Cystic kidney disease: what do we know now; what might we know in 10 years time?

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NHS Foundation Trust

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Cystic kidney disease

Outline:

- Phenotypic spectrum
- Diagnostic genetic testing
- Disease progression
- Treatment
- Registries

Classification of Renal Cystic diseases

- Phenotypic spectrum
- Diagnostic genetic testing
- Disease progression
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I. Polycystic kidney diseases

a. ARPKD (*PKHD1*)
b. ADPKD (*PKD1* and *PKD2*)
c. Acquired renal cystic disease
d. GCKD

II. Congenital abnormalities of the kidney and urinary tract (CAKUT)

a. Renal adysplasia
b. Renal hypoplasia
c. Abnormalities of form, position and number
d. Ureteral and urethral abnomalities

III. Tubulointerstitial diseases ± cysts

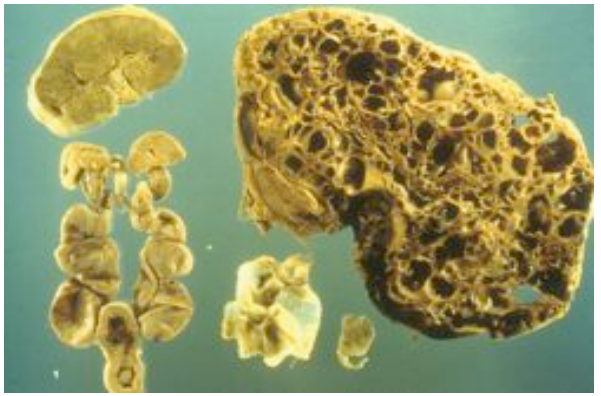
a. Renal tubular dysgenesis
b. NPHP
c. Medullary cystic diseases
d. BBS

IV. Cystic neoplasms and neoplastic cysts

a. Including VHL

V. Miscellaneous

a. Simple cysts
b. Meduallry sponge kidney
c. Localised cystic disease



Bonsib 2010

Renal cystic diseases in practice:

- Clinical setting
- Referrer
- Novel therapies
- New molecular tests

CAKUT (renal adysplasia, obstruction, syndromic-*HNF1B*)

Ciliopathies including ARPKD (Hepatorenal fibrocystic diseases)

Ciliopathies including NPHP

- ADPKD
- other AD diseases
- acquired disease

What do we know now?

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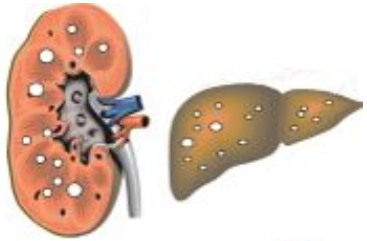
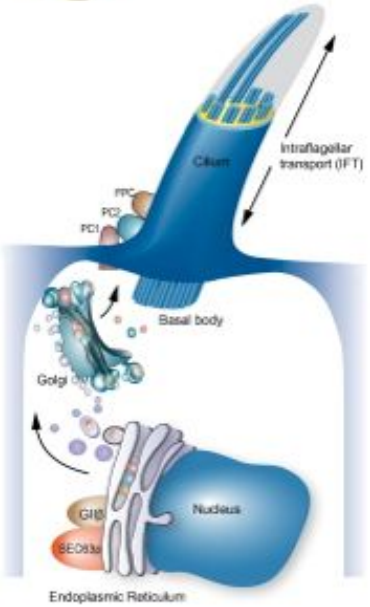
- Renal cysts are seen in many hundreds of recognisable syndromes and mendelian diseases
- Many are linked to abnormalities of the renal primary cilium





I. Polycystic kidney diseases
II. CAKUT
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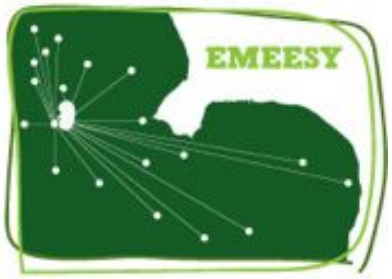
IV. Cystic neoplasms and neoplastic cysts
V. Miscellaneous

