Prognostic Biomarker Qualification: Case Study: ADPKD and TKV

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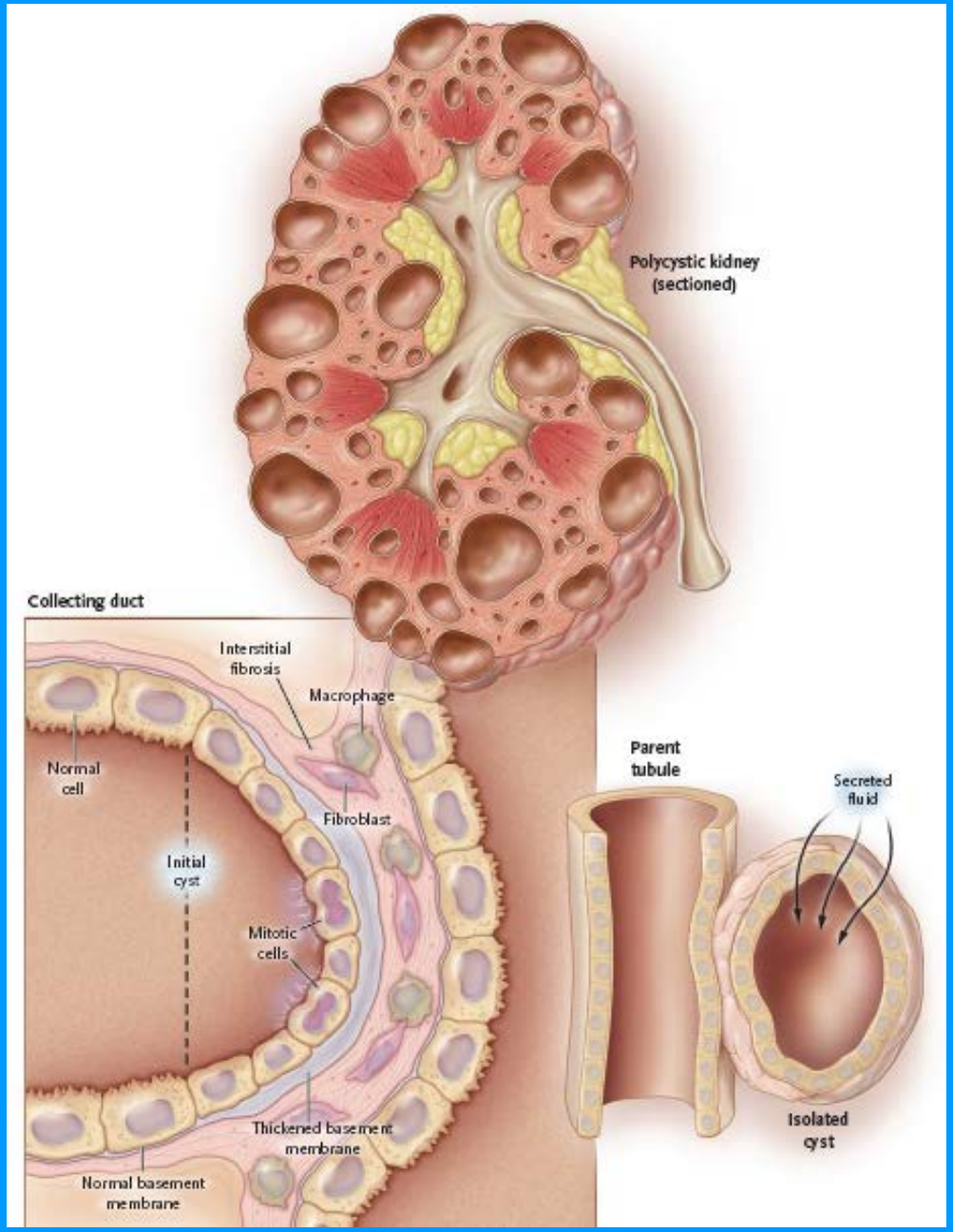
Disclosures

- Research Support:
  - Boston Scientific
- Consultation
  - Otsuka, Kadmon, Sanofi-Genzyme

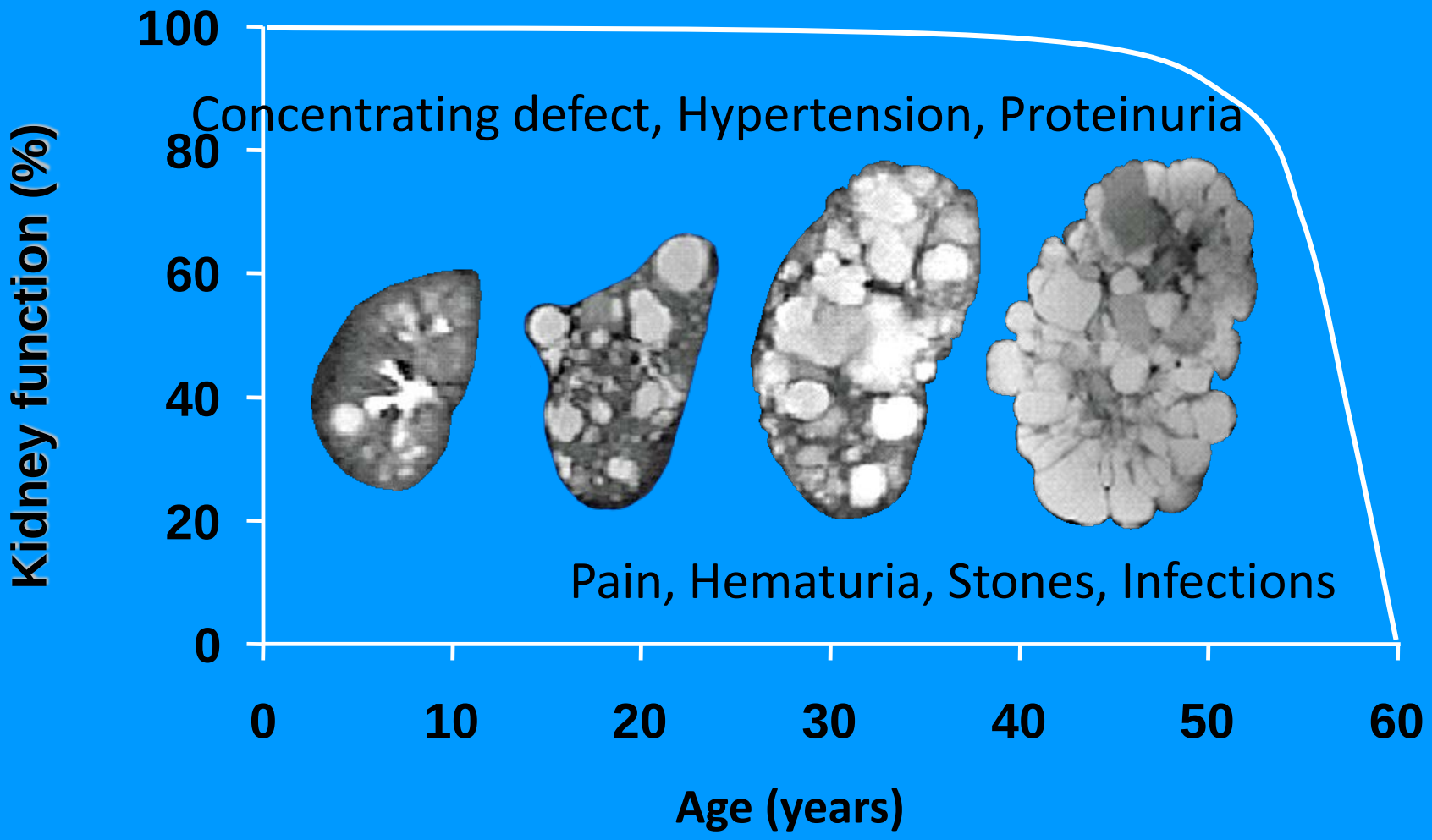
ADPKD

- 4th leading cause of ESRD
- No race/gender favored
- >3,000,000 worldwide
- Cysts
  - — Kidneys
  - —Liver
  - —Pancreas
  - —Spleen
  - —Brain
- Begin *in utero*
- Develop in tubules
- Separate from tubules
- Isolated sacs



