THE UNIVERSITY OF SYDNEY

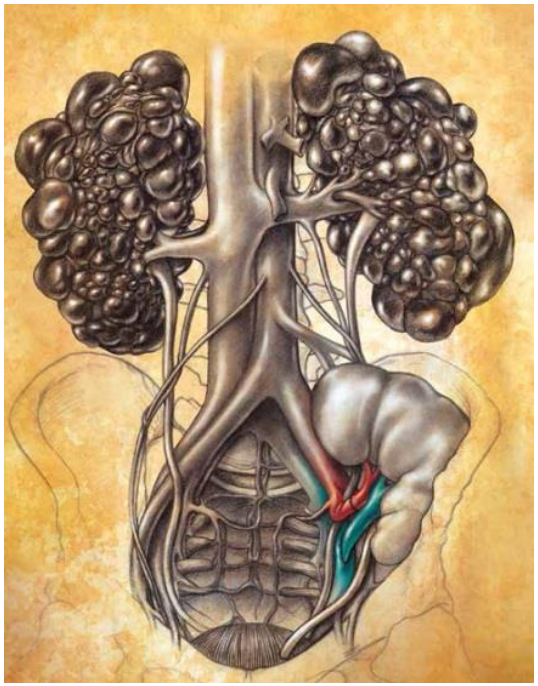
Westmead Millennium Institute for Medical Research

NSW GOVERNMENT Health Western Sydney Local Health District

UPDATE ON PATHOGENESIS & TREATMENT OF ADPKD

David Harris

20/11/19



Imaging

Genetics

Pathogenesis

Treatment

- **Disease modifying drugs**
- **Water**
- **Basic optimised management**

IMAGING

THE LANCET

Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1

David Ravine, Robert N Gibson, Rowan G Walker, Leslie J Sheffield, Priscilla Kincaid-Smith, David M Danks

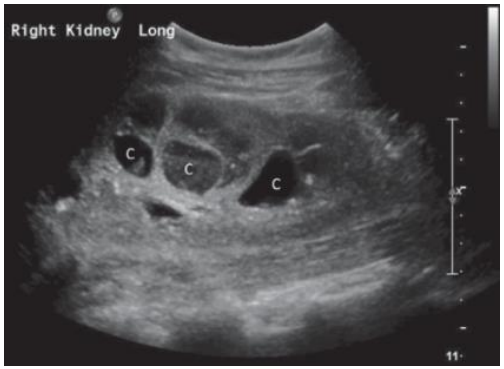


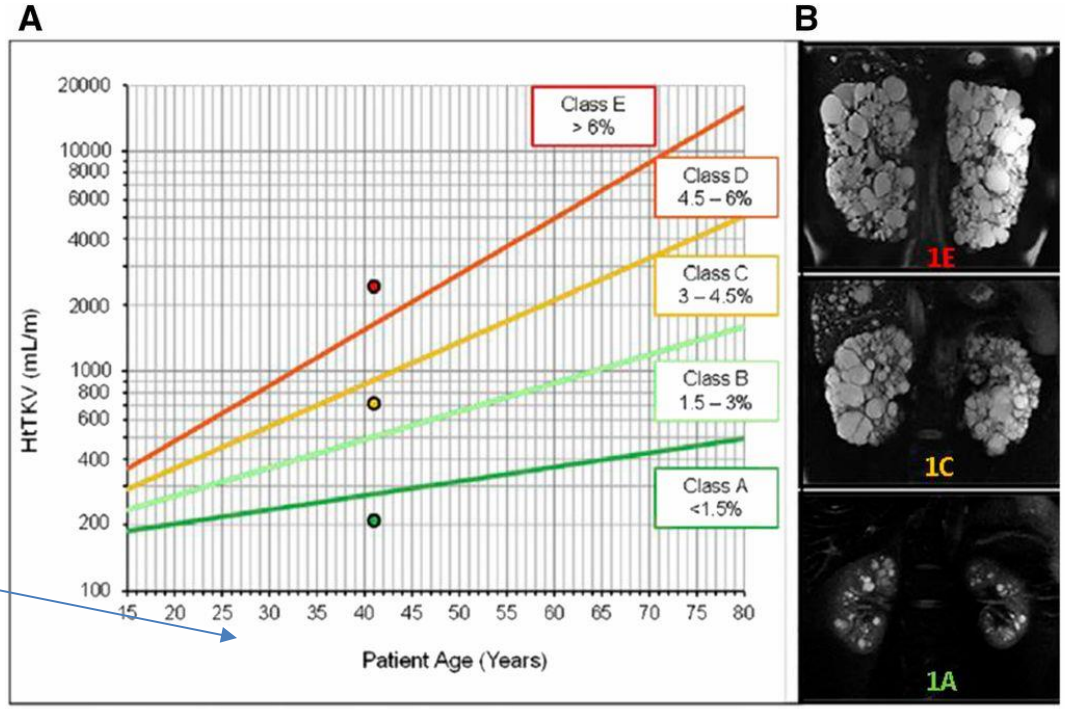
TABLE. PEI-RAVINE CRITERIA FOR THE DIAGNOSIS OF ADPKD BY RENAL ULTRASOUND EXAMINATION*[2]

Age (years)	Positive family history†	Number of renal cysts required to establish diagnosis	PPV, sensitivity	Number of renal cysts required to exclude diagnosis
15–29	Yes	≥3 (unilateral or bilateral)	PPV = 100%, sensitivity = 81.7%	Normal ultrasound does not exclude the diagnosis
30–39	Yes	≥3 (unilateral or bilateral)	PPV = 100%, sensitivity = 82–96%	Normal ultrasound does not exclude the diagnosis
40–59	Yes	≥4 (at least 2 in each kidney)	PPV = 100%, sensitivity = 90%	<2 (NPV = 100%, specificity = 98.2%)
≥60	Yes	≥8 (at least 4 in each kidney)	PPV = 100%, sensitivity = 100%	<2
Any age‡	No	≥10 cysts in each kidney with renal enlargement ± hepatic cysts		NA

ABBREVIATIONS: ADPKD = autosomal dominant polycystic kidney disease; NA = not applicable; NPV = negative predictive value; PPV = positive predictive value.
* Criteria based on the use of conventional 3-5 MHz ultrasound probe with cyst size typically being above 1 cm in diameter. CT, MRI and more sensitive ultrasound probes detect smaller cysts and therefore the above criteria are not applicable to these imaging modalities.
† Genotype unknown.
‡Criteria based on expert opinion.

Ravine et al. Lancet 343: 824, 1994: Pei et al. J Am Soc Nephrol 20: 205, 2009; Rangan Med Today, 2014

