



# ADPKD Summit

“Addressing the Need for Clinical Endpoints in ADPKD”



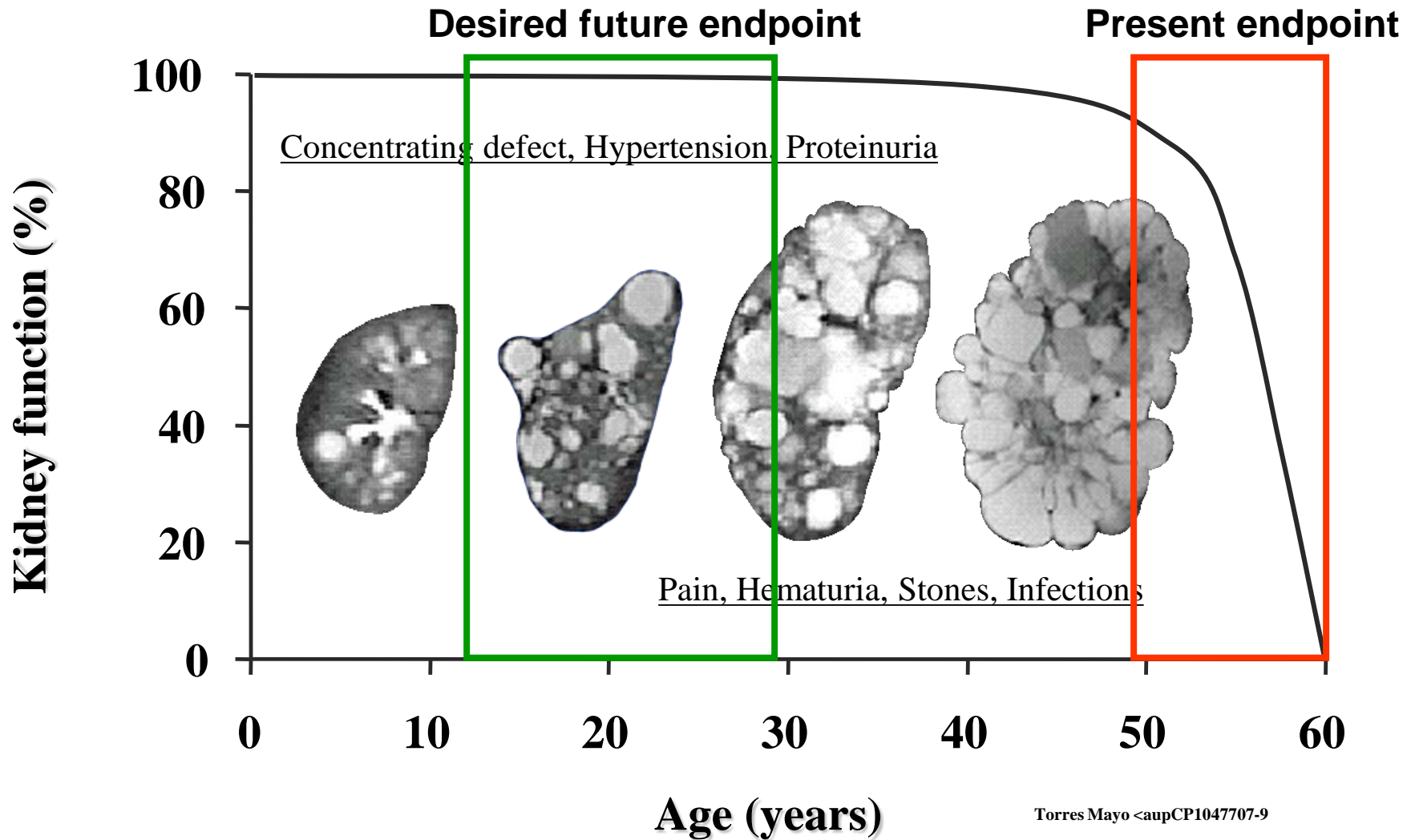
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Polycystic Kidney Disease



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### “Addressing the Need for Clinical Endpoints in ADPKD”

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8:00 am	Breakfast	
8:30 am	Welcome / Objectives	Steve Broadbent
8:45 am	Patient Perspectives	“PKD Patient’s Perspective” Dr. David Baron and Dr. Ron Perrone
9:05 am	Starting Point	“Obstacles to Developing Medical Products for ADPKD” Dr. Frank Czerwiec and Dr. Ron Perrone
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4:00 pm	Close	



- **Francesco Emma** (Bambino Gesù Children's Hosp)
- **Amy Porter** (Critical Path Institute)\*
- **Gary Lundstrom** (Critical Path Institute)\*
- **Kitty Bogy** (Critical Path Institute)\*
- **Steve Broadbent** (Critical Path Institute)\*
- **Dione Kobayashi** (Cydan Development)
- **James McArthur** (Cydan Development)
- **Martin Williams** (Cydan Development)
- **Romaldas Maciulaitis** (European Medicines Agency)\*
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- **Cynthia Beam** (Vertex Pharmaceuticals)
- **Dan Bowers** (Vertex Pharmaceuticals)
- **Joe Mancini** (Vertex Pharmaceuticals)

\* ADPKD Planning Committee

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# ADPKD: A Personal Experience

David A. Baron, Ph.D. - Chief Scientific Officer  
PKD Biomarker Summit - July 14, 2016

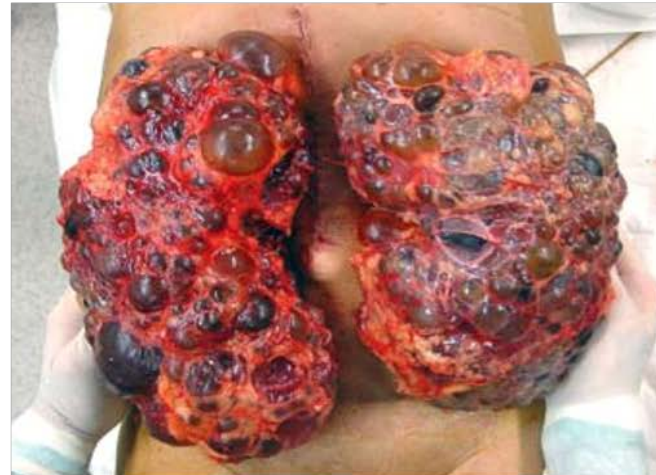
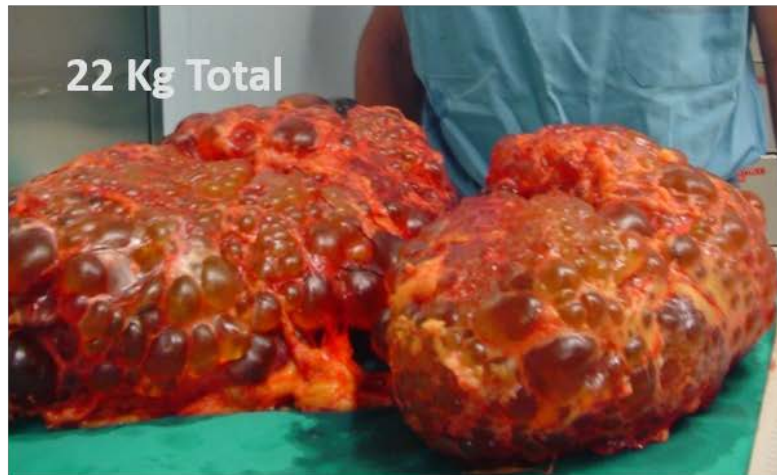
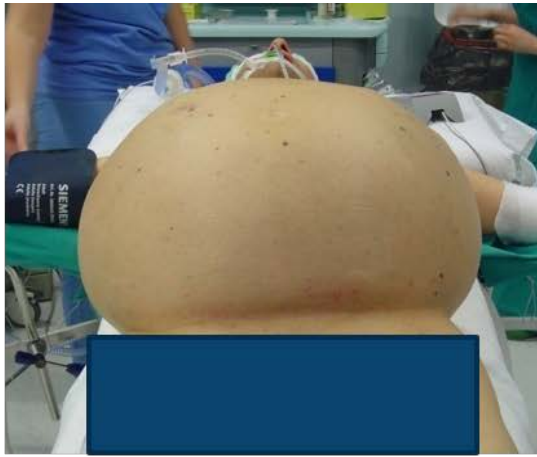


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- ADPKD is the most common monogenetic, potentially fatal disease typically affecting many members of a family
- ADPKD phenotypes are diverse yet share much in common
- The correlation of genotype with phenotype and the potential contribution of modifier genes is under active investigation
- ADPKD, despite its name, is a systemic disease affecting many organs and tissues



Courtesy  
J. Grantham



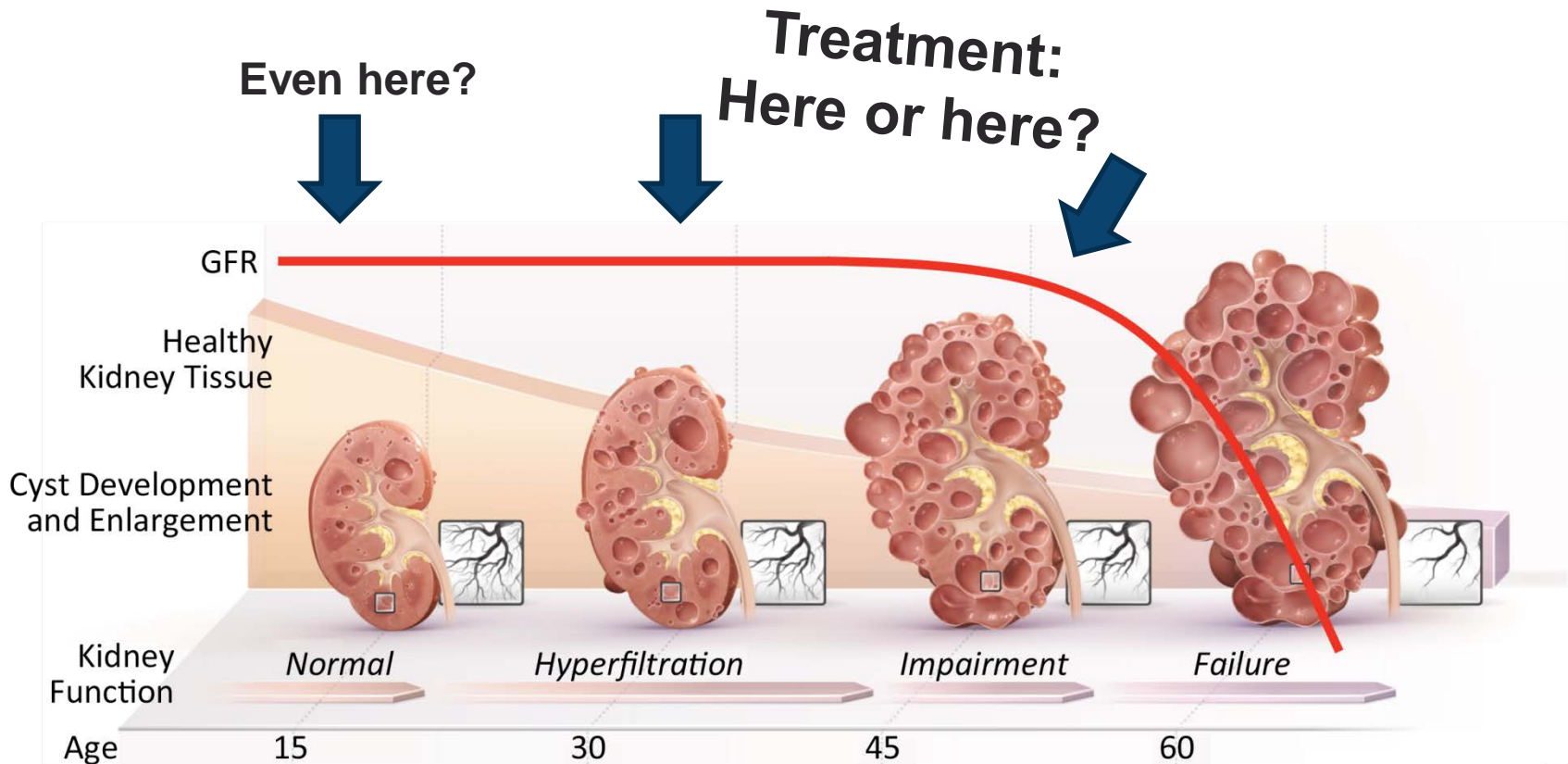
- I am 6½ years post-transplant (12/09) and thanks in part to many of you, I continue to work to facilitate the development of new therapies for ADPKD
- In my “generation”:
  - Advances in transplantation immunology
  - Advances in cardiovascular therapies
  - Advances in the basic science of ADPKD
    - Molecular genetics
    - Cellular and molecular mechanisms
    - Biophysical and molecular biology of ADPKD proteins
  - However, no therapeutic advances (US)

- ADPKD is a progressive disease starting prenatally, but may not be diagnosed until the third or fourth decade of life
- ADPKD costs governments large sums of money for renal replacement therapy alone
- 10% of cases represent spontaneous mutations
- The regulatory path to approval of new and novel ADPKD therapeutics is not well defined

- I consider myself an “average” yet unique ADPKD patient
- Pre-transplant
  - Increasingly refractory hypertension (common)
  - Hematuria (common)
  - UTIs (more common in women)
  - Retroperitoneal bleed requiring transfusion
  - Electrolyte imbalance (high K<sup>+</sup>) requiring hospitalization
  - Flank and back pain and intermittent acute pain (common)
  - Fatigue and sleep disturbances (common)
  - Psychiatric: depression, anxiety, guilt, cognitive deficits (collectively common)

- Near-transplant
  - Finding a living donor (uncertainty, anxiety, navigating difficult data)
  - Work-ups disclosing thyroid cysts (biopsy) and findings on chest X-ray
- Post-transplant
  - Polyuria and nocturia
  - Upper endoscopy: cysts (cancer?) near common bile duct in pancreas
  - Urosepsis and hospitalization
  - Bilateral laparoscopic nephrectomy
  - Mycophenolate microscopic colitis: dose titrations
  - Monthly labs: dose adjustments
  - Bicuspid aortic valve, aortic root aneurism, mitral valve defect -implications
  - MRA of Circle of Willis for berry aneurisms (negative)
  - Cysts in male reproductive tract (poorly researched)
  - Multiple basal and squamous cell skin cancers (Moh's surgeries)

- Kidney stones
- Arachnoid membrane cysts
- Dolichoectasias
- Mitral valve prolapse
- Abdominal wall hernias
- Diverticulosis and diverticulitis
- Increased risk of non-skin cancer (post-transplant)
- Increased risk of prior dialysis on transplantation
- Endothelial dysfunction (vascular phenotype)



GFR: glomerular filtration rate.

Adapted from: [Grantham JJ, et al. N Eng J Med 2006; 354\(20\):2122-30.](#)

- I am truly fortunate to have been able to help organize and participate in this summit
- As CSO of the PKD Foundation, I owe those with ADPKD a clear regulatory path to new therapeutics and treatments whether they be small molecules, biologics, or molecular genetic interventions
- The collective patients' voice must be considered, many of whom are still afraid to “come out”

- If a therapeutic with a favorable benefit/risk were available when I was 18, I would have taken it without certainty that ESRD was in my future
- I took and continue to take antihypertensives and statins for decades without any assurance that they will prevent a fatal sequela of cardiovascular disease
- I represent the growing chorus of ADPKD patients who not so long ago were hesitant to even acknowledge their condition



- ADPKD has protean effects on patients and families alike
- The biomedical science of ADPKD is entering a renaissance
- ADPKD is best treated early
- ADPKD is an important target not only for Pharma, but for governments
- A clear regulatory path to approval is urgently needed to speed therapeutic development



# Thank You!

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# Obstacles to Development of Medical Products in ADPKD

**Dr. Ronald Perrone and Dr. Frank Czerwiec**



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- The disease of polycystic kidneys in adults ..... first shows signs or symptoms after the age of 30-40, and progresses mercilessly .....
- The genetically determined disease process is latent for many years, and then becomes manifest in a kidney tissue ***which has apparently developed and functioned normally.***

