer SC, et al. A painful inheritance--patient perspectives on living with polycystic kidney disease: thematic synthesis of qualitative research. Nephrology Dialysis Transplantation. 2015 May 1;30(5):790–800.

Take home points: Symptom burden and impact of PKD

- Although renal dysfunction in a late finding, complications and symptoms often present before GFR decline
- Even early stage PKD has a substantial symptom burden, impact on quality of life and psychological impact on patients

Predicting renal prognosis in PKD

Predictors of progression in PKD

Table 2. Univariate Cox analysis

Variable	Patients (*n*)	Univariate HR (95% CI)	*P* Value
Sex			
Female	732		
Male	609	1.3 (1.0 to 1.4)	0.017
Hypertension before age 35 yr			
No	788		
Yes	357	3.1 (2.6 to 3.8)	<0.001
Macroscopic hematuria before age 35 yr			
No	964		
Yes	150	2.9 (2.2 to 3.7)	<0.001
Cyst infection before age 35 yr			
No	1012		
Yes	84	2.1 (1.5 to 3.0)	<0.001
Flank pain related to cysts before age 35 yr			
No	938		
Yes	170	2.6 (1.9 to 3.4)	<0.001
≥1 urologic complication before age 35 yr (hematuria, pain, or cyst infection)			
No	824		
Yes	294	2.4 (2.0 to 3.0)	<0.001

HR for risk of ESRD at 60yrs

Other studies exist which confirm these criteria, as well as changes in albuminuria and urine concentrating capacity

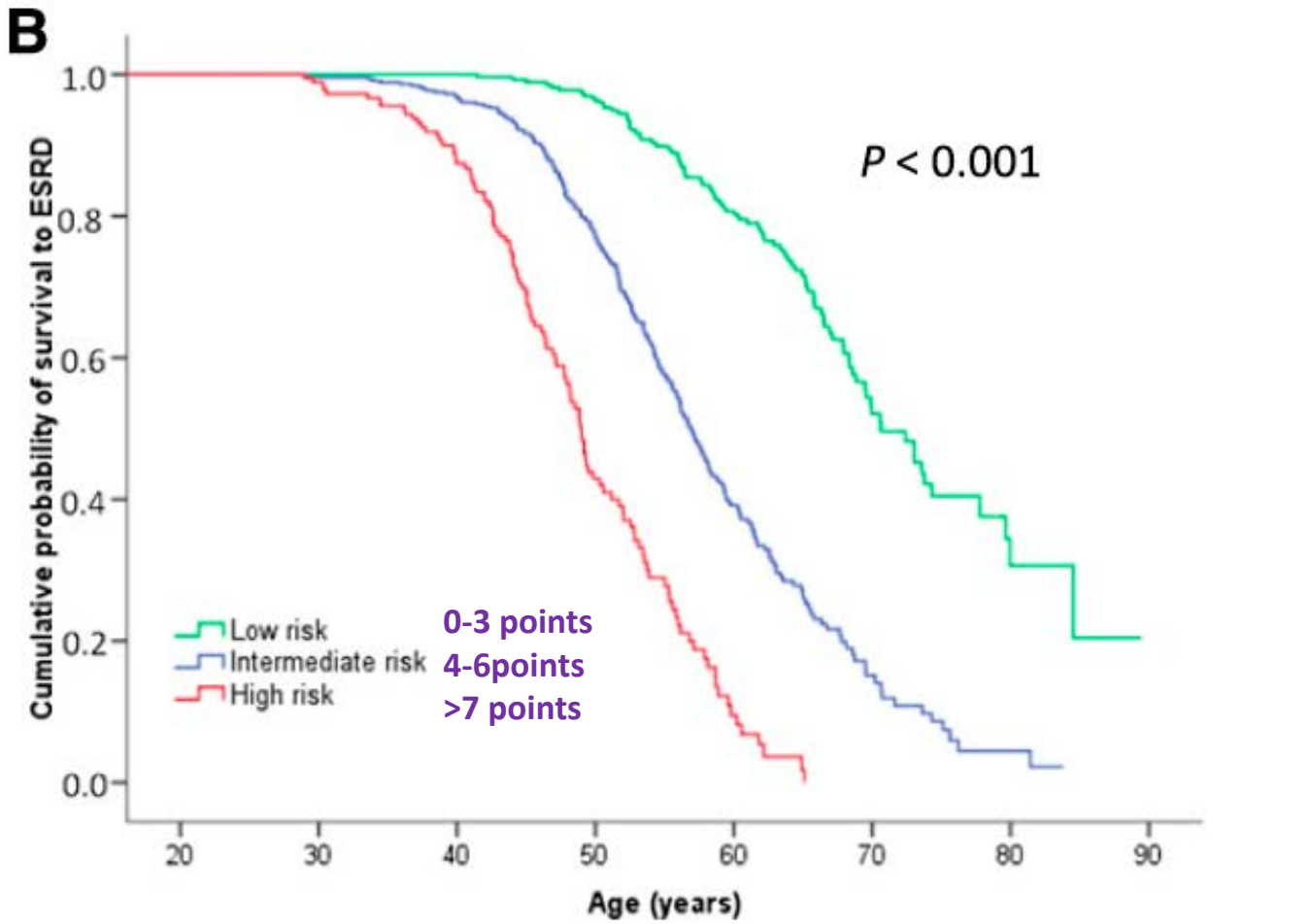
These are not *predictors* of progression, they are ***signs that substantial progression has already occurred***

J Am Soc Nephrol 27: ●●●–●●●, 2015. doi: 10.1681/ASN.2015010016

Clinical markers and the PRO-PKD score

PROPKD score	
Factor	**Points**
Male	1
Hypertension before age 35	2
First urologic event before age 35	2
PKD2 mutation	0
Non truncating PKD1 mutation	2
Truncating PKD1 mutation	4

- A scoring system based on a mix of clinical and genetic factors
- Can only be used in patients with a history of urologic events



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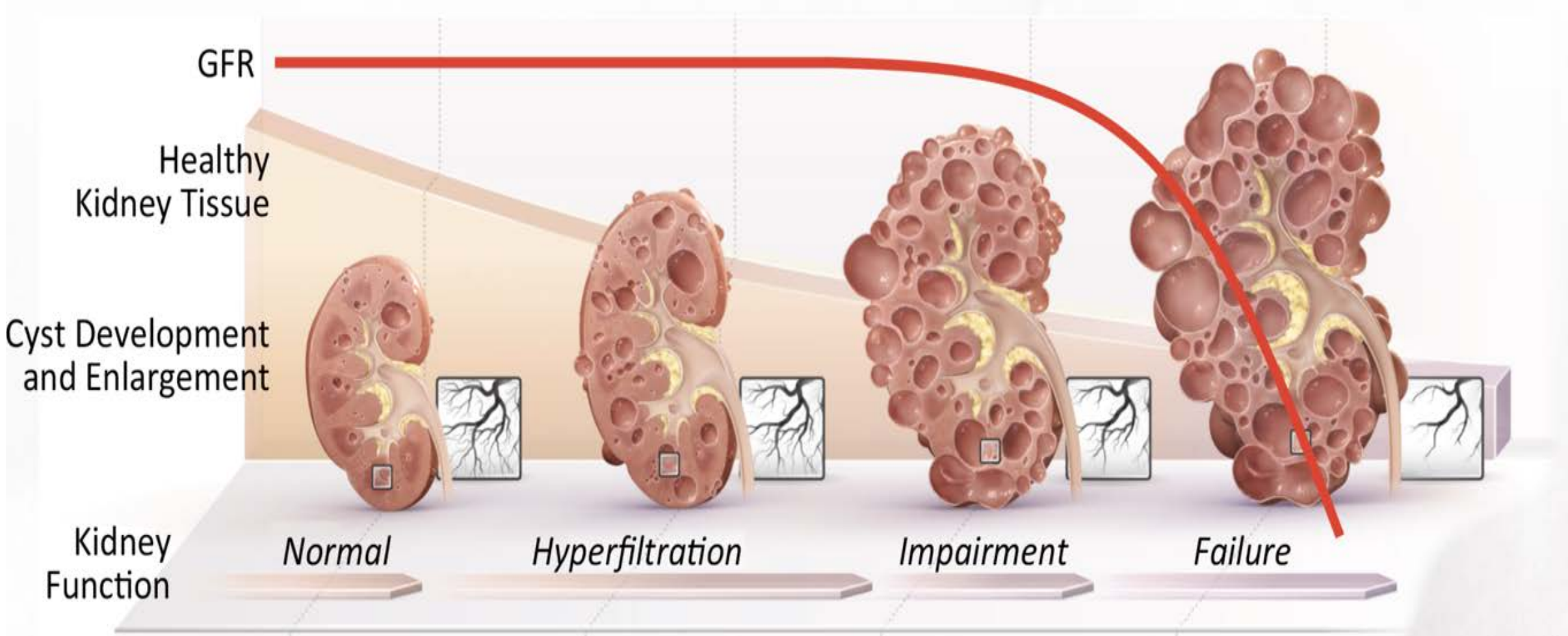

GFR
Healthy Kidney Tissue
Cyst Development and Enlargement
Kidney Function
Normal
Hyperfiltration
Impairment
Failure

Kidney size/Total kidney volume (TKV)

- In many cases, genetics are too variable to firmly predict progression, and clinical markers appear too late in the disease course

- Since kidney size precedes renal dysfunction, changes in kidney size have been examined as a marker of prognosis and disease progression. A dynamic marker like this would help quantify the progression of an individual patient

