Autosomal Dominant Polycystic Kidney Disease: Issues Regarding Diagnosis

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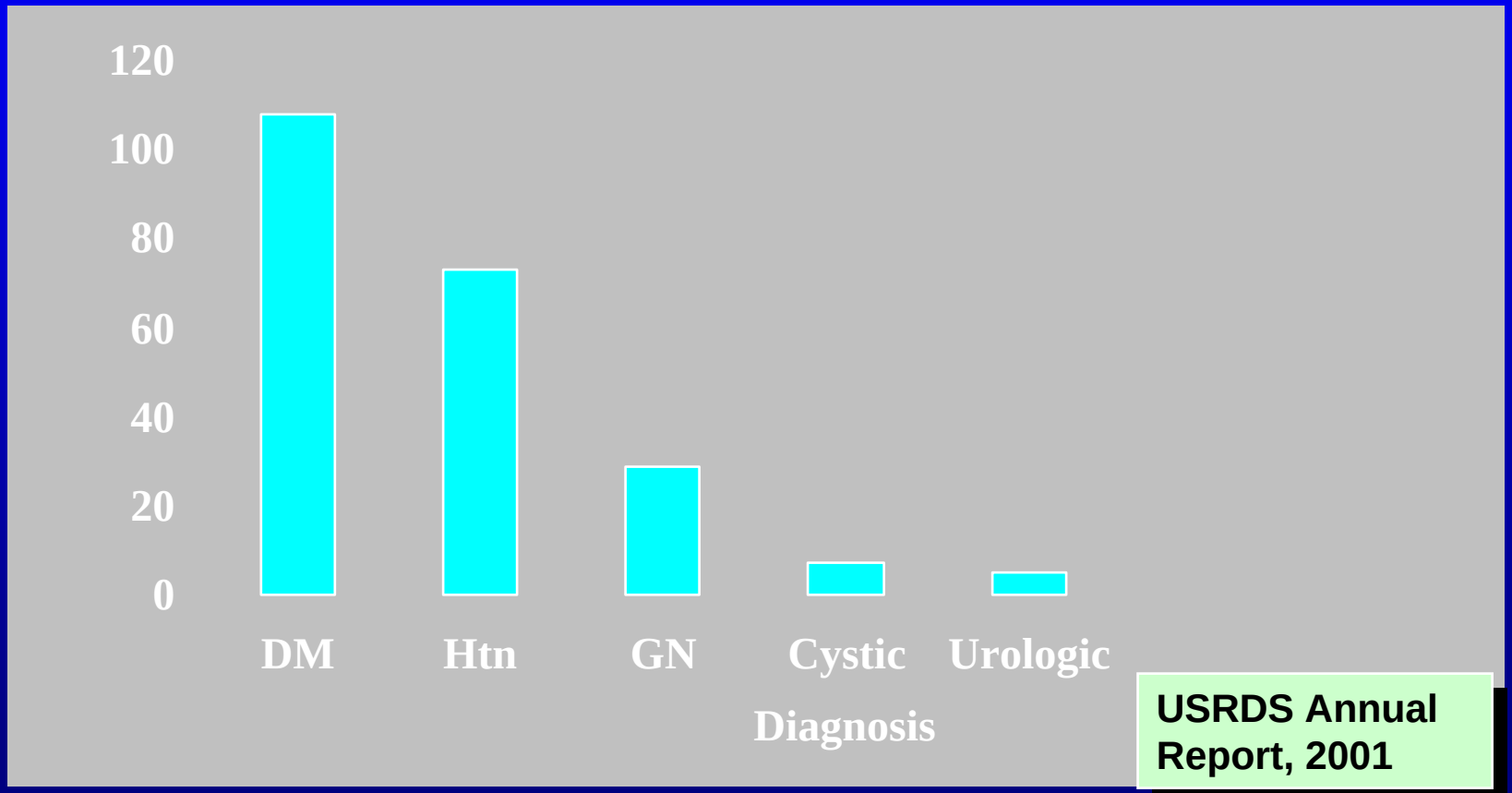
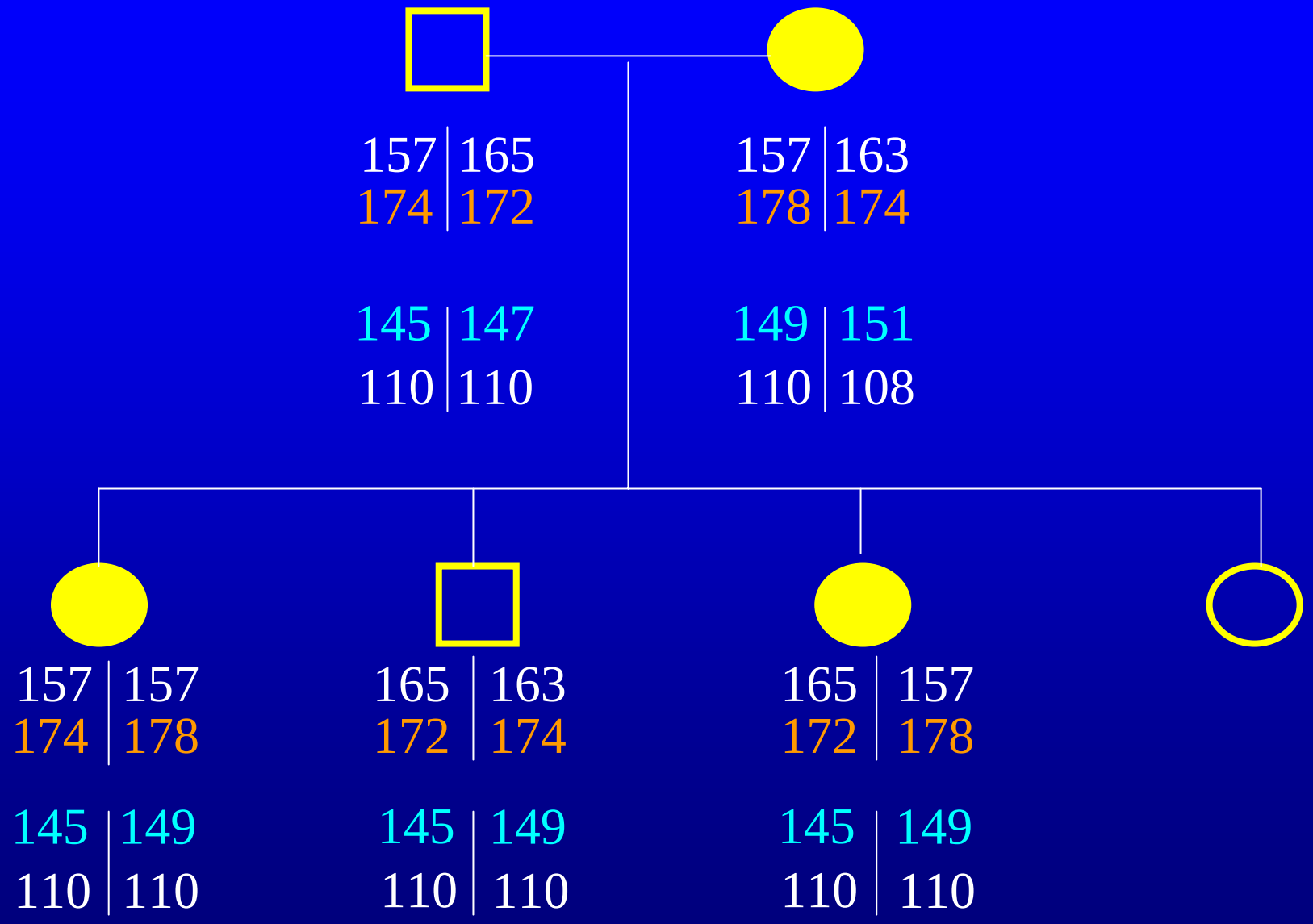
Mendelian Disorders of the Kidney

