BCRenal

THE UNIVERSITY OF BRITISH COLUMBIA
Faculty of Medicine

Modern Management of Polycystic Kidney Disease

Rationale, tools and management of ADPKD in the KCC

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Nov 29, 2018

Outline

New insights into ADPKD and Rationale for an ADPKD clinic

- Better understanding of PKD
- New tools and treatments for PKD

Goals and anticipated management of ADPKD within the KCC

- Current state of PKD in BC
- Alignment of PKD care with KCC framework
- Best practices development and working group

Disclosures

Relevant to this topic, I disclose the following from Otsuka Canada Pharmaceuticals Inc:

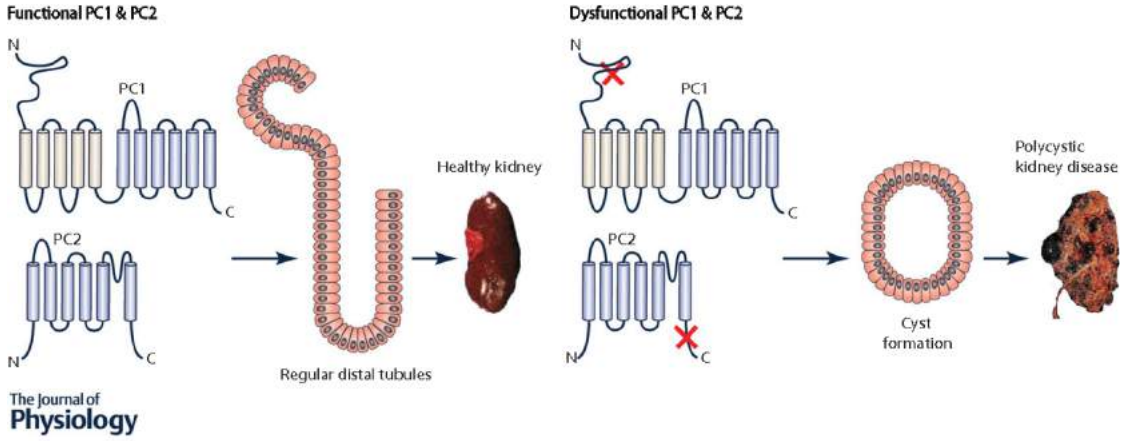
- An unrestricted grant to the BCPRA to assist in creation of the PKD registry
- Honoraria for participation in advisory boards, consultancy groups and development of educational material related to PKD

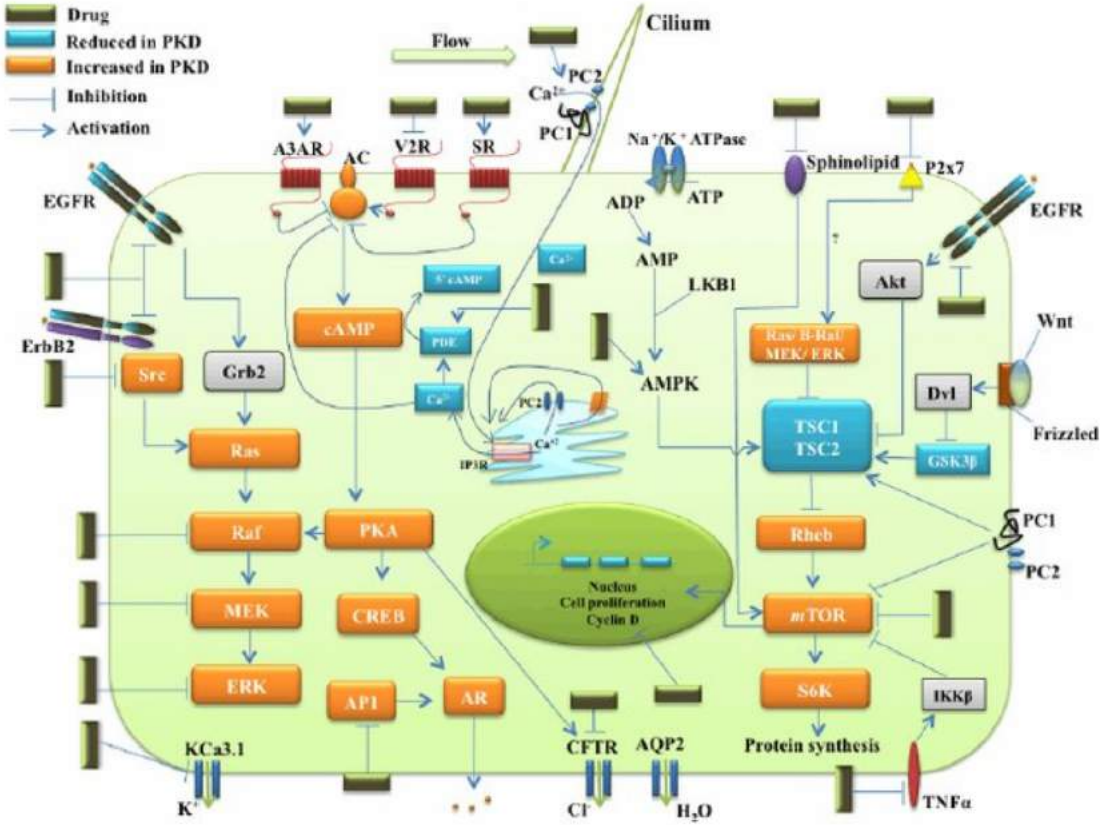
Epidemiology

- 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.

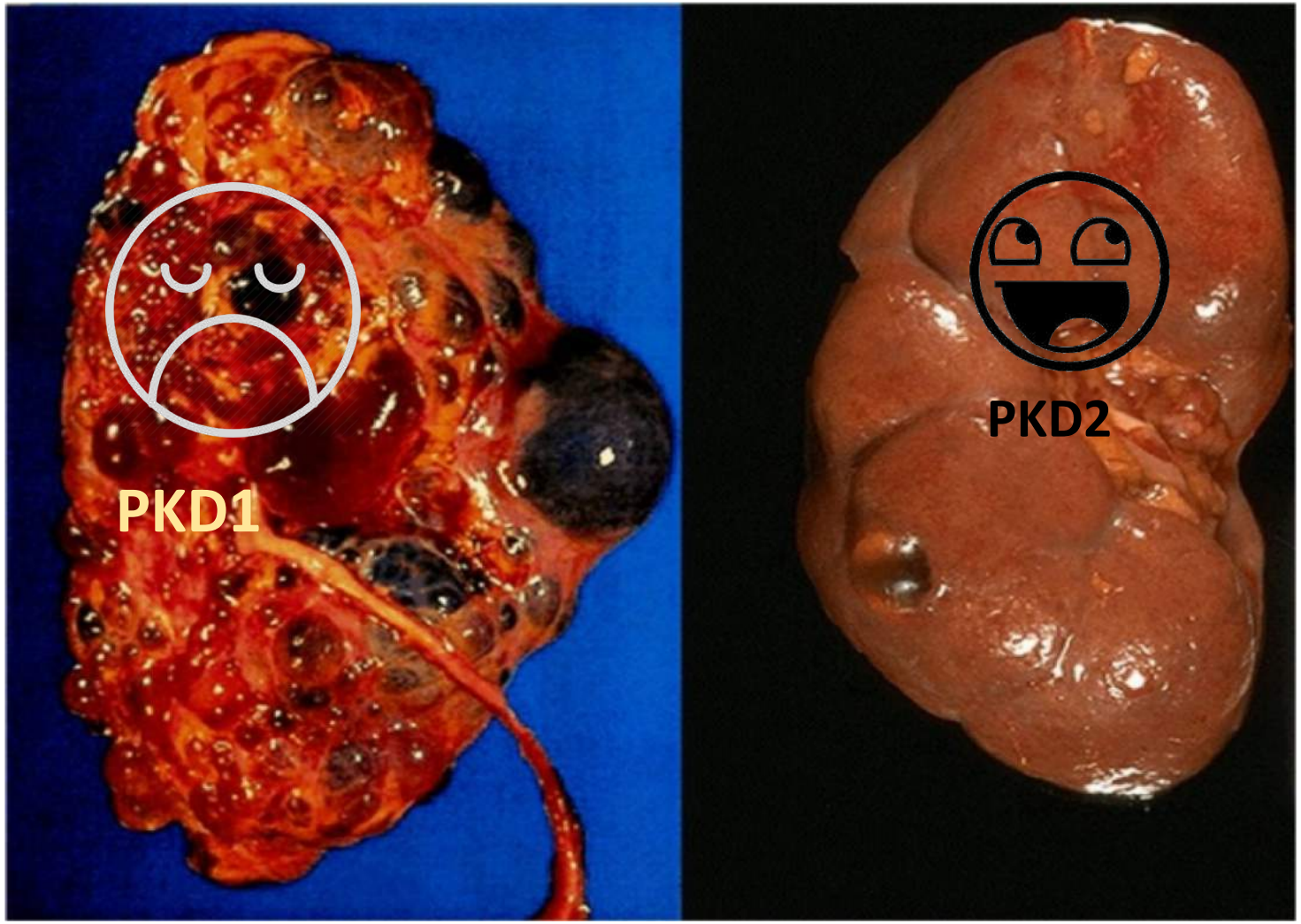
- Of patients with an identifiable etiology of ESRD, ADPKD is the 4th leading cause of ESRD in Canada

ADPKD is a more complex disease than previously appreciated

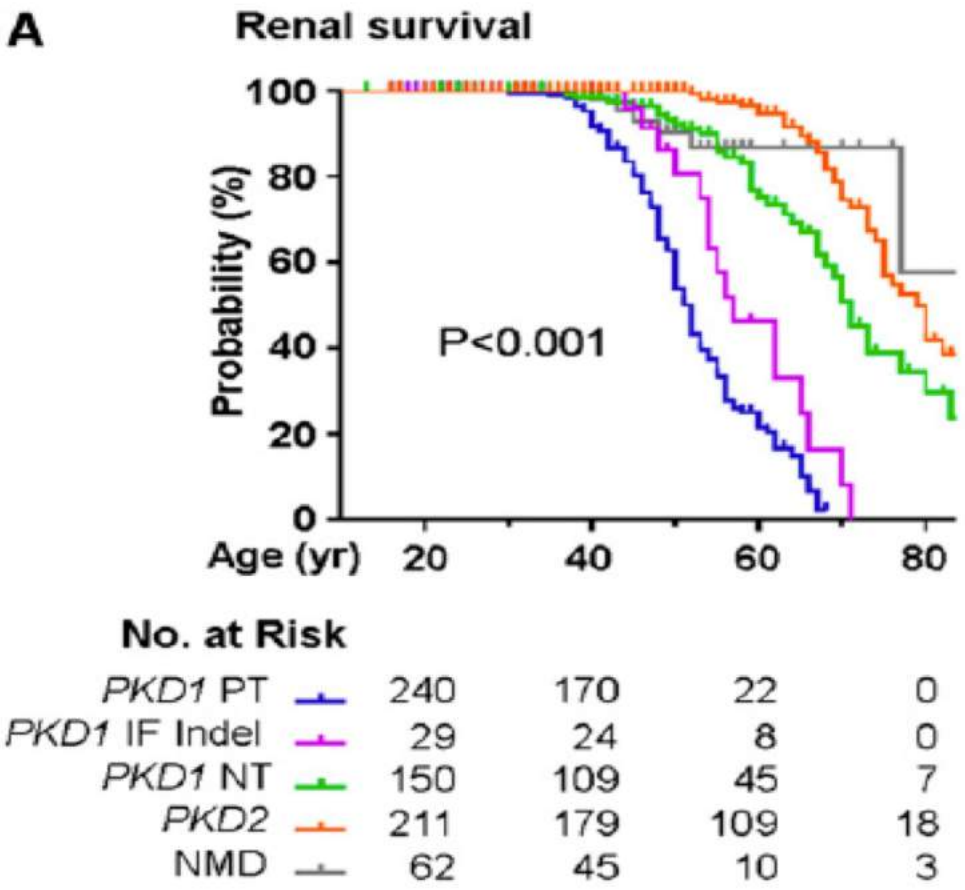

Functional PC1 & PC2
N
PC1
C
PC2
N
C
Regular distal tubules
Healthy kidney
Dysfunctional PC1 & PC2
N
PC1
C
PC2
N
C
Cyst formation
Polycystic kidney disease
The Journal of Physiology