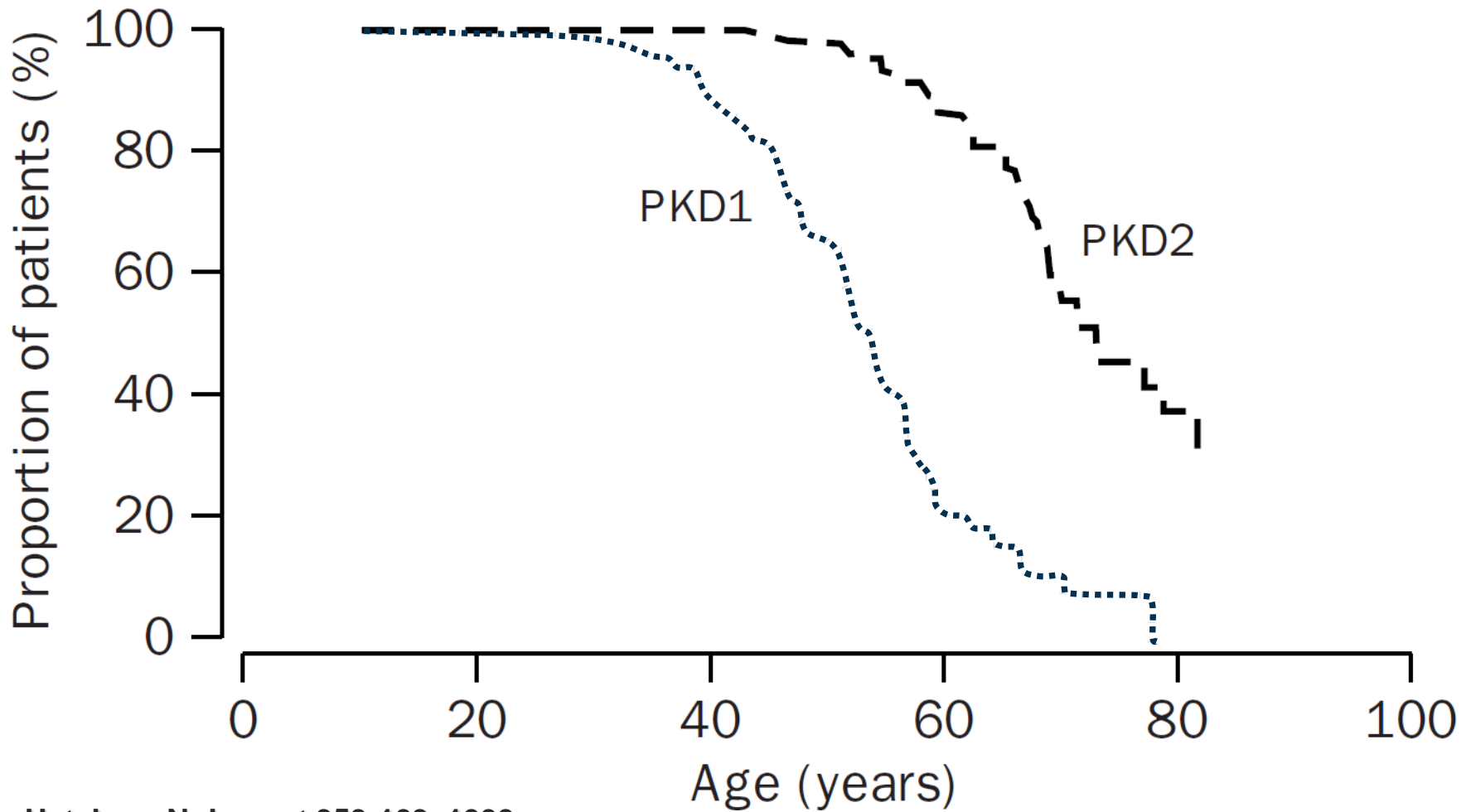
- GFR remains stable for many years, while enormous structural derangement of kidneys occurs; more rapid decline with GFR <60

Males 5 - 6 ml/min/year; Females 4 - 5 ml/min/year (MDRD)

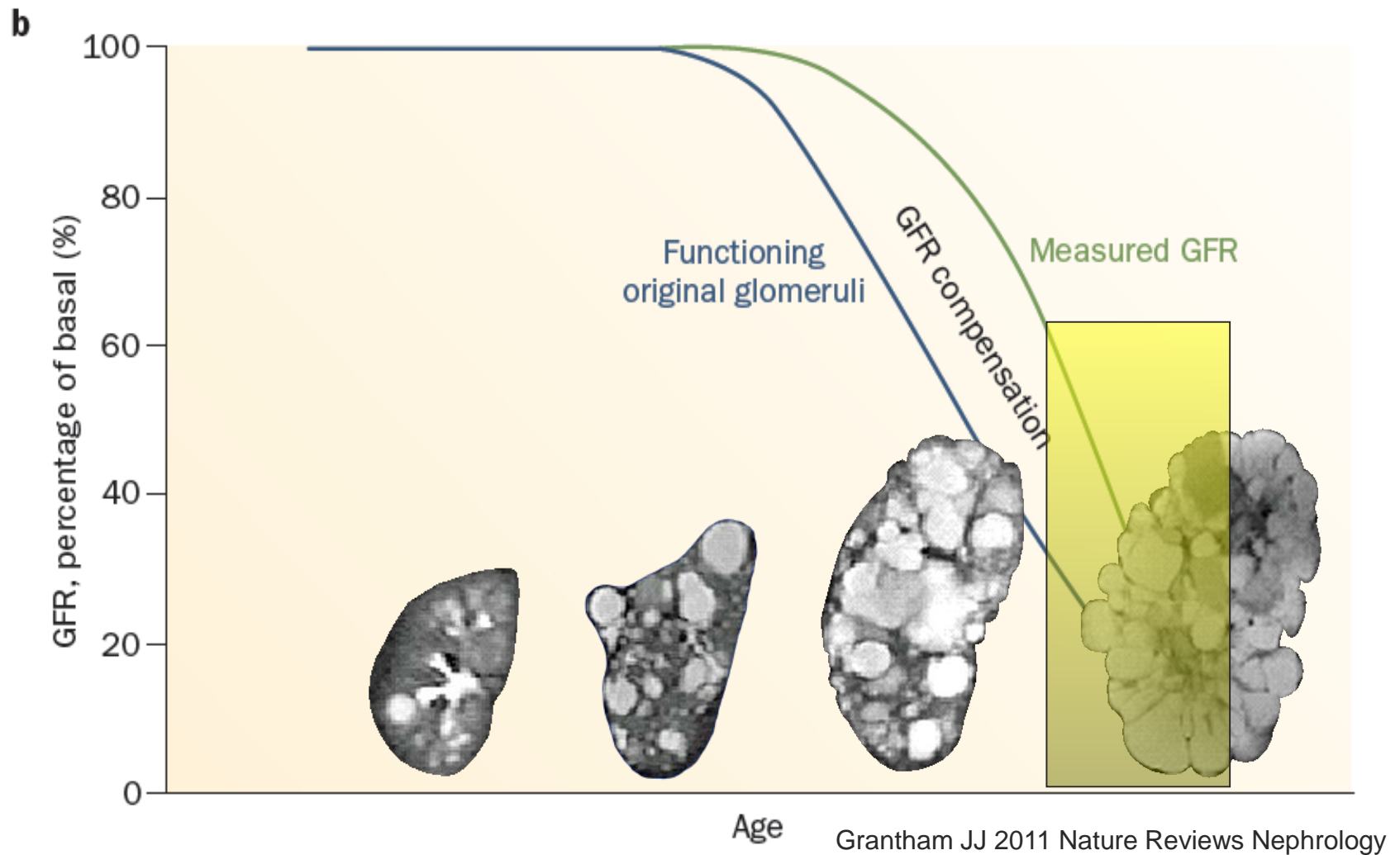
CKD Stage	Stage 1	Stage 2	Stage 3
N	162	216	84
eGFR <sub>CKD-EPI</sub> Decline (95% Confidence interval mL/min/1.73m <sup>2</sup> /year)	- 2.55 (-3.20 to -1.90)	-3.90 (-4.42 to -3.37)	-5.36 (-6.19 to -4.53)

Torres VE et al., CJASN 2016

- Progression of ADPKD to renal failure takes on average 56 years



Hateboer N; Lancet 353:103, 1999

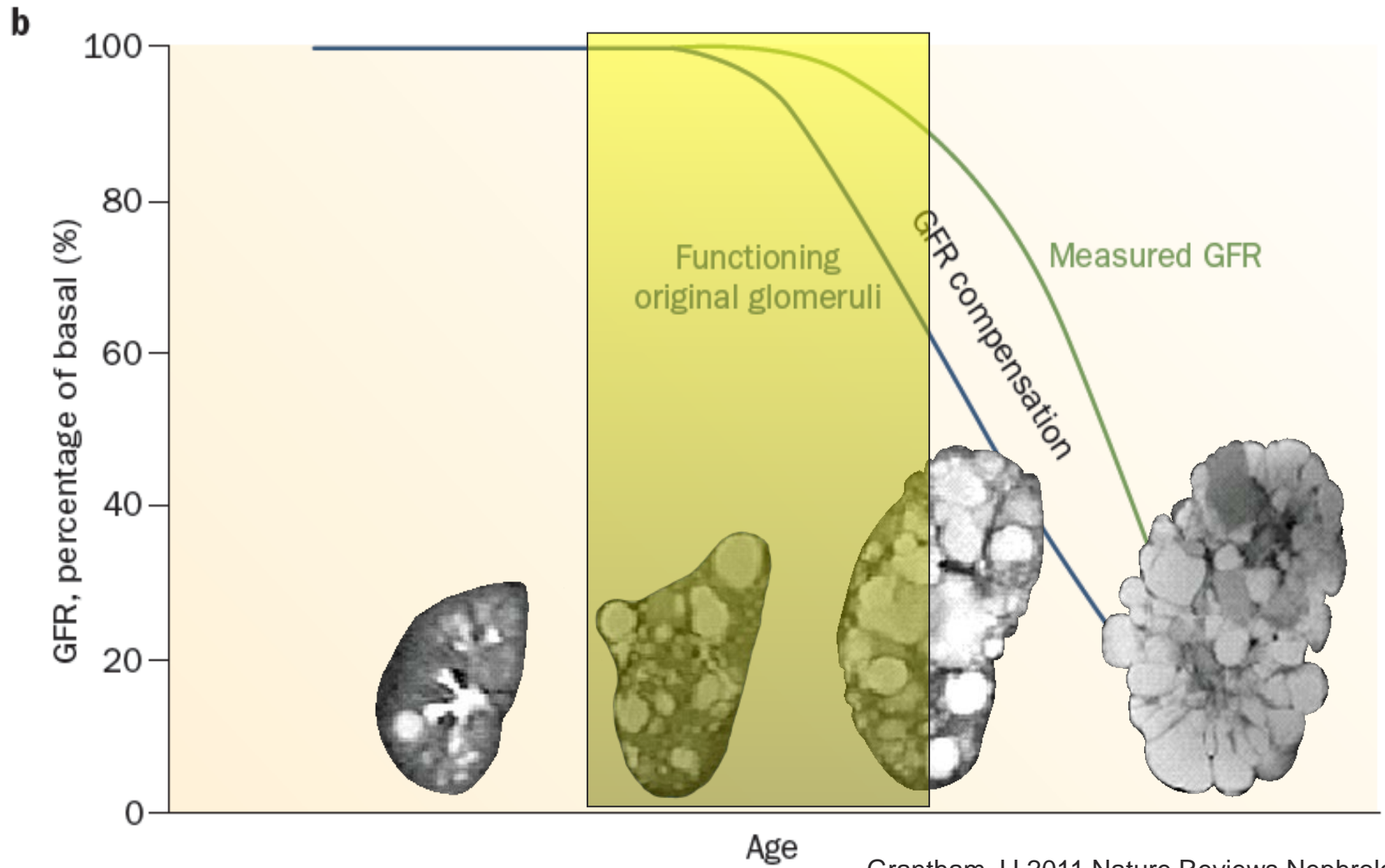




# Large Differences in Outcomes Arise from Small Absolute Changes in Early Biomarkers

- **RENAAL Trial<sup>1</sup>**: (N=1513, age 31-70 yrs, NIDDM, mean SCr=1.9 mg/dL, losartan vs. placebo)
  - **↓16% DbI SCr/ESRD/Death → 0.8 mL/min/1.73m<sup>2</sup>/year difference**  
15% reduction in eGFR decline (4.4 vs. 5.2 mL/min/1.73m<sup>2</sup>/year)
- **IDNT Trial<sup>2</sup>**: (N=1715, 30-70 ( $\bar{x}$ =59) yrs, NIDDM, SCr 1.0<sub>♀</sub>, 1.2<sub>♂</sub>-3.0 mg/dL,  $\bar{x}$ =1.67, irbesartan vs. placebo)
  - **↓23% DbI SCr/ESRD/Death → 1.0 mL/min/1.73m<sup>2</sup>/year difference**  
15% reduction in Creatinine clearance decline (5.5 vs. 6.5 mL/min/1.73m<sup>2</sup>/year)
- **AASK Trial<sup>3,4</sup>**: (N=1094, 18-70 ( $\bar{x}$ =54) years, HTN, eGFR 20-65 mL/min/1.73m<sup>2</sup>,  $\bar{x}$ = 46, ramipril vs. amlodipine)
  - **↓38% DbI SCr/ESRD/Death → 1.16 mL/min/1.73m<sup>2</sup>/year difference**  
36% reduction in eGFR decline (chronic slope = 2.07 vs. 3.22 mL/min/1.73m<sup>2</sup>/year)

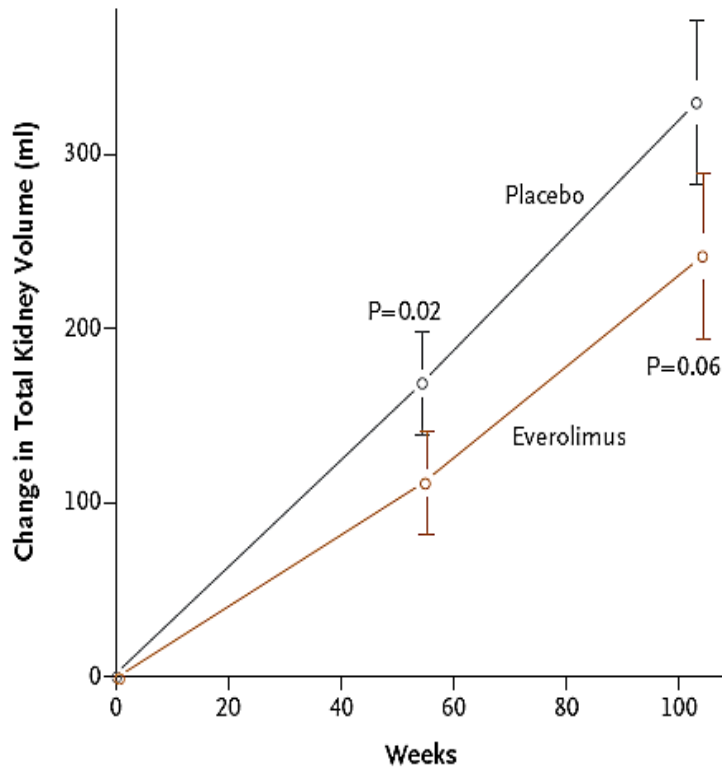
<sup>1</sup> Brenner BM, NEJM 2001, <sup>2</sup> Lewis EJ, NEJM 2001. <sup>3</sup> Wright JT, JAMA 2002, <sup>4</sup> Agodoa LY, JAMA 2001



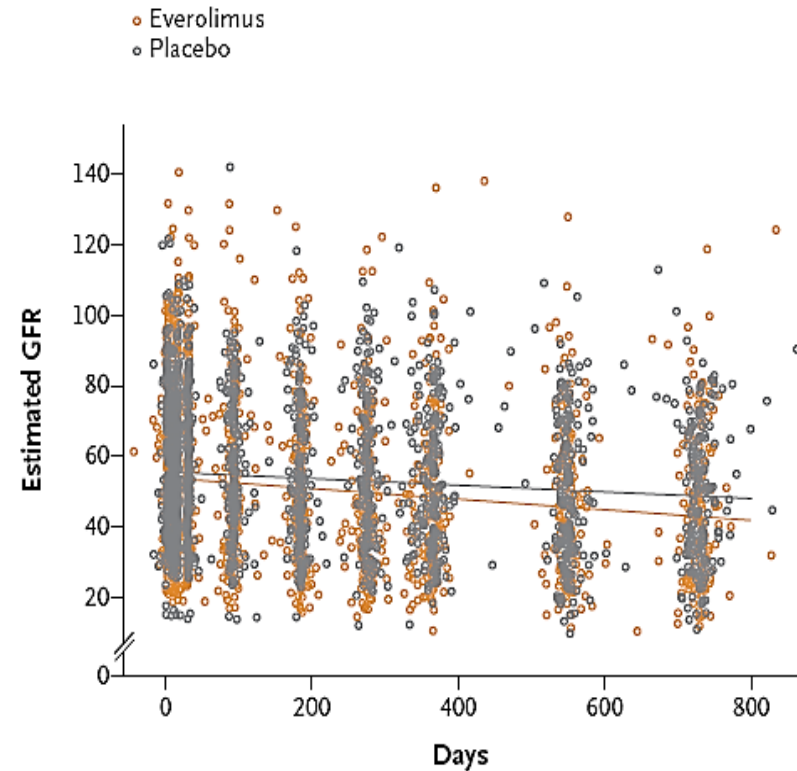
Grantham JJ 2011 Nature Reviews Nephrology

- Studying late disease carries a risk of false negatives
  - Late failure may not apply in early disease
- Studying early disease carries a risk of false:
  - Positive: Use of intermediate surrogate may not predict true outcome
  - Negative: Acute effects and relatively small eGFR changes in CKD1
- Missing data:
  - subjects are employed; family obligations
  - studies are long leading to decaying compliance, especially if differences in treatment tolerability
- Distinguish toxicities/SAEs from natural history
- Potential unblinding bias
- Inability to use historical data
- Uncertainty in use of regulatory discretion

# A False Negative Result?



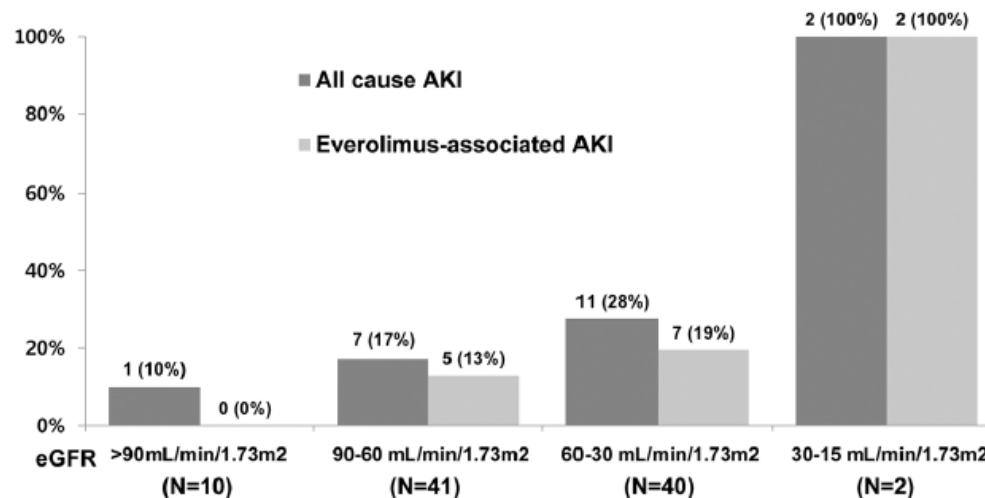
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Walz G et al, 2010 NEJM

