BCKD19
BC KIDNEY DAYS

Advances in management of ADPKD: a comprehensive approach

Fouad T. Chebib, MD, FASN
Assistant Professor of Medicine
Mayo Clinic College of Medicine and Science

Disclosures

- No conflict of interest

MAYO CLINIC

BCKD19
BC KIDNEY DAYS

Objectives

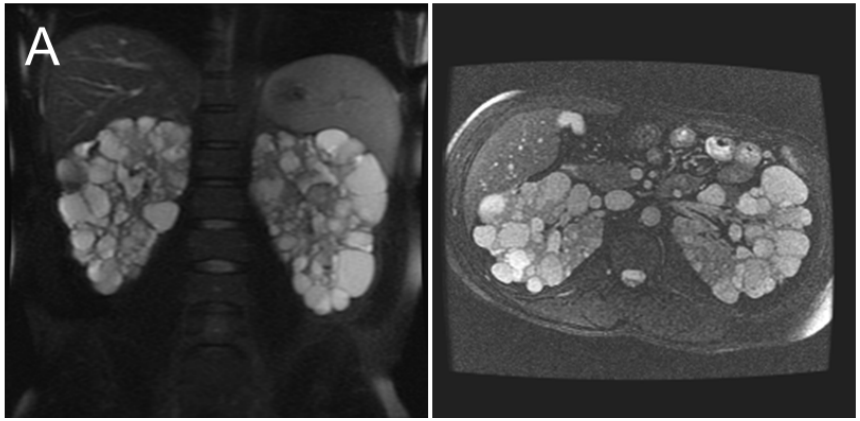
- Updates in diagnosis and prognosis of ADPKD
- Advances in management of ADPKD patients:
  - Multidisciplinary and comprehensive approach
  - Role of disease-modifying treatments

MAYO CLINIC

BCKD19 BC KIDNEY DAYS

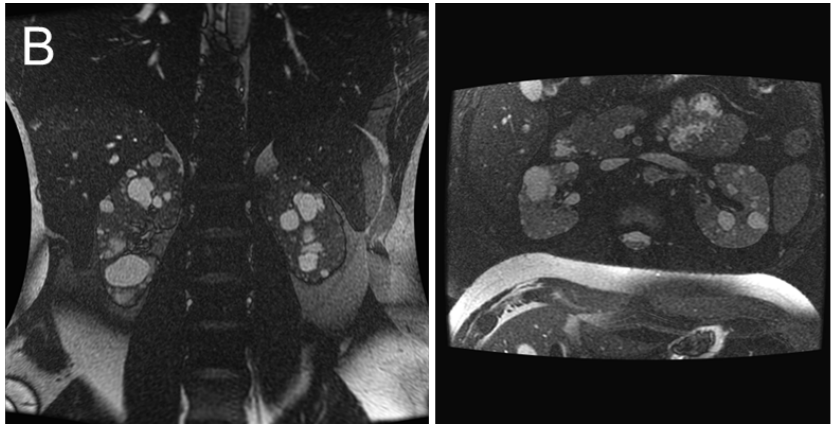
Two patients with renal cysts

27 yo male
eGFR 91 ml/min



Estimated onset of ESKD in **13** years
Disease-modifying treatment

27 yo male
eGFR 91 ml/min

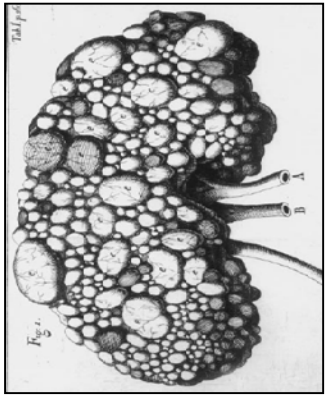


Estimated onset of ESKD in **43** years
Basic optimized management

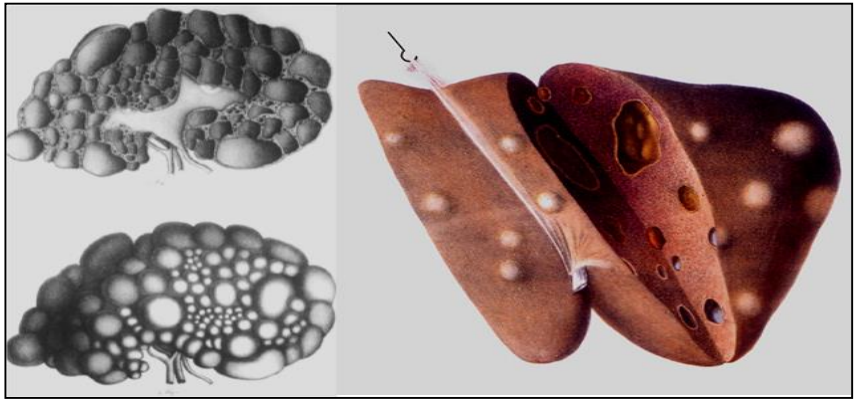
MAYO CLINIC

BCKD19
BC KIDNEY DAYS

For centuries… an illness without cure



Galeazzi
1757



Cruveilhier
1835

Rayer
1841

"The cystic degeneration of the kidneys,
once it reaches the point where it can be detected or suspected during life,
is an illness without cure".

Rayer 1841

MAYO CLINIC

BCKD19
BC KIDNEY DAYS

Autosomal Dominant Polycystic Kidney Disease

1:500 -1:1000

12.5 million patients worldwide

More than 50% of patients reach kidney failure by age 50

MAYO CLINIC

BCKD19
BC KIDNEY DAYS

Milestones in ADPKD

Pierre Rayer

Cystic degeneration = illness without cure

1841

1585

Bathory (King of Poland)

1888

Polycystic Kidney disease coined by Felix Lejars

1989

cAMP-dependent fluid secretion

1994

Identification of *PKD1*

1996

Identification of *PKD2*

2003

V2R antagonists in PKD animal models

2006

TKV marker of progression (CRISP)

2010

1st clinical trial mTOR inh.

2012

1st successful trial (TEMPO3/4)

2014

Mayo Classification

HALT PKD

Octreotide (ALADIN)

2015

Tolvaptan approval In Europe/Canada

Tolvaptan approval In Japan

2016

TKV accepted as prognostic biomarker by FDA

2017

REPRISE

2018

FDA Approval: JYNARQUE

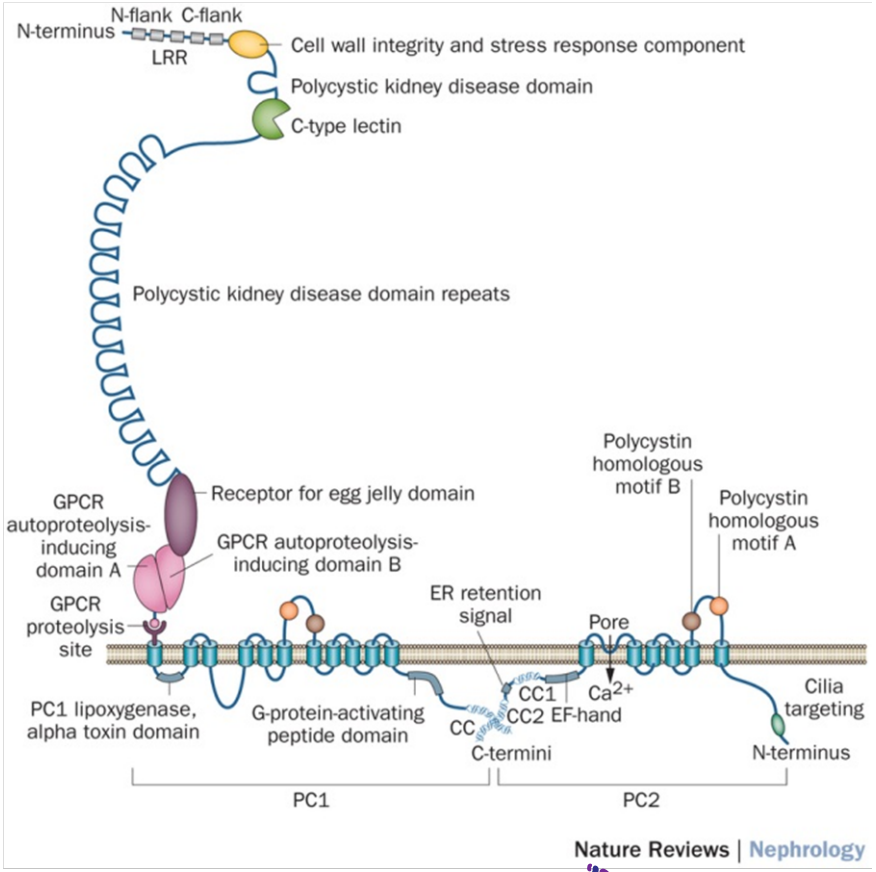
Lanreotide (DIPAK1 trial)

Current trials:
- Lixivaptan (EliSA)
- Venglustat (Staged-PKD)
- Bardoxolone (FALCON)
- Water prescription (PREVENT-ADPKD)

MAYO CLINIC

BCKD19 BC KIDNEY DAYS

	PKD1	PKD2
Gene location	16p13.3	4q21
Protein product	**Polycystin 1**	**Polycystin 2**
Year gene discovered	1994	1996
No. of known pathogenic mutations in gene	>1270	>200
Function of protein product	Receptor, adhesion molecule (not well known)	Ca^{2+}-permeable nonselective cation channel
Proportion of ADPKD cases	64-85%	15-36%
No of cysts	More numerous	Less numerous
Mean Age at ESRD incidence	58.1 yrs	79.7 yrs

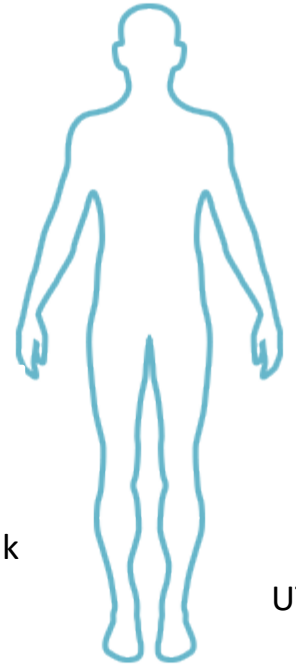


Chebib and Torres. (2016) AJKD

Chebib *et al.* (2015) *Nat. Rev. Nephrol.*

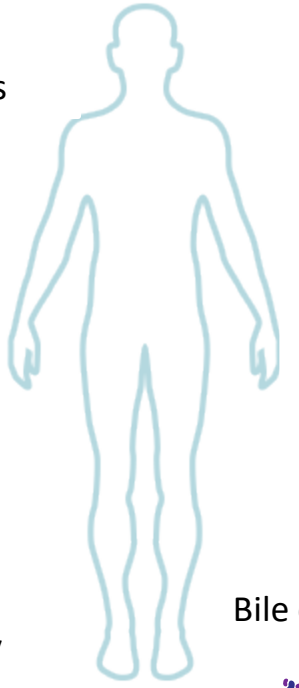
Systemic disease

RENAL MANIFESTATIONS



- Kidney stones
- Palpable kidneys
- Polyuria
- Abdominal/flank pain
- Hypertension
- Hematuria
- Nocturia
- Recurrent UTI/cyst infection

EXTRA-RENAL MANIFESTATIONS



- Vascular dissections
- Hepatic cysts
- Seminal vesicle, dura, arachnoid cysts
- Pancreatic cysts
- Diverticulosis
- Male infertility
- Intracranial aneurysms
- Valvular heart disease
- Intraductal papillary mucinous neoplasms
- Abdominal wall hernias
- Bile duct compression

MAYO CLINIC

BCKD19 BC KIDNEY DAYS

Case

43 year old patient with ADPKD and CKD stage 5 presents for follow up with his three children:

- Son (41 y.o.) had renal ultrasound with no cysts
- Daughter (36 y.o) had CT scan with >15 cysts on each kidney
- Son, 29 y.o, had abdominal MRI with one renal cyst

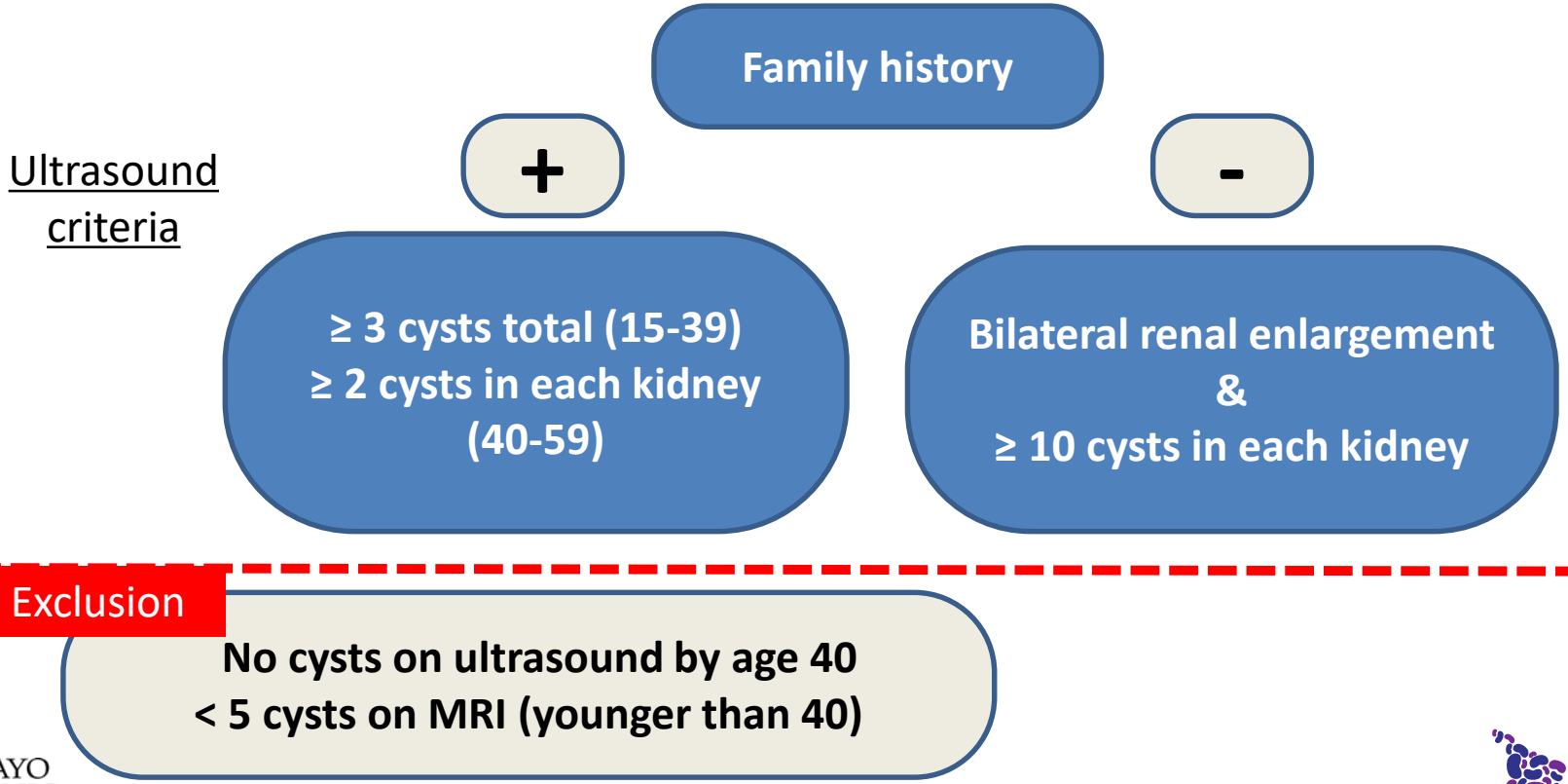
Do any of my kids have ADPKD? Any additional testing needed?

