Modern Management of Autosomal Dominant Polycystic Kidney Disease

Advances in care and Developing a Common Approach to a Rare Disease

Micheli Bevilacqua, MD, FRCPC, MHA, CHE
Fraser Health Division of Nephrology
Chair, BC Renal Kidney Care Committee
BC Renal PKD Network Medical Lead
Clinical Assistant Professor, UBC Division of Nephrology

Outline

- Epidemiology, natural history of ADPKD
- Predicting individual renal prognosis in ADPKD
  - Imaging based prognostication
- Treatments to delay renal progression in ADPKD
- BC Experience with a provincial ADPKD Network
  - Developing a shared approach to a (relatively) rare disease

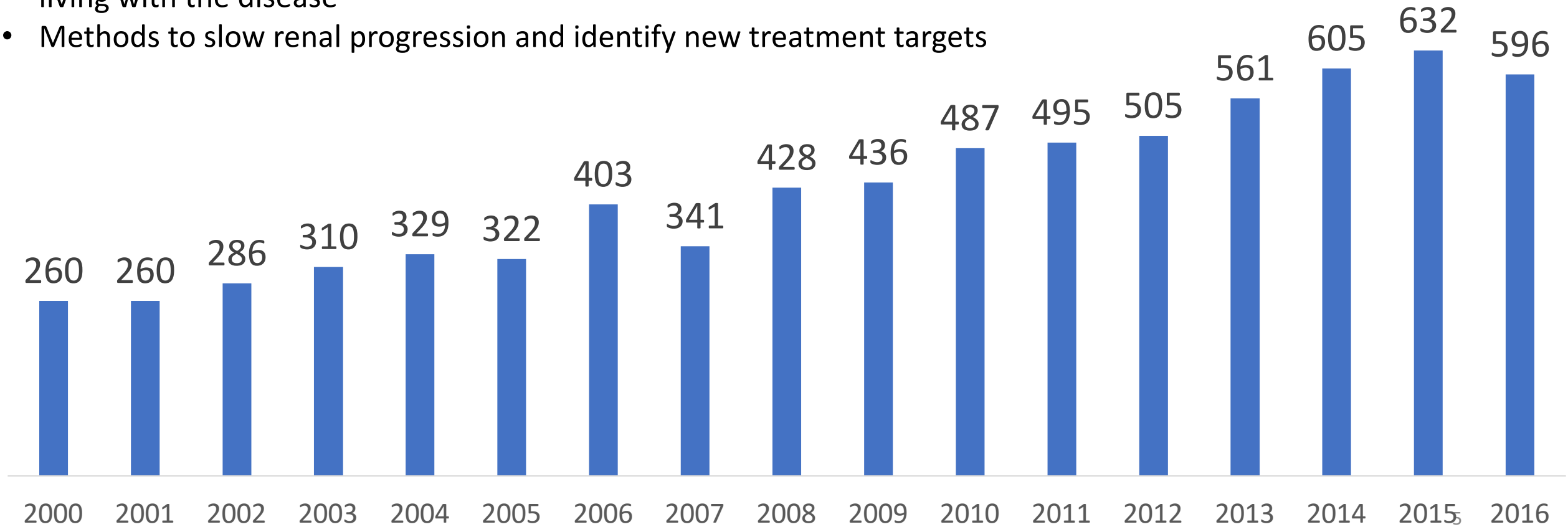
Disclosures

- I disclose the following:
  - Otsuka Pharmaceuticals Canada (advisory fees and grants)
    - Who manufacture the vasopressin antagonist tolvaptan
  - Sanofi Canada (advisory fees)

Epidemiology and Natural History of PKD

This is an exciting time in PKD research!

- Better understanding of the disease
- Better understanding of the course experienced by individual people living with the disease
- Methods to slow renal progression and identify new treatment targets



Epidemiology

- Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder, affecting between 1-2.5/1000 live births
  - ~4500 to over 10000 British Columbians living with the disease.

- There is no racial predilection; it affects all groups equally
  - The genes (esp. PKD1) are prone to mutation

- Of patients with an identifiable etiology of ESRD, ADPKD is the 4th leading cause of ESRD in Canada, comprises ~10% of the patient we see

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 fairly good *if big enough*, 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

Differential diagnosis of multiple renal cysts

Table 2 | Differential diagnosis of other renal cystic diseases

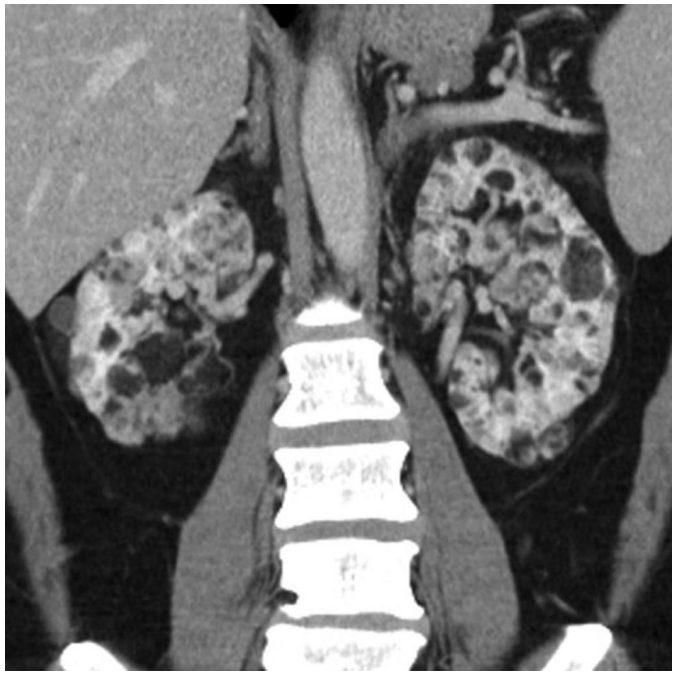
Disorder	Inheritance	Family history	Clinical features
Autosomal-recessive polycystic kidney disease	AR	Siblings (25%)	~1 in 20,000. Neonatal deaths in 30%; Potter's phenotype; biliary dysgenesis (congenital hepatic fibrosis, intrahepatic bile duct dilatation), resulting in portal hypertension and cholangitis.
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*.

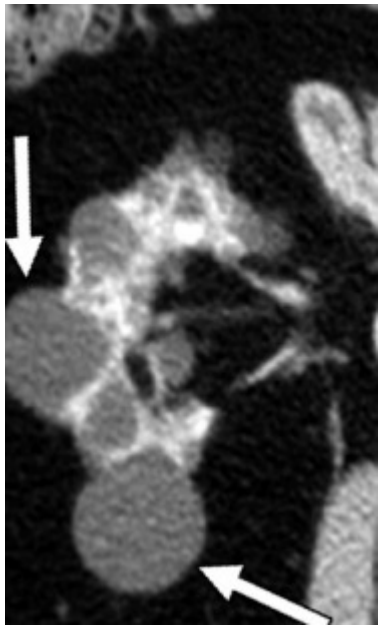
These can often be differentiated via imaging

ADPKD = diffuse bilateral cystic involvement AND leads to renal enlargement

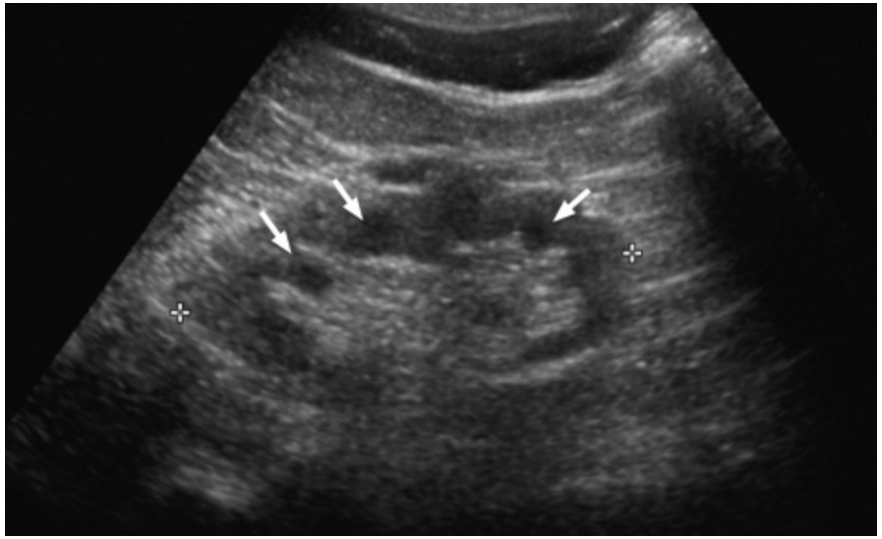
Chapman et al, 2015



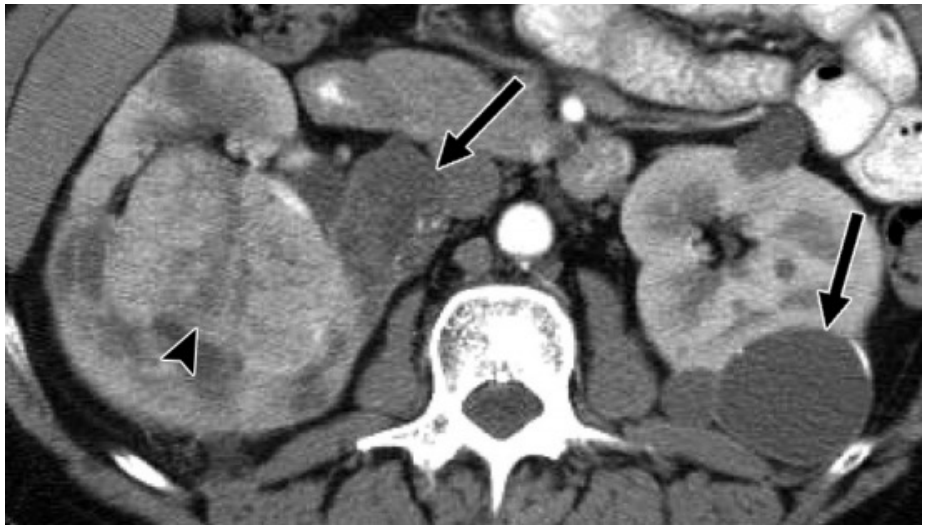
TSC: cysts + AMLs



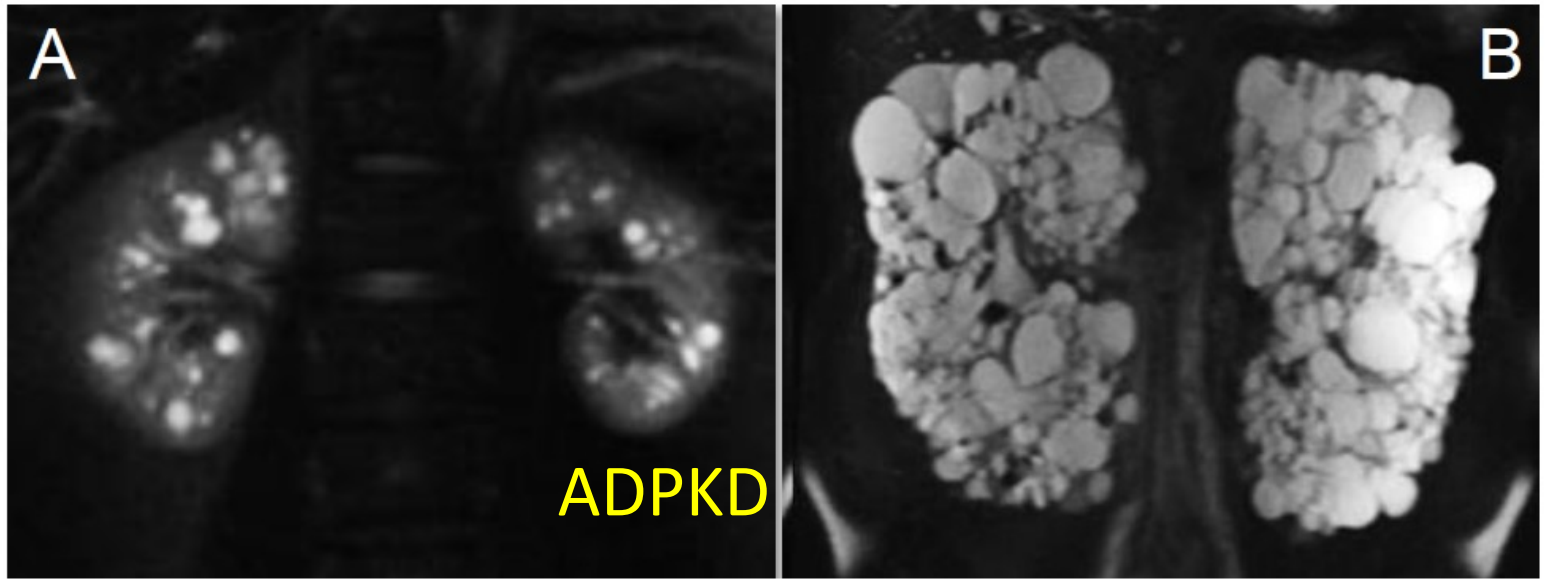
Acquired multicystic disease



Medullary cystic dz's



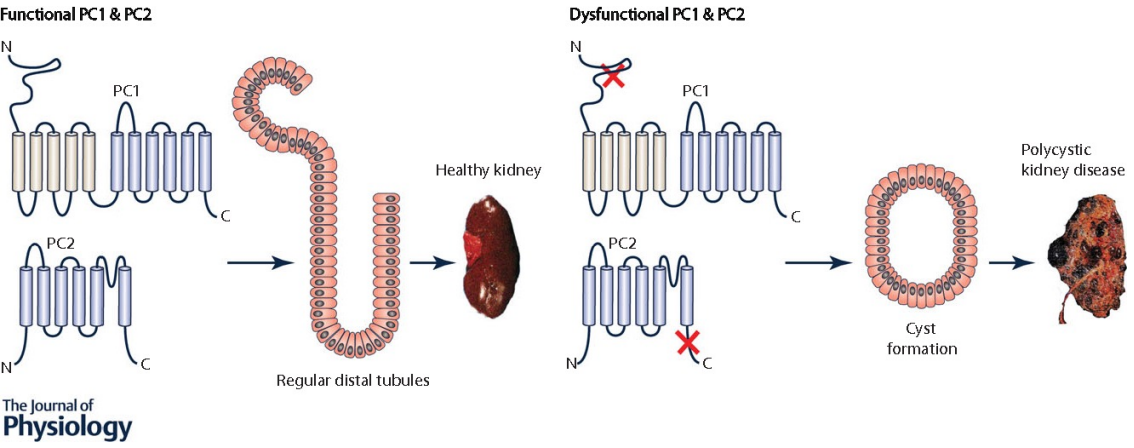
VHL: cyst +RCC

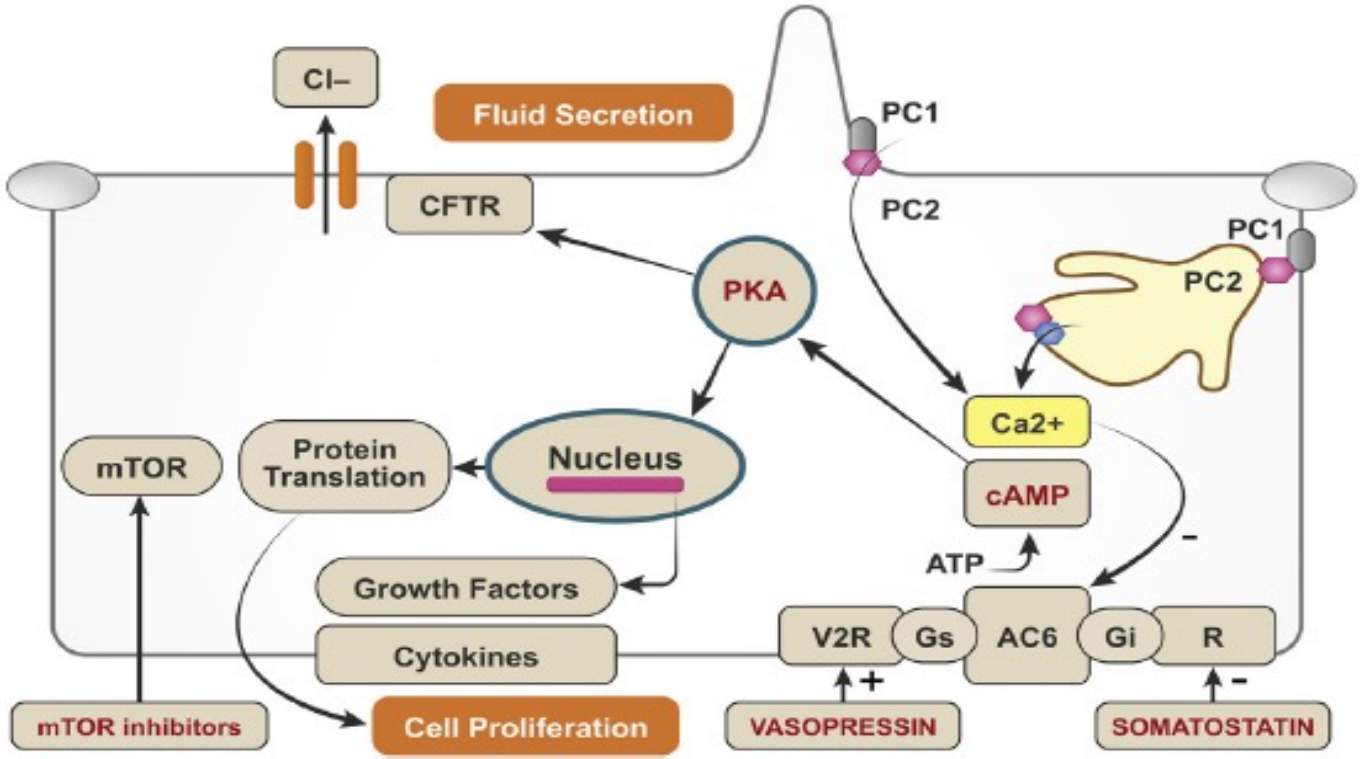


Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 877

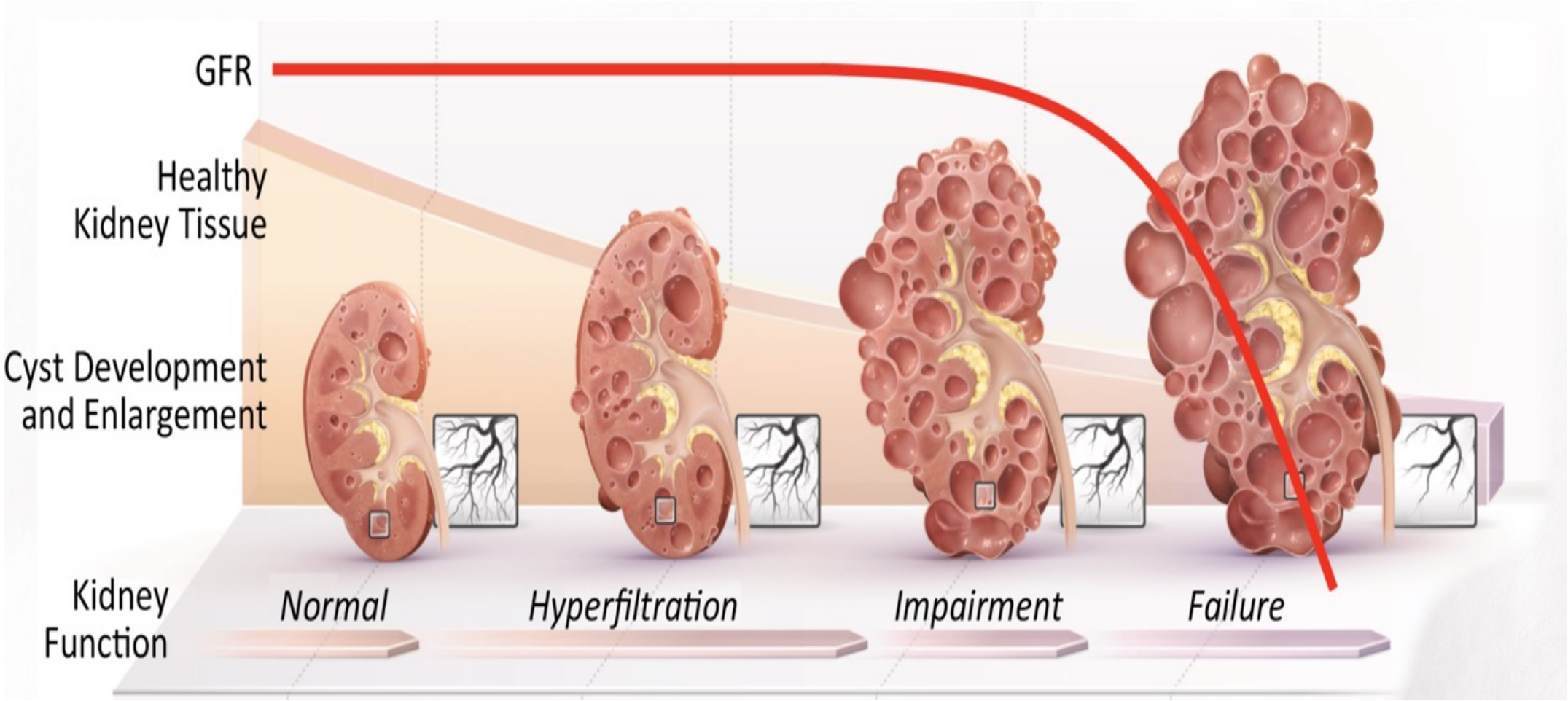
Katabathina VS, Kota G, Dasyam AK, Shanbhogue AKP, Prasad SR. Adult Renal Cystic Disease: A Genetic, Biological, and Developmental Primer. RadioGraphics. 2010 Oct;30(6):1509–23.