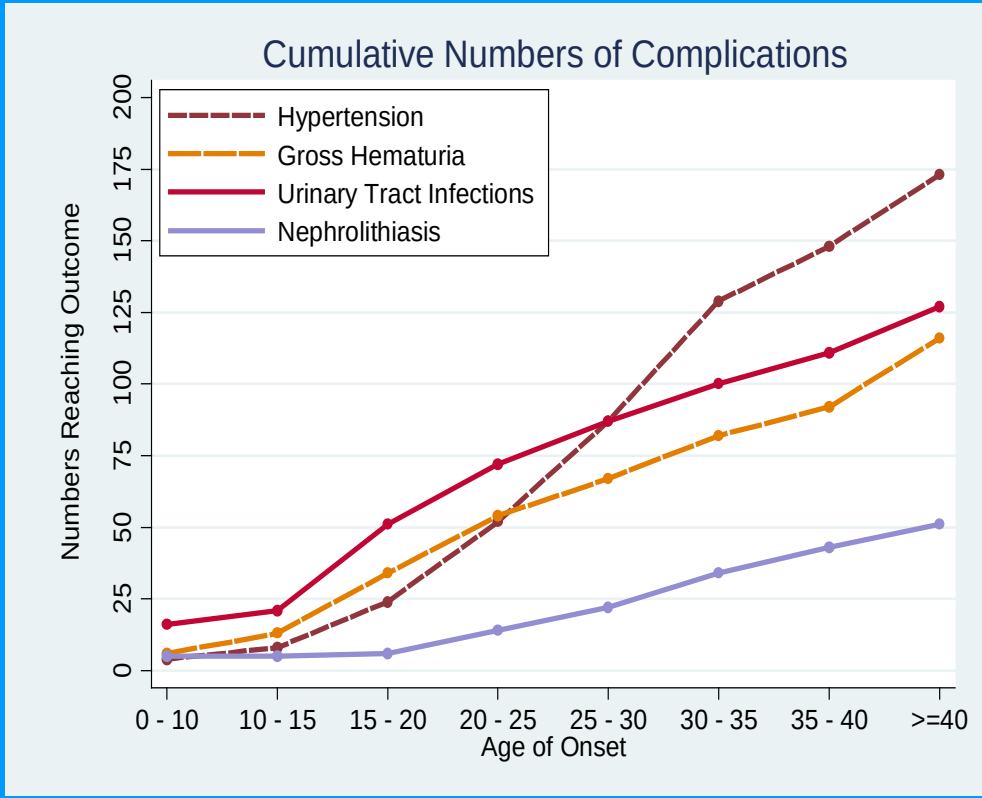
Grantham JJ. *N Engl J Med*. 2008;359:1477-1485.

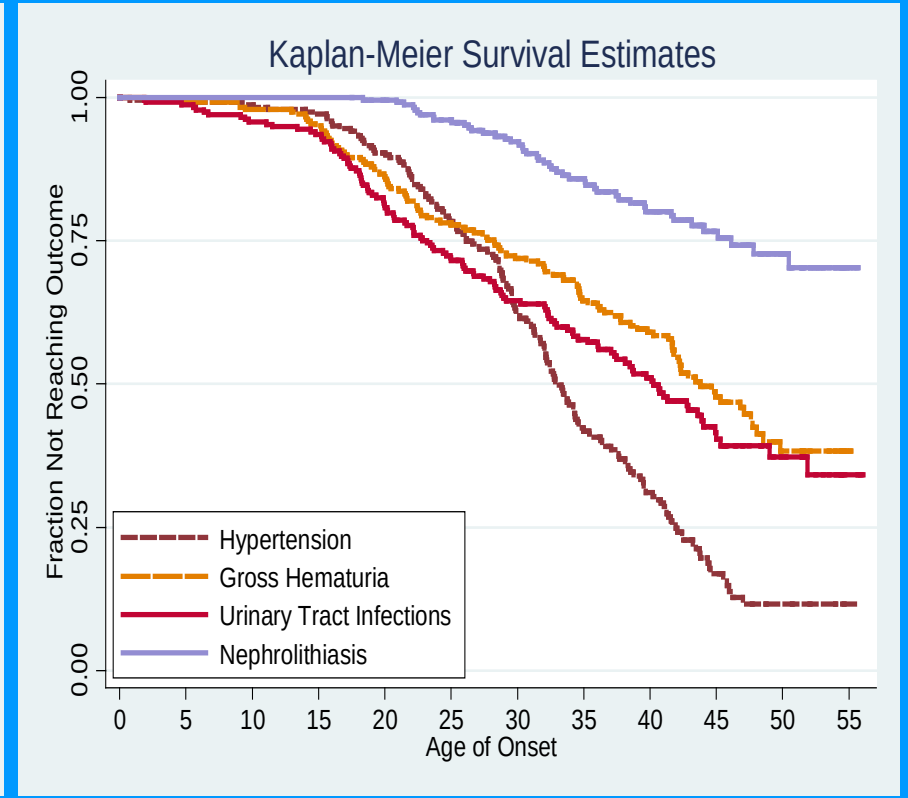
ADPKD Progression



Torres Mayo <aupCP1047707-9

ADPKD patients suffer renal complications prior to loss of kidney function





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

NIH CRISP Studies; Rahbari-Oskoui, *ASN Renal Week*, 2010.

Characteristics of ADPKD That Associate with ESRD

- **Genotype:** > 95% PKD1 individuals demonstrate **renal cysts** by age 30
- **Hypertension:** occurs in 60% with intact renal function by age 30
- **Proteinuria:** is not a common feature of this disease, but has important prognostic implications
- **Gross hematuria**: > 50% will have had an episode by age 40

ALL CHARACTERISTICS HAVE NOW BEEN SHOWN TO MEDIATE THEIR RISK THROUGH KIDNEY VOLUME

CRISP

Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease

Prospective longitudinal observational study with annual protocolized visits, MRIs and GFR measurements