- Much of the following data has come from the CRISP investigators

Change in kidney size precedes change in renal function

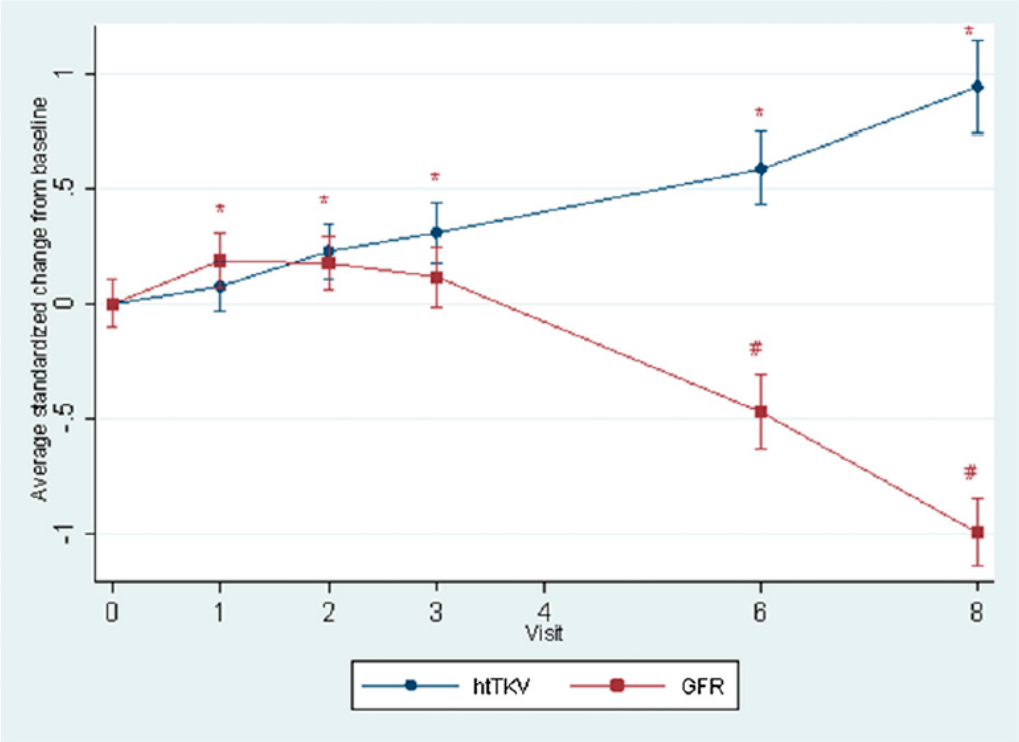


Figure 2. | **Average standardized change in htTKV and iothalamate GFR**. htTKV determined at baseline and iothalamate GFR at baseline and five subsequent visits until year 8 (n=93 with complete data). P<0.01 based on paired t test comparing each year to baseline for htTKV (*) and GFR (#). htTKV, height-adjusted total kidney volume.

- While a statistically significant difference in GFR did not arise until 6 years of follow-up, a detectable and significant change in TKV was detectable at 1 year follow up

Clin J Am Soc Nephrol 7: 479–486, 2012.

TKV as a predictor of renal outcomes

Table 3. Baseline predictors of CKD stage 3 endpoint

Variable	AUC	Sensitivity	Specificity	Cut Point	95% CI of AUC	*P* Value*
htTKV (cc/m)	0.84	0.74	0.7	600	(0.79, 0.90)	
Serum creatinine (mg/dl)	0.75	0.58	0.81	1.1	(0.67, 0.82)	0.02
BUN (mg/dl)	0.76	0.63	0.79	16	(0.70, 0.83)	0.04
Urine albumin (mg/d)	0.70	0.66	0.67	30	(0.61, 0.78)	0.002
MCP-1 (pg/mg)	0.75	0.80	0.62	410	(0.68, 0.83)	0.02
Baseline age (yr)	0.66	0.60	0.65	35	(0.59, 0.74)	<0.001

AUC, area under the curve; 95% CI, 95% confidence interval; htTKV, height-adjusted total kidney volume; MCP-1, monocyte chemotactic protein-1.

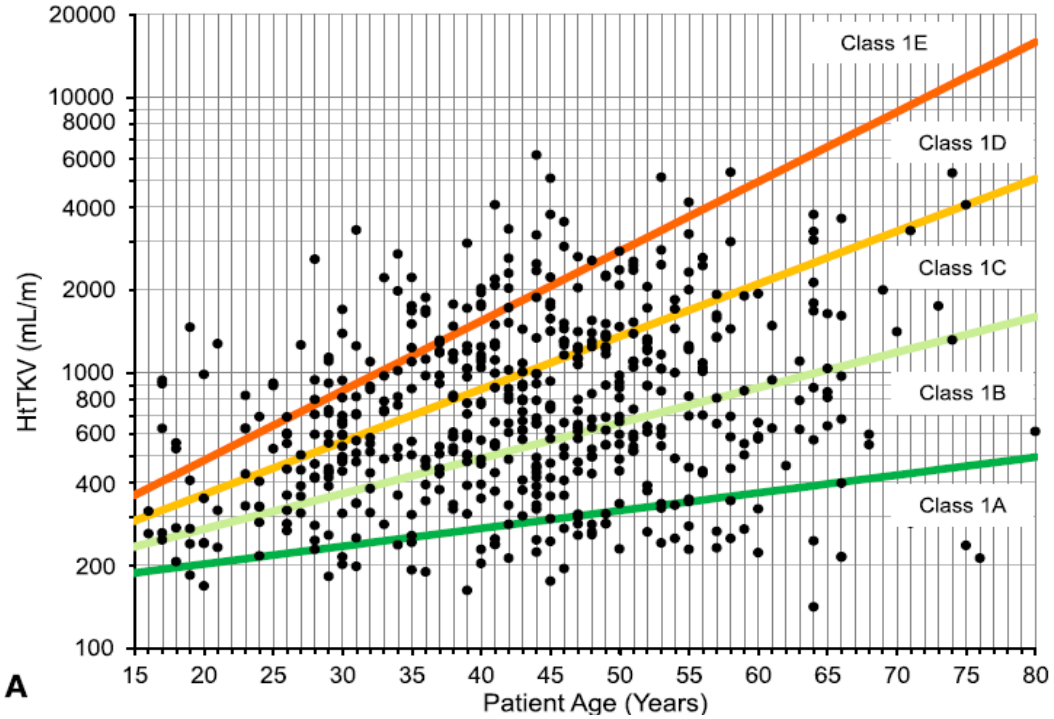
- In this study of the CRISP cohort, total kidney Volume (TKV) at baseline was found to be a better predictor of risk of GFR <60 over 8 years of follow-up than baseline age, baseline renal function or proteinuria

At present, this appears to be the best predictor of renal progression for ***early stage*** PKD

Clin J Am Soc Nephrol 7: 479–486, 2012.

Mayo classification categorizes rate of kidney growth

Class	Average annual change in TKV
1A	<1.5%
1B	1.5-3
1C	3-4.5
1D	4.5-6
1E	>6%



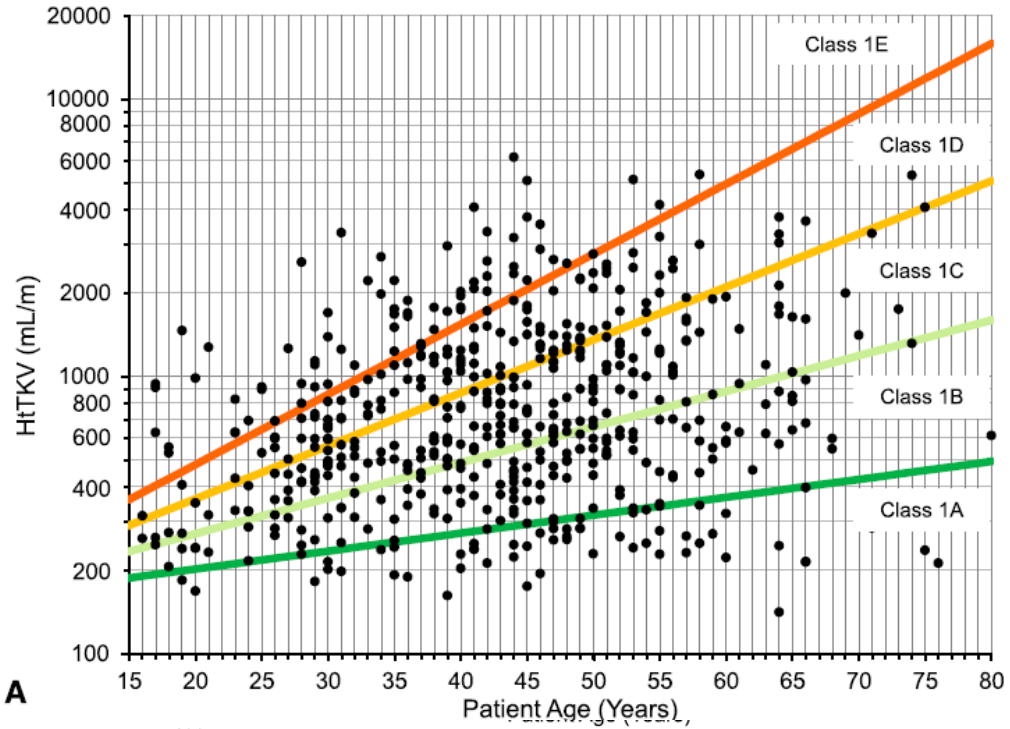
The 1A-1E classification is best thought of as a ***velocity of growth classification*** – the classes refer to the average annual growth in htTKV