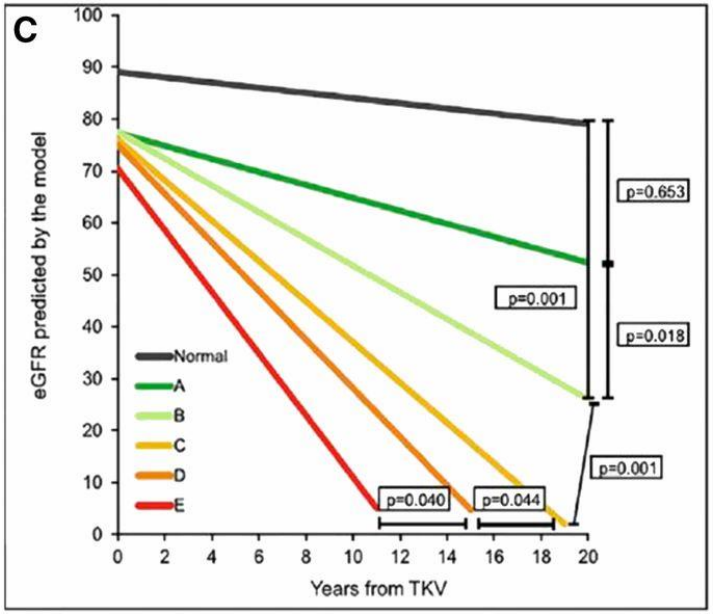
Mayo imaging classification



class stable

htTKV + age
→ predict eGFR decline

Good predictor in typical not atypical disease

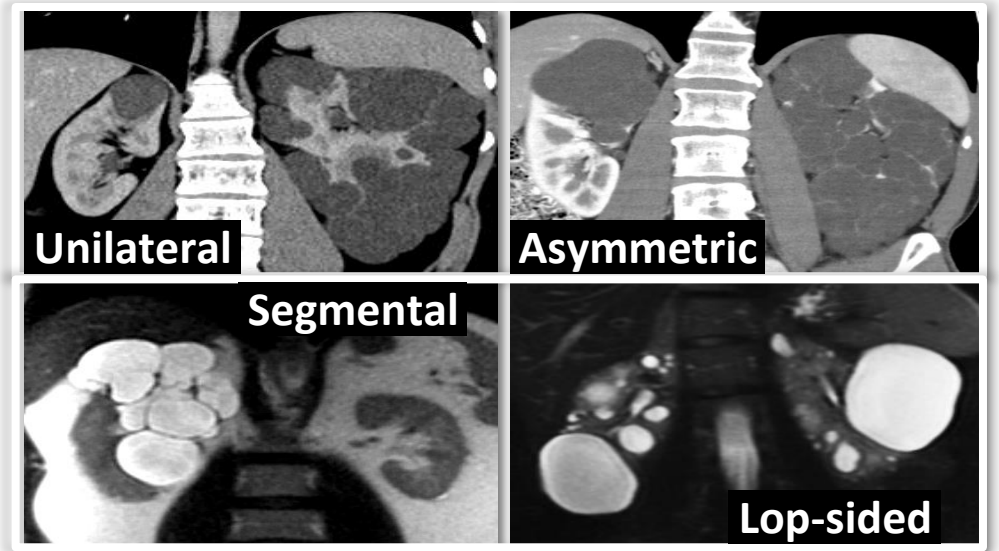


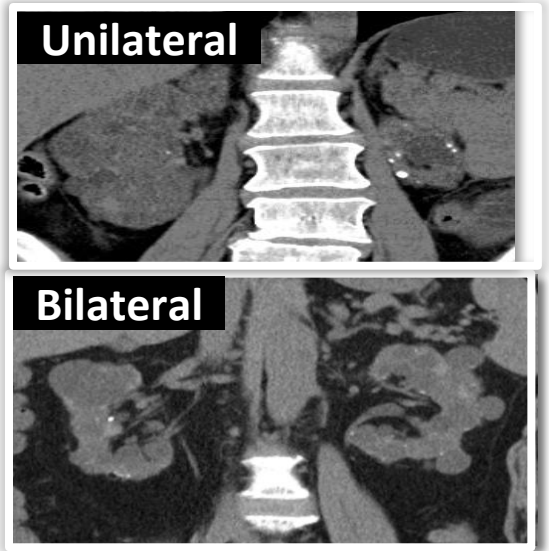
	Estimated eGFR slope (ml/min/SA per year)	
	Male	*Female*
Class 1A	-0.23	0.03
Class 1B	-1.33	-1.13
Class 1C	-2.36	-2.43
Class 1D	-3.48	-3.29
Class 1E	-4.78	-4.58

Fouad T. Chebib et al.
JASN 2018;29:2458-2470

Typical vs atypical disease

	Class	Sub-class	Term	Description
95%	1 Typical ADPKD			**Cyst distribution is bilateral and diffuse with relatively even contribution to TKV**
5%	2 Atypical ADPKD	A	*Unilateral*	Normal contralateral kidney with ≤2 cysts
			Asymmetric	Mild involvement of contralateral kidney with 3–9 cysts and <30 % of TKV
			Segmental	Involvement only one pole of one or both kidneys
			Lop-sided	Mild replacement of kidney tissue with ≤5 cysts accounting for ≥50% TKV
		B	*Bilateral presentation w/ acquired unilateral atrophy*	Atrophy of contralateral kidney
			Bilateral presentation w/ bilateral kidney atrophy	Length <14.5 cm, atrophy of parenchyma and SCr ≥ =1.5 mg/dL

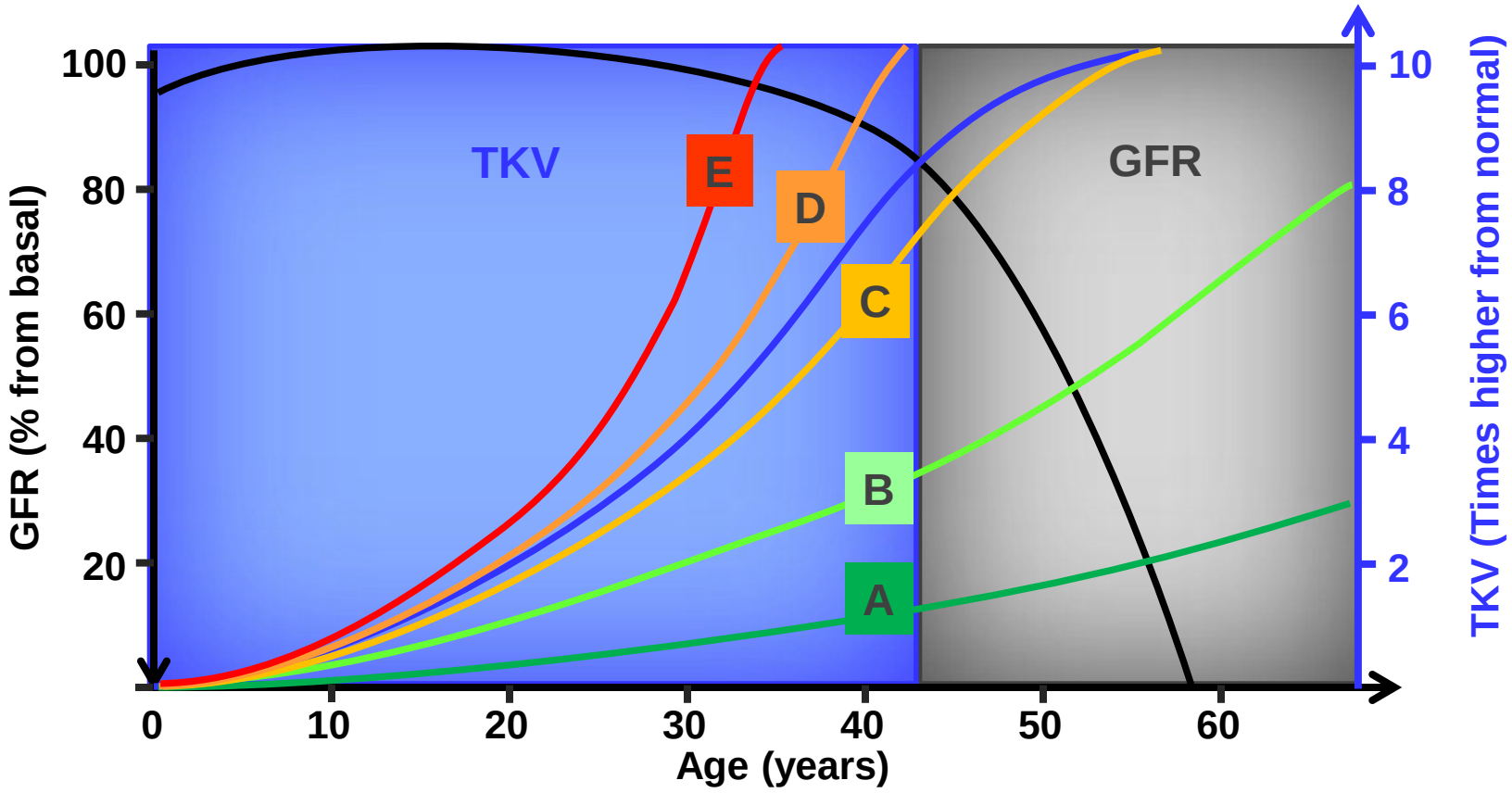




TKV as a Prognostic Biomarker

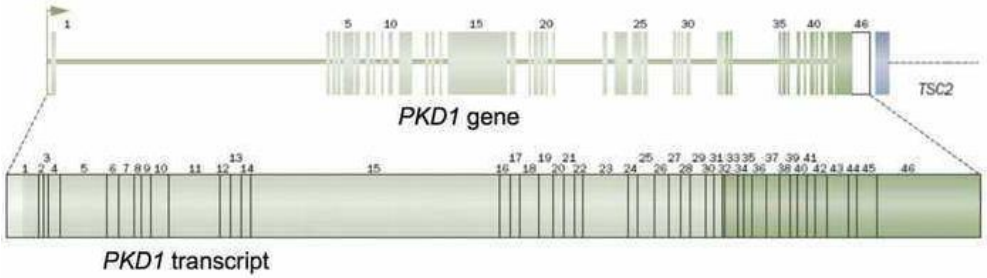
CT & MR useful for differential diagnosis and to establish prognosis

TKV to monitor disease progression requires high precision



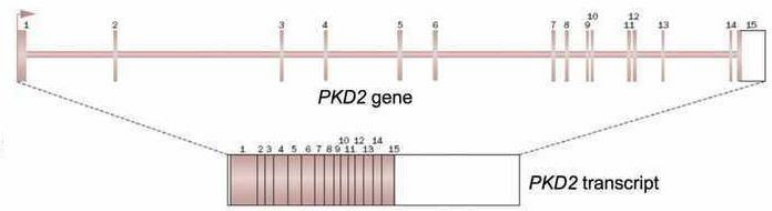
TKV is a good predictor at earlier stages, GFR better during late stages