Drug
Reduced in PKD
Increased in PKD
Inhibition
Activation
Flow
Cilium
PC2
PC1
A3AR
AC
V2R
SR
Na+/K+ ATPase
Sphinolipid
P2x7
EGFR
ADP
ATP
AMP
LKB1
Akt
EGFR
ErbB2
Src
Grb2
cAMP
PDE
AMPK
Wnt
Dvl
Frizzled
Ras
Ras/ B-Raf/ MEK/ ERK
TSC1 TSC2
GSK3β
Raf
PKA
Rheb
PC1
PC2
Nucleus
Cell proliferation
Cyclin D
MEK
CREB
mTOR
ERK
AP1
AR
S6K
IKKβ
KCa3.1
CFTR
AQP2
Protein synthesis
TNFα
K+
Cl-
H2O

Different faces of PKD



It gets more complicated…



There are a huge number of individual mutations, many of uncertain prognostic significance

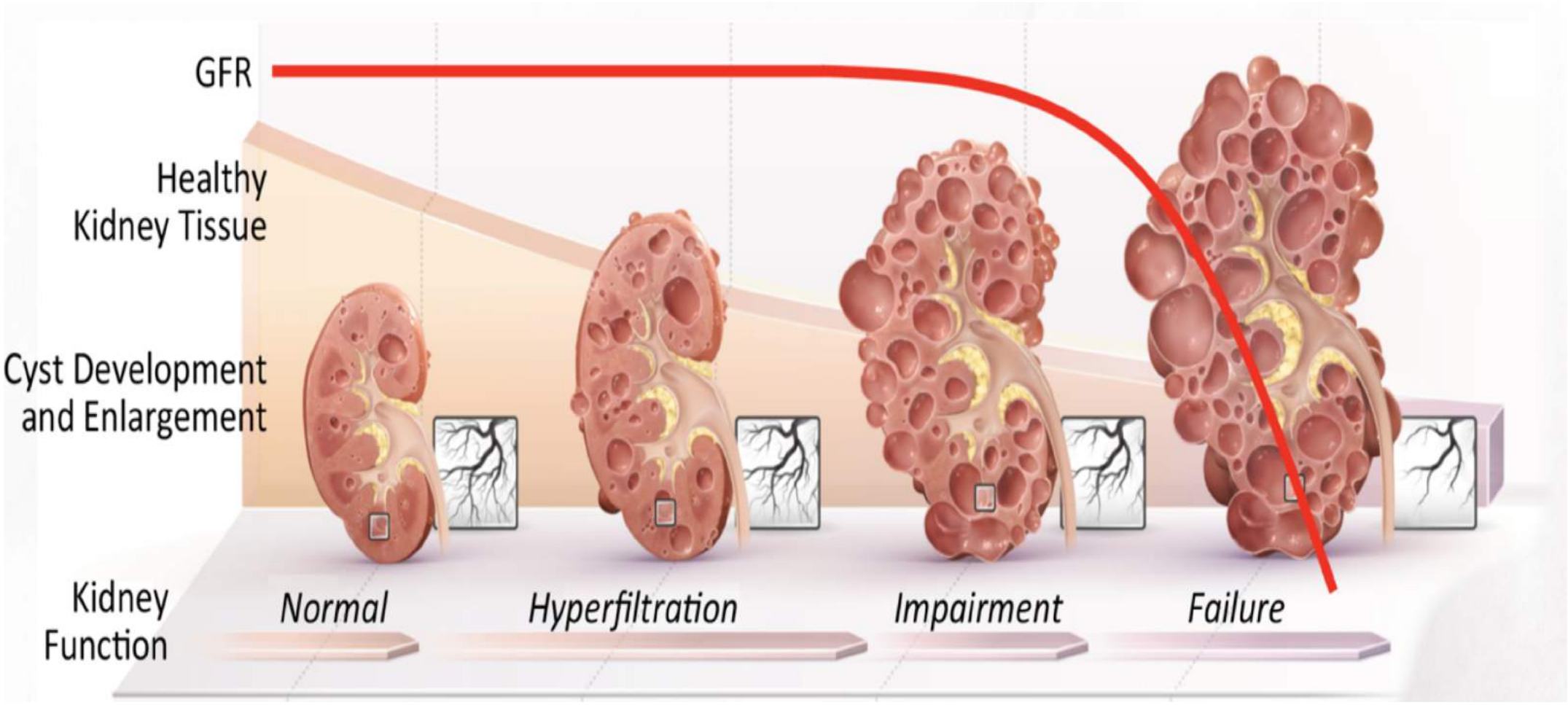
<u>Mayo PKD mutation database</u>

- 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

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.

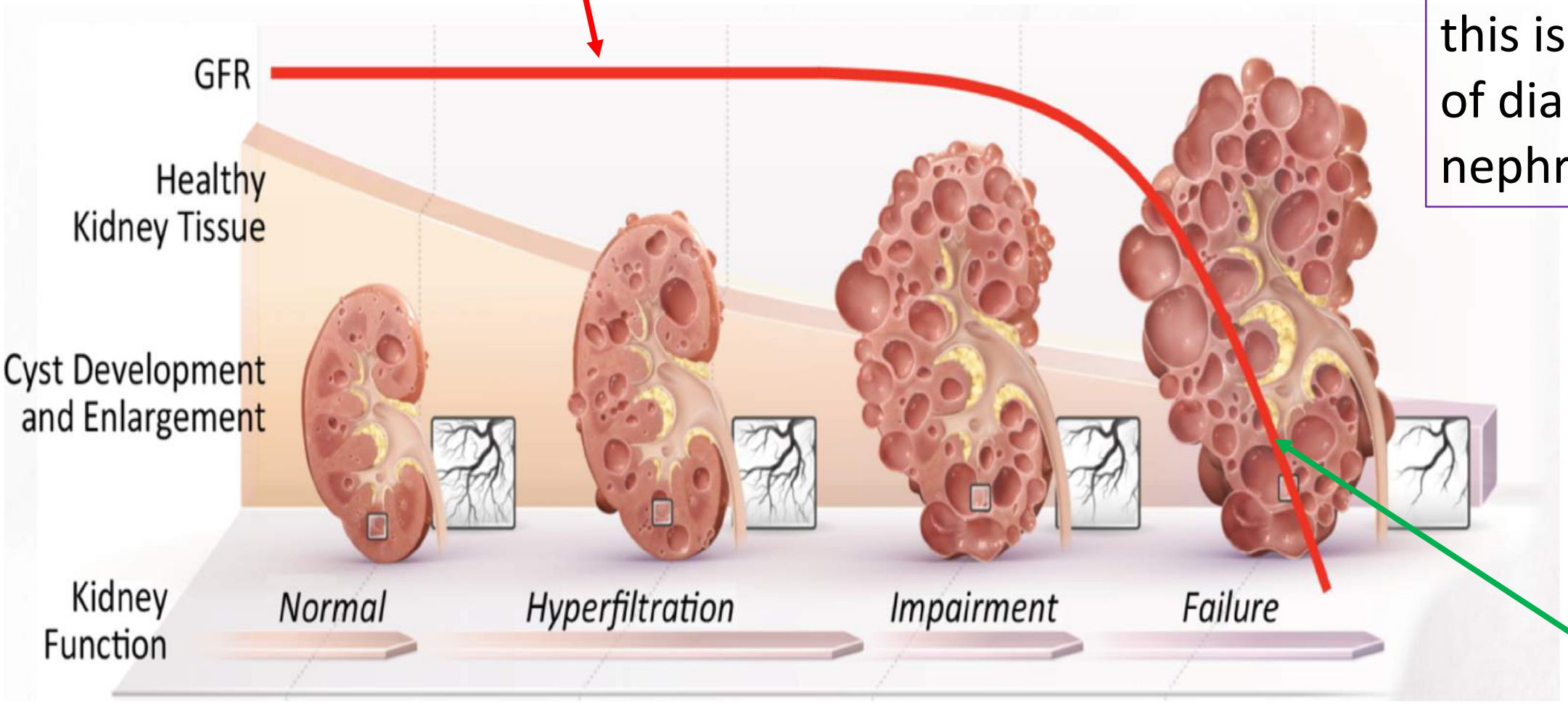
Modern understanding of ADPKD disease course