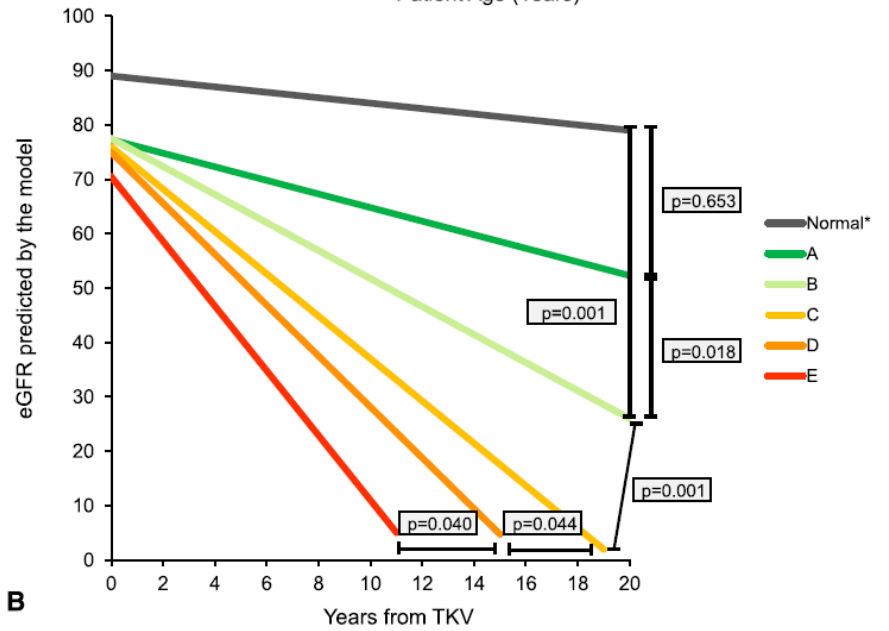
J Am Soc Nephrol 26: 160–172, 2015.

Mayo class predicts rate of GFR loss

Class	Average annual change in TKV	Average annual decrease in eGFR
1A	<1.5%	0.23
1B	1.5-3	1.33
1C	3-4.5	2.63
1D	4.5-6	3.48
1E	>6%	4.78

The average GFR comes from >8 years of CRISP and Mayo clinic follow-up data





J Am Soc Nephrol 26: 160–172, 2015.

Take home points: Predicting progression of PKD

Clinical/ lab abnormalities predict disease progression but they are late findings

Assessment of kidney size is the best early predictor of renal prognosis

- ❖Providing patients with an individualized prognostication of their renal disease (based on assessment of renal size in early stages) is becoming standard of care
- ❖Disease modifying treatments will target early stage patients and there is a substantial symptom burden even in early stage PKD

Take home point: Early management of PKD

- All PKD patients should have a detailed clinical assessment including prognostication of renal progression

For this reason, early referral to nephrology is recommended for all PKD patients

- This is a significant difference compared to the general CKD population where delayed referral is appropriate

Treatment of PKD

Measures to slow renal decline in ADPKD

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 11, 2014 VOL. 371 NO. 24

Blood Pressure in Early Autosomal Dominant Polycystic Kidney Disease

Robert W. Schrier, M.D., Kaleab Z. Abebe, Ph.D., Ronald D. Perrone, M.D., Vicente E. Torres, M.D., Ph.D., William E. Braun, M.D., Theodore I. Steinman, M.D., Franz T. Winklhofer, M.D., Godela Brosnahan, M.D., Peter G. Czarnecki, M.D., Marie C. Hogan, M.D., Ph.D., Dana C. Miskulin, M.D., Frederic F. Rahbari-Oskoui, M.D., Jared J. Grantham, M.D., Peter C. Harris, Ph.D., Michael F. Flessner, M.D., Ph.D., Kyongtae T. Bae, M.D., Charity G. Moore, Ph.D., M.S.P.H., and Arlene B. Chapman, M.D., for the HALT-PKD Trial Investigators*

HALT-PKD trial

- P: 558 hypertensive PKD patients with GFR > 60ml/min
- I: Low blood pressure target (95/60-110/75)
- C: Standard BP target (120/70-130/80)

(Also looked at combination RAS blockade – negative results, will not discuss here)

- O: Primary outcome was change in TKV. Secondary outcomes included decrease in renal function and proteinuria
- Study design: Double-blind RCT

Table 1. Demographic, Clinical, and Laboratory Characteristics at Baseline, According to Study Group of the 2-by-2 Factorial Design Trial.*

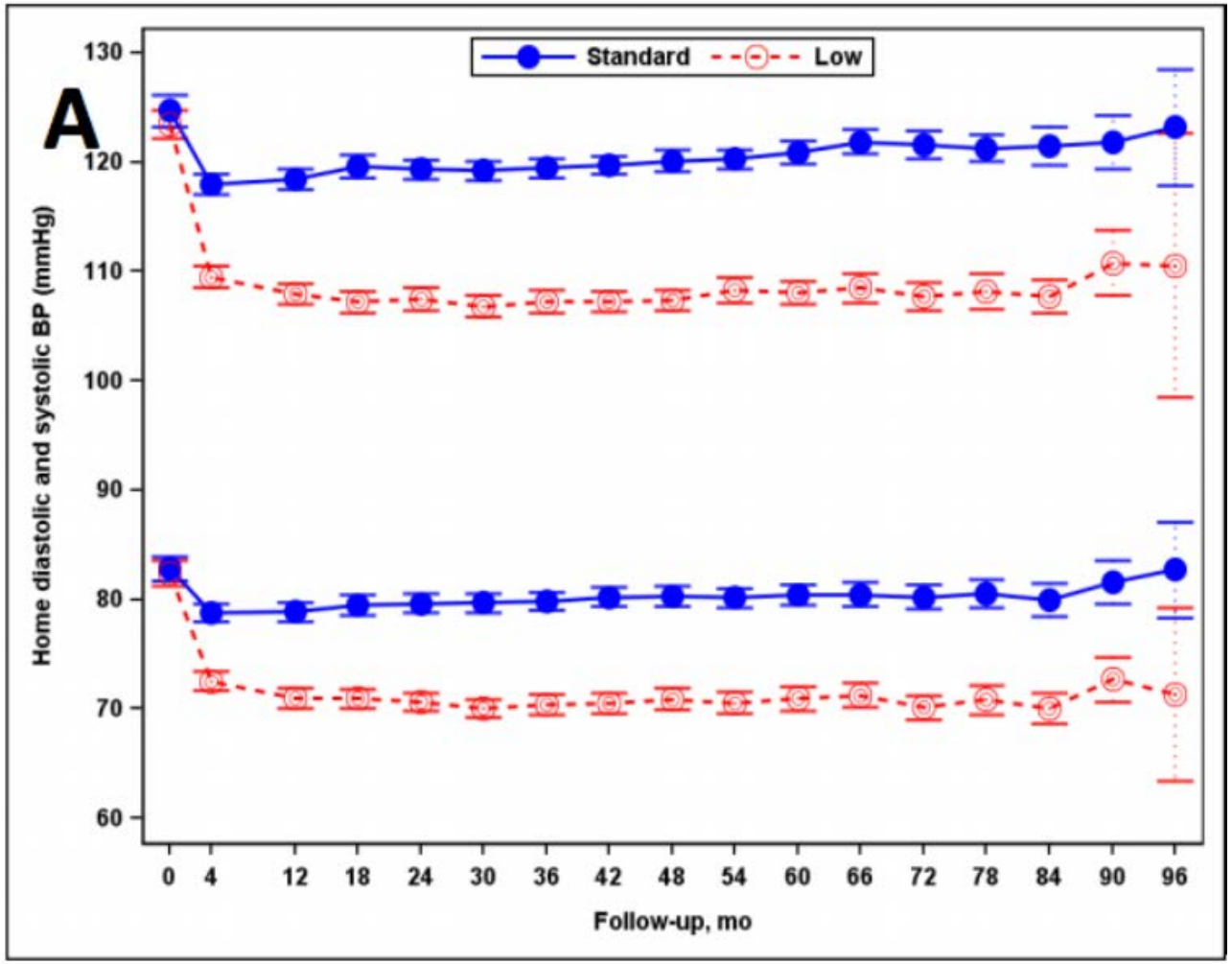
Characteristic	Lisinopril–Telmisartan (N=273)	Lisinopril–Placebo (N=285)	Standard Blood Pressure (N=284)	Low Blood Pressure (N=274)
Age — yr	37.0±8.3	36.3±8.3	36.3±8.4	36.9±8.2
Male sex — no. (%)	141 (51.6)	142 (49.8)	143 (50.4)	140 (51.1)
Race — no. (%)†				
White	255 (93.4)	262 (91.9)	258 (90.8)	259 (94.5)
Black	6 (2.2)	8 (2.8)	7 (2.5)	7 (2.6)
Other	10 (3.7)	17 (6.0)	18 (6.3)	9 (3.3)
Data missing	2 (0.7)	0	2 (0.7)	0
PKD genotype — no./total no. (%)‡				
PKD1	190/252 (75.4)	192/260 (73.8)	204/260 (78.5)	178/252 (70.6)
PKD2	42/252 (16.7)	42/260 (16.2)	34/260 (13.1)	50/252 (19.8)
No mutation detected	20/252 (7.9)	26/260 (10.0)	22/260 (8.5)	24/252 (9.5)
Body-mass index§	27.4±5.2	27.1±5.1	27.3±5.4	27.1±4.9
Estimated GFR — ml/min/1.73 m²¶	90.4±17.5	92.6±17.4	91.7±17.8	91.4±17.2
Urinary aldosterone — μg/24 hr	12.2±10.0	12.2±9.1	13.0±10.6	11.4±8.2
Urinary albumin — mg/24 hr				
Median	19.3	17.6	19.1	17.7
Interquartile range	12.7–35.2	11.7–30.6	12.8–31.8	11.7–33.3
Total kidney volume — ml	1264.6±786.2	1164.0±661.0	1240.6±747.1	1185.2±704.0
Renal blood flow — ml/min/1.73 m²	607.7±195.3	609.2±216.2	592.4±206.1	624.7±205.3
Left-ventricular-mass index — g/m²	64.1±13.2	63.7±12.9	63.8±13.8	63.9±12.2

