Disclosure of Interests

- Otsuka: Consulting, Research Grants
- Pfizer Inc: Consulting
- Sanofi/Genzyme: Consulting
- NIDDK: CRISP, HALT and Modifier Research Grants

What Endpoints Should be Used in Clinical Trials for Autosomal Dominant Polycystic Kidney Disease?

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Fact 1:Kidney and Cyst Volume are Determinants of Renal Outcomes in ADPKD

- Renal cysts are the first verifiable primary manifestation of ADPKD
- Cyst formation ALWAYS precedes:
  - flank pain
  - hypertension
  - gross hematuria
  - reduced GFR
  - nephrolithiasis
  - kidney infections
- The inverse correlation between kidney volume and function has been observed for over 30 years in ADPKD

[1]Thomsen *Urol Rad* 3:85, 1981; [2]Chapman *Kid Int* 64:1035, 2003; [3]Fick-Brosnahan *AJKD* 39:1127, 2002; [4]Lee *Nephron Clin Pract* 103:c173, 2006; [5]Tokiwa Clin Exp Neph March 2011; [6]*Meijer CJASN* 5:1091, 2010;

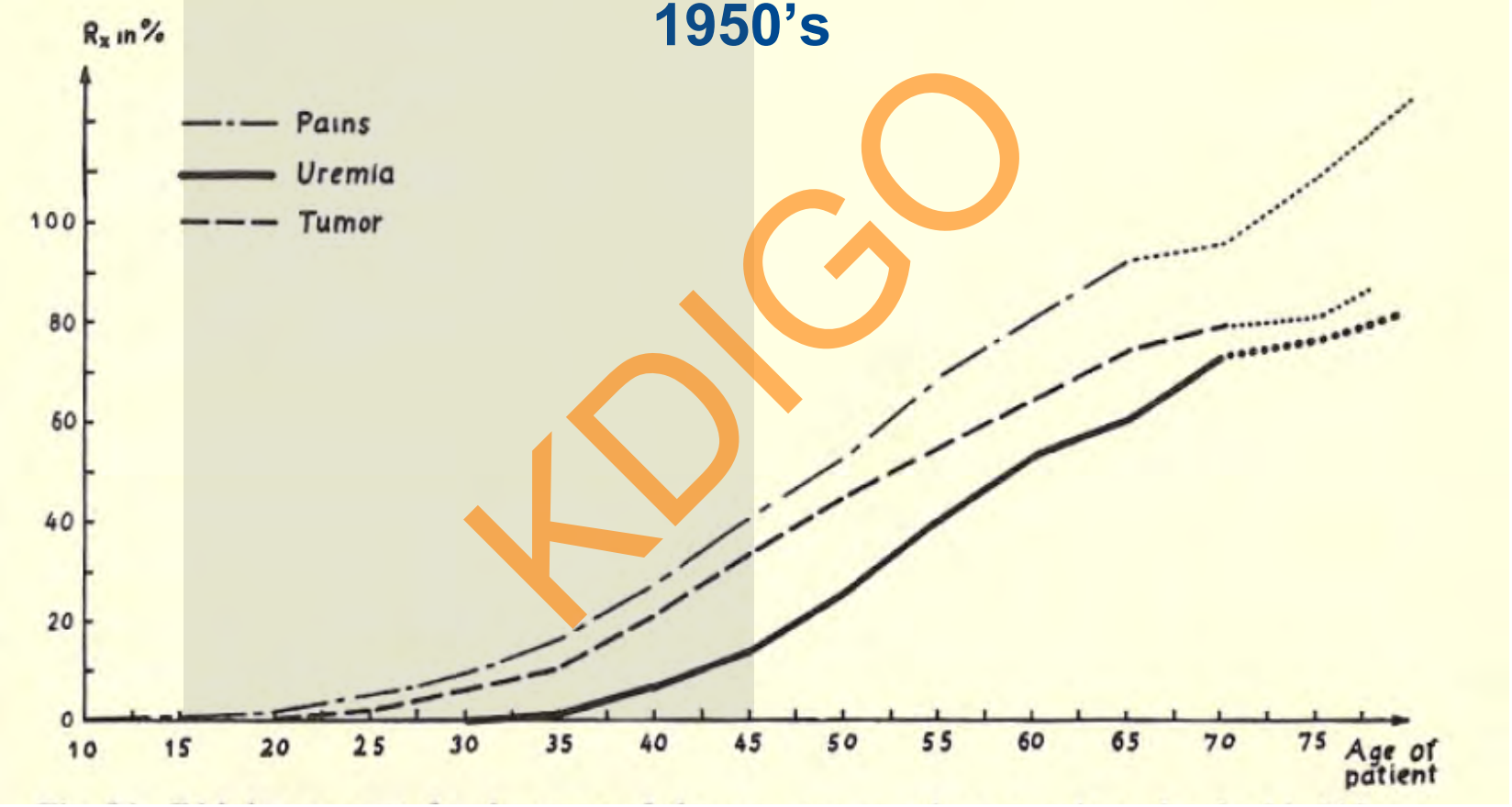
FACT 2: Renal Characteristics of ADPKD Associate with ESRD

- **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
- **Renal insufficiency:** progression to renal failure in > 80 % of all PKD patients

ALL CHARACTERISTICS HAVE NOW BEEN SHOWN TO MITIGATE THEIR RISK THROUGH TKV

FACT 3: PKD Patients suffer from Renal Complications Prior to Loss of Kidney Function:

Initially: 284 ADPKD patients longitudinally in the 1950's



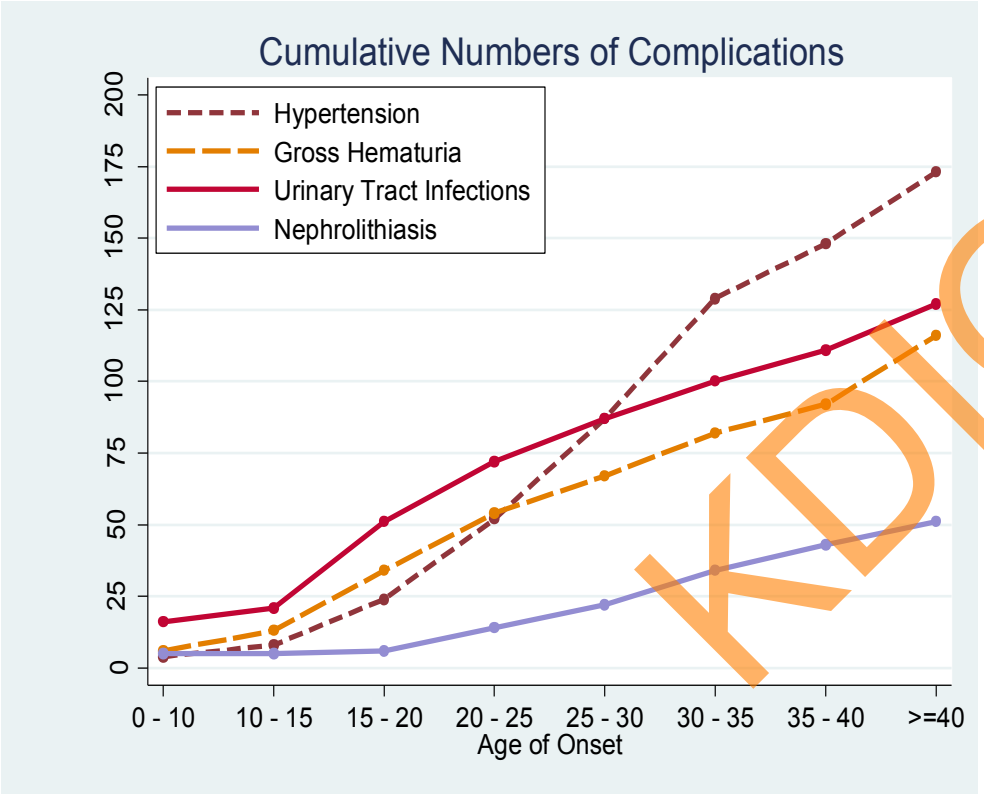
O.Z. Dalgaard 1957. 284 patients longitudinal study; 350 cases clinical data; *uremia* = BUN > 100 mg/dl

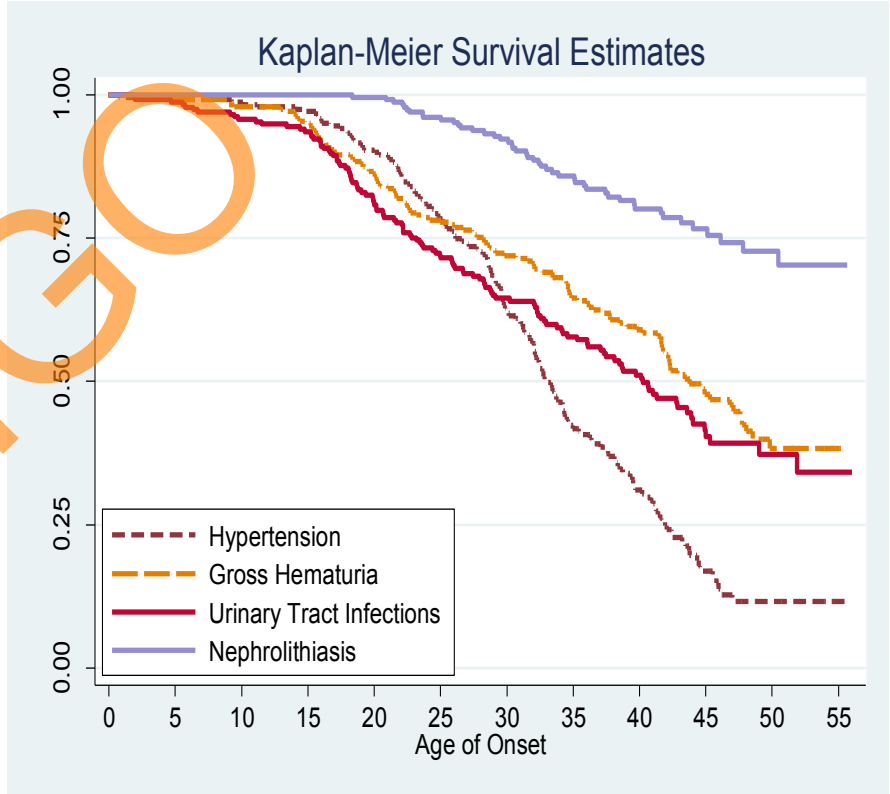
NIH CRISP Natural History Study Participants Demonstrate Frequent Renal Complications

Baseline Parameter	N=241
Mean Age	33.8 (± 9) years
Mean Age of Diagnosis	24.5 (± 9) years
Mean TKV	1076 (± 670) ml
Mean Serum Creatinine Concentration	1.0 (± 0.2) mg/dl
Mean Glomerular Filtration Rate	98.2 (± 24.9) ml/min/1.73m²
Medical History	
Hypertension	69.3 %
Gross Hematuria	40.7 %
Nephrolithiasis	16.2 %
Flank/Kidney Pain	80.1 %

Chapman, *Kidney International* CRISP 2003; Grantham, *NEJM* CRISP 2006;

Age of onset of renal complications in the CRISP population





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

NIH CRISP Studies; Rahbari-Oskoui, *ASN Renal Week*, 2013.