- Off-target effects may explain everolimus’ “dissociation” of eGFR and TKV in ADPKD: “Unexpectedly, a significant reduction in the TKV ( $P = 0.02$ ) coincided with a significant worsening of renal function and a drop in estimated GFR ( $P = 0.004$ ) after 1 year of treatment with everolimus ... Among male patients with ADPKD who had an estimated GFR of less than 60 ml per minute, those in the everolimus group had a significantly more rapid decline in the estimated GFR than did those in the placebo group. This was not seen among male patients with an estimated GFR of 60 ml per minute or more ... “  
Walz G 2011 NEJM Letter

- Recent evidence suggests everolimus is associated with AKI in CKD 2-4



**Figure 2** Incidence of AKI according to baseline eGFR categories in the RCC group. The incidence of all-cause AKI and everolimus-associated AKI increased progressively with decreasing eGFR ( $P = 0.029$  and  $P = 0.004$  for trend, respectively).  
Ha SH 2014 BMC Cancer

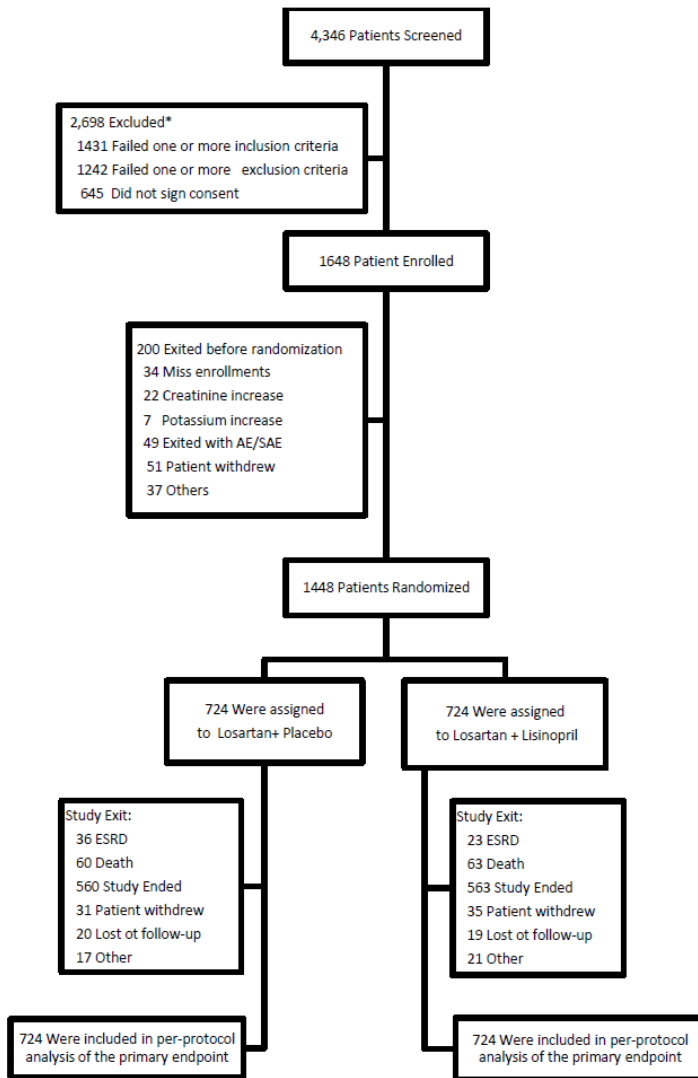
### VA NEPHRON-D Trial

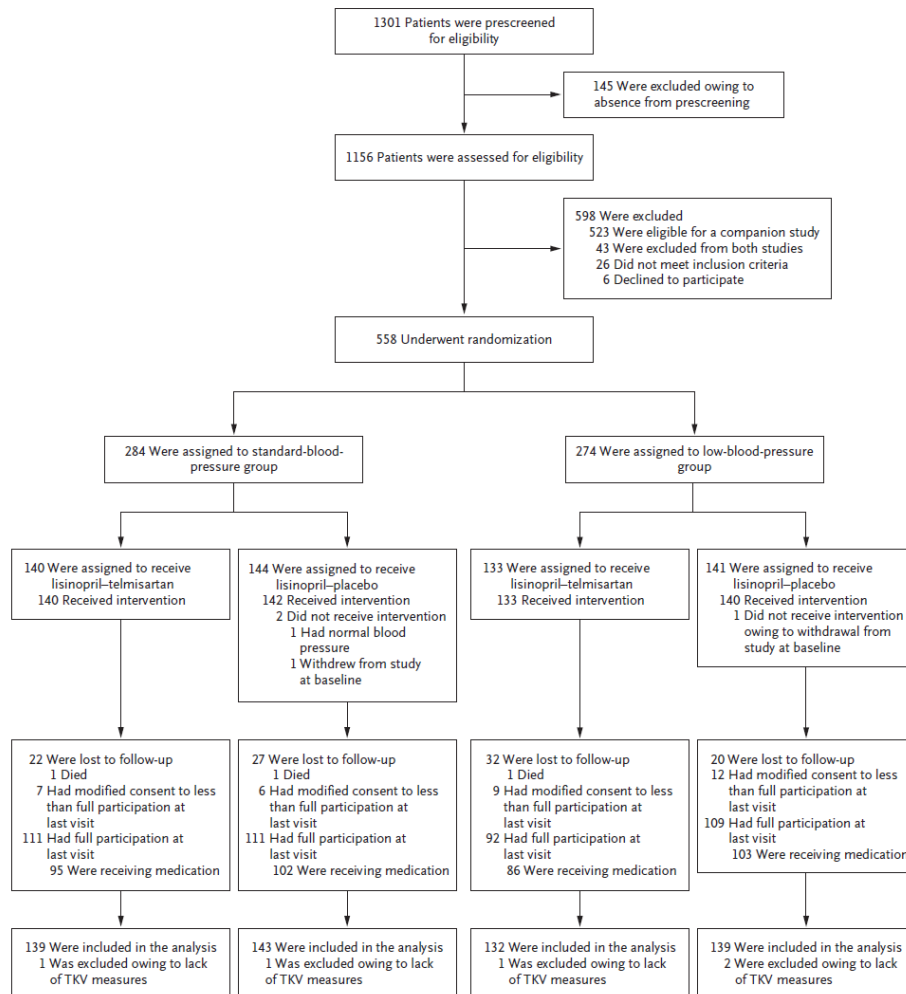
Losartan ± Lisinopril in T2DM (CKD 2-4) x 2.2 yrs

- Conducted at 32 VA Medical Centers
- 1° Endpoint: eGFR Reduction\*, ESRD, Death
- 10% of subjects had missing data (balanced):
  - 66 patients withdrew
  - 39 patients were lost to follow-up
  - 38 patients data was missing for “Other” reasons
- **Despite “captive” population & governmental eMR system:**
- Protocol stipulates: *“For the primary endpoint and other survival endpoint ... assume that the missing data is non-informative (ignorable) and censor ...”*. Terminated by IDMC due to lack of efficacy & signals of hyperkalemia & AKI in dual-treatment arm

\*>50% reduction if < 60 mL/min/1.73m<sup>2</sup>,  
>30 mL/min/1.73m<sup>2</sup> reduction if ≥ 60 mL/min/1.73m<sup>2</sup>

Fried LF et al. 2013 NEJM





## HALT-PKD “A”

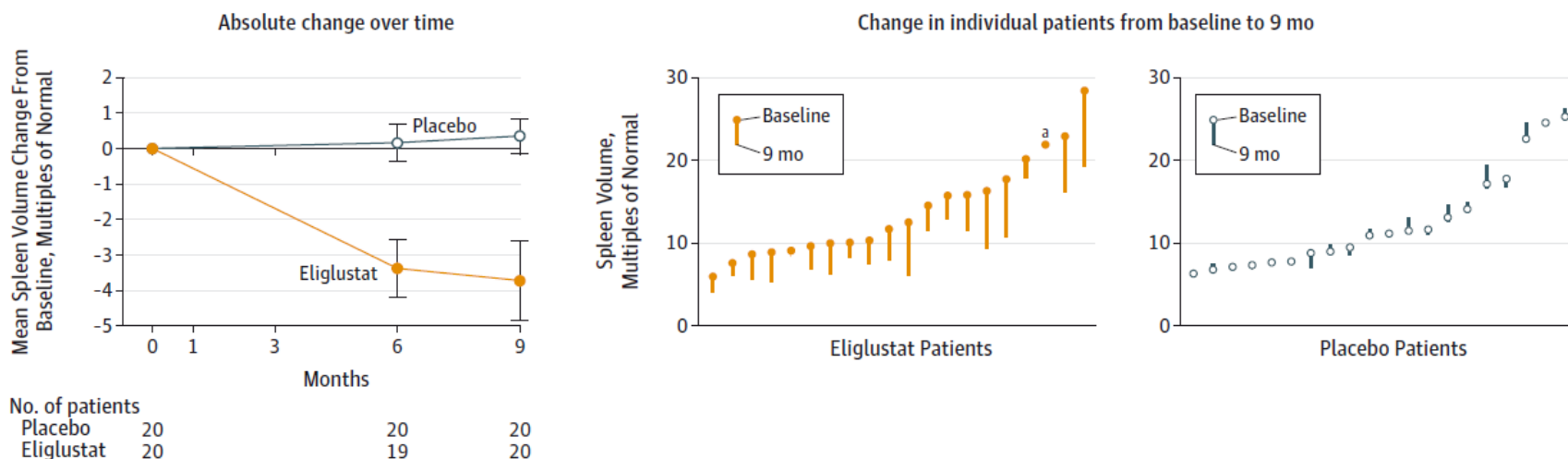
- 2x2 Low/Standard BP & Lisinopril ± Telmesartan in ADPKD (CKD 1-2) x 8 years
- Conducted at 7 Tertiary PKD Centers
- 1° Endpoint: TKV %Change/year
- 2° Endpoint: eGFR Change/year
- 24% of subjects had incomplete data:
  - 18% of patients were lost to follow-up
    - 24% on dual-therapy, low-BP
    - 15-19% in other arms
  - 6% of patients withdrew early
  - 9% completed trial off study medications

Protocol stipulates: “Although missing data are not expected to be an overly large problem (assuming that the participant population for this disease is very enthusiastic about the study), the random regression methods are somewhat robust to this problem. Obtaining two of the four observations of the primary outcome variable is essential, however.”

Schrier RW et al., 2014 NEJM

# Key Gaucher's Approval Trial: 9 Month-Effects on Organ Size in 39 Patients

Figure 2. Changes in the Primary End Point of Spleen Volume in the Intention-to-Treat Population



Benefits for also seen in secondary outcomes of Liver volume, hematocrit and platelet count.

Mistry PK et al., 2015 JAMA

**For another Gaucher disease (Type 1) drug program:** *“Due to the orphan nature of Type I Gaucher Disease, and the limitations of the submitted clinical studies, the determination of the clinical effectiveness of ELELYSO® will rely more on clinical judgment than on the statistical rigor usually required for larger controlled studies.” ... “However, due to the current product shortage issues which persist with CERZYZME, a request for an additional request for a pre-market adequate and well-controlled study is deemed burdensome. Further long term data (e.g. up to 5 years of total exposure) from the PB-06-003 study could suffice and be obtained by DGIEP via a post-marketing requirement.”*

Vali B et al., 2011 FDA Statistical Review for ELELYSO™



- ADPKD progresses slowly
- Trials, by necessity, are long and expensive
- Potential subjects in the ages of interest have family and work commitments, limiting ability to participate in multi-year trials
- Earlier endpoints needed
  - Minimize false positive and negative results
  - Low cost
  - Predictive of efficacy
- A regulatory framework that respects patient and family acceptance of short-term benefit despite uncertainty about future delay in ESRD is desirable



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# Regulatory Requirements for Drug Approval and Approval Pathways

Dr. Romaldas Mačiulaitis and Dr. Aliza Thompson



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The views presented in this presentation/these slides are those of the author and should not be understood or quoted as being made on behalf of the European Medicines Agency and/or its scientific committees.

- Terminology
- Approval Pathways in Europe and the US
- Evidentiary considerations related to surrogate endpoints
- Endpoints for clinical trials in ADPKD



- Clinical Outcome
- Biomarker
- Surrogate Endpoint

*\*BEST (Biomarkers, EndpointS, and other Tools) Resource used as source for FDA definitions. The BEST Resource was developed by the FDA and NIH to address the need for harmonization of terms used in translational science and medical product development and specifically terms related to study endpoints and biomarkers.*

- **Clinical Outcome: Significant overlap in definitions/concepts**
  - **FDA (BEST Resource):** An outcome that describes or reflects how an individual feels, functions or survives (*BEST Resource*). The FDA has also referred to an endpoint that describes how an individual feels, functions or survives as a “clinically meaningful endpoint.”
  - **EMA:** No single/set definition, but generally used to refer to an endpoint that measures **clinical benefit** (*based on ICH E8*). Clinical outcomes can range from “improvement of **symptoms**” to “delay of disease **progression**” or “prolonging **survival**”.



- **Biomarker: FDA and EMA definitions are similar; BEST definition shown below.**
  - A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.
  - Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives.

- **Surrogate endpoint: Again, overlapping definitions/concepts**
  - **FDA (BEST Resource):** An endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather **is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.**

From a U.S. regulatory standpoint, surrogate endpoints and potential surrogate endpoints can be **characterized by the level of clinical validation: validated surrogate endpoint, reasonably likely surrogate endpoint, candidate surrogate endpoint**



- **Surrogate endpoint:**

- **EMA:** An endpoint that is intended to **relate** to a clinically important outcome but does not in itself measure a clinical benefit.

Surrogate endpoints may be used as **primary endpoints** when appropriate (when the surrogate is *reasonably likely* or *well known* to *predict clinical outcome*) and *validated* (based on ICH E8 and E9).

# Regulatory Pathways

## Marketing Authorizations (MA) in Europe

### National MA procedures:

- Marketing Authorizations
- Mutual Recognition Procedures
- Decentralized Procedures

### Centralized MA procedures:

- Full (“Standard”) MA
- Conditional MA
- MA under Exceptional Circumstances
- Accelerated MA

## Approval Pathways in the US

- Traditional Approval
- Accelerated Approval

Standard MA	Conditional MA	MA under Exceptional Circumstances	Accelerated MA
Full B/R assessment	Positive B/R pre MA and agreed plan to generate data for full B/R	Positive B/R pre MA, without full B/R assessment	Evidence requirements for applications to be assessed are the same as for other applications; possible option after PRIME procedure
Valid for 5 years (renewable)	Valid for 1 years (renewable)	Valid for 5 years (renewable)	
Specific post MA conditions are possible (e.g., PASS, PAES)	Specific post MA obligations +/- conditions		
Prerequisite (at least one): obligatory or optional scope for centralized procedure	Prerequisite (at least one): seriously debilitating, or life threatening, emergency situation, orphan medicine, UMN, extent to fulfill UMN	Prerequisite (both): very rare condition, comprehensive information not possible based on current scientific knowledge	Prerequisites (all): major interest for public health and therapeutic innovation; UMN, extent to fulfill UMN, evidences
B/R – benefit risk ratio; MA – Marketing Authorization; PAES - Post Authorization Efficacy Study; PASS – Post Authorization Safety Study; UMN – unmet medical need			

- Positive Benefit/Risk
  - Irrespective of full, conditional, or exceptional type of MA
  - Further B/R profiling can/should be requested after MA, based on type of MA and comprehensiveness of premarketing data
- Benefit proven by showing a clinically relevant effect, employing endpoint(s) representing clinical or surrogate outcomes as per
  - ICH Topics E8/E9 provisions
  - Disease specific guidelines, e.g., cardiovascular, renal guideline
  - Product specific scientific advise/protocol assistance, including joint EMA/HTA, pilot adaptive pathways to patients, and PRIME procedures

- Traditional Approval
  - Approval based on a clinical outcome/clinically meaningful endpoint (i.e. an endpoint that reflects how a patient feels, functions or survives) or a validated surrogate endpoint
- Accelerated Approval
  - Approval based on an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality
  - In the US, this is the only pathway that provides the opportunity to resolve issues related to effectiveness (i.e., verify the benefit) in the post-marketing setting



## Additional Conditions/Requirements:

- Product must be for a serious or life-threatening disease or condition **AND** provide a meaningful advantage over available therapies
- For drugs granted accelerated approval, postmarketing confirmatory trials are generally required to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit
- Approval of a drug may be withdrawn if trials fail to verify clinical benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug

# Evidentiary considerations related to surrogate endpoints



**What the law says:** Discusses, in general terms, the evidence needed to support a “reasonably likely surrogate” but not a validated surrogate endpoint