Young: Age 37

Preserved kidney function: eGFR 90

Rapid progressing disease: Big kidneys at a young age

Achieved BP


A
Standard
Low
Home diastolic and systolic BP (mmHg)
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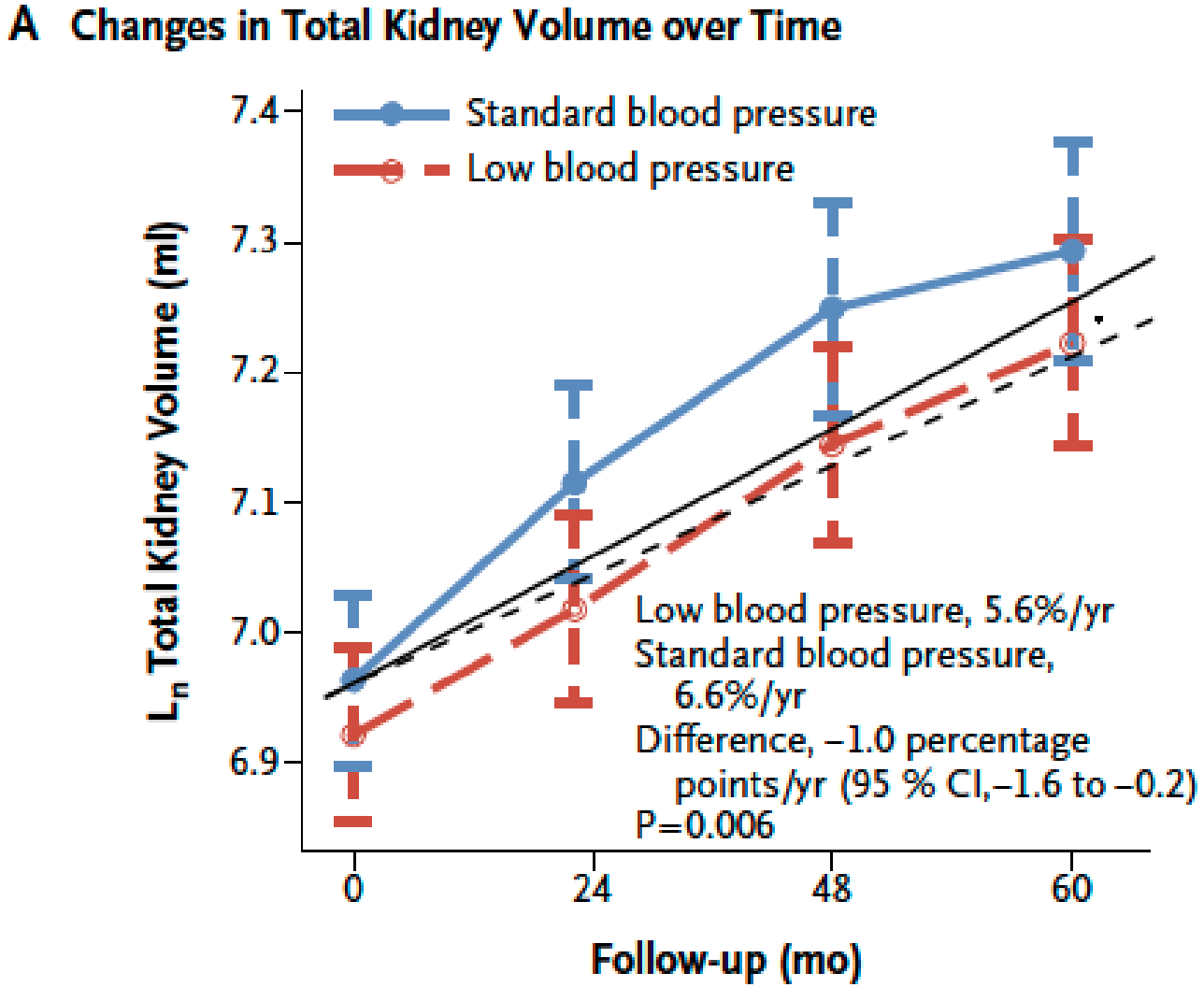
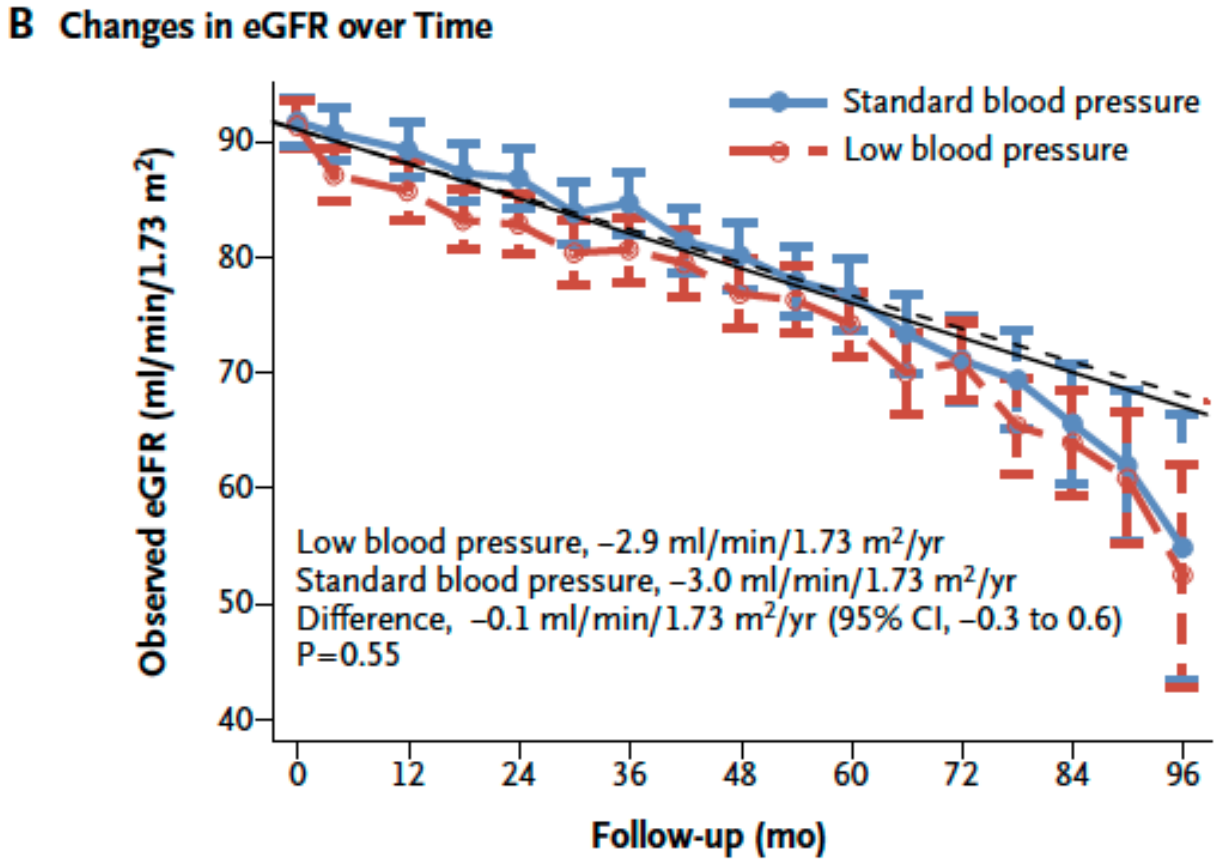
Follow-up, mo