Increased Kidney Volume Associates with Renal Complications in ADPKD

Renal Complication	N	Mean Volume per Kidney ± SD		P-value
		Complication Present	Complication Absent	
Loss of GFR	220	598 ± 368	366 ± 168	<0.0001
Hypertension	241	628 ± 48	352 ± 33	<0.0001
Gross Hematuria	191	820 ± 87	588 ± 52	<0.03
Microalbuminuria	49	853 ± 87	535 ± 52	<0.01
Proteinuria	270	1190 ± 93	578 ± 32	<0.0001

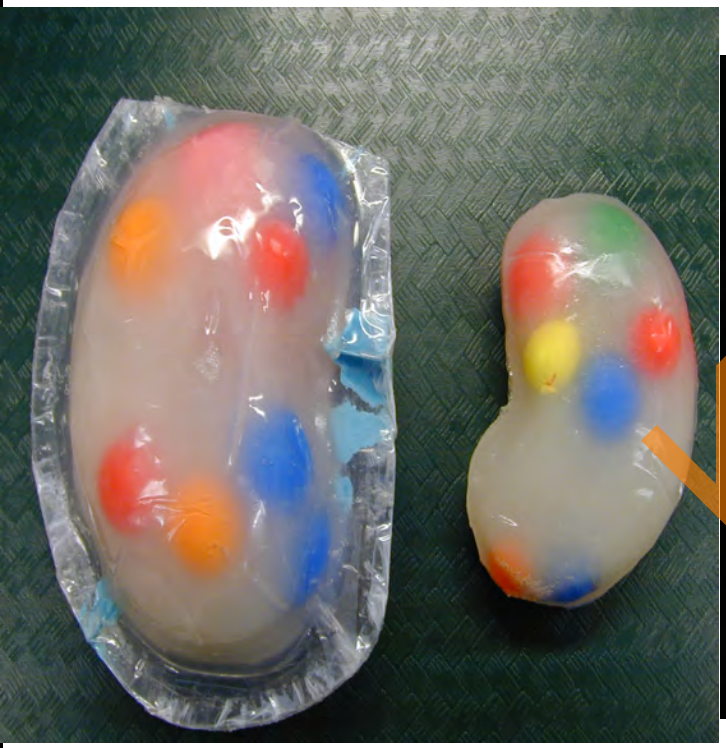
Grantham, Chapman and Torres *Clin J Am Soc Nephrol* 1:148–157, 2006.

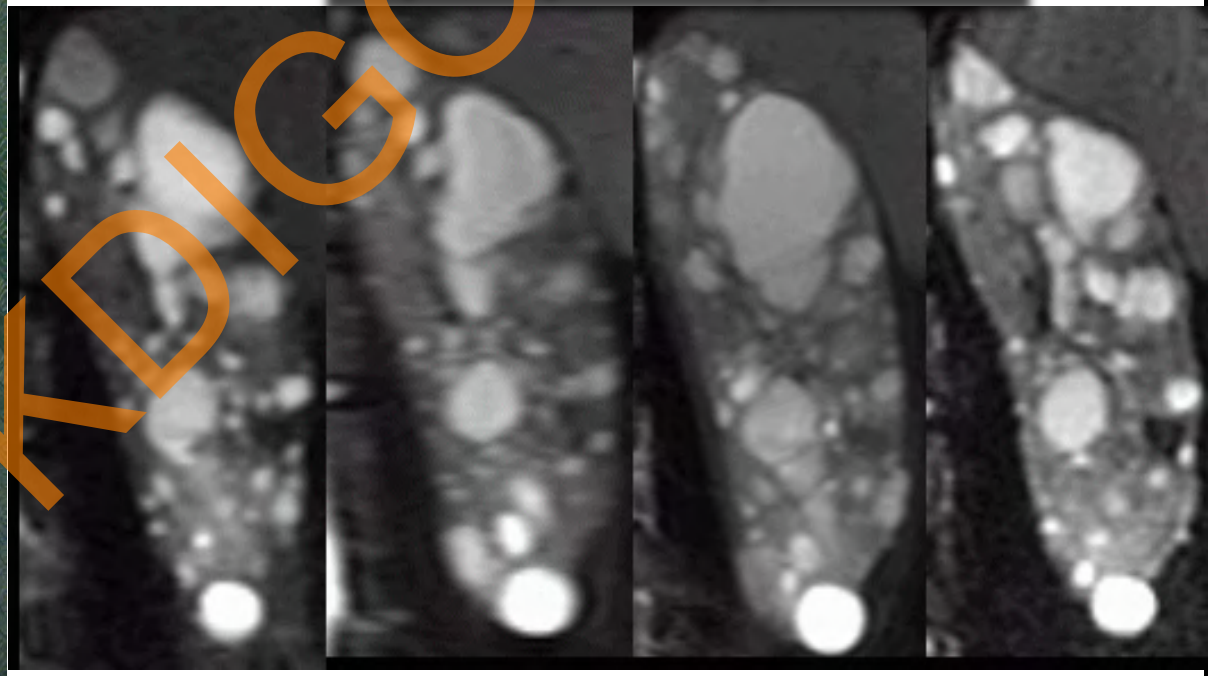
FACT 5: Total Kidney Volume can be measured accurately and reliably in ADPKD

Inter-observer variability: 2.1%

Intra-observer variability:2.4%

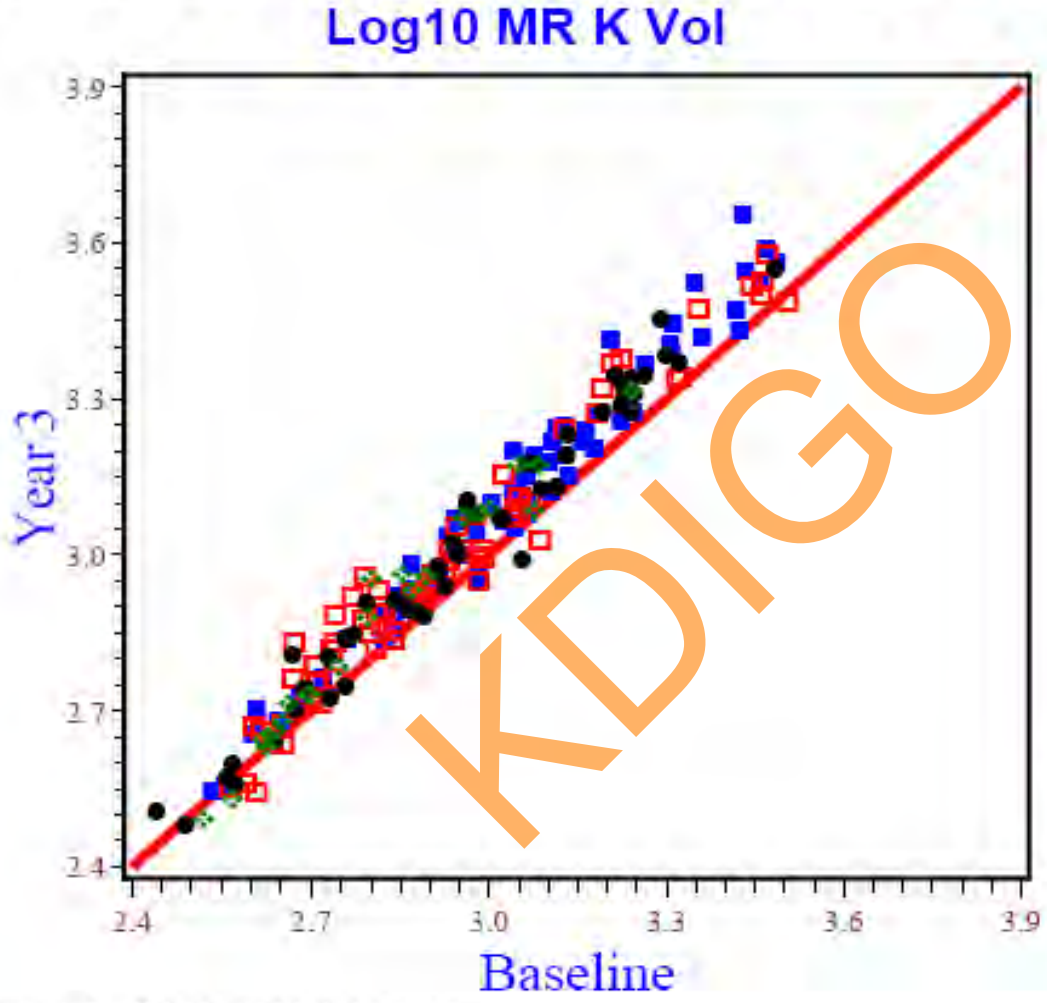
Day-to-day variability: 2.4%





Bae for the CRISP study *Clin J Am Soc Nephrol* 1:148–157, 2001.