ADPKD pathophysiology: more complicated than previously recognized





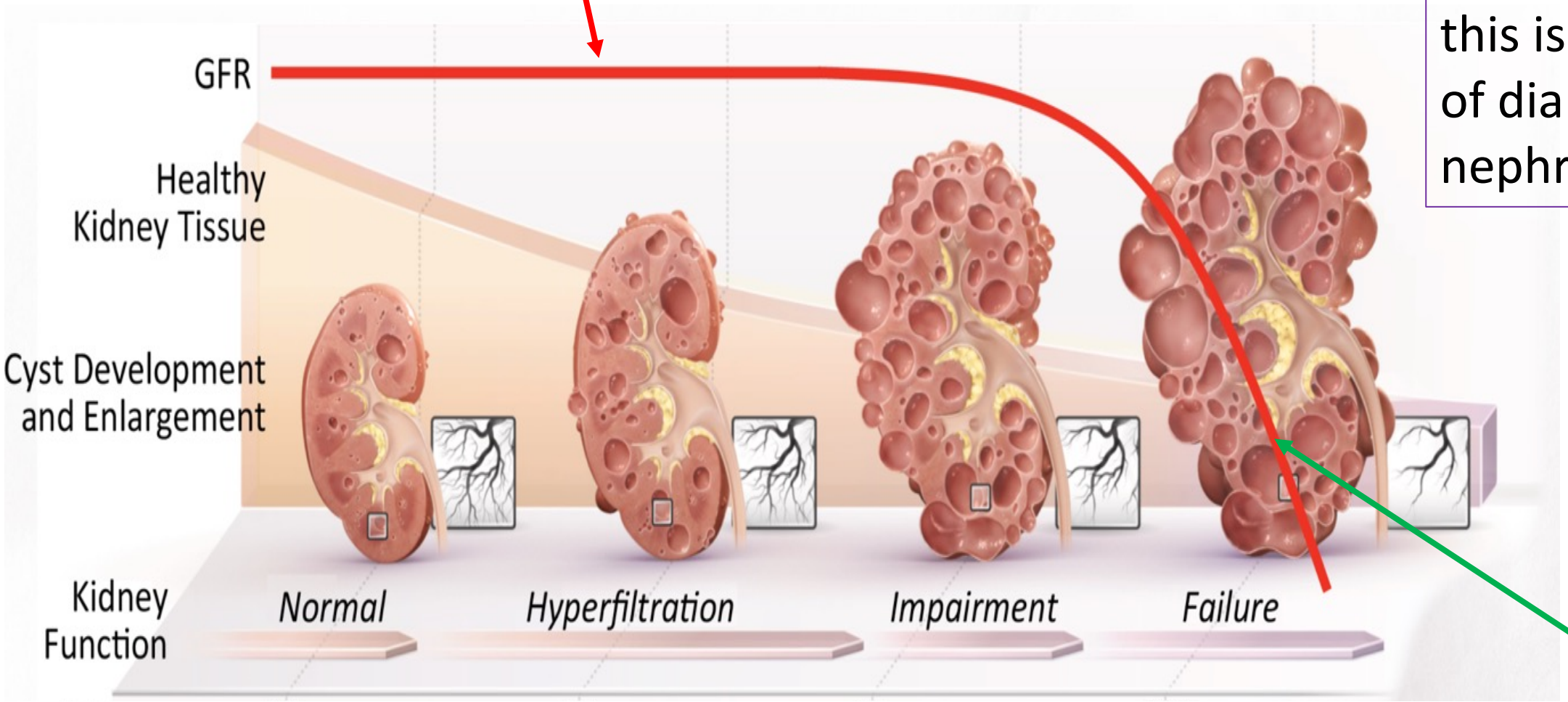
Modern understanding of ADPKD natural history



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

Maintained GFR in the setting of renal parenchymal loss = hyperfiltration

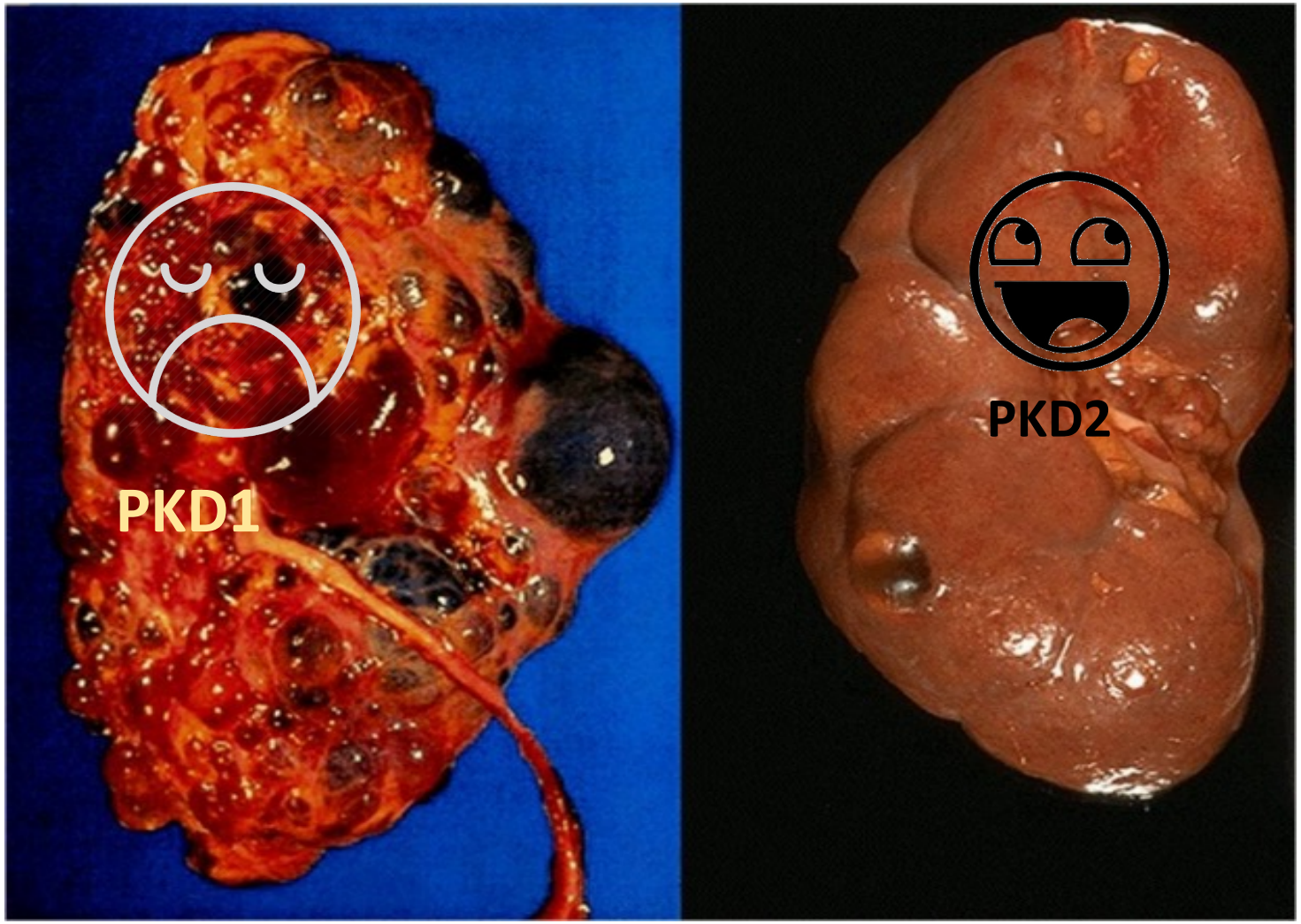
A good way to conceptualize this is to think of diabetic nephropathy



Upwards of 5-6ml/year decline

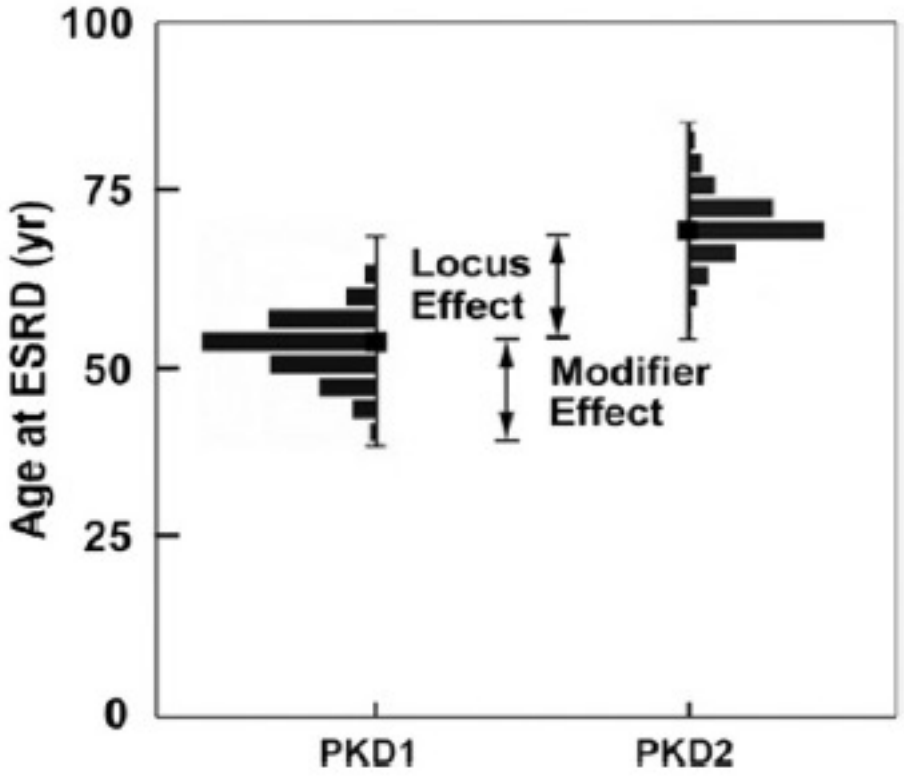
The disease course is variable one, with the early disease marked by cyst proliferation and expansion with little renal dysfunction followed by a precipitous decline. The corollary here is that by the time there is a change in GFR, significant cyst expansion and proliferation has already occurred

Genetics in PKD: Traditional understanding



It is more complicated than 1 vs 2…

Substantial variability



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

<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

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

Take home points: Natural history

- Imaging based diagnosis of PKD is age dependent
- There is a list of differential diagnoses for bilateral renal cystic disease
- 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 individual patients that limits clinical utility

Predicting renal prognosis in ADPKD

Conventional predictors of progression in PKD

Table 2. Univariate Cox analysis

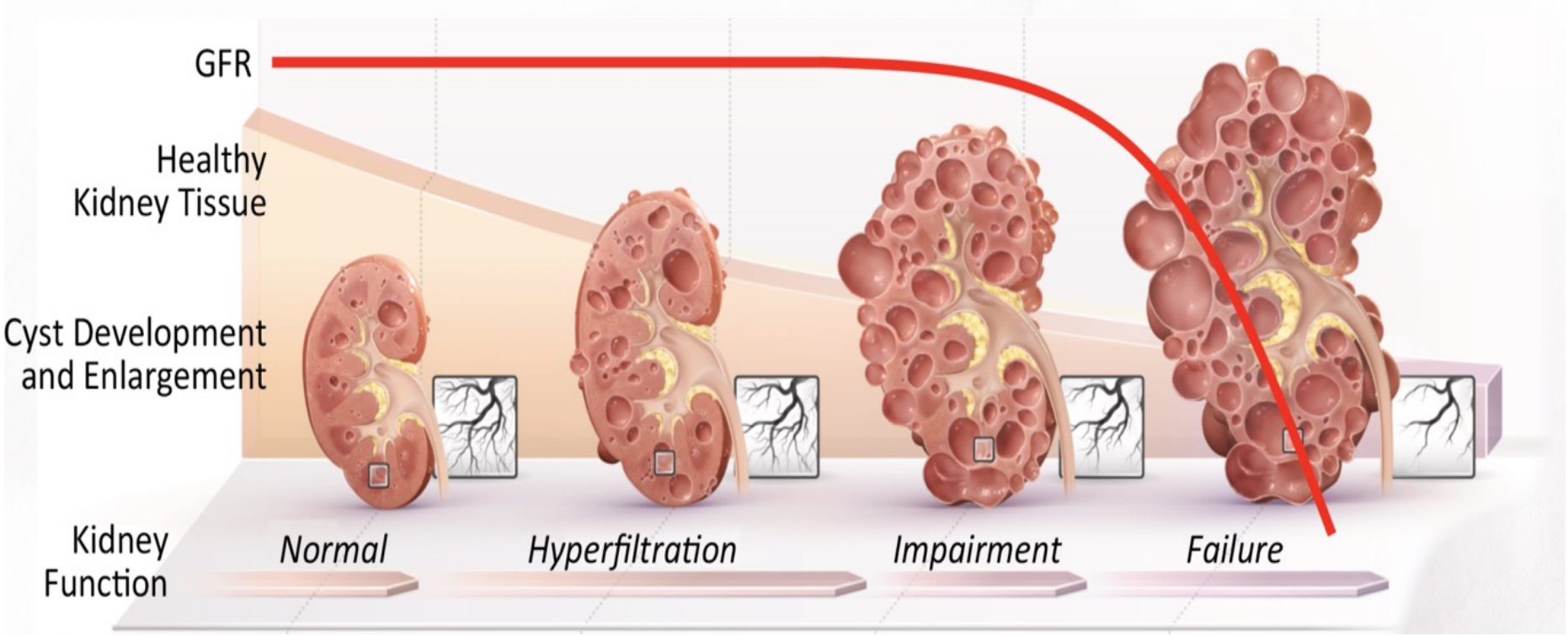
Variable	Patients (*n*)	Univariate HR (95% CI)	*P* Value
Sex			
Female	732		
Male	609	1.3 (1.0 to 1.4)	0.017
Hypertension before age 35 yr			
No	788		
Yes	357	3.1 (2.6 to 3.8)	<0.001
Macroscopic hematuria before age 35 yr			
No	964		
Yes	150	2.9 (2.2 to 3.7)	<0.001
Cyst infection before age 35 yr			
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

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

HR's for risk of ESRD at 60yrs

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

Kidney size/Total kidney volume (TKV)



This is a dynamic marker of the individual's specific PKD phenotype

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

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.

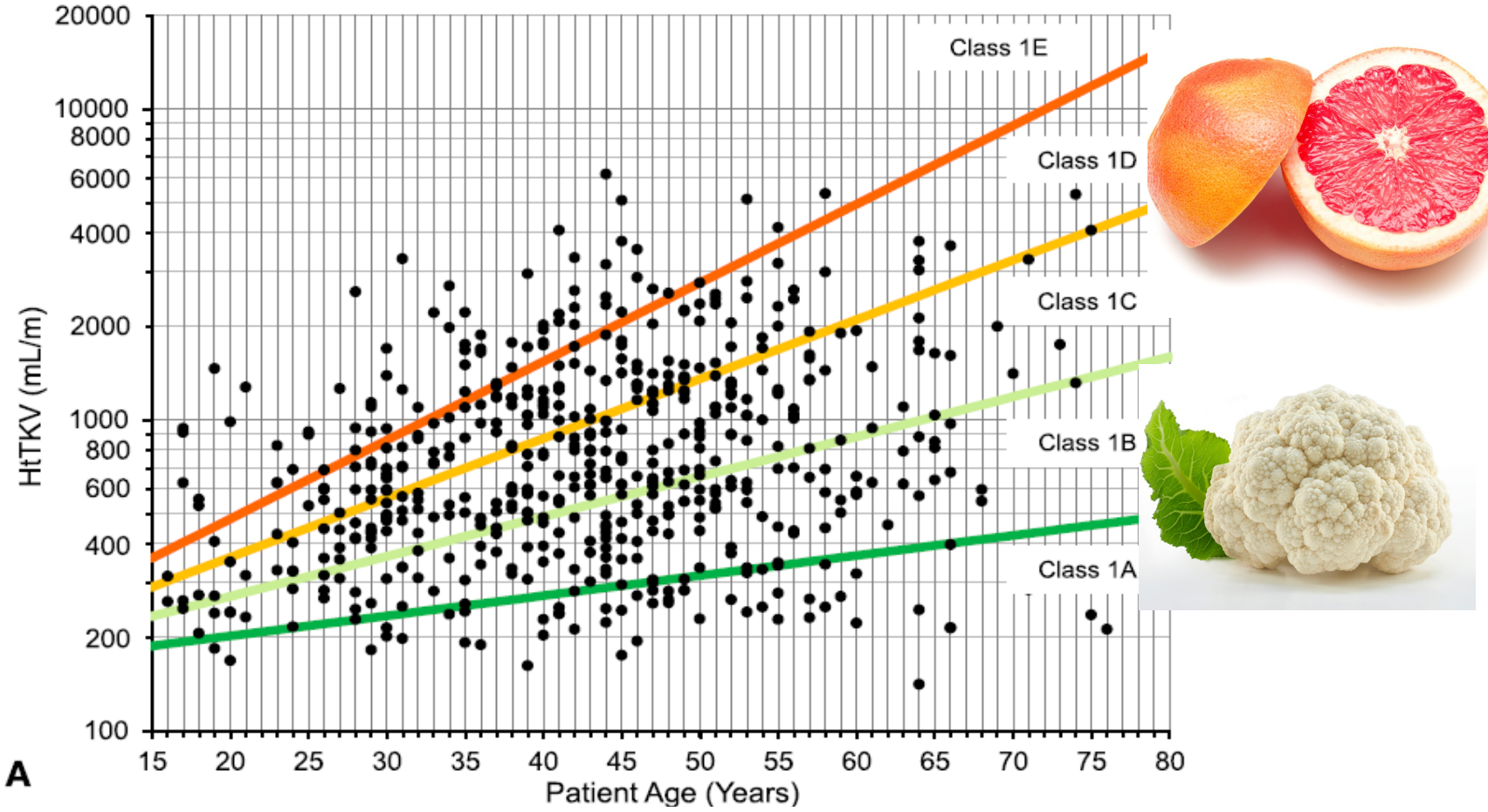
- In this study of the CRISP cohort, total kidney Volume (TKV) at baseline was found to be a better predictor of risk of GFR <60 over 8 years of follow-up than baseline age, baseline renal function or proteinuria

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.