Effect on TKV



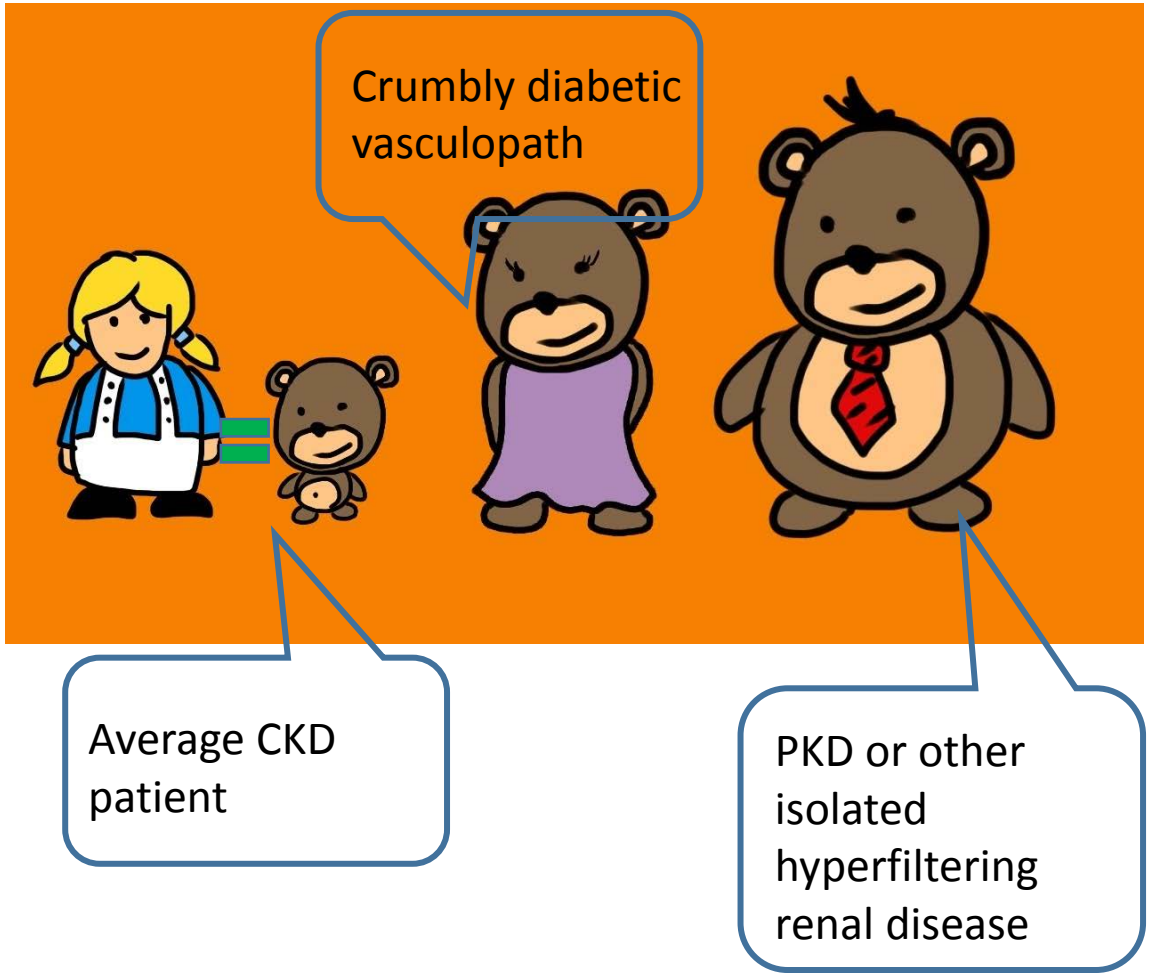
Effect on rate of GFR decline

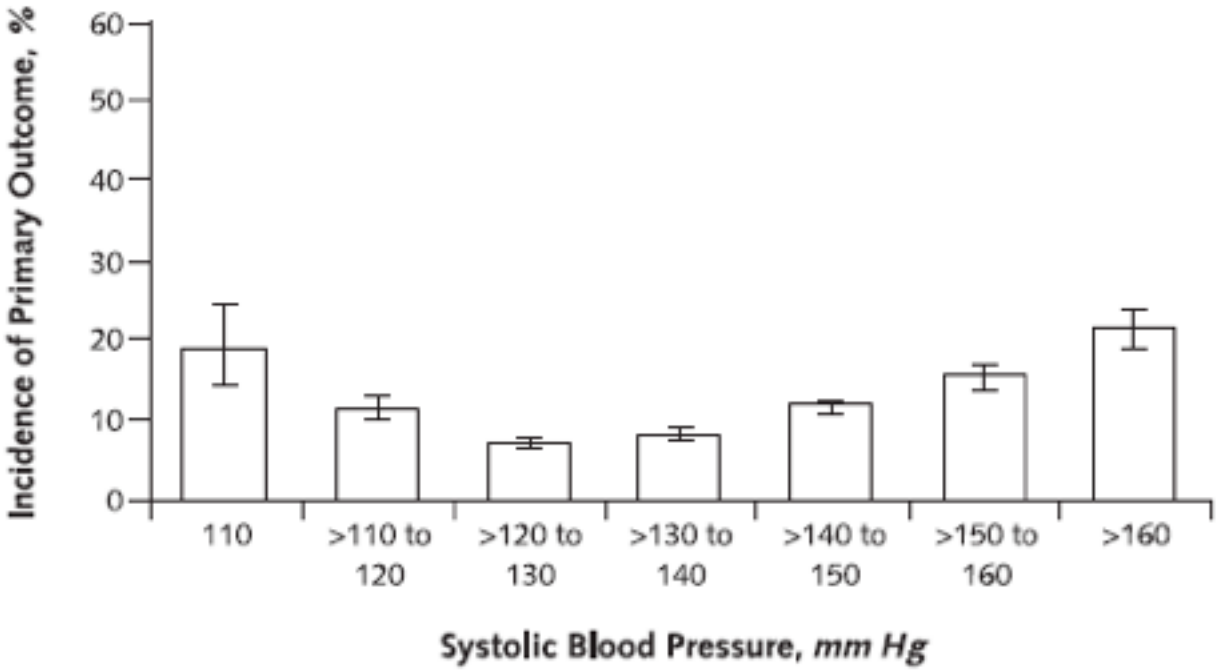


Secondary outcomes

- Albuminuria was reduced by 3.77% in the low target group vs 2.43% in the standard target group ($p<0.001$)
- Dizziness/light-headedness were more common in the low target group [80.7 vs 69.4 ($p=0.02$)]. Despite this, >75% of participants completed the study at their assigned BP target

Opinion: How Goldilocks got misinterpreted

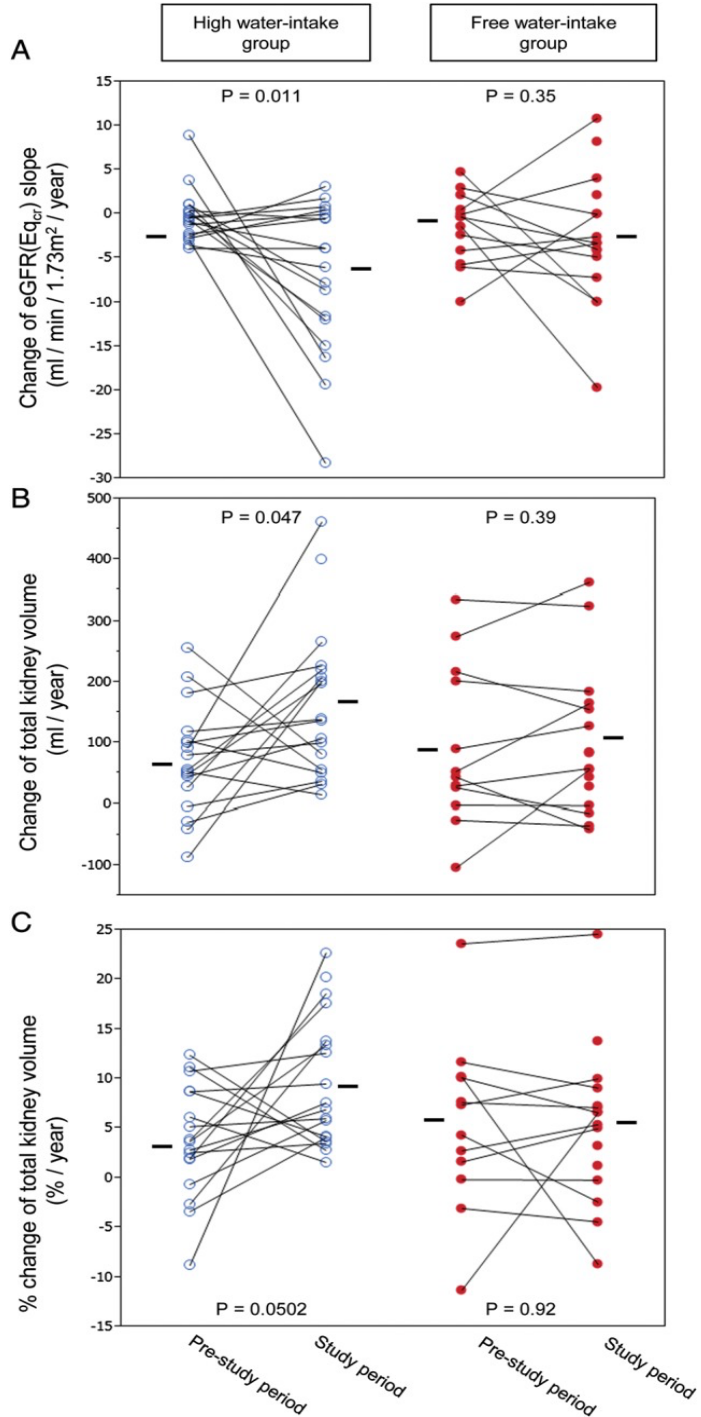




Ann Intern Med. 2006;144:884-893.