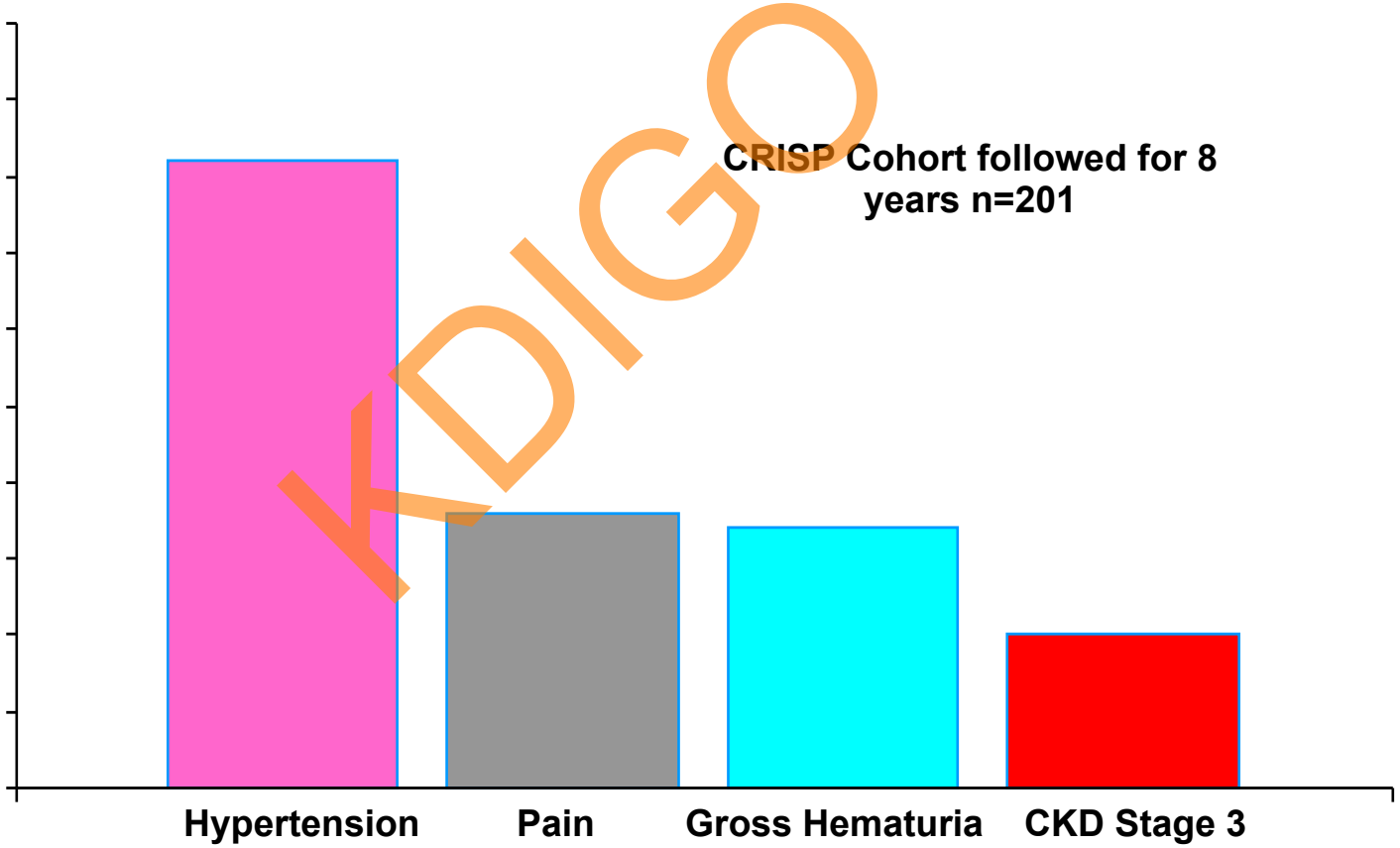
CHANGE in TOTAL KIDNEY VOLUME, BL-YR3



5.3 % Average (-5.3 to 17.5%) yearly increase in renal size

Grantham NEJM 354:2122-2130, 2006

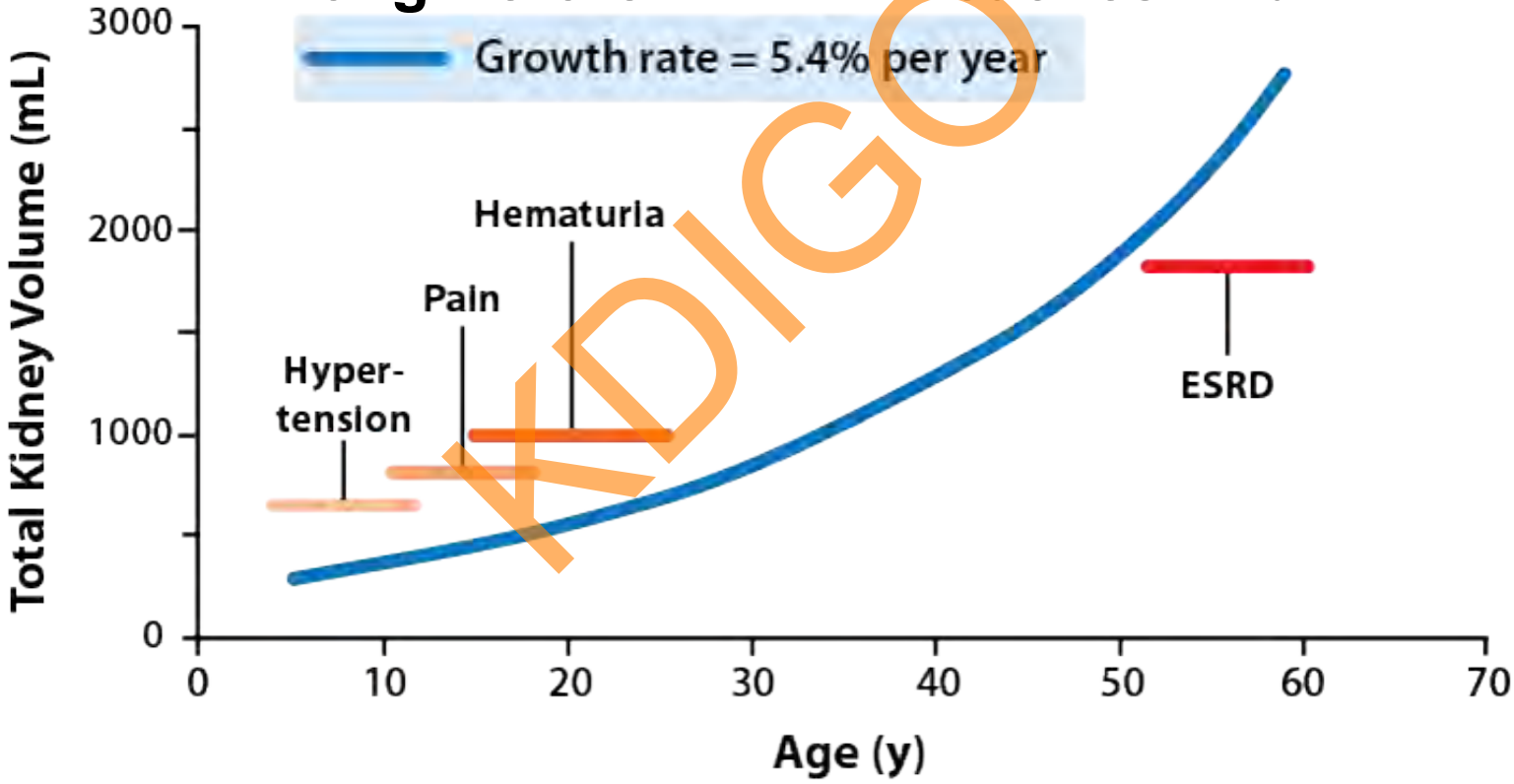
Risk of Clinical Events Increases with Every 100ml Increase in TKV



NIH CRISP Studies
Rahbari-Oskui, *ASN week* 2013

Progressive Rise in Total Kidney Volume

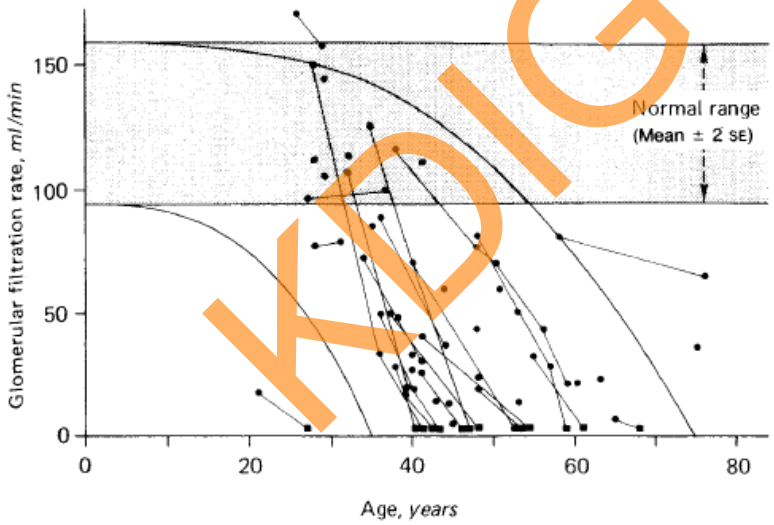
Signs and Symptoms of Injury Develop Long Before ADPKD Reaches End



Grantham JJ. 2012. Unpublished.