Age 15-45 yrs

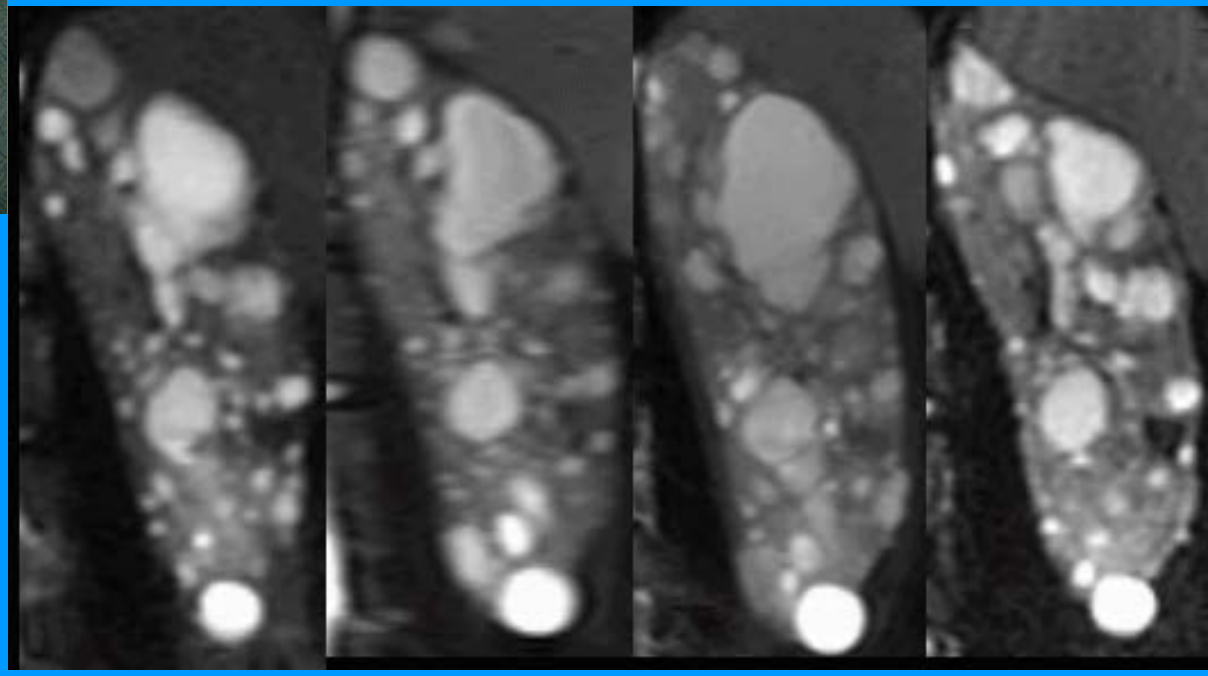
eGFR >70 ml/min

2/3 with hypertension <35 yrs or PrU >300 mg/d

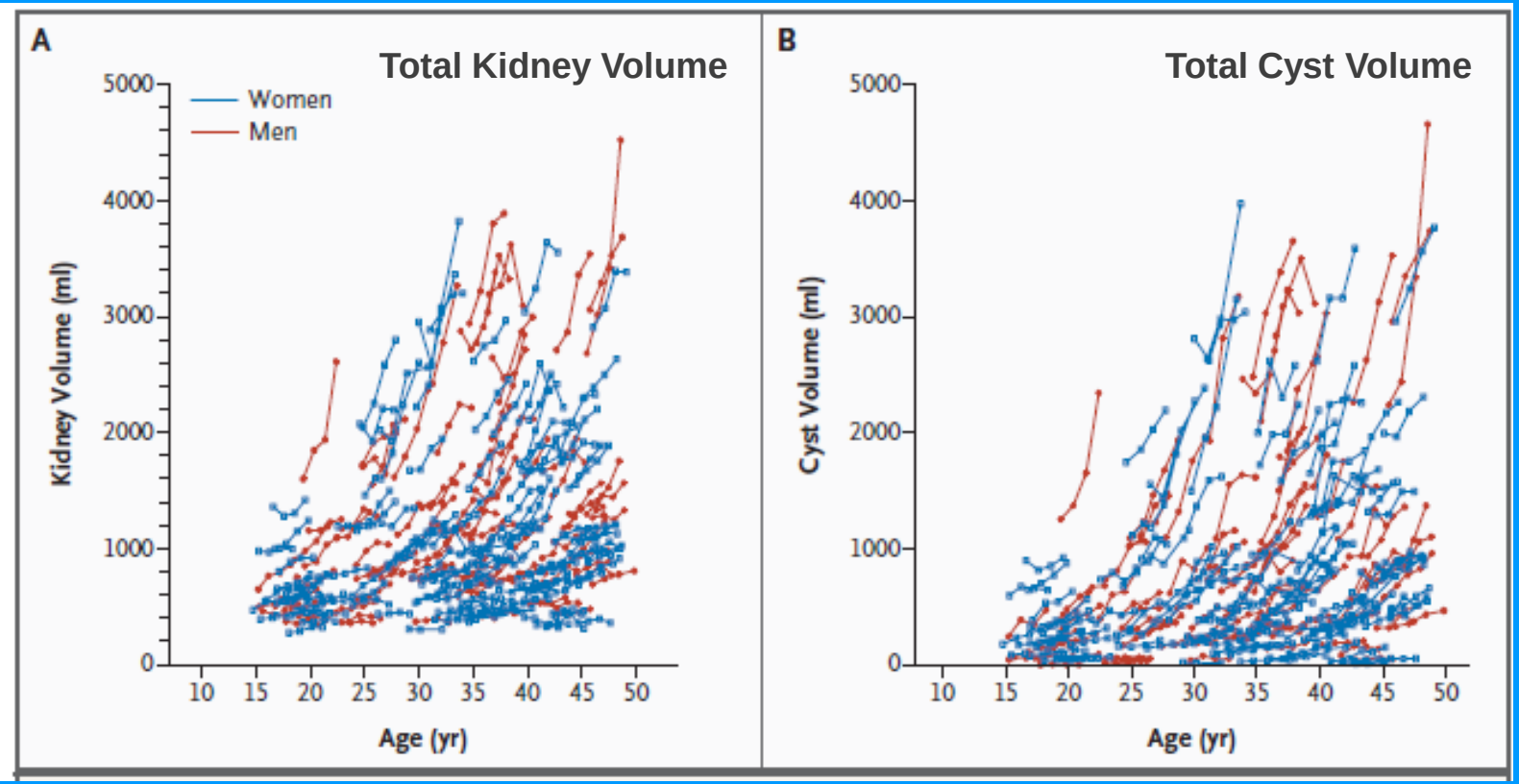
Inter-observer variability: 2.1%

Intra-observer variability:2.4%

Day-to-day variability: 2.4%



Increased Kidney Volume is Due to Increased Cyst Volume

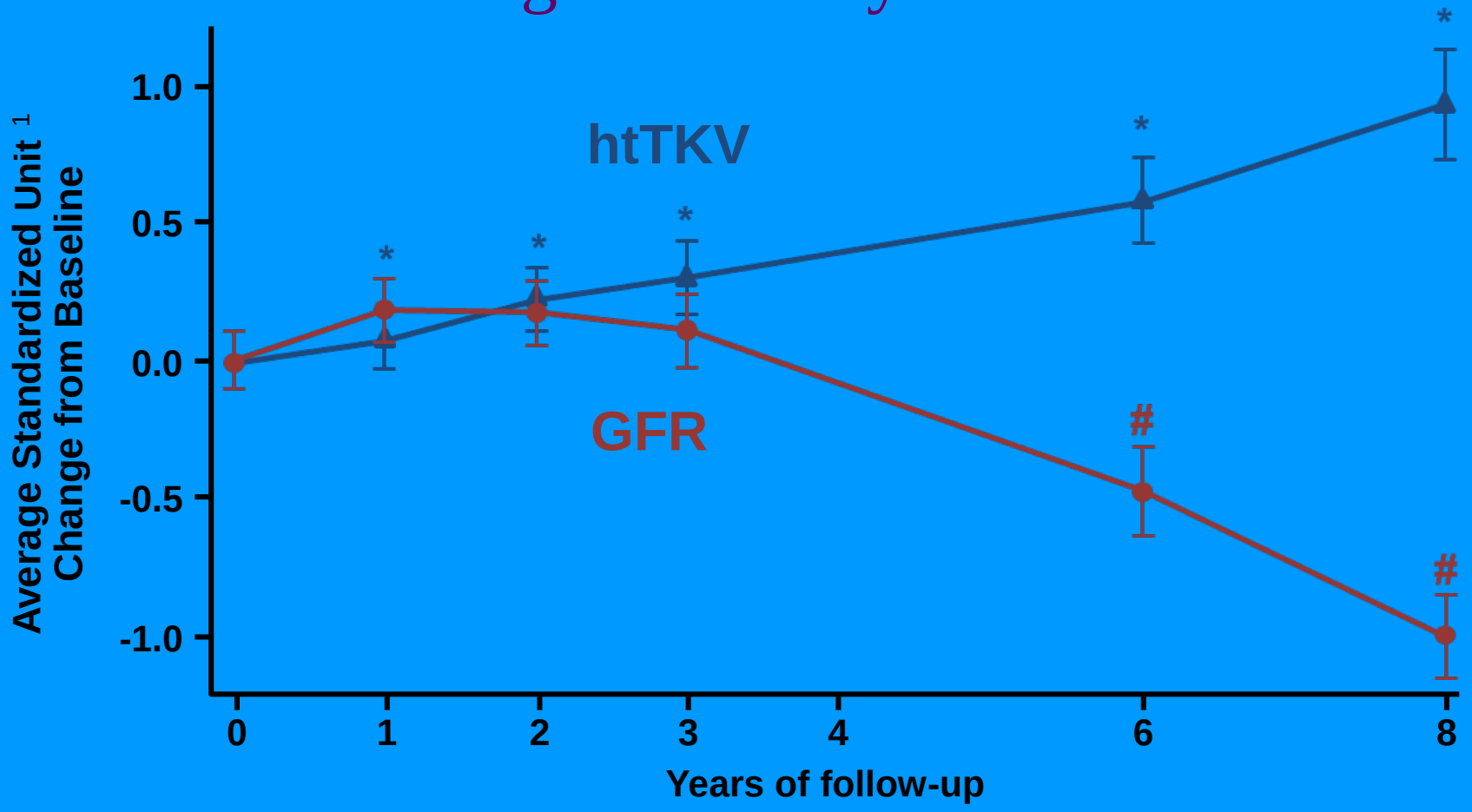


Kidney growth is highly variable and each individual has their own growth curve

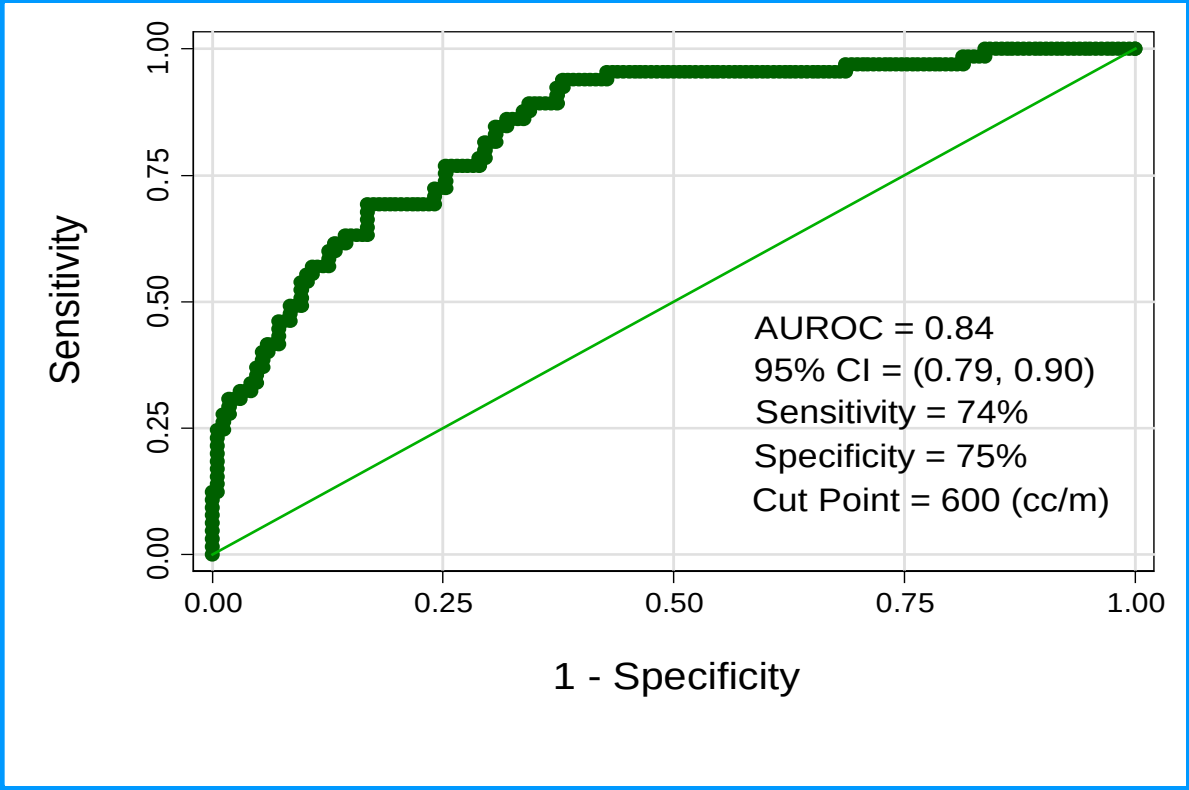
Measurement variability= Inter-observer 2.1%, Intra-observer 2.4%, Day-to-Day 2.4%

Grantham, *NEJM* CRISP 2006; Chapman *Kidney Int* 64; 1035–1045, 2003

Change in Kidney Volume Precedes Change in Kidney Function



p<0.05 for htTKV change from baseline; # p<0.05 for GFR change from baseline; htTKV=Height-adjusted total kidney volume; [1] Percent Change Standardized to a common unit;
NIH CRISP Studies; Chapman CJASN 7:479, 2012



Baseline predictors of CKD Stage 3 endpoint

Variable	Units	AUC	Sensitivity	Specificity	Cut-point	95%CI of AUC	P*