- A: Only daughter has ADPKD, no additional testing
- B: Cannot exclude ADPKD in younger son
- C: Need an abdominal CT scan for older son

MAYO CLINIC

BCKD19 BC KIDNEY DAYS

How to diagnose or exclude ADPKD?



MAYO CLINIC

BCKD19
BC KIDNEY DAYS

Imaging diagnostic criteria of ADPKD

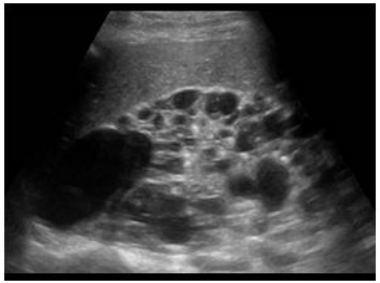
Positive family history		
	Ultrasound-based	**CT/MRI based**
Age 15-39	≥ 3 cysts (total)	**> 10 cysts (total)**
Age 40-59	≥ 2 cysts in each kidney	Not determined
Age > 60	≥ 4 cysts in each kidney	Not determined
Negative family history		
Any age	≥ 10 cysts in each kidney (bilateral kidney enlargement)	Not determined

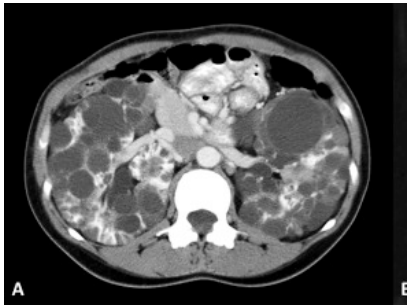
MAYO CLINIC

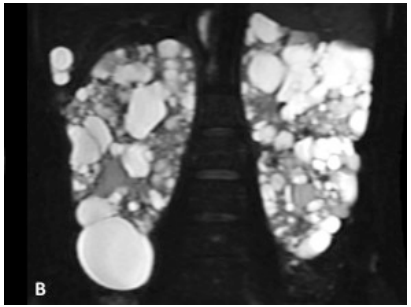
BCKD19 BC KIDNEY DAYS

Imaging modalities

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







MAYO CLINIC

When and how to screen?

- All adult patients at risk of APDKD (positive family history)
  - Discuss implications such as health/life insurance, employment, psychosocial,..
- Initial modality: Ultrasound
- Younger patients/kidney donors: CT/MRI

MAYO CLINIC

BCKD19 BC KIDNEY DAYS

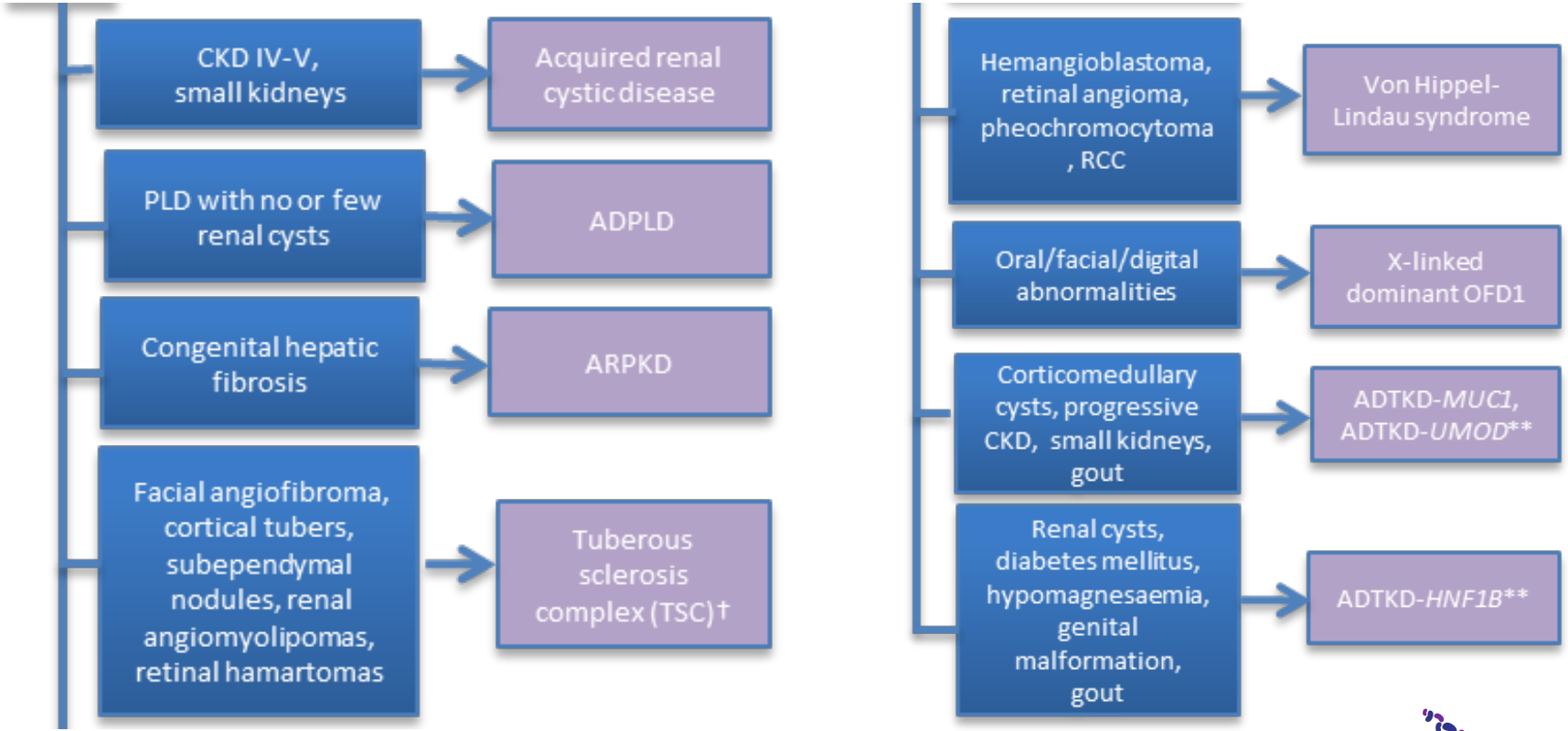
Family history

- Helpful more in diagnosis than in prognosis
  - *PKD1*: One relative w/ ESRD onset ≤ 50 yo
  - *PKD2*: One relative w/ ESRD onset ≥ 70 yo
- Negative in 10% to 15% :
  - De novo mutations (5% of cases)
  - Mild disease from *PKD2* mutations and non-truncating *PKD1* mutations
  - Mosaicism
  - Unavailability of parental medical records

MAYO CLINIC

BCKD19 BC KIDNEY DAYS

Differential Diagnosis



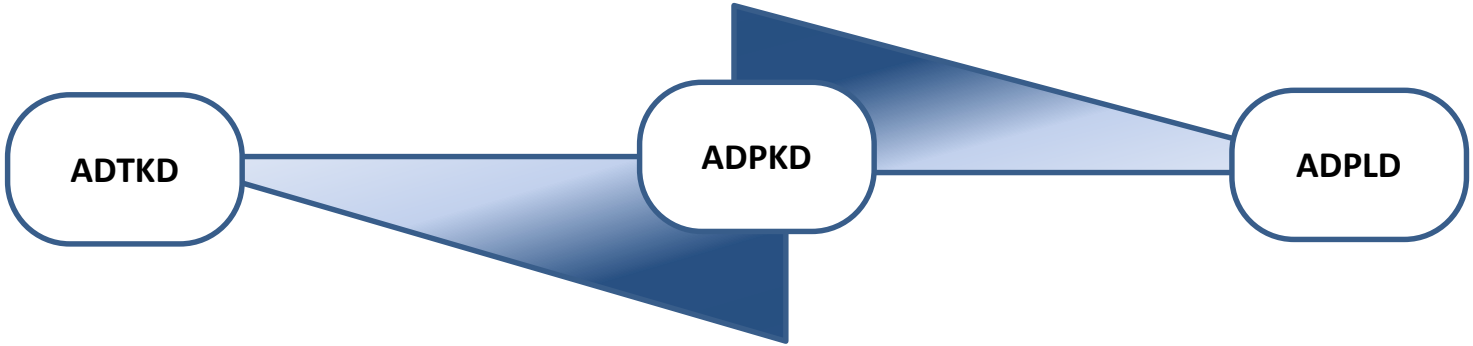
MAYO CLINIC

Chebib and Torres. (2016) AJKD

BCKD19 BC KIDNEY DAYS

The genetic spectrum of renal cystic diseases

Interstitial fibrosis ..... **Renal cysts** ..... **Liver cysts**



MUC1
UMOD
HNF1B

DNAJB11

PKD1
PKD2

ARPKD

PKHD1

GANAB

PRKCSH
SEC63
LRP5
ALG8
SEC61B

MAYO CLINIC

BCKD19 BC KIDNEY DAYS

Case - continued

You diagnosed the 36 yo daughter with ADPKD.

Her serum creatinine is 1.2 mg/dL; She has had one episode of gross hematuria in the past, her BP is 142/89 mm Hg, her UA shows Uosm of 728 mOsm/Kg and Albumin/creatinine of 580 mg/g.

She would like to know when she would reach end stage kidney disease?

- A: 43 yo similar to her father
- B: We can't predict
- C: Would need to measure TKV

MAYO CLINIC

BCKD19 BC KIDNEY DAYS

Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP)

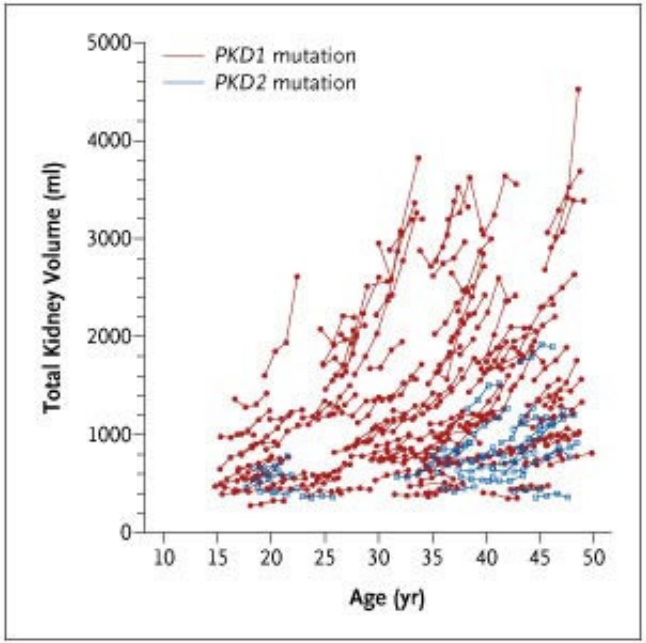


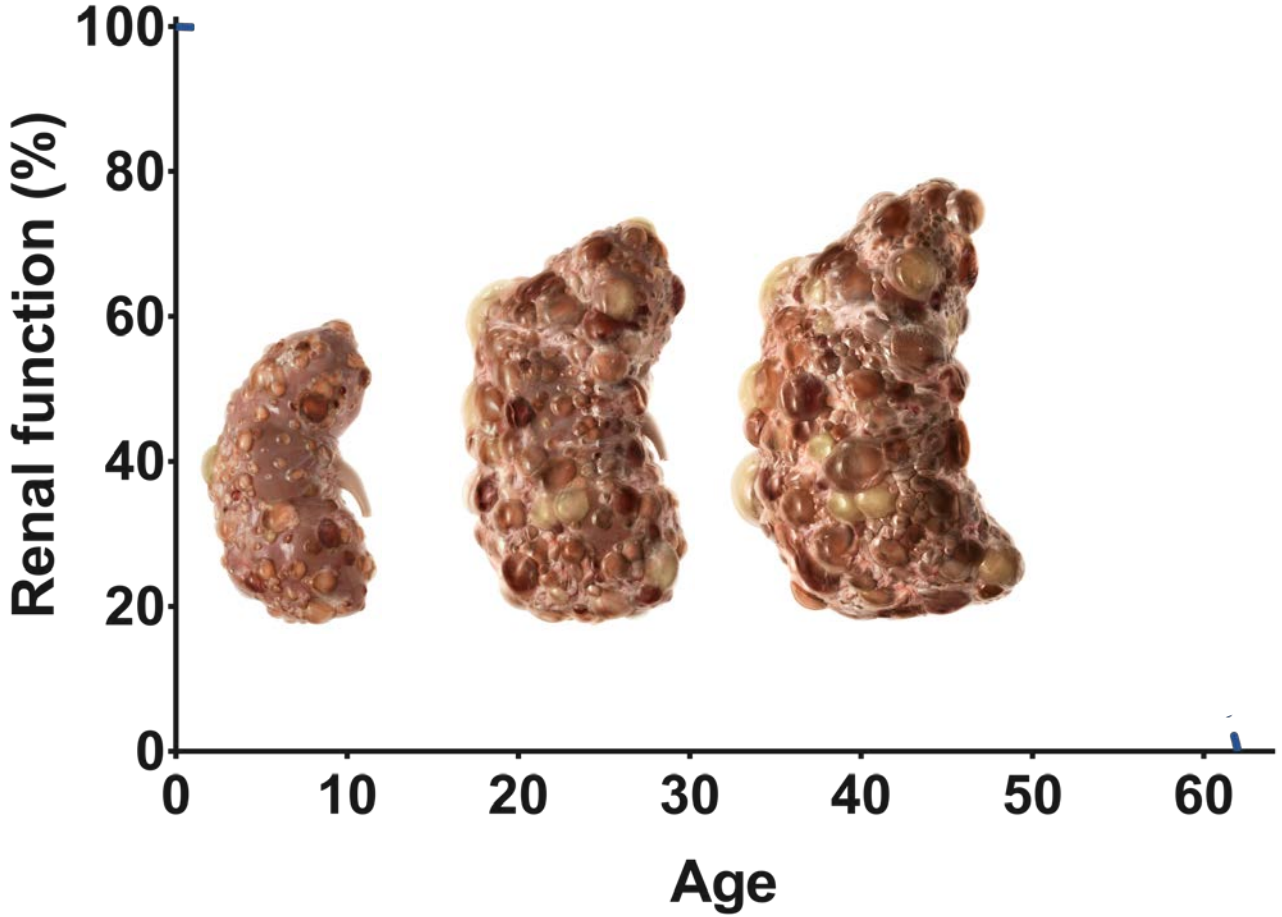
Table 1. Relationship between Total Kidney Volume and Glomerular Filtration Rate.