FACT 6: Kidney Volume predicts GFR in an age and time dependent fashion

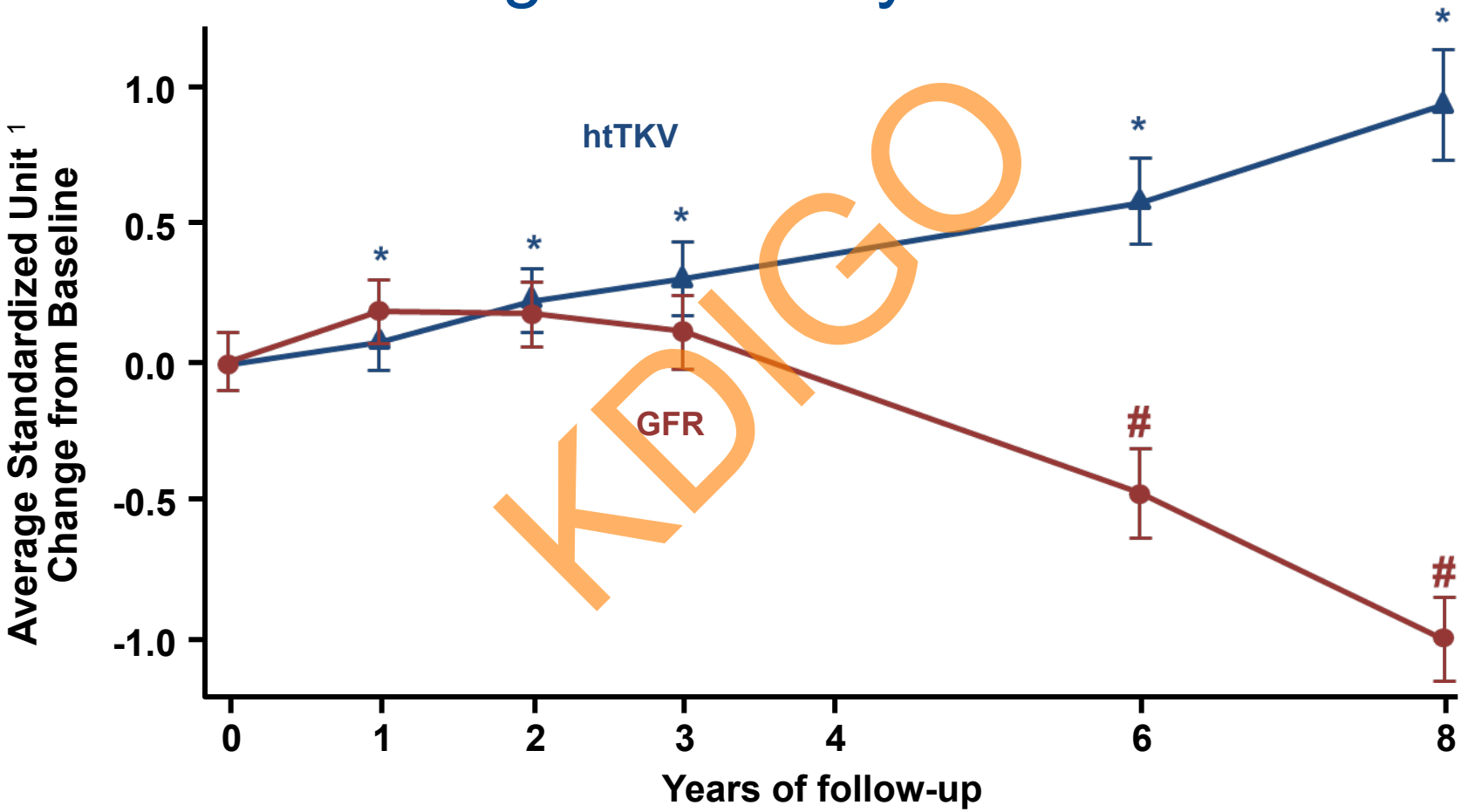
- Kidney enlargement begins *in utero* and continues at a rate characteristic of each individual
- TKV associates inversely with kidney function in 7 cross-section and 3 longitudinal studies
- Kidney enlargement precedes renal insufficiency by many years



44 Patients Age 21-75
Mean GFR 61.9 ml/min

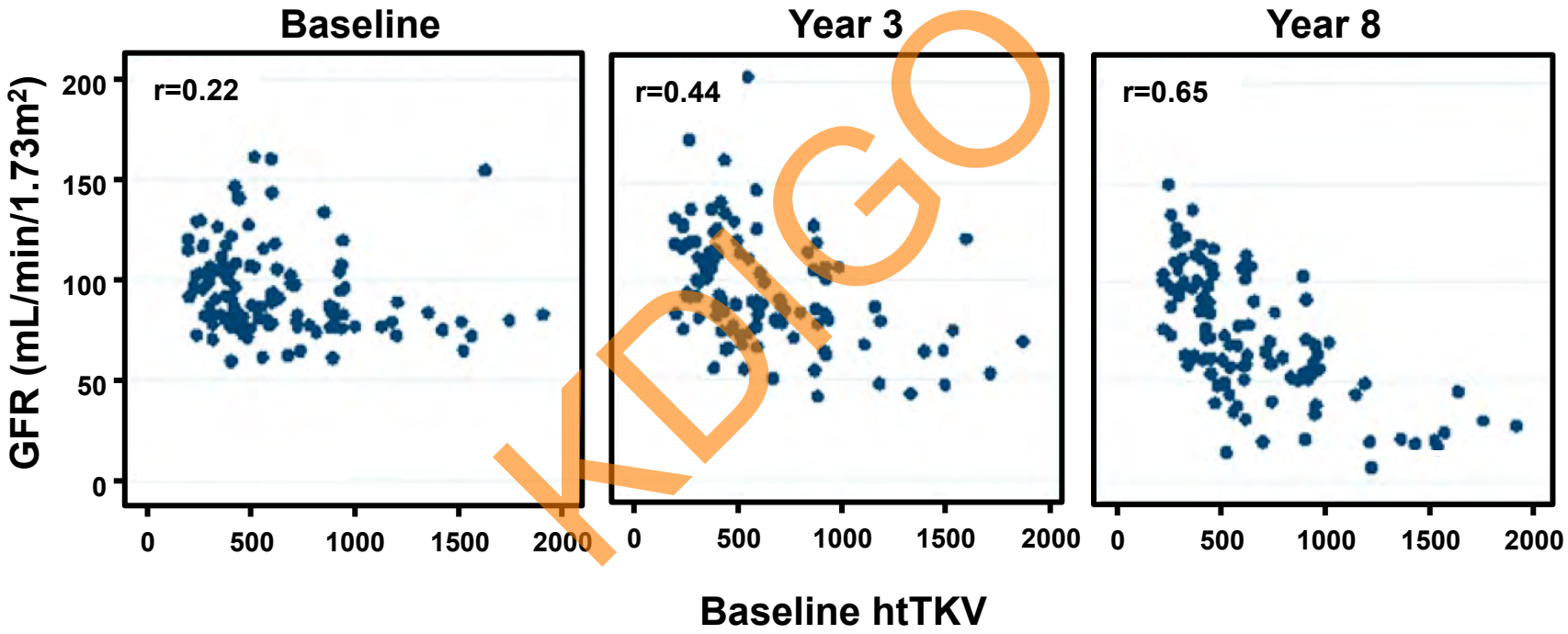
- TKV predicts onset of renal insufficiency (2012 CRISP (n=241;, 2013 PKDOC (n=1066)).

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

Future Decline in Renal Function is Predicted by Baseline Kidney Volume



The relationship improves significantly with longer follow-up time

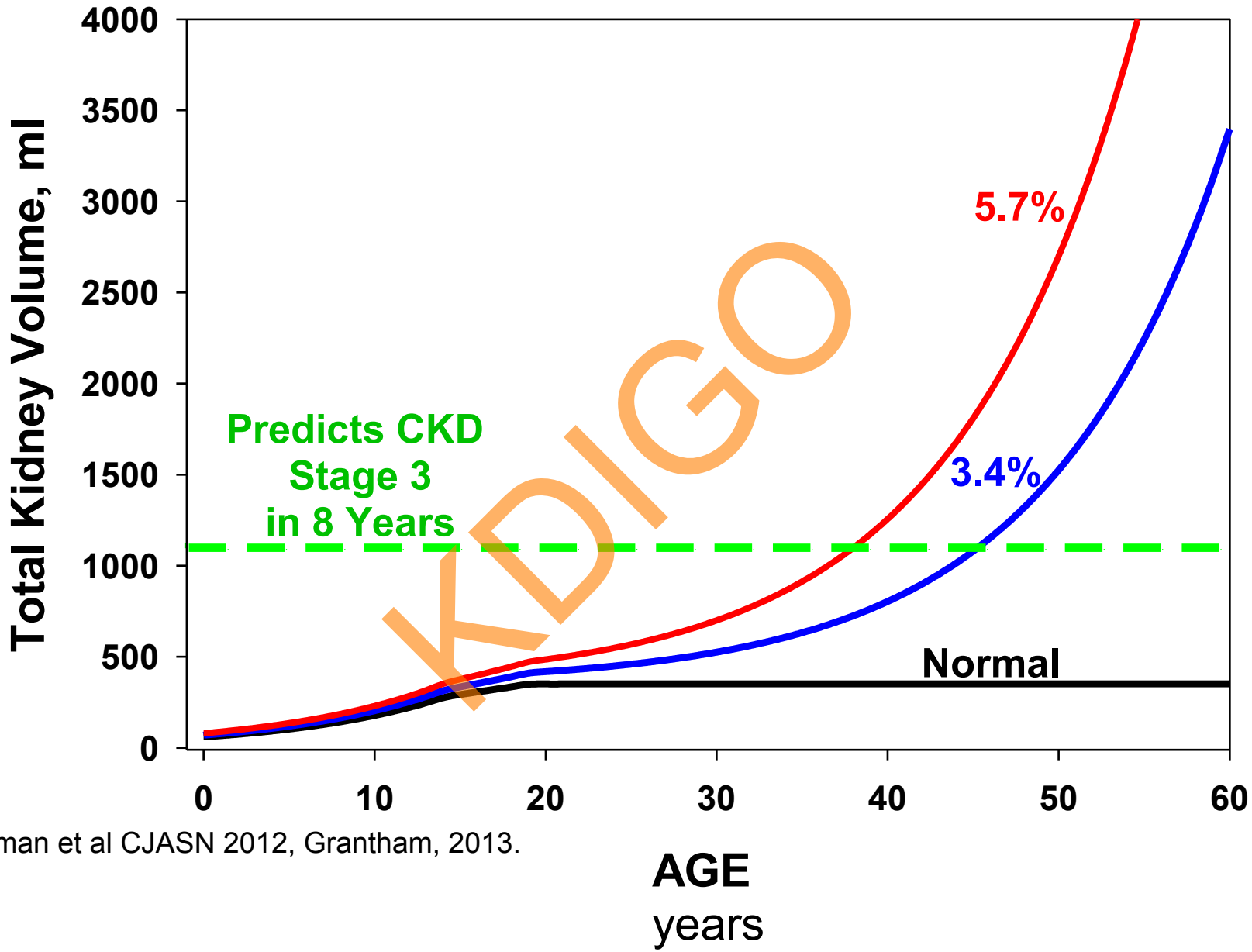
NIH CRISP Studies; htTKV=height-adjusted total kidney volume; GFR by iothalamate clearance