**What FDA guidance documents say:**

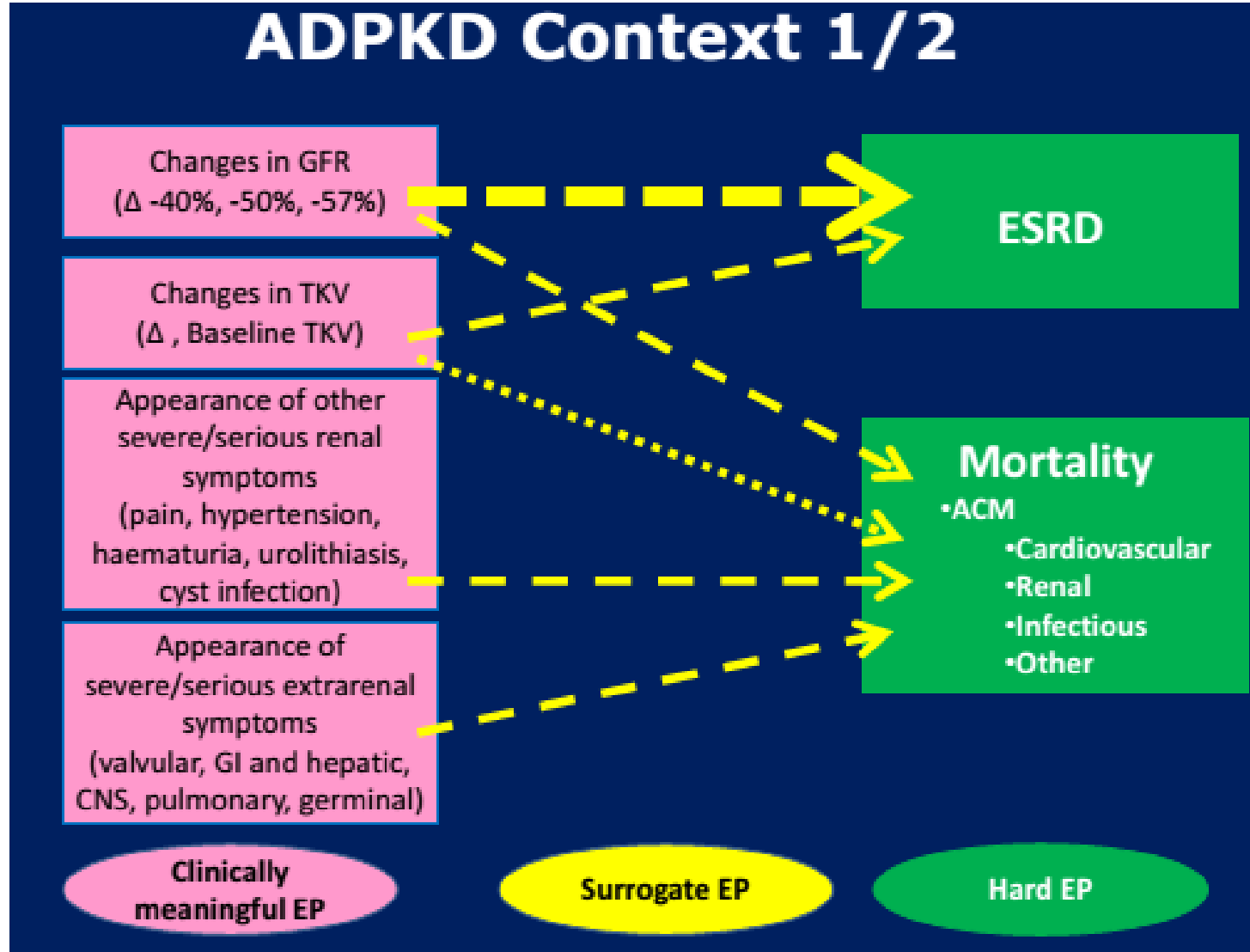
- FDA has issued a guidance document that contains fairly granular guidance on evidence that should be considered when evaluating a “reasonably likely surrogate” supporting accelerated approval.
- At present, no FDA guidance document contains a detailed discussion of the evidence needed to establish a “validated surrogate endpoint” supporting traditional approval, however FDA has stated that the standard is high

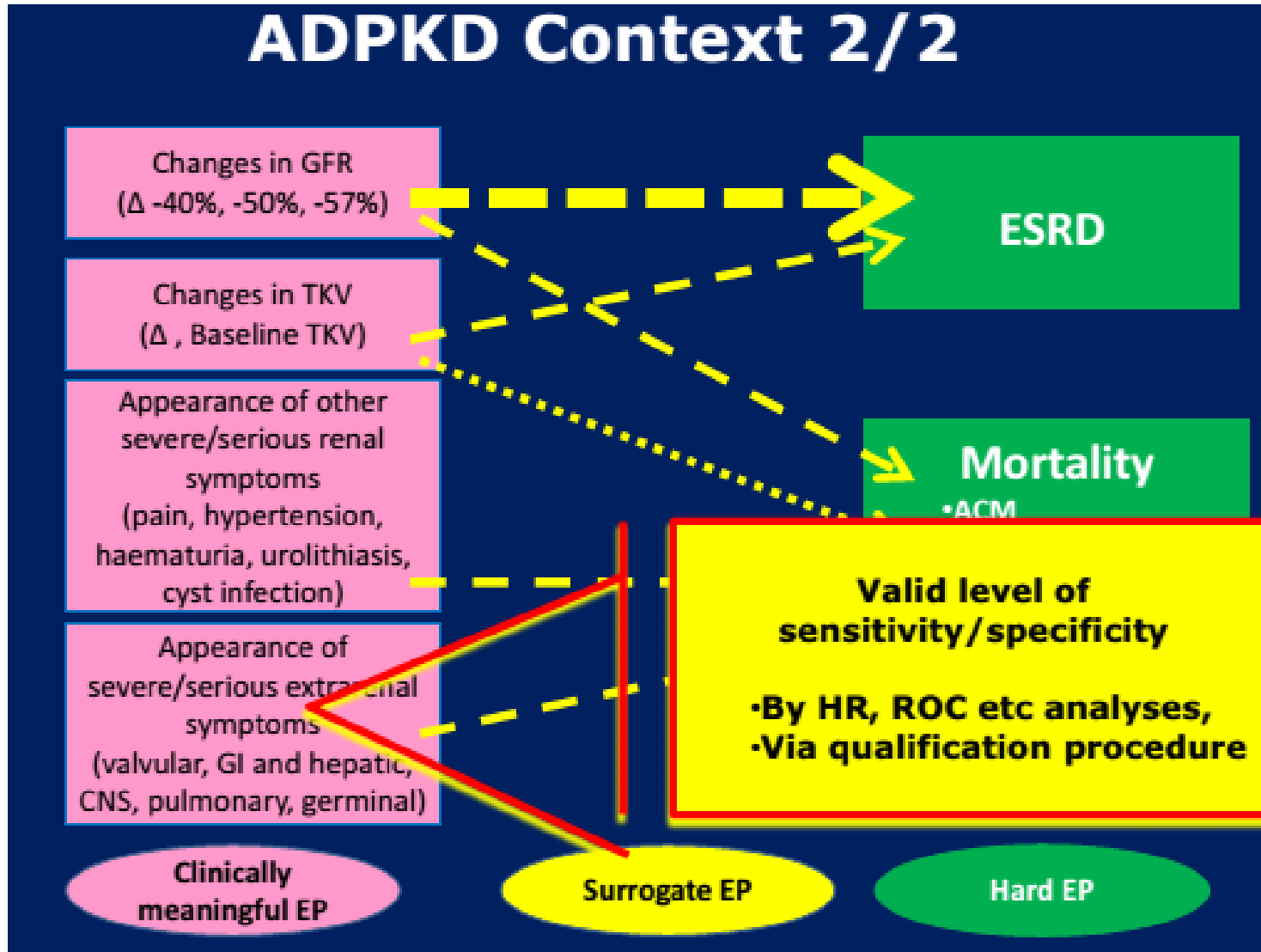
*“Because of the substantial risk of adversely affecting the public health if a biomarker is falsely accepted as a surrogate endpoint, **robust scientific evidence is needed to justify qualification of a biomarker for use as a surrogate endpoint.** There have been **numerous biomarkers that represented plausible surrogate endpoints** (e.g. reduced rate of ventricular premature beats following a heart attack, cardiac output in congestive heart failure, increased HDL cholesterol in patients with coronary artery disease). **However, when tested in outcome trials, these biomarkers have failed to predict the expected clinical benefit.** It has generally not been clear whether this represented an erroneous expectation of a relationship of the biomarker to the outcome or an unrecognized off-target effect of the drug... “*

-Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools, issued January 2014

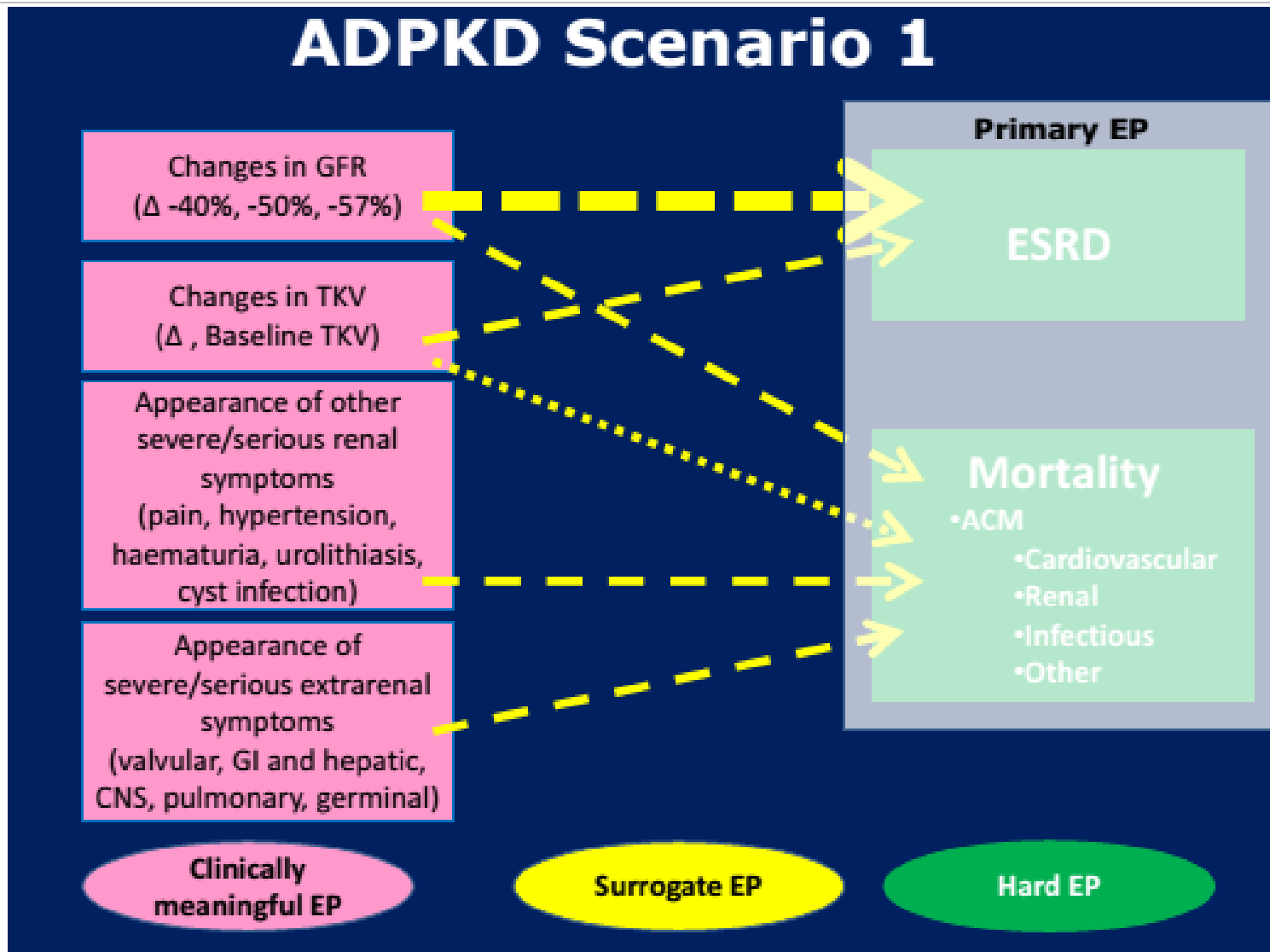
- **Biologic plausibility:** whether surrogate is on pathophysiologic pathway leading to clinical outcome of interest (causal? necessary intermediate?)
- **Strength and consistency of epidemiologic data** supporting relationship between surrogate and clinical outcome of interest
- **Whether treatment effects on surrogate have been shown to predict treatment effects on clinical outcome of interest** (with drugs in the same/related pharmacologic class? with drugs from distinct pharmacologic classes/ regardless of the mechanism of the intervention?)

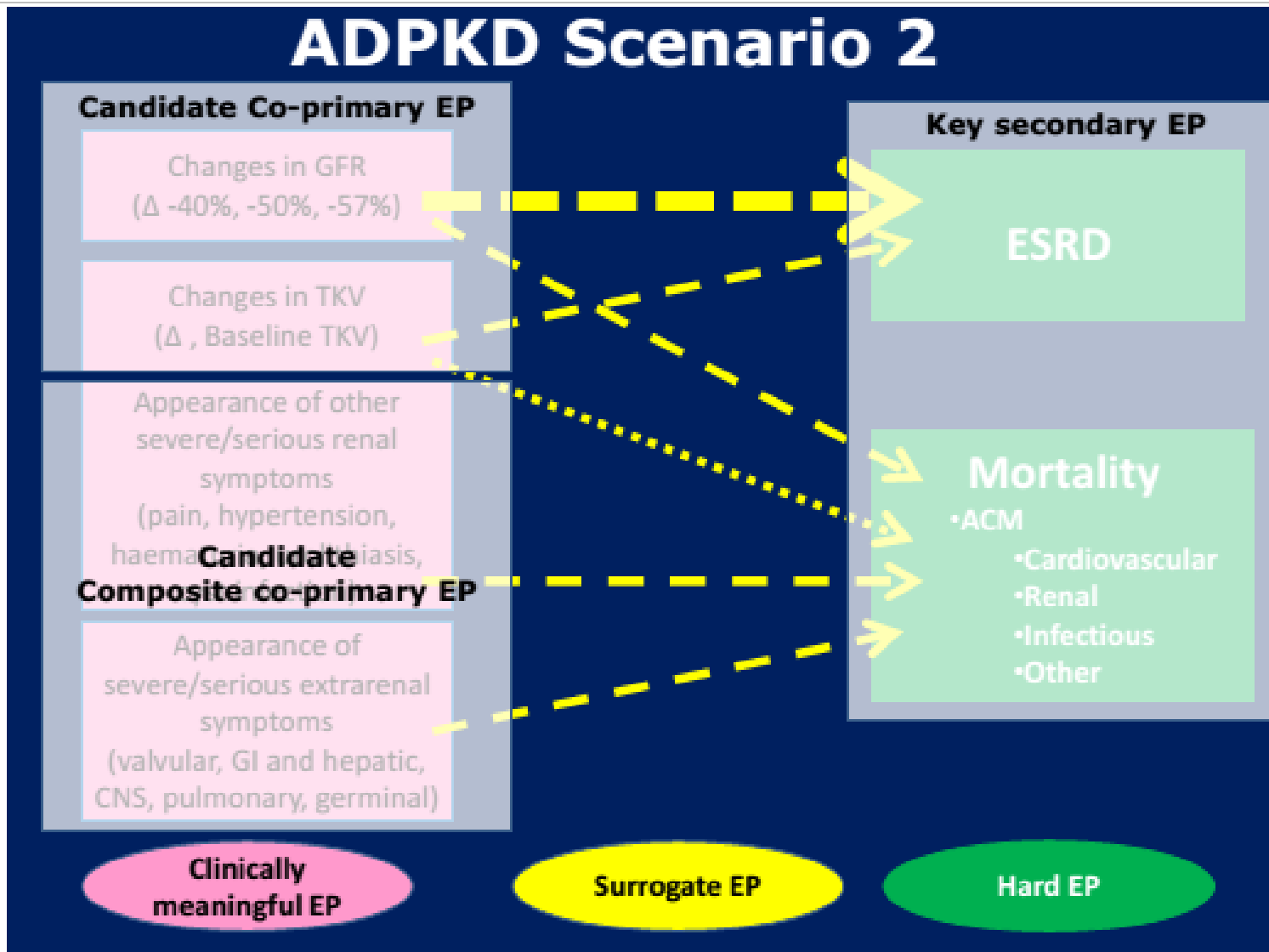
# Endpoints in ADPKD











Potential endpoints *	Comments
<b>Decline in GFR/irreversible loss of renal function</b>	Endpoint could be slope-based, loss of a prespecified magnitude, or hard outcome (end stage disease defined by chronic dialysis, transplantation or sustained GFR < 15)
<b>Chronic pain, acute pain episodes, other important symptoms associated with the disease</b>	Endpoint could be based on a Patient Reported Outcome measure or assessed in some other way (e.g., initiation or escalation of pain medication usage)
<b>Other Renal Complications: Nephrolithiasis, cyst hemorrhage, renal cyst infection</b>	Should be further discussion about how to define clinically significant events for the purpose of registration trials
<b>Onset or worsening of hypertension</b>	May be a noisy endpoint; careful thought should be given with regard to how to optimize the design of the trial to capture effects on onset or worsening of hypertension

\*Not intended to be a comprehensive list; composite endpoints acceptable

More on Total Kidney Volume as a  
surrogate endpoint in the next  
session...



## Developing therapies to treat early stages of ADPKD:

- **Studies supporting drug approval are often conducted in patients with more advanced disease. Why?** From an efficacy perspective, patients with more advanced disease are more likely to progress to the outcome of interest (as compared to those who are early in the disease course). Hence, enrolling patients with more advanced disease makes it easier to detect a treatment effect (if one exists) in trials that are smaller and of shorter duration than the trials would be if patients with early stage disease were enrolled.
- **A perspective (Dr. Thompson's):** At least as relates to developing therapies to treat slowly progressively chronic kidney diseases, **we often encourage sponsors to enrich their trials with patients with more advanced disease, not so much because we think earlier stages of disease should not be treated, but because we view it as a “tool” or rather means to get the data needed to understand whether a therapy is effective.**

## **Developing therapies to treat early stages of ADPKD** (Dr. Thompson's perspective):

- If it is thought a therapy will also be effective in treating patients with more advanced disease (e.g., those that have already begun to manifest significant changes in eGFR), one could conduct separate trials in patients with early and more advanced stages of disease, or enroll both population into a single trial as a means to provide the efficacy data needed to support approval.
- Obviously, studying a therapy in patients with more advanced disease will not help one detect a treatment effect if the therapy is only thought to be effective early in the course of the disease. And yet, to understand the benefit of such a therapy (and how to use the therapy in clinical practice), I believe it is important for development programs to collect some data on efficacy (or lack thereof) in patients at later stages of disease.