Variable	Total Kidney Volume			Glomerular Filtration Rate	
	Baseline Intercept	Slope	Slope	Baseline	Slope
	ml	*ml/yr*	*%/yr*	*ml/min*	*ml/min/yr*
Total kidney volume and age — mean ±SD (no. of patients)					
<750 ml and <30 yr	506±109 (45)	25.9±22.0 (45)	4.70±3.80 (45)	114±24.7 (47)	2.88±12.1 (46)
<750 ml and ≥30 yr	572±130 (48)	23.0±22.2 (48)	3.70±3.42 (48)	108±24.2 (49)	1.03±7.06 (48)
750–1500 ml and <30 yr	978±193 (28)	53.4±36.1 (28)	5.33±3.15 (28)	122±30.8 (28)	−0.38±7.66 (28)
750–1500 ml and ≥30 yr	1052±191 (61)	55.4±44.0 (61)	5.16±3.88 (61)	101±26.8 (61)	−1.62±10.9 (61)
>1500 ml and <30 yr	1859±333 (12)	173±81.3 (12)	9.48±4.61 (12)	99.6±23.8 (13)	−2.69±10.2 (12)
>1500 ml and ≥30 yr	2155±543 (38)	144±92.2 (38)	6.76±3.78 (38)	94.0±29.2 (38)	−5.04±5.86 (39)
P values for analysis-of-variance factors					
Total-kidney-volume group		<0.001	<0.001	0.009	0.005
Age group		0.20	0.02	0.005	0.20
Interaction		0.30	0.24	0.15	0.95

MAYO CLINIC

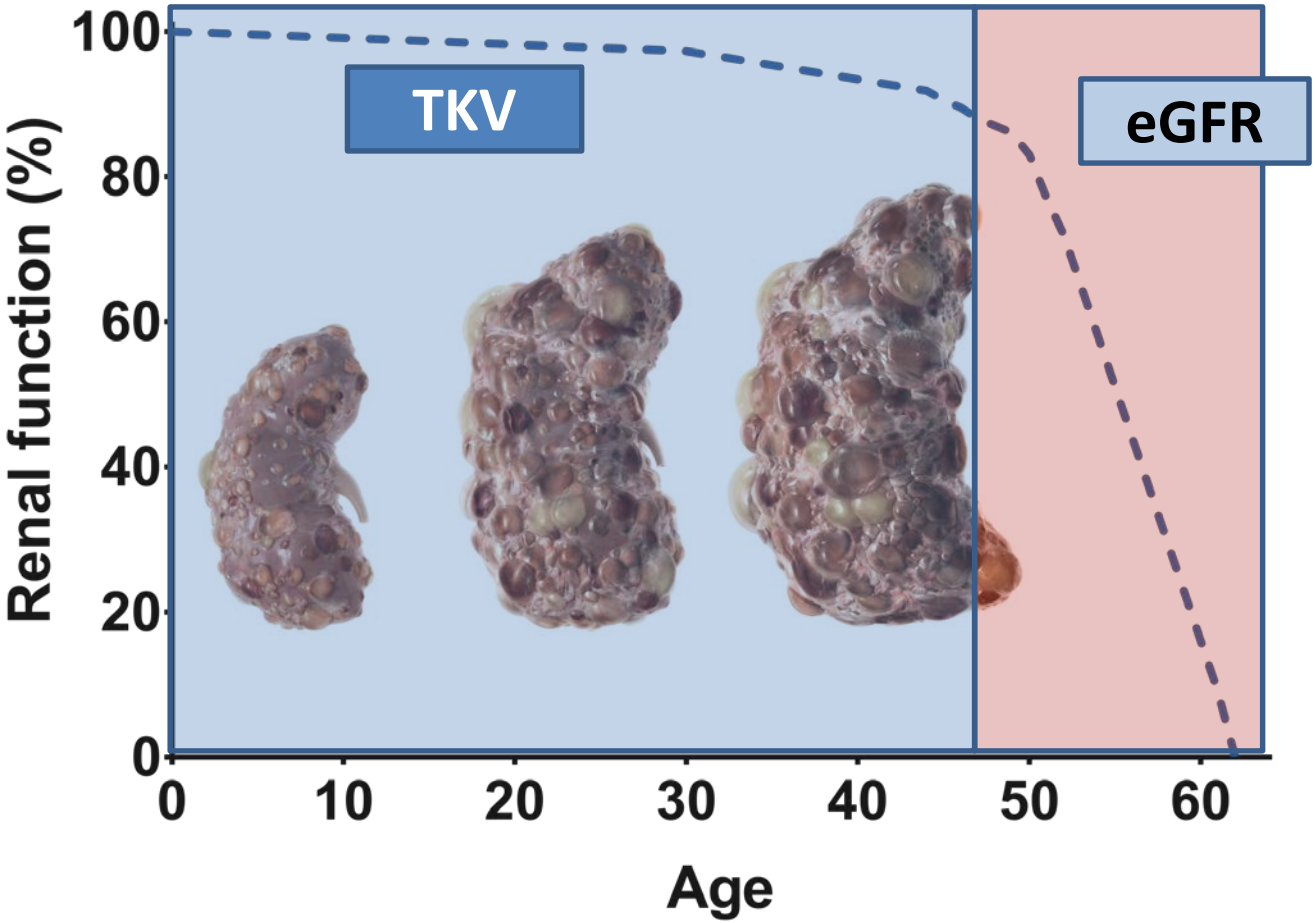
Grantham JJ et al. N Engl J Med 2006;354:2122-2130.

BCKD19 BC KIDNEY DAYS



MAYO CLINIC

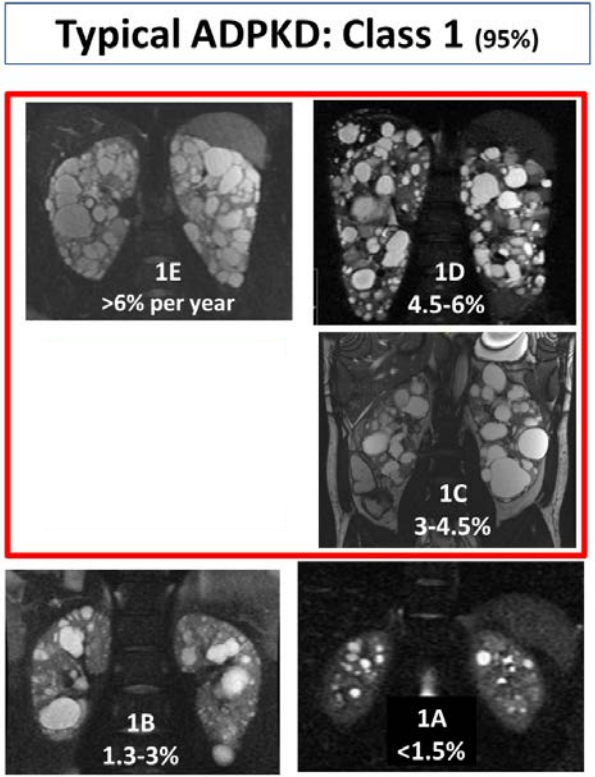
BCKD19
BC KIDNEY DAYS

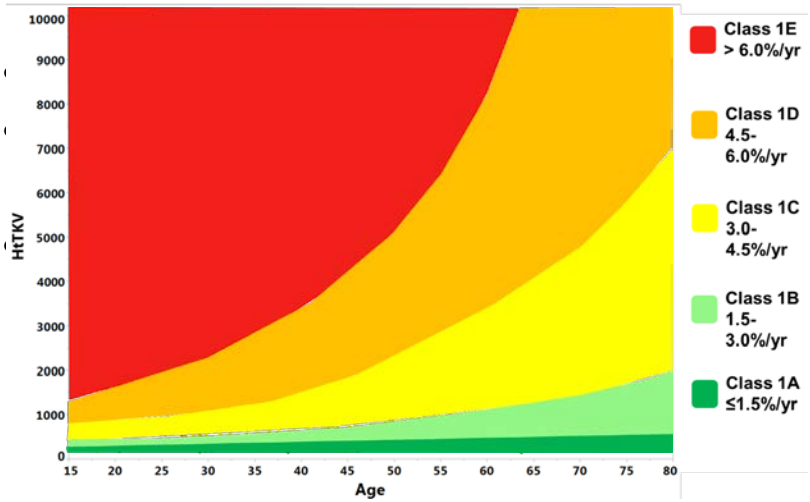


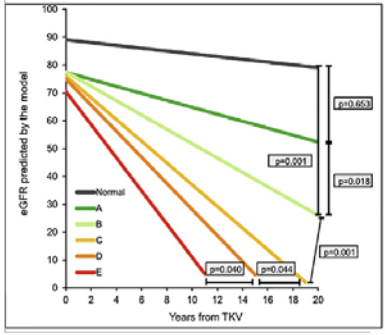
MAYO CLINIC

BCKD19
BC KIDNEY DAYS

Mayo ADPKD classification







	Estimated eGFR slope (ml/min/SA per year)	
	Male	*Female*
Class 1A	-0.23	0.03
Class 1B	-1.33	-1.13
Class 1C	-2.36	-2.43
Class 1D	-3.48	-3.29
Class 1E	-4.78	-4.58

MAYO CLINIC

Irazabal et al. JASN 2015

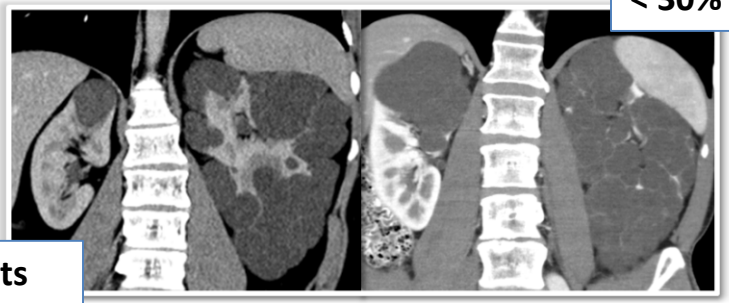
BCKD19
BC KIDNEY DAYS

Atypical ADPKD: Class 2 (5%)

Focal disease (2A)

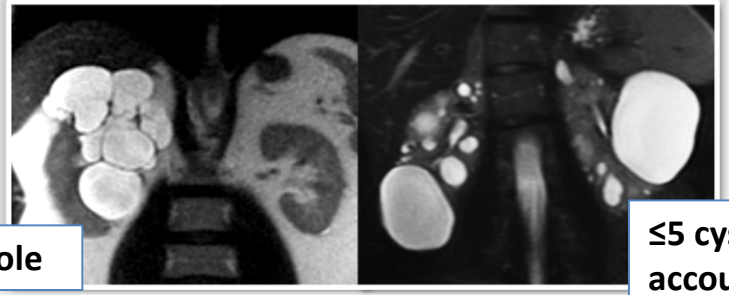
3-9 cysts
< 30% of TKV

0-2 cysts



Unilateral Asymmetric

One pole



Segmental Lop-sided

≤5 cysts account for ≥50% TKV

Parenchymal atrophy (2B)

Unilateral

Enlargement in one kidney

atrophy in the other

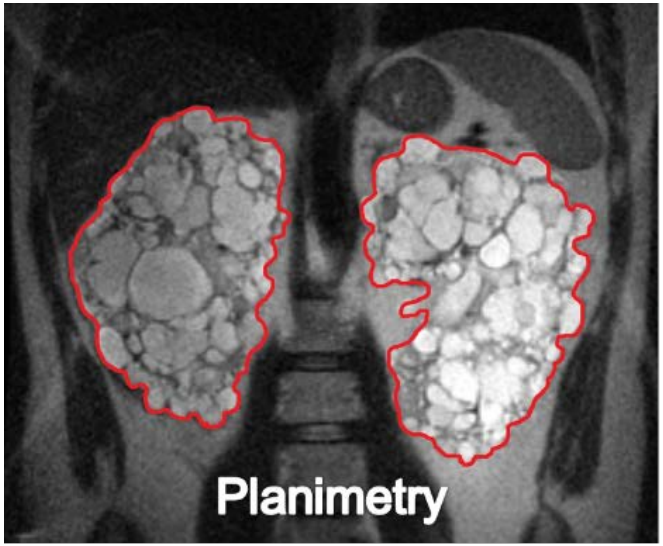
Bilateral

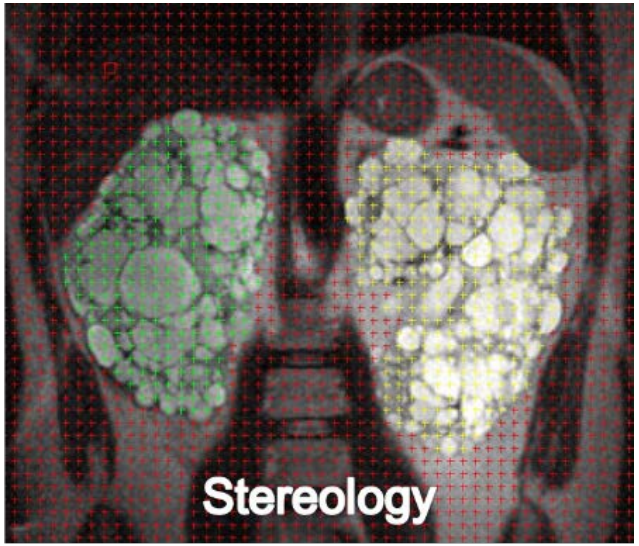
- Creat ≥1.5
- No kidney enlargement (<14.5 cm)
- replacement of kidney tissue by cysts
- Parenchymal atrophy