Water

- Theoretical basis – inhibition of ADH release and therefore less activity via V2R
- Numerous studies with conflicting results – no demonstrable impact on renal progression
- Low risk treatment, many patients do this as far as tolerated
- Data from tolvaptan studies demonstrate that it is possible to drink enough water to suppress ADH, but it is very difficult and only a minority of patients can do so



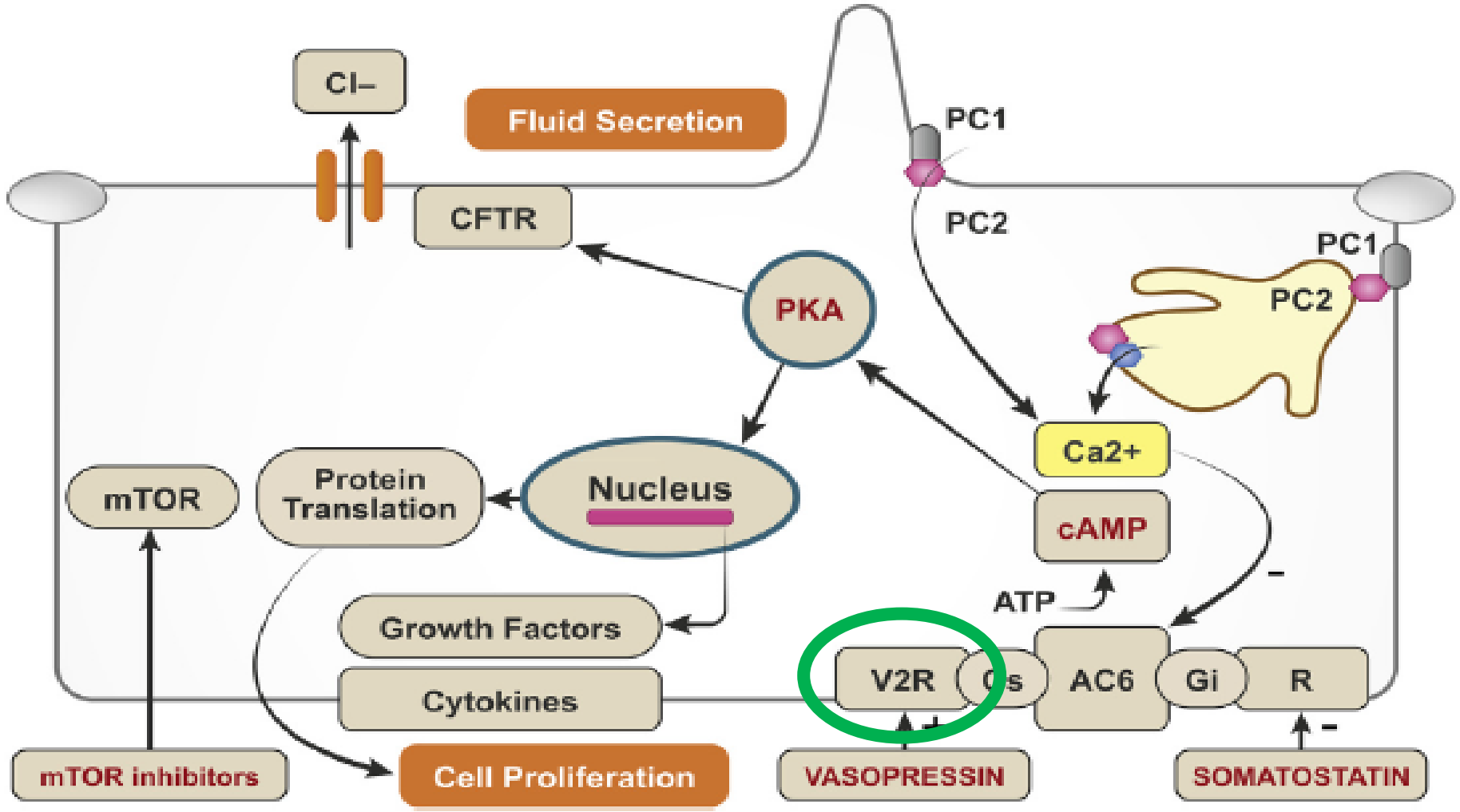
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D.,
Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D.,
Jared J. Grantham, M.D., Eiji Higashihara, M.D., Ph.D., Ronald D. Perrone, M.D.,
Holly B. Krasa, M.S., John Ouyang, Ph.D., and Frank S. Czerwiec, M.D., Ph.D.,
for the TEMPO 3:4 Trial Investigators*

Refresher on ADPKD pathophysiology



TEMPO 3:4 trial

- P: 1445 patients 18-50 years old with ADPKD and TKV >750 ml and GFR > 60ml/min
- I: Tolvaptan; dosed BID, titrated to max tolerated dose with goal 90/30mg
- C: Placebo. High fluid intake and hypertension management with RAS blockade in both groups
- O: Primary outcome was change in TKV. Secondary outcomes included decrease in renal function and pain events
- Study design: Double-blind, placebo controlled RCT

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Tolvaptan (N=961)	Placebo (N=484)
Male sex — no. (%)	495 (51.5)	251 (51.9)
Age — yr	39±7	39±7
Race — no. (%)†		
White	810 (84.3)	408 (84.3)
Asian	121 (12.6)	62 (12.8)
Other	30 (3.1)	14 (2.9)
Stratification factor — no. (%)		
Hypertension	765 (79.6)	382 (78.9)
Estimated creatinine clearance <80 ml/min	242 (25.2)	130 (26.9)
Total kidney volume <1000 ml	197 (20.5)	101 (20.9)
Medical history — no. (%)		
Hematuria	338 (35.2)	164 (33.9)
Kidney pain	496 (51.6)	239 (49.4)
Nephrolithiasis	187 (19.5)	109 (22.5)
Urinary tract infection	290 (30.2)	164 (33.9)
Anemia	105 (10.9)	48 (9.9)
Proteinuria	233 (24.2)	116 (24.0)
Current medication — no. (%)		
Angiotensin-converting–enzyme inhibitor	419 (43.6)	199 (41.1)
Angiotensin-receptor blocker	307 (31.9)	165 (34.1)
Angiotensin-converting–enzyme inhibitor, angiotensin-receptor blocker, or both	683 (71.1)	350 (72.3)
Beta-blocker	171 (17.8)	94 (19.4)
Calcium-channel blocker	180 (18.7)	104 (21.5)
Diuretic	32 (3.3)	14 (2.9)

Table 1. (Continued.)

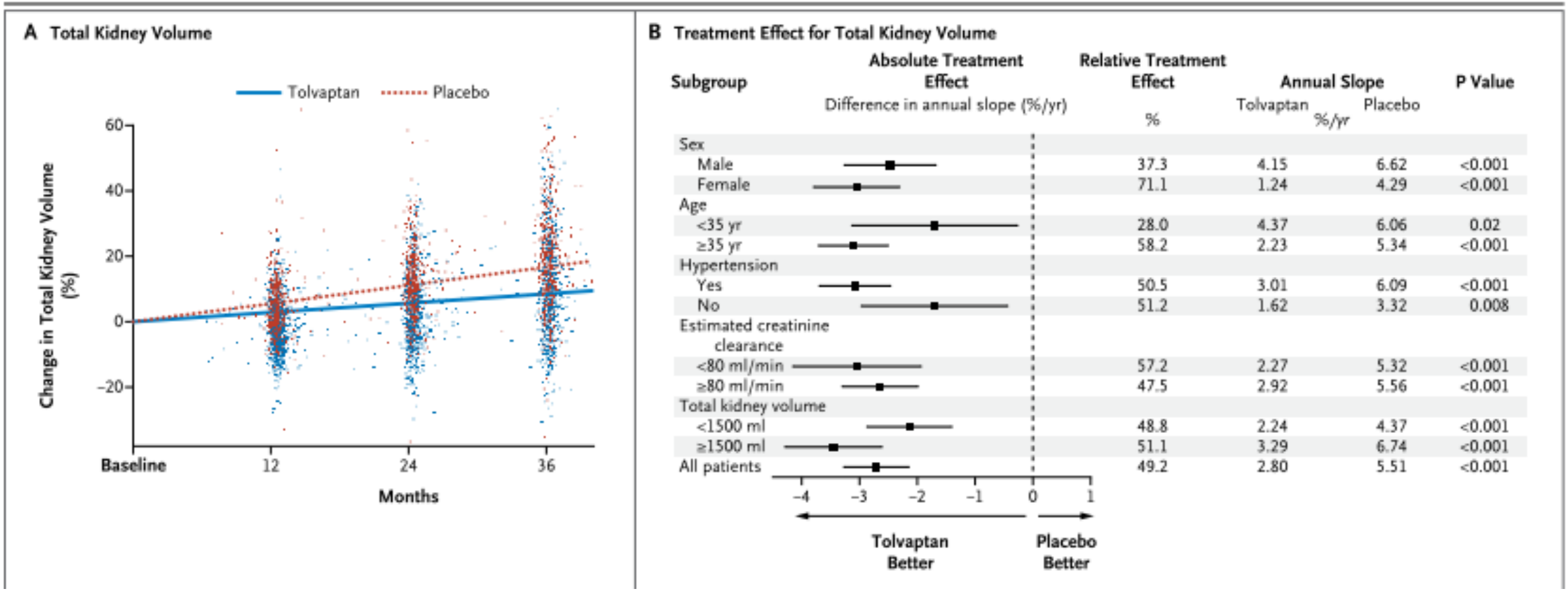
Characteristic	Tolvaptan (N=961)	Placebo (N=484)
Height — cm	173.5±10.4	173.6±7.8
Weight — kg	79±18	79±18
Blood pressure — mm Hg		
Systolic	128.6±13.5	128.3±13.5
Diastolic	82.5±9.9	82.5±9.3
Total kidney volume — ml	1705±921	1668±873
Height-adjusted total kidney volume — ml/m	979±515	958±483
Serum creatinine — mg/dl‡	1.05±0.30	1.04±0.32
Reciprocal of serum creatinine — $(mg/ml)^{-1}$	102.27±27.21	104.30±35.60
Estimated creatinine clearance — ml/min§	104.08±32.76	103.80±35.60
Estimated GFR — ml/min/1.73 m^2¶	81.35±21.02	82.14±22.73
Urinary albumin-to-creatinine ratio	7.2±14.3	8.6±21.7