GENETICS



PKD1
80%

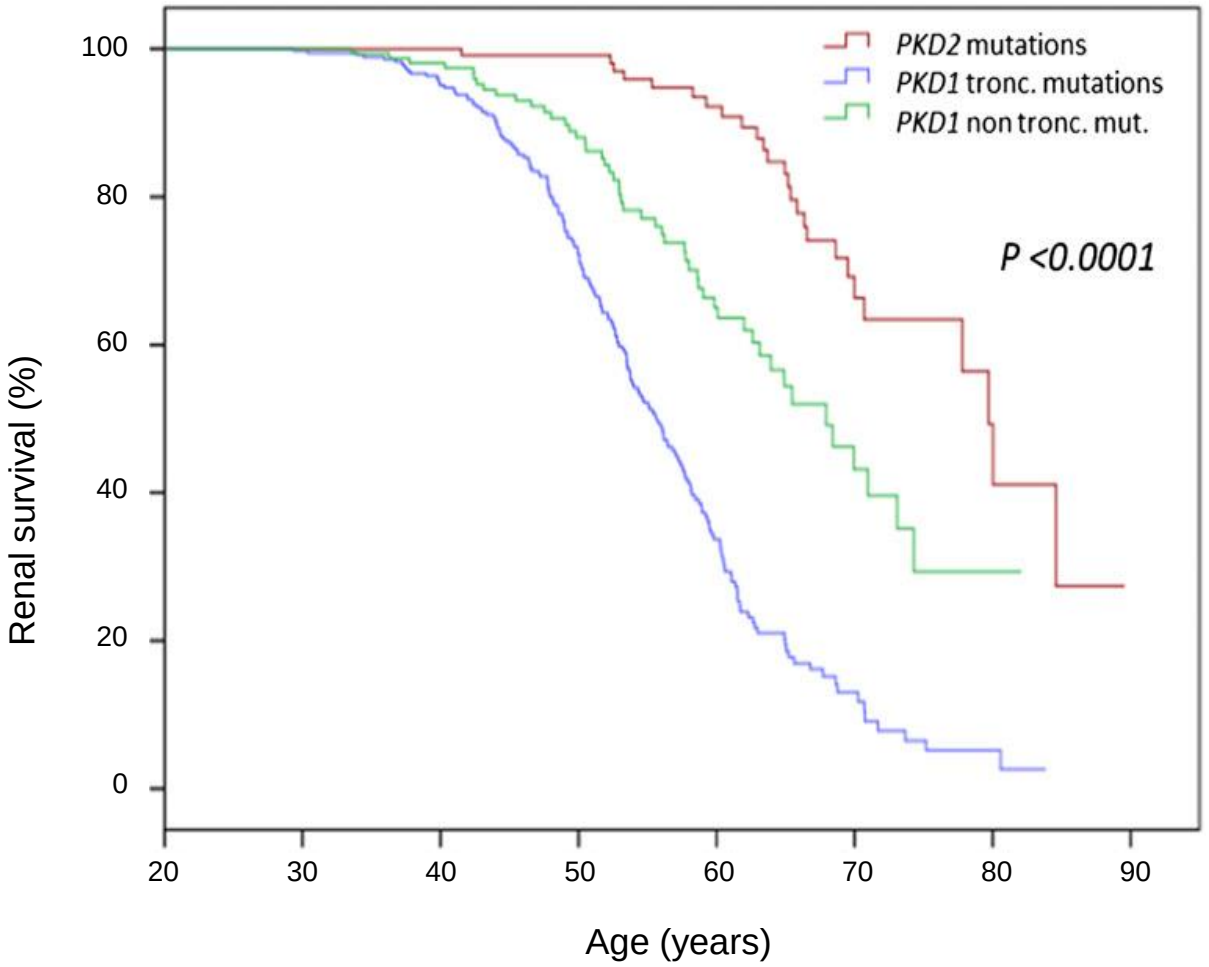
- **Large gene** 16p13.3, 53kB, 46 exons, 15 kB mRNA
- encodes polycystin-1 protein, a **transmembrane receptor** for an unknown ligand
- **No hot spots**; mutations throughout the gene, mutation of gene 5' portion *may* have more severe phenotype
- **Numerous mutations**: Mayo Clinic Database >2300 mutations
- **Mutation screening labour-intensive** (only 30% of mutations are recurrent)
- **Pseudogenes (**highly homologous but generally non-functional copies of genes)



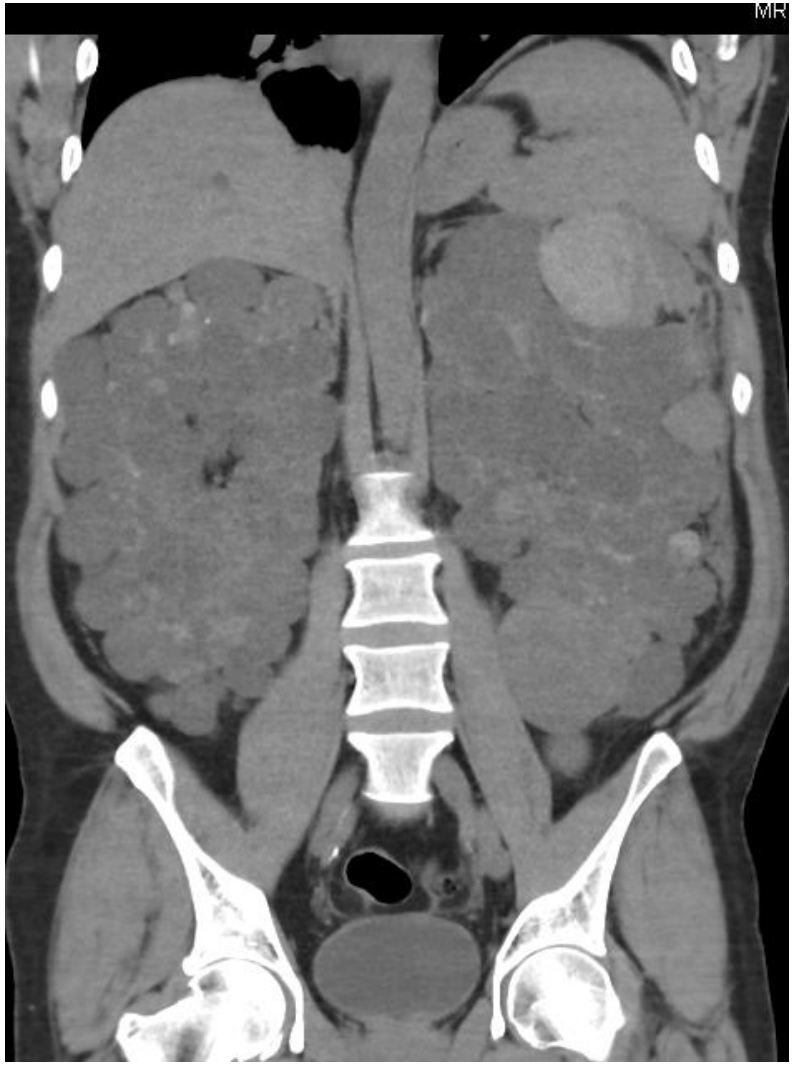
PKD2
15%

- **Smaller gene** 4q21-q23, 15 exons, 5 kB mRNA
- encodes polycystin-2 protein, **calcium ion channel**
- Mutations throughout the gene
- >200 mutations
  (truncated protein, unique to a single family; missense mutations much less common)