TKV Mayo classification
Categorizing 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%



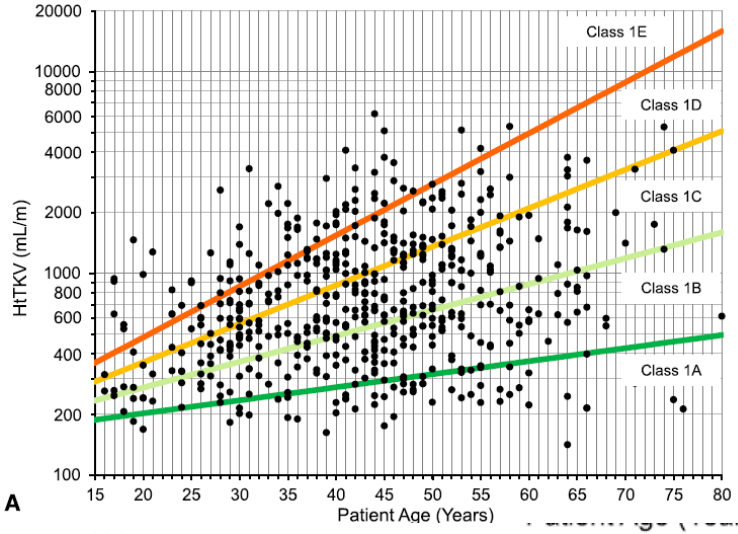
The 1A-1E classification is best thought of as a ***velocity of growth classification*** – the classes refer to the average annual growth in htTKV

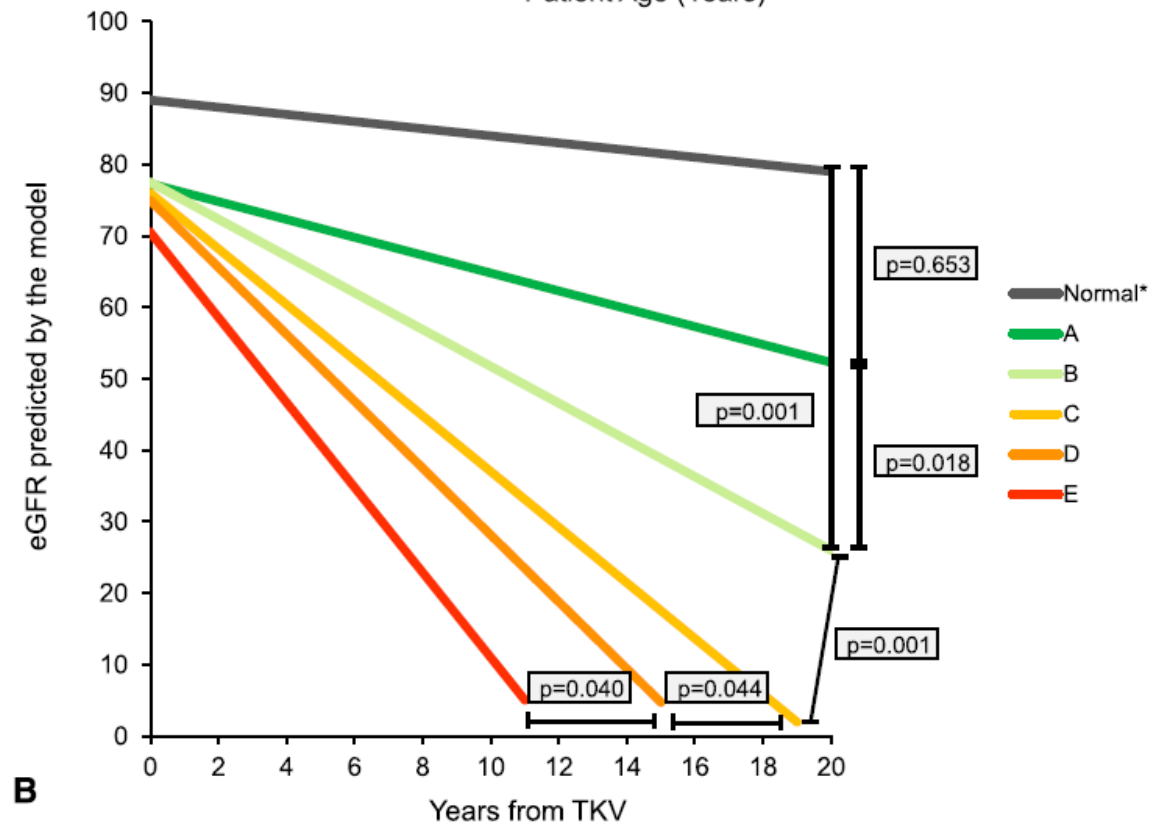
J Am Soc Nephrol 26: 160–172, 2015.

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



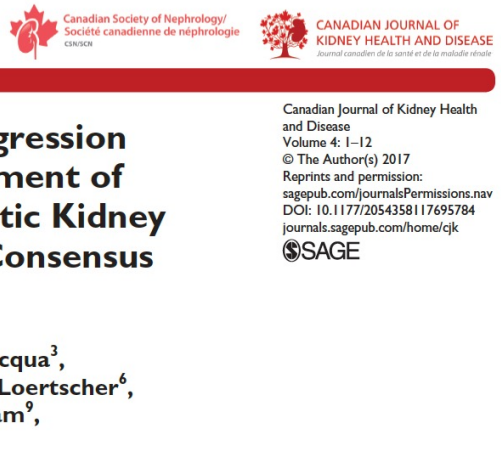


J Am Soc Nephrol 26: 160–172, 2015.

Insights from the Canadian Consensus Document

2.1. We recommend that a baseline assessment of renal size be undertaken in patients with ADPKD.

- This information will help provide individual prognostication
  - Determine the subset of ‘rapid progressors’ versus those with a more favorable renal prognosis
- This information will be key in treatment decisions


Canadian Society of Nephrology/ Société canadienne de néphrologie
CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE
Original Research Article
Canadian Journal of Kidney Health and Disease
Volume 4: 1–12
© The Author(s) 2017
Reprints and permission: sagepub.com/journalsPermissions.nav
DOI: 10.1177/2054358117695784
journals.sagepub.com/home/cjk
SAGE

Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease: A Canadian Expert Consensus

Steven Soroka[1], Ahsan Alam[2], Micheli Bevilacqua[3], Louis-Philippe Girard[4], Paul Komenda[5], Rolf Loertscher[6], Philip McFarlane[7], Sanjaya Pandeya[8], Paul Tam[9], and Daniel G. Bichet[10]

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 (i.e., before there is GFR loss)

- Providing patients with an individualized prognostication of their renal disease in PKD is now standard of care

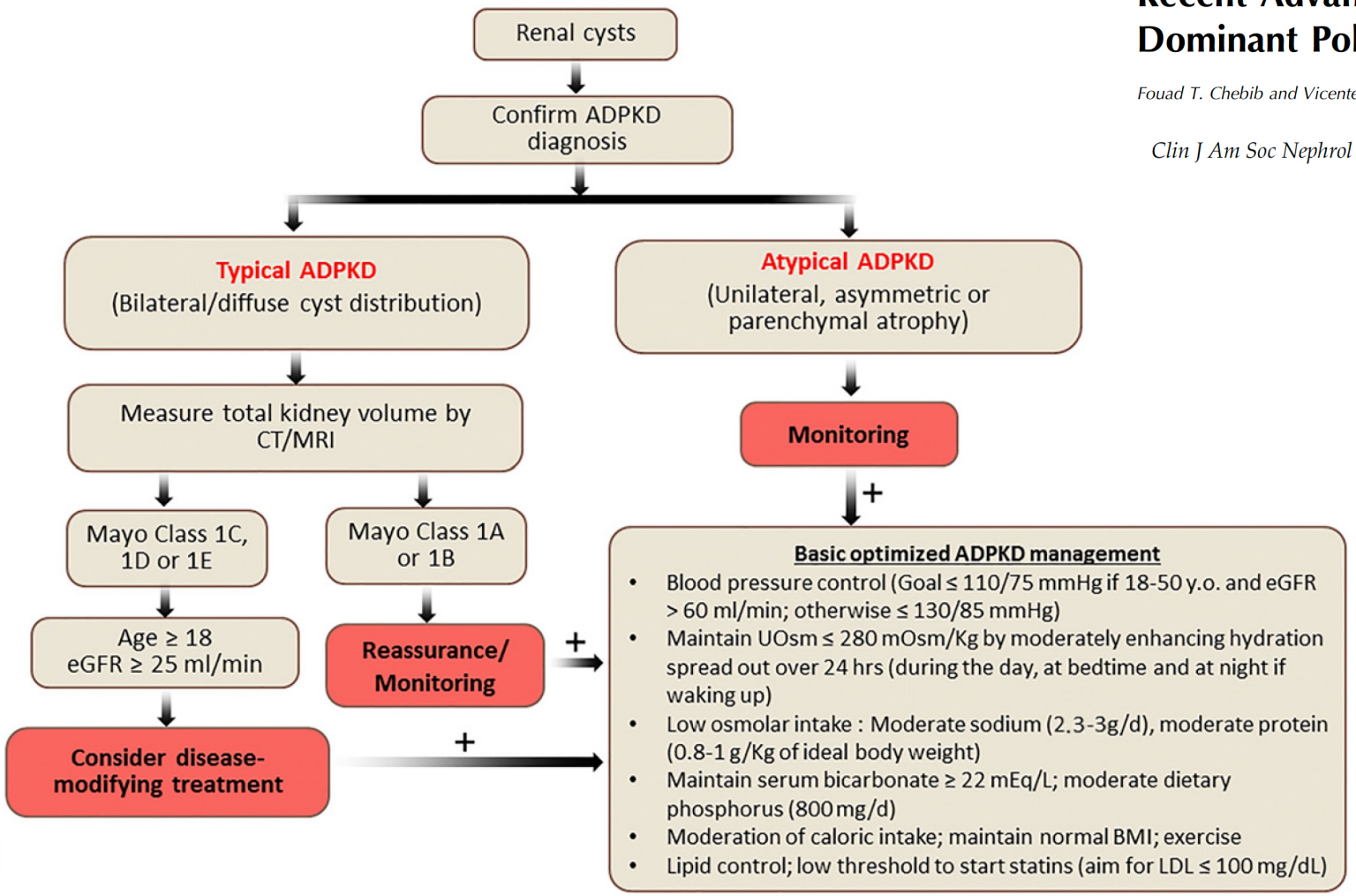
For these reasons, early nephrology assessment of PKD (and other inherited renal diseases) is helpful

Treatment of PKD

Measures to slow renal decline in ADPKD

A new management paradigm for ADPKD

Targeted and non-target treatments



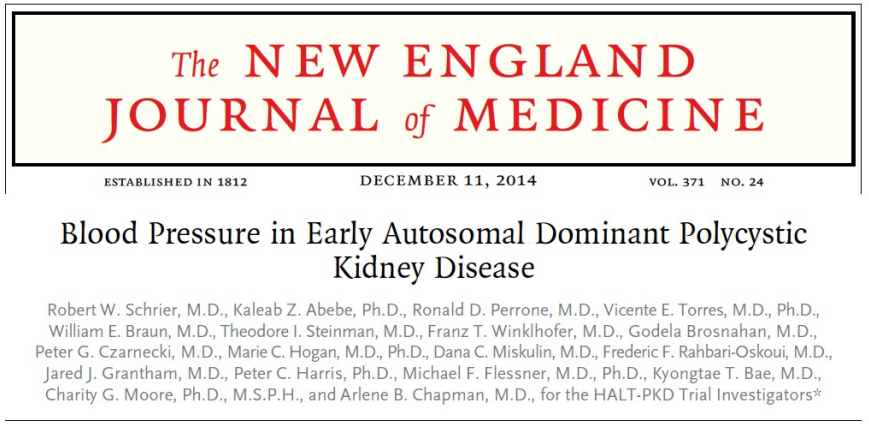
Recent Advances in the Management of Autosomal Dominant Polycystic Kidney Disease

Fouad T. Chebib and Vicente E. Torres

Clin J Am Soc Nephrol 13: ●●●–●●●, 2018. doi: https://doi.org/10.2215/CJN.03960318

MAYO CLINIC

BP Management: 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

After years of discussion now generally accepted as an endpoint in *early* PKD

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

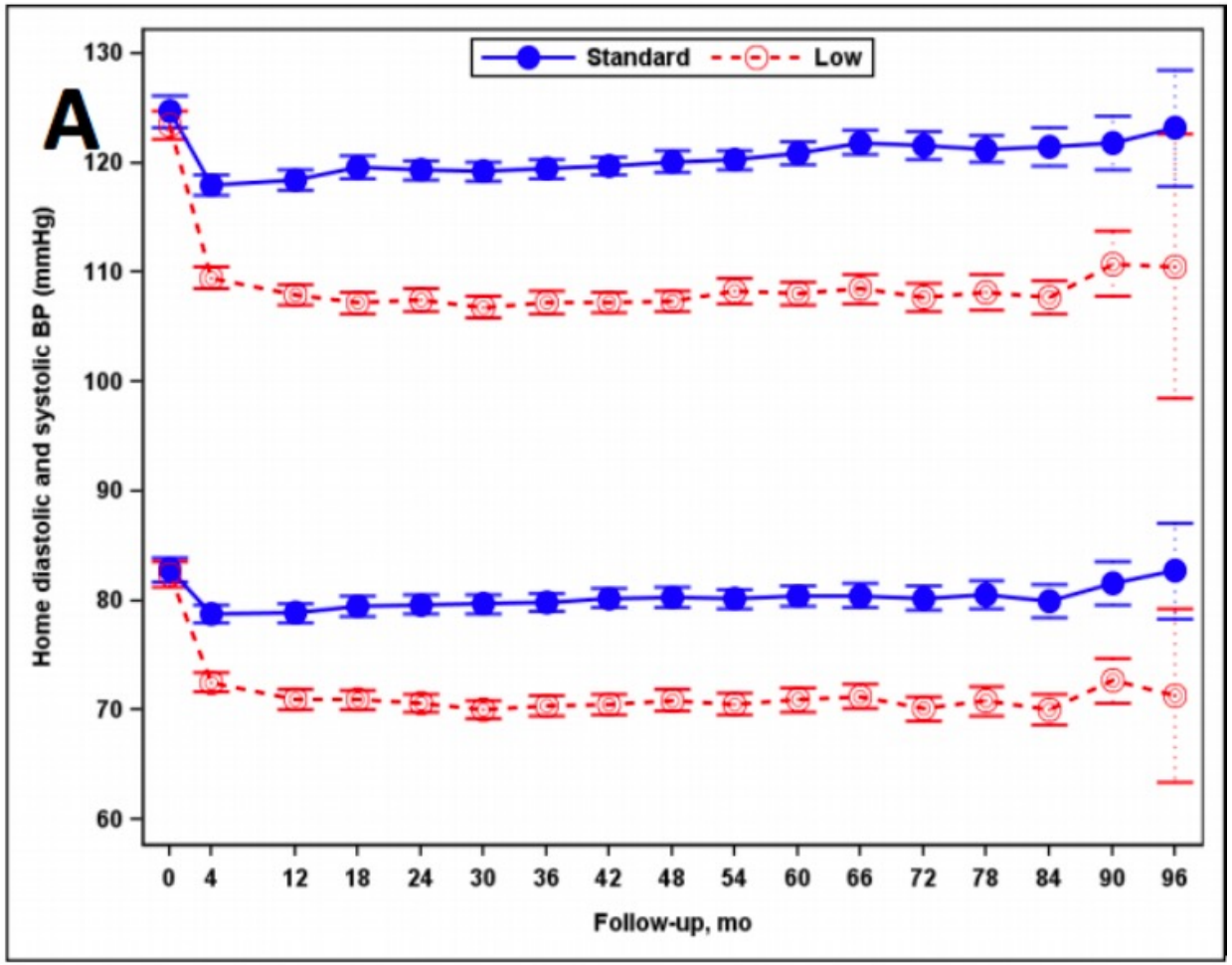
Characteristic	Lisinopril–Telmisartan (N=273)	Lisinopril–Placebo (N=285)	Standard Blood Pressure (N=284)	Low Blood Pressure (N=274)
Age — yr	37.0±8.3	36.3±8.3	36.3±8.4	36.9±8.2
Male sex — no. (%)	141 (51.6)	142 (49.8)	143 (50.4)	140 (51.1)
Race — no. (%)†				
White	255 (93.4)	262 (91.9)	258 (90.8)	259 (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 m^2¶	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 m^2	607.7±195.3	609.2±216.2	592.4±206.1	624.7±205.3
Left-ventricular-mass index — g/m^2	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