Chapman *CJASN* 7:479, 2012

ROC AUC Values predicting CKD Stage 3 within 8 years in CRISP Participants

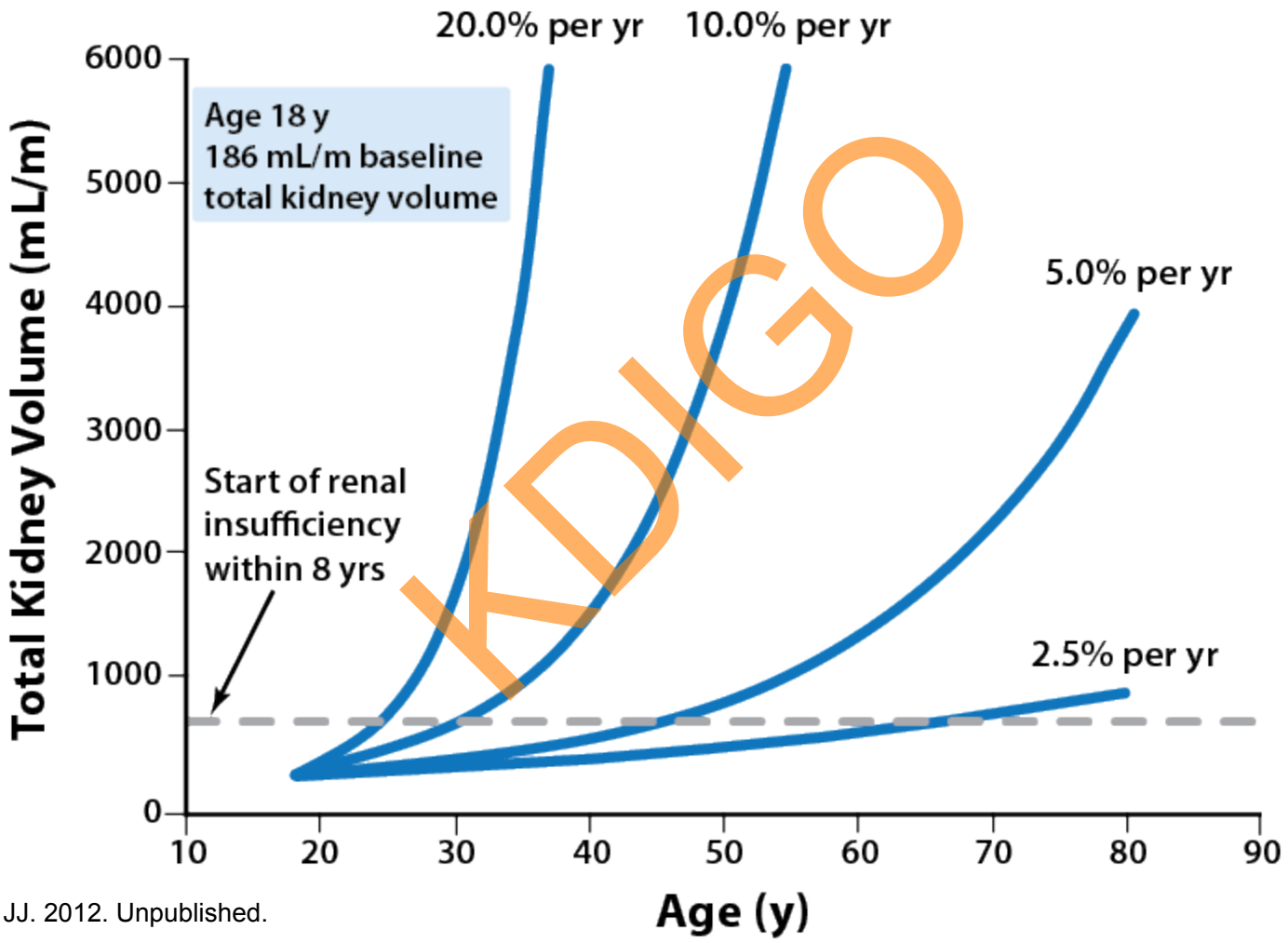
	htTKV	Serum* Creatinine	Serum Blood* Urea Nitrogen	Urinary* MCP1	Urine Albumin* Excretion	Age*
sensitivity (%)	75	64	51	81	63	64
specificity (%)	74	81	79	62	67	65
correctly classified (%)	75	76	74	67	66	65
ROC	0.850	0.770	0.760	0.760	0.690	0.680
Cut Point	600	1.1	16	410	30	35

* P<0.05 ROC htTKV vs. others



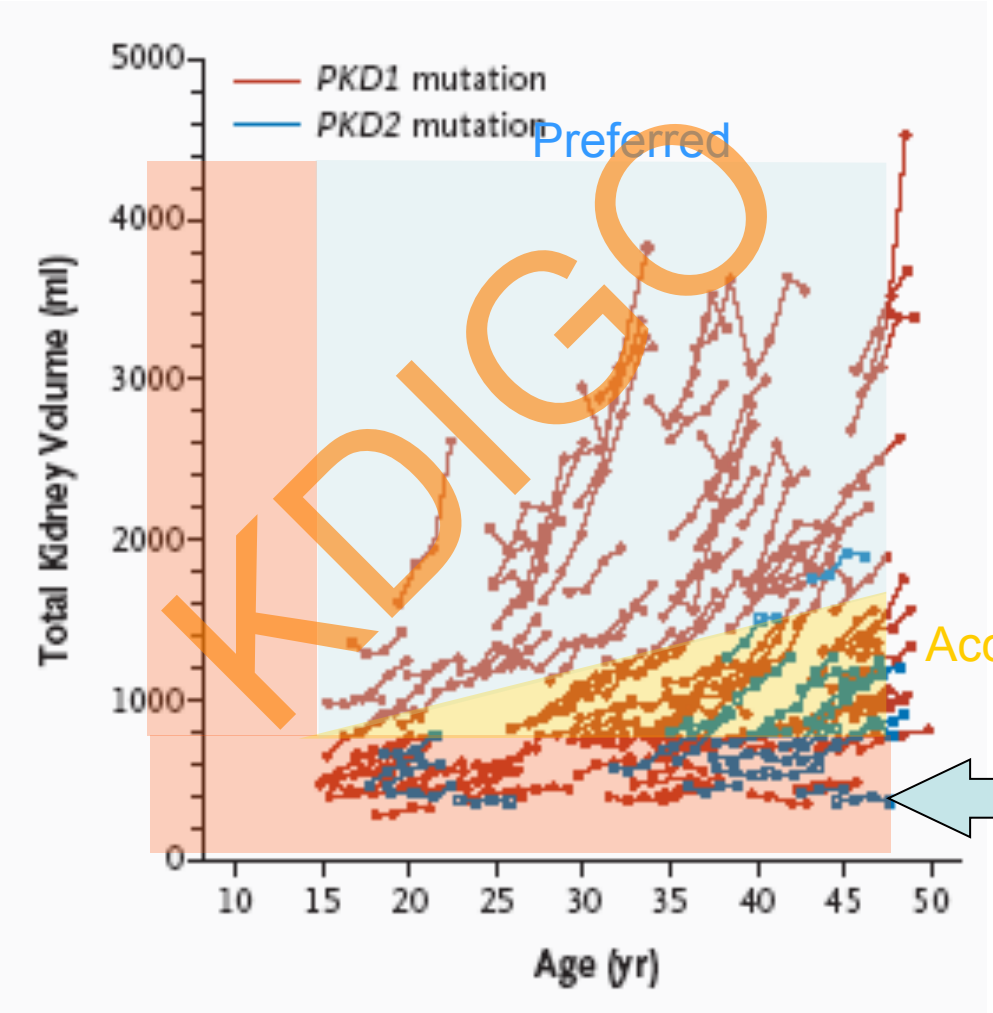
Chapman et al CJASN 2012, Grantham, 2013.

Effect of Kidney Growth Rate on Development of ESRD



Grantham JJ. 2012. Unpublished.

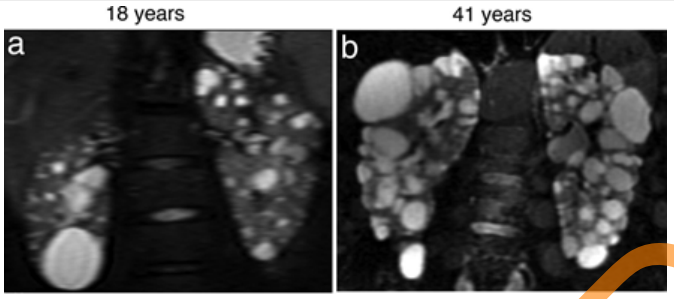
Appropriate Selection of ADPKD Patients to Test New Interventions



J.J. Grantham 2006 NEJM 354:2128

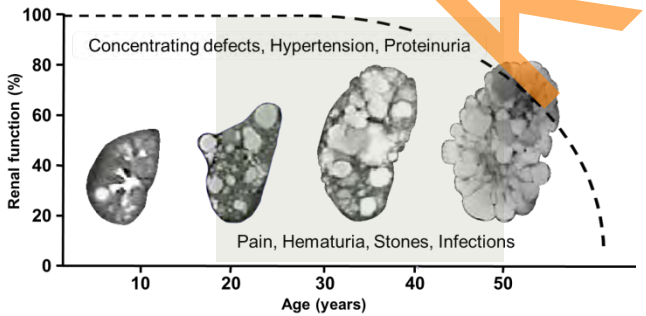
Interventional trials designed based on disease natural history