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

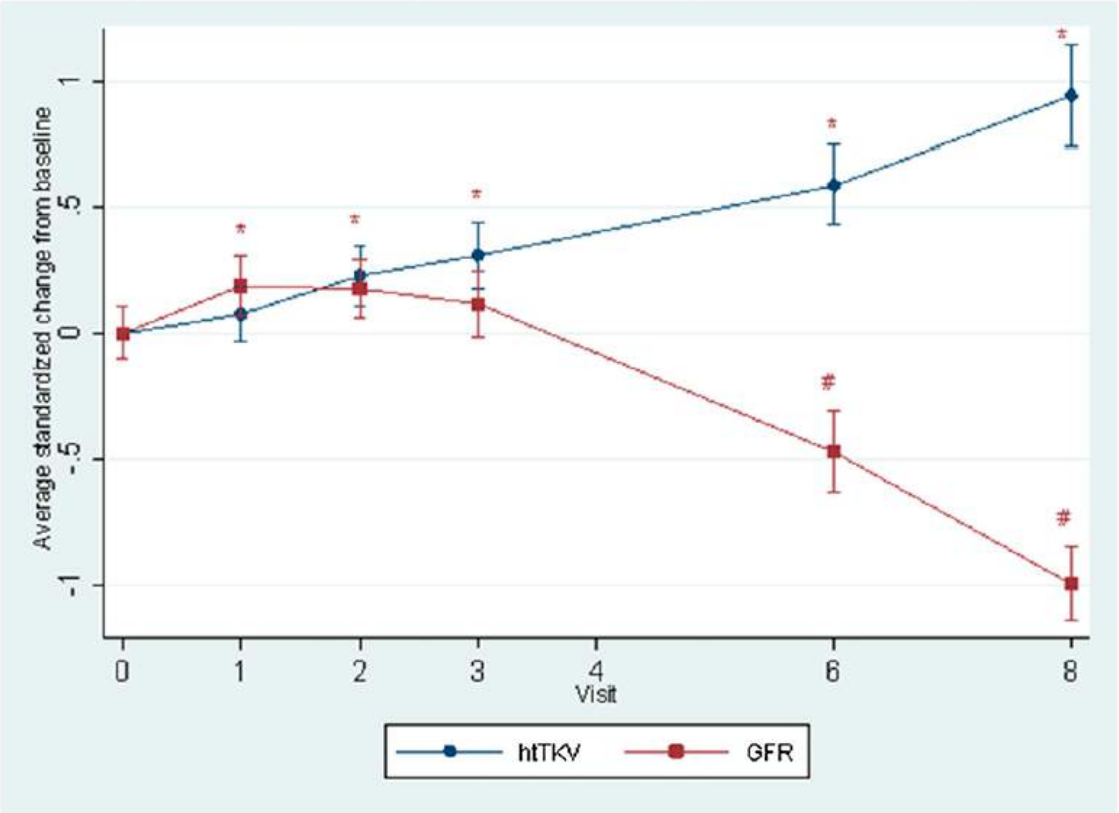


Upwards of 5ml/year decline

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

Tools to evaluate ADPKD are becoming more specialized

Changes in kidney size precede change in renal function



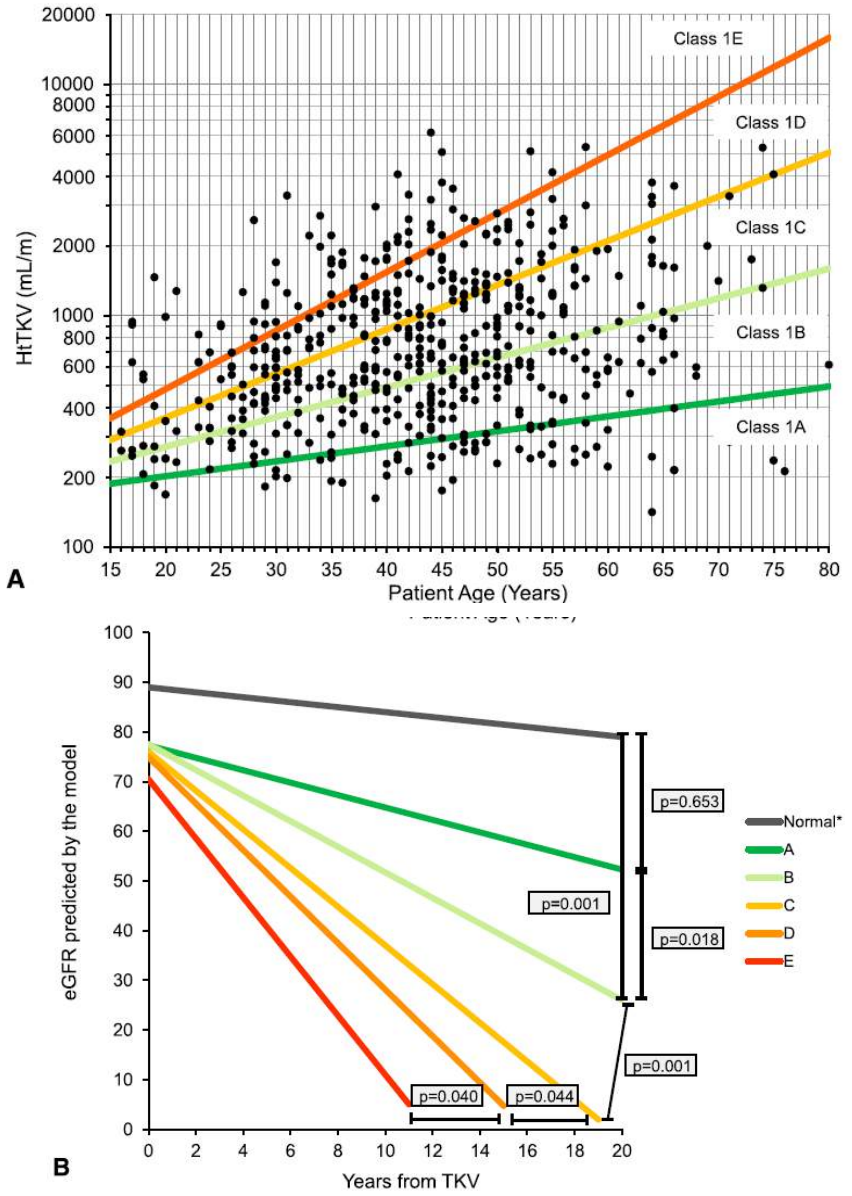
Significant changes in kidney volume can be detected years before changes in GFR

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.

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

TKV-based prognostication: the Mayo classification

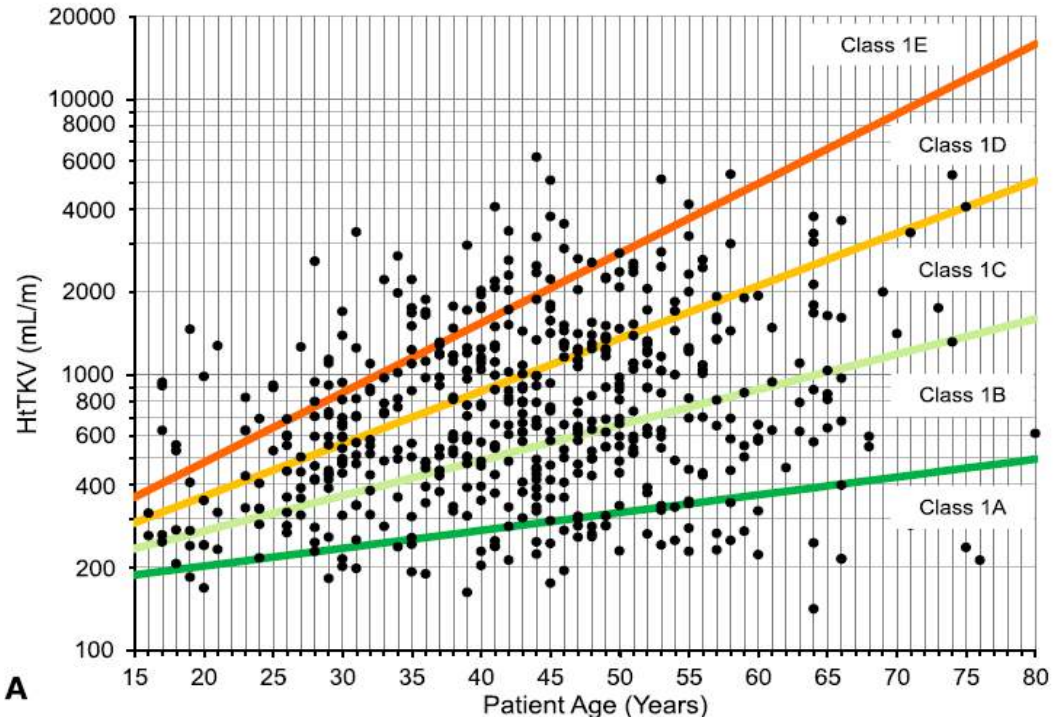
At present this appears to be the most robust individualized predictor of **early stage** progression in PKD patients (i.e., before GFR declines)



J Am Soc Nephrol 26: 160–172, 2015.

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%



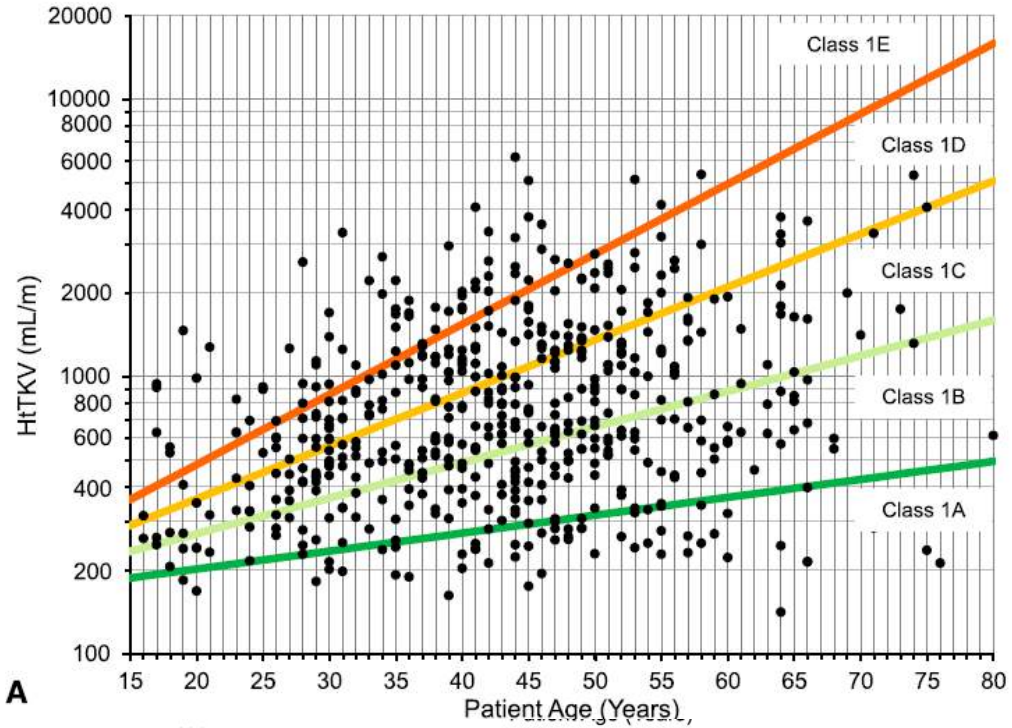
The 1A-1E classification is best thought of as a ***velocity of growth classification*** – the classes refer to the average annual growth in htTKV

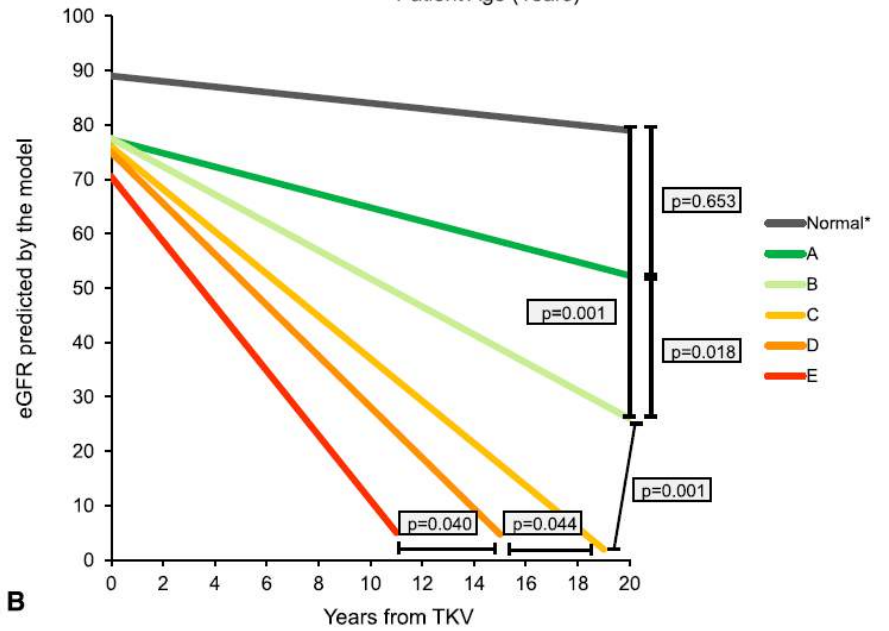
J Am Soc Nephrol 26: 160–172, 2015.

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.