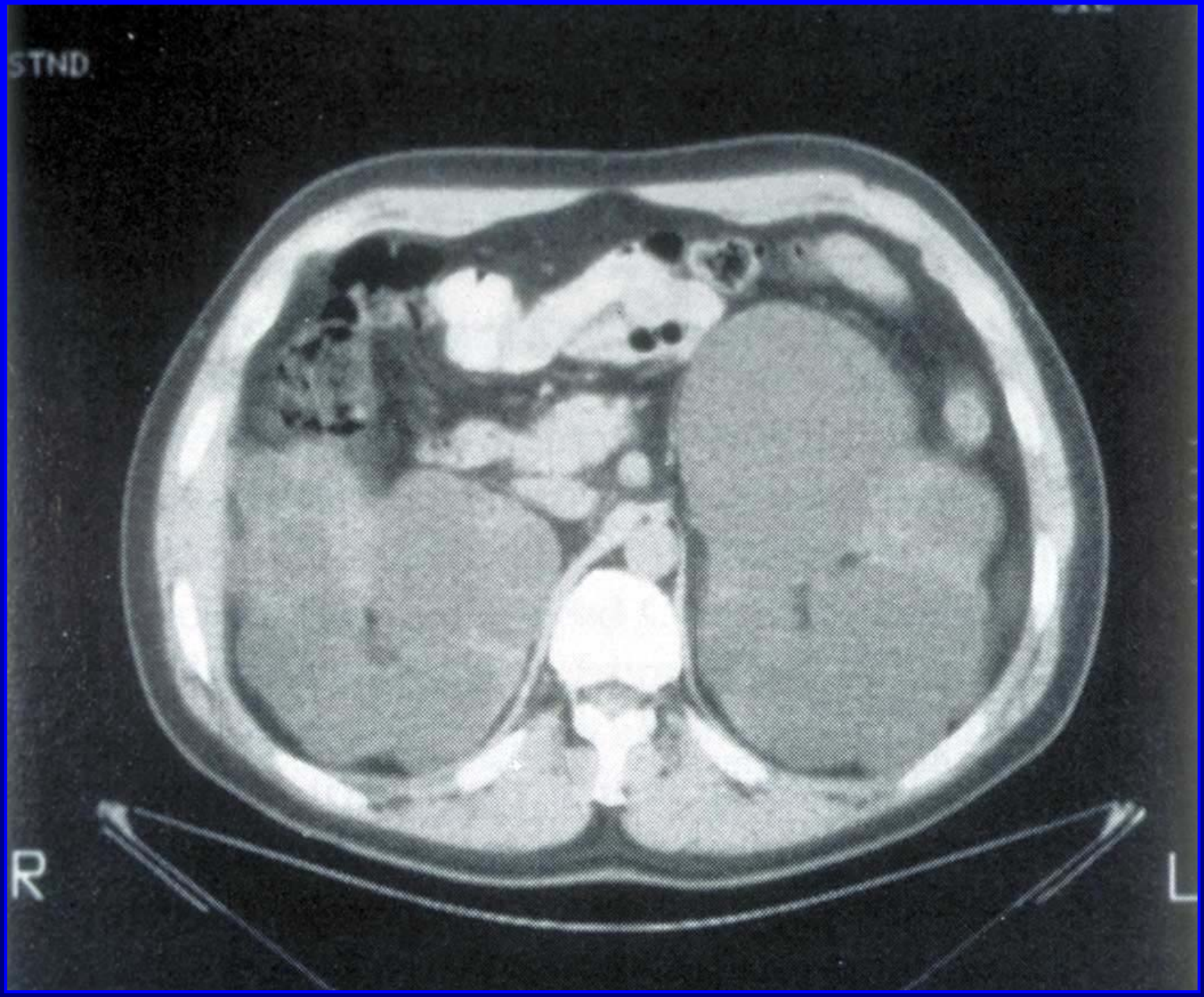
Autosomal Dominant *ADPKD*	50% chance of inheritance, men and women, vertical transmission through generations
Autosomal Recessive *ARPKD*	25% chance of inheritance, men and women, parents asymptomatic carriers
X-Linked *Alports'*	Affected mother: males and females offspring: 50% chance of inheriting disease
	Affected father: females 50% chance of inheriting disease

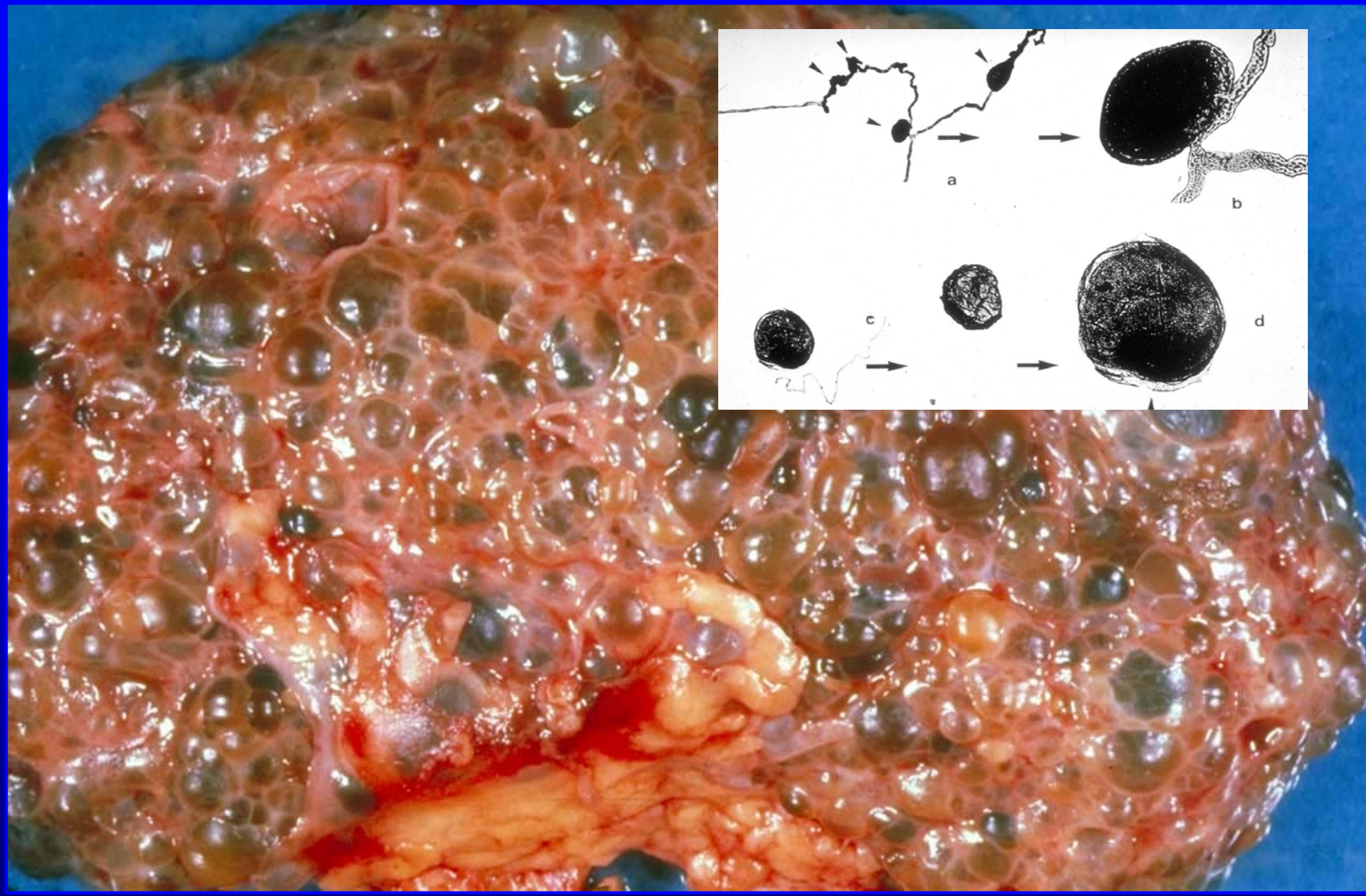
Incidence of ESRD by Diagnosis in the USA, 1996-1998