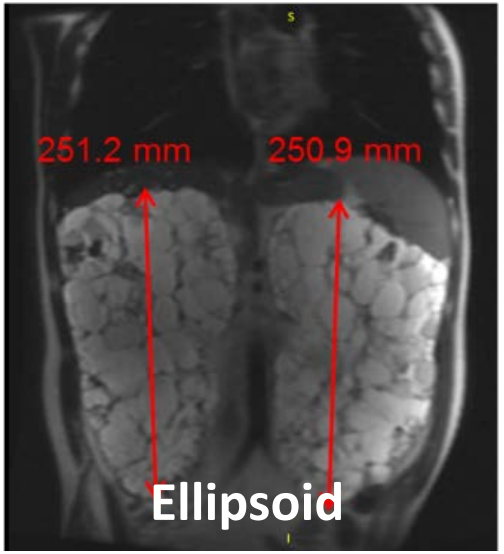
MAYO CLINIC

BCKD19 BC KIDNEY DAYS

Total Kidney Volume (TKV) = FDA approved prognostic biomarker in ADPKD







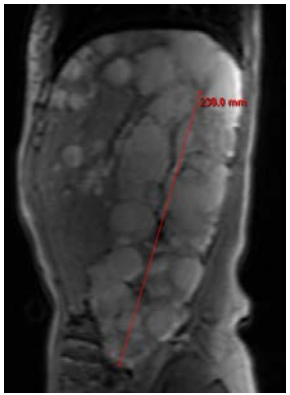
Gold standard

MAYO CLINIC

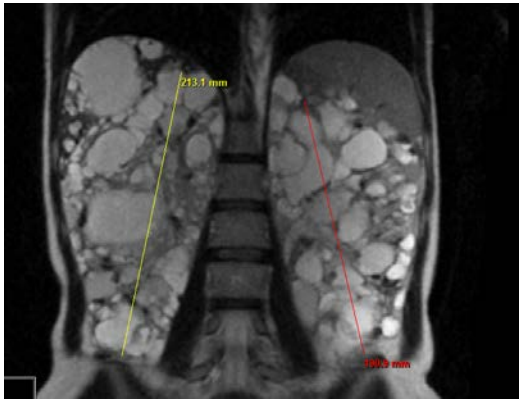
BCKD19 BC KIDNEY DAYS

Mayo ADPKD Calculator/prognosticator

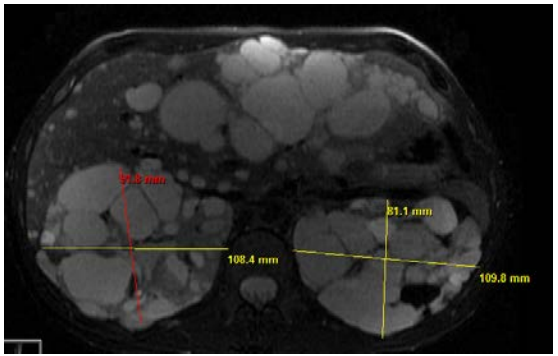
Step 1: Maximal sagittal length



Step 2: Max. Coronal length



Step 3: Max. width and depth



MAYO CLINIC

BCKD19
BC KIDNEY DAYS

Mayo ADPKD Calculator/prognosticator

Step 4: Calculate TKV

1 — Kidney Volume Calculator based on Ellipsoid equation (π/6xLxWxD) from MRI or CT image

Required Data Entry

Right Kidney		Left Kidney	
Sagittal Length (mm)	230	Sagittal Length (mm)	190.9
Coronal Length (mm)	213.1	Coronal Length (mm)	190.9
Width (mm)	91.8	Width (mm)	81.1
Depth (mm)	108.4	Depth (mm)	109.8

Calculated Results

Right Kidney Volume (mL)	1139.8	Left Kidney Volume (mL)	878.3
		Total Kidney Volume (mL)	2018.1

Clear All | Calculate Volumes

Step 5: Determine Mayo Classification

2 — ADPKD Classification using Kidney Volume Calculator

Required Data Entry		Calculated Results	
Patient Height (m)	1.74	Height Adjusted TKV (mL/m)	1159.8
Patient Age (years)	36	ADPKD Classification	1D

Clear All | Calculate Classification

Step 6: Estimate future eGFR/time to ESRD

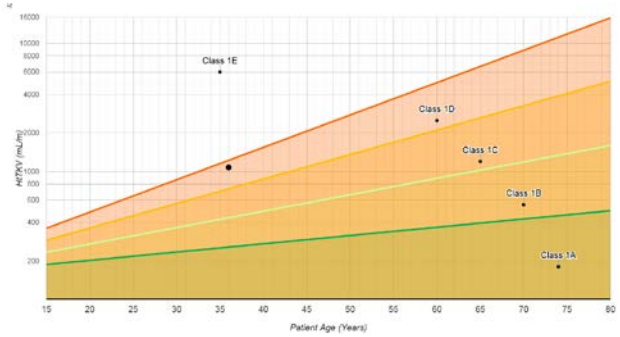
4 — Prediction of Future eGFR based on Classification

Required Data Entry		Calculated Results	
Serum Creatinine (mg/dL)†	1.2	Current eGFR (mL/min/1.73m2)	58.1
Age (years)	36	Future eGFR (mL/min/1.73m2)	10.7
Race (AA/O)‡	o		
Gender (M/F)	f		
ADPKD Classification	1D		
Future time (years)	12		

Clear All | Calculate Current and Future eGFR

† This equation is only valid with creatinine essays that are traceable to IDMS
‡ AA = African American; O = All ethnic groups other than African American