ADPKD carries a higher disease burden than is recognized

Extra-renal manifestations of PKD

KIDNEY-RELATED

Pain and discomfort

Kidney stones

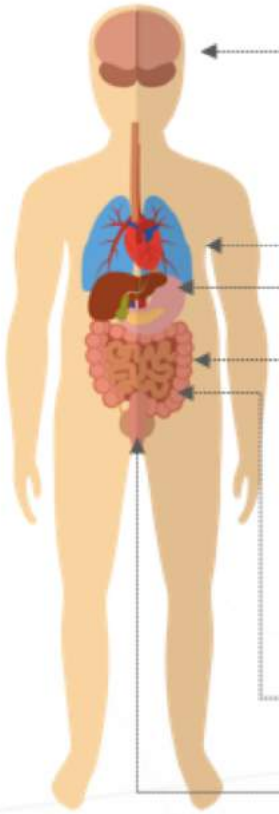
Cyst bleeds

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)

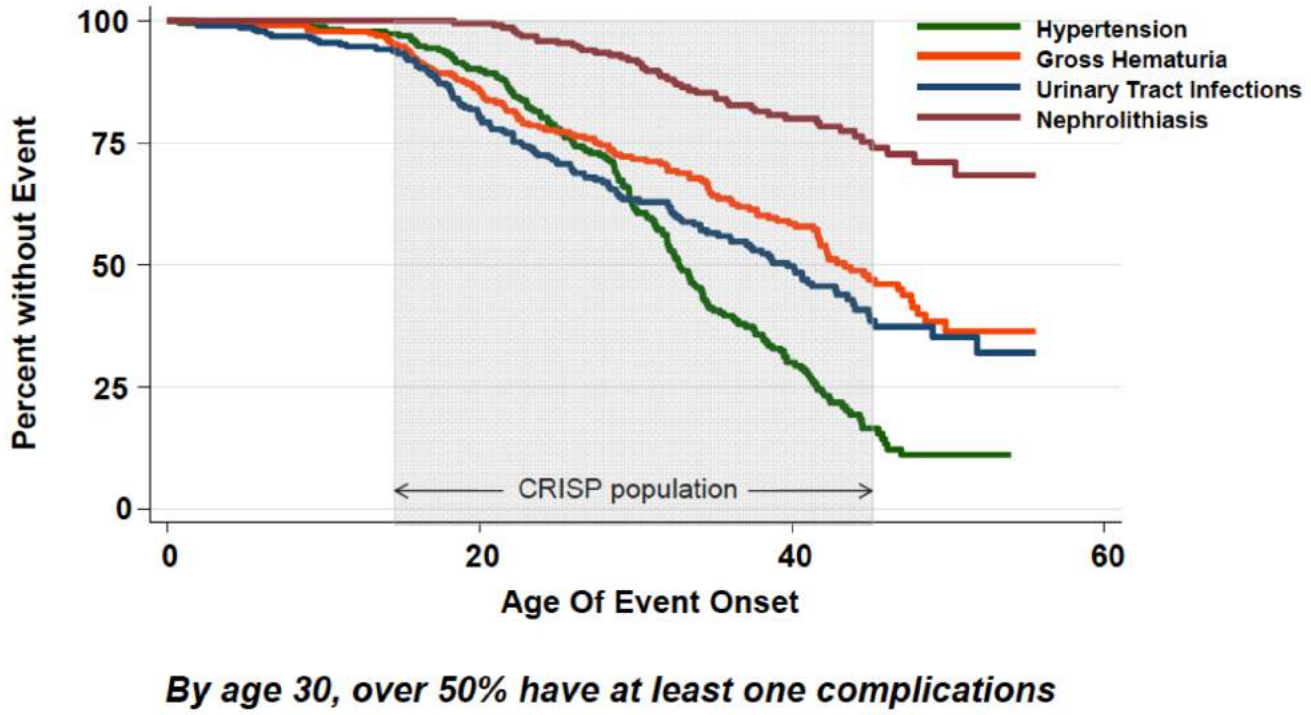
Seminal vesicle cysts

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.

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.

CK-35

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.

Abdominal symptoms

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

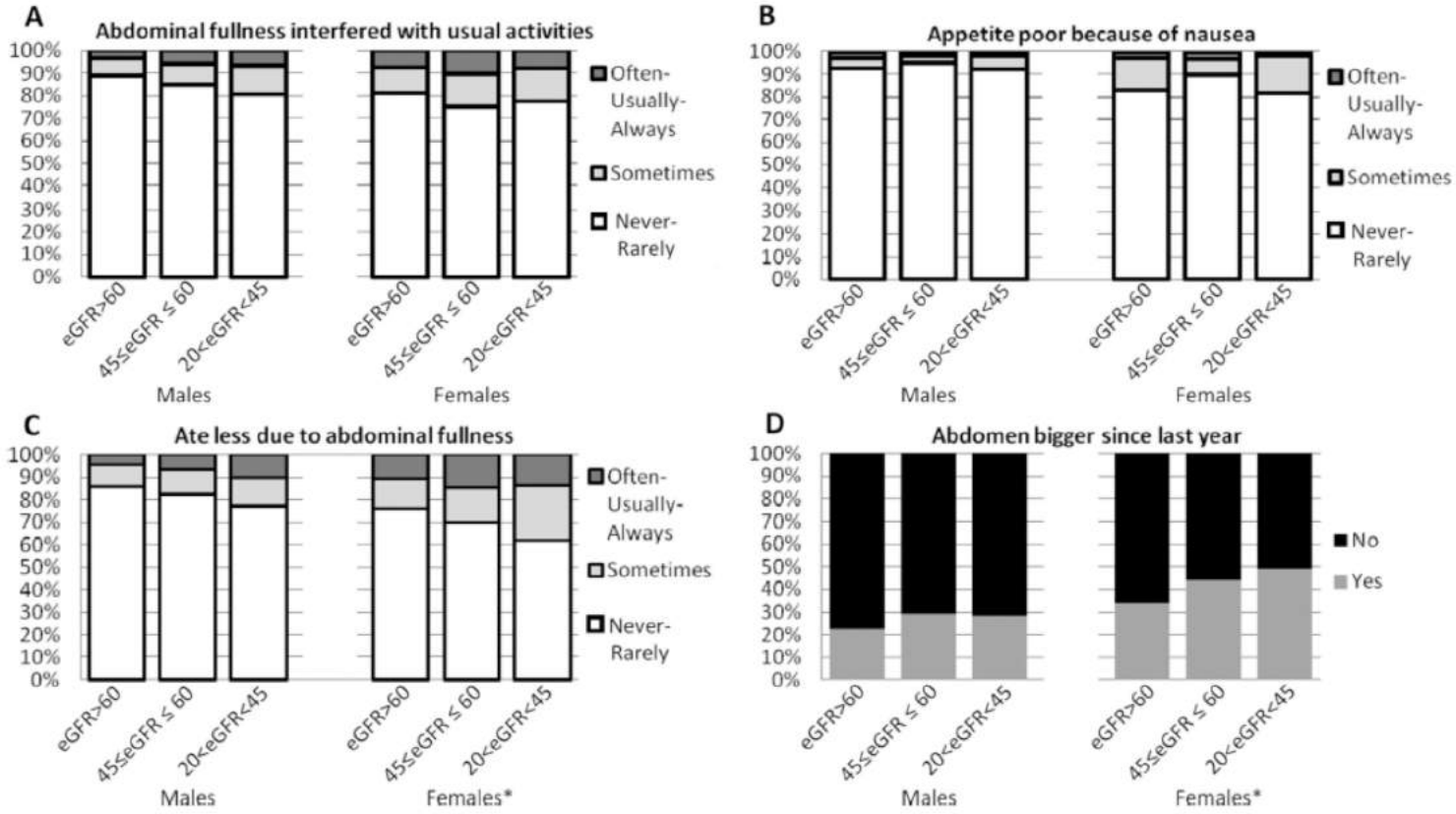
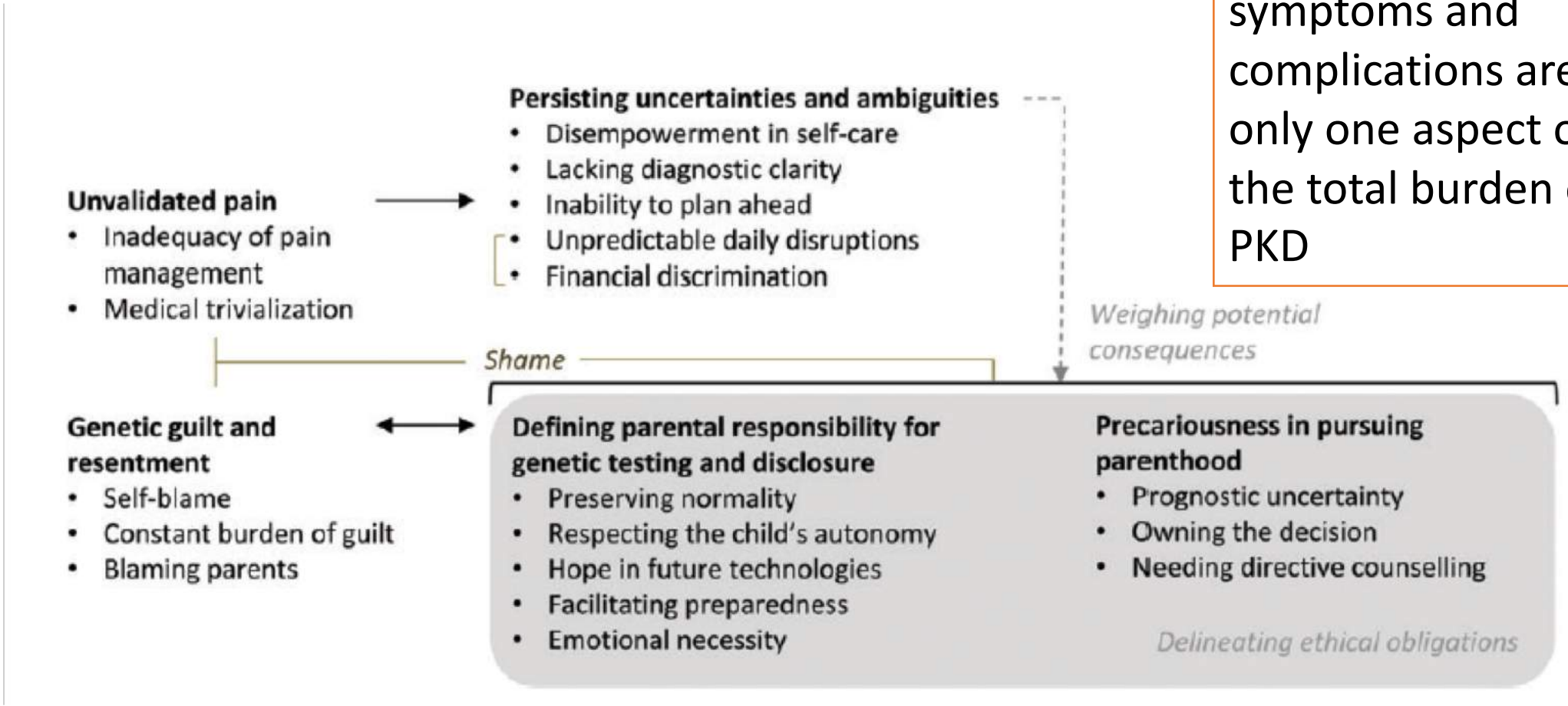


Figure 1. ADPKD patients' reports of frequency of abdominal symptoms

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.

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.