## **Developing therapies to treat early stages of ADPKD** (Dr. Thompson's perspective):

- Whether a therapy is only expected to have efficacy early in the course of disease also has bearing on the use of TKV as a surrogate and so I'll circle back to this issue in the next session.





# Thank You!

[www.c-path.org](http://www.c-path.org)



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# Break

10:30 am - 10:40 am



### “Addressing the Need for Clinical Endpoints in ADPKD”

Time	Description	Comments / Notes
8:00 am	Breakfast	
8:30 am	Welcome / Objectives	Steve Broadbent
8:45 am	Patient Perspectives	“PKD Patient’s Perspective” Dr. David Baron and Dr. Ron Perrone
9:05 am	Starting Point	“Obstacles to Developing Medical Products for ADPKD” Dr. Frank Czerwiec and Dr. Ron Perrone
9:25 am	Regulatory Perspectives	“Regulatory Requirements for Drug Approval and Approval Pathways” Dr. Aliza Thompson and Dr. Romaldas Mačiulaitis
9:45 am	Break	
10:00 am	Addressing Unmet ADPKD Needs (Part 1)	“Can TKV be Qualified/Accepted as a Surrogate Endpoint?” Moderator: Dr. Ron Perrone; Introduction: Dr. Arlene Chapman
11:30 am	Lunch	
12:15 pm	Addressing Unmet ADPKD Needs (Part 2)	“What are Other / Additional Endpoints that should be Considered?” Introduction and Moderator: Dr. Albert Ong
1:45 pm	Break	
2:00 pm	Addressing Unmet ADPKD Needs (Part 3)	“How Do We Address the Challenges in Using Available Regulatory Pathways?” Moderator: Dr. David Baron; Introduction: Dr. Frank Czerwiec
3:30 pm	Wrap-Up / Next Steps	Steve Broadbent
4:00 pm	Close	



# Addressing Unmet ADPKD Needs Part 1: Can TKV be Qualified/Accepted as a Surrogate Endpoint?

**Dr. Ron Perrone and Dr. Arlene Chapman**

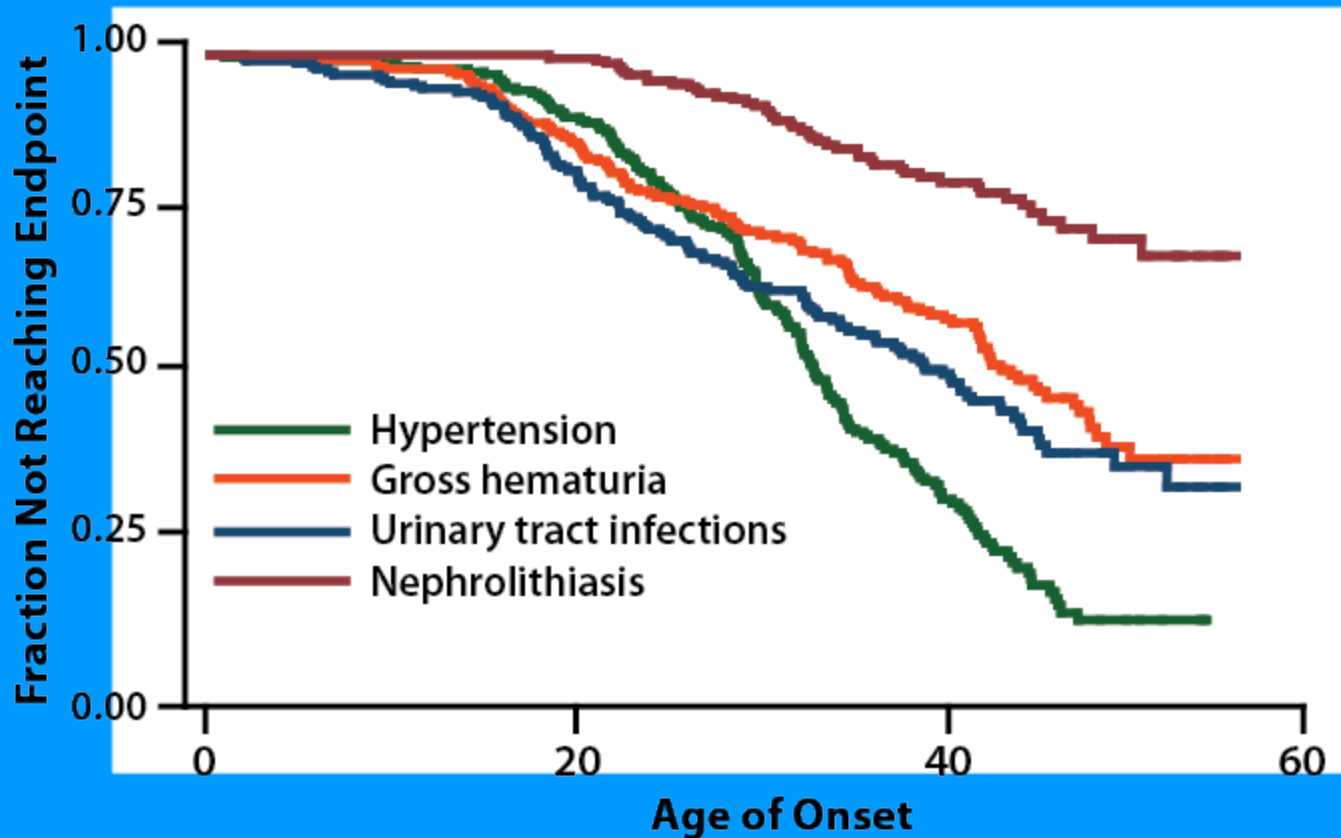


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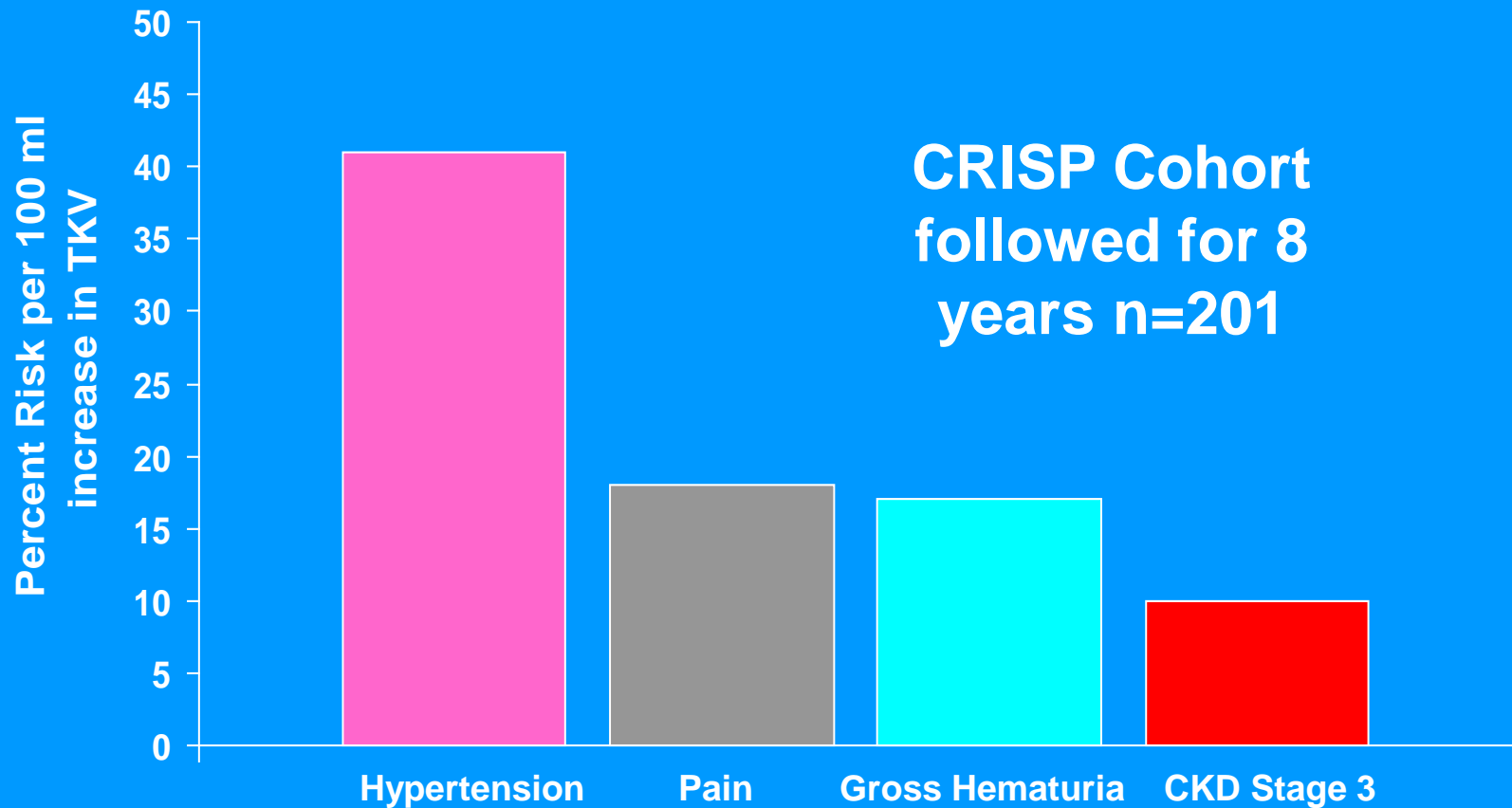
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# Renal Morbidities Associated With ADPKD



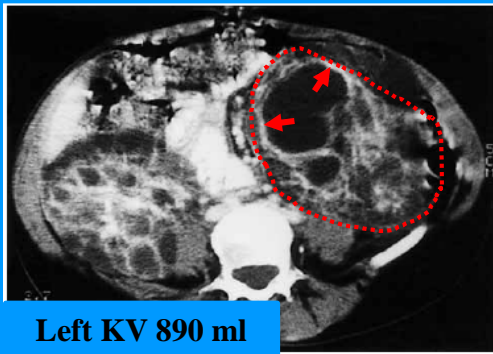
*By age 30, over 50% have at least one complication*

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



# Renal Events in ADPKD Result in Significant Pain

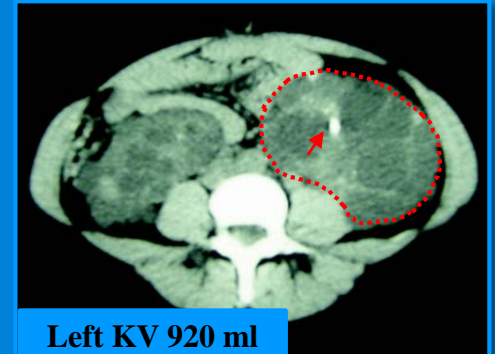
## Cyst Infection



Left KV 890 ml

- 20 Y Female
- Acute left flank pain
- eGFR 106

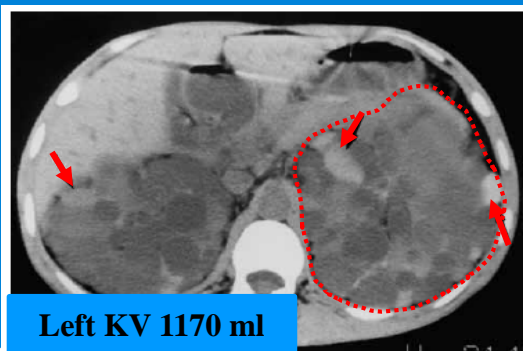
## Nephrolithiasis



Left KV 920 ml

- 35 Y Male
- Acute left flank pain

## Cyst Hemorrhage



Left KV 1170 ml

- 32 Y male
- Acute onset left flank pain
- eGFR 80

## Nephrectomy for Pain



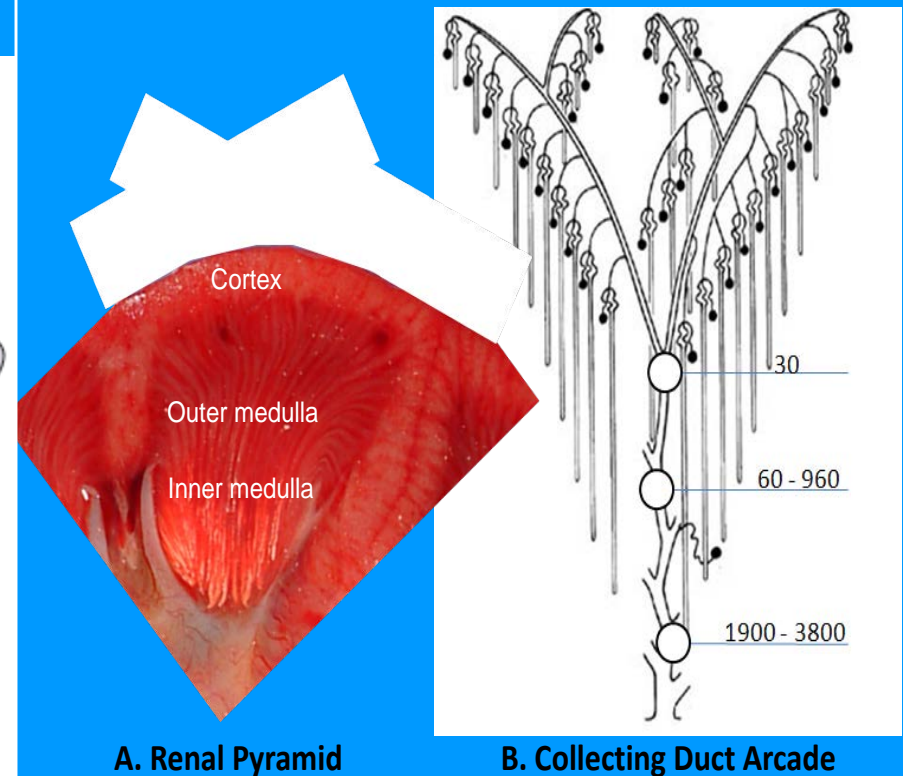
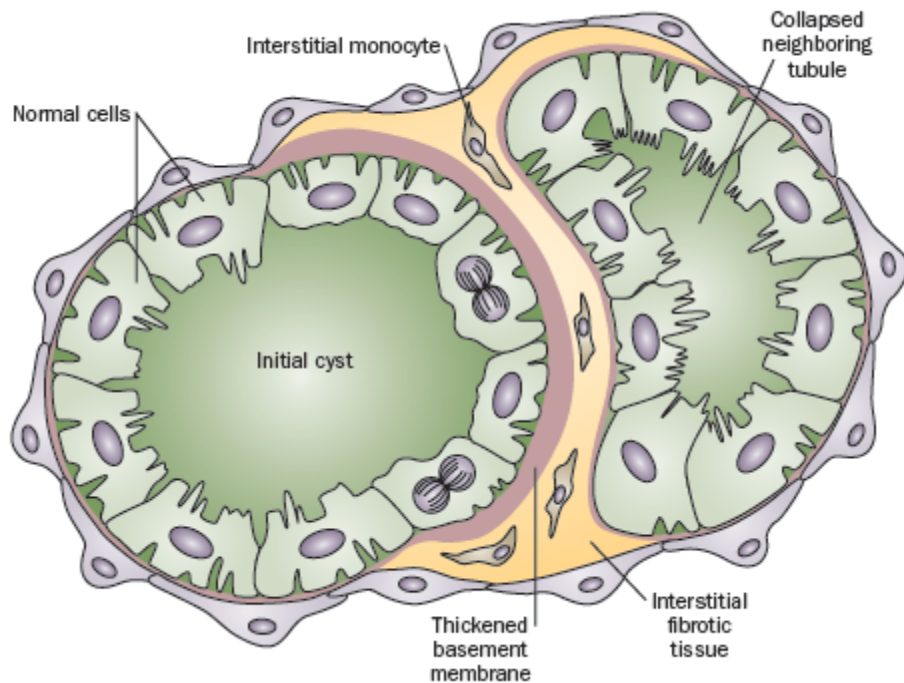
- 52 Y Male
- Chronic pain
- Kidney Weight: 21.5 kg

# Renal Cysts are the Hallmark and Primary Protagonists of Progressive Renal Insufficiency

## Cysts

- Compress adjacent tubules
- Generate interstitial inflammation
- Obstruct urine flow