Trial Population
Mid-Stage ADPKD



Significant cystic burden for age

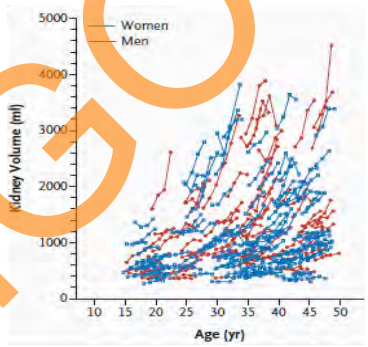
TKV ≥ 750 ml Age 18-50



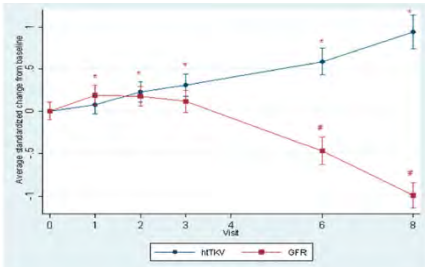
Preserved kidney function

CKD 1-3: eCrCl >60 ml/min

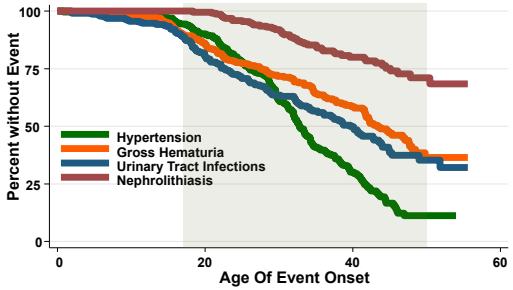
Endpoints: Disease Specific Modifiable Outcomes



Cyst Growth by TKV



Kidney Function Decline

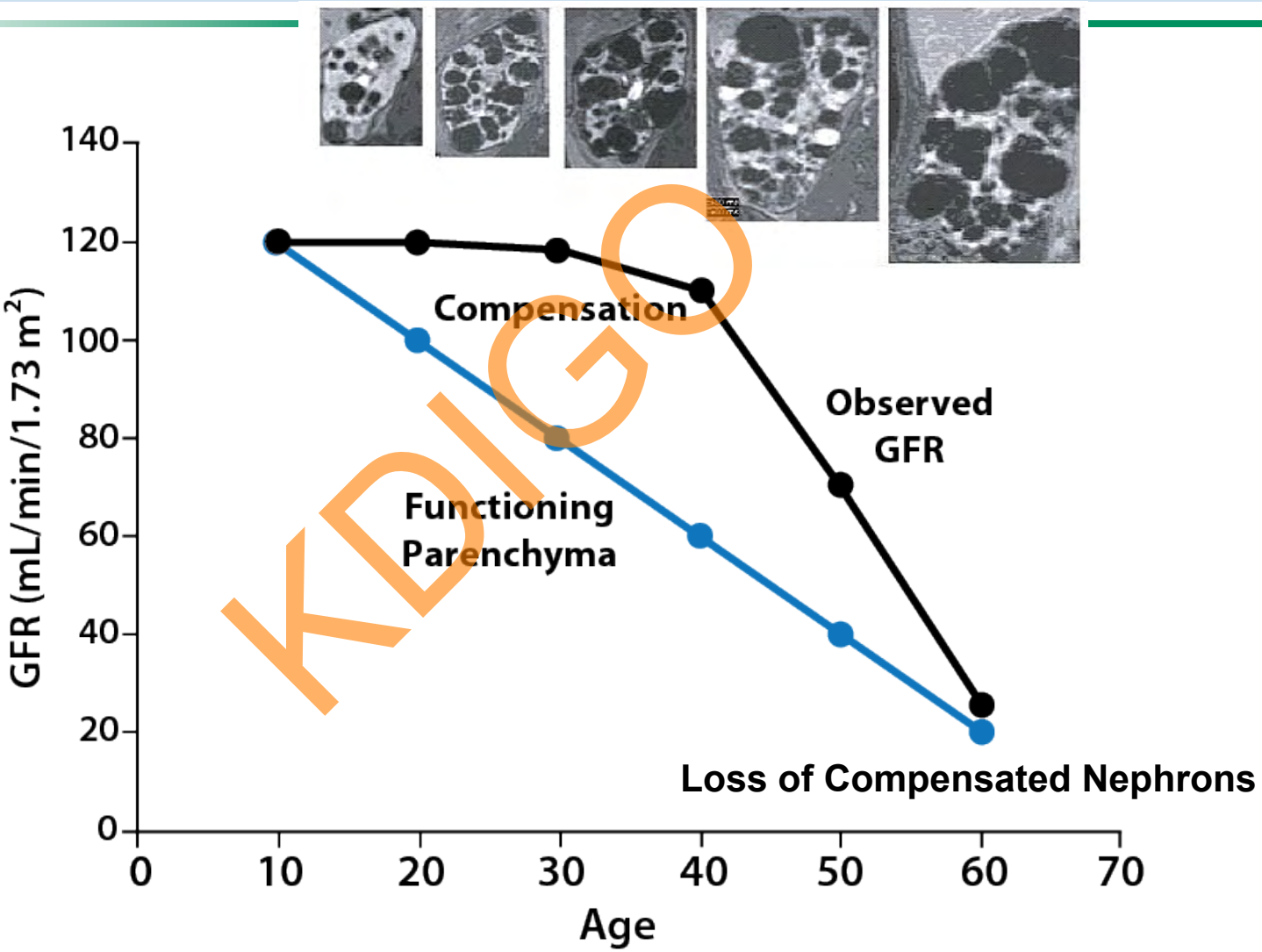


Progression related events

GAPS IN KNOWLEDGE:

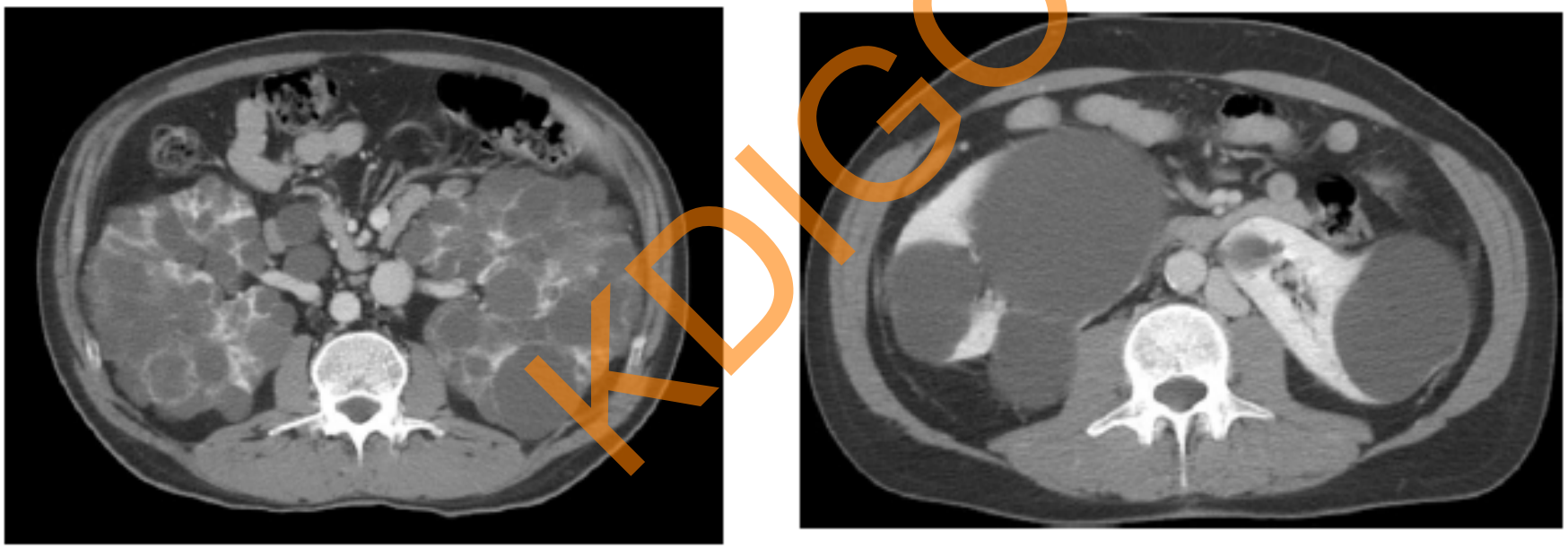
- Knowledge regarding the characteristics of renal clinical, TKV and GFR events in African Americans
- Knowledge regarding the characteristics of renal clinical, TKV and GFR events in Asians
- Potential contribution of individual cyst conformation to future loss of kidney function
- Features of TKV when kidney function begins to decline

GFR Compensation for Loss of Parenchyma



Grantham JJ et al. *Clin J Am Soc Nephrol*. 2006;1:148-157.