Class 1D

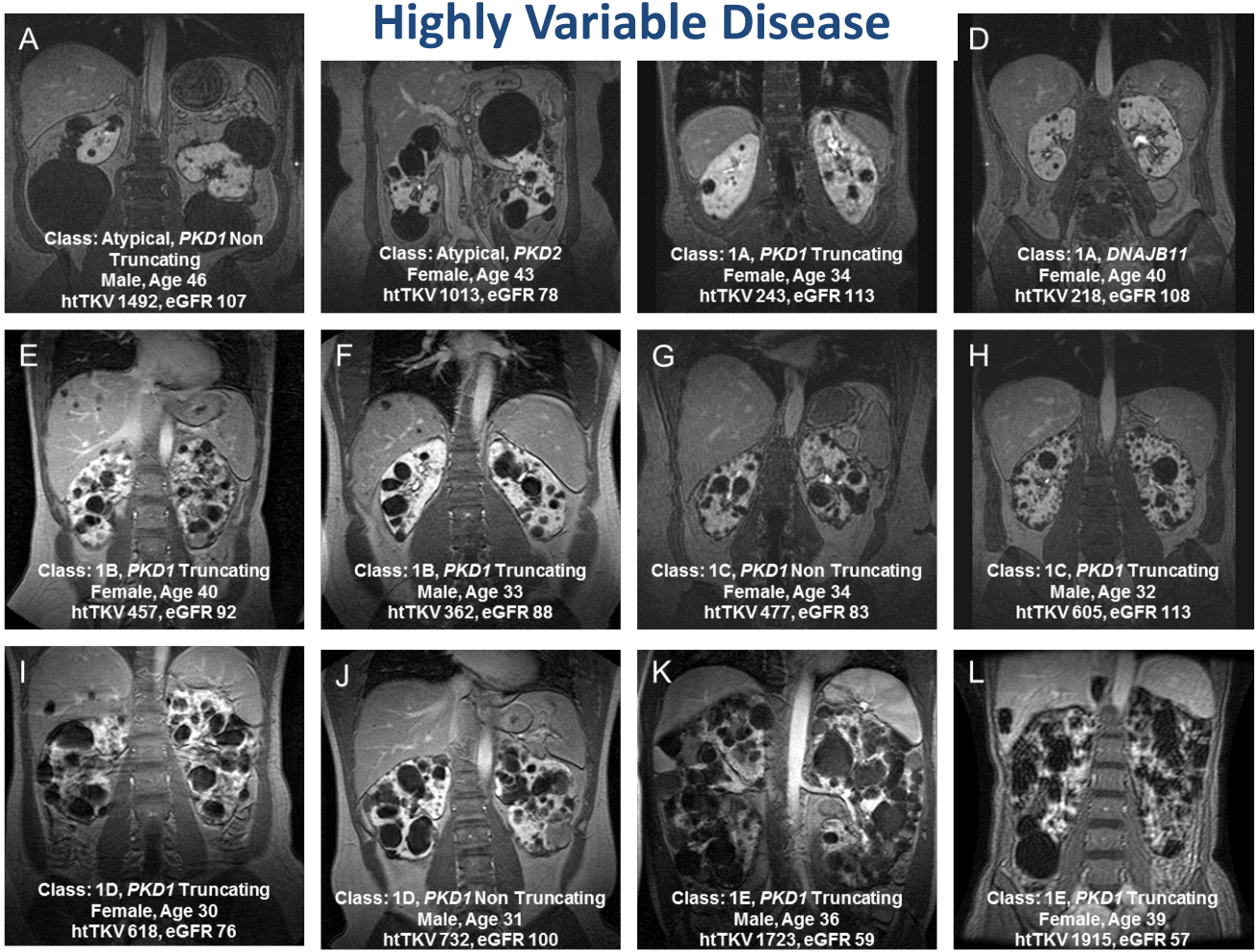


ESRD in 12 years
At age 48

MAYO CLINIC

BCKD19 BC KIDNEY DAYS

Highly Variable Disease

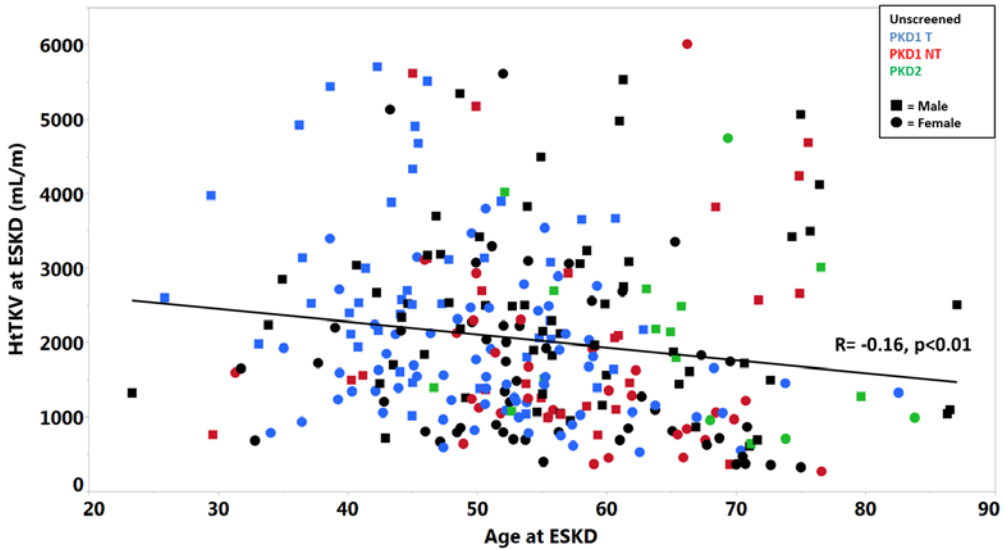


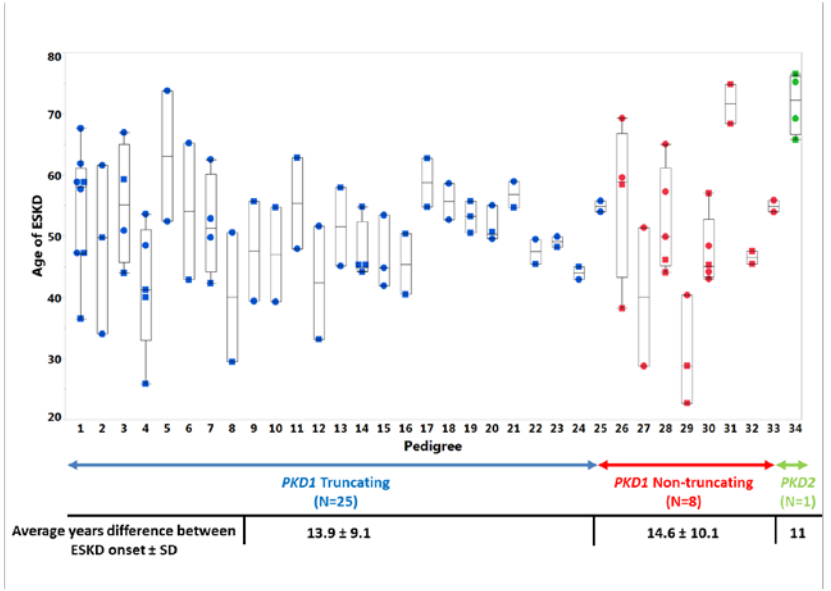
Chebib and Torres, CJASN, 2018

MAYO CLINIC

BCKD19 BC KIDNEY DAYS

ADPKD is a highly variable disease





MAYO CLINIC

Chebib et al., unpublished data

BCKD19 BC KIDNEY DAYS

Case - continued

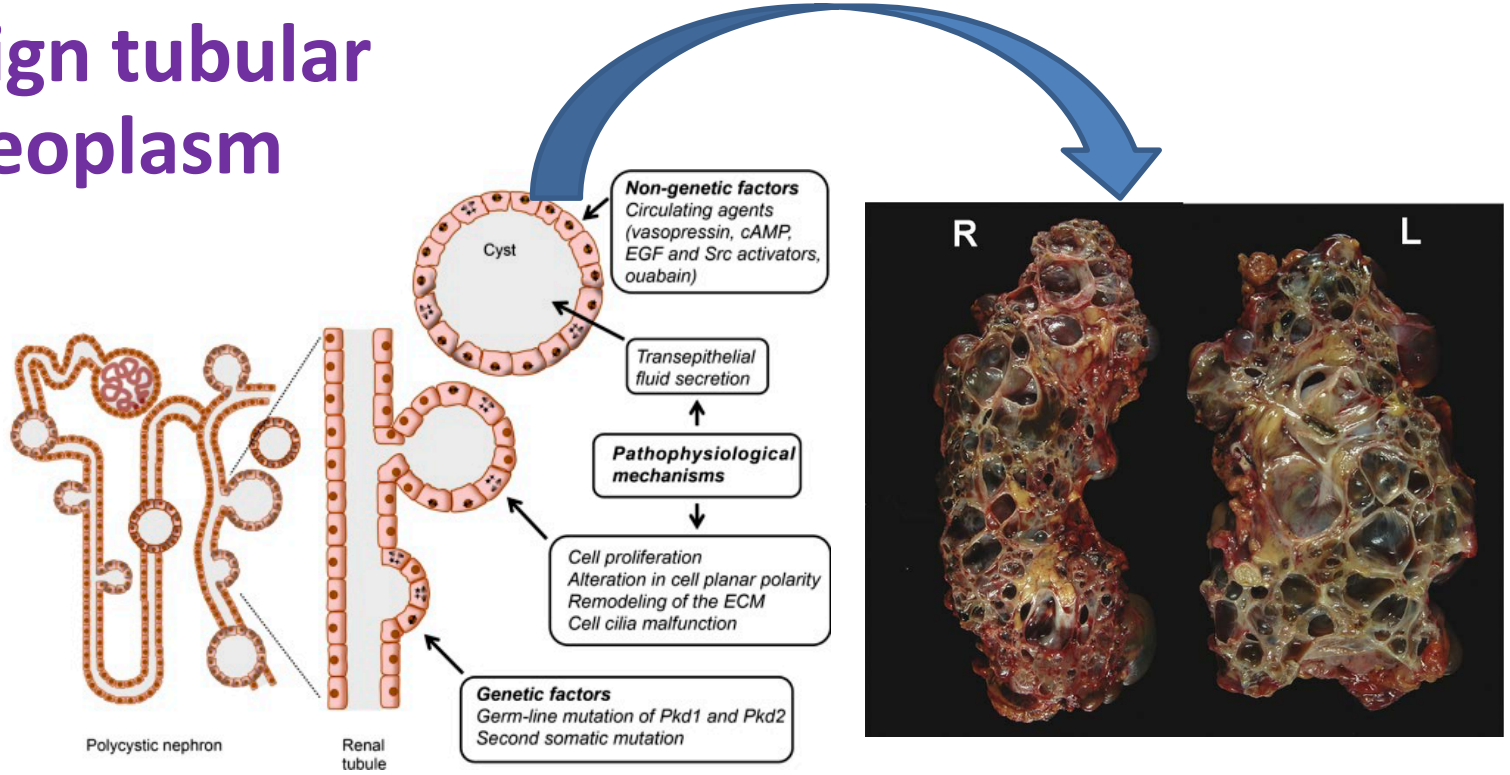
Now that she understands that is she has rapid progressive disease, she would like to know what are her **options to slow her disease progression.**

- A: Water prescription
- B: PKD diet
- C: V2R antagonist or Tolvaptan
- D: Tight blood pressure control with ACEI/ARB
- E: All of the above

MAYO CLINIC

BCKD19 BC KIDNEY DAYS

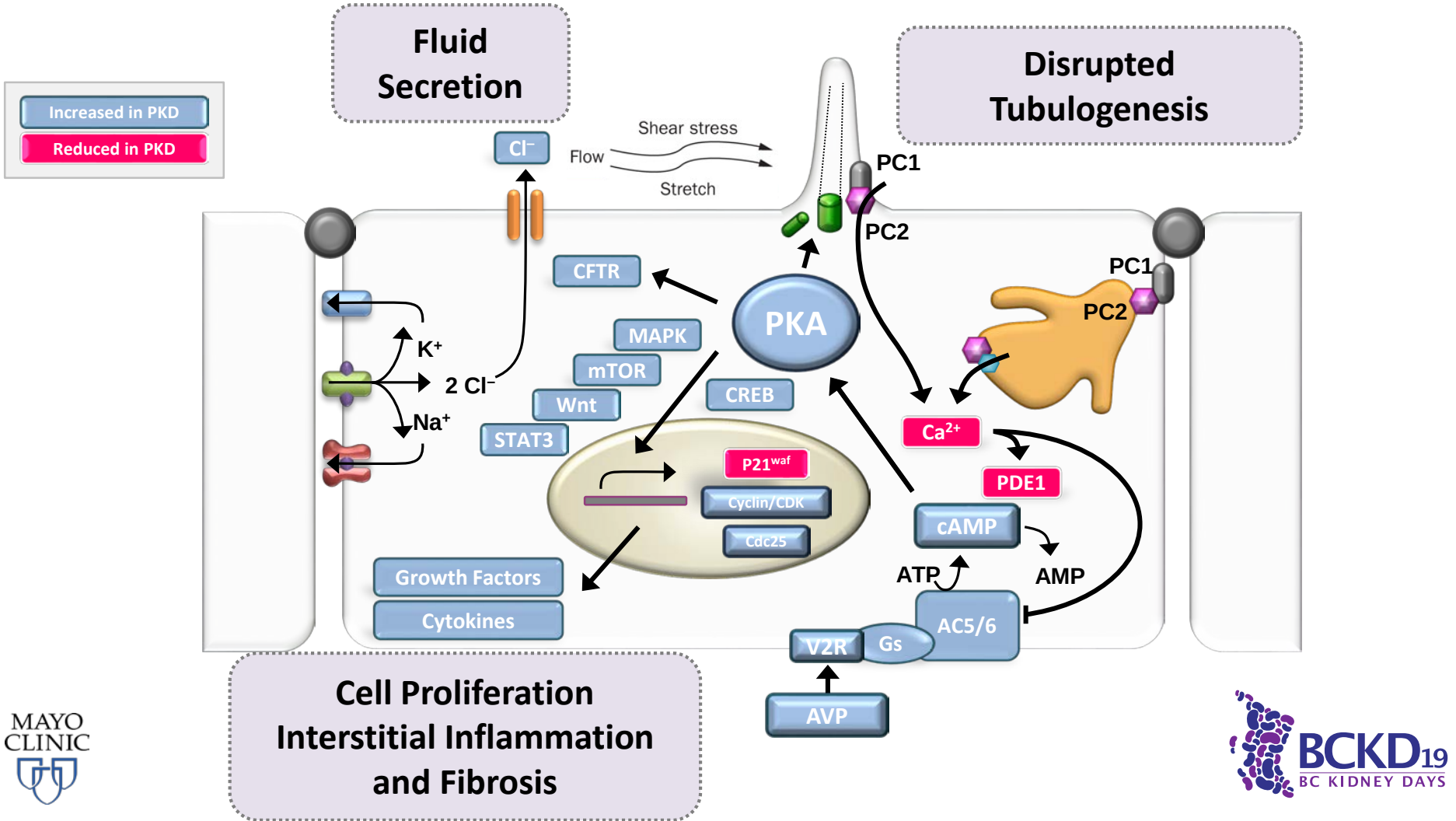
Benign tubular neoplasm



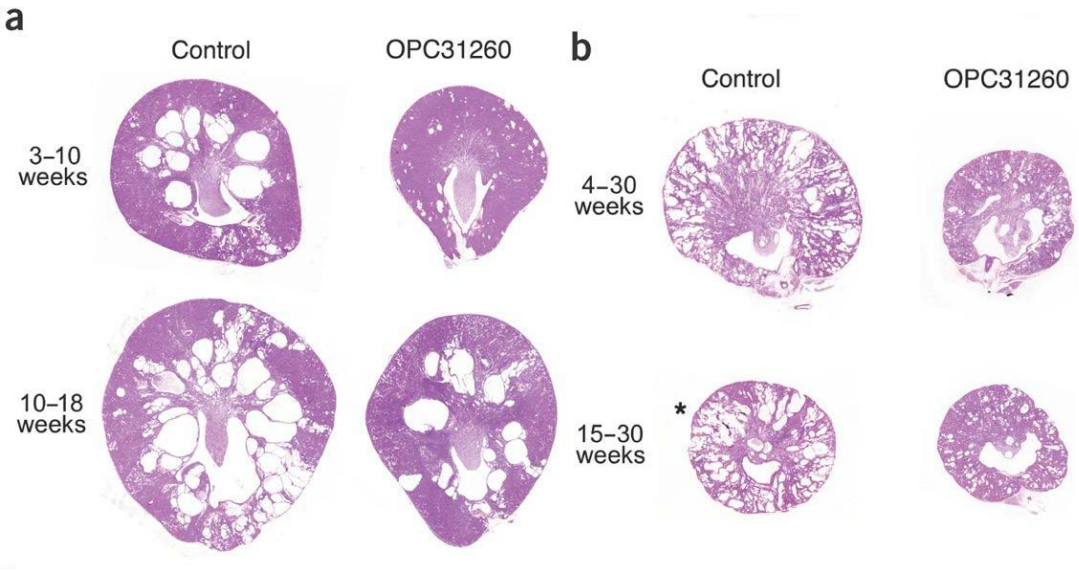
- Cyst formation begins in utero and continues throughout life
- Originate from only 1-5% nephrons

MAYO CLINIC

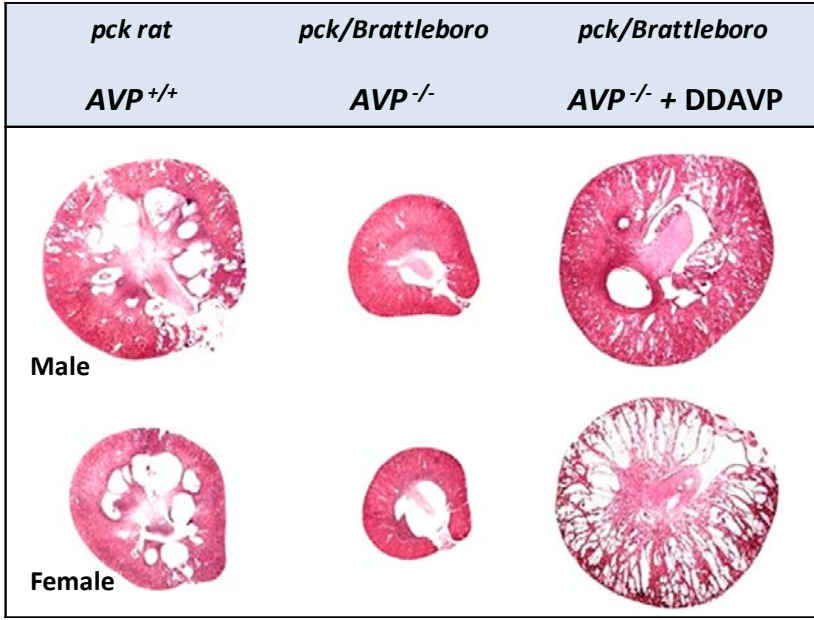
BCKD19 BC KIDNEY DAYS


Increased in PKD
Reduced in PKD
Fluid Secretion
Disrupted Tubulogenesis
Cl⁻
Shear stress
Flow
Stretch
PC1
PC2
CFTR
PKA
MAPK
mTOR
Wnt
STAT3
CREB
K⁺
2 Cl⁻
Na⁺
Ca2+
PDE1
cAMP
ATP
AMP
AC5/6
V2R
Gs
AVP
P21waf
Cyclin/CDK
Cdc25
Growth Factors
Cytokines
Cell Proliferation
Interstitial Inflammation
and Fibrosis
MAYO CLINIC
BCKD19
BC KIDNEY DAYS

Rationale for Vasopressin receptor (V2) antagonists in ADPKD



Gattone et al Nature medicine, (2003)



Wang et al JASN 19:102, 2008.

MAYO CLINIC

BCKD19 BC KIDNEY DAYS

TEMPO Program (2004-2017)

(Tolvaptan Efficacy and Safety in Management of PKD and Outcomes)

Clinical Trials to Test Efficacy and Safety

Study	Design	Dates	Number of Participants
TEMPO 3:4	RCT, double blind	3years (2007-2012)	1,445 patients
TEMPO 4:4	Open label extension	2 years (2010-2016)	871 patients
REPRISE	Randomized withdrawal, Double blind	1 year (2014-2017)	1,370 patients

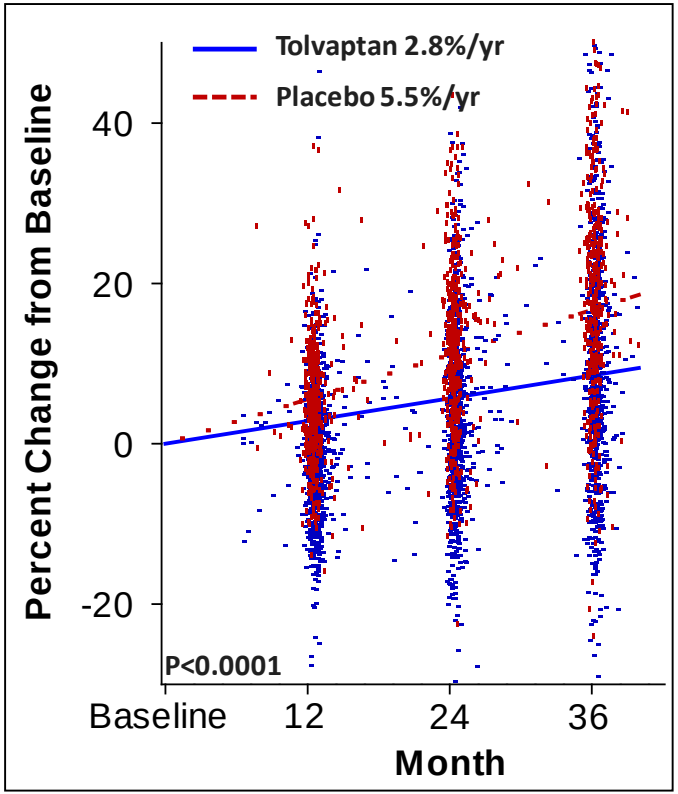
MAYO CLINIC

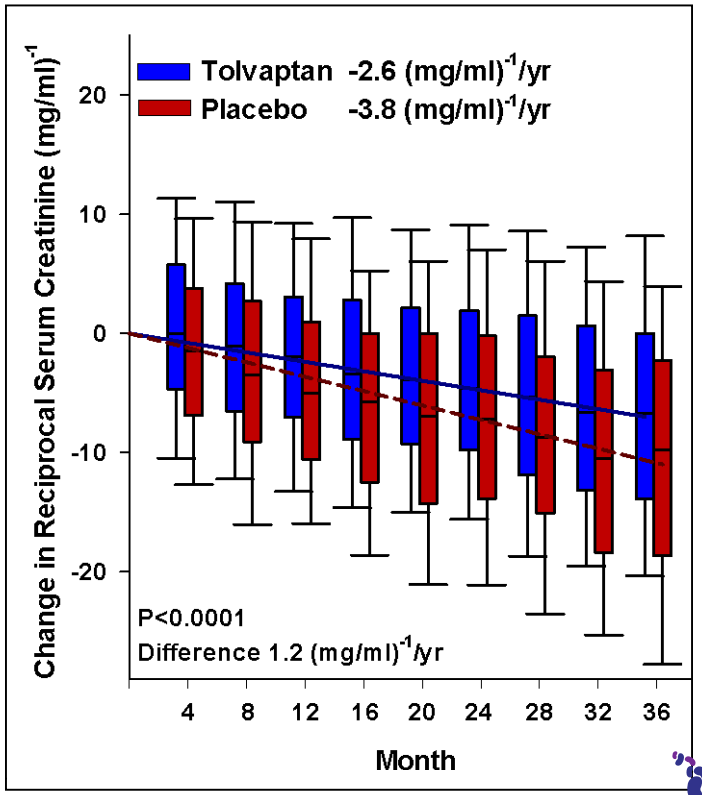
BCKD19 BC KIDNEY DAYS

TEMPO 3:4

Tolvaptan Slowed:

Increase in TKV





Tolvaptan Slowed:

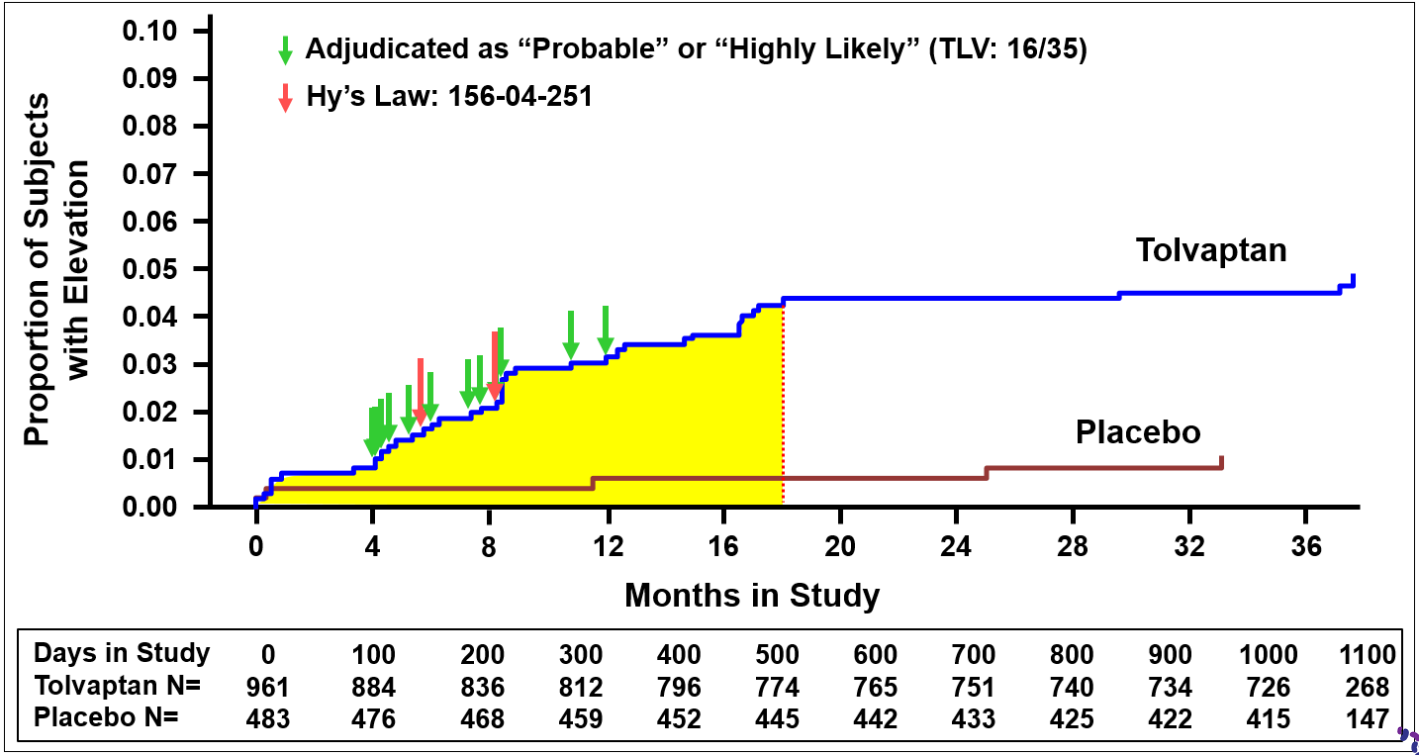
Decline in GFR

MAYO CLINIC

Torres et al. N Engl J Med 367:2407, 2012

BCKD19 BC KIDNEY DAYS

Drug-induced hepatotoxicity



Days in Study	0	100	200	300	400	500	600	700	800	900	1000	1100
Tolvaptan N=	961	884	836	812	796	774	765	751	740	734	726	268
Placebo N=	483	476	468	459	452	445	442	433	425	422	415	147

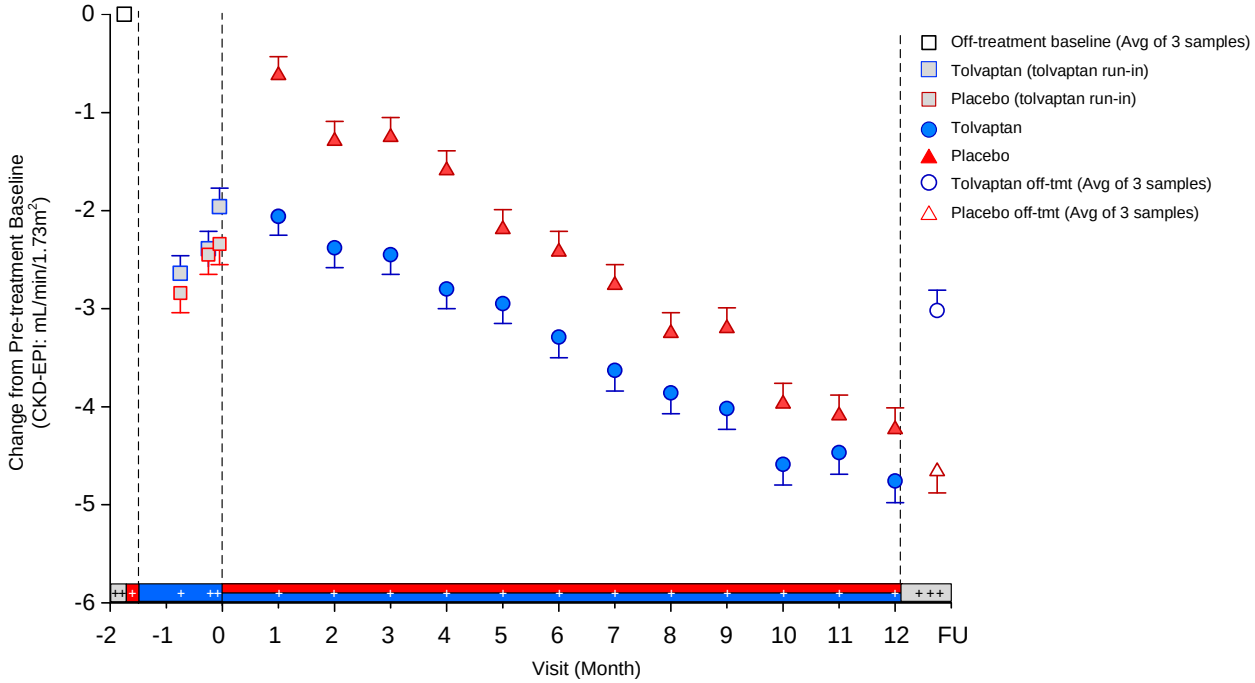
MAYO CLINIC

Watkins Drug Saf. 38:1103-13, 2015.

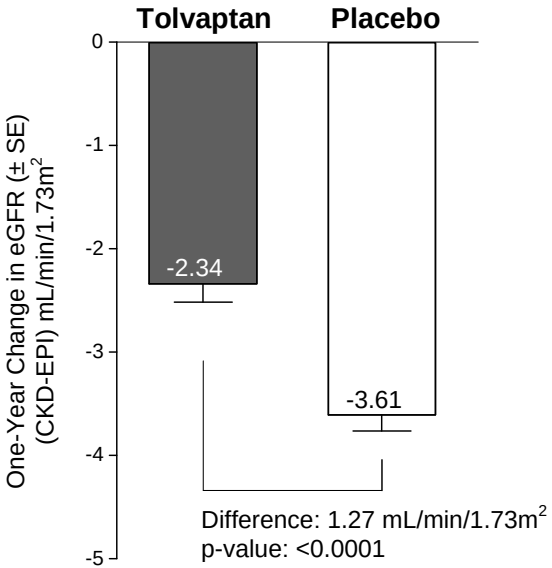
BCKD19 BC KIDNEY DAYS

REPRISE Trial

Change from Baseline eGFR by study period



One-year Change in eGFR



MAYO CLINIC

Torres et al. NEJM 377:1930-1942, 2017.

BCKD19 BC KIDNEY DAYS

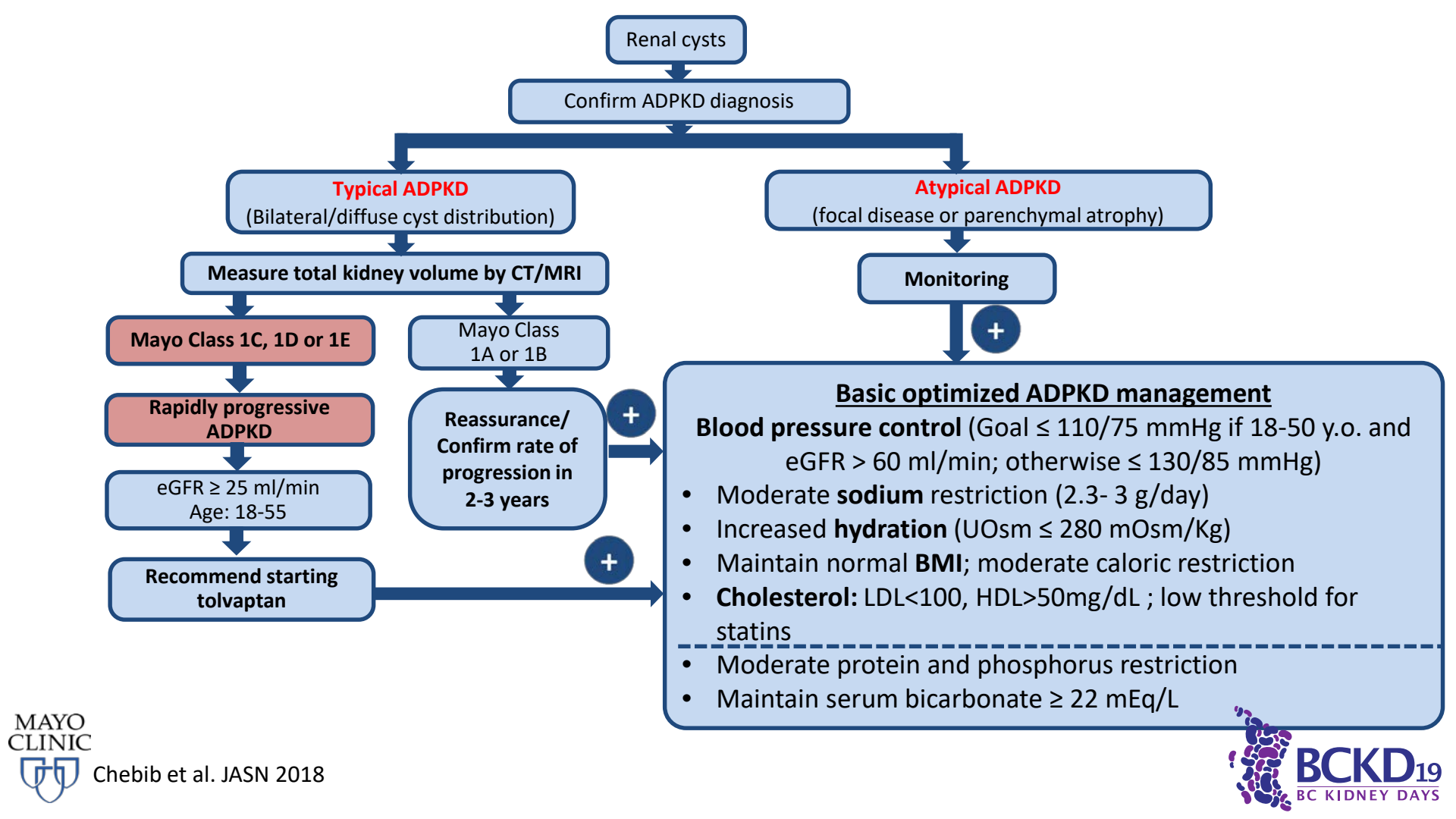
Countries Where Tolvaptan Is Approved for ADPKD

Region	Labelled Indication for ADPKD*
Japan	Documentation of 5% rate of TKV increase No age or CKD restriction
Canada	No age or CKD restriction; expert recommendation: TEMPO 3:4 criteria, Mayo class E, D ,possibly C
European Union	Adults with CKD 1 through CKD 3, (extended to CKD4) Evidence of rapidly progressive disease
United States	Adults **at risk** of rapidly progressing kidney disease
Also approved in Australia, South Korea, Hong Kong, Switzerland, and Nordic countries	

*by Regulatory Agencies; other restrictions may be imposed by individual country reimbursement decisions.