USRDS Annual Report, 2001


157 | 165
174 | 172
145 | 147
110 | 110
157 | 163
178 | 174
149 | 151
110 | 108
157 | 157
174 | 178
145 | 149
110 | 110
165 | 163
172 | 174
145 | 149
110 | 110
165 | 157
172 | 178
145 | 149
110 | 110


STND
R
L


a
b
c
d

Current Criteria for a Diagnosis of ADPKD

Family History

< 30 years:

2 cysts bilaterally

30-60 years:

4 cysts bilaterally

➢ 60 years:

8 cysts bilaterally

No Family History

5 cysts distributed bilaterally with a consistent phenotype

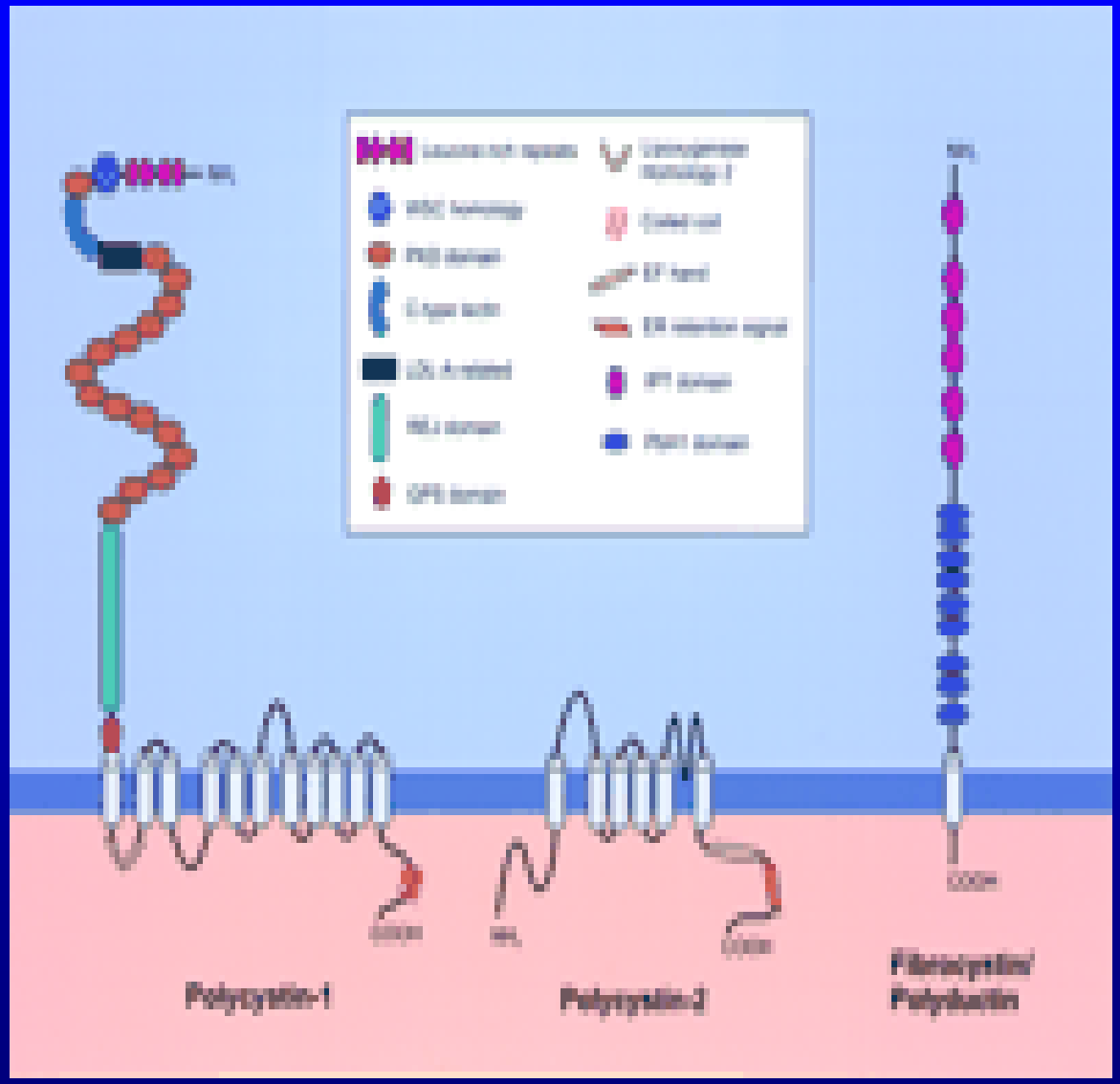
Ravine et al, Lancet 1994

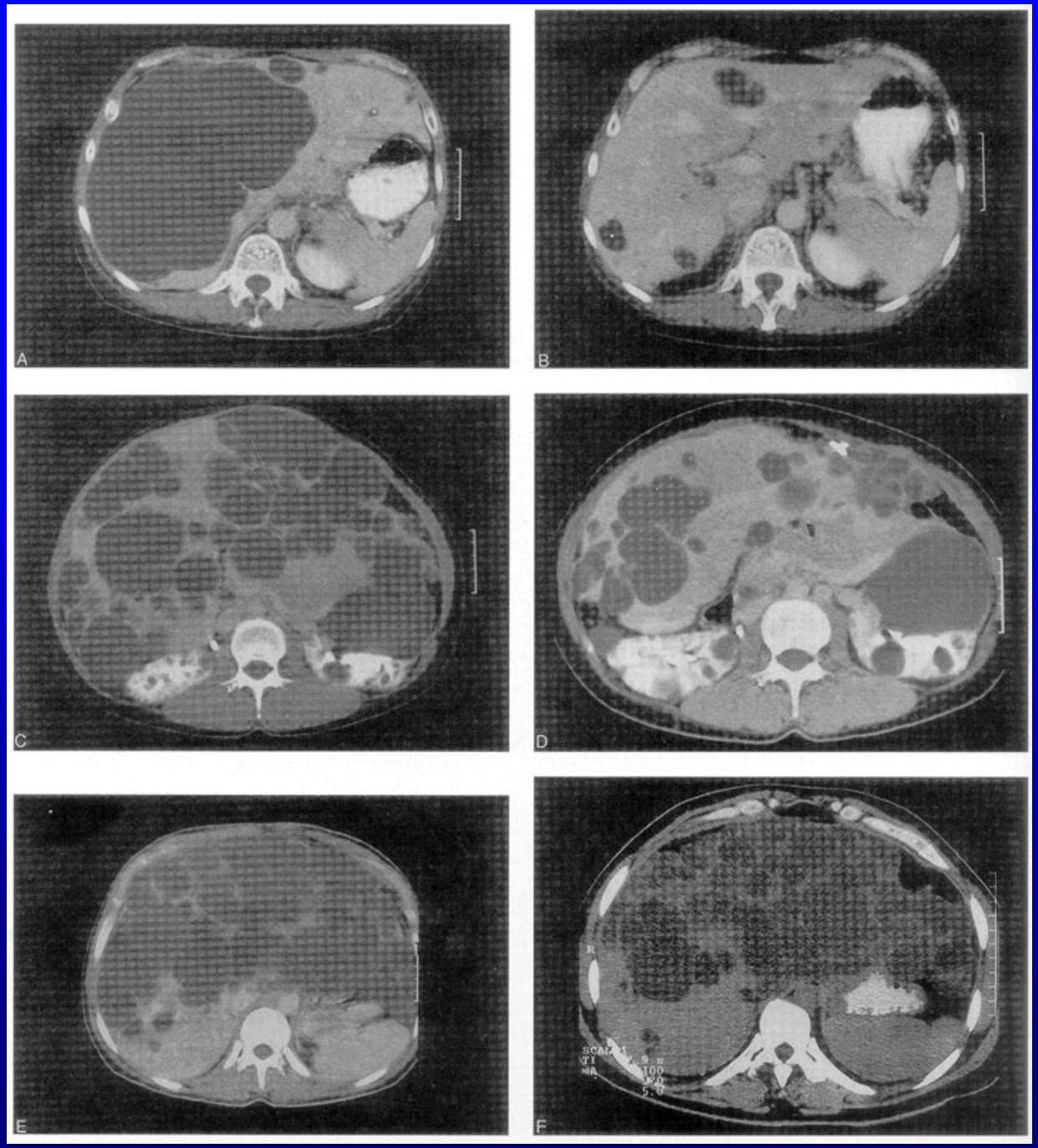
Phenotypic Characteristics of ADPKD

- > 95% PKD1 individuals demonstrate **renal cysts** by age 30
- > 50% of PKD1 individuals demonstrate **liver cysts** by age 30
- 5-8% of PKD individuals demonstrate asymptomatic **intracranial aneurysms**
- **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