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	y	0.66	0.60	0.65	35	(0.59, 0.74)	< 0.001

QUALIFICATION OF TOTAL KIDNEY VOLUME AS A PROGNOSTIC BIOMARKER FOR USE IN CLINICAL TRIALS EVALUATING PATIENTS WITH AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

RD Perrone, JF Marier, MS Mouksassi, F Czerwiec, K Romero, E Dennis, D Miskulin, A Chapman, B Gitomer, and VE Torres for the PKD Outcomes Consortium

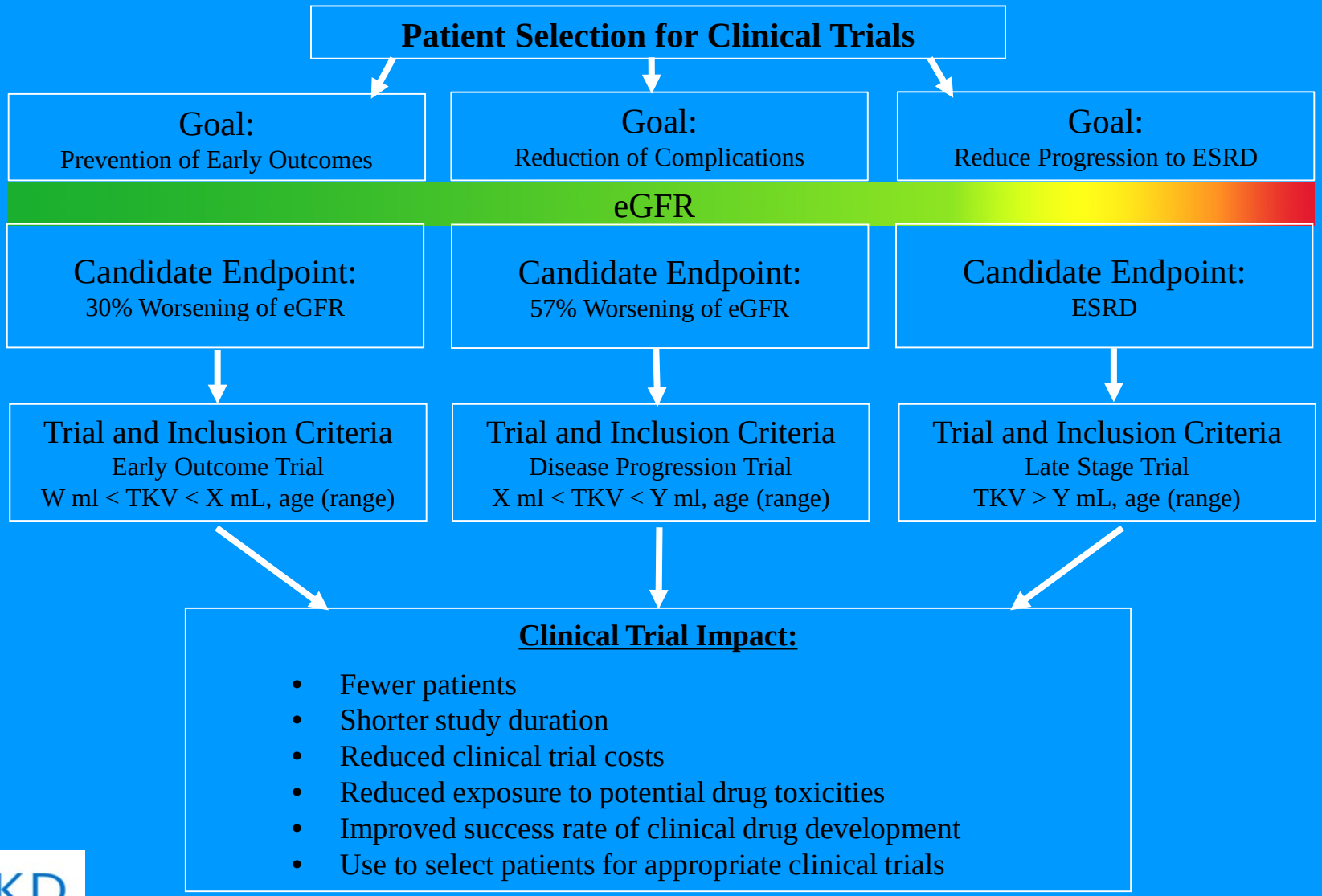
PKD CONSORTIUM CRITICAL PATH INSTITUTE

Primary Research Objectives

- Determine the predictive value of TKV, baseline eGFR, baseline age and other prognostic factors (e.g., sex, PKD mutation, race) in estimating the risk of worsening of eGFR and ESRD to support the regulatory qualification of TKV as a prognostic biomarker for use in clinical trials.
- Develop a joint model that can simultaneously assess longitudinal TKV measurements and the probability of disease outcome. Use the above joint model as a drug development tool (DDT) for trial enrichment strategies.