Heterogeneity due to affected gene and allele

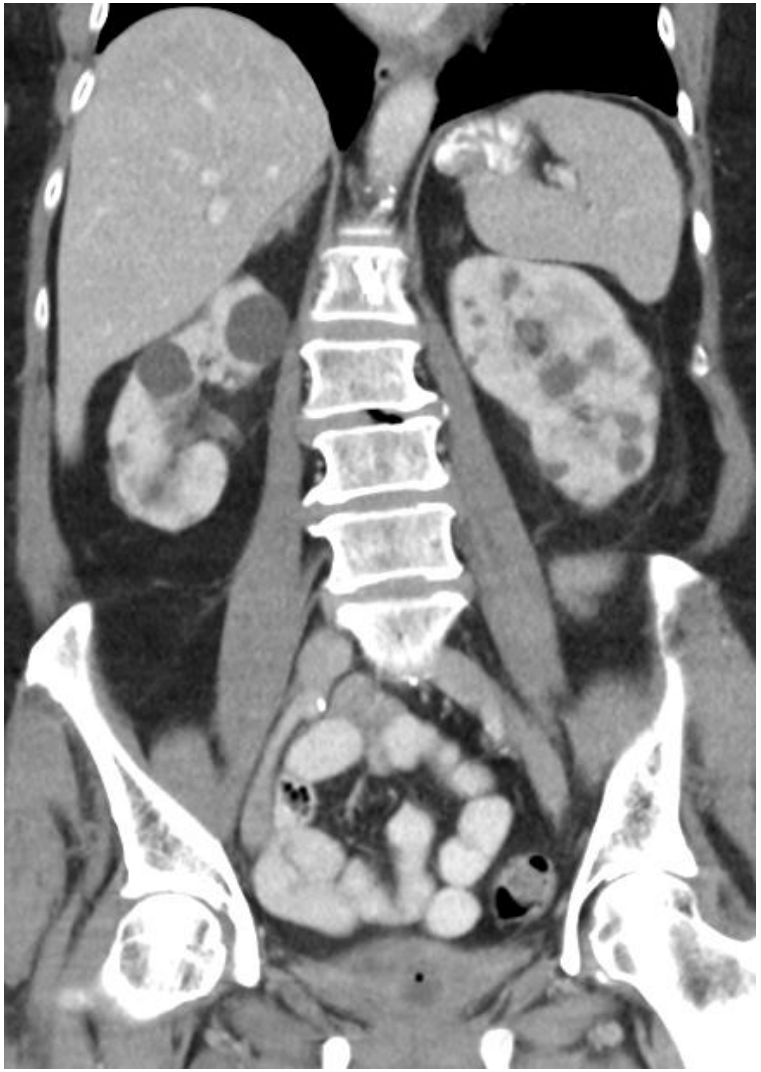


Cornec-Le Gall JASN 2013;24:1006



PKD1

- 47 year old male
- Cr 300 μmol/L
- eGFR 20 ml/min/1.73m ^{2}
- CKD Stage 4



PKD2

- 72 year old female
- Cr 77 μmol/L
- eGFR 66 ml/min/1.73m ^{2}
- CKD Stage 2

Next Generation Sequencing in PKD

- ***Options for testing***
  - **Single gene**
  - **Targeted panel**
  - **Exome: WES, 1% 30Mb, detects 98% of known PKD1 variants, potential ascertainment bias**
  - **Genome: WGS, 3Gb, needed to detect 2%, copy number variants, structural variants, other variant types**

- ***Multiple genes associated with PKD: genomic approaches allow testing of all of these in one go***

- ***Other genes***
  - **GANAB (glucosidase II alpha subunit) & DNAJB11: small bilateral kidney cysts**
  - **HNF1b: MODY**
  - **UMOD: ADTKD-UMOD**
  - **MUC1: MCD**

- ***10% of families with mild ADPKD, no mutation is detected:***
  - **deep intronic mutations, extra-genic mutations, another locus (? – probably not), wrong diagnosis – phenocopy**

- ***up to 10% of patients have a negative family history (even after parental U/S screening), and 25% of these cases are due to de novo mutations***

Indications for Genetic Testing

- ***NOT the first line diagnostic test***
- **When a *definitive diagnosis* is required in young persons**
  - **eg potential living-related donor in an affected family with equivocal imaging data**
  - **predictive testing in adults**
- **To provide *diagnostic clarity***
  - **eg a negative family history of ADPKD when alternative causes of cystic kidney disease are considered**
- **In couples requesting *genetic counselling & family planning***
- **In cases of marked *clinical discordance*, eg very early onset disease or very mild disease**

Genetic counselling in ADPKD

informed consent essential

Result

Nothing found: wrong genes, wrong technology, or condition not genetic

VOUS (variant of uncertain significance)

- **difference found ?normal ?pathogenic**
- **uninformative for diagnosis or predictive testing of family**

Pathogenic mutation:

- **diagnosis made**
- **inheritance – can test other family members**
- **recurrence risk – options for family planning**

Emotional impact:

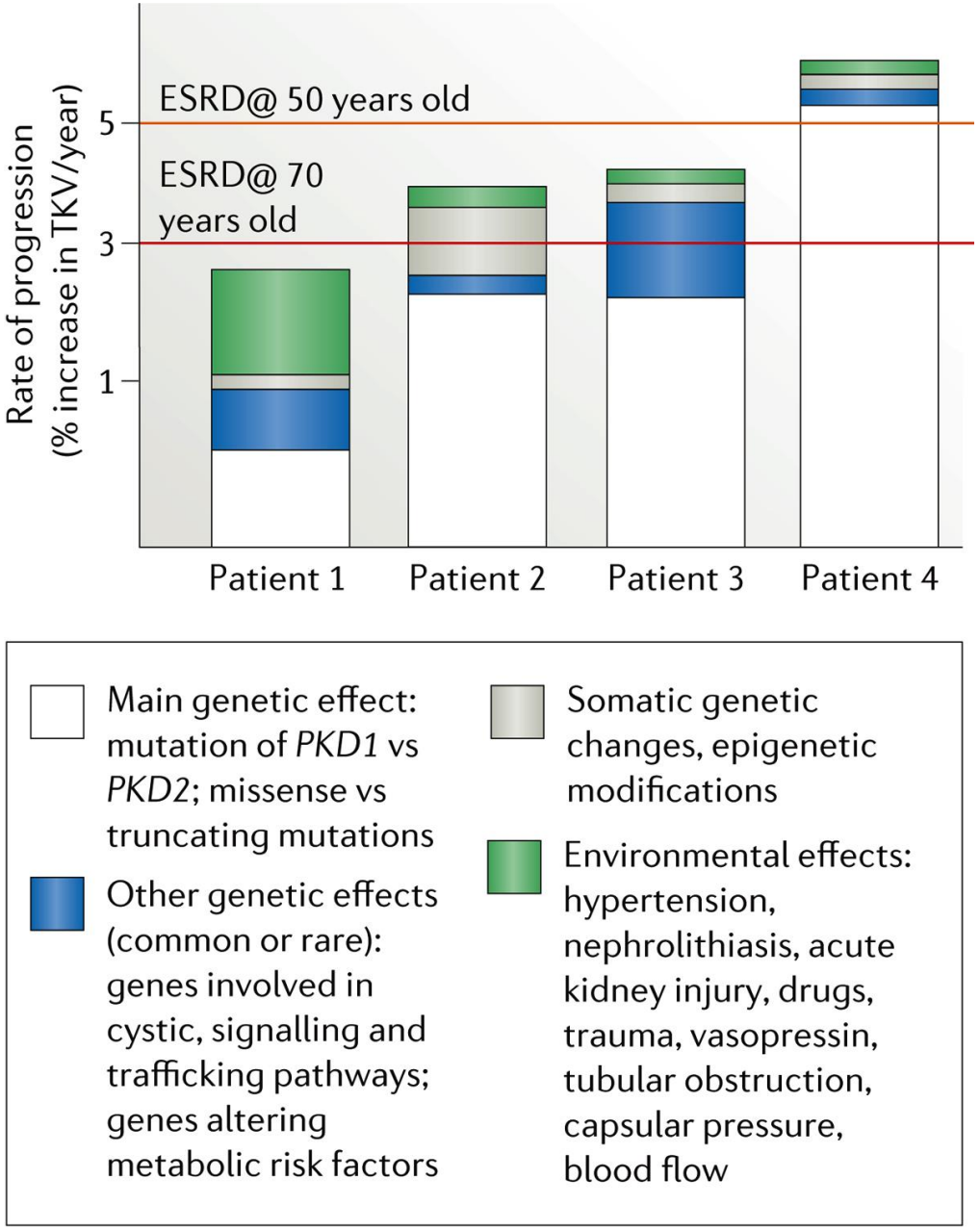
certainty vs uncertainty, implications for family, unexpected result

Pragmatic aspects:

insurance (voluntary moratorium on use of result), future employment

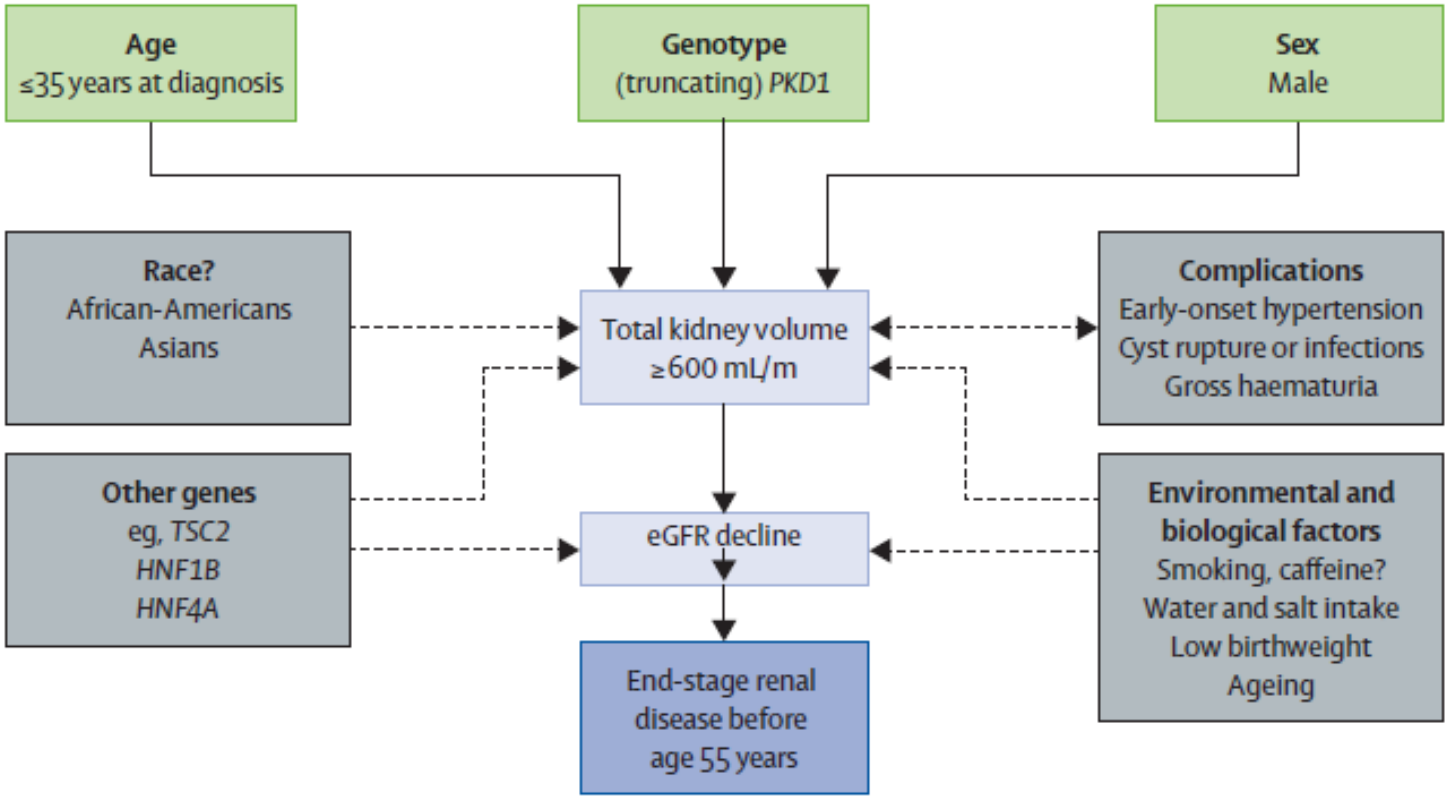
PATHOGENESIS

Genetic & environmental effects on polycystin protein dosage explains rate of ADPKD cyst progression

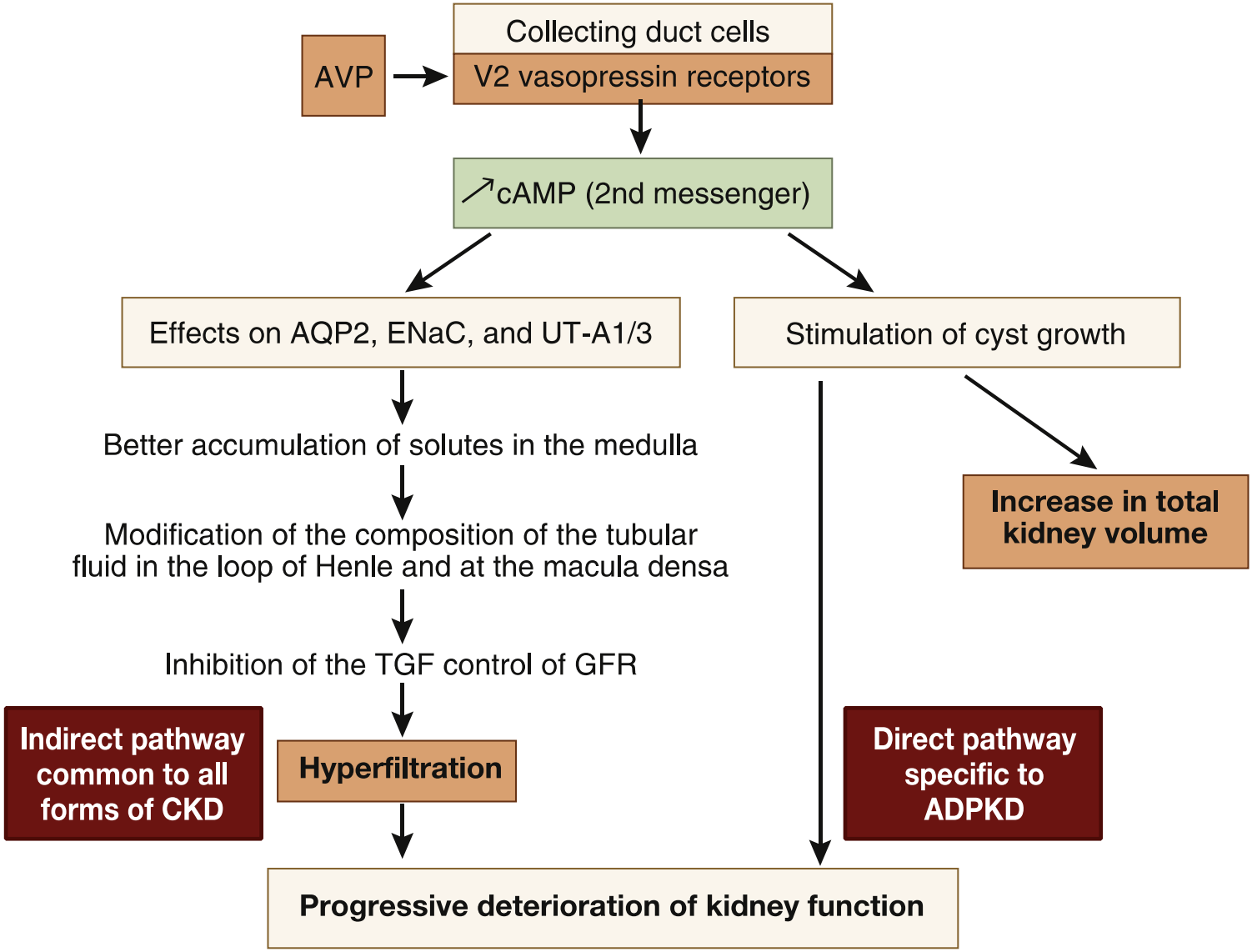


Lanktree & Chapman.
***NRN* 2017;127**

Factors relevant to the prediction of disease progression in ADPKD



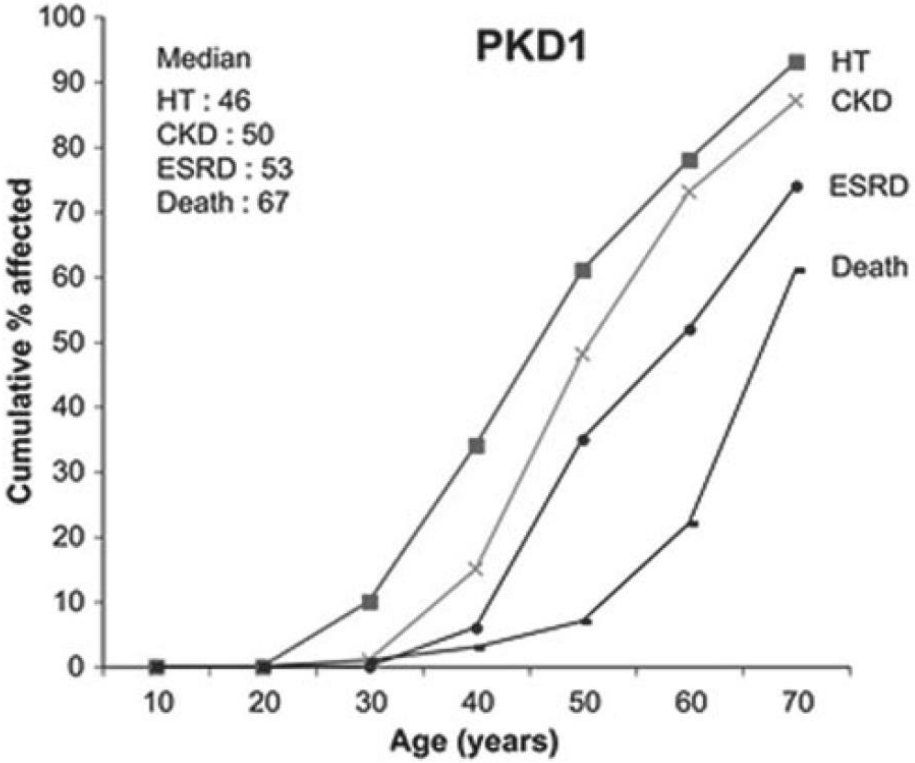
Ong ACM et al. Lancet *2015;385: 993–2002*



Bankir L, Bichet DG. KI 2019;96:19–22

TREATMENT

Why treat ADPKD?