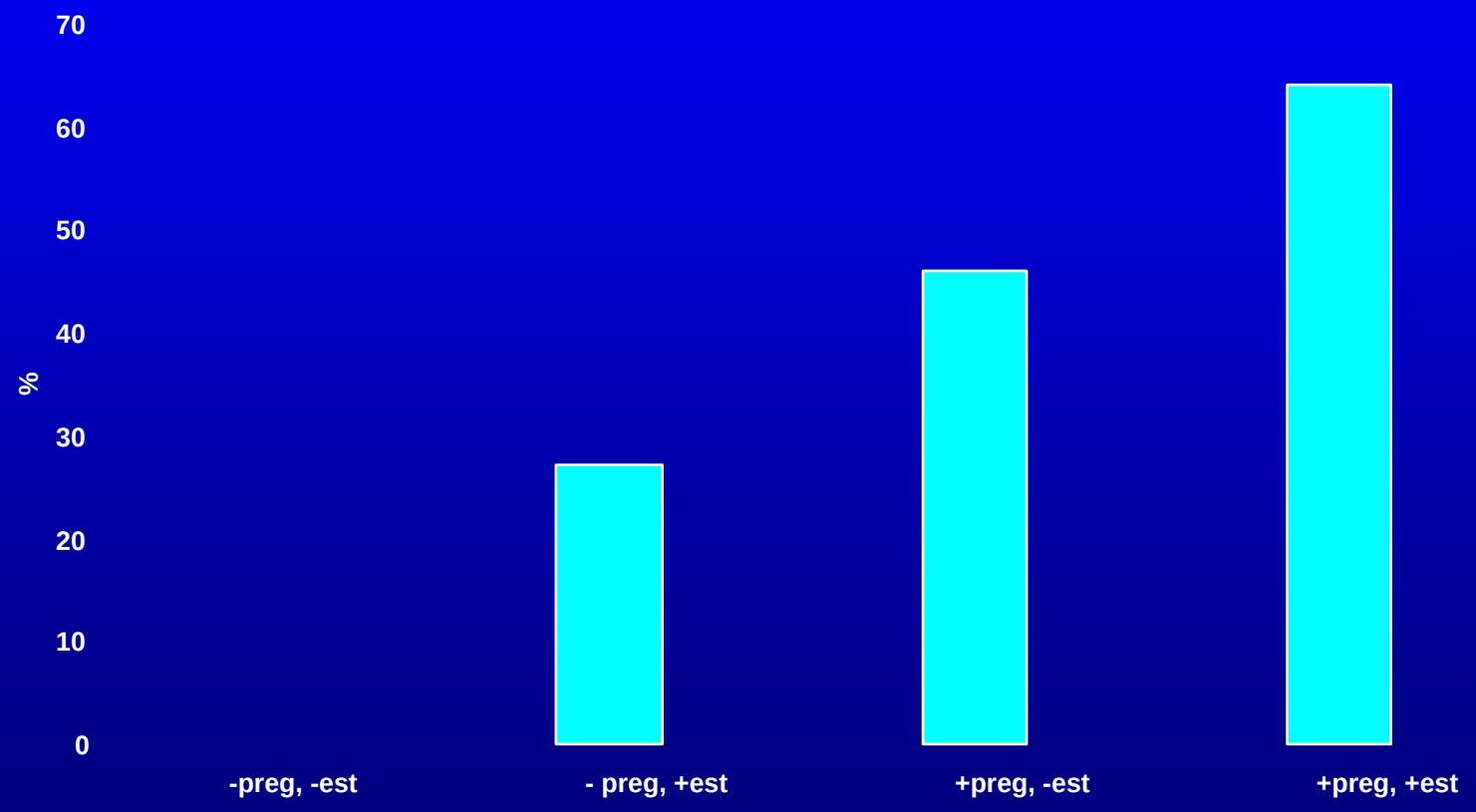
CYSTIC DISEASES OF THE KIDNEY

Disease	Freq	Chrom	Gene	Protein	Function
ADPKD	1:1,000	16p13.3 4q 21.2	Pkd1 Pkd2	Polycystin1 Polycystin2	Receptor? Ca activated cation channel
ARPKD	1:20,000	6q24.2	PKHD	Fibrocystin/ polyductin	Receptor
VHL	1:25,000	3p14.1	VHL	vhl	Tumor Suppressor
TSC	1:20,000	9q34.3 16p13.3	TSC1 TSC2	hamartin tuberin	Tumor Suppressor
MCD	1:50,000	16p13.1	?	?	?
FJN	1:15,000	2p13.1	NPHP1 NPHP4	nephrocystin	Cell-cell adhesion


Polycystin-1
Polycystin-2
Fibrocystin/
Polyductin


A
B
C
D
E
F

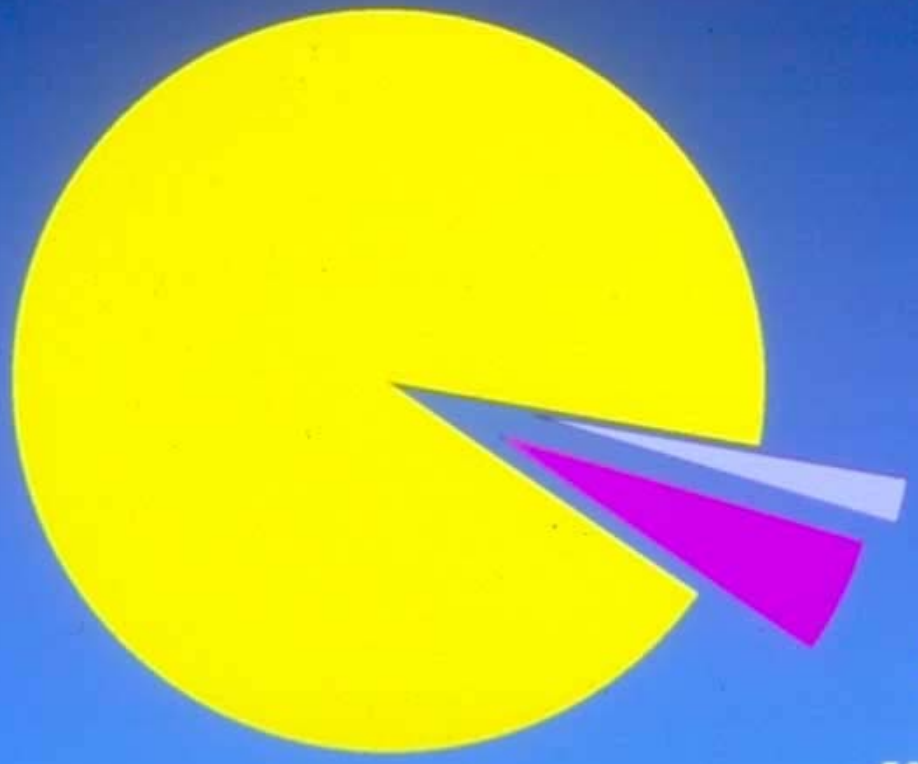
Prevalence of hepatic cystic disease in 85 ADPKD women stratified by pregnancy and estrogen use



Prospective screening for ICA in asymptomatic ADPKD subjects

	Torres (1990)	Chapman (1992)	Huston (1993)	Ruggieri (1994)
Method	CT/MRI	CT/Angio	MRA	MRA
n	96	88	85	93
ICA	0	4	9	10
Susp (n)	11	4	-	-
FH (%)	10	10	12	12