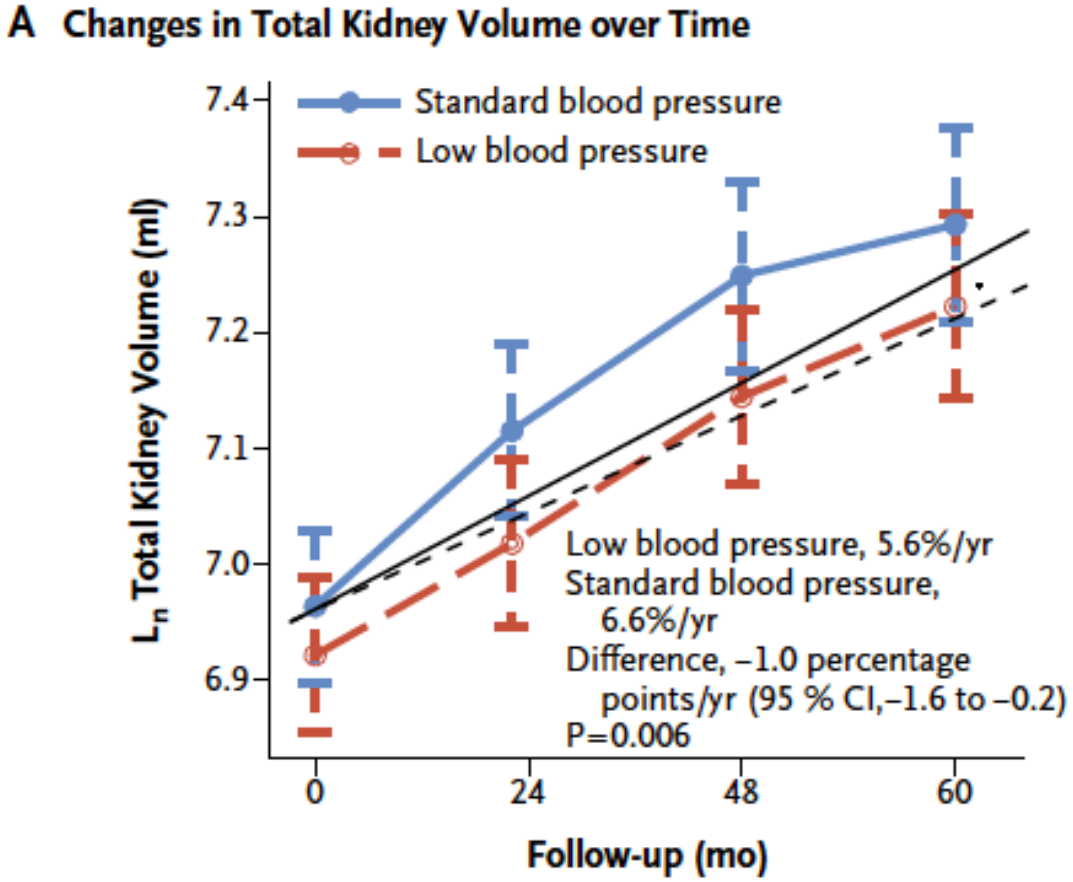


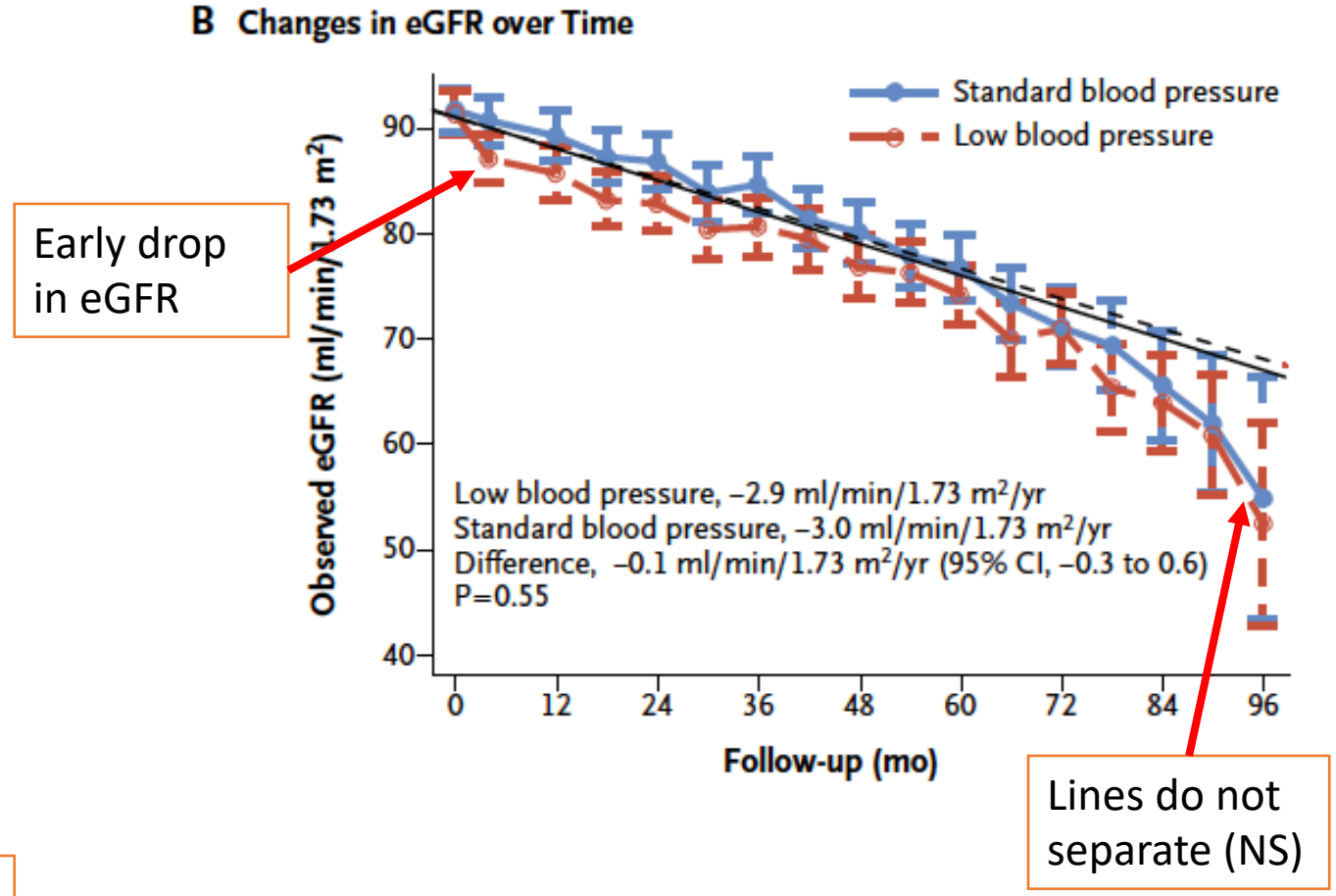
120/80

110/70

Median = 2 drugs

Results





Early drop in eGFR

Lines do not separate (NS)

14.2% slower rate of TKV increase

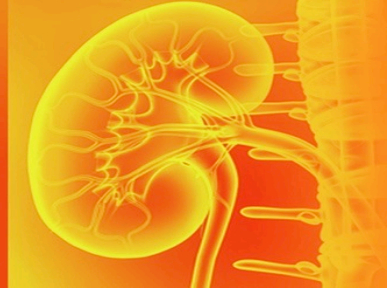
Secondary outcomes

- Albuminuria was reduced by 3.77% in the low target group vs an increase of 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

Does this effect make sense?

- Recall, PKD is a hyper-filtering and eventually fibrotic disease. At some point, RAS blockade and targeting snGFR makes sense
  - The proteinuria difference also supports this line of reasoning
- We also know that changes in renal blood flow occur simultaneously (or may precede) increases in TKV
  - Potential role of RAAS early in disease process
- This trial was in young patients with single system disease and preserved GFR – tend to better tolerate lower blood pressures
- Note that the low BP group happened to have more PKD2 – this may have exaggerated the effect, but both groups were still dominated by PKD 1 patients (>70%) and baseline TKV was similar

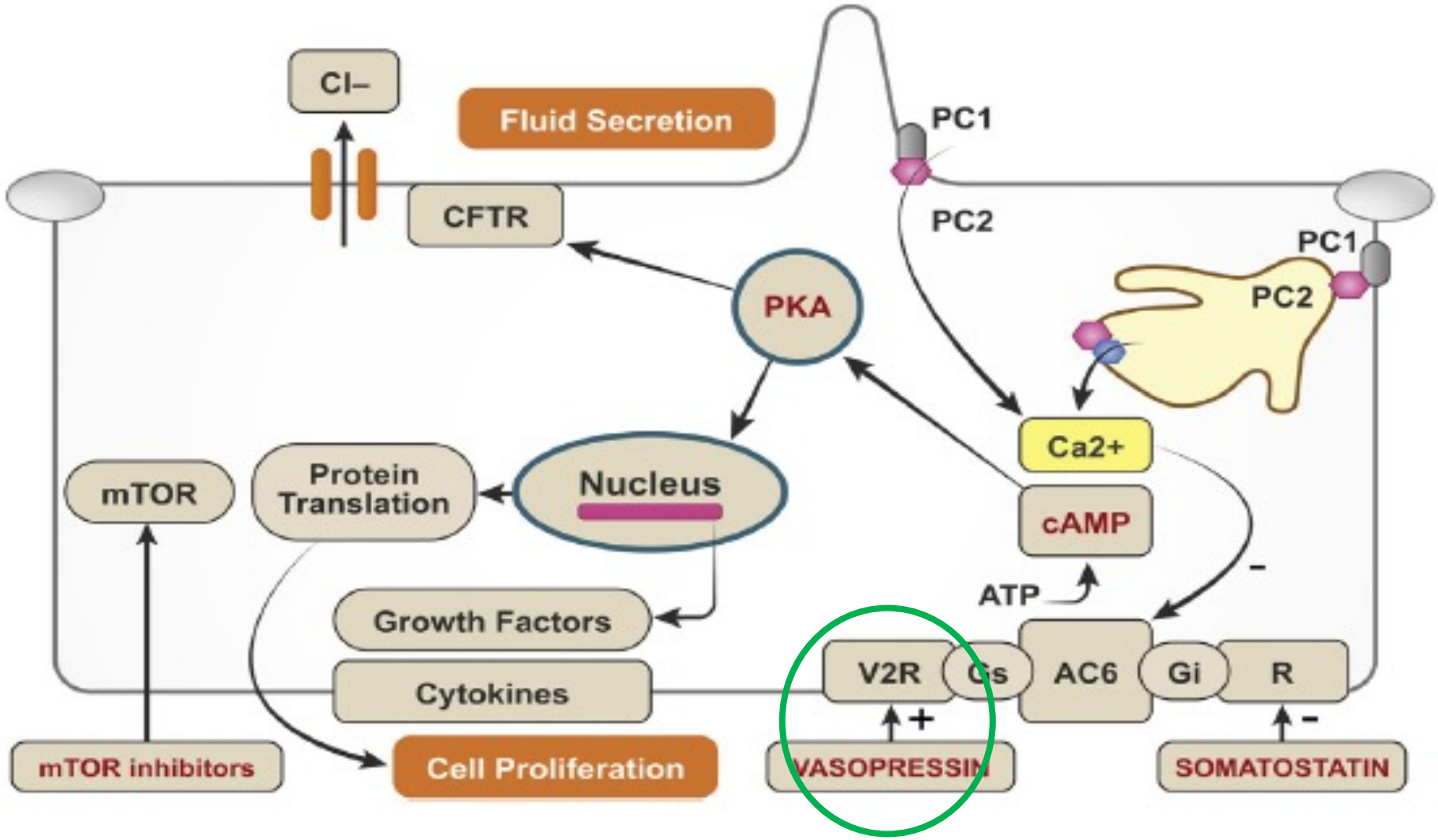
Insights from the Canadian Consensus Document



1. *We recommend that patients with ADPKD who are <50 years old with eGFR >60 ml/min/1.73 m^2 and without significant cardiovascular comorbidities should have a target BP of ≤110/75 mmHg, realizing that in some patients an individual target may be needed.*

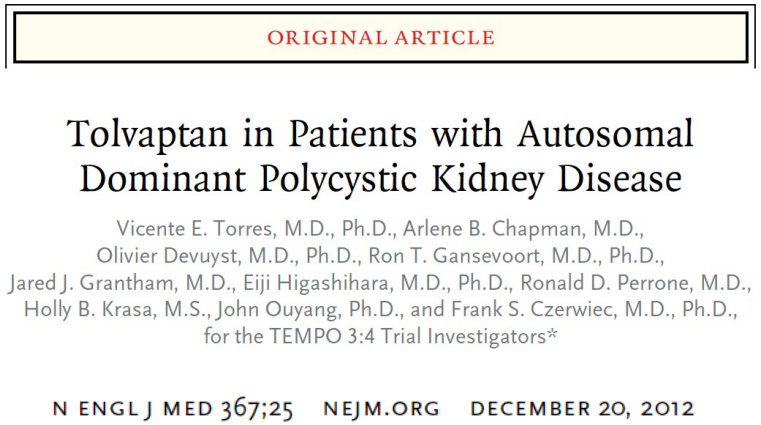
In my experience, *early stage* patients tolerate this quite well, and as seen in the trial, can often meet this goal with 1-2 drugs

Role of vasopressin in ADPKD



Vasopressin blockade: 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 (Target 140/90)
- O: Primary outcome was change in TKV. Secondary outcomes included decrease in renal function and pain events
- Study design: Double-blind, placebo controlled RCT


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*

N ENGL J MED 367;25 NEJM.ORG DECEMBER 20, 2012

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.)

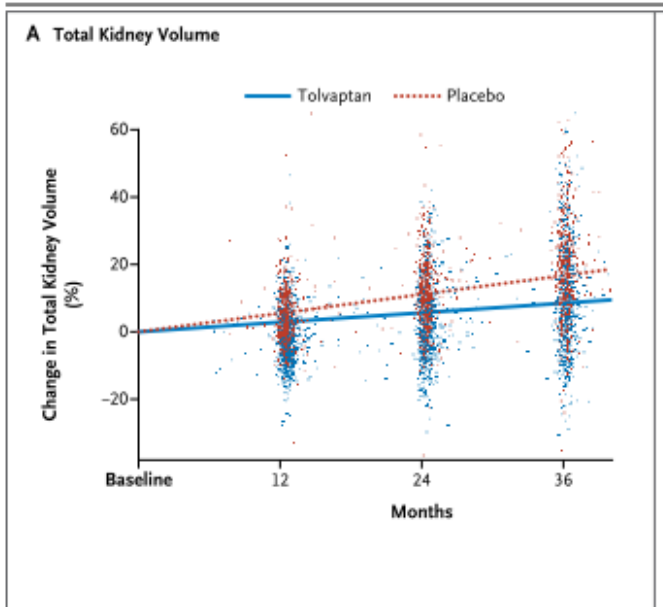
Characteristic	Tolvaptan (N=961)	Placebo (N=484)
Height — cm	173.5±10.4	173.6±7.8
Weight — kg	79±18	79±18
Blood pressure — mm Hg		
Systolic	128.6±13.5	128.3±13.5
Diastolic	82.5±9.9	82.5±9.3
Total kidney volume — ml	1705±921	1668±873
Height-adjusted total kidney volume — ml/m	979±515	958±483
Serum creatinine — 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

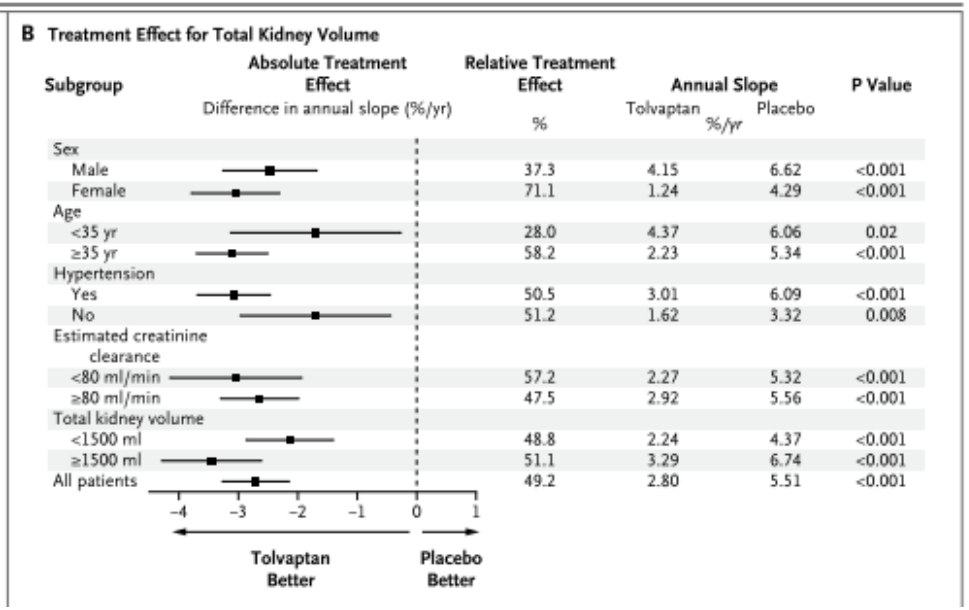
91umol/l

Young: Age 39

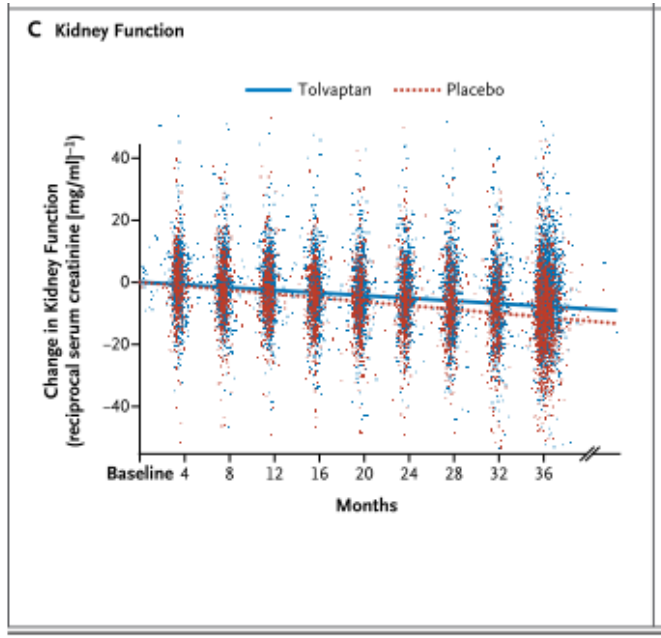
Preserved kidney function: eGFR 81

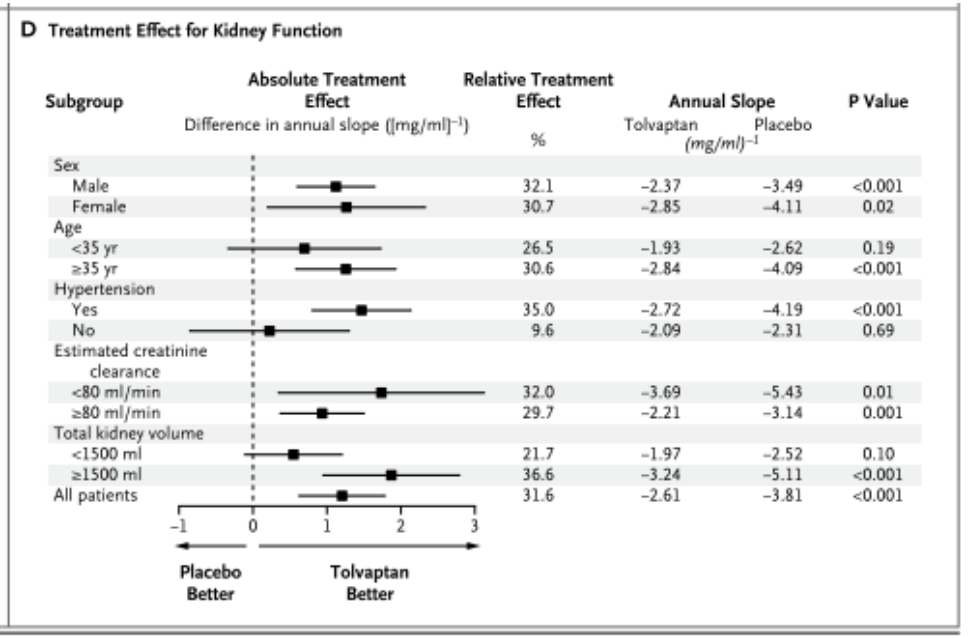
Rapid progressing disease: Big kidneys at a young age (~1700ml TKV)





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





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 (~1ml per year slower GFR slope)