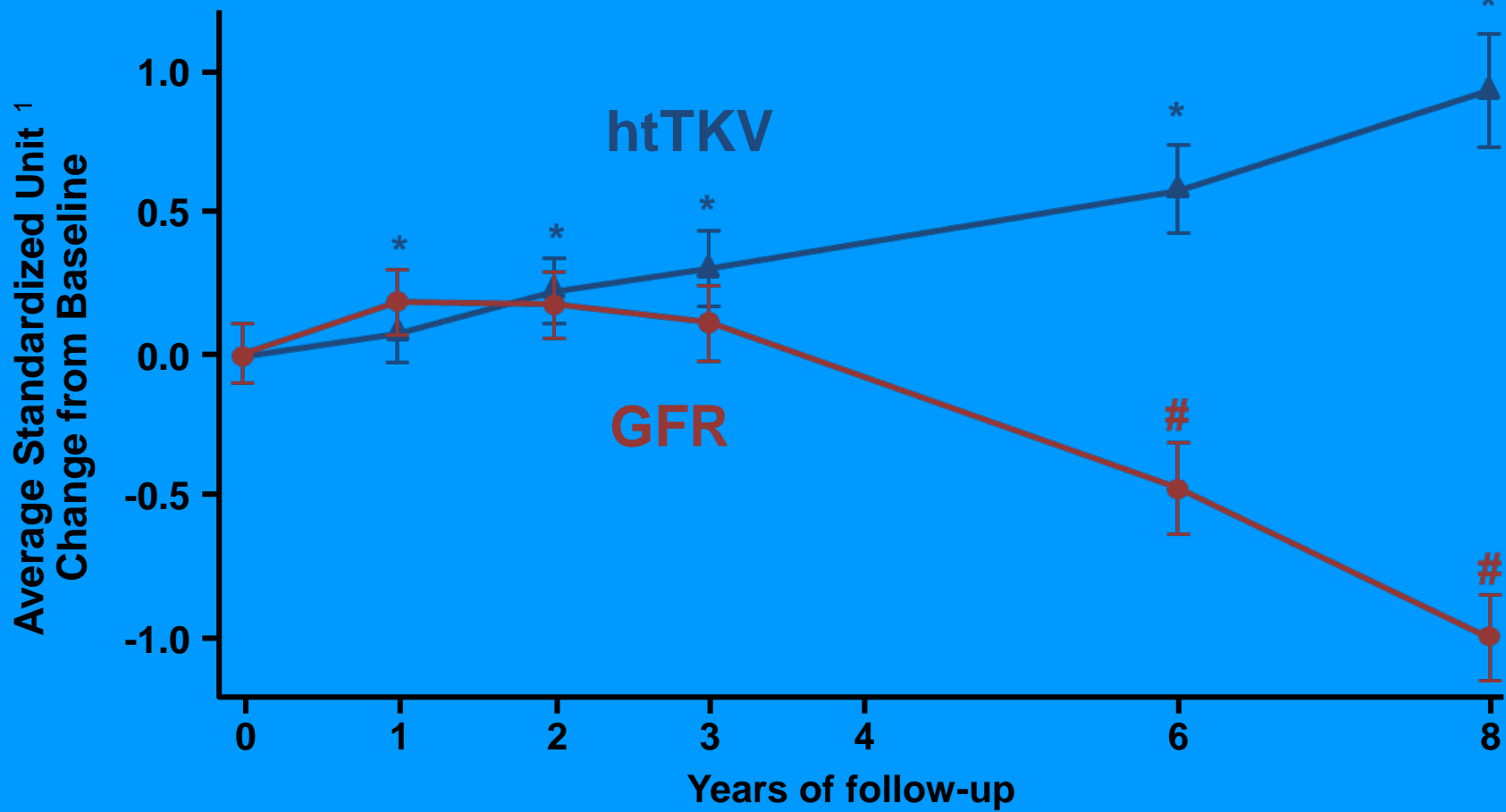
- Collecting duct cysts important
- Drain upstream nephrons



A. Renal Pyramid

B. Collecting Duct Arcade

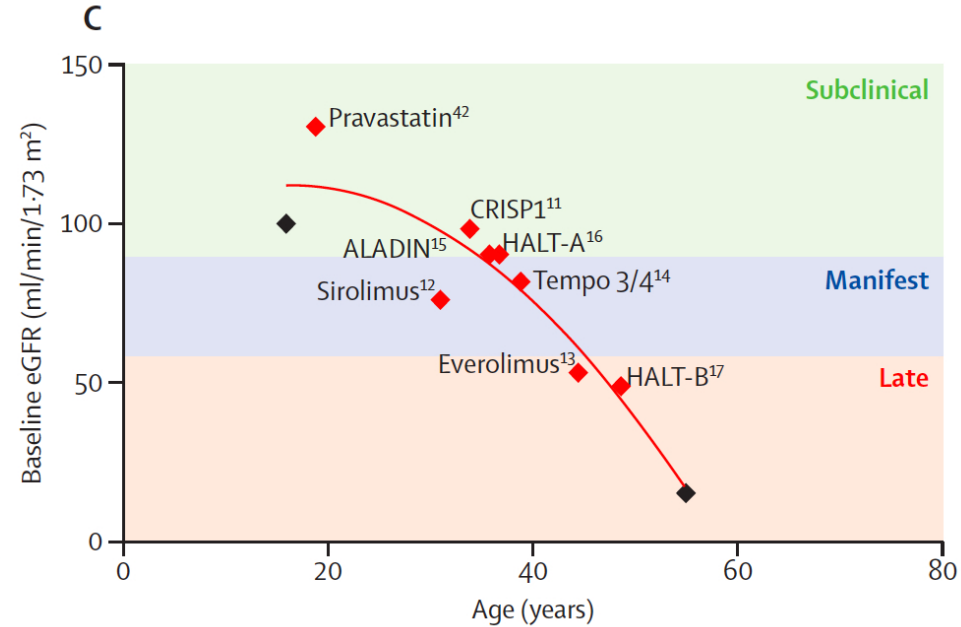
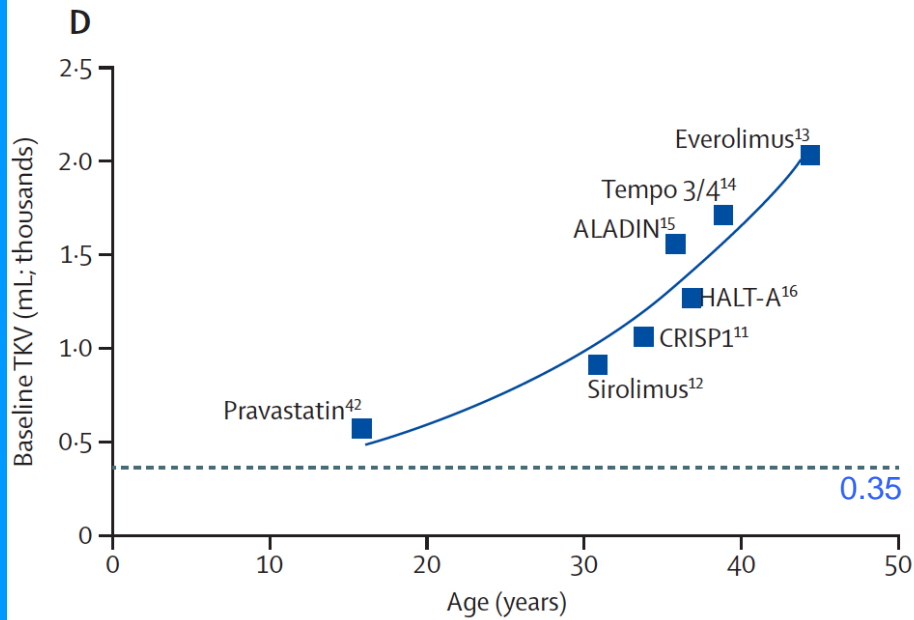
# Change in Kidney Volume Precedes Change in Kidney Function



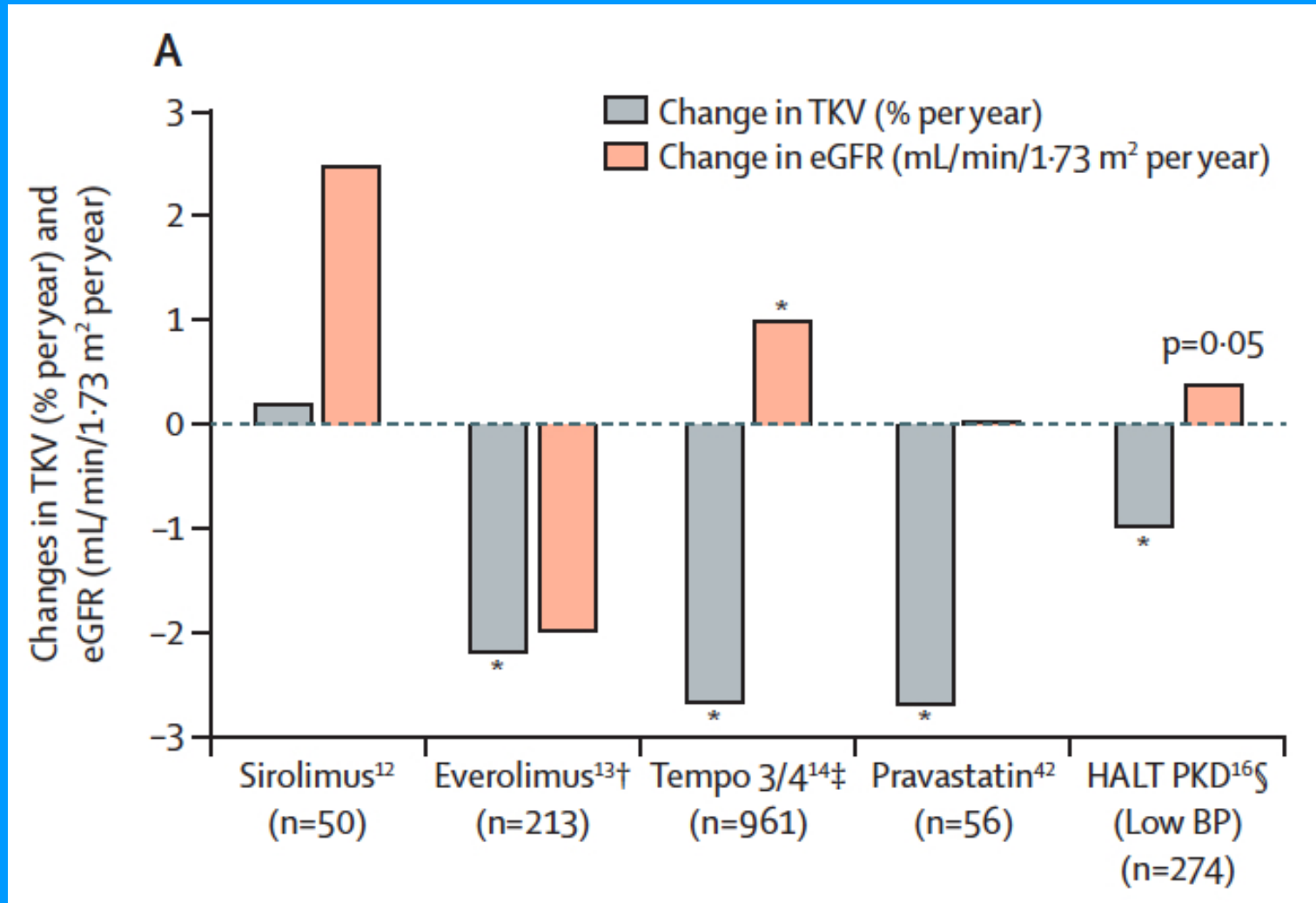
p<0.05 for htTKV change from baseline; # p<0.05 for GFR change from baseline; htTKV=Height-adjusted total kidney volume; <sup>1</sup> Percent Change Standardized to a common unit; NIH CRISP Studies; Chapman CJASN 7:479, 2012



# Baseline TKV and eGFR in ADPKD clinical trials



# Effect of therapeutic interventions

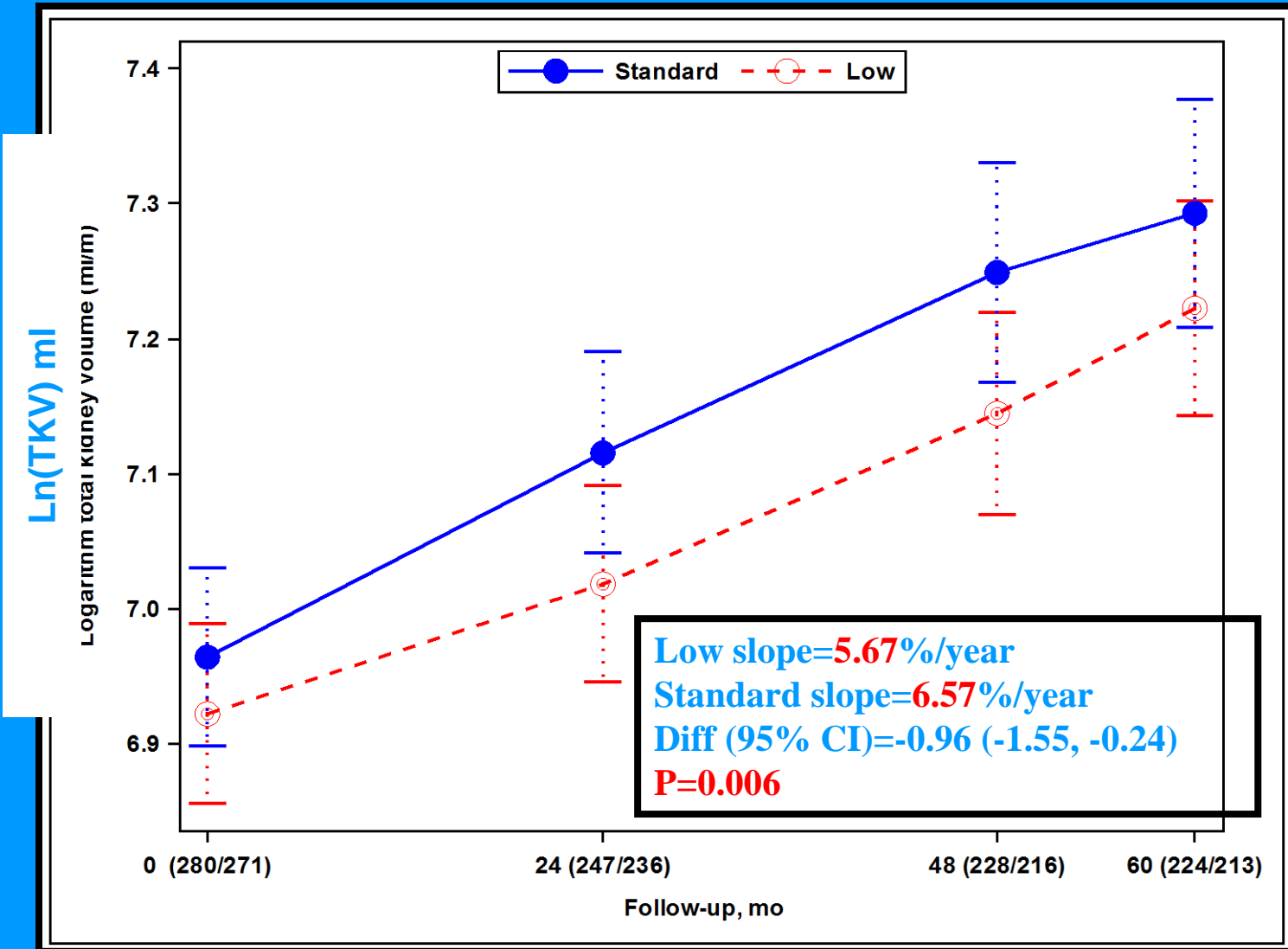


# Classification of ADPKD patients

## Pre-specified imaging findings

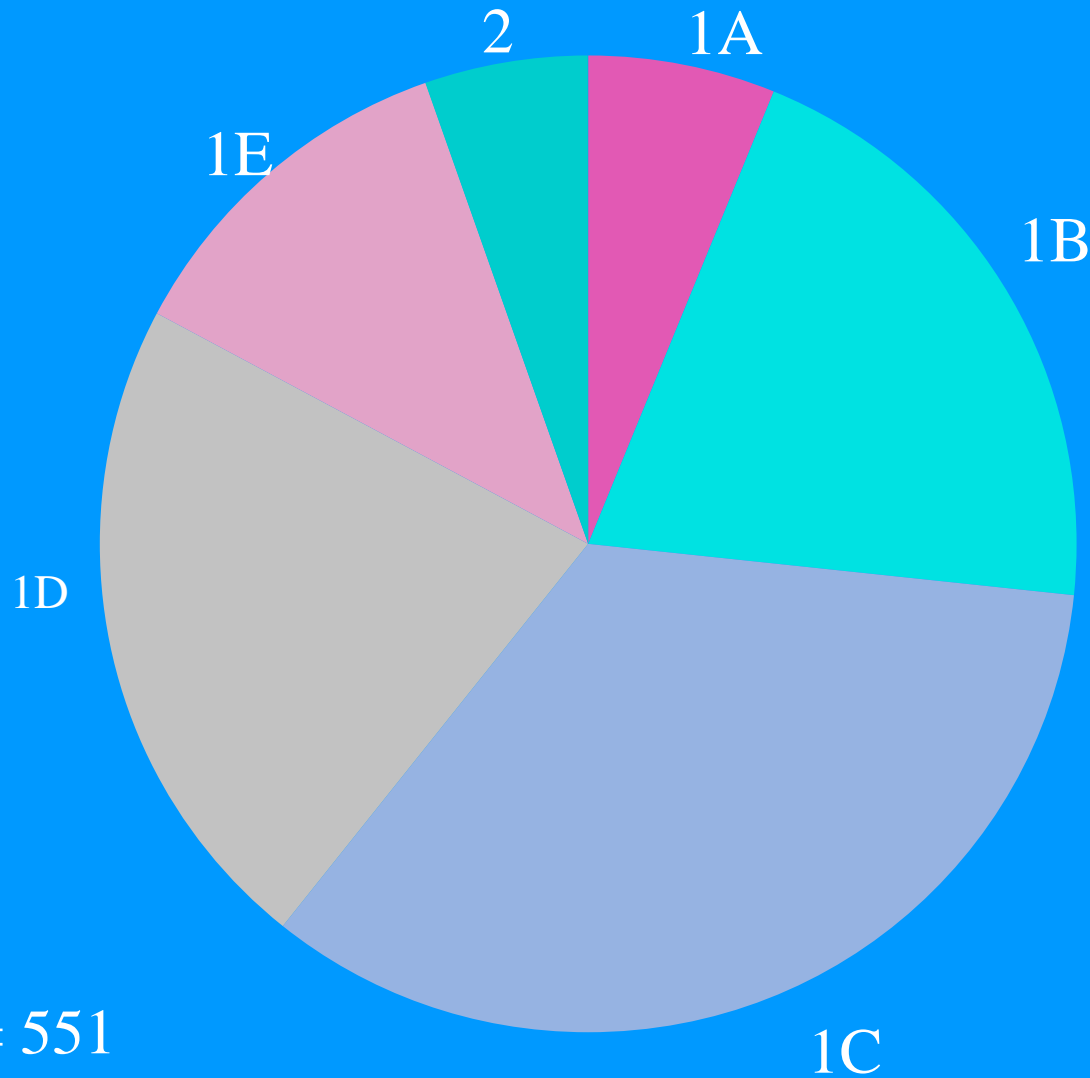
Class	Sub class	Term	Description
1	Typical ADPKD		<b>Cyst distribution is bilateral and diffuse with relatively even contribution to TKV</b>
2	A	<i>Unilateral</i>	Normal contralateral kidney with $\leq 2$ cysts
		<i>Asymmetric</i>	Mild involvement of contralateral kidney with 3-9 cysts and $< 30\%$ of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