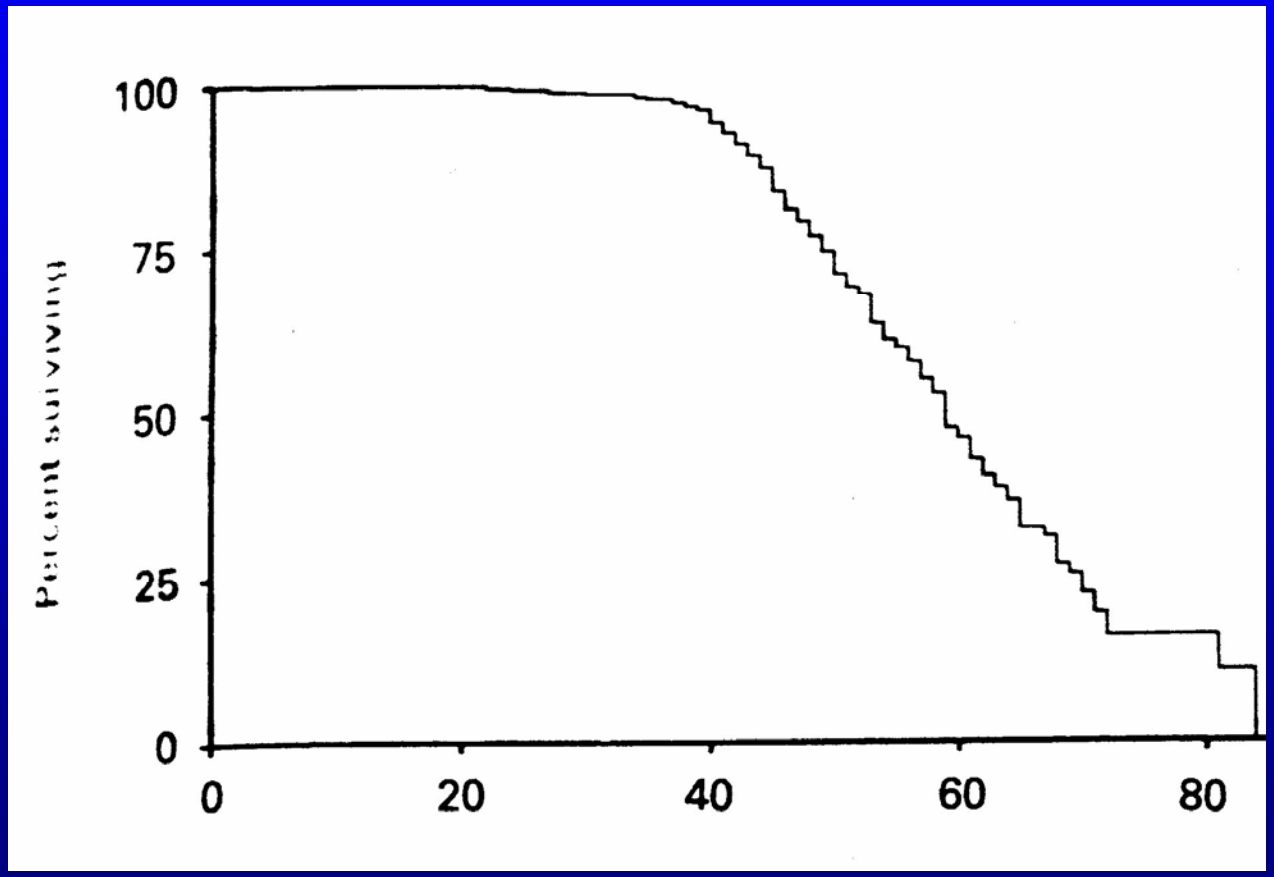
DISTRIBUTION OF 22 RICA AMONG 219 FAMILIES (CONFIRMED RICA)