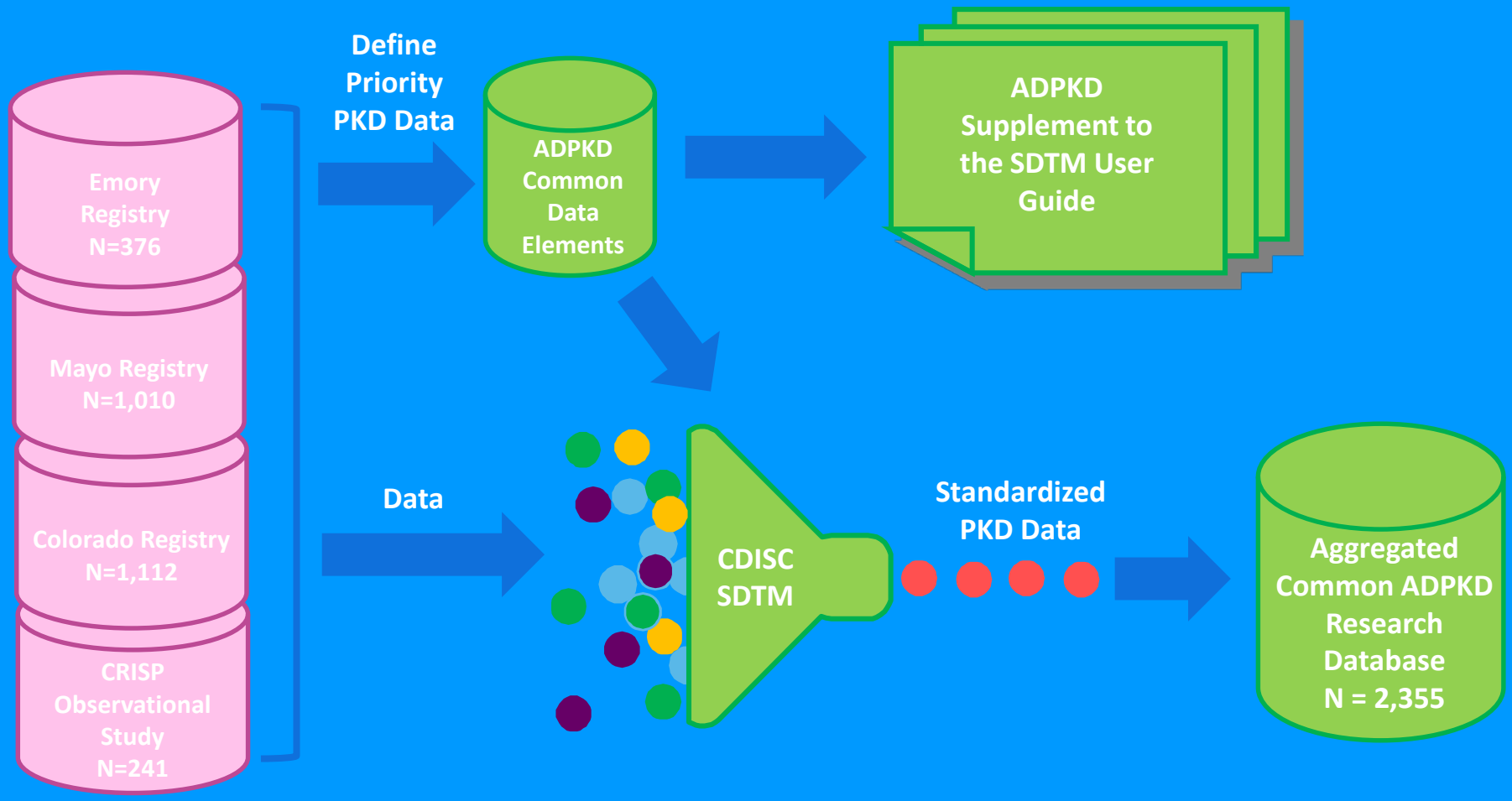
PKD CONSORTIUM CRITICAL PATH INSTITUTE

Decision Tree for Use of Baseline TKV for Prognostic Clinical Trial Enrichment



PKD CONSORTIUM CRITICAL PATH INSTITUTE

PKDOC Data Overview and Summary



PKD CONSORTIUM CRITICAL PATH INSTITUTE

Trial Enrichment Using TKV: Highest Risk of Progression

Follow-Up Times (Years)	Probabilities of Avoiding 30% Worsening of eGFR							
	TKV < 1 L				TKV ≥ 1 L			
	Age: < 40 years		Age: ≥ 40 years		Age: < 40 years		Age: ≥ 40 years	
	eGFR ≥ 50 mL/min	eGFR < 50 mL/min	eGFR ≥ 50 mL/min	eGFR < 50 mL/min	eGFR ≥ 50 mL/min	eGFR < 50 mL/min	eGFR ≥ 50 mL/min	eGFR < 50 mL/min
1	0.991	0.992	0.992	0.991	0.984	0.982	0.985	0.979
2	0.980	0.980	0.981	0.979	0.963	0.959	0.966	0.953
3	0.950	0.949	0.951	0.947	0.907	0.899	0.915	0.884
4	0.917	0.916	0.918	0.913	0.852	0.839	0.863	0.815
5	0.887	0.888	0.889	0.884	0.805	0.789	0.818	0.757

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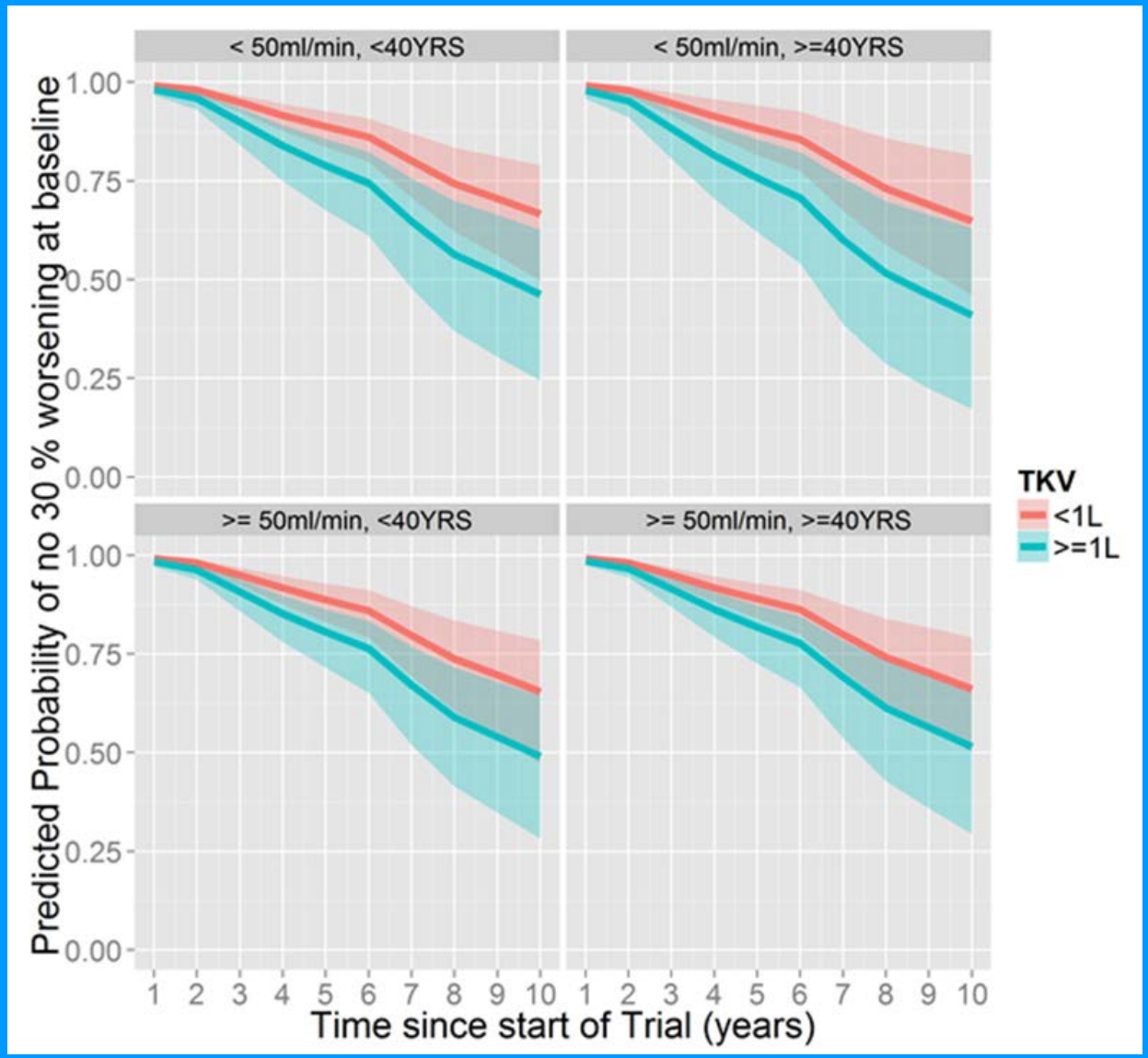
Predicted Probability at Baseline of Avoiding a 30% Decline in eGFR: Effect of Baseline TKV