Treatments for ADPKD are becoming more specialized

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*

ORIGINAL ARTICLE

Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease

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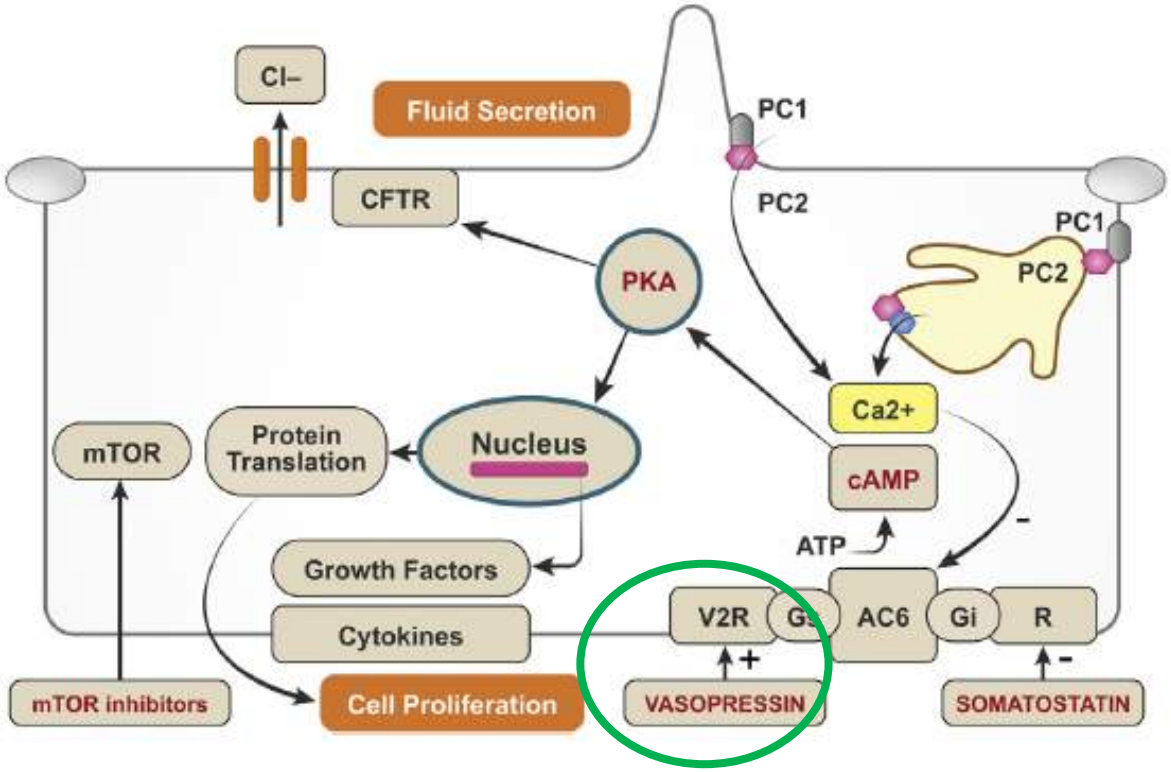
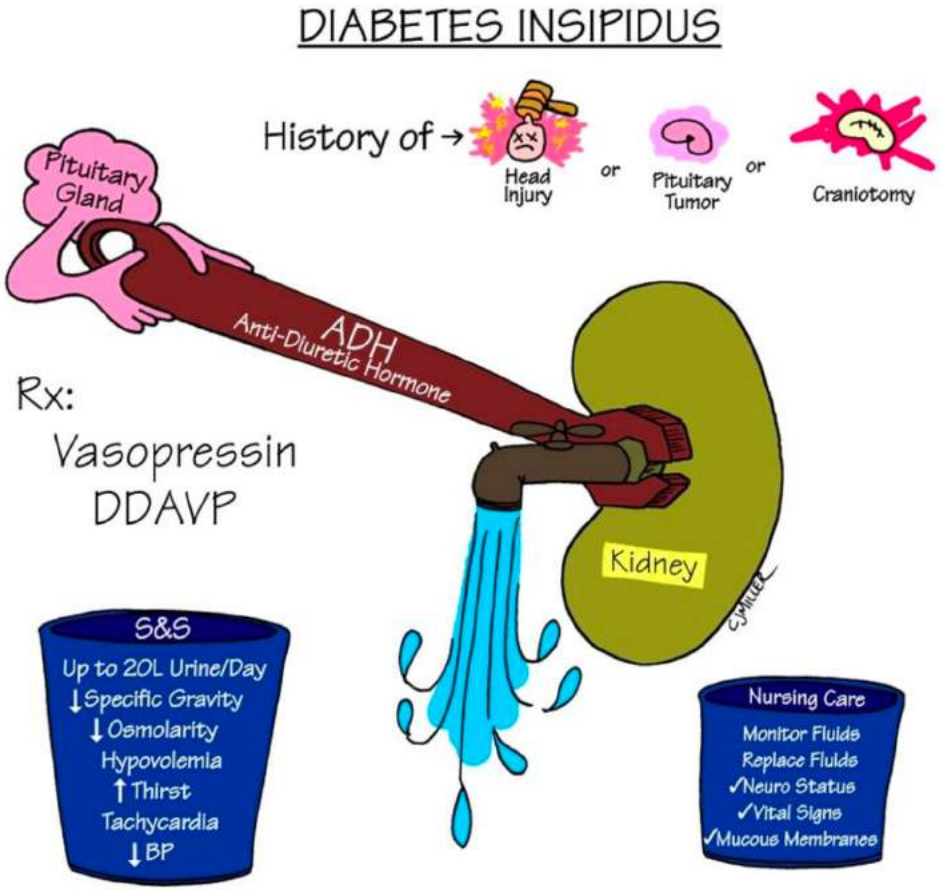
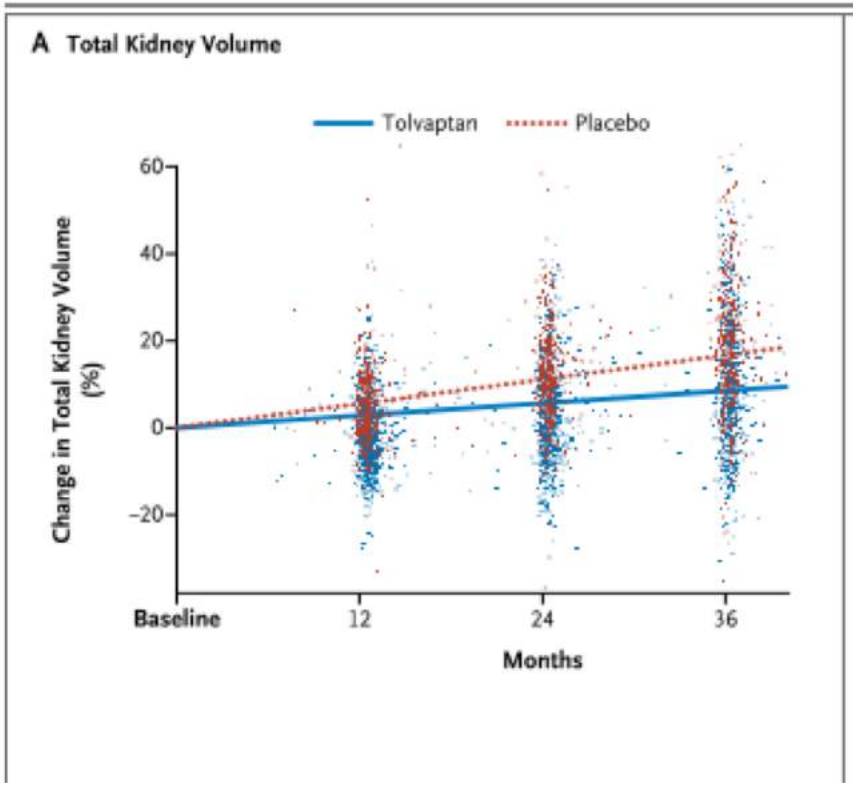
How tolvaptan (vasopressin 2 receptor antagonist) works





Results in early(earlier) stage patients

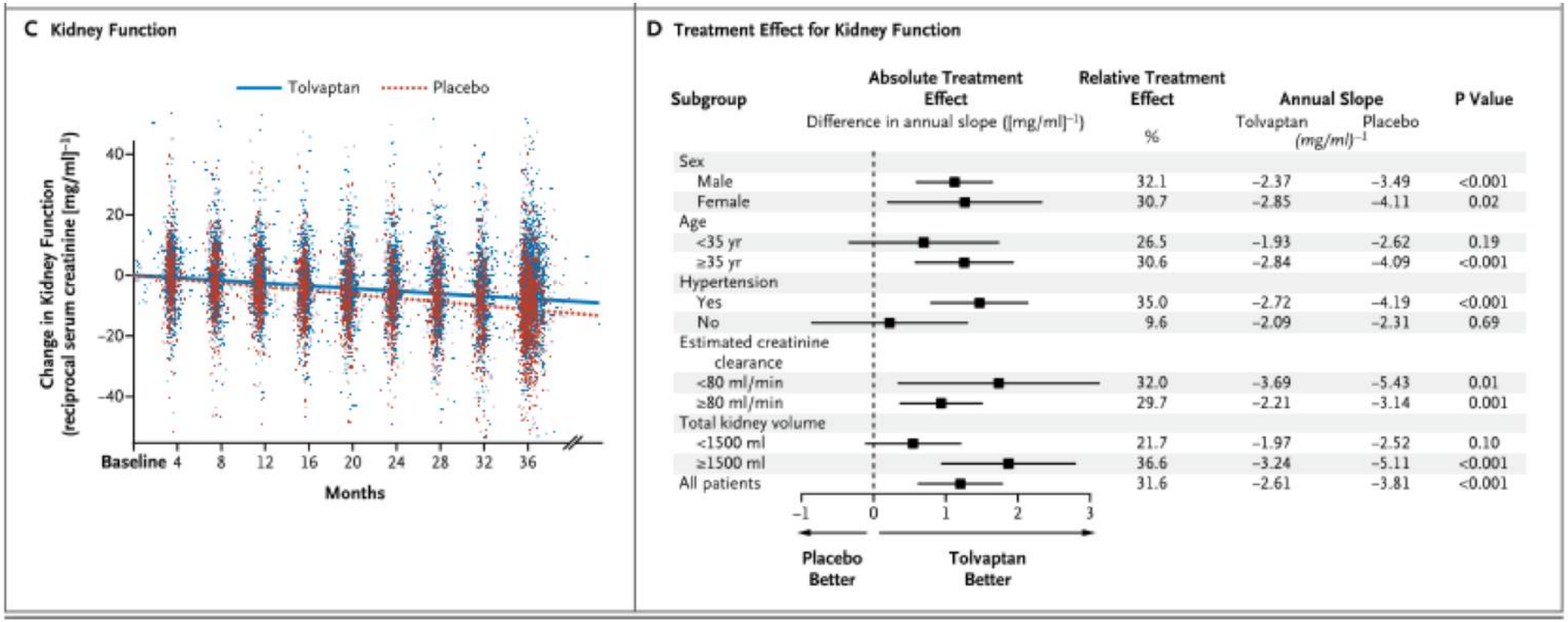


B Treatment Effect for Total Kidney Volume

Subgroup	Absolute Treatment Effect: Difference in annual slope (%/yr)	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