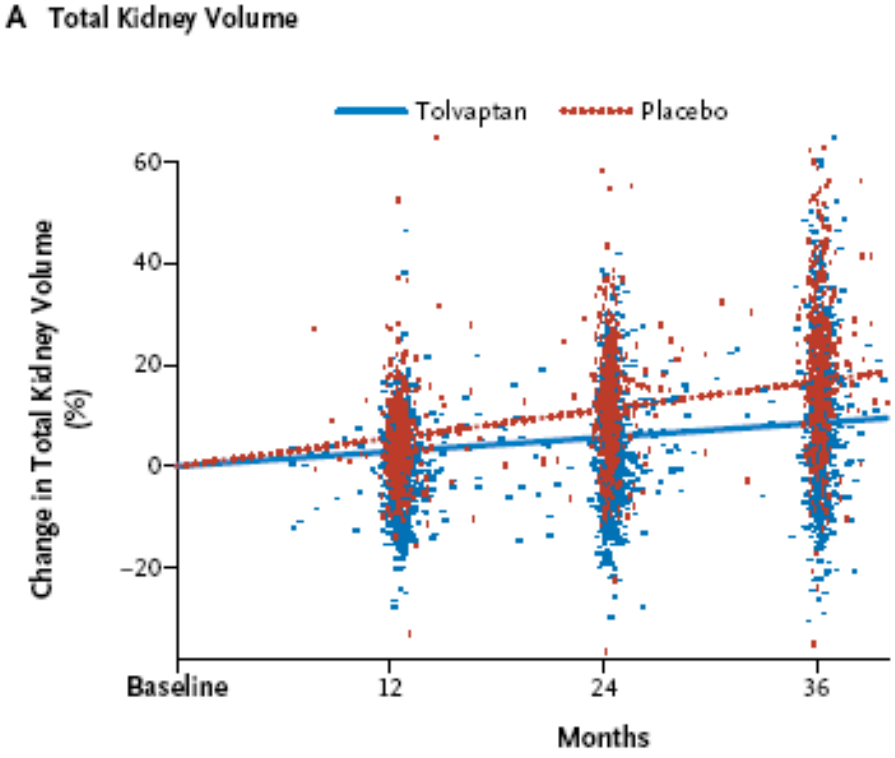


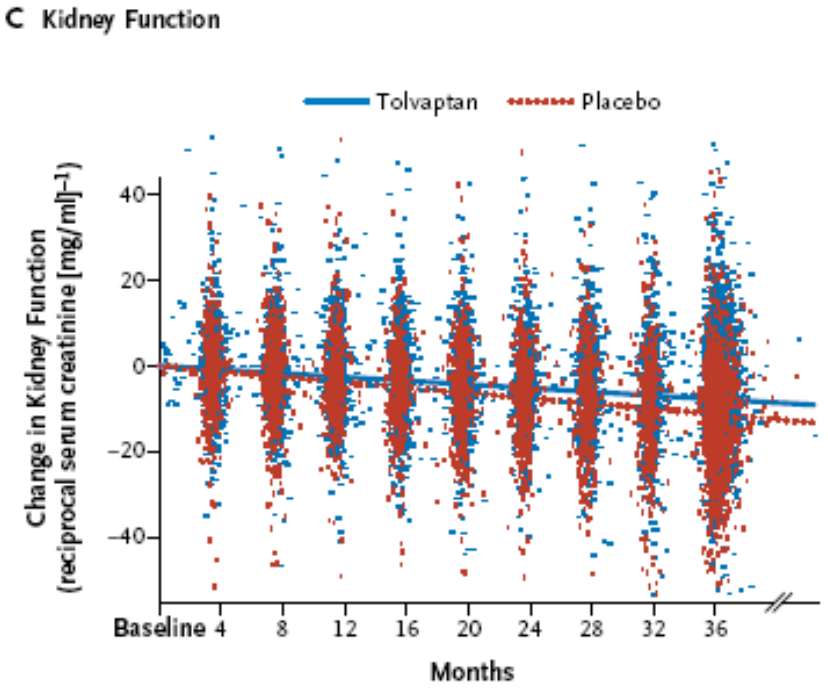
Dicks 2006 CJASN 1:710

Symptom	Prevalence
Back pain	51%
Often, usually, always	20%
Abdominal pain	28%
Prescription pain meds	12%

Miskulin 2014 AJKD 63:214

Tolvaptan attenuates early-stage human ADPKD
TEMPO 3:4



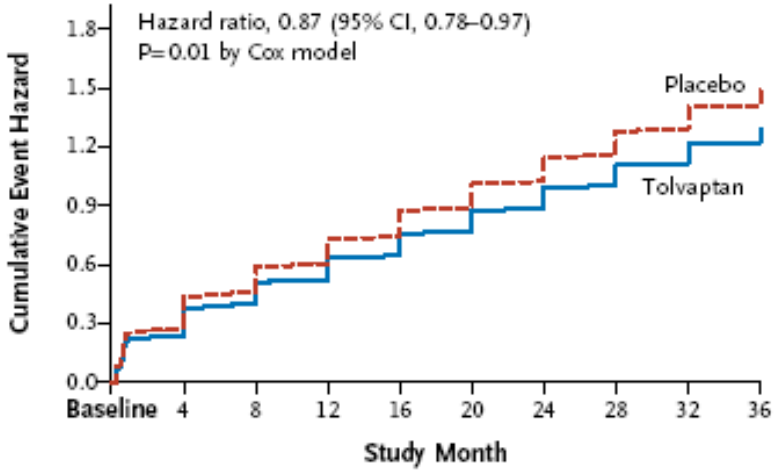


Torres et al. N Engl J Med 2012

Tolvaptan attenuates early-stage human ADPKD

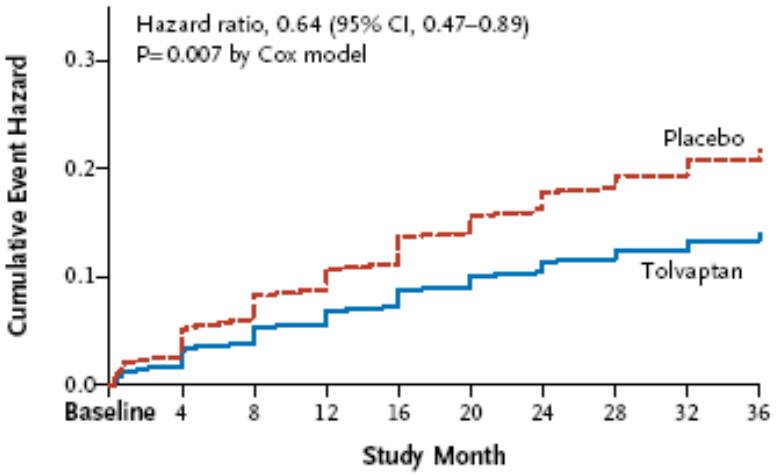
TEMPO 3:4

B Risk of ADPKD-Related Composite Events



No. at Risk										
Tolvaptan	961	870	835	811	792	776	763	752	744	642
Placebo	483	472	463	454	446	438	428	422	418	359