91umol/l

Young: Age 39

Preserved kidney function: eGFR 81

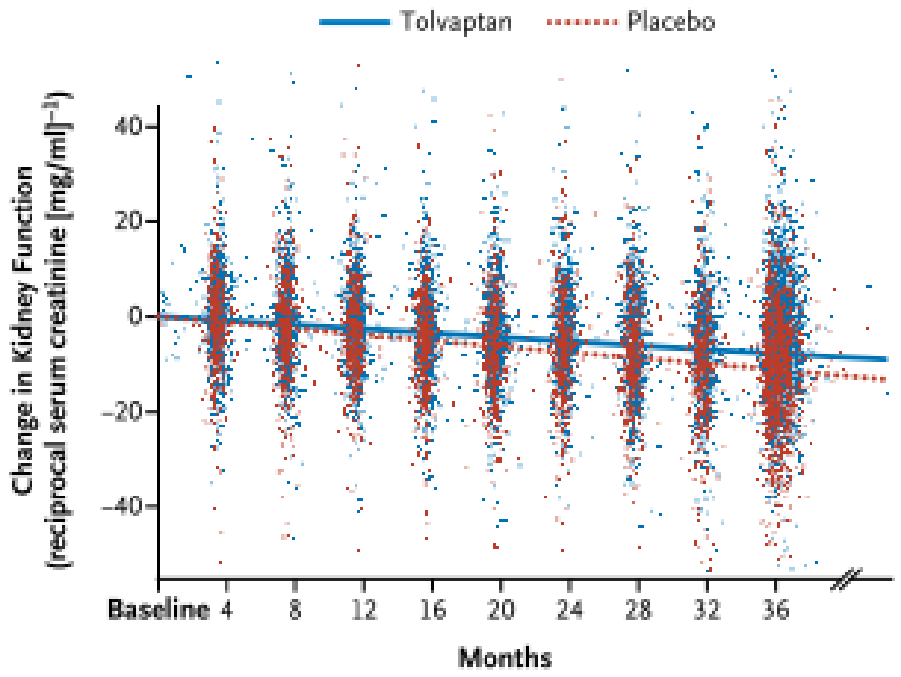
Rapid progressing disease: Big kidneys at a young age



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

- Increase in TKV was 2.8%/year(2.3-3.1%) in the tolvaptan group vs. 5.5%/year (5.1-6.0%) in the placebo group

C Kidney Function



D Treatment Effect for Kidney Function

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

- Slope of reciprocal of creatinine (which varies directly with GFR) was-2.61/year compared to -3.81/year in the placebo group. This corresponds to a GFR slope of -2.72ml/min/year vs. -3.70ml/min/year

Table 2. Most Common Adverse Events and Serious Adverse Events.*

Event	Tolvaptan (N=961)	Placebo (N=483)
	no. of patients with event (%)	
Adverse events more common in tolvaptan group		
Thirst	531 (55.3)†	99 (20.5)
Polyuria	368 (38.3)†	83 (17.2)
Nocturia	280 (29.1)†	63 (13.0)
Headache	240 (25.0)	120 (24.8)
Pollakiuria‡	223 (23.2)†	26 (5.4)
Dry mouth	154 (16.0)	59 (12.2)
Diarrhea	128 (13.3)	53 (11.0)
Fatigue	131 (13.6)	47 (9.7)
Dizziness	109 (11.3)	42 (8.7)
Polydipsia	100 (10.4)†	17 (3.5)
Adverse events more common in placebo group		
Hypertension	309 (32.2)	174 (36.0)
Renal pain	259 (27.0)§	169 (35.0)
Nasopharyngitis	210 (21.9)	111 (23.0)
Back pain	132 (13.7)	88 (18.2)
Increased creatinine level	135 (14.0)	71 (14.7)
Hematuria	75 (7.8)†	68 (14.1)
Urinary tract infection	80 (8.3)§	61 (12.6)
Nausea	98 (10.2)	57 (11.8)
Serious adverse events more common in tolvaptan group		
Alanine aminotransferase elevation	9 (0.9)	2 (0.4)
Aspartate aminotransferase elevation	9 (0.9)	2 (0.4)
Chest pain	8 (0.8)	2 (0.4)
Headache	5 (0.5)	0
Serious adverse events more common in placebo group		
Pyelonephritis	5 (0.5)	5 (1.0)
Renal-cyst infection	6 (0.6)	4 (0.8)
Renal-cyst hemorrhage	3 (0.3)	4 (0.8)
Renal pain	1 (0.1)	4 (0.8)
Appendicitis	1 (0.1)	4 (0.8)
Nephrolithiasis	2 (0.2)	3 (0.6)
Urinary tract infection	1 (0.1)	3 (0.6)
Hypertension	1 (0.1)	3 (0.6)

- 23% vs. 13.8% in the placebo group discontinued the drug
- 8.3% of all tolvaptan patients discontinued due to aquaretic symptoms
- 1.3% of patients in the tolvaptan group discontinued the drug due to liver enzyme abnormalities

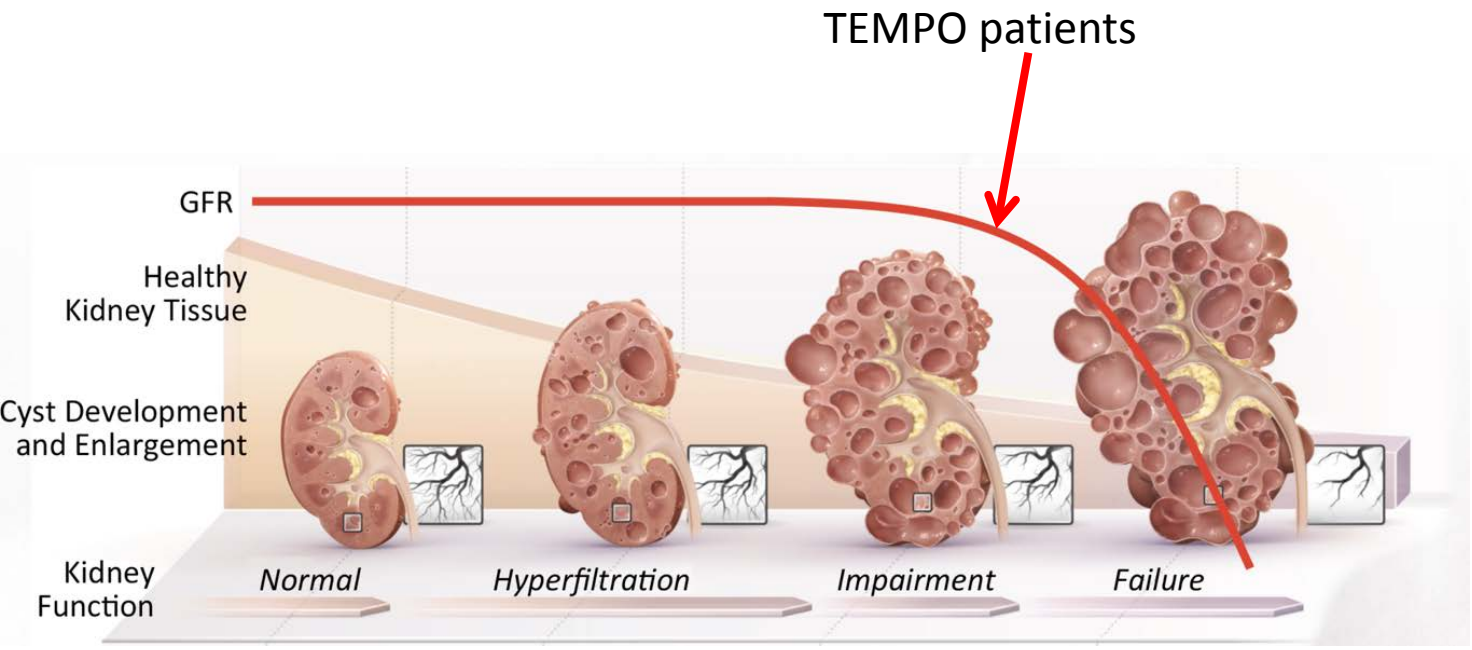
HyperNa 2.8% vs. 1.0% (NS)

Adverse effects – increased transaminases

- Overall, 4.9% with tolvaptan vs. 1.2% in the placebo group had abnormal liver enzymes
- 2 patients (0.02%) in the tolvaptan arm had AST/ALT >3xULN *and* bilirubin >2xULN. This pharmacologic entity is a specific type of drug induced liver damage deemed 'Hy's Law' and carries an approximate 10% mortality
  - The two patients that met this criteria had their liver injury occur at 4 and 5 months of treatment. The first had complete recovery at 3 months, the second had mild persistent increase in transaminases
- To compare to other drugs associated with AST/ALT increases:
  - INH: up to 20%
  - MTX: 15%
  - Amiodarone: 3-6%
  - Lipitor: <2%

As a result there is Health Canada mandated hepatic monitoring when using tolvaptan ('Blood for drug')

Applicability of findings to other ADPKD patients



Variable	TEMPO inclusion criteria	Actual mean values of pts entered
Age	18-50	39
GFR	>60ml/min, randomization stratified to >80 or <80	81ml/min. ~25% < 80ml/min, remainder >80ml/min
TKV	>750 ml	~1700ml
BP	Not a criterion, randomization stratified to present or absent	128/82. Hypertension present in ~80% of patients, ~72% on RAAS blockade
Proteinuria	Not a criterion	7-8mg/mmol