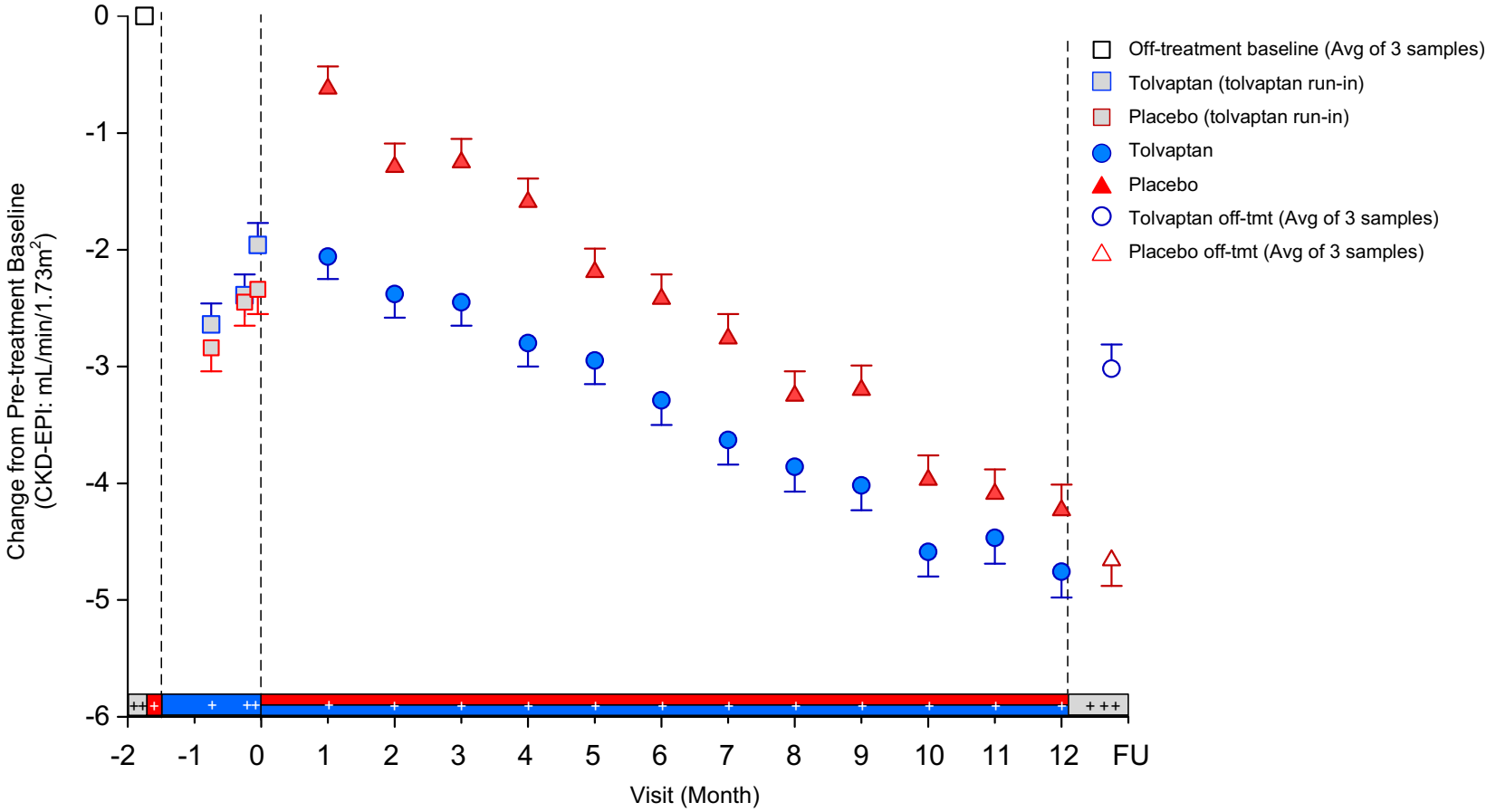
Increase in TKV was 2.8%/year(2.3-3.1%) in the tolvaptan group vs. 5.5%/year (5.1-6.0%) in the placebo group

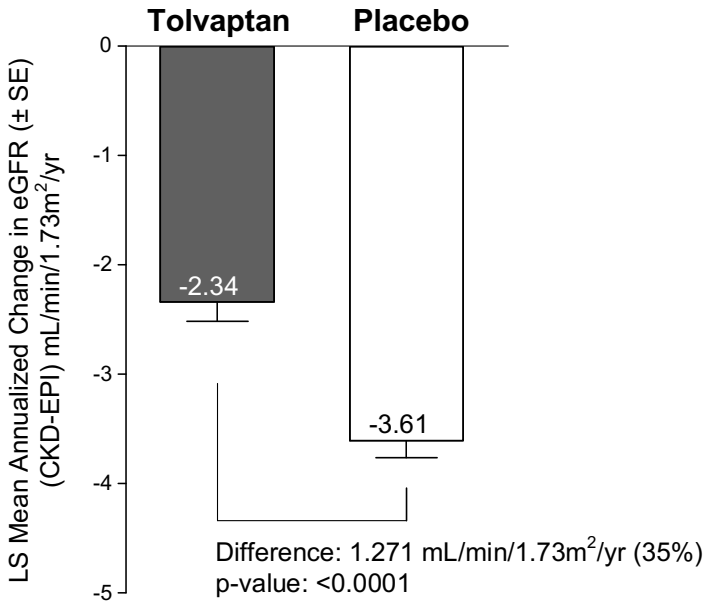
Results in early(earlier) stage patients



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

Results in later stage patients



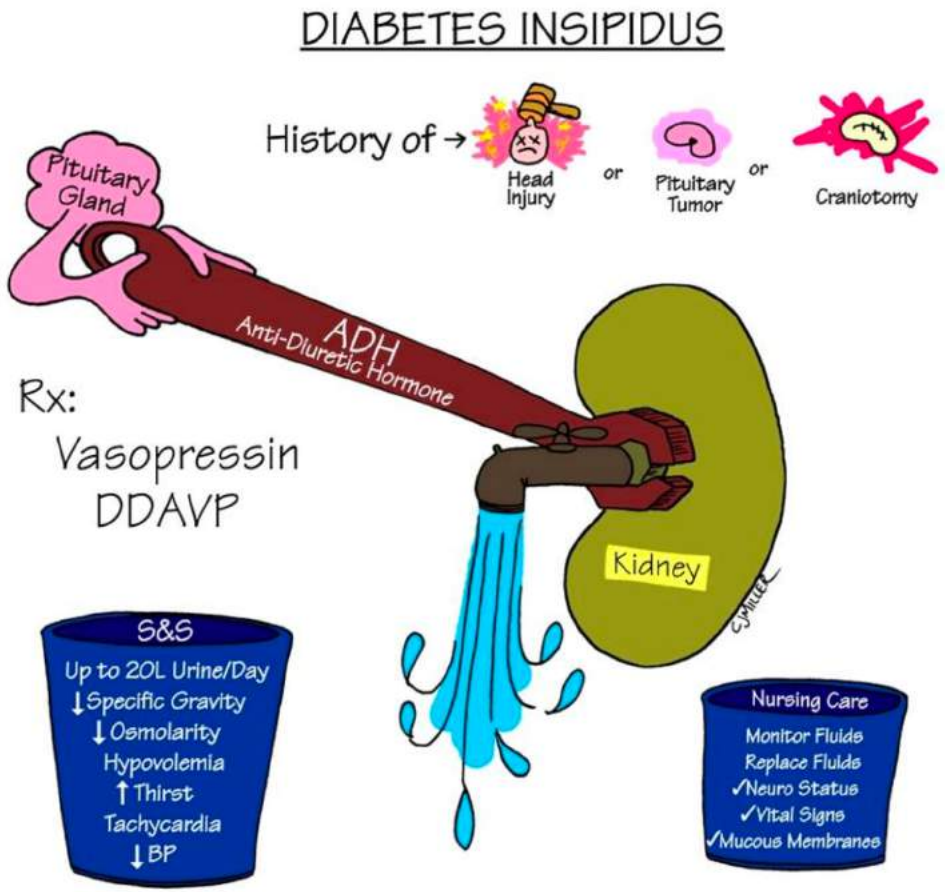


Adverse effects - aquaretic symptoms

This is a difficult drug for patients to work into their lives

It induces a different disease to slow the existing one

- There is a high rate of side effects and discontinuation

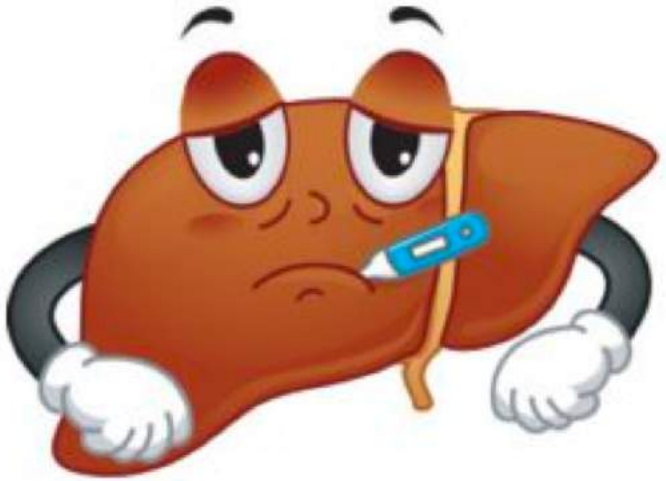


Dealing with aquaretic symptoms

- Judicious approach to dose titration
- Minimizing dietary solute intake (primarily salt and protein)
- Treat this like a ‘sick day’ medication - or more accurately, a ‘convenience day’ or ‘cheat day’ medication

Increased transaminases and need for monitoring

- Overall, there is a 4-5% rate of increased liver enzymes with tolvaptan
  To compare to other drugs associated with AST/ALT increases:
  - INH: up to 20%
  - MTX: 15%
  - Amiodarone: 3-6%
  - Lipitor: <2%



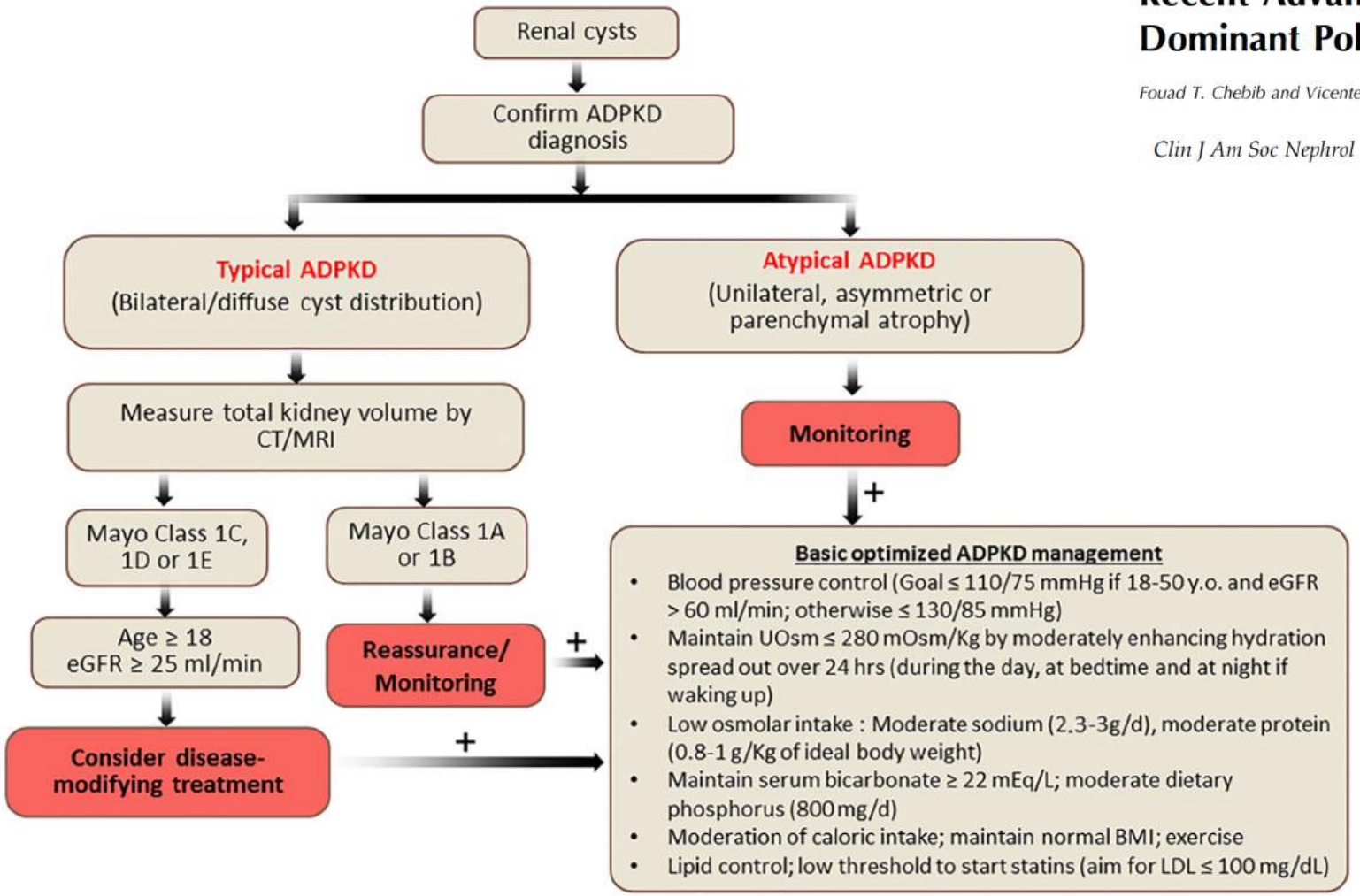
- But in the trials, 3 patients had AST/ALT >3xULN *and* bilirubin >2xULN.
  - Signal of much worse liver injury called **Hy's Law**