# Annualized % Change in TKV



# Post-Hoc Analysis: HALT PKD Study A

## Distribution of Patients by Class at Baseline

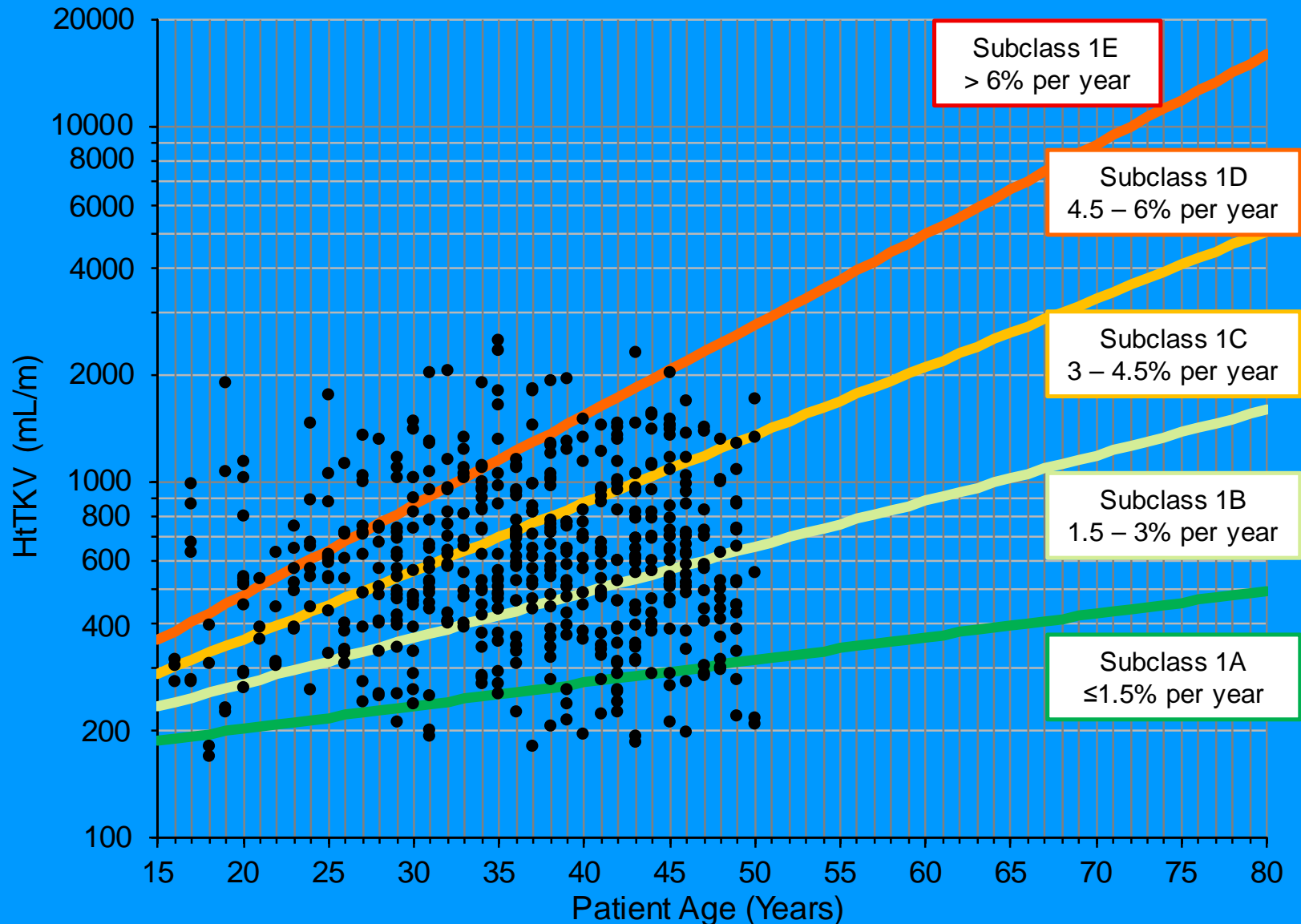


Class 1: 94.6%

Class 2: 5.4%

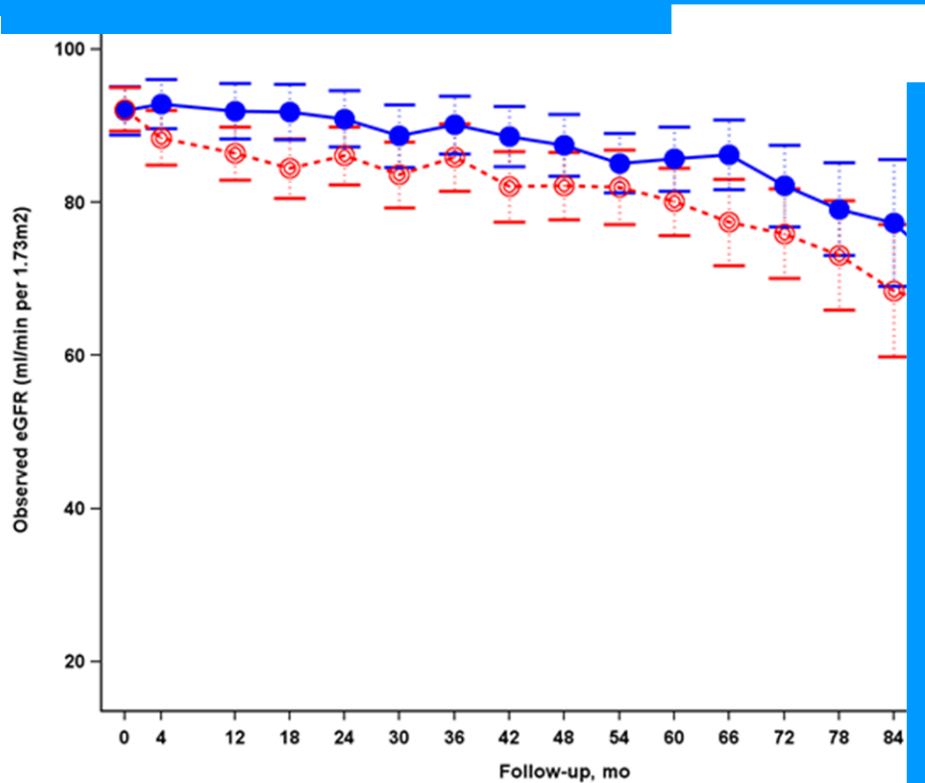
N = 551

# Image Classification of HALT PKD Study A Patients

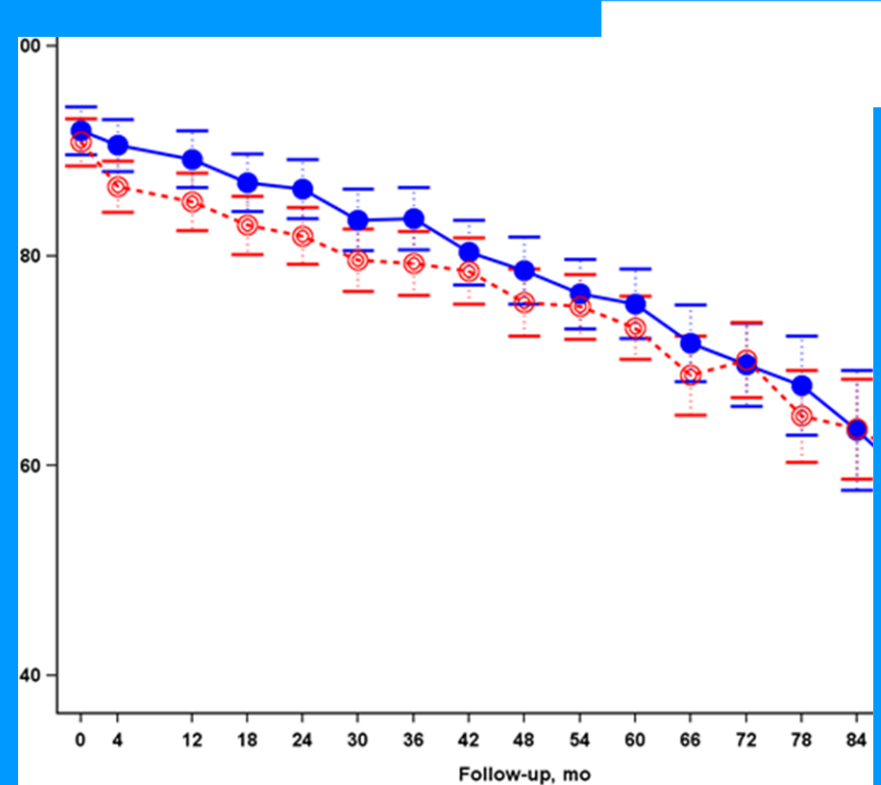


# eGFR Changes by Class at Baseline

## Class 1A and 2



## Class 1D and 1E



Standard BP

Low BP

# Value of Image Classification of ADPKD

## HALT PKD Study A as a Model

- 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



## Issues to consider:

- Does the type of intervention matter?
- Does the stage of disease matter?
- Does the imaging modality used matter?
- Is there sufficient evidence now to use TKV as a surrogate endpoint?
- What if any, are the limitations to consider TKV as a surrogate endpoint?



## Session: Can TKV be Qualified/Accepted as a Surrogate Endpoint?

Aliza Thompson



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- I think it is fair to say that there is a “diversity of opinion” within the FDA about whether TKV should be accepted as a surrogate endpoint for a treatment’s effect on progression to end-stage kidney disease in ADPKD.
- There has also been some discussion (but not a lot) about whether treatment effects on TKV could be used as a surrogate endpoint for a treatment’s effect on some of the later symptomatic manifestations of ADPKD.
- In the next few slides, I will provide (I hope) a reasonable description of what we have told sponsors about the acceptability of TKV as a surrogate endpoint. Obviously, you’ll have an opportunity to hear more from others at the FDA during the discussion.

- As discussed in the prior talk, accelerated approval allows for approval of a drug on the basis of a surrogate endpoint that is reasonably likely to predict clinical benefit. For drugs granted accelerated approval, postmarketing trials are generally required to verify the clinical benefit.
- We have told sponsor that **we would be willing to consider a “substantial” treatment effect on total kidney volume that persists after treatment withdrawal (i.e., one that does not reflect a reversible pharmacologic effect on total kidney volume but rather a structural effect on the disease) as a “reasonably likely” surrogate for effects on progression to end stage kidney disease** and hence basis for accelerated approval.
- Our concern (and the road block to date) : It seems unlikely that patients would remain on placebo for long after the drug is on the market, and hence we think it would be difficult to assure completion of a postmarketing trial verifying the clinical benefit. More on this issue in the afternoon session...

## Other issues that need to be worked out...

- What magnitude of an effect on TKV is needed/large enough to affect the outcome? Can we leverage existing data to better understand this issue?
- For therapies that are only thought to be effective early in the course of the disease, one also needs to consider whether the effect on TKV operates over a large enough fraction of the disease course as to lead to clinical benefit.

Generally speaking, there is greatest confidence in a candidate surrogate when there are data from intervention trials showing that treatment effects on a candidate surrogate endpoint reliably predict treatment effects on an outcome.

One perspective on the data supporting TKV as a validated surrogate endpoint: To date, the data supporting TKV as a surrogate endpoint in ADPKD have been mixed. On the one hand, there are epidemiologic data that show a relationship between increased renal volume and later renal function decline. However, findings in intervention trials, such as a phase 2 trial of everolimus (Walz et al, N Engl J Med 2010; 363:830-840) and the HALT-PKD trial (Schrier et al, N Engl J Med 2014; 371:2255-2266), have raised questions and concerns about the ability of treatment effects on TKV to reliably predict treatment effects on the progressive loss of renal function.

Although we haven't accepted TKV as a validated surrogate endpoint for full approval, we have indicated that we would view treatment effects on TKV as supportive of efficacy (i.e., could be used to help address the need for "substantial evidence of effectiveness").

I think it's also fair to say that if a therapy showed efficacy in later stages of disease, one could use effects on TKV in patients with early stages of disease as a means to extend the claim/indication to that population.

# Lunch

12:25 pm – 1:00 pm





### “Addressing the Need for Clinical Endpoints in ADPKD”

Time	Description	Comments / Notes
8:00 am	Breakfast	
8:30 am	Welcome / Objectives	Steve Broadbent
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3:30 pm	Wrap-Up / Next Steps	Steve Broadbent
4:00 pm	Close	



## Addressing Unmet ADPKD Needs Part 2: What are Other / Additional Endpoints that should be Considered?

Dr. Albert Ong



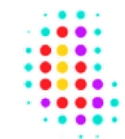
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# Other Additional Clinical Endpoints in ADPKD (Part 2)

Albert Ong  
Professor of Renal Medicine  
University of Sheffield, UK  
ADPKD Summit Meeting  
Bethesda



SheffieldKidneyInstitute



**Kidney Genetics Group**

Academic Unit of Nephrology  
University of Sheffield



The  
University  
Of  
Sheffield.

# Other potential end-points

- **Biomarkers of disease activity**
  - equivalent, additive or superior to TKV?
- **Clinical signs of disease onset**
  - early, preceding significant changes in TKV
- **Symptoms related to disease progression**
  - sensitivity of tools to measure, relationship to TKV

# Psychological impact of ADPKD on Quality of life

- Genetic predisposition → profound psychological burden
- **Uncertainty** about the future (renal prognosis)
- **Fear** (observed the effects in relatives)
- **Guilt** about risk to ones children
- Patient perspectives of adverse emotional strain & negative impact on quality of life **under recognised** (esp. early)
- Exacerbated by physical manifestations:  
fear of renal failure, rupture of an intracranial aneurysm
- Overall infrequently reported

# ADPKD and Quality of Life (QOL)

- **Health** “state of complete physical, mental and social well-being, not merely absence of disease” (WHO 1946)
- **QOL** multidimensional concept (1968)  
“individuals’ **perception of their position in life** in the context of the **culture and value** systems in which they live, in relation to their **goals, expectations, standards and concerns**”. (WHO 1994)
- How does **ADPKD** influence **QOL**?

# Sheffield ADPKD Psychosocial risk & QOL - Methods

Designed a postal questionnaire combining:

- KDQOL-SF1.3 (Quality of Life)
- 9 item Patient Health Questionnaire (PHQ-9, Depression)
- Multidimensional Scale of Perceived Social Support (MSPSS)  
– perception of interpersonal relationships

A novel, modified, Genetic psychosocial risk instrument (GPRI),  
**GPRI\_ADPKD** (psychosocial impact of living with ADPKD)

- 349 patients, **not** on renal replacement therapy

# Sheffield ADPKD Psychosocial risk & QOL - Conclusion

Patients with ADPKD report:

- Worse quality of life
- Increased psychosocial risk
- Depression

as kidney function declines and/or kidney size increases.

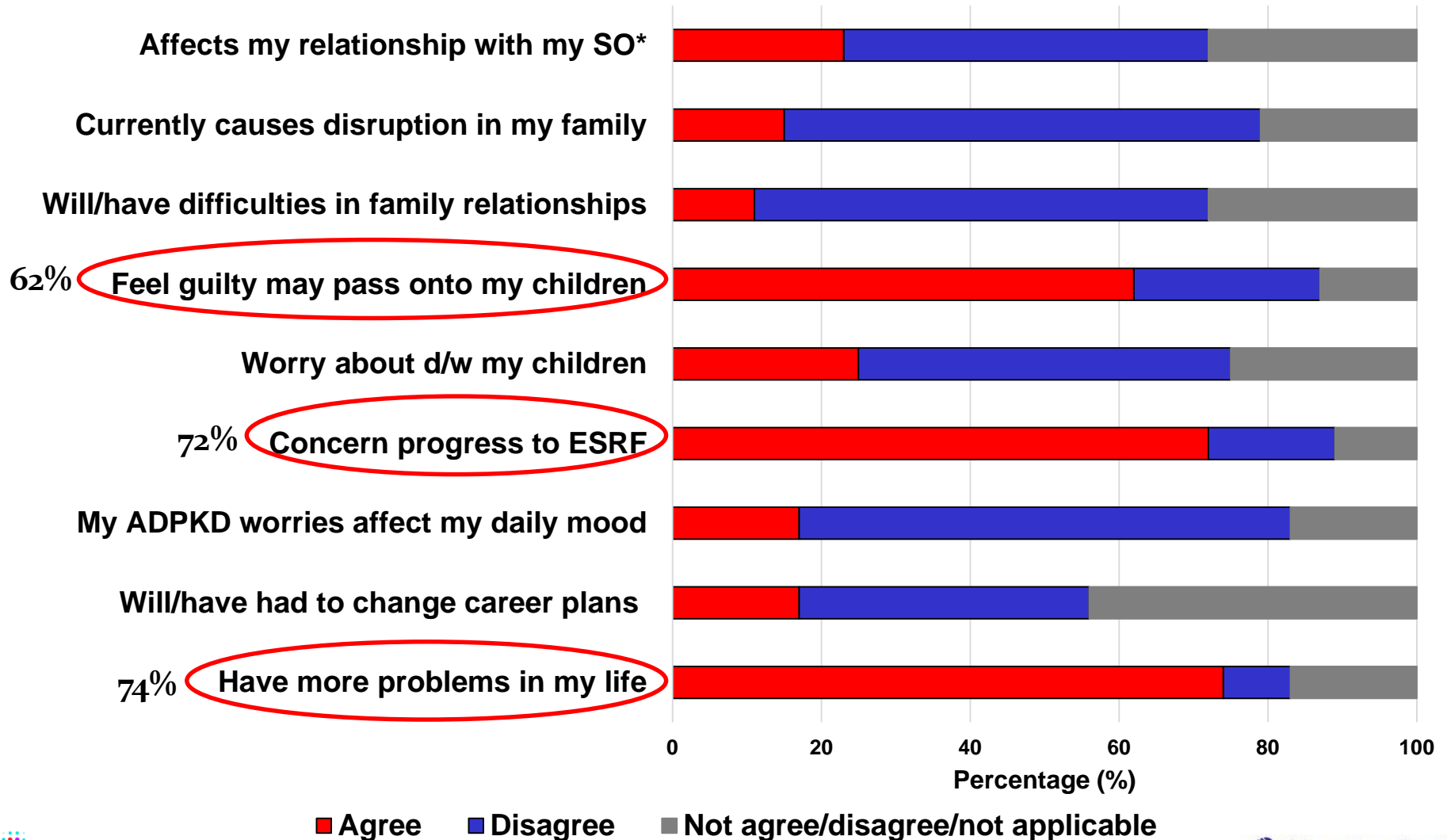
Female gender – uniform, independent risk for adverse psychological wellbeing

**Highlights** the need to improve the recognition & provide support services for patients & their families



# Sheffield ADPKD Psychosocial risk & QOL – Results (5)

\*SO significant other



Simms, NDT 2015

# Patient's perspective on being diagnosed with ADPKD

“My diagnosis came at a really difficult time, I was struggling with all the usual adjustments to having 2 young children and I was looking forward to getting my body back & feeling healthy again. The diagnosis was **like a cloud forming over me**. Knowing **how it affected my mother and grandfather**. It was especially hard knowing that I **may have passed it on** to my children without knowing that was a risk when they were conceived. I was also **worried about their future**; watching their mother struggle, getting ill and worrying about me as I had done with my mother.”