- TEMPO 3:4 enrolled a very specific group of ADPKD patients in that they had relatively preserved (but not normal) renal function and massive kidneys at about age 40; in other words they were at high risk of declining rapidly
- The fact that the placebo arm had a -3.7ml/min/year GFR slope reinforces this
- There are ongoing trials on these patients as well as patients with lower GFR

Identifying candidates for tolvaptan

- Essentially the current data points to efficacy in patients who are rapidly progressing but still early in their disease course
- This indication may change when more data is published
- Canadian guidelines for treatment will be published later this year
- Early prognostication of all PKD patients is critical to help identify the rapidly progressing patients who will be candidates for this, and any other treatments that emerge
  - The future will likely be multi-targeted treatment of PKD, directed at rapid progressors, early in their disease course
  - In the pipeline: mTOR inhibitors, SS analogues, TZDs, metformin, statins

Delaying renal progression in PKD

- A stricter blood pressure target may help slow progression of PKD
- Not all patients can tolerate such low blood pressure, but the young, early stage PKD patients here tolerated it quite well
  - I would attempt aggressive target in most PKD patients, especially with preserved GFR
  - If they do not tolerate the low target, back off
- High fluid intake may have some benefit and is fairly benign
- Tolvaptan (and other disease modifying treatments) is likely to be most effective in those with preserved renal function but rapidly progressing disease

Extra-renal manifestations of PKD

Extra-renal manifestations of PKD

KIDNEY-RELATED

Pain and discomfort

Kidney stones

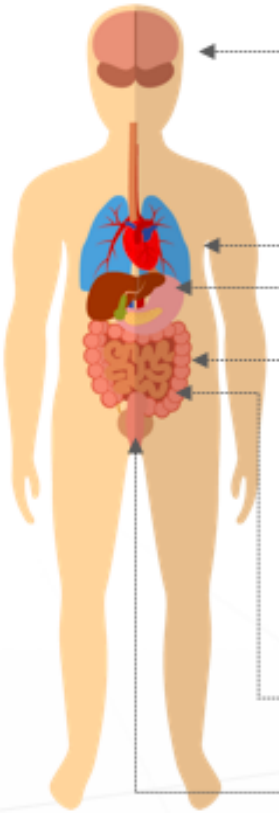
Cyst bleeds

Infected cysts

High blood pressure

Blood in urine

Worsening kidney function / kidney failure



NON-KIDNEY-RELATED

Brain aneurysm*

Cardiovascular*
(e.g., heart valve problems)

Liver cysts

Hernias of the abdomen

Diverticulosis*
(outpouchings of the large intestine)

Seminal vesicle cysts

Not everybody with ADPKD will experience all of these complications

*Less frequent

ADPKD: Autosomal Dominant Polycystic Kidney Disease
Adapted from www.endpkd.ca; and Harris PC, et al. Gene Reviews, last updated June 11, 2015.

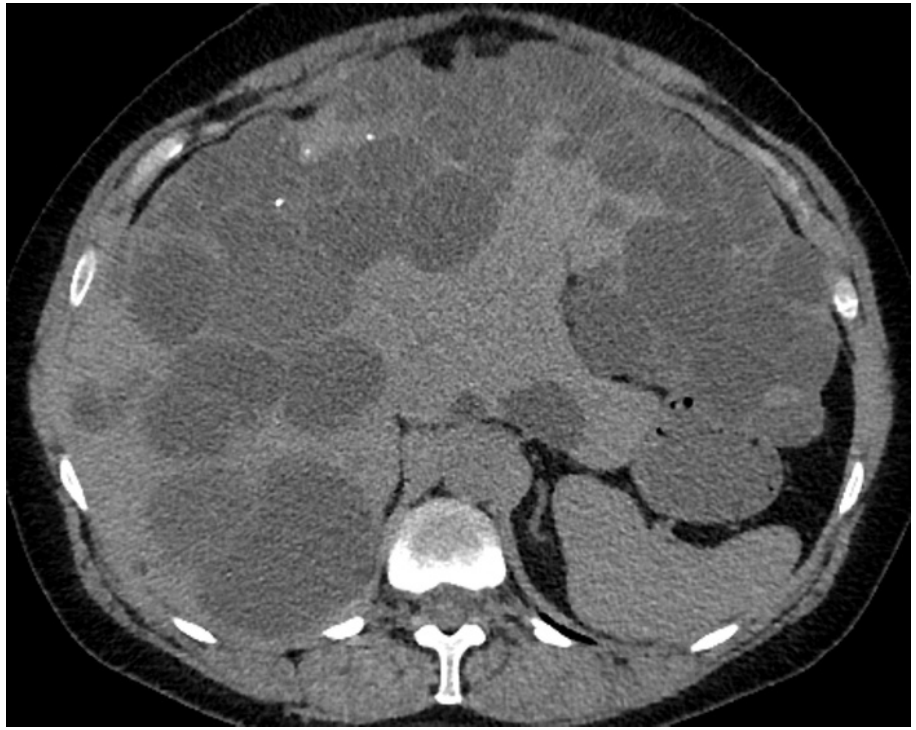
Intracranial aneurysms

- Occur in ~10% of PKD compared to ~2-3% in general population
- The only clear risk factor is a family history of ICA rupture
- Role of screening unclear
  - Mostly small ICA, unclear significance
  - Repair risky
- Screening recommended for those with:
  - Prior ICA rupture, family Hx, high risk profession, **patient anxiety**
- If doing screening and monitoring (MRA or CTA)
  - Repeat q6–24 months if positive
  - Repeat q5-10 years if negative

Opinion for those with ICAs, this is another reason for aggressive BP control

Liver involvement in PKD

- Liver cysts occur in >80% of PKD patients
- Most are asymptomatic; ~20% have abdominal symptoms
- Impact on liver function is rare, but occurs
- Estrogen is a risk factor – more common in women, avoid HRT
- The renal treatments we will discuss do not impact liver cysts
  - Somatostatin analogues are being studied



Summary

- There is substantial disease progression including symptoms and impact on patients that occur before you see any change in GFR
- There are imaging based tools available to help predict patient's disease course in PKD
  - PKD patients should all have at least one assessment of renal size
- There is good data for a lower blood pressure target in PKD
  - This is a good time to review blood pressure control in your PKD patients
- Tolvaptan can be considered in patients with rapidly enlarging kidneys but preserved GFR

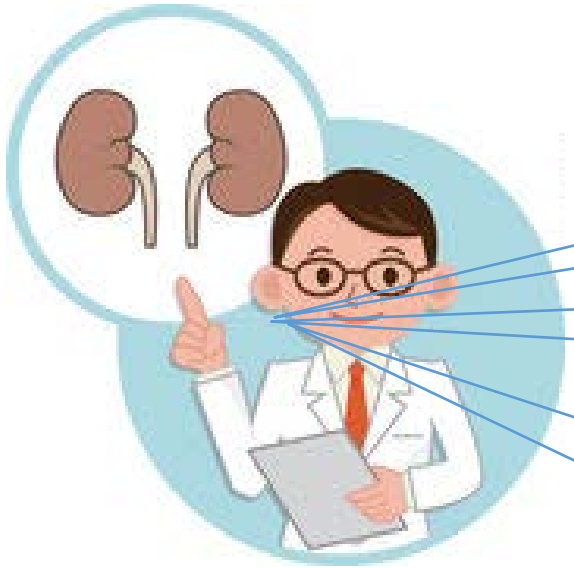
Summary

Early assessment of PKD patients and identification of rapid progressors is the cornerstone of modern PKD management

- Please consider early nephrology referral for all your PKD patients, at least for an initial assessment

- Remember to ask about affected family members and any screening

What we have done with PKD in the past

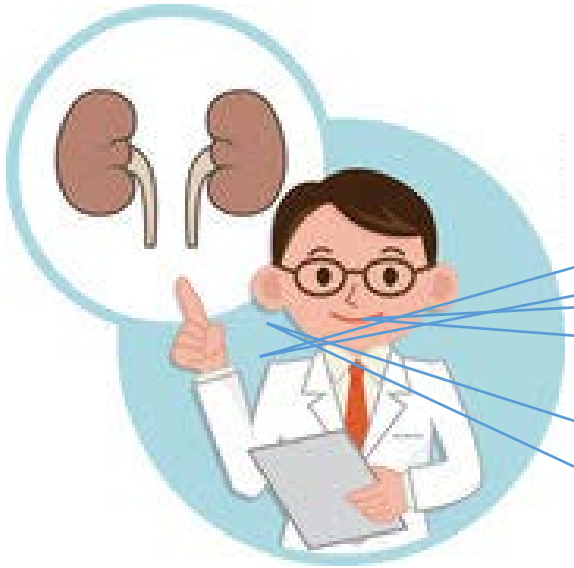


Let’s confirm the diagnosis and then we will tell you about screening your family members

Drink lots of water, keep your BP in the normal range and do your bloodwork. See you in 6-12 months.

When your GFR drops, we’ll start talking about transplant and dialysis

What we should aim for now



Tell us what your family screening, reproductive, financial, symptom and renal failure concerns are and we will discuss those

We will use imaging and other tools to more accurately predict your renal progression as early as possible

We will discuss treatments like BP and water that apply to everyone with PKD and will assess whether you are a candidate for disease specific treatments

Questions?

Thank you for attending this talk and for your interest!

If any questions arise, feel free to contact me at:

Mike.bevilacqua@bcpra.ca