D Risk of Clinically Significant Kidney Pain



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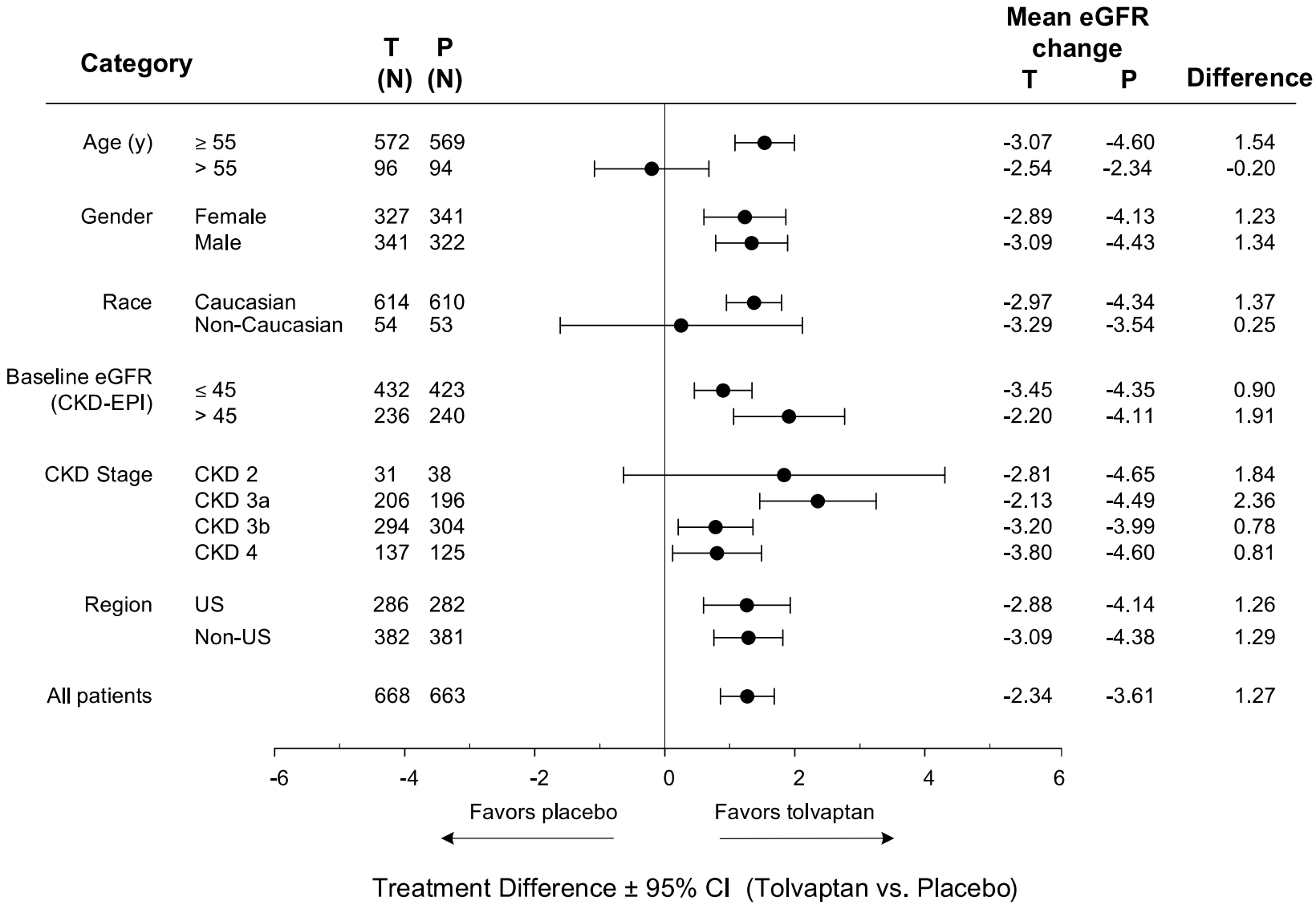
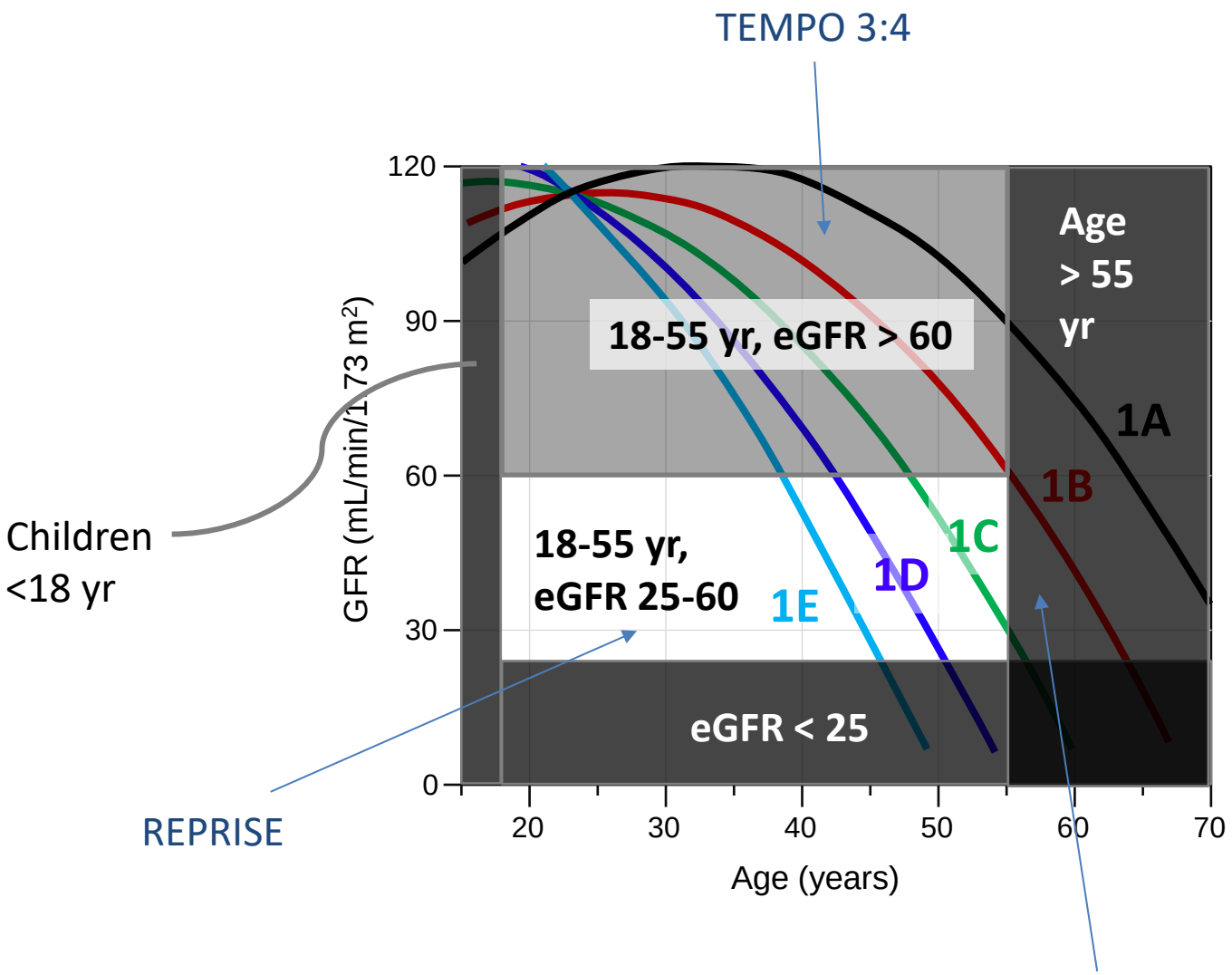


Torres VE et al. *REPRISE*. NEJM 2017

eGFR & age can identify patients that benefit from tolvaptan



Pts >55 yr did not benefit in REPRISE because 1A or 1B

Tolvaptan

CRITERIA FOR PERSCRIPTION

age 18-55

eGFR 30-89 mL/min/1.73 m^2 *AND*

rapidly progressing disease

eGFR decline ≥ 5 mL/min/1.73 m^2 in 1y

or, ≥ 2.5 mL/min/1.73 m^2 pa in 5y (PBS)

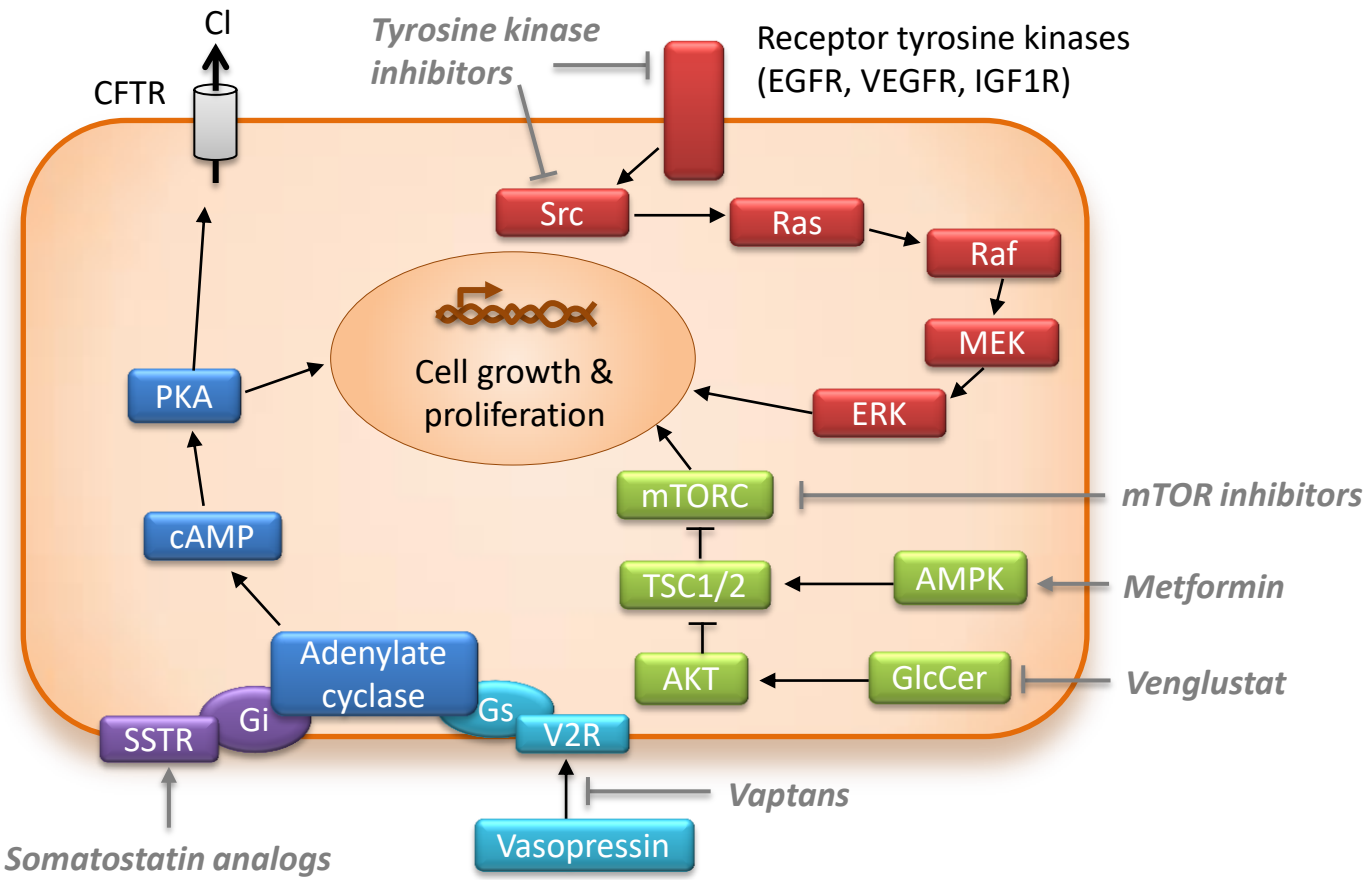
Mayo class 1C-1E (+/- 1B after observation)