Predicted Probability at Baseline of Avoiding a 30% Decline in eGFR

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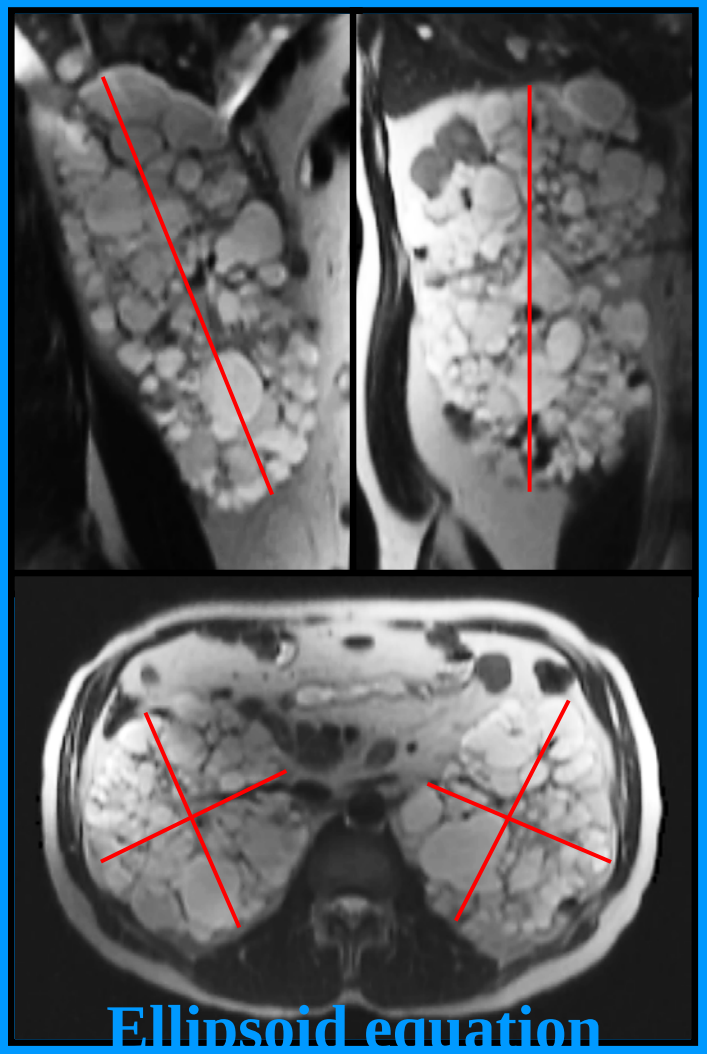
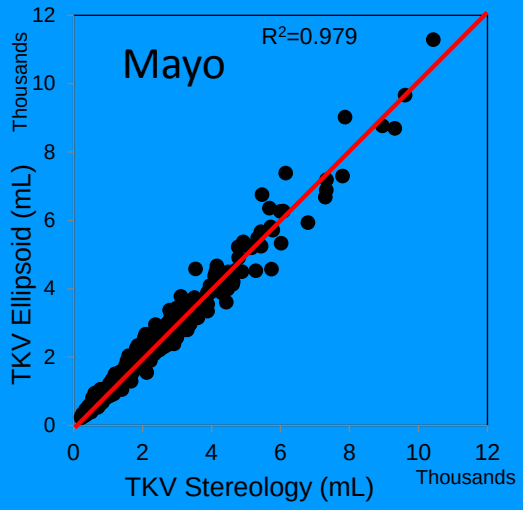
Classification of ADPKD patients Pre-specified imaging findings

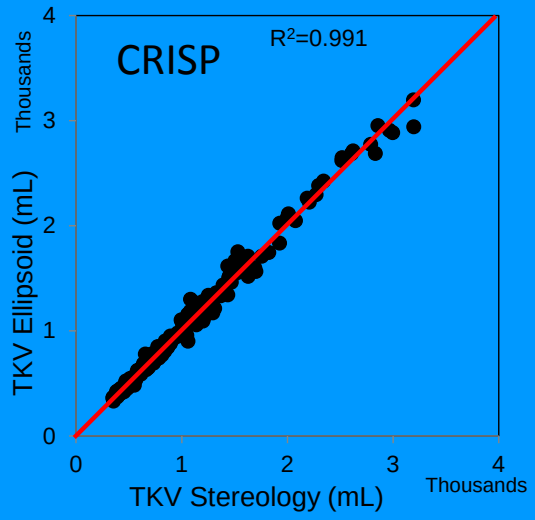
Class	Sub class	Term	Description
1 Typical ADPKD			**Cyst distribution is bilateral and diffuse with relatively even contribution to TKV**
2 Atypical ADPKD	A	*Unilateral*	Normal contralateral kidney with ≤2 cysts
		Asymmetric	Mild involvement of contralateral kidney with 3-9 cysts and <30 % of TKV.
		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

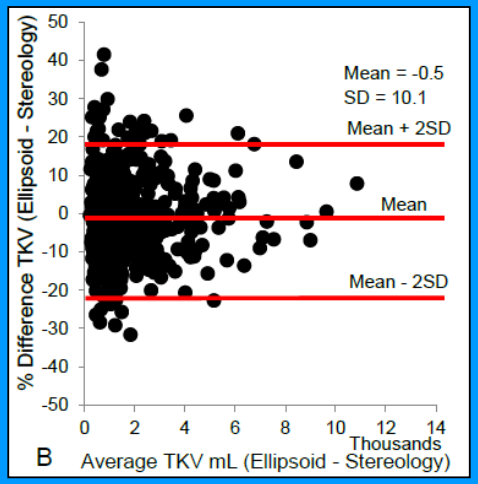
Irazabal. J Am Soc Nephrol 26: 160–172, 2015