- The injury is reversible with drug discontinuation

- There is **mandatory** hepatic monitoring while on tolvaptan (monthly at first then q3 months)

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

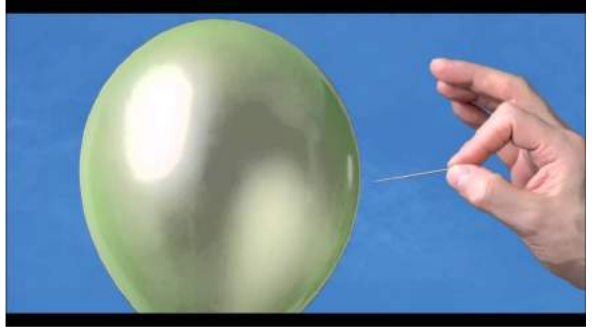
MAYO CLINIC

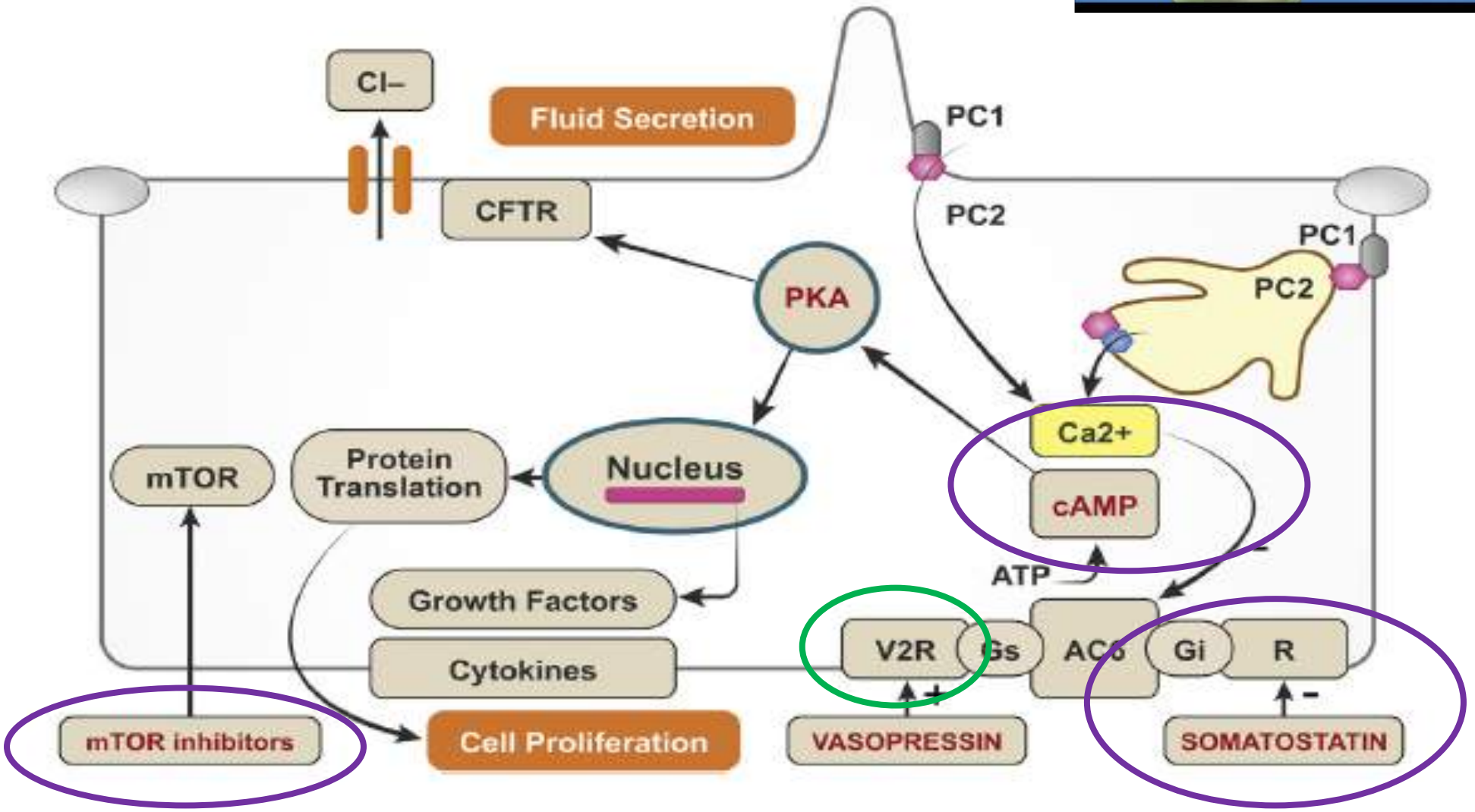
Table 2. Basic optimized management of adult patients with ADPKD

Intervention	Goal	Methods to Achieve Goal	Evidence[a]
Intensive BP control	≤110/75 mm Hg in: 1. 18–50-year-olds 2. eGFR>60 ml/min per 1.73 m^2 3. Particularly: Mayo Clinic class 1 C–E Intracranial aneurysm Valvular heart disease	Early detection is essential[b] By order of preference: 1. ACEI/ARB 2. α/β or cardioselective β-blocker 3. Dihydropyridine CCB 4. Diuretic Dietary Approaches to Stop Hypertension (DASH)-like diet at early stages	Grade 1B
	≤130/85 mm Hg in: 1. Other adult hypertensives		
Sodium	Moderate restriction (2.3–3 g/d)	Counseling	Grade 1C
	Adjust for extrarenal losses (hot climate, runners, sauna, bowel disease) if appropriate	Dietitian follow-up Monitor 24-h urine sodium	
Hydration	Moderately enhanced hydration spread out over 24 h (during the day, at bedtime, and at night if waking up)	Counseling	Grade 1C
	Maintain urine osmality ≤280 mOsm/kg	Monitor first morning urine osmality, plasma copeptin if available Water prescription(L)=$\frac{\text{24-hour urine solute load(mOsm)}}{280}$ + Insensible loss($\int$ 0.5 L)	
Protein	0.8–1.0 g/kg of ideal body wt	Dietitian Monitor protein intake: 6.25×(urine urea nitrogen in g/d+[0.03×weight in kilogram])	Grade 1C
Phosphorus	Moderate diet phosphate restriction (800 mg/d)	Dietician Read food labels and watch for food additives containing phosphates Use of phosphate binders not different from other advanced CKD when needed	Grade 2C
Acid base	Maintain plasma bicarbonate within the normal range (≥22 mEq/L)	Increase fruits/vegetables (2–4 cups/d) Oral sodium bicarbonate if needed	Grade 2B
Caloric intake	Maintain normal BMI Moderation in caloric intake	Dietitian follow-up Regular exercise	Grade 1C
Lipid control	Aim for serum LDL ≤100 mg/dl	Dietician Regular exercise Statin if needed (ezetimibe if intolerant to statin)	Grade 2B

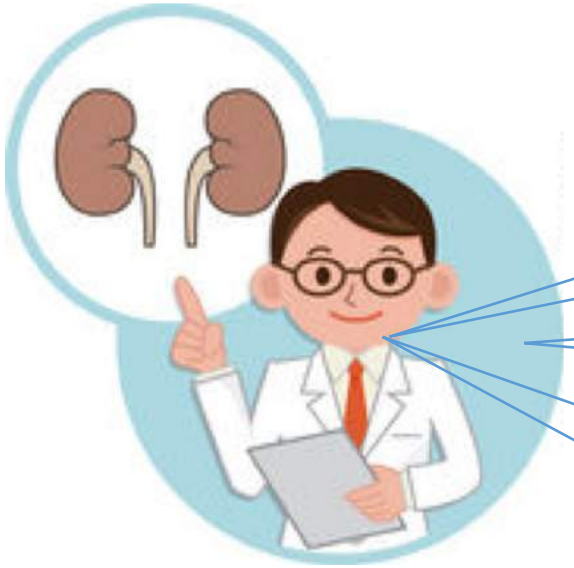
ADPKD, autosomal dominant polycystic kidney disease; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blocker; BMI, body mass index.
[a]Grading of levels of evidence is provided in Supplemental Table 1.
[b]Screen children at risk every 3 years starting at age 5 years. Children with hypertension should be referred and managed by experts in pediatric hypertension.

Other targets in PKD





What we have done with PKD in the past

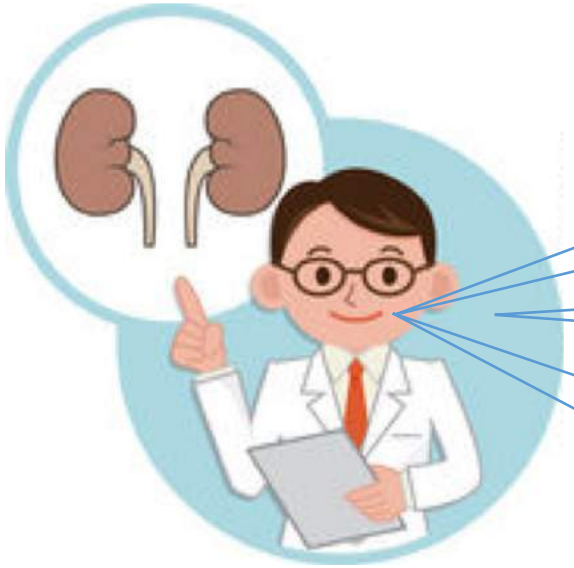


Let’s confirm the diagnosis and then we will tell you about screening your family members

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 need to do with ADPKD now

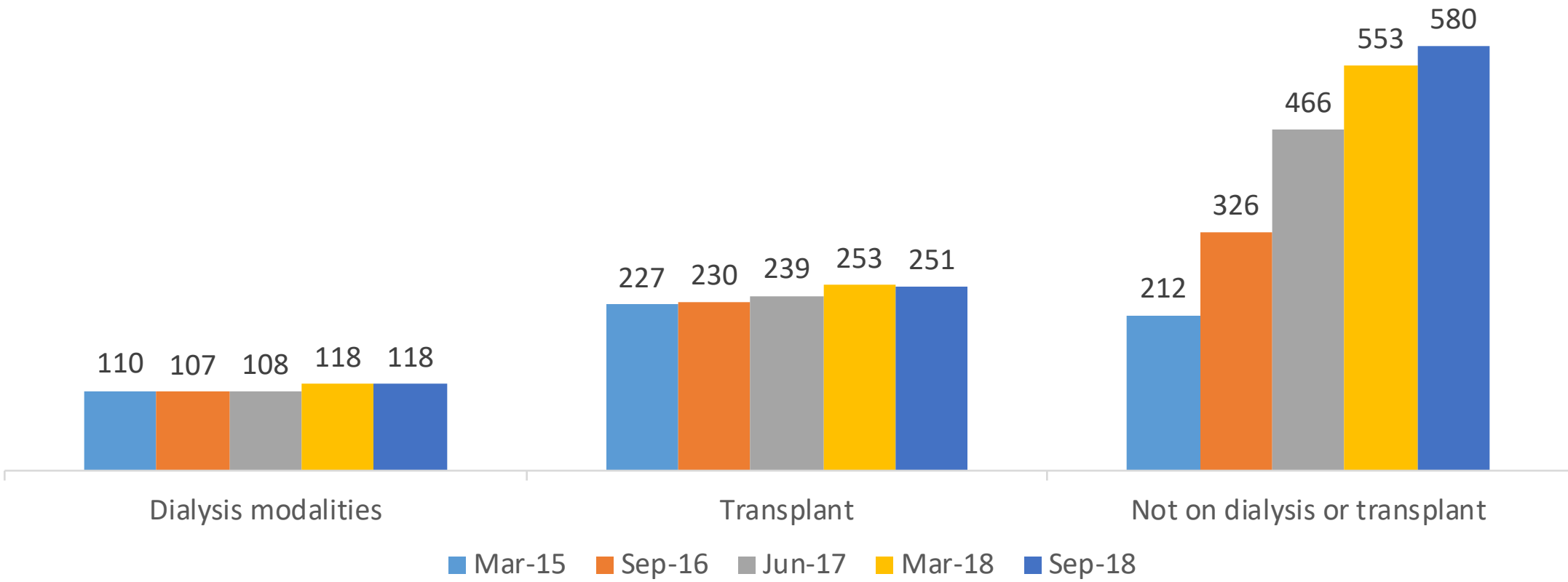


Tell us what your family screening, reproductive, financial, symptom and renal failure concerns are and we will discuss those