CONTRAINDICATIONS

inability to handle aquaretic side effects *(up to 9L!; occupation or lifestyle)*
hypotension & hypovolemia
pregnancy & lactation
uncorrected hypernatremia
inability to sense or respond to thirst
significant liver injury not due to PLD *(elevated AST/ALT in 6%)*
urinary tract obstruction

DOSE

Start with lowest dose available, esp. if well-preserved GFR
Titrate up, aiming for first morning U_{Osm} < 280-300


Cl
CFTR
Tyrosine kinase inhibitors
Receptor tyrosine kinases (EGFR, VEGFR, IGF1R)
Src
Ras
Raf
MEK
ERK
Cell growth & proliferation
PKA
cAMP
mTORC
mTOR inhibitors
TSC1/2
AMPK
Metformin
AKT
GlcCer
Venglustat
Adenylate cyclase
Gi
Gs
SSTR
V2R
Vaptans
Vasopressin
Somatostatin analogs

Targets of Treatment

- **Current targets**
  - *Cell signals driving proliferation*: vaptans, somatostatin analogues, mTOR inhibitors, metformin, venglustat, tyrosine kinase inhibitors
  - *Uncertain mechanism of action*: bardoxolone, pravastatin, PPARγ agonists
- **Future targets**
  - *Metabolic reprogramming*: Warburg, caloric restriction
  - *Inflammation*
  - *Epigenetic mechanisms*: nicotinamide
  - *Others*: Ciliary signals (+ & -), noncoding RNAs, cell cycle regulators, CFTR, crystal deposition

Clinical Trials in ADPKD

NIH U.S. National Library of Medicine
ClinicalTrials.gov

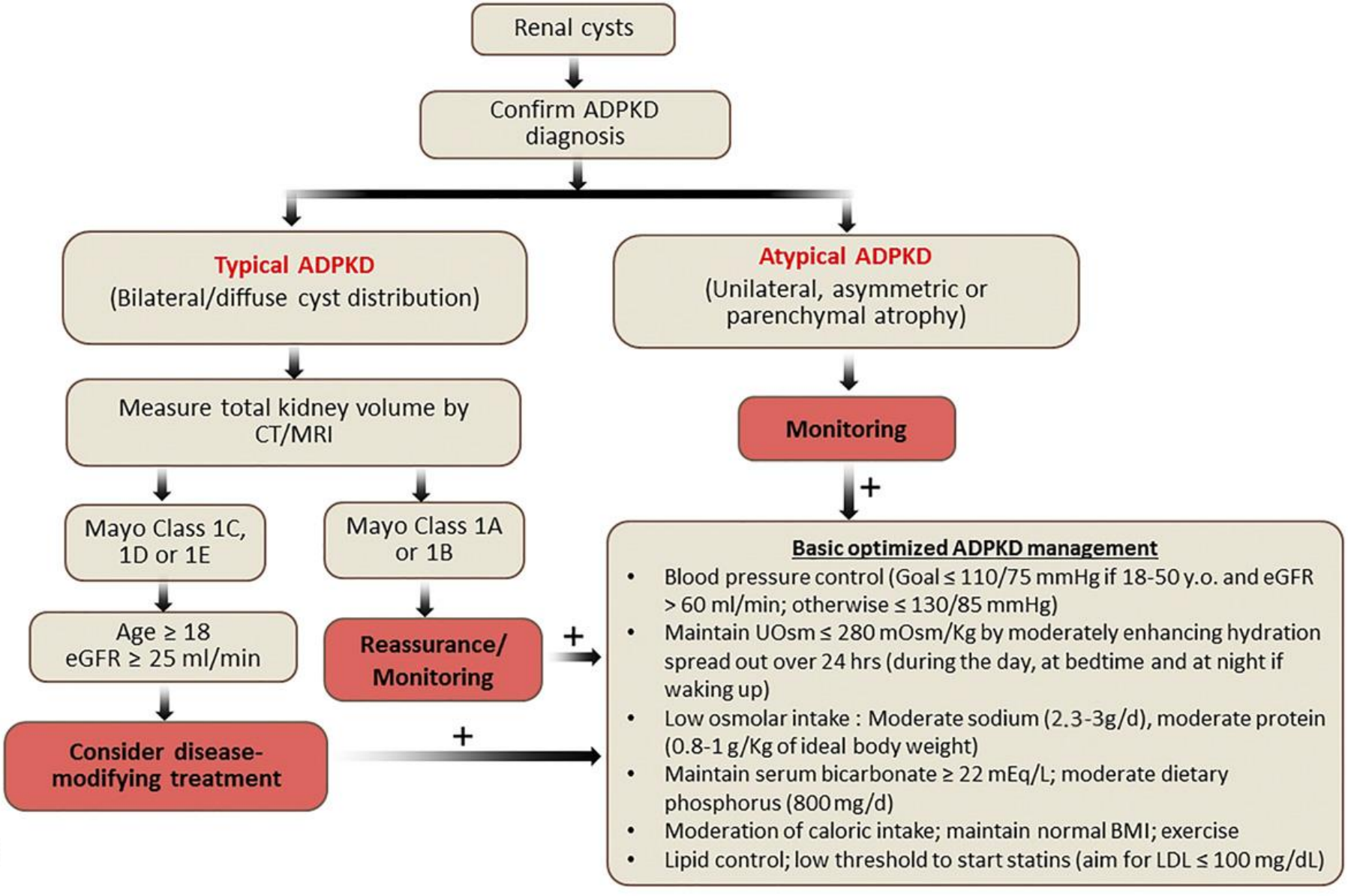
Accessed 12th Sept 2019

Multiple Small Molecule Interventions

Molecule	Mechanism of Action	Repurposed	Phase	Sponsor
Lixivaptan	V2R antagonist	Yes	Phase 2	Palladio Bio
Tesevatinib	Tyrosine Kinase Inhibitor	Yes	Phase 2	Kadmon
Venglustat	Glucosylceramide synthase inhibitor	Yes	Phase 2/3	Sanofi-Genzyme
Bardoxolone	Nrf2 inhibitor	Yes	Phase 2	Reata
Pravastatin	HMG CoA Inhibitor	Yes	Phase 4	Uni Colorado
Metformin	AMPK Inhibitor	Yes	Phase 4	Tufts, Uni Colorado, AKTN

Public Health Interventions

Intervention	Mechanism of Action	Primary Outcome	Sponsor
Caloric Restriction	Multiple (AMPK, TORC)	Feasibility	University of Colorado
Niacinamide	Tyrosine Kinase Inhibitor	TKV	University of Kansas
Water*	Reduction of vasopressin release	TKV	Westmead Hospital
Water	Reduction of vasopressin release	TKV	Rogosin Institute



Chebib FT & Torres VE. CJASN 2018;13 ***(a great review!)***

Basic optimized ADPKD management

- **BP** (1B)
  - *ACEI/ARB first-line, then cardioselective β-blocker*
  - *consider <110/75 if <50 yr, CV disease*
- **Liberal water intake** (1C)
  - *Uosm ≤280 mosm/kg*
  - *24h*
- **Salt restriction** < 80-100mmol/d (1C)
- **Protein restriction** 0.8-1.0g/kg IBW/d (1C)
- **Moderate caloric intake, avoid obesity, regular exercise** (1C)
- **Avoid high phosphorus diet** (2C)
- **Acid-base: bicarbonate** ≥ 22mmol/l (2B)
- **Total cholesterol** < 4.0mmol/L (2B)
- **No smoking**
- **Limit caffeine**

Rapid-progressors with preserved kidney function

Consider enrolling in a clinical trial!

Summary

US: preferred screening method, Pei-Ravine criteria

MRI (or CT): for differential diagnosis & complications
for prognosis (TKV, Mayo classification in typical ADPKD)

TKV early, GFR late

Genetic testing: for diagnostic clarity, genetic counselling (with informed consent!), clinical discordance

Heterogeneity: affected gene & mutation, polycystin dose (genetic & environmental effects), other genes, age, complications

Vasopressin: central role

Disease modifying drugs: esp. vaptans

Water: possible role

Importance of basic optimised management, especially BP


#SydNYE