MAYO CLINIC

BCKD19 BC KIDNEY DAYS



MAYO CLINIC

Chebib et al. JASN 2018

BCKD19 BC KIDNEY DAYS

Basic optimized management

(Based on studies specific to ADPKD)

Intervention	Goal	Methods to achieve goal
Intensive blood pressure control	**≤110/75 mmHg** in: 1) 18-50 year-old 2) eGFR > 60 ml/min/1.73 m^2 3) Particularly: a) Mayo Class 1 C- E b) Intracranial aneurysm c) Valvular disease **≤130/80 mm Hg** in: 1) other adult hypertensives	Early detection is essential <u>By order of preference:</u> 1. ACEI or ARB 2. Alpha-beta or cardioselective beta blocker 3. Diuretic (not with tolvaptan) 4. Dihydropyridine CCB DASH like diet at early stages
Sodium	Moderate restriction (2.3-3 g/d) Adjust for extrarenal losses (hot climate, runners, sauna, bowel disease) if appropriate	• Counseling • Renal dietitian follow-up • Monitor 24-hr urine sodium
Hydration	Moderately enhanced hydration spread out over 24 hrs (during the day, at bedtime and at night if waking up). Maintain UOsm ≤ 280 mOsm/Kg	• Counseling • Monitor first morning Uosm, plasma copeptin if available

Water prescription

Low Osmolar diet
Low salt, low protein

Water intake

Target of morning
Uosm ≤ 280 mOsm/Kg

Water prescription (L)* = $\frac{\text{24hr urine volume (L) x Uosm}}{280}$

Water prescription (L) = $\frac{1000}{280}$ = 3.5 L

Water prescription (L) = $\frac{600}{280}$ = 2.1L

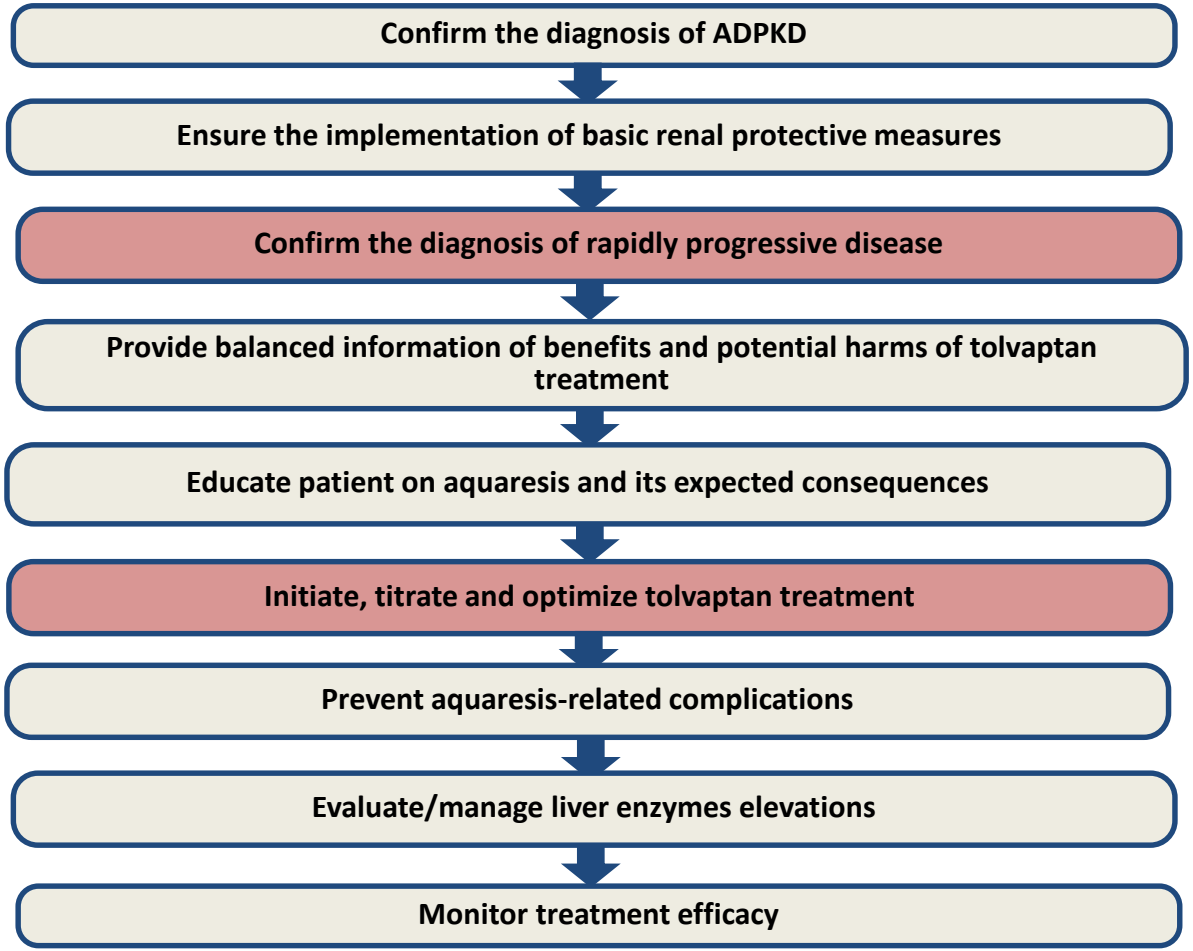
MAYO CLINIC

Basic optimized management
(Based on studies specific to ADPKD)

Intervention	Goal	Methods to achieve goal
Caloric intake	Maintain normal BMI Moderation in caloric intake	• Renal dietitian follow-up • Regular exercise
Lipid control	Aim for serum LDL ≤ 100 mg/dL	• Renal dietician • Regular exercise • Statin if needed (ezetimibe if intolerant to statin)

MAYO CLINIC

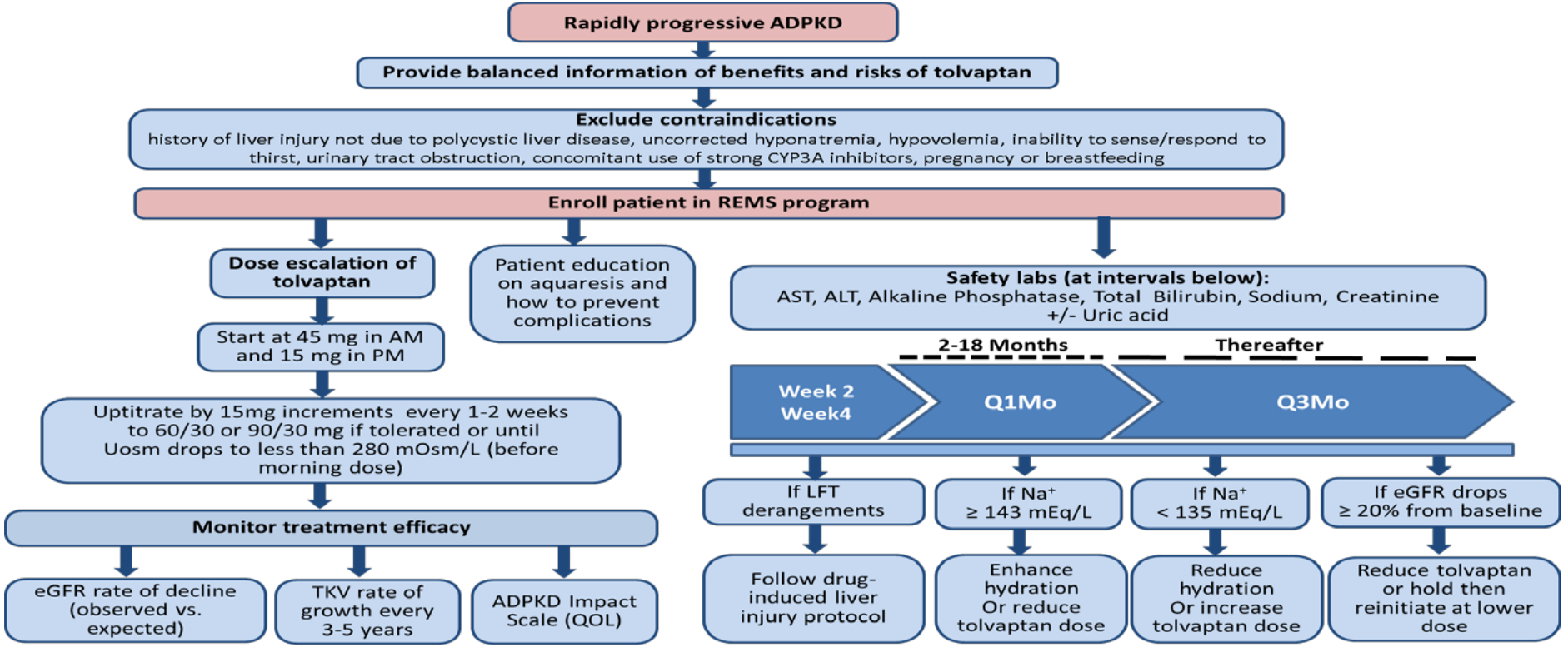
BCKD19 BC KIDNEY DAYS



MAYO CLINIC

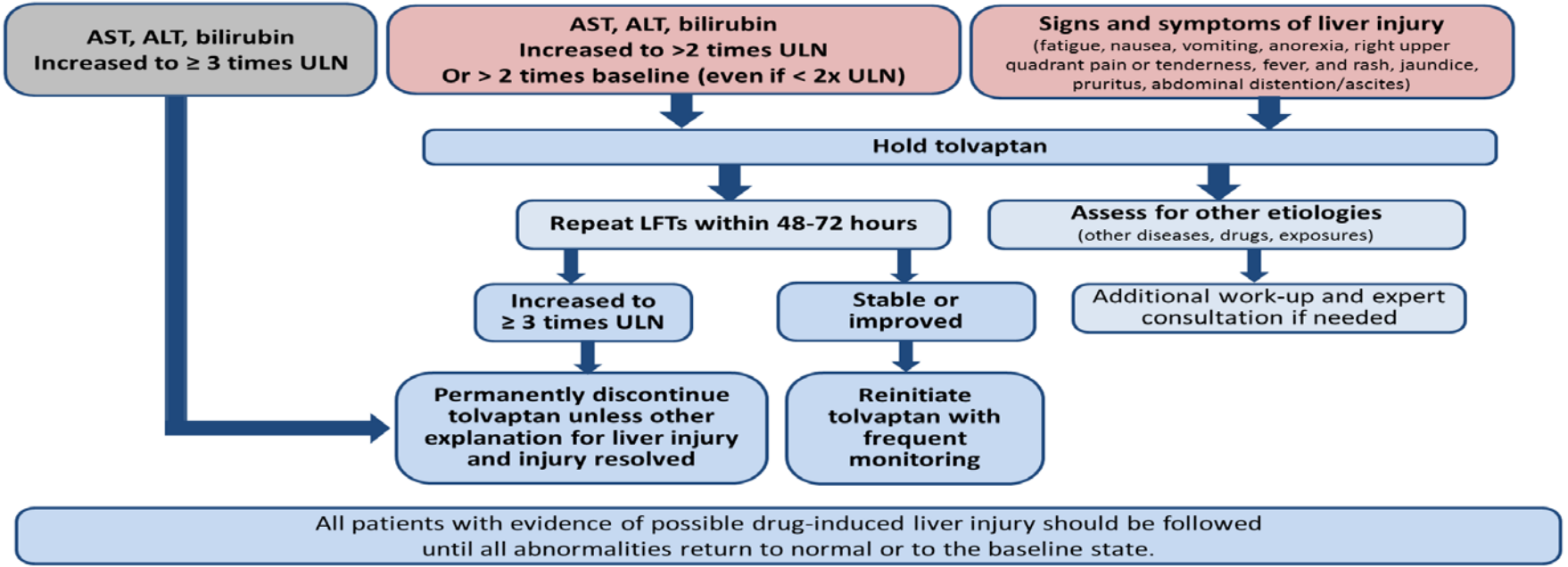
Chebib et al. JASN 2018

BCKD19 BC KIDNEY DAYS



Chebib et al. JASN 2018

Evaluation and management of liver enzymes elevations

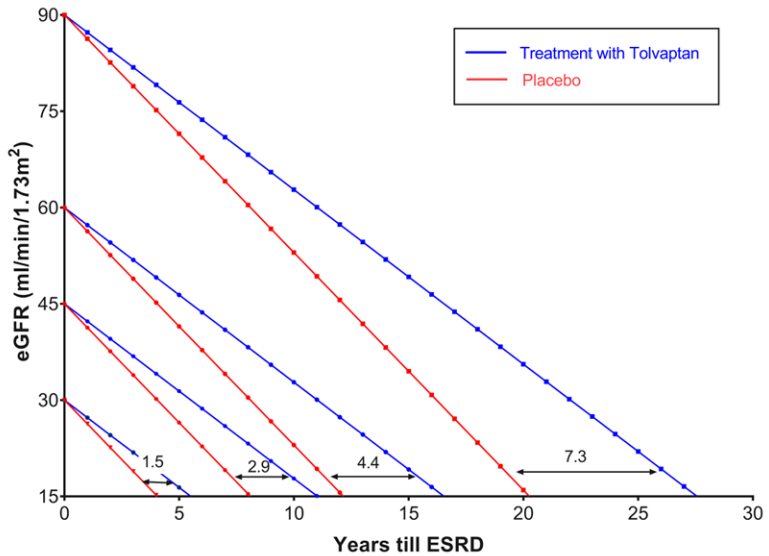


MAYO CLINIC

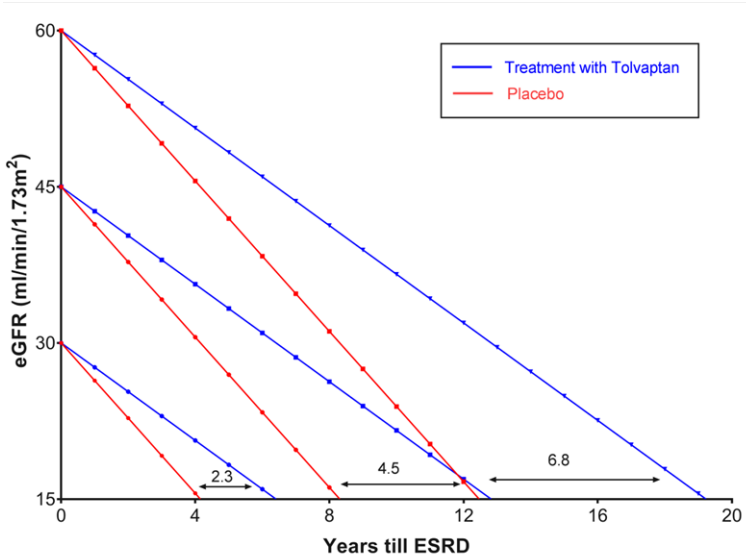
BCKD19 BC KIDNEY DAYS

Hypothetical extrapolations of the effect of tolvaptan in delaying the need of renal replacement therapy