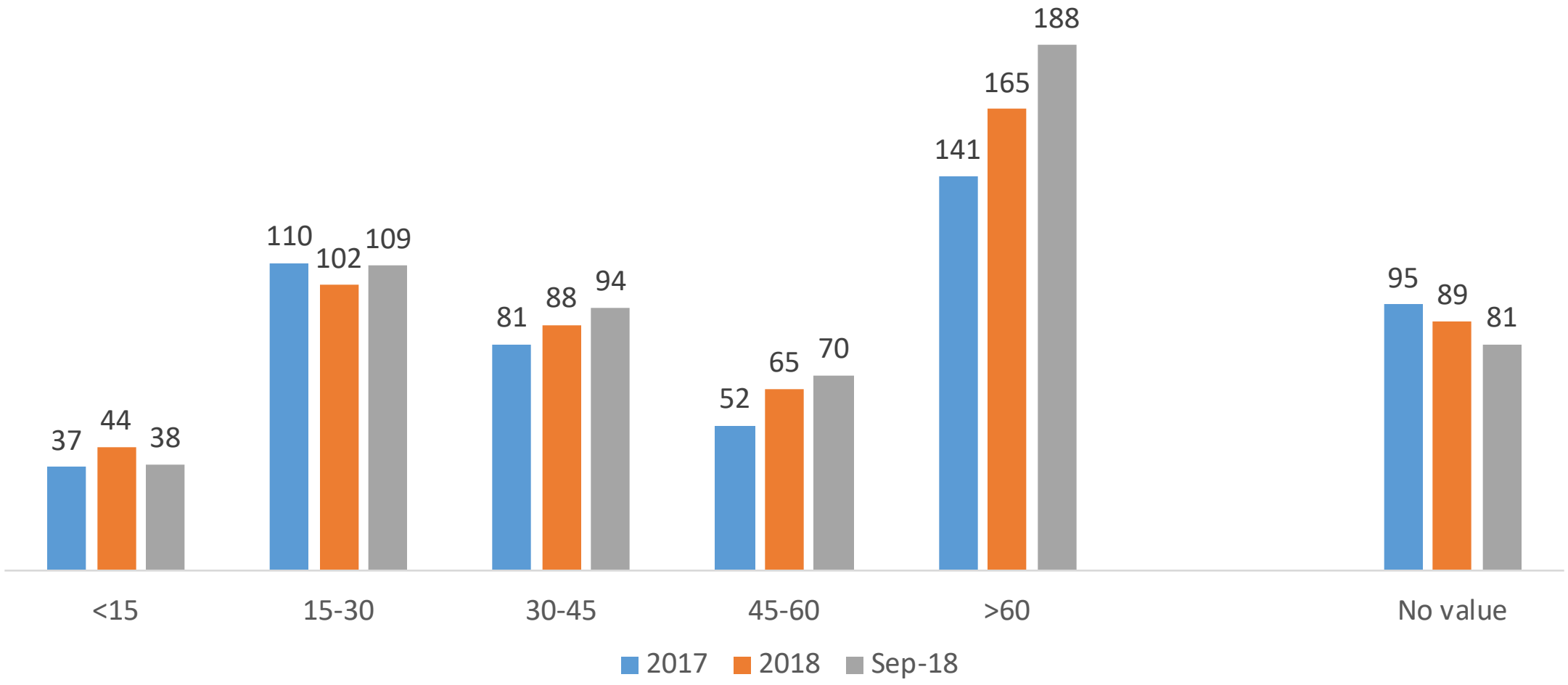
We will use imaging and other tools to more accurately predict your renal progression

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

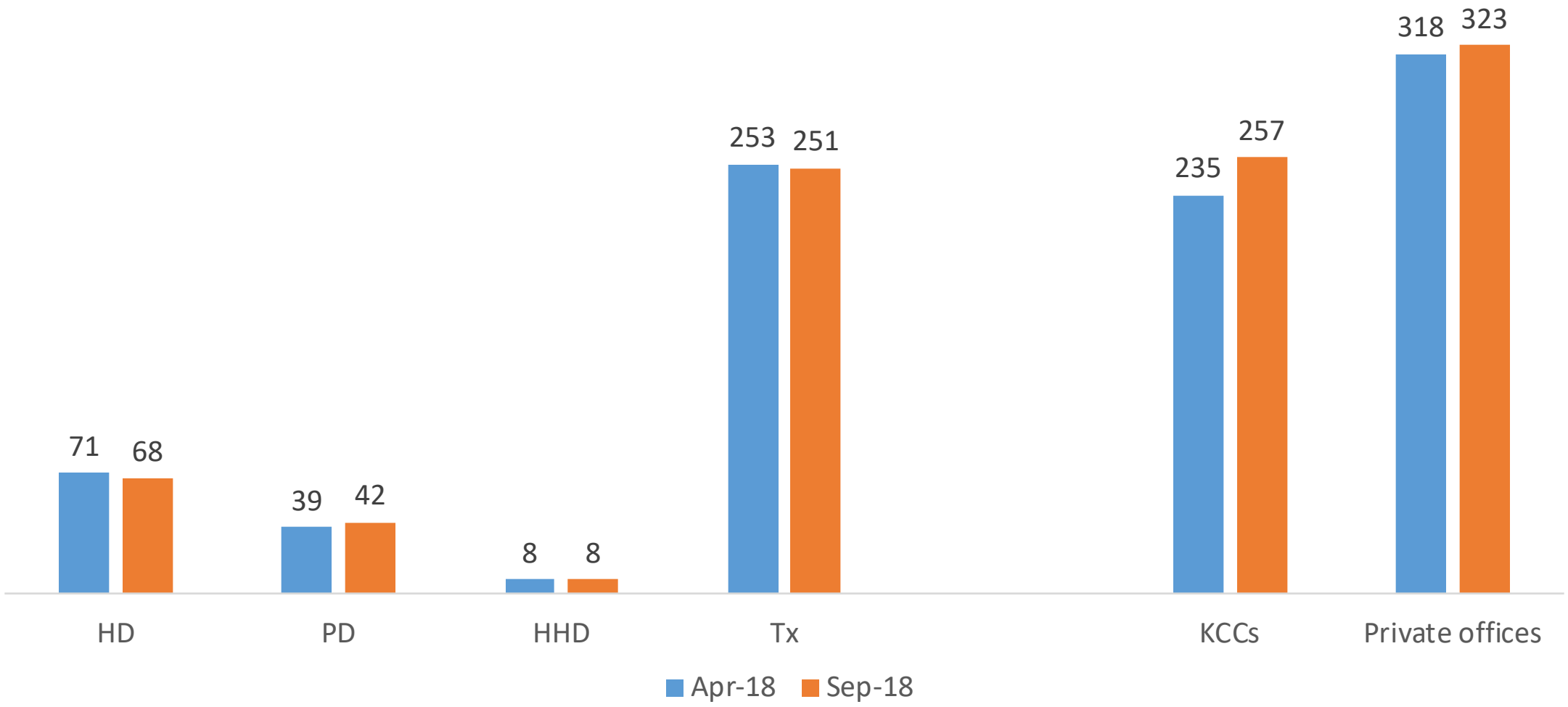
PKD patients in BC that we know of (ADPKD registry)



Many of the patients identified are early stage



Many are in KCC, more are not



Modern management of ADPKD aligns with goals of KCC

- Early identification and care
  - All documents (KCC best practices, ADPKD guidelines) suggest early referral
- Evaluation of risk of progression, implementation of tailored treatment strategies
- Interprofessional programs focusing on different aspects of the disease process and experience

Table 2. Basic optimized management of adult patients with ADPKD

Intervention	Goal	Methods to Achieve Goal	Evidence[a]
Intensive BP control	≤110/75 mm Hg in: 1. 18–50-year-olds 2. eGFR>60 ml/min per 1.73 m^2 3. Particularly: Mayo Clinic class 1 C–E Intracranial aneurysm Valvular heart disease ≤130/85 mm Hg in: 1. Other adult hypertensives	Early detection is essential[b] By order of preference: 1. ACEI/ARB 2. α/β or cardioselective β-blocker 3. Dihydropyridine CCB 4. Diuretic Dietary Approaches to Stop Hypertension (DASH)-like diet at early stages	Grade 1B
Sodium	Moderate restriction (2.3–3 g/d) Adjust for extrarenal losses (hot climate, runners, sauna, bowel disease) if appropriate	Counseling Dietitian follow-up Monitor 24-h urine sodium	Grade 1C
Hydration	Moderately enhanced hydration spread out over 24 h (during the day, at bedtime, and at night if waking up) Maintain urine osmality ≤280 mOsm/kg	Counseling Monitor first morning urine osmality, plasma copeptin if available Water prescription(L) = $\frac{\text{24-hour urine solute load(mOsm)}}{280}$ + Insensible loss($\int$ 0.5 L)	Grade 1C
Protein	0.8–1.0 g/kg of ideal body wt	Dietitian Monitor protein intake: 6.25×(urine urea nitrogen in g/d+[0.03×weight in kilogram])	Grade 1C
Phosphorus	Moderate diet phosphate restriction (800 mg/d)	Dietician Read food labels and watch for food additives containing phosphates Use of phosphate binders not different from other advanced CKD when needed	Grade 2C
Acid base	Maintain plasma bicarbonate within the normal range (≥22 mEq/L)	Increase fruits/vegetables (2–4 cups/d) Oral sodium bicarbonate if needed	Grade 2B
Caloric intake	Maintain normal BMI Moderation in caloric intake	Dietitian follow-up Regular exercise	Grade 1C
Lipid control	Aim for serum LDL ≤100 mg/dl	Dietician Regular exercise Statin if needed (ezetimibe if intolerant to statin)	Grade 2B

ADPKD, autosomal dominant polycystic kidney disease; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blocker; BMI, body mass index.
[a]Grading of levels of evidence is provided in Supplemental Table 1.
[b]Screen children at risk every 3 years starting at age 5 years. Children with hypertension should be referred and managed by experts in pediatric hypertension.

Coming soon: Best practices for management of ADPKD in the KCC

- Goal will be a complement to existing best practices
- How to implement modern treatment strategies within the KCC
- Not a standalone document, not meant to be a standalone clinic

SHAMELESS PLUG

- Working group formed, but we would love to have you!
  - Email me if you would like to join
- Seeking multidisciplinary input, involvement from across the province

Summary

- Our understanding of ADPKD is evolving, new treatment strategies
- Modern management includes predicting risk of progression, tailoring treatments
- There are a host of management strategies encompassing many dimensions of care to consider in ADPKD
- The KCC framework is well suited to these needs, with some specific adjustments for ADPKD patients
  - Stay tuned for the best practices document and let me know if you want to be involved!

Questions/comments