> 1 ANEURYSM
2% OF FAMILIES
11 ANEURYSMS
50% OF ANEURYSMS

1 ANEURYSM
5% OF FAMILIES
11 ANEURYSMS
50% OF ANEURYSMS

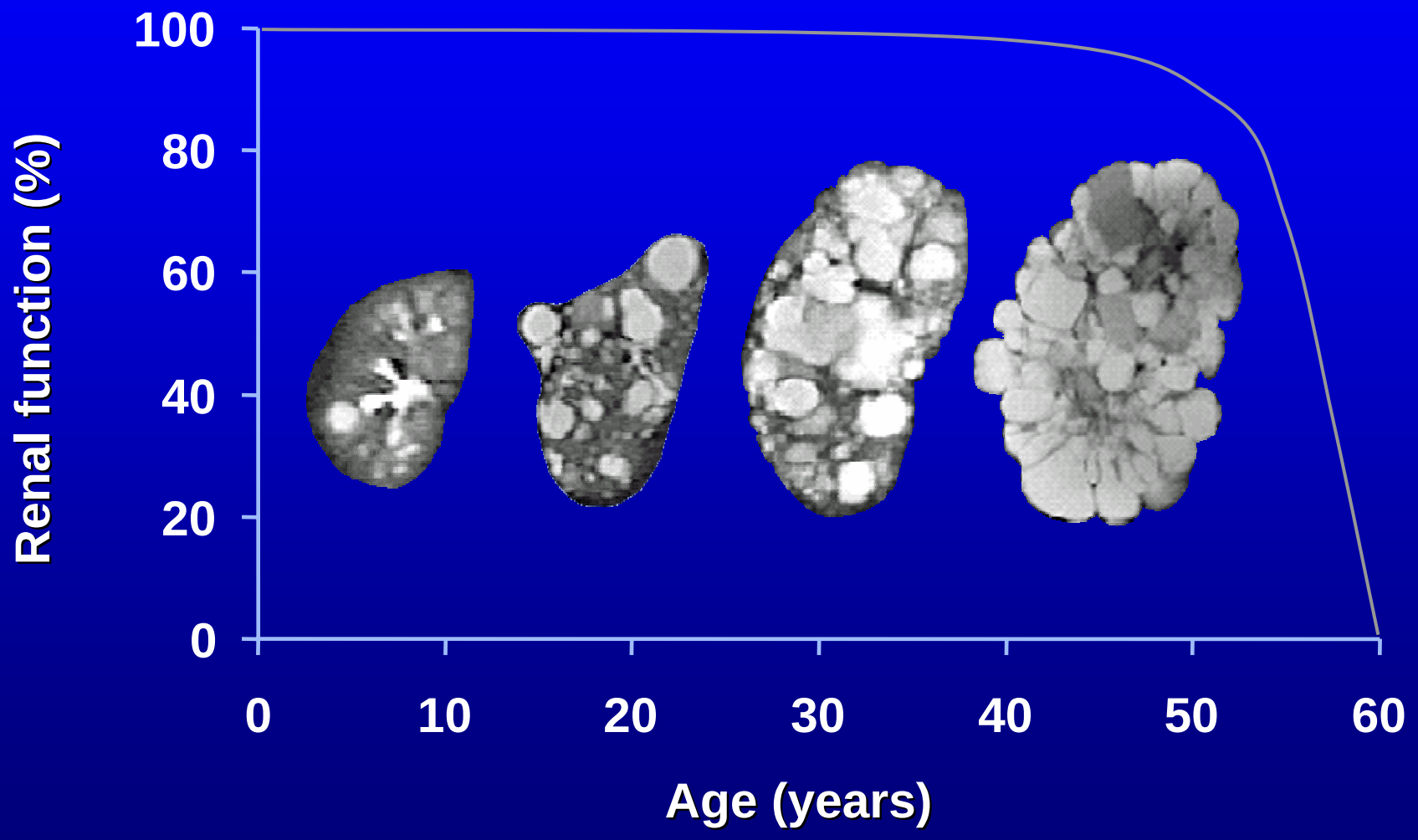
Cumulative Survival of ADPKD



Mean Age of ADPKD Patients with SCr > 1.5 mg/dl

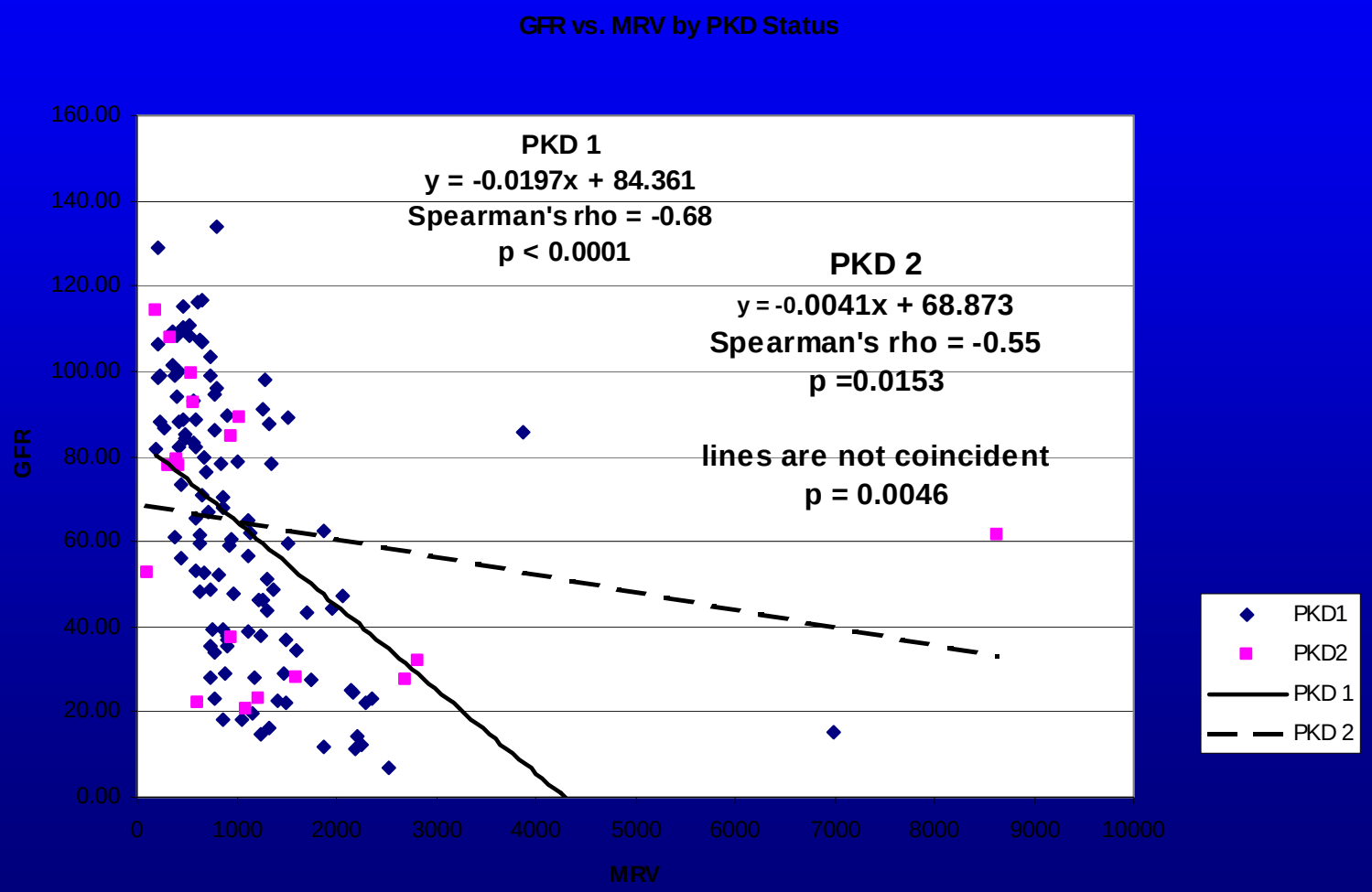
Manifestation	Yes	No
Male	41	54
PKD1 Gene	49	70
Hypertension	47	66
Hypertension + male	40	85

When to Treat and What to Measure?