A- Based on TEMPO3:4



B- Based on REPRISE



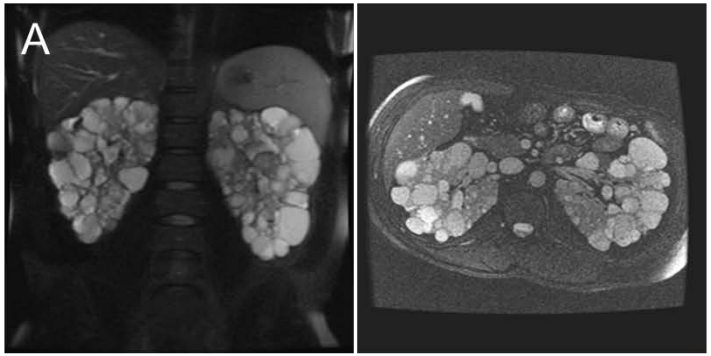
	TEMPO3:4	REPRISE
Placebo	-3.7 ml/min/1.73m^2/year	-3.61 ml/min/1.73m^2/year
Tolvaptan	-2.72 ml/min/1.73m^2/year	-2.34 ml/min/1.73m^2/year

MAYO CLINIC

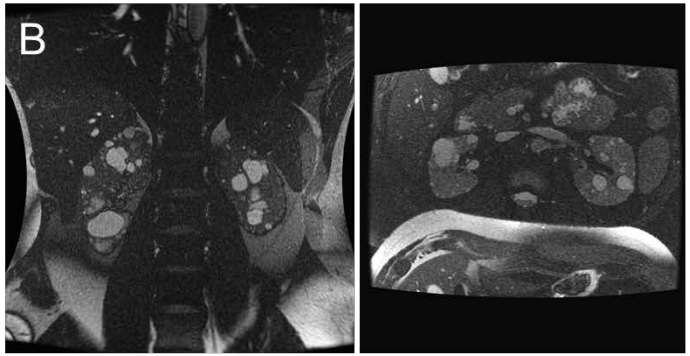
Chebib et al. JASN 2018

BCKD19 BC KIDNEY DAYS

To treat or not to treat?



Patient A: 27 y.o male with eGFR 91 ml/min and TKV of 2064 ml



Patient B: 27 y.o male with eGFR 91 ml/min and TKV of 652 ml

MAYO CLINIC

BCKD19 BC KIDNEY DAYS

Acknowledgments

Chebib.fouad@mayo.edu

This session is held in memory of

R.K & A.K Sandu

BCKD19
BC KIDNEY DAYS

Basic optimized management
(Based on studies in the general CKD population)

Intervention	Goal	Methods to achieve goal
Protein	0.8-1.0 g/Kg of ideal body weight	• Renal dietitian • Monitor protein intake: • 6.25 x [urine urea nitrogen in g/day + (0.03 x weight in kg)]
Phosphorus	Moderate diet phosphate restriction (800mg/d)	• Renal dietician • Read food labels and watch for food additives containing phosphates • Use of phosphate binders not different from other advanced CKD when needed
Acid base	Maintain plasma bicarbonate within the normal range (≥ 22 mEq/L)	• Increase fruits/vegetables (2-4 cups/d) • Oral sodium bicarbonate if needed

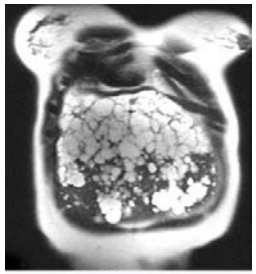
MAYO CLINIC

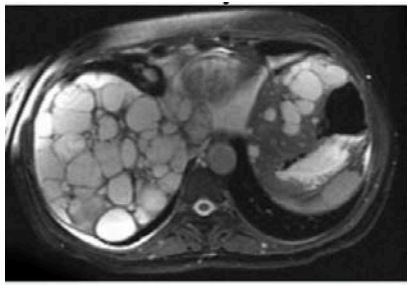
BCKD19 BC KIDNEY DAYS

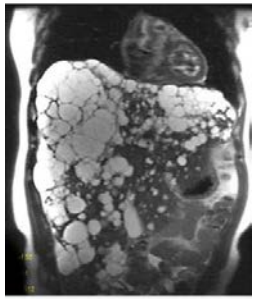
ICA screening

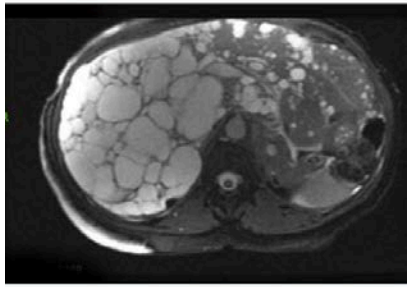
- Occurs more frequently in ADPKD compared to general population
- **9-12%** with ADPKD vs. 2-3%
- If positive family history (ICA/sudden death): prevalence increases to **25%**
- Screen if:
  - High risk occupation
  - Preop major surgery (Transplant, liver resection)
  - Positive family history.
    - If negative MRA: repeat every 5 years

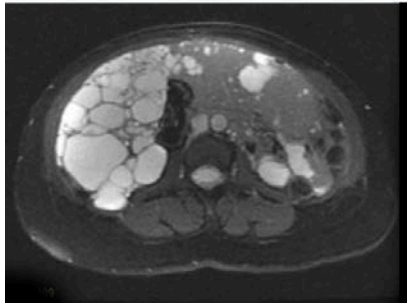
Severe PLD



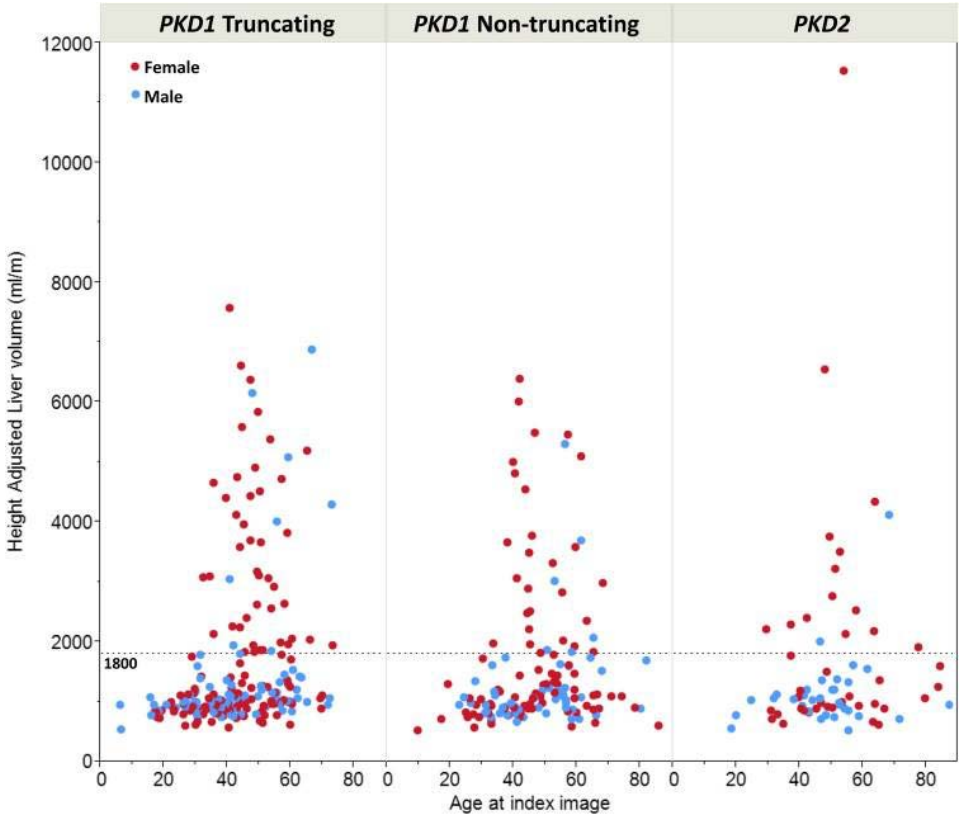






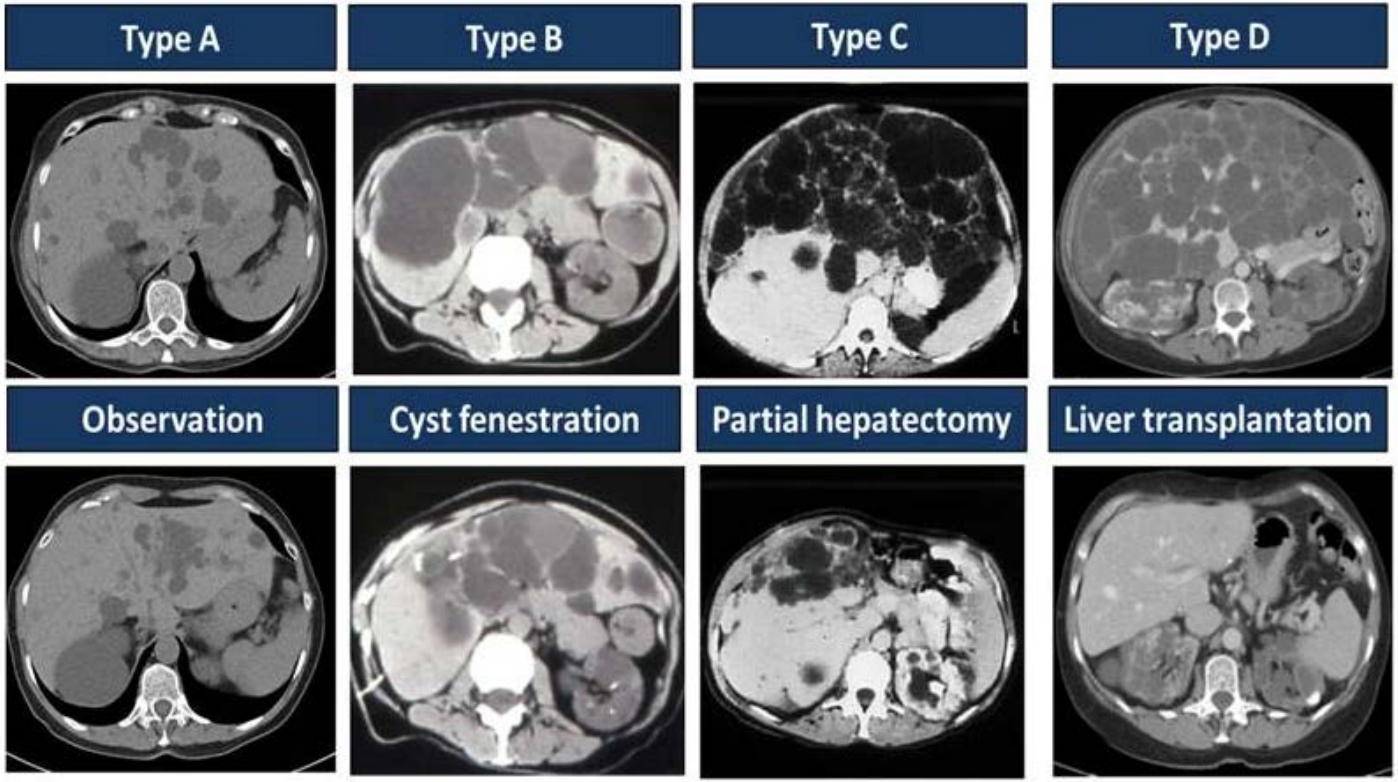


Effect of PKD genotype on PLD severity



Chebib et al Nephrol Dial Transplant, (2016)

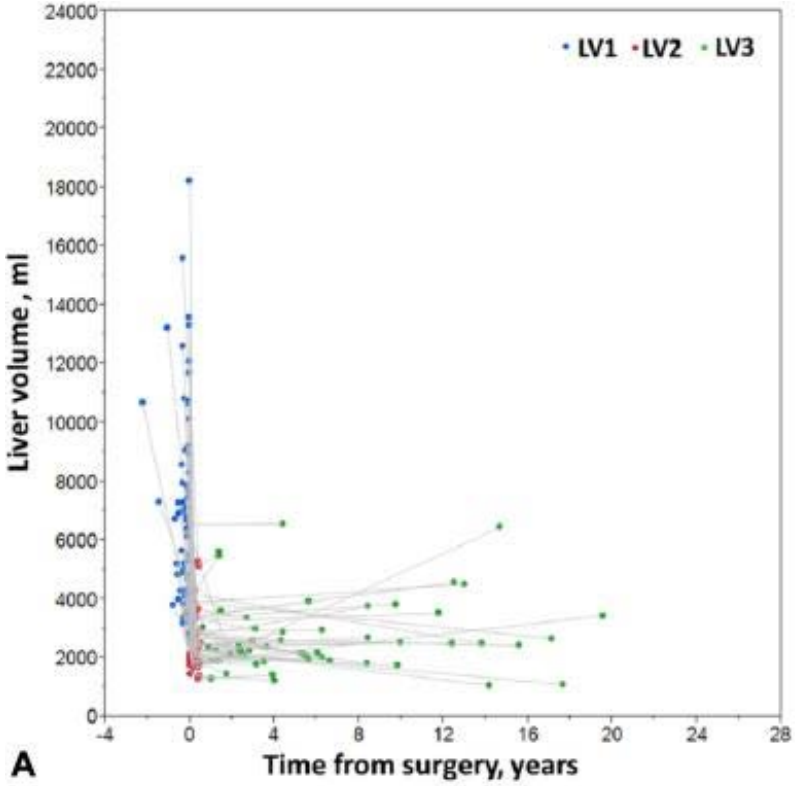
Mayo PLD classification



Chebib et al J Am Coll Surg, (2016)

Partial Hepatectomy

Sustained long-term reductions in LV after PHCF can be achieved in selected patients with severe, highly symptomatic PLD



Chebib et al J Am Coll Surg, (2016)