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

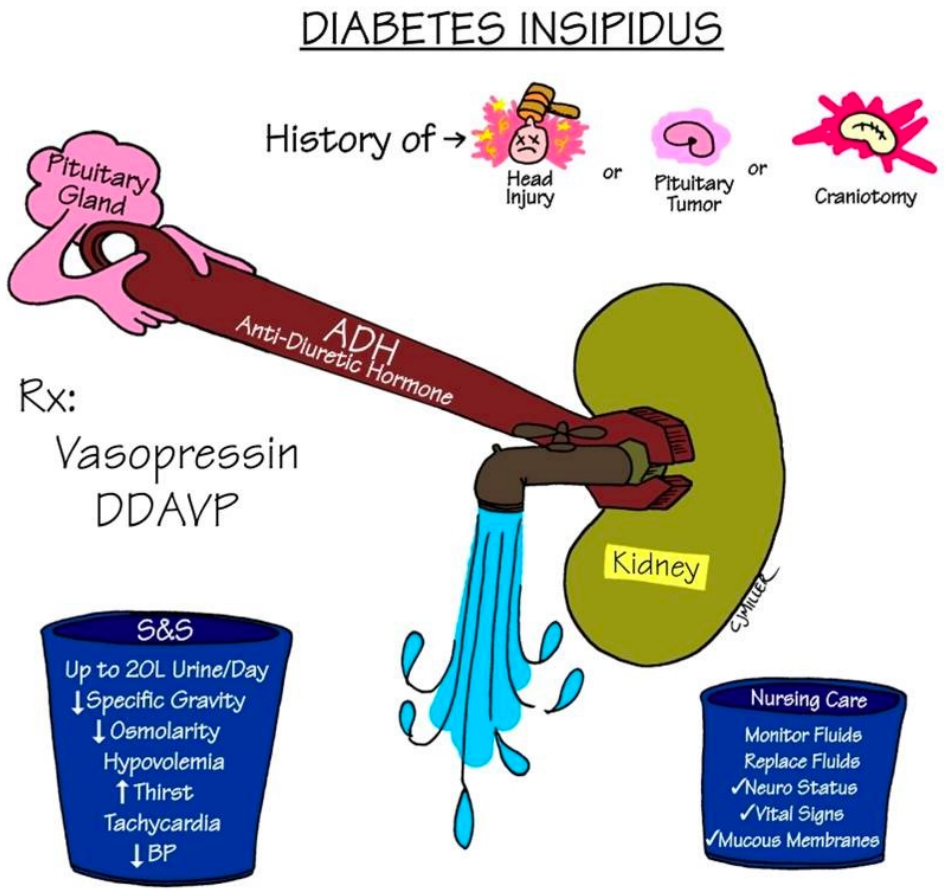
Event	Tolvaptan (N=961)	Placebo (N=483)
	no. of patients with event (%)	
Adverse events more common in tolvaptan group		
Thirst	531 (55.3)†	99 (20.5)
Polyuria	368 (38.3)†	83 (17.2)
Nocturia	280 (29.1)†	63 (13.0)
Headache	240 (25.0)	120 (24.8)
Pollakiuria‡	223 (23.2)†	26 (5.4)
Dry mouth	154 (16.0)	59 (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 - aquaretic symptoms

- In the treatment group, 55% took the maximal dose (total 120 mg daily)
- 23% vs. 13.8% in the placebo group discontinued the drug; 8.3% of all patients discontinued due to aquaretic symptoms
- In the real world we have strategies to help with this including dosing, timing and targeting urinary solute
  - ‘Real world’ discontinuation rates are closer to 10% in Canada



Increased transaminases and need for monitoring

- Overall, 4.9% with tolvaptan vs. 1.2% in the placebo group had abnormal liver enzymes

- 3 patients (0.02%) in the tolvaptan arm had AST/ALT >3xULN *and* bilirubin >2xULN. Hy's Law = BAD

- To compare to other drugs associated with AST/ALT increases:
  - INH: up to 20%
  - MTX: 15%
  - Amiodarone: 3-6%
  - Lipitor: <2%

Mandatory hepatic monitoring while on tolvaptan

REPRISE: Inclusion Criteria

Key Inclusion Criteria:

- Diagnosis of ADPKD (Pei-Ravine criteria)
- Tolvaptan naïve
- 18-55y; eGFR 65 – 25 mL/min

  OR
- 56-<66y; eGFR 44 – 25 mL/min
  and evidence of eGFR decline >2mL/min/yr

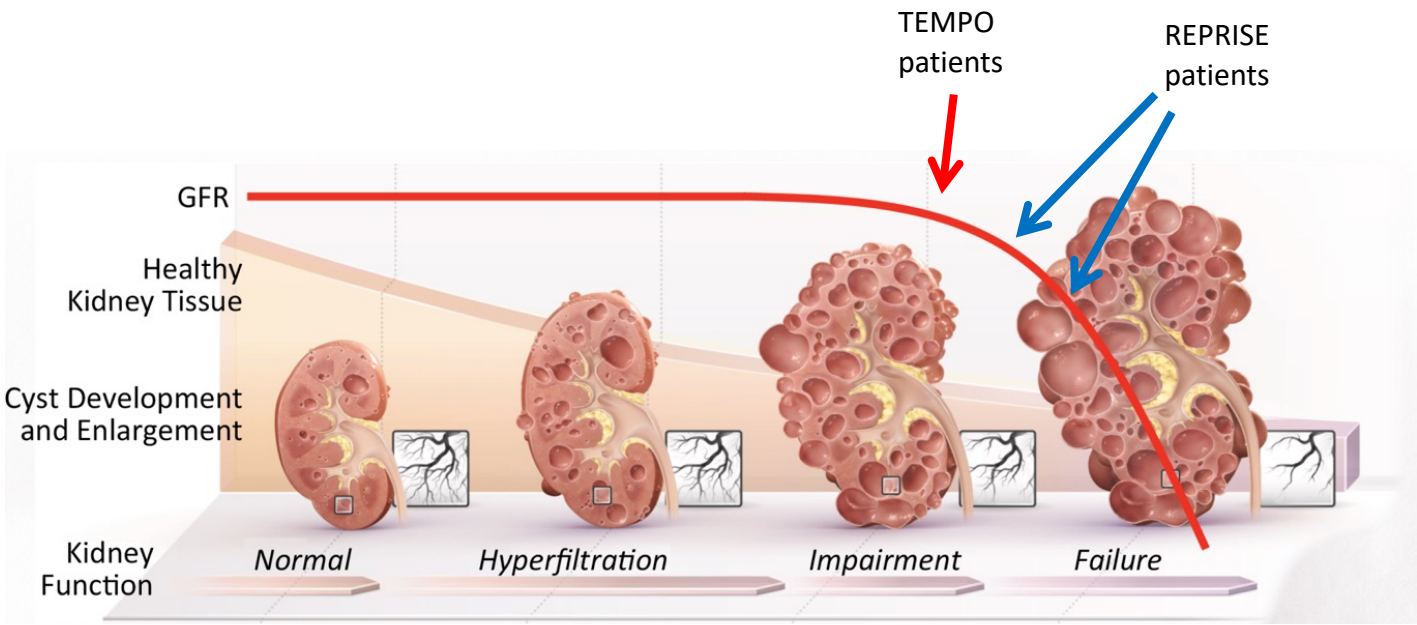
- Randomized withdrawal, placebo controlled study

The goal was to identify a group of rapidly progressing patients who were later in their disease course

ORIGINAL ARTICLE

Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease

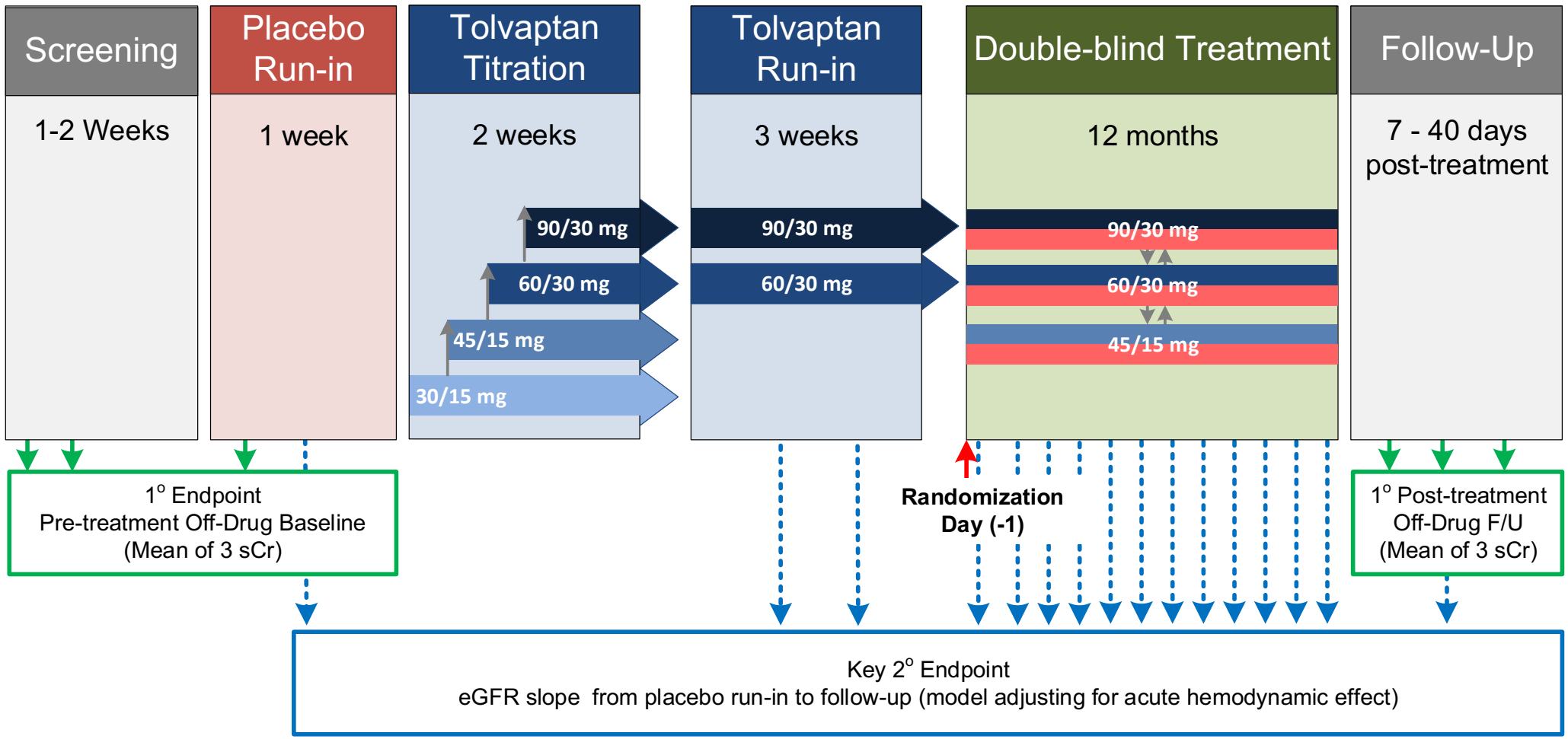
Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D., Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D., Ronald D. Perrone, M.D., Gary Koch, Ph.D., John Ouyang, Ph.D., Robert D. McQuade, Ph.D., Jaime D. Blais, Ph.D., Frank S. Czerwiec, M.D., Ph.D., and Olga Sergeyeva, M.D., M.P.H., for the REPRISE Trial Investigators*



Trial design and endpoints

Efficacy
-vs-
Effectiveness

Randomized-withdrawal, Placebo-controlled, Double-blind,



Baseline Characteristics

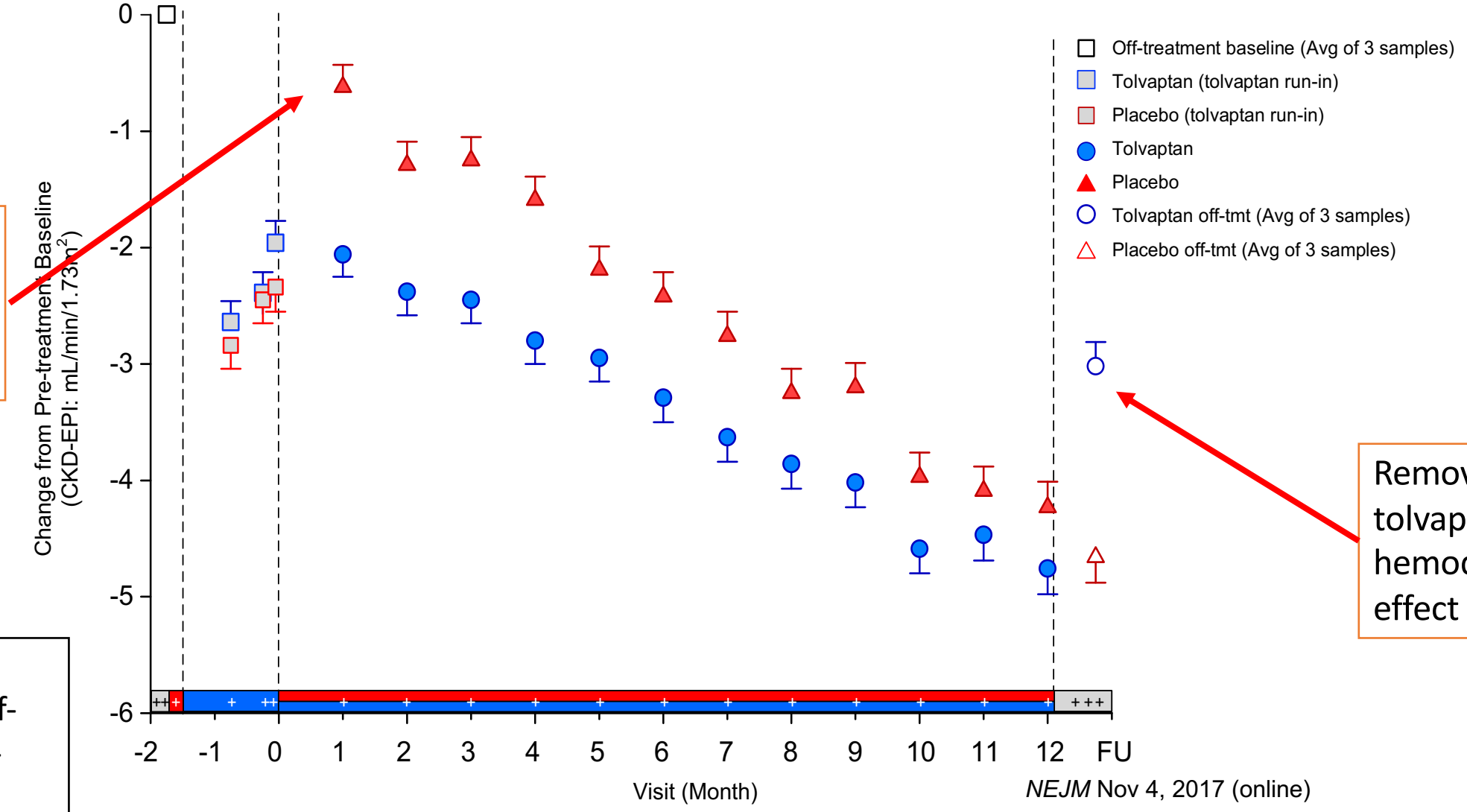
Characteristic	Tolvaptan (N=683)	Placebo (N=687)
Age, years (SD)	47.3 (8.2)	47.2 (8.2)
Male gender, n (%)	347 (50.8)	333 (48.5)
Height, cm (SD)	174 (10)	173 (10)
Weight, kg (SD)	84.6 (19.9)	81.6 (19.3)
BMI, kg/m^2 (SD)	28.0 (5.8)	27.7 (5.6)
Race, n (%)		
Caucasian	626 (91.7)	632 (92.0)
Asian	22 (3.2)	19 (2.8)
Black	25 (3.7)	23 (3.3)
Other	10 (1.5)	13 (1.9)
Positive family history for PKD; n, (% yes)	514/679 (75.7)	529/687 (77.0)
Blood Pressure, mmHg (SD)		
Systolic	129.3 (13.8)	129.9 (14.5)
Diastolic	82.1 (9.6)	82.6 (9.7)
$eGFR_{CKD-EPI}$, $mL/min/1.73m^2$ (SD)	40.7 (10.9)	41.4 (11.2)
CKD Stage, n (%)		
CKD 2	32 (4.7)	39 (5.7)
CKD 3a	209 (30.6)	202 (29.4)
CKD 3b	303 (44.4)	315 (45.9)
CKD 4	139 (20.4)	128 (18.6)
Hypertension; n, (% yes)	634 (92.8)	640 (93.2)
Taking RAAS inhibitor	595 (87.1)	581 (84.6)
History of Kidney Pain, n, (% yes)	338/675 (50.1)	344 /679 (50.7)
Dose at end of single-blind tolvaptan, mg/day, n (%)		
60/30	118 (17.3)	124 (18.0)
90/30	565 (82.7)	563 (82.0)

Older than TEMPO (47 years vs 37)

Predominantly Caucasian

Lower kidney function with good representation of the spectrum of stages 3+4

Change from baseline eGFR



Removal of tolvaptan hemodynamic effect

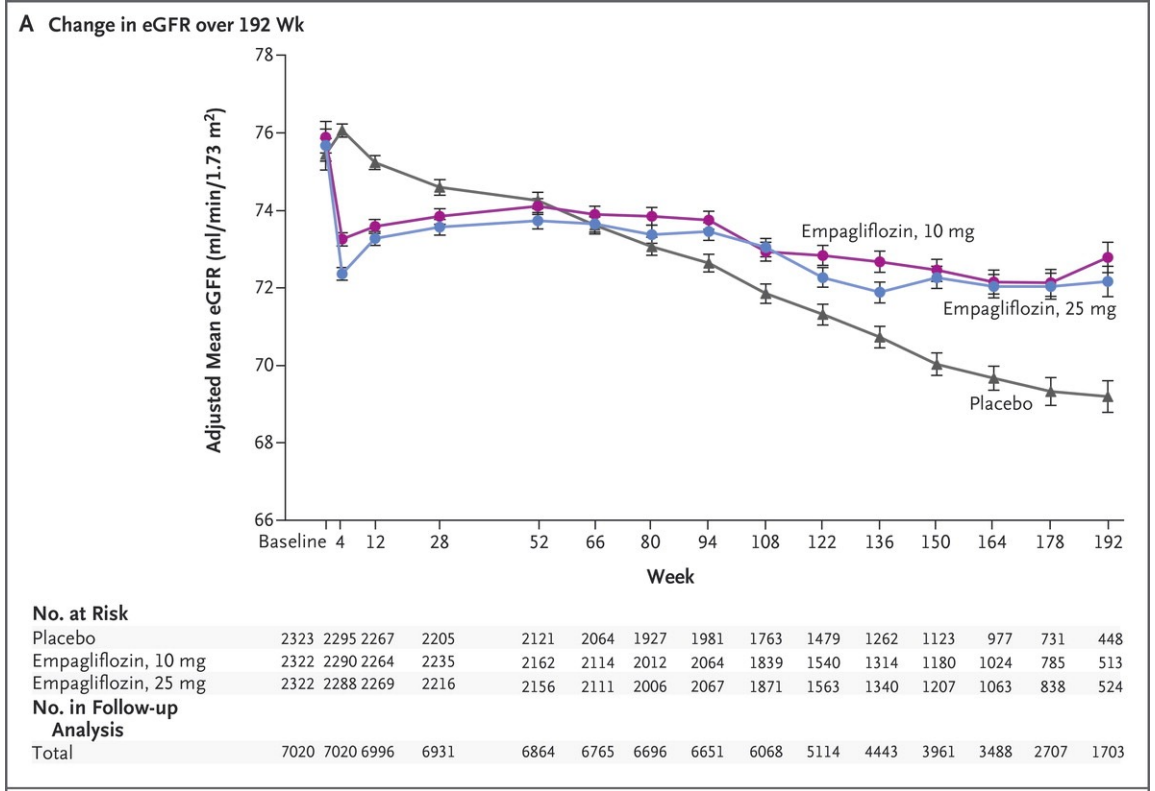
Removal of tolvaptan hemodynamic effect

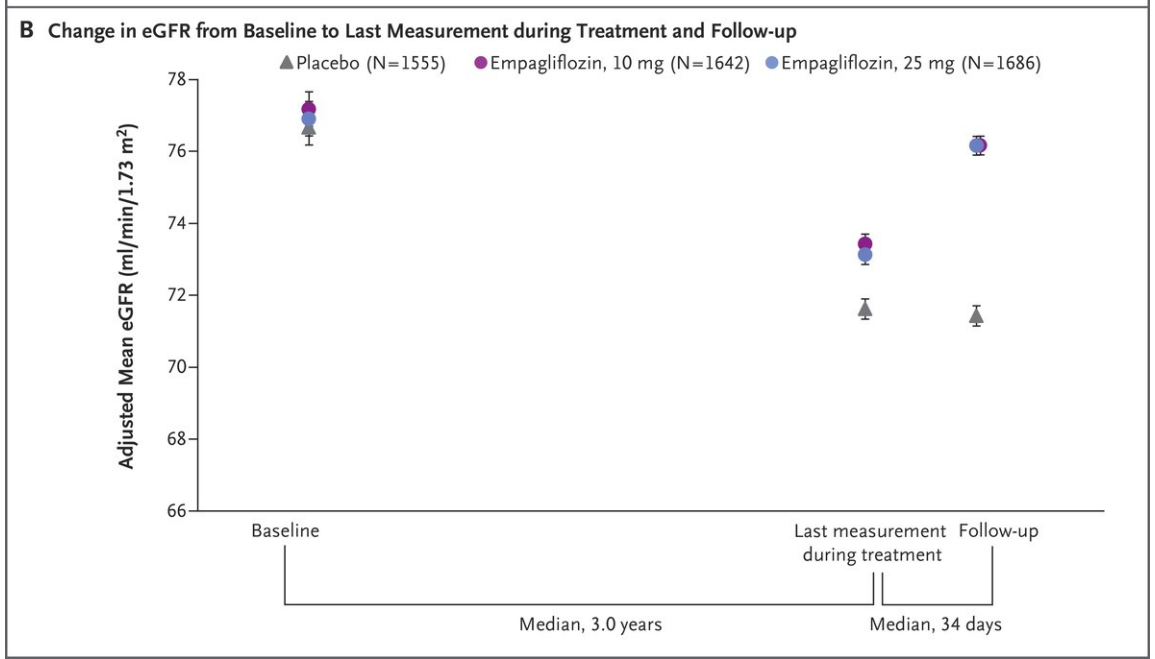
Final eGFR comparison is off-treatment to off-treatment