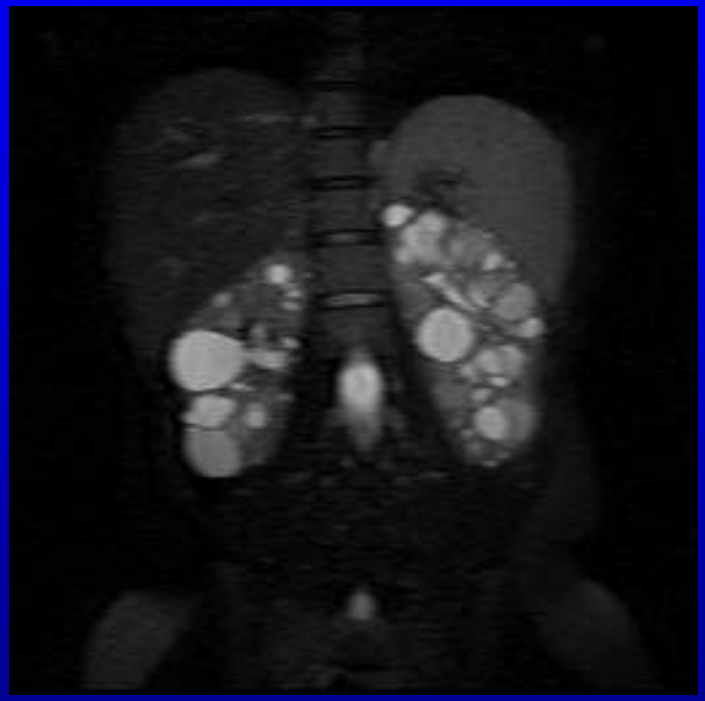


CP1047707-9

PKD1 vs PKD2

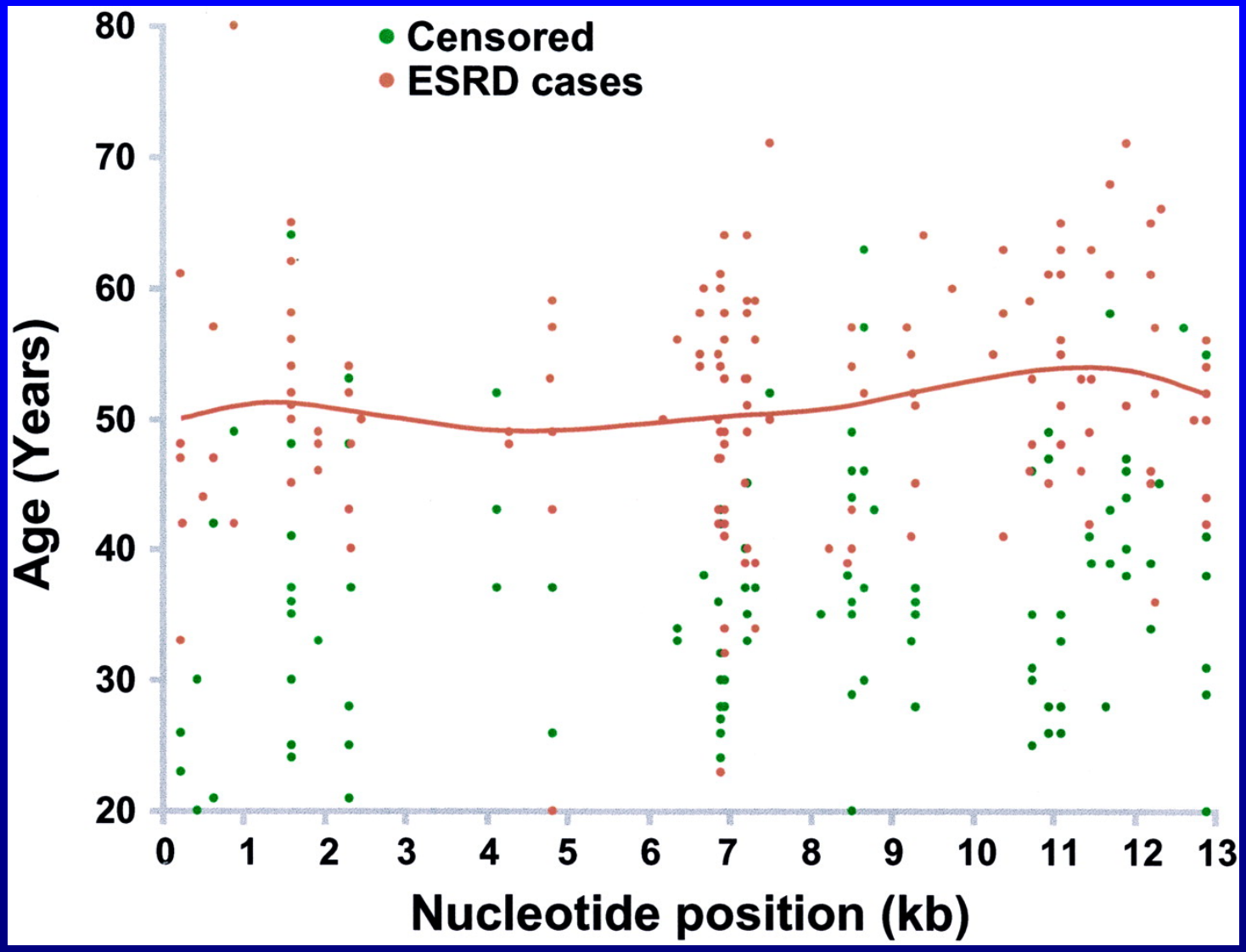

GFR vs. MRV by PKD Status
PKD 1
y = -0.0197x + 84.361
Spearman's rho = -0.68
p < 0.0001
PKD 2
y = -0.0041x + 68.873
Spearman's rho = -0.55
p =0.0153
lines are not coincident
p = 0.0046
GFR
MRV
160.00
140.00
120.00
100.00
80.00
60.00
40.00
20.00
0.00
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
PKD1
PKD2
PKD 1
PKD 2

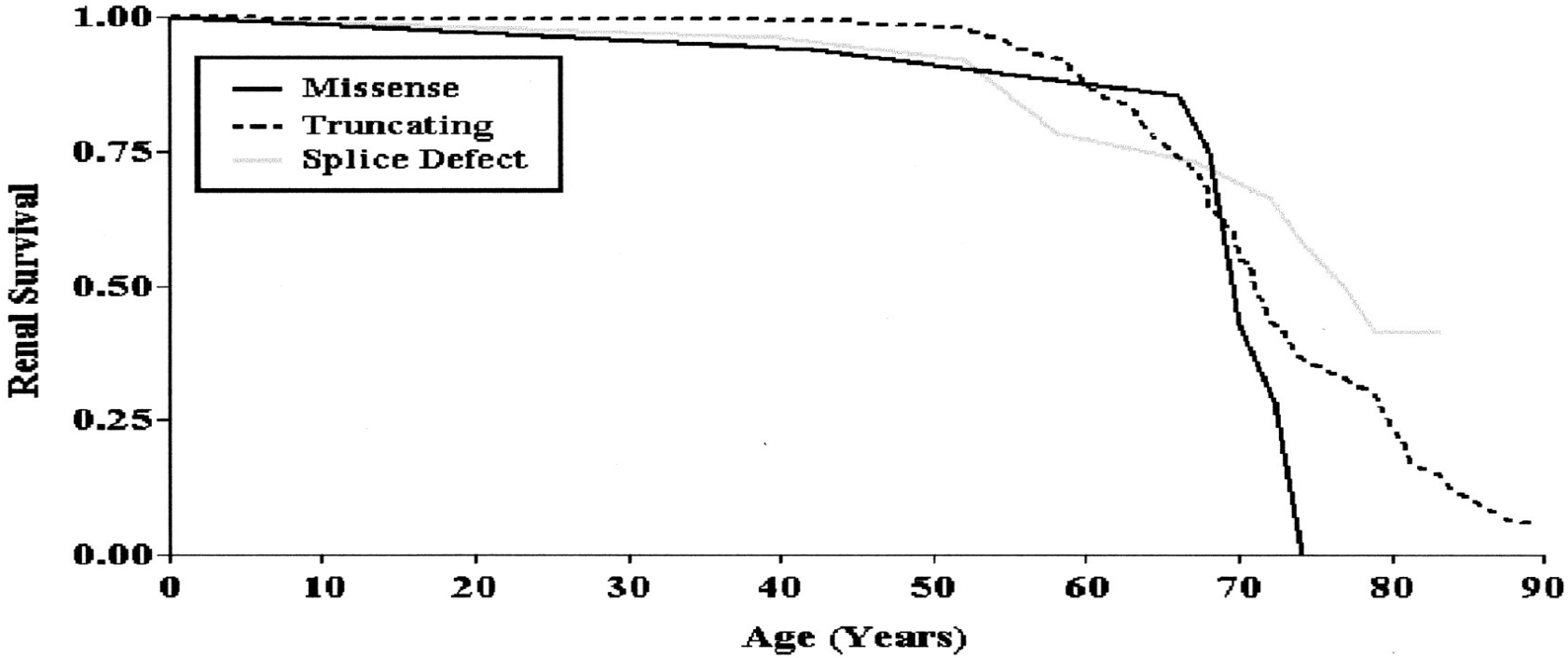
PKD2 mutation type and disease severity

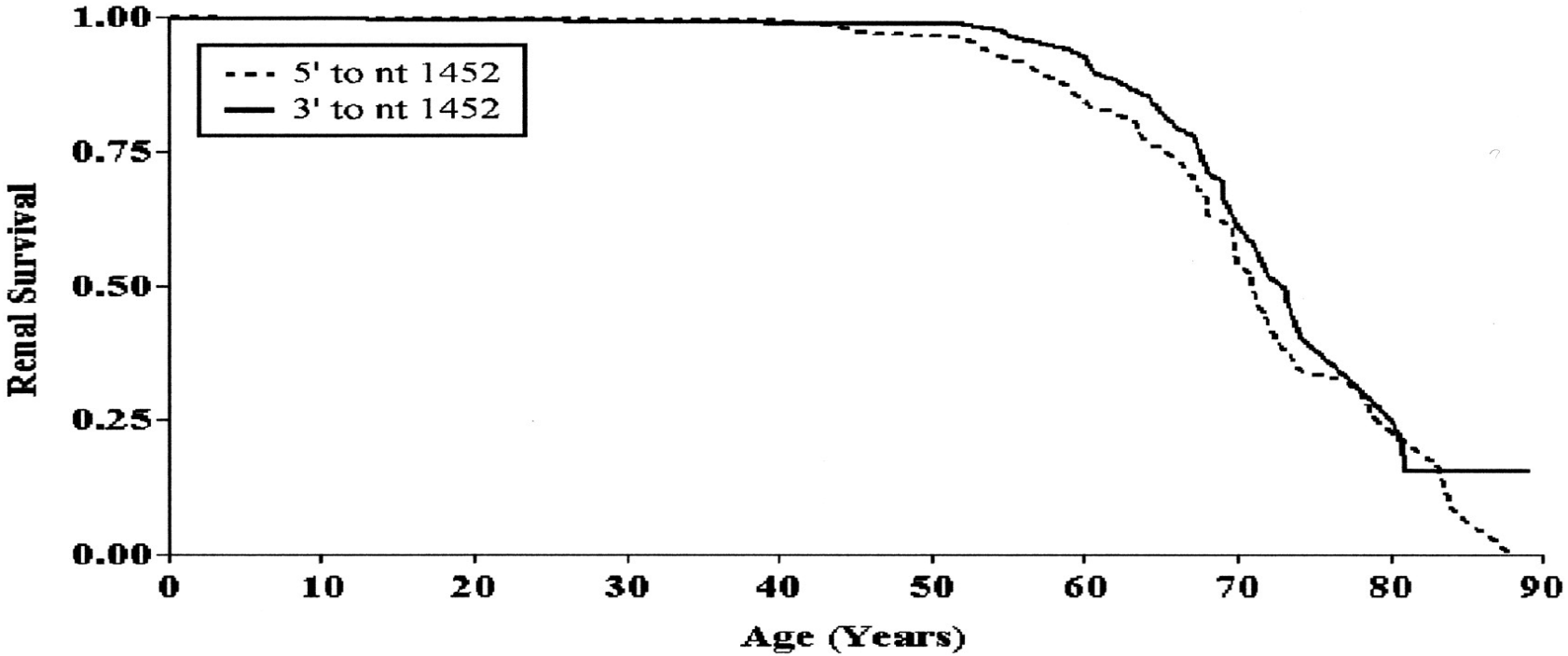


41 year old normotensive man, serum creatinine 1.1 mg/dl, splicing defect, IVS

19 year old hypertensive woman, serum creatinine 1.2 mg/dl, ins/del Exon 11


Censored
ESRD cases
Age (Years)
80
70
60
50
40
30
20
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Nucleotide position (kb)