# Further research in ADPKD and Quality of Life

- ADPKD KDIGO supplement, Chapman et al. KI 2015
  - research agenda: develop & validate ADPKD specific tools to measure psychosocial impact.
  - strategies to manage psychosocial issues
- European ADPKD Forum 2015 ([www.pkdinternational.org](http://www.pkdinternational.org))

## What does ADPKD mean for patients & families?

**“Profound emotional impact”:**

**Loss** – of the life hoped to live

**Uncertainty** – progression, family planning

**Fear** – ESRF, health insurance/occupation, children

Associated anxiety/depression

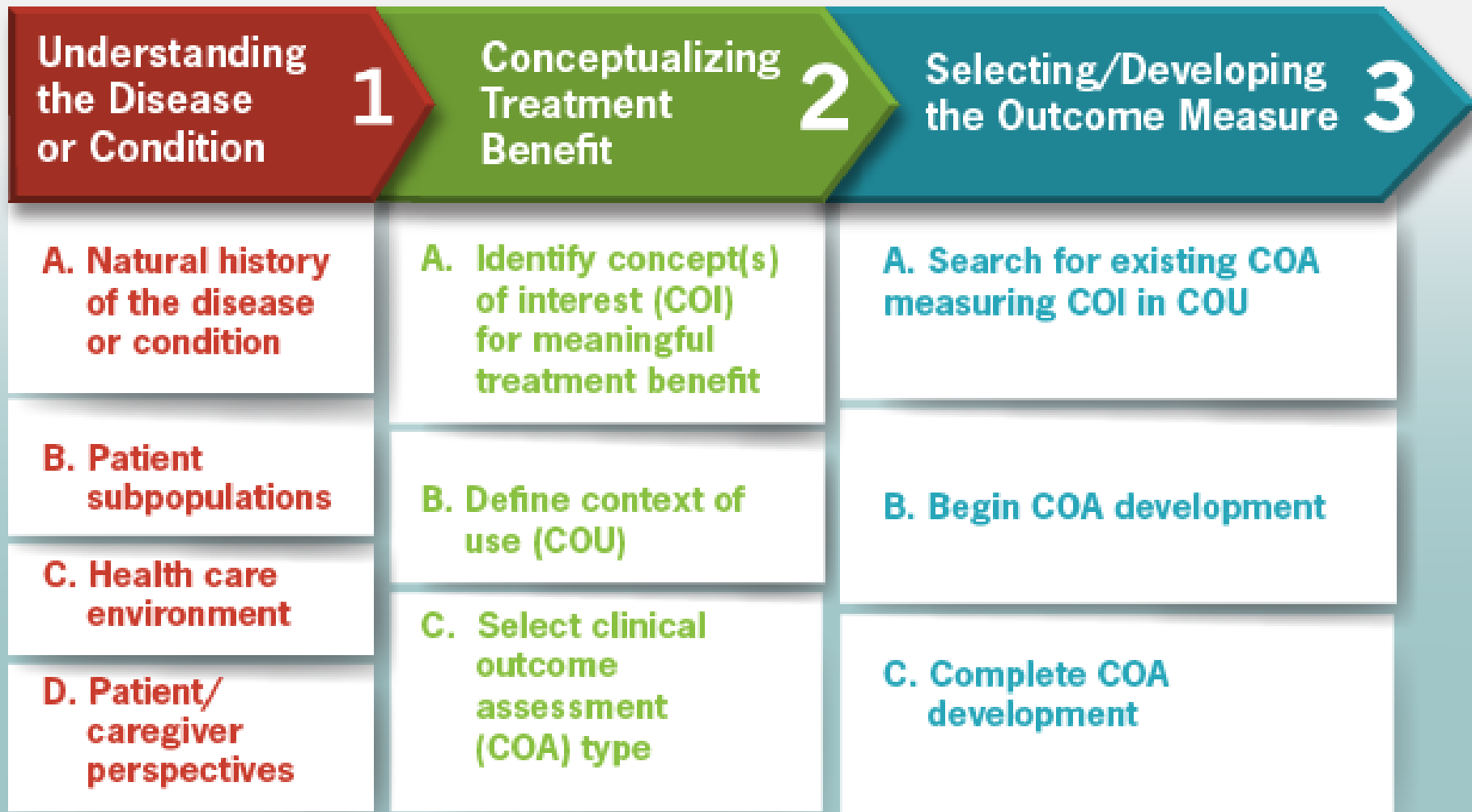
# Further research in ADPKD and Quality of Life (3)

**Patient perspectives** psychosocial impact living with ADPKD  
(> 18yrs, any stage CKD inc. RRT) Tong, NDT 2015

- Systematic review of qualitative studies. Identified 5 themes:  
**pain** (unvalidated/management),  
**uncertainties** (diagnosis, future),  
**genetic guilt** (family relationships, children),  
**parenthood** (anxiety of pursuing)  
**parental responsibilities** (PGD, normality vs disclosure)

Need for patient & MDT involvement to develop services

Roadmap to  
**PATIENT-FOCUSED OUTCOME MEASUREMENT**  
in Clinical Trials





## Understanding the Disease or Condition **1**

### A. Natural history of the disease or condition

- Onset/Duration/Resolution
- Diagnosis
- Pathophysiology
- Range of manifestations

### B. Patient subpopulations

- By severity
- By onset
- By comorbidities
- By phenotype

### C. Health care environment

- Treatment alternatives
- Clinical care standards
- Health care system perspective

### D. Patient/caregiver perspectives

- Definition of treatment benefit
- Benefit-risk tradeoffs
- Impact of disease

## Conceptualizing Treatment Benefit **2**

### A. Identify concept(s) of interest (COI) for meaningful treatment benefit, i.e., How a patient:

- Survives
- Feels (e.g., symptoms)
- Functions

### B. Define context of use (COU) for clinical trial:

- Disease/Condition entry criteria
- Clinical trial design
- Endpoint positioning

### C. Select clinical outcome assessment (COA) type:

- Patient-Reported Outcome (PRO)
- Observer-Reported Outcome (ObsRO)
- Clinician-Reported Outcome (ClinRO)
- Performance Outcome (motor, sensory, cognition)

## Selecting/Developing the Outcome Measure **3**

### A. Search for existing COA measuring COI in COU:

- Measure exists
- Measure exists but needs to be modified
- No measure exists
- Measure under development

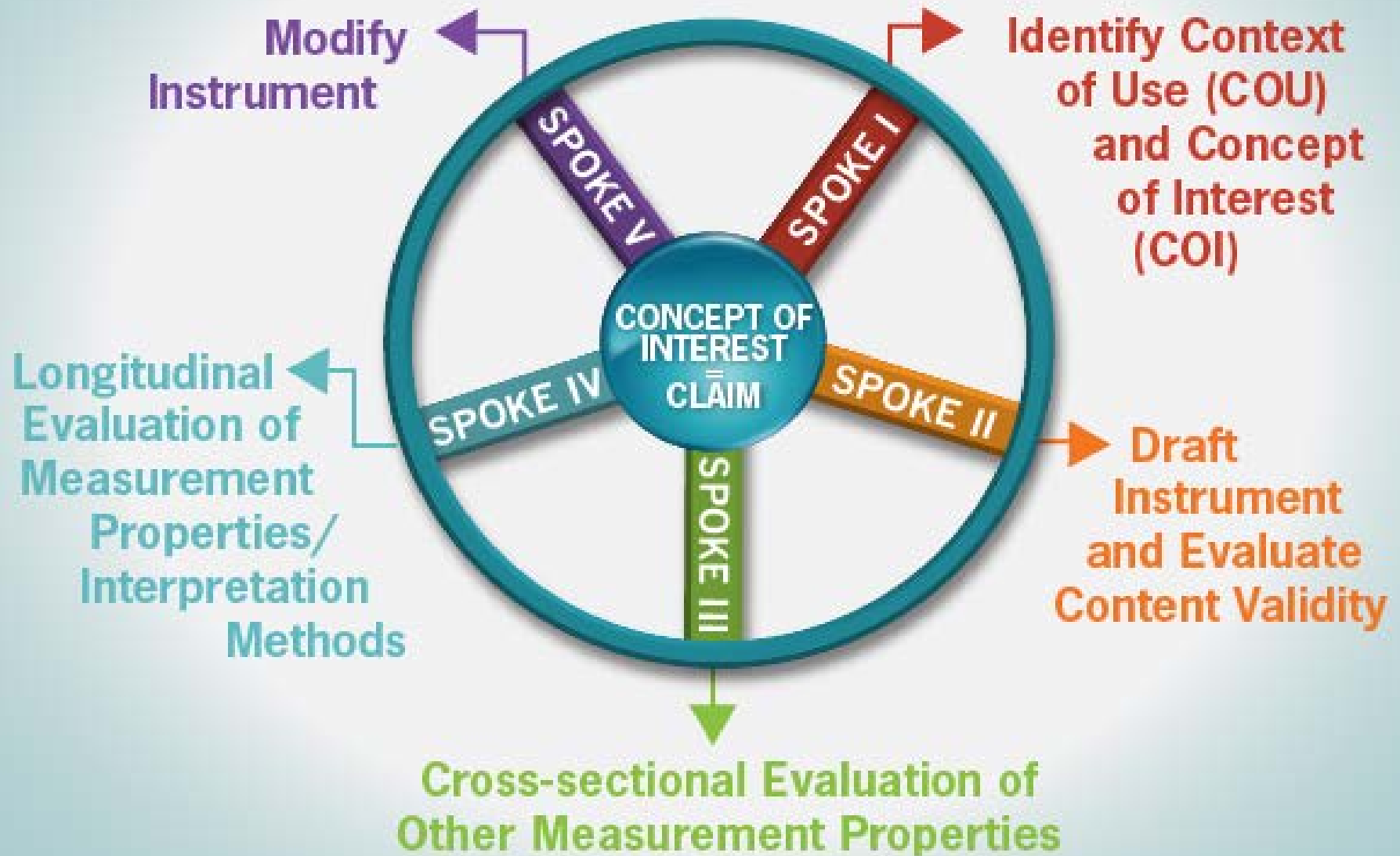
### B. Begin COA development

- Document content validity (qualitative or mixed methods research)
- Evaluate cross-sectional measurement properties (reliability and construct validity)
- Create user manual
- Consider submitting to FDA for COA qualification for use in exploratory studies

### C. Complete COA development:

- Document longitudinal measurement properties (construct validity, ability to detect change)
- Document guidelines for interpretation of treatment benefit and relationship to claim
- Update user manual
- Submit to FDA for COA qualification as effectiveness endpoint to support claims

# Qualification of **CLINICAL OUTCOME ASSESSMENTS** (COAs)



# Evidentiary Considerations for Performance Outcomes (For Discussion)

## V. Modify Instrument

- Identify a new COU
- Change instrument content (**includes procedures for administration/data collection**)
- Translate and culturally adapt
- Evaluate modifications using spokes I – IV
- Document all changes

**Consider submitting to FDA for qualification of new COA, as appropriate.**

## IV. Longitudinal Evaluation of Measurement Properties/ Interpretation Methods

- Assess ability to detect change and construct validity
- Identify responder definition(s)
- Provide guidelines for interpretation of treatment benefit and relationship to claim
- Document all results
- Update user manual

**Submit to FDA for COA qualification as effectiveness endpoint to support claims.**

## III. Cross-sectional Evaluation of Other Measurement Properties

- Assess score reliability and construct validity
- Confirm administration procedures & training materials
- Prepare user manual
- Document measure development

**Consider submitting to FDA for COA qualification for use in exploratory studies prior to longitudinal evaluation.**



## I. Identify Context of Use and Concept of Interest

- Obtain **patient and SME input** to determine concept of interest (concept measured should be of relevant and important to patients)
- Determine intended population
- Determine intended application/characteristics (type of scores, mode and frequency of administration)
- Perform literature/expert review
- Develop hypothesized conceptual framework (if the performance outcome is a composite of multiple scores)
- Position COA within a preliminary endpoint model

## II. Select or Create Instrument and Evaluate Content Validity

- **Define tasks that are intended to reflect aspects of daily functioning consistent with the concept of interest and patient population**
- **Generate evidence based on patient input that the tasks are appropriate for the population and reflect the concept of interest**
- **Develop administration procedures & training materials**
- **Pilot test Perfo to obtain patient and administrator input (including documentation of understanding) prior to larger scale studies**
- **Refine (as needed) and finalize instrument content**
- **Other ???**



# Break

2:30 pm – 2:40 pm



### “Addressing the Need for Clinical Endpoints in ADPKD”

Time	Description	Comments / Notes
8:00 am	Breakfast	
8:30 am	Welcome / Objectives	Steve Broadbent
8:45 am	Patient Perspectives	<b>“PKD Patient’s Perspective”</b> Dr. David Baron and Dr. Ron Perrone
9:05 am	Starting Point	<b>“Obstacles to Developing Medical Products for ADPKD”</b> Dr. Frank Czerwiec and Dr. Ron Perrone
9:25 am	Regulatory Perspectives	<b>“Regulatory Requirements for Drug Approval and Approval Pathways”</b> Dr. Aliza Thompson and Dr. Romaldas Mačiulaitis
9:45 am	Break	
10:00 am	Addressing Unmet ADPKD Needs (Part 1)	<b>“Can TKV be Qualified/Accepted as a Surrogate Endpoint?”</b> Moderator: Dr. Ron Perrone; Introduction: Dr. Arlene Chapman
11:30 am	Lunch	
12:15 pm	Addressing Unmet ADPKD Needs (Part 2)	<b>“What are Other / Additional Endpoints that should be Considered?”</b> Introduction and Moderator: Dr. Albert Ong
1:45 pm	Break	
2:00 pm	Addressing Unmet ADPKD Needs (Part 3)	<b>“How Do We Address the Challenges in Using Available Regulatory Pathways?”</b> Moderator: Dr. David Baron; Introduction: Dr. Frank Czerwiec
3:30 pm	Wrap-Up / Next Steps	Steve Broadbent
4:00 pm	Close	



# Addressing Unmet ADPKD Needs Part 3: Addressing the Challenges

Dr. David Baron and Dr. Frank Czerwiec



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- ADPKD is systemic, not just a kidney disease
- Science advances, but no treatments yet (for US)
- Need defined regulatory paths for drug approval
- Patients want therapies that:
  - are preventative (prevent RRT as long as possible)
  - not just palliative (RRT)
  - can start early to modify disease progression
  - have favorable benefit/risk, even if RRT delay is uncertain
- Many patients remain afraid to “come out”, only a few have shared their “voice”

- Slow Disease Progression (from birth, 6 decades to feared outcomes)
- Difficult to measure, clinically unrelatable endpoints
  - TKV – what does it mean to the patient; does it track the disease?
  - eGFR – what level of change is clinically relevant?
- Focus on secondary prevention at end of progression (ESRD)
- Desire to establish disease modification at first signs of progression (TKV)
- Use of surrogates is complicated and fraught with uncertainty
- Trials are difficult to perform to standard of “well-conducted”
  - Studied at tertiary “ADPKD centers of excellence”
  - Missing data
  - Non-compliance
- While rare, flexibility afforded rare diseases is uneven

# Regulatory Requirements

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- Definitions:
  - Endpoints
    - Outcomes vs Biomarkers
    - Meaningful vs Surrogate Endpoints
      - Surrogates: Validated (established) vs Reasonably Likely vs Candidate
- Approval Pathways:
  - US, EU, Canada, PMDA & Others?
  - Standard vs. Accelerated vs Conditional
  - Levels of Evidence
- Current thinking on Endpoints
  - A variety of options
  - A variety of scenarios

- Outcomes
  - Mortality
  - ESRD
  - ACM
  - Renal complications/symptoms
  - Non-renal complications/symptoms
- Surrogates:
  - eGFR
  - Total Kidney Volume (TKV)
  - ADPKD Outcomes (Composites?)
- More to be added based on final slides

## How do we address the challenges using available regulatory pathways?

- Incorporating the patient “voice”
- “Early” versus “Late” trials
- Reasonable endpoint(s) to target
- Evidence & confidence
- Overcoming regulatory uncertainty

## Discussion





# Thank You!

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