Cyst Distribution (Renal Parenchyma), in Atypical Forms of ADPKD, May Add Relevant Clinical Information in Addition to TKV



Antiga, et al, *CJASN* 2006

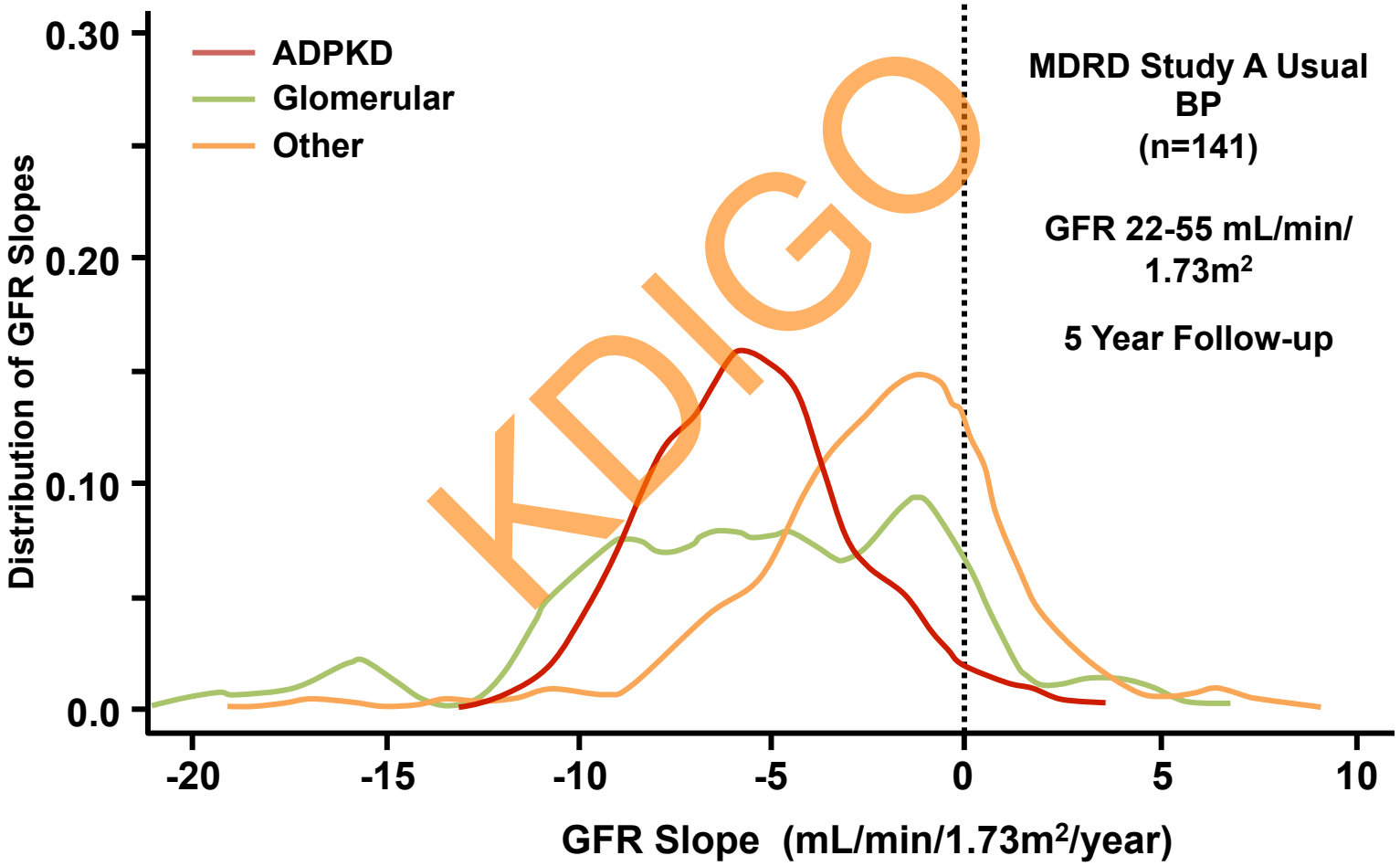
Controversy 1: Which is the most appropriate imaging modality to monitor ADPKD patients for TKV

- TKV measurements in clinical trials are done to detect small changes in TKV accurately over a relatively short period of time
- TKV measurements done clinically are performed to risk stratify individuals for progression to renal failure and to monitor progression over longer periods of time

Controversy 2: What role if any does TKV have in monitoring patients in later stages of PKD

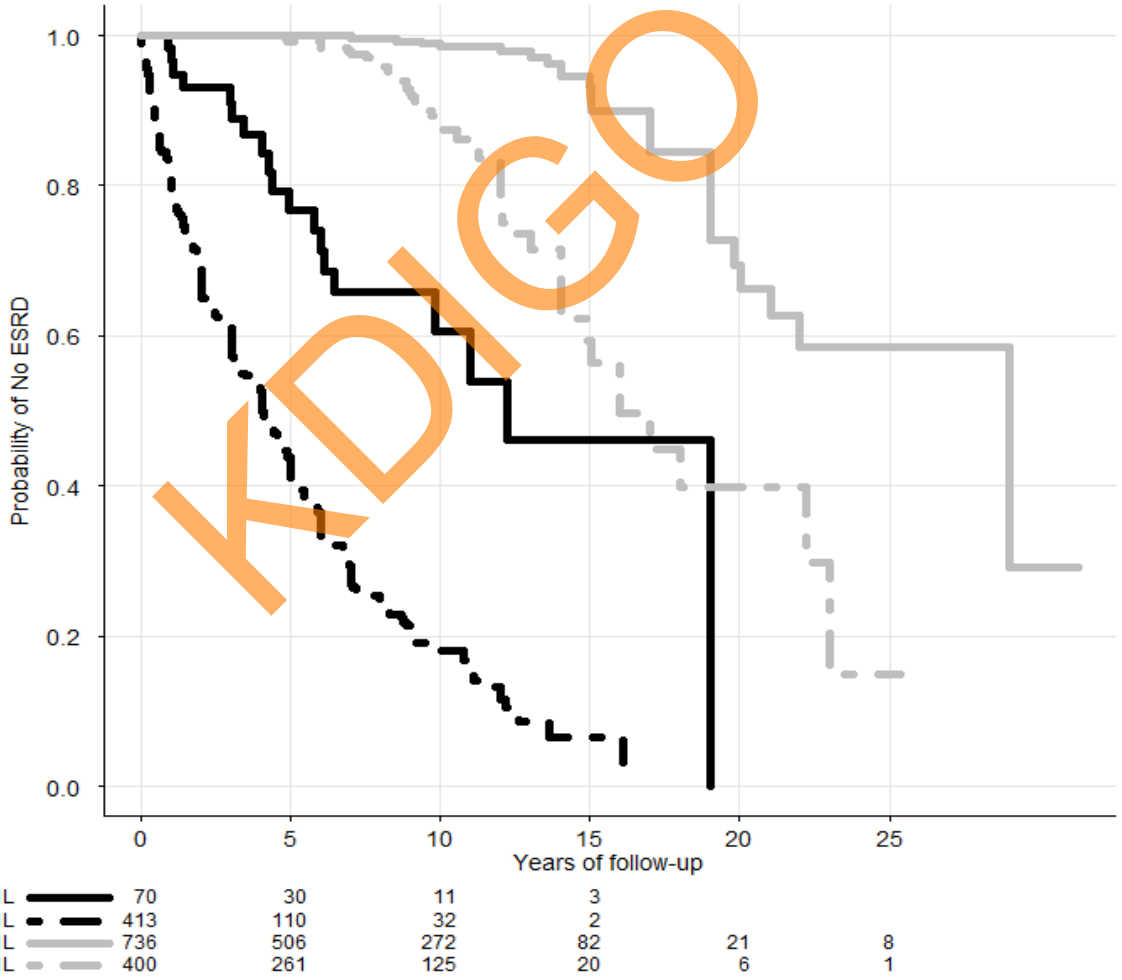
- At what stage of CKD, is monitoring of kidney function alone adequate to measure disease progression?
- Does TKV provide additive information regarding assessment of disease progression in later stages?

Fact 7: Kidney Function Declines in ADPKD Rapidly in the Late Stages of Disease



Klahr *JASN* 5:2037-2047, 1995; *MDRD Study*

Risk of progressing to ESRD with TKV > or < 1 L and eGFR < or > 50ml/min



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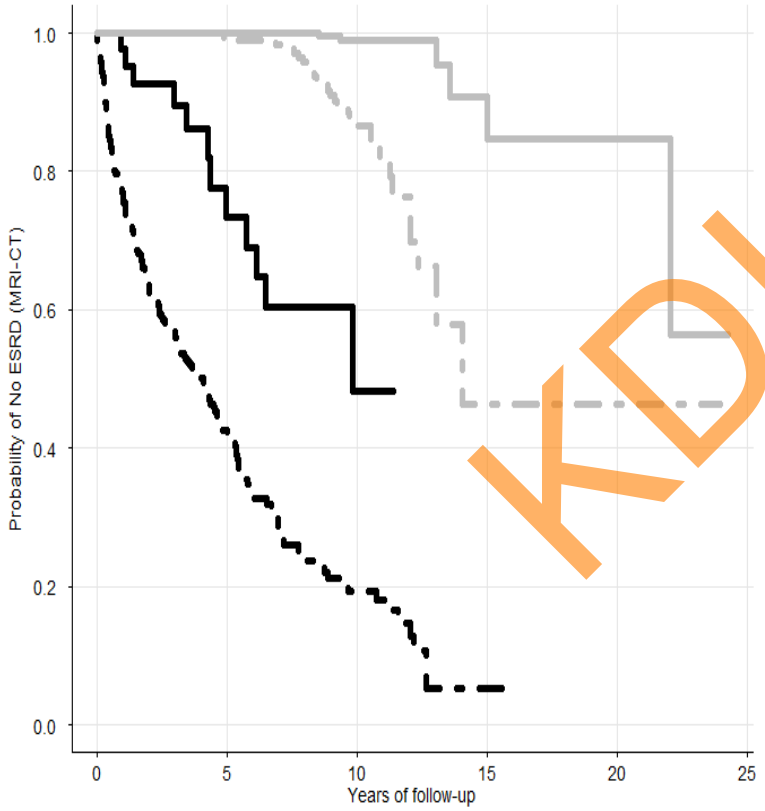
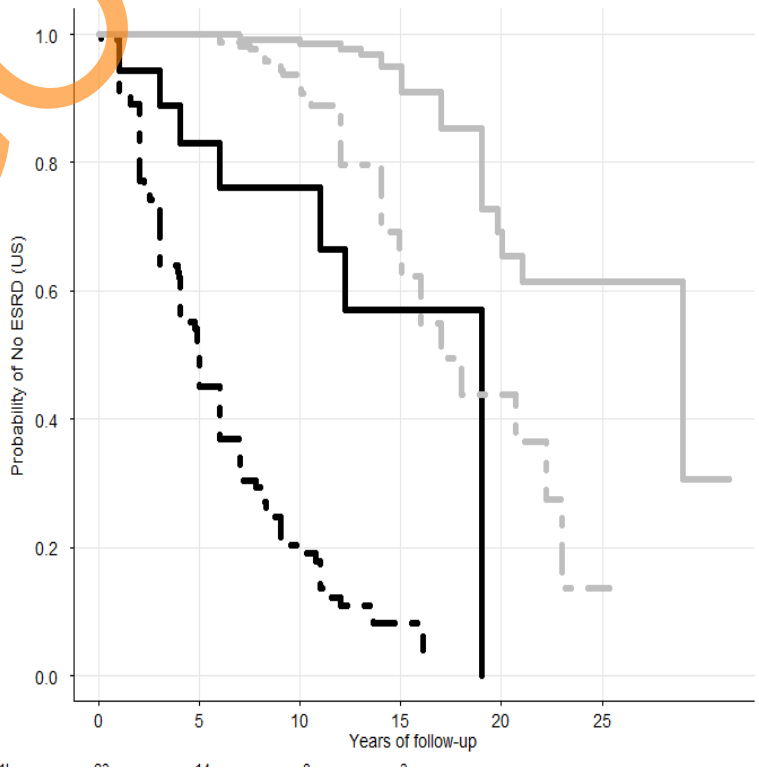
Comparison of US vs. CT/MRI estimates of TKV and risk for progression to ESRD