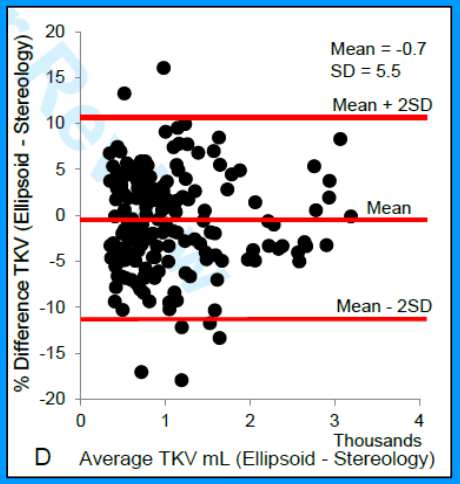
TKVe correlates strongly with TKVs











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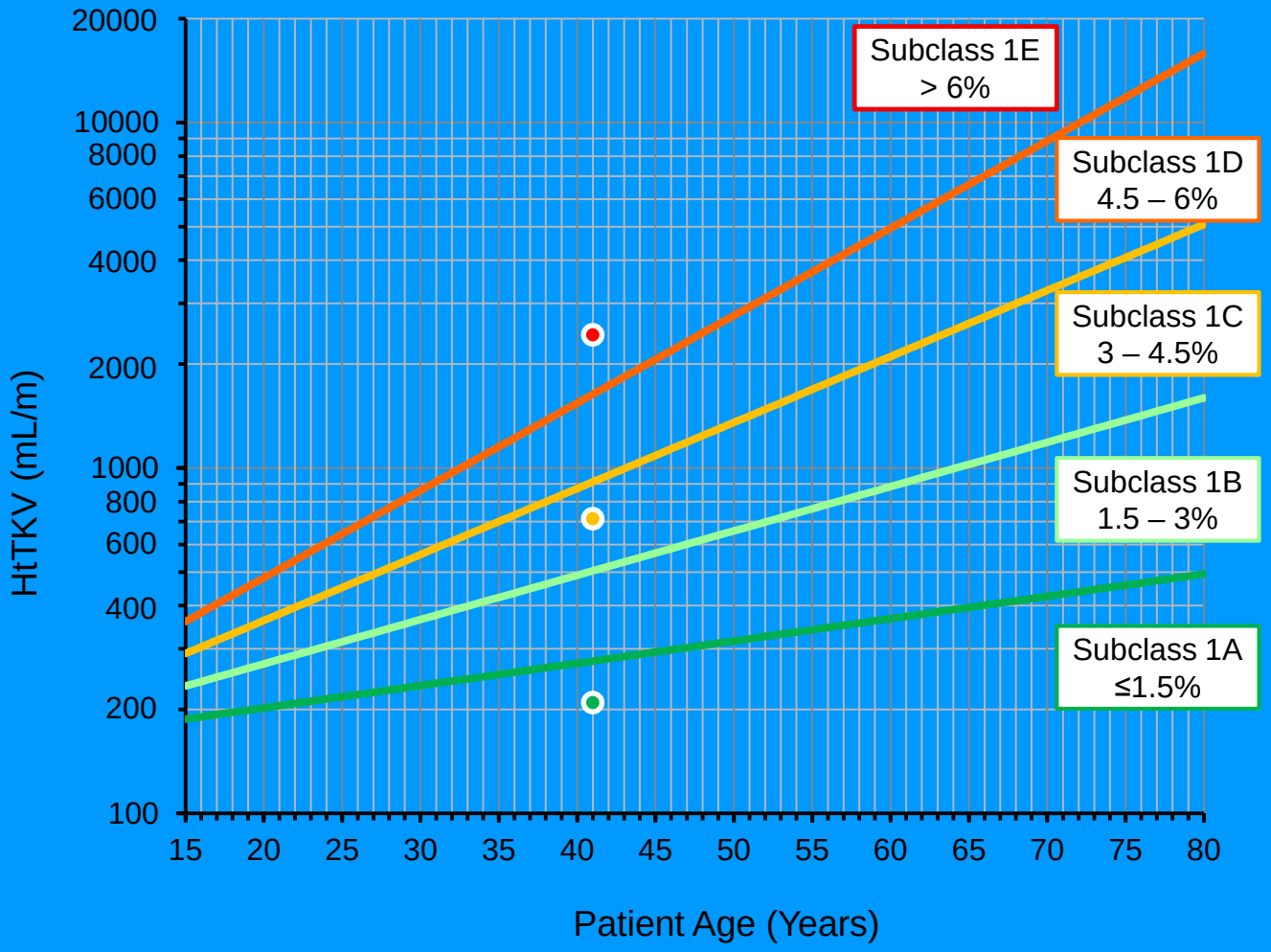
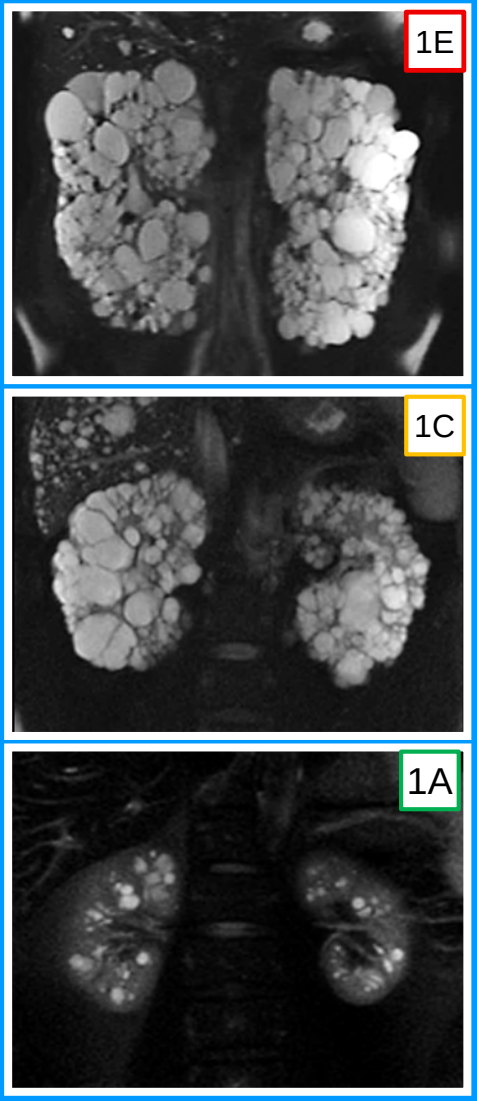
Irazabal. J Am Soc Nephrol. 26: 160–172, 2015

Classification by Estimated Rate of Growth (from age and starting HtTKV = 150 ml/m)