NEJM Nov 4, 2017 (online)

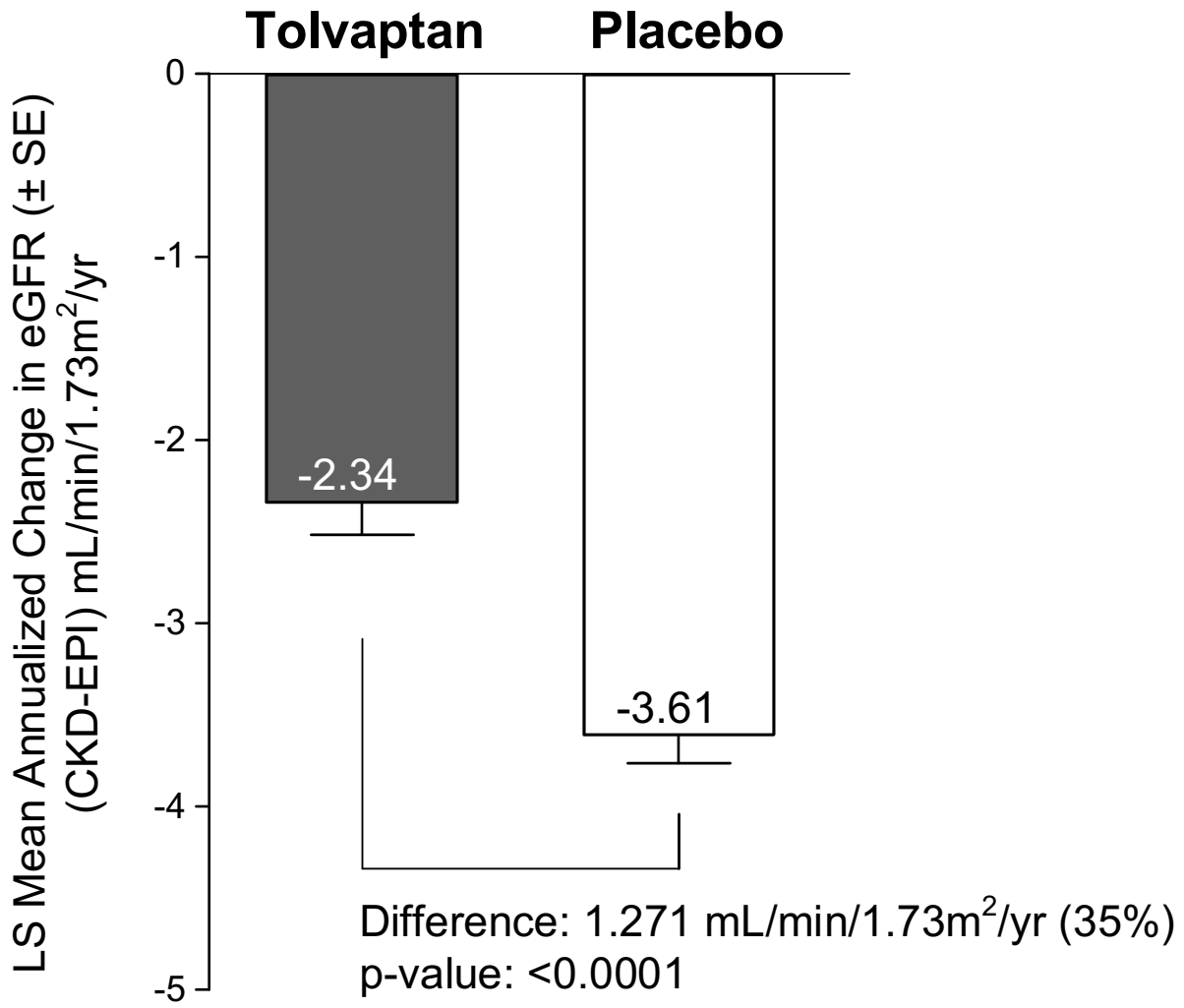
Comparison: EMPA-REG

- Another drug with a known, reversible hemodynamic effect on GFR
- Comparison of pre-treatment eGFR to post-treatment eGFR (off drug to off drug)

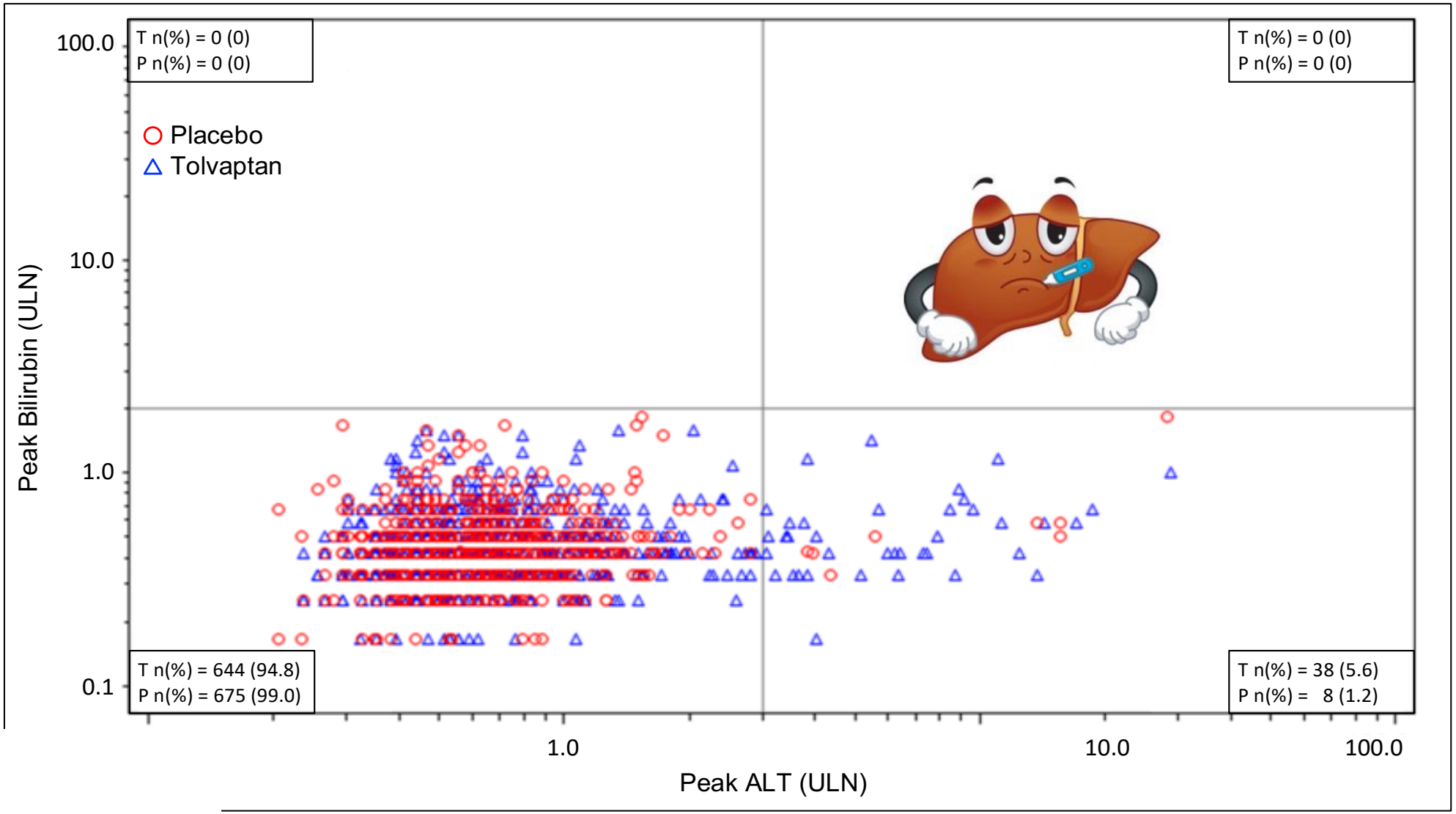




One year change in eGFR in REPRISE



Hepatotoxicity in REPRISE



REPRISE: Conclusions

- This was a drug efficacy trial, designed with FDA input
  - Randomized withdrawal, selection for rapid progressors, 1 year follow-up
- Primary outcome was met: tolvaptan slowed the decline in renal function by 1.3 mL/min/1.73m2/year
- Subgroup analysis shows consistent effect ***except*** the >55 group which appear to be slower progressors to start with

- Safety:
  - Consistent with previous tolvaptan trials
  - More transaminase increases but none reached Hy's Laboratory criteria in setting of monthly labwork

What we now know about tolvaptan in ADPKD

Effects of tolvaptan on TKV

- In patients at high risks of progression before substantial kidney function loss, tolvaptan slows rate of kidney growth

Effects on eGFR

- Tolvaptan has been demonstrated to slow the rate of eGFR decline in 2 large RCTs across a broad range of GFR stages.
  - A consistent treatment effect across 3 studies (2 RCT and open label) is encouraging to see

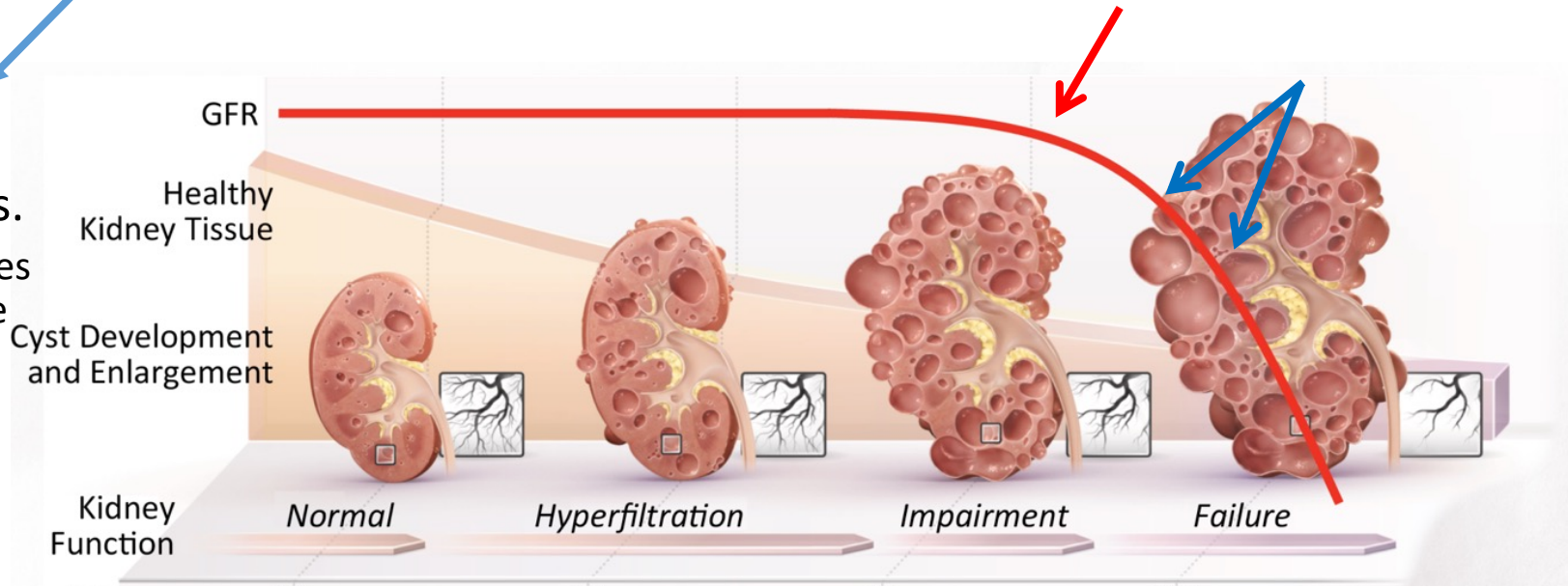
Safety Results

- The safety profile of tolvaptan was similar across clinical trials
- Rates of increased liver enzymes are similar across studies (4-6%)
  - The potential risk of permanent or life-threatening hepatocellular injury has decreased from 1:3000 in 2013 to 1:6200

Seeing a consistent 1-1.2ml/yr effect is encouraging, but long-term effect is still extrapolation

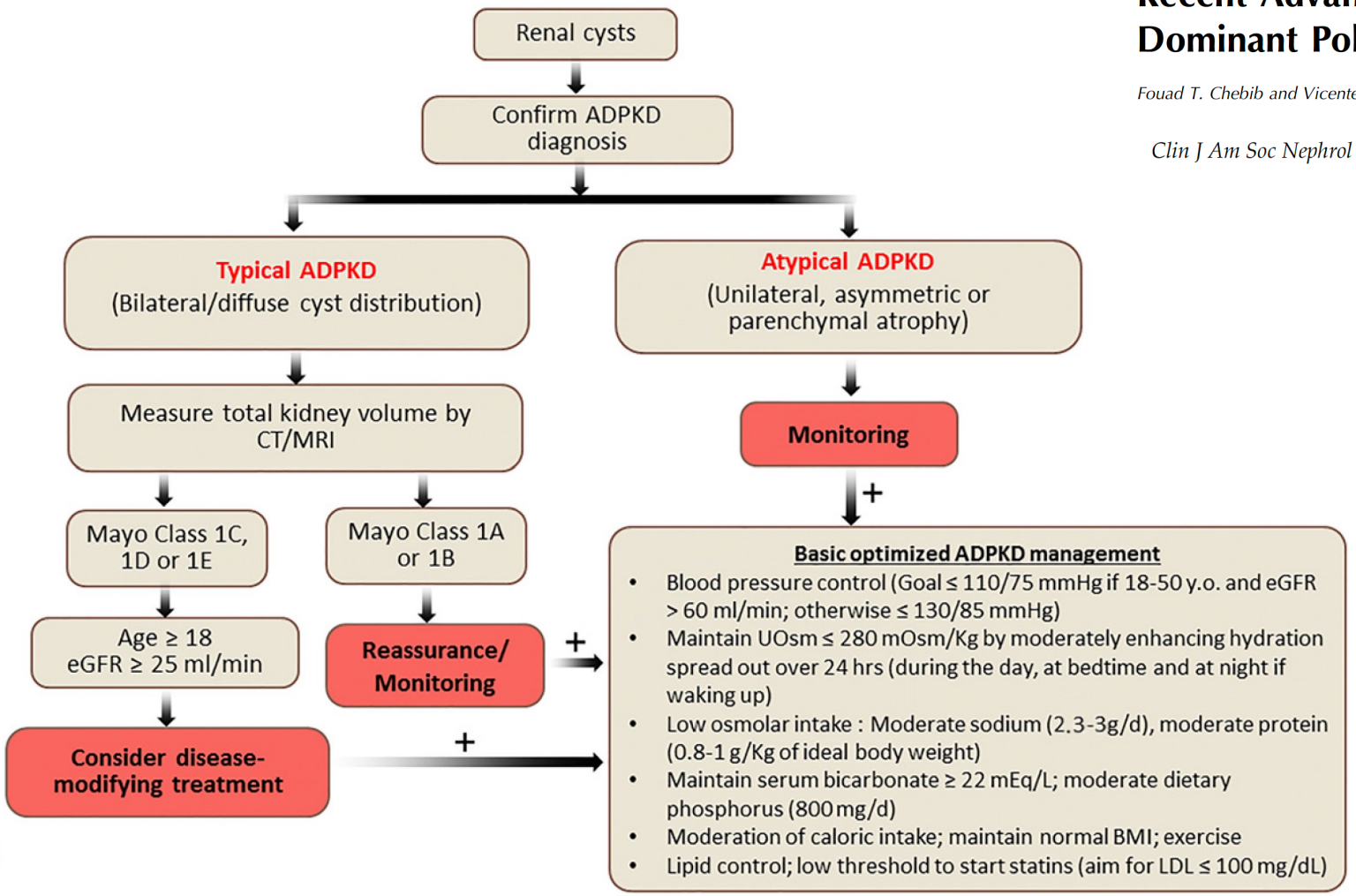
TEMPO patients

REPRISE patients



A new management paradigm for ADPKD

Targeted and non-target treatments



Recent Advances in the Management of Autosomal Dominant Polycystic Kidney Disease