CT/MRI

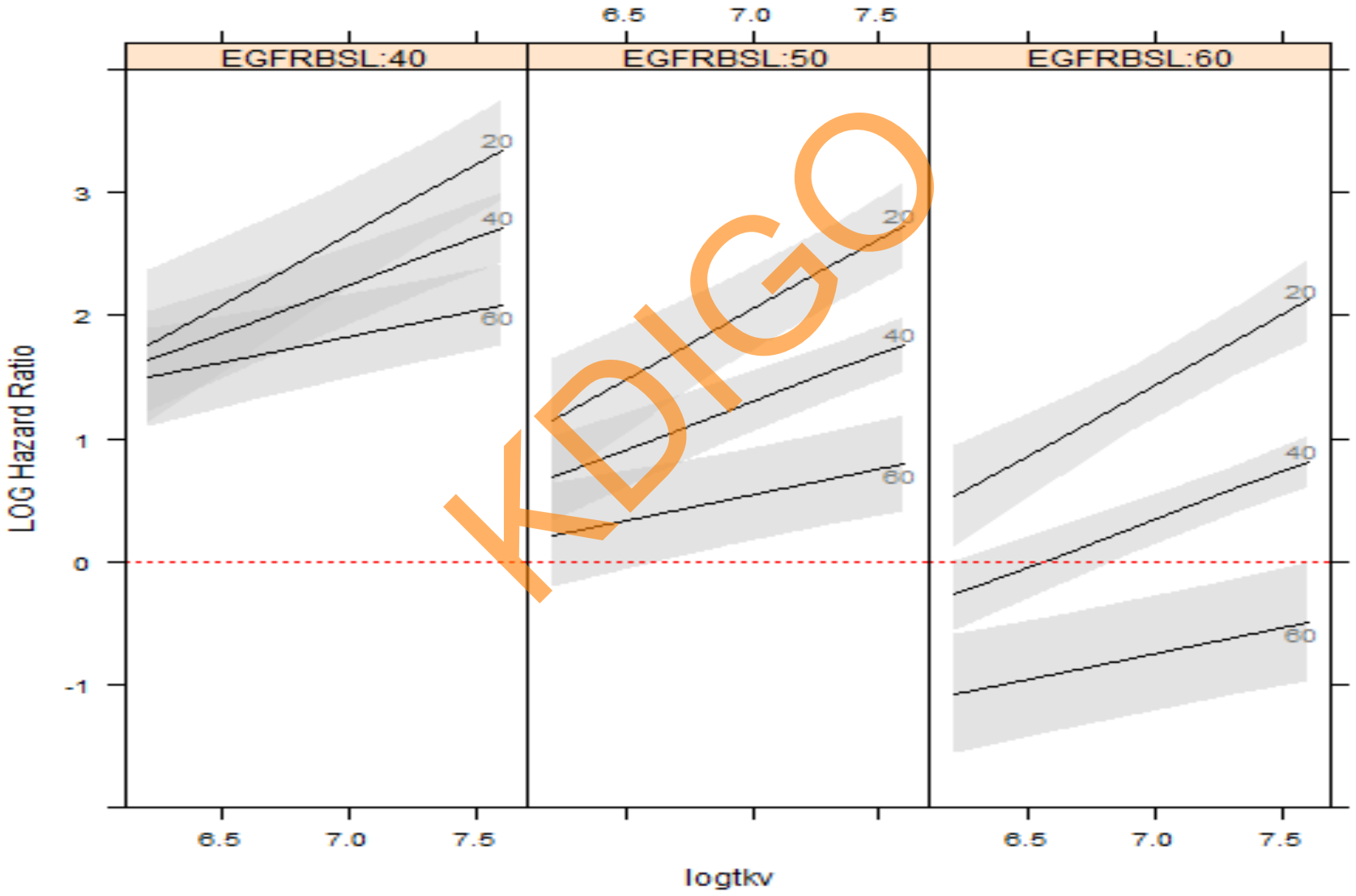


ULTRASOUND

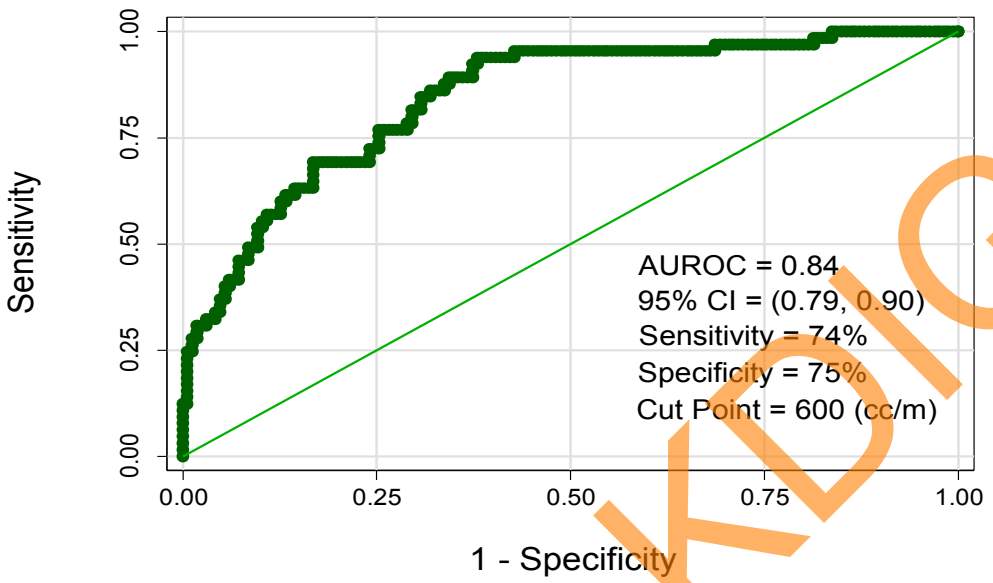


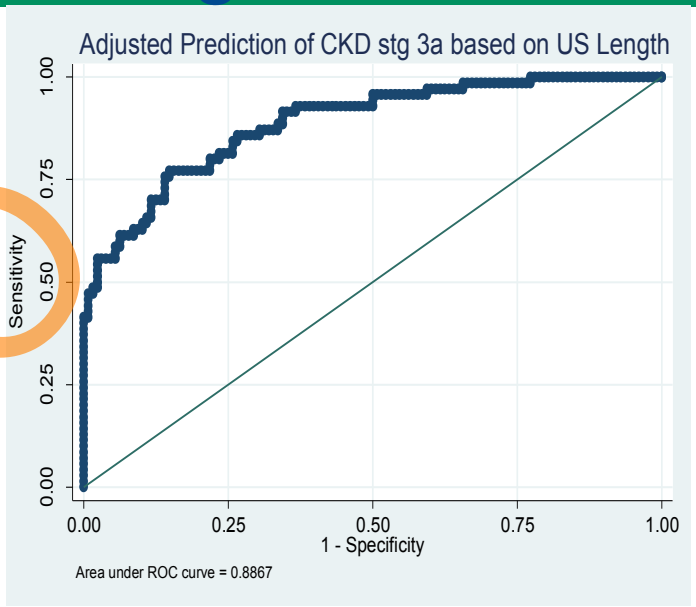
PKD DOC, CPATH, in preparation2010.

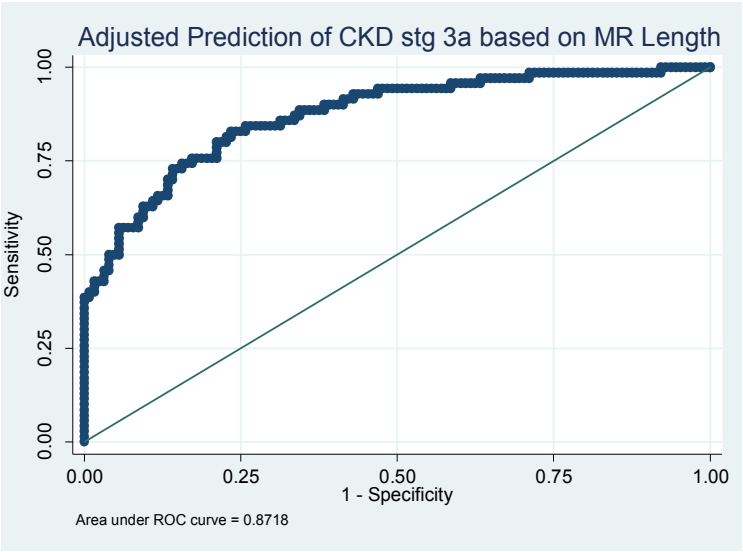
Relative Risk of Progression to ESRD based on TKV at age 20, 40 or 60 years



Ultrasound and MR Renal Length Predicts Future CKD Stage 3







NIH CRISP Studies; Chapman et al, *ASN Renal Week*, 2010.

Summary

TKV is needed in RCT in ADPKD, both for subject enrichment AND as a primary endpoint

TKV alone currently provides predictive information regarding renal disease progression in ADPKD

While MR remains the imaging modality of choice in RCT, other less expensive and invasive imaging modalities such as ultrasound may be used for risk prediction and management of ADPKD