Missense
Truncating
Splice Defect
Renal Survival
1.00
0.75
0.50
0.25
0.00
0
10
20
30
40
50
60
70
80
90
Age (Years)


5' to nt 1452
3' to nt 1452
Renal Survival
1.00
0.75
0.50
0.25
0.00
0
10
20
30
40
50
60
70
80
90
Age (Years)

Attitudes Regarding Pre-symptomatic Testing for ADPKD

	+PKD N=141	At Risk N=137		P value
Self testing	X	97%		
Offspring	88%	89%		NS
Prenatal	65%	50%		0.09
Terminate	4%	8%		NS

Insurance Issues in Pre-ESRD Patients

- 88% have medical insurance
- Only 25% disclosed health status to employer and only 35% disclosed to their insurer
- 57% chose their jobs due to insurance availability
- 37% did not change jobs due to insurance
- 30% previously denied insurance converage

Screening At Risk Asymptomatic ADPKD Individuals

	Before 1951	1951-1974	After 1974
+FH Diagnosis	38%	55%	48%
Mean Age	39	27	24

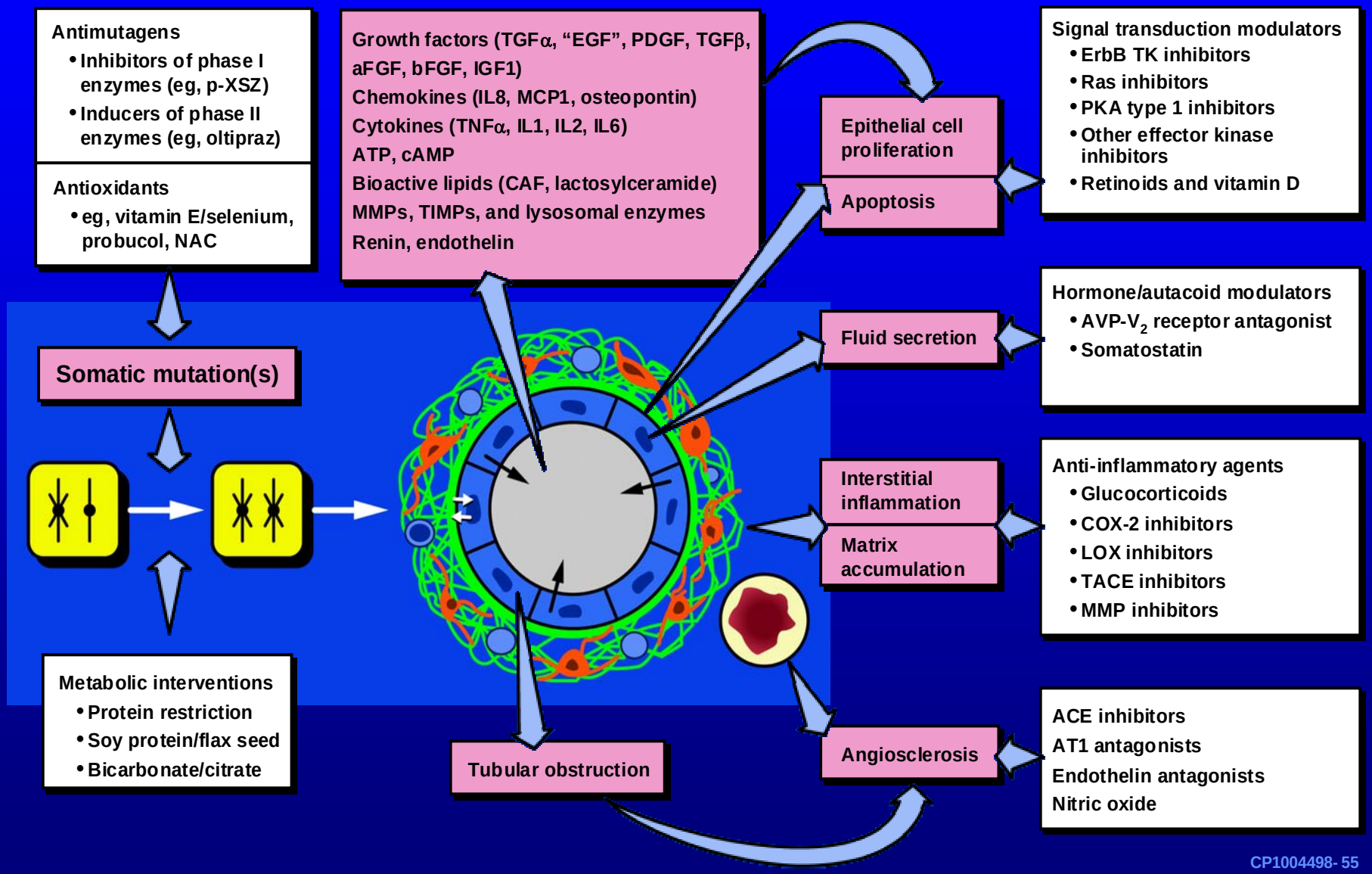
Limitations of Genetic Testing in PKD

- Identifies the mutation approximately 85% of the time
- Full sequencing is necessary to reach this level of identification
- Cost of mutation screening is extremely high
- High polymorphism rate in PKD1

Indications for genetic testing

- Possible donor for transplant
- Family planning
- Unclear phenotypic diagnosis

Prospects for Therapy in PKD



Acknowledgements

- GCRC Nursing and Laboratory Staff
- Hypertension and Renal Disease Research Center
- All of the ADPKD participants

Center for Medical Genomics

- Neil Lamb PhD
- Ashima Amin BS

Chapman Lab

- Sharon Langley MS
- William Paxton MD, PhD
- Janine Ladson, MPH

HALT PKD CLINICAL TRIALS NETWORK

NIH Funded Consortium to Initiate Interventional Trials to Slow or Halt Progression of ADPKD

HALT PKD CLINICAL TRIALS NETWORK

- Initiation of an interventional trial involving 1200 subjects at four clinical centers to determine the benefit of maximum blockade of the renin-angiotensin-aldosterone system

Hypothesis

- Activation of the RAAS and hypertension play important and independent roles in structural progression of renal cystic disease and in the loss of renal function in ADPKD

Specific Aims Study A

- To study the efficacy of combination ACEI/ARB therapy vs. ACEI therapy alone and low vs. standard blood pressure control on the rate of change of renal volume in hypertensive ADPKD individuals with intact renal function (GFR>60 ml/min)

Specific Aims for Study B

- To determine the efficacy of combination ACEI/ARB therapy vs ACEI alone with standard blood pressure control (SBP<130 mmHg and BPD<80 mm Hg) on the rate of doubling of serum creatinine, ESRD and death in ADPKD individuals with moderate renal insufficiency (GFR: 30-60 ml/min)

ADPKD Background

- Most common genetic renal disease
- 1 in 700-1000 individuals
- 4.7% of ESRD
- Systemic disorder

  Liver and pancreatic cysts

  CNS aneurysms

  Cardiac abnormalities

ADPKD Background

- Caused by at least 2 genes
- PKD1 on chr. 16 and PKD2 on chr. 4
- 85% of disease associated with mutation in PKD1 gene

ADPKD Background

- Genes encode membrane proteins
- Polycystin-1 and polycystin-2 interact to form new class of calcium channel