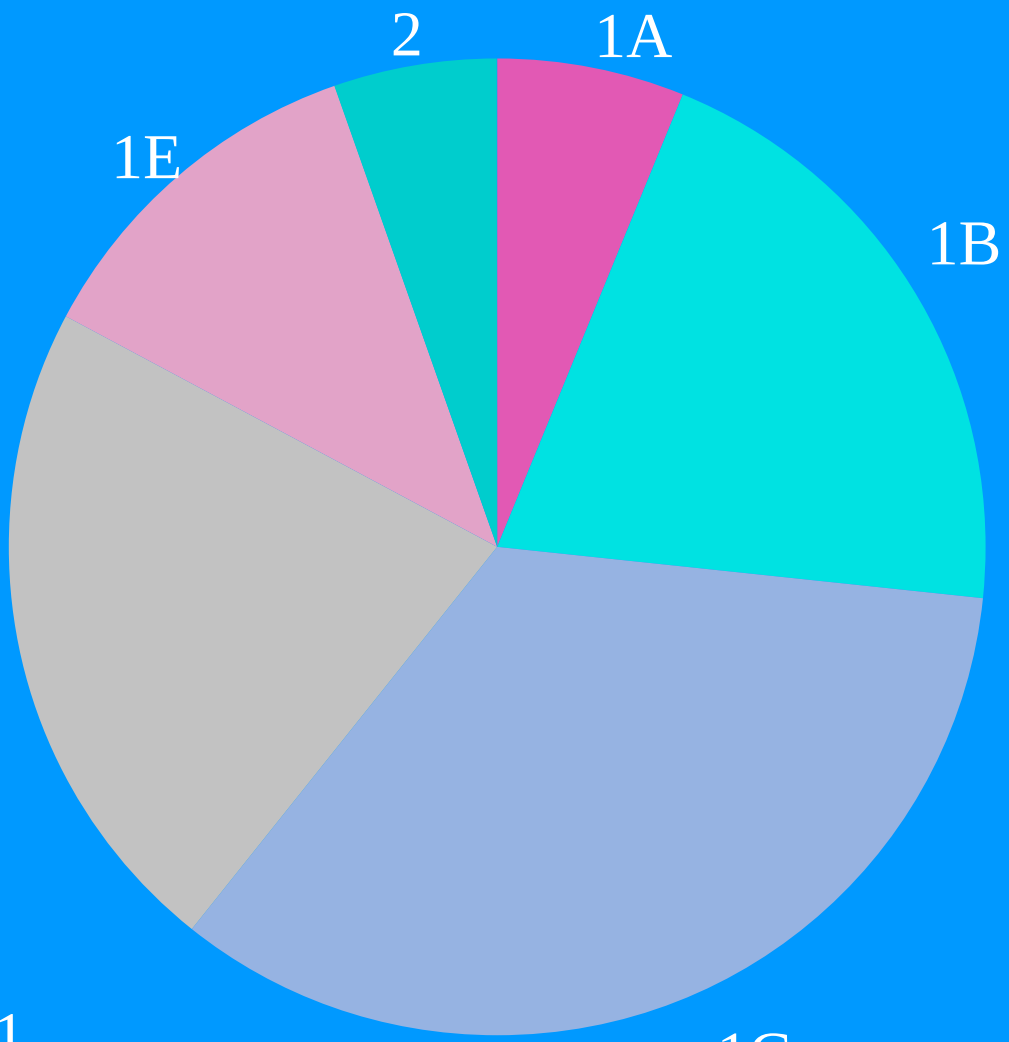




Irazabal. J Am Soc Nephrol 26: 160–172, 2015

Post-Hoc Analysis: HALT PKD Study A

Distribution of Patients by Class at Baseline

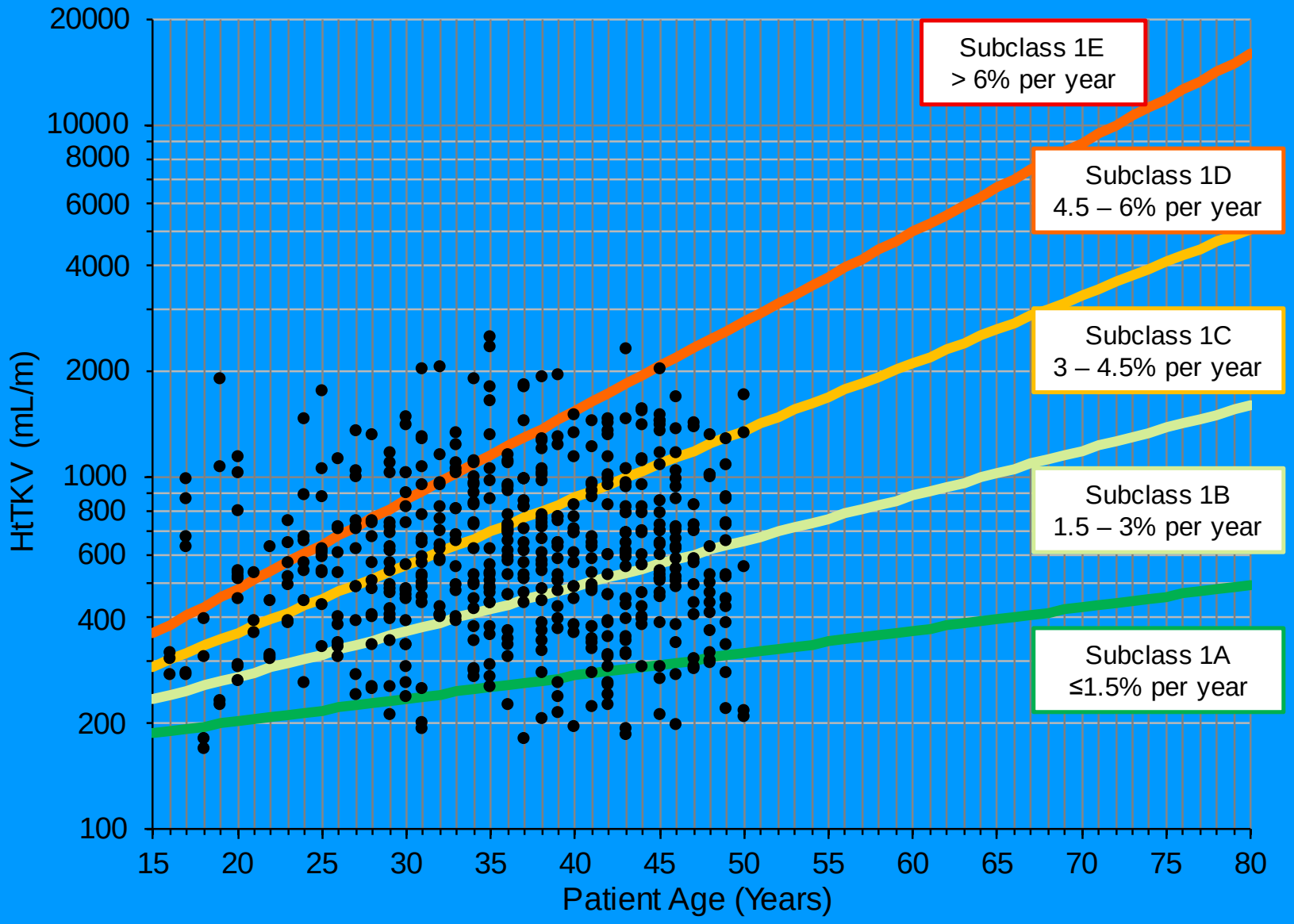


Class 1: 94.6%

Class 2: 5.4%

N = 551

Image Classification of HALT PKD Study A Patients

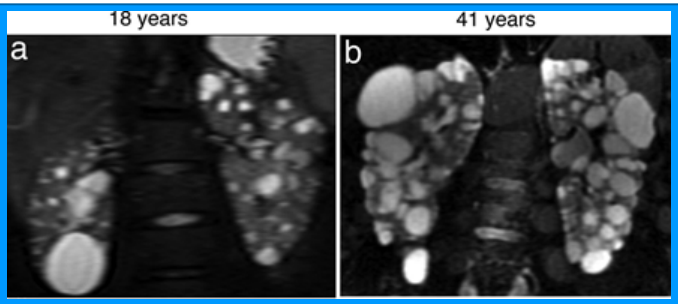


Value of Image Stratification of ADPKD
HALT PKD Study A as a Model

- Class severity associates with greater rates of TKV increase and eGFR decline
- Changes in TKV and eGFR are negatively correlated
- The treatment effect of low BP increases with class severity
- In the patients with the most severe disease (class D-E), low BP associates with slower eGFR decline after month 4 and overall
- Restriction of enrollment to class 1D-E patients would have detected a stronger low BP effect on TKV growth and EGFR decline, with a much lower number of patients (187 vs 551)
- These results stress the importance of optimal patient selection to reduce the cost and the chance of a type II error

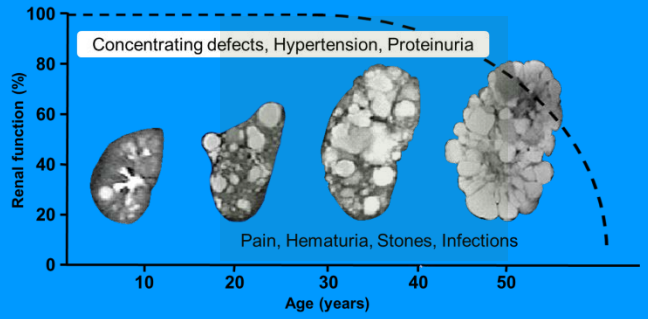
Interventional trials designed based on disease natural history

Trial Population
Mid-Stage ADPKD



Significant cystic burden for age

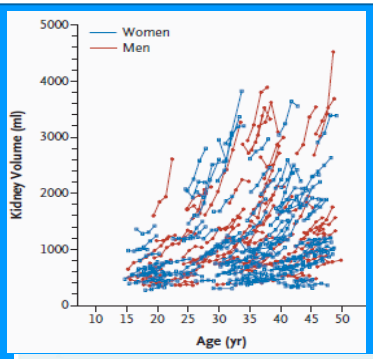
TKV ≥ 750 ml Age 18-50



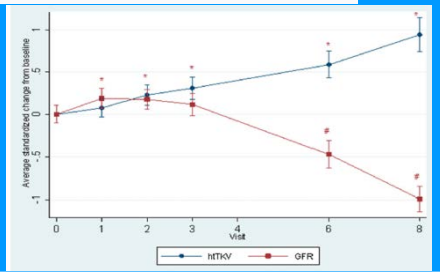
Preserved kidney function

CKD 1-3: eCrCl >60 ml/min

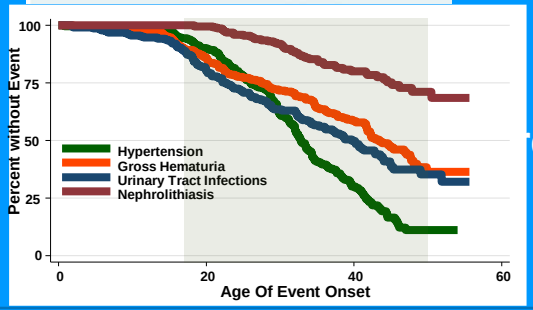
Endpoints: Disease Specific Modifiable Outcomes



Cyst Growth by TKV



Kidney Function Decline



Progression related events

Thanks for your attention!