Fouad T. Chebib and Vicente E. Torres

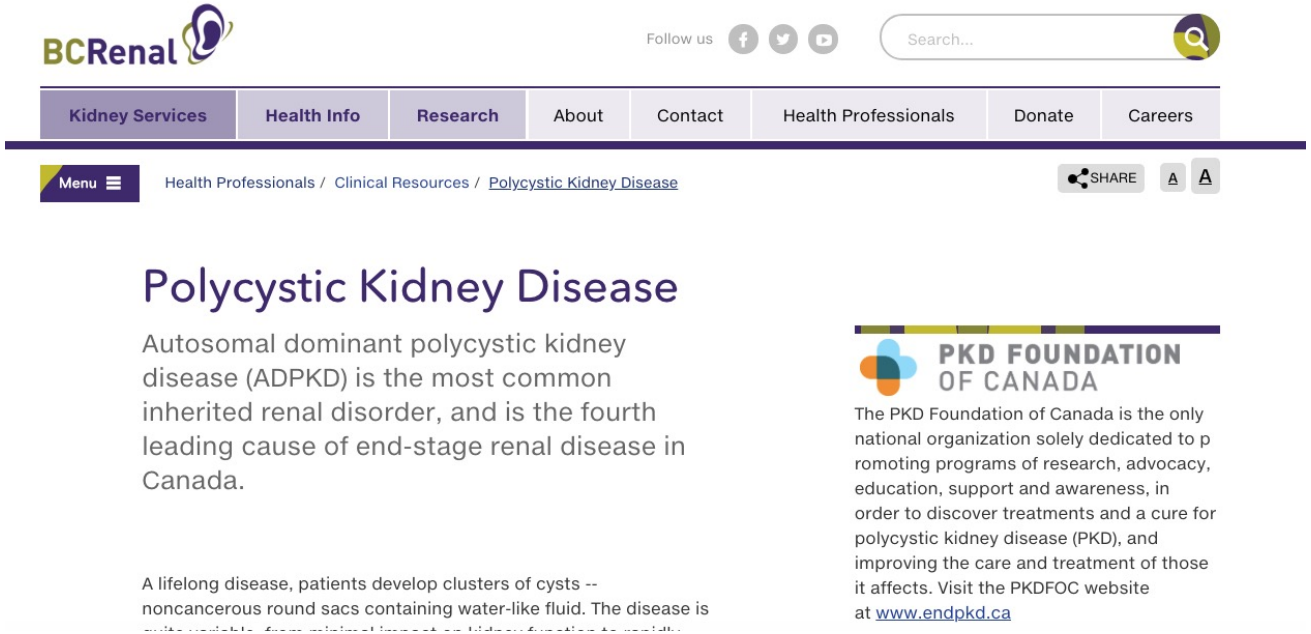
Clin J Am Soc Nephrol 13: ●●●–●●●, 2018. doi: https://doi.org/10.2215/CJN.03960318

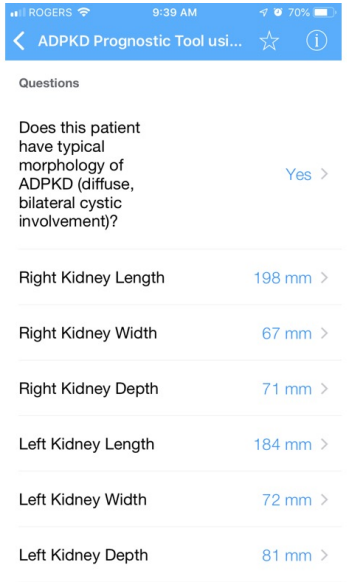
MAYO CLINIC

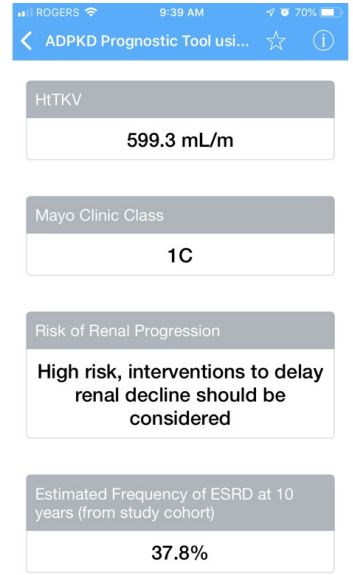
Translating evidence into clinical care

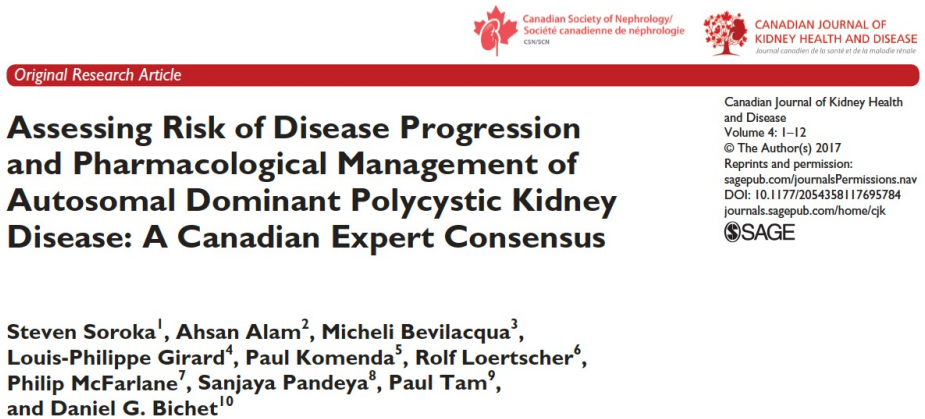
Creating a common approach to a rare(ish) disease

1st attempt: A host of standardized tools to support ADPKD care, *many* talks given





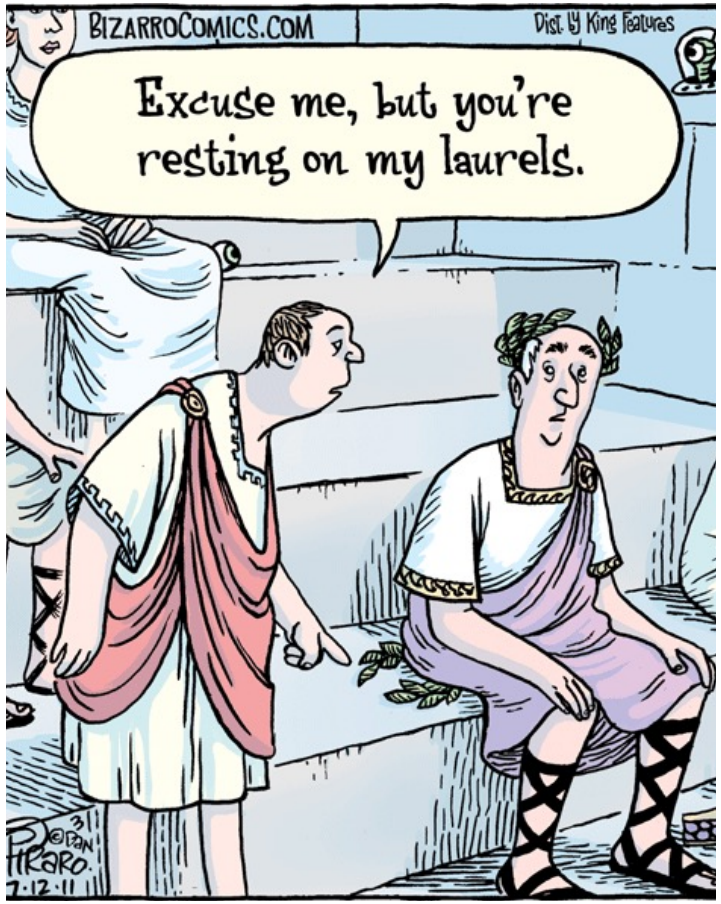




Did these tools translate into practice? Results of BC ADPKD needs assessments

- **Wide** variability in practice
  - Settings in which patients are seen
  - Frequency of visits, labs, screening investigation
  - Use of imaging and other tests

- Uncertainty around use of new tools and treatments
  - BP targets
  - Use of imaging – people know they *should* do TKV but uncertainty remains in interpreting results
  - Use of tolvaptan treatment: patient selection, dose titration

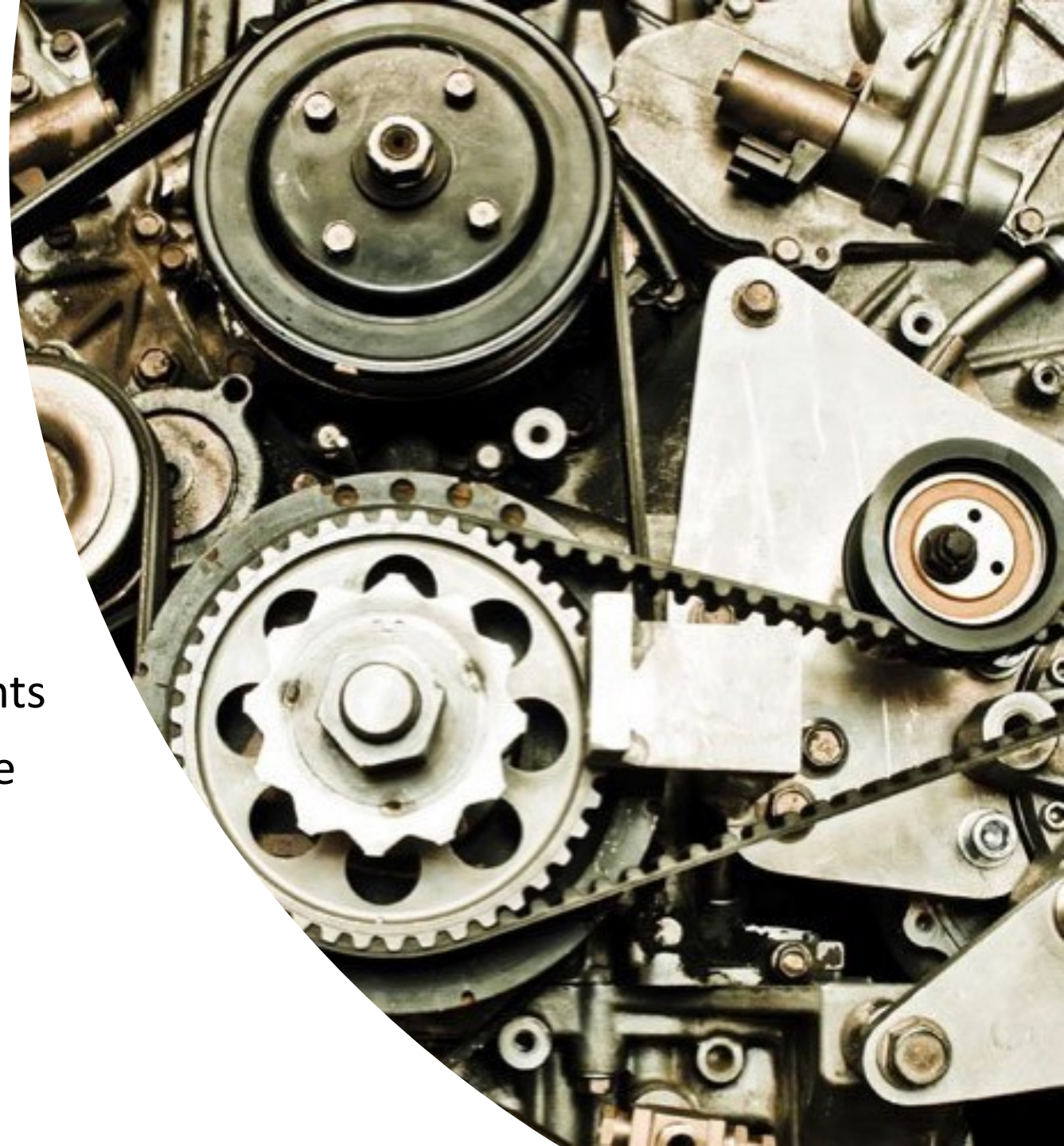


Phase 2: Developing a Provincial ADPKD network

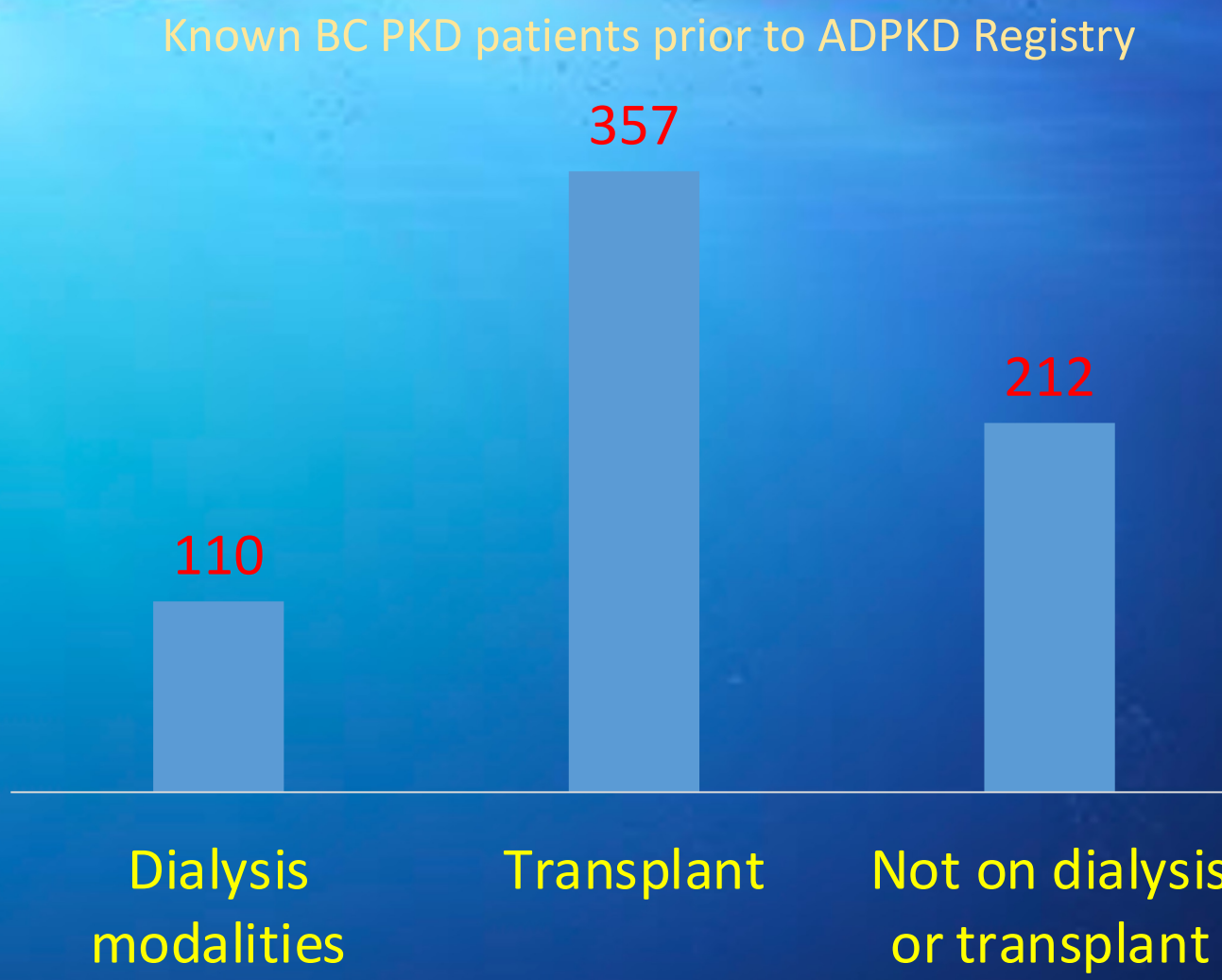
Vision: Creation of a *comprehensive provincial network* of PKD care in order to evaluate, *standardize* and enhance the care of British Columbians living with ADPKD in an *equitable* and sustainable fashion.

Components of an ADPKD network

- ADPKD Registry
- ADPKD Clinician Network
- Modernizing ADPKD Imaging
- Supporting and evaluating ADPKD treatments
- Knowledge Sharing of BC ADPKD experience



First, find the patients



Why build a patient registry?

Potential reasons to create a registry

- Research
- Collect data for clinical/QI purposes
- Collect data for administrative purposes
- Research

An important point to remember is that in this case the registry was layered on top of a *pre-existing* renal database

- Starting from scratch would be an entirely different initiative

BC ADPKD registry purpose statement

To gather comprehensive data on ADPKD in BC that will allow us to:

- Understand the burden of disease, current treatment patterns and patient outcomes
- Inform QI in ADPKD care at both the provincial level and the local/individual clinician level
- Assist with ongoing research efforts through registry level data as well as facilitating patient identification for future trials

These are ranked in priority order - it is primary meant as a clinical tool to complement existing data collection

Our registry is a first in Canada and now amongst the largest database of PKD patients anywhere

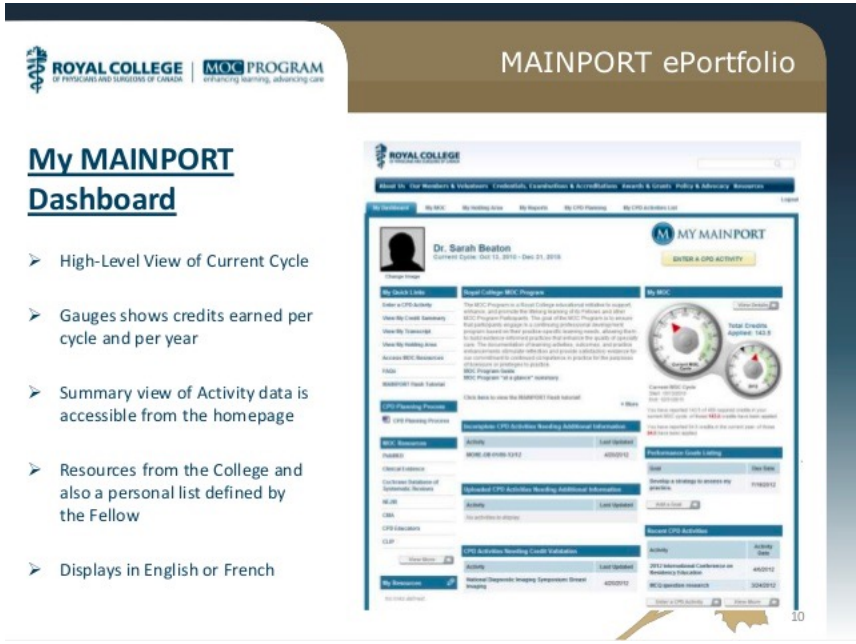
Capturing patients in a registry

- Automatic/already done for patients in CKD clinics, dialysis modalities, transplant
  - Rare to non-existent in many private nephrologists offices
- The registration process takes about 2 min
  - We focus on the ‘need to have’ rather than the ‘nice to have’
  - Seems small but this is a new step in clinic workflow for some, need to minimize that burden
- In the first instance we had a financial incentive
  - Made life easier, *not* sustainable
- Now there is no longer financial incentive, expectation registration is part of workflow
- Needs to be clear benefit if people are going to participate

Benefit to clinicians: Facilitating QI/ practice audits

In Progress: Plan is first facilitated, then as a self-assessment

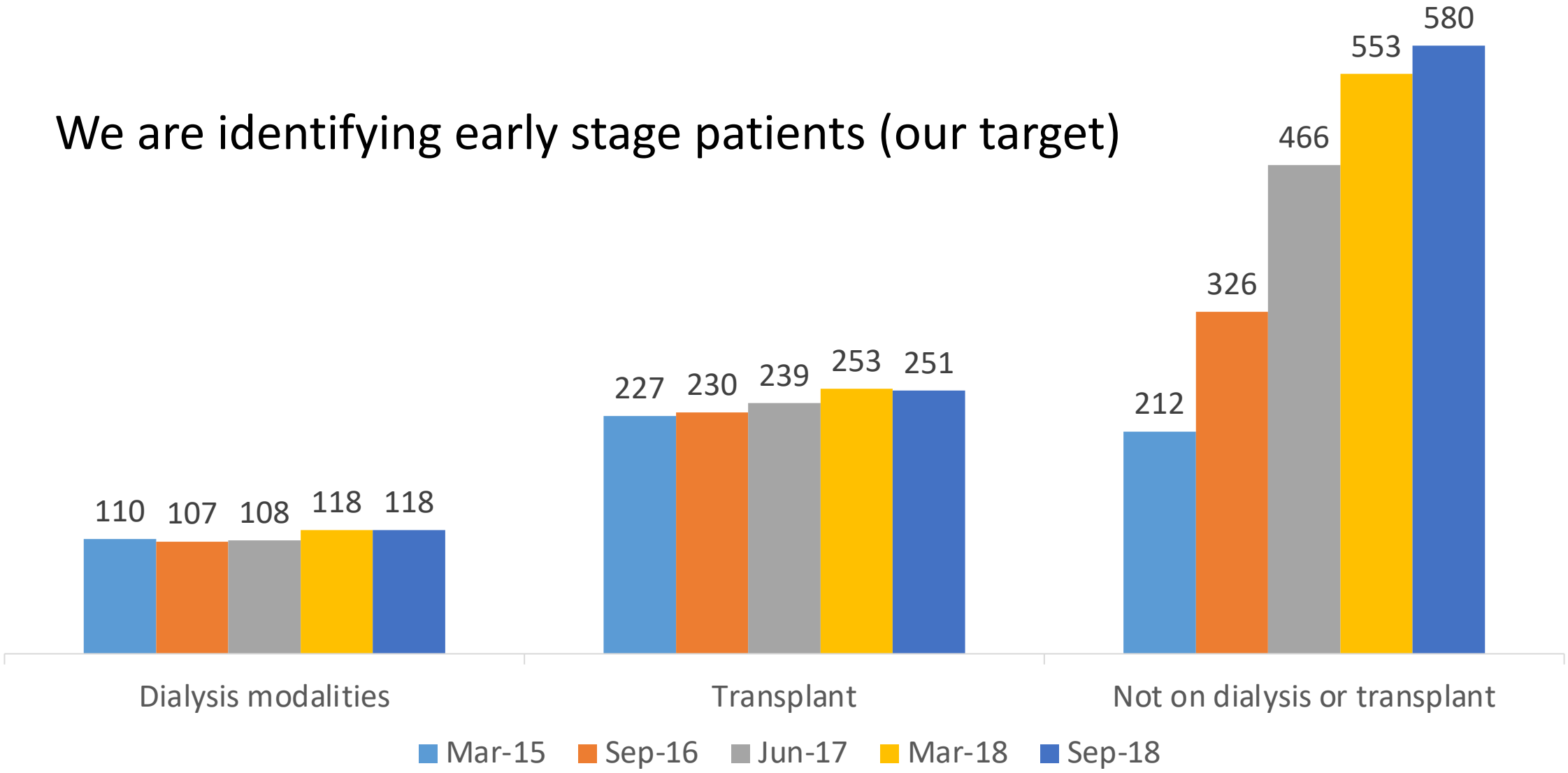
- How many PKD patients do I have?
- Where are they in their disease trajectory?
- Where are they treated?
- How are they treated?
  - BP
  - Meds
- Quick way to identify candidates as new treatments/data emerge



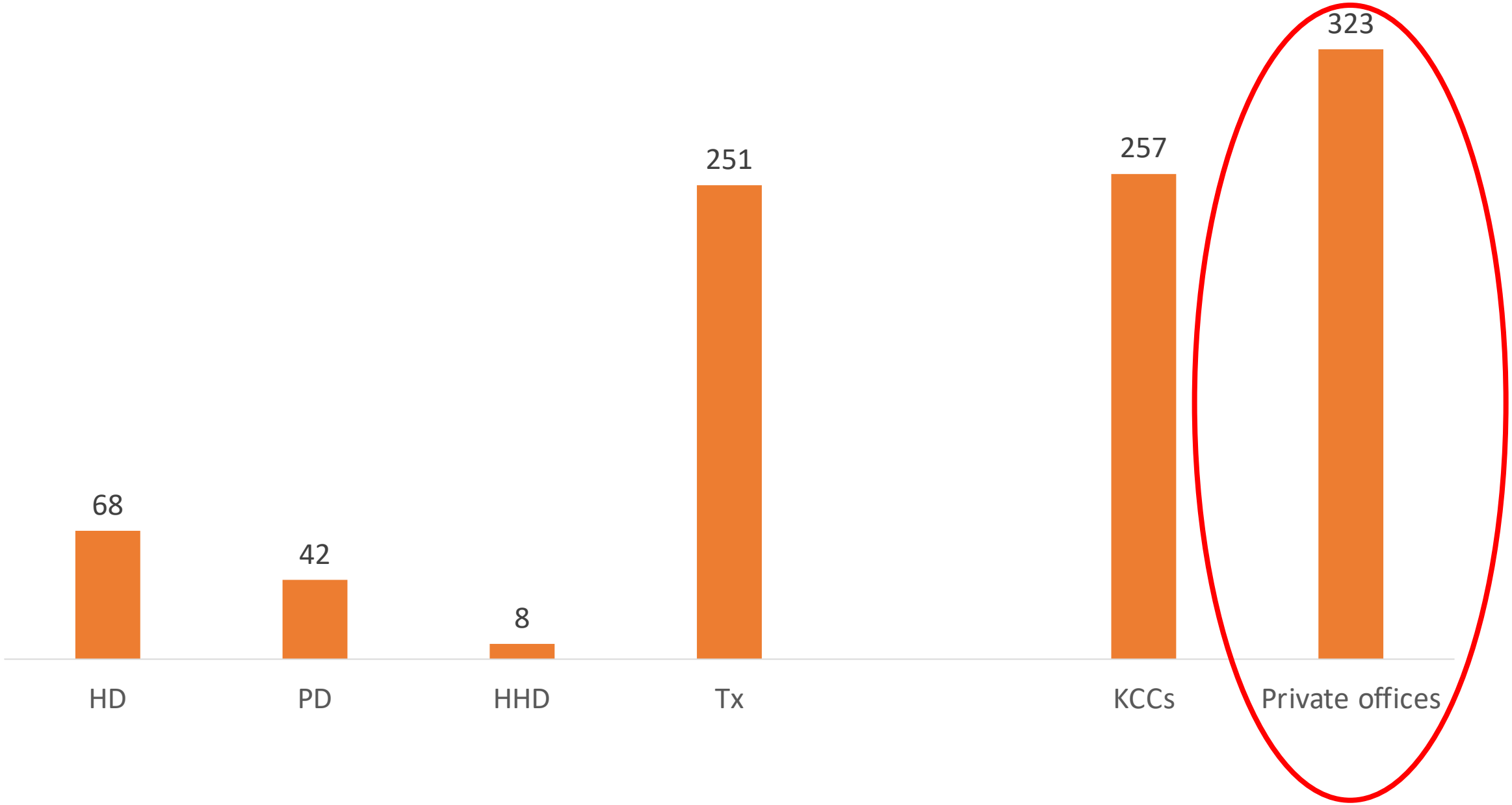
Category 3!!!

Results so far

We are identifying early stage patients (our target)



Where are PKD patients managed?

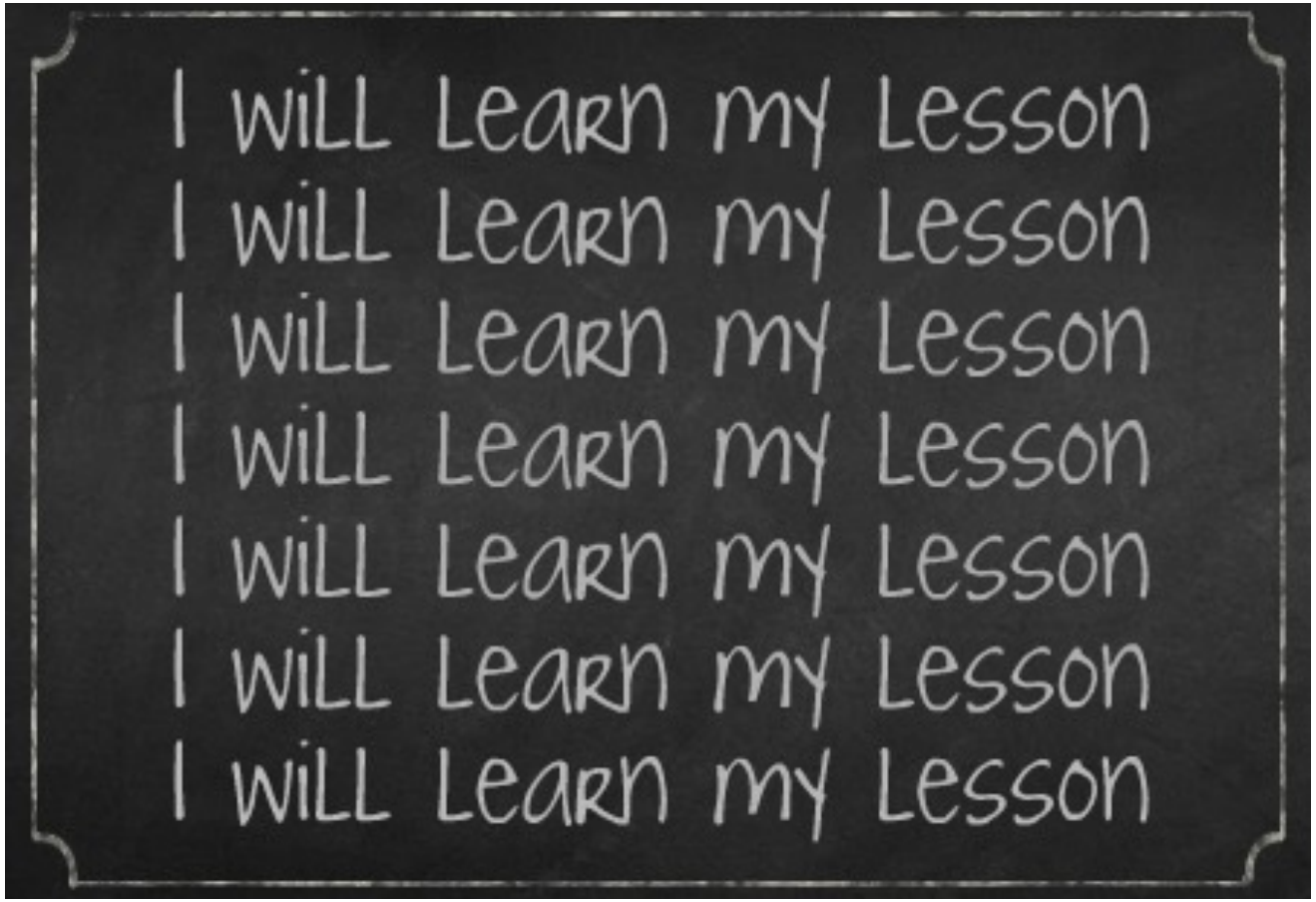


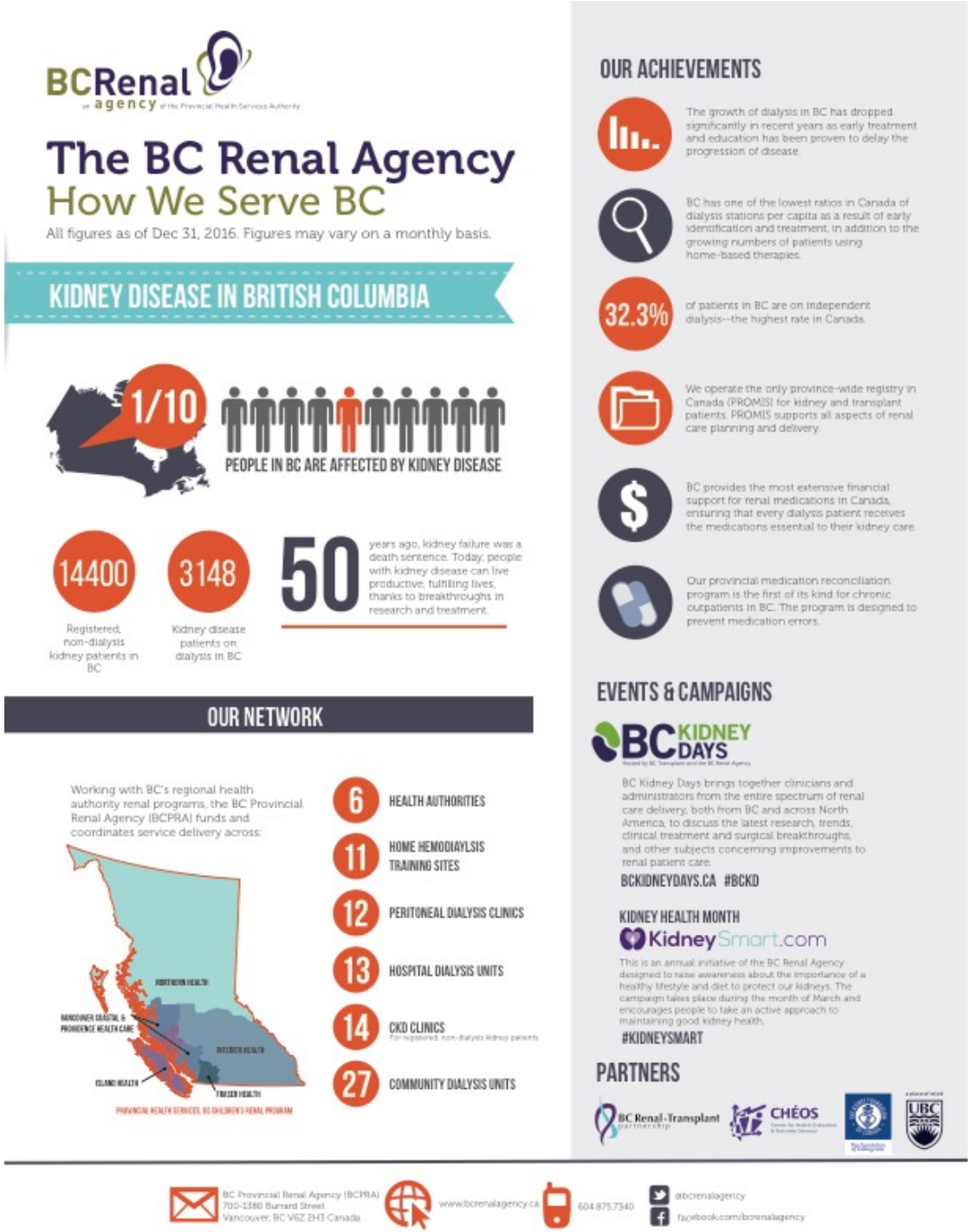
Lessons learned from building the PKD registry

1. To get a comprehensive picture, we need to think beyond acute care and existing clinics that usually target more advanced patients

2. Spend time determining your essential data set/requirements

3. Engaging providers in different practice settings is a challenge
   - If you are introducing a new task, however small, there needs to be a clear benefit to the end user





Phase 3: Coordinate ADPKD care across BC

Two broad approaches to sub-specialized disease-specific care

1. Specialized clinics with ultra-specialized providers
2. Developing specialized tools to help local providers deliver best care

In progress: Best Practices for management of ADPKD

- Experience in doing this with other aspects of CKD care
- The goal is to enable consistent ADPKD management regardless of where patients live and receive their care
- Guidelines being formed via a working group
  - Multidisciplinary input
  - Patient partners included in development

BEST PRACTICES:
KIDNEY CARE CLINICS

Spring 2014
Submitted by the Kidney Care Advisory Committee

ADPKD Best Practices: Content

- Clinical decision support
  - Use of medications
  - Approach to ordering tests (imaging)
  - Screening and management of complications (e.g. aneurysm)

- Clinical tools
  - Clinic visit sheets and associated materials
  - Patient education materials and resources

- Logistics
  - Frequency of clinic visits
  - Standardized requisitions, investigations

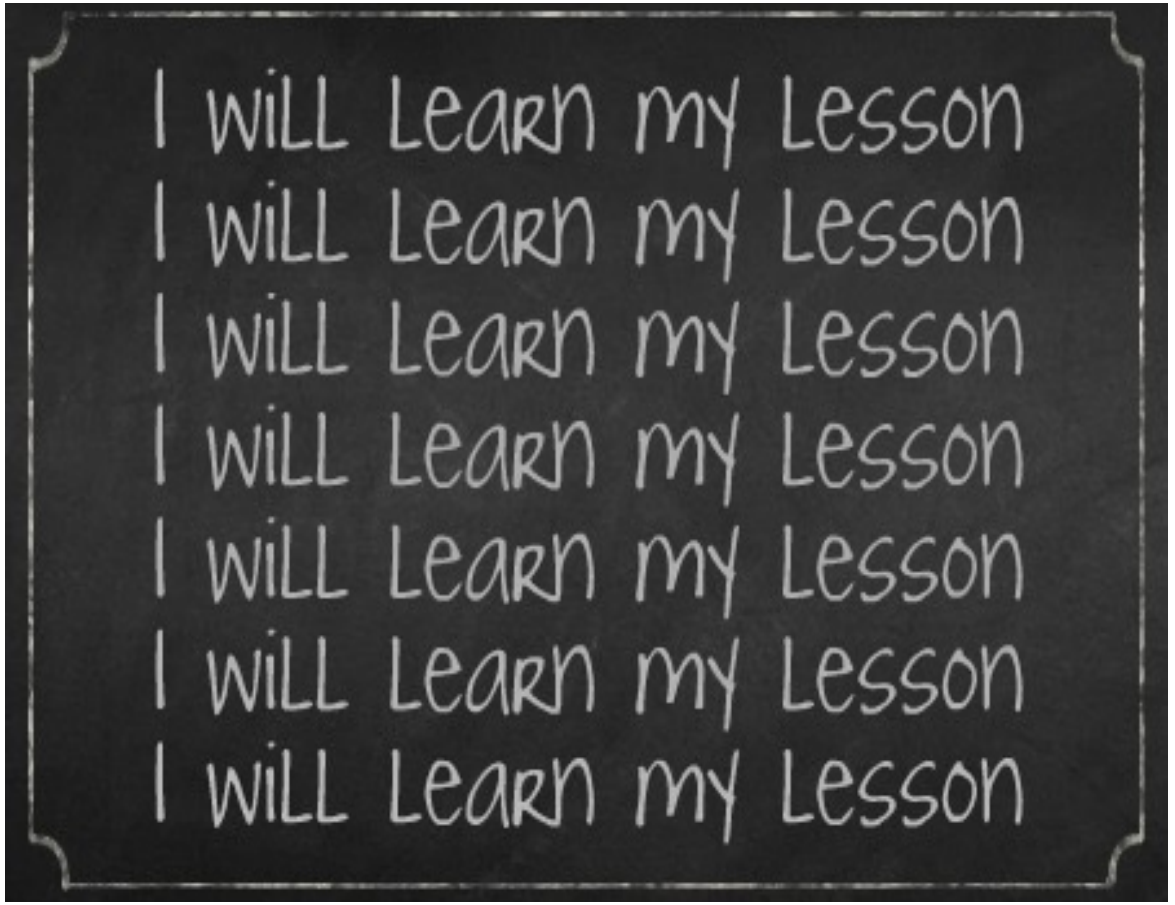
**There are no clear guidelines around much of this in the literature! Our approach when there is uncertainty and high variability is to at least aim for consensus, consistency and then evaluate

Lessons learned from establishing a clinical network for a rare(ish) disease

You will have to deal with uncertainty

- In the absence of guidance we found a high level of practice variability amongst BC nephrologists
  - Much of this appropriate as there is no 'right' answer
- We cannot let the lack of published guidelines be an excuse for inconsistent clinical management
- Even if the right answer is unclear, high variability does not serve anyone well; examine the current state, reach consensus, standardize and evaluate

Engage all stakeholders (including patients!!) in this process



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 blood pressure in the normal range and do your bloodwork. See you back in 6-12 months.

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

What we 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

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

Summary

- Our understanding of ADPKD is evolving, new treatment strategies are emerging
- Modern ADPKD management includes predicting risk of progression, tailoring treatments
  - The concept of identifying risk/speed of progression is now a mainstay of ADPKD care
- Improving care of (relatively) rare diseases requires a collaborative approach
- Variability in the face of uncertainty is a good opportunity for consensus building (remember to evaluate afterwards!)

Questions?