Bergmann and Weiskirchen 2012



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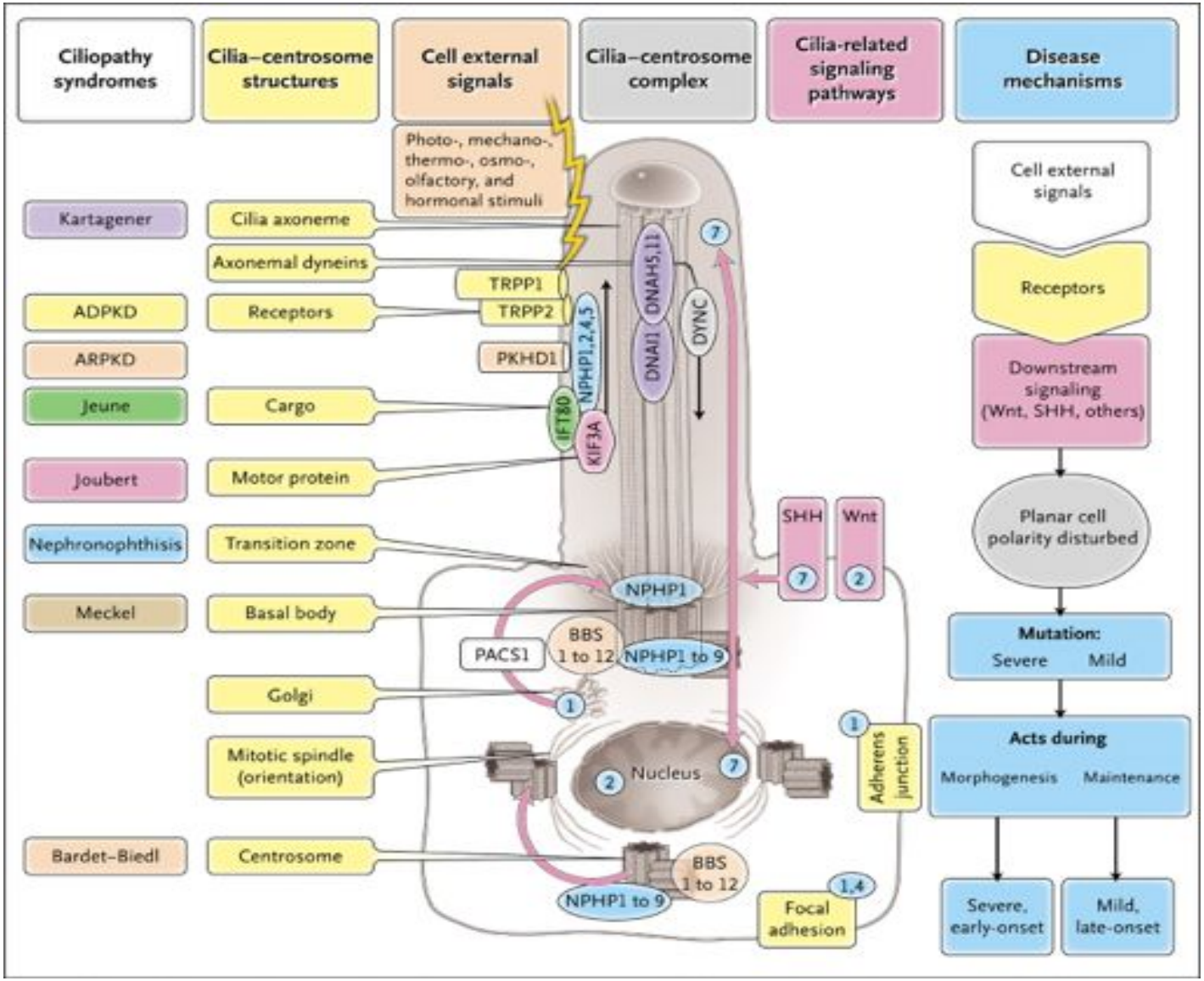

Hildebrandt F et al. N Engl J Med 2011;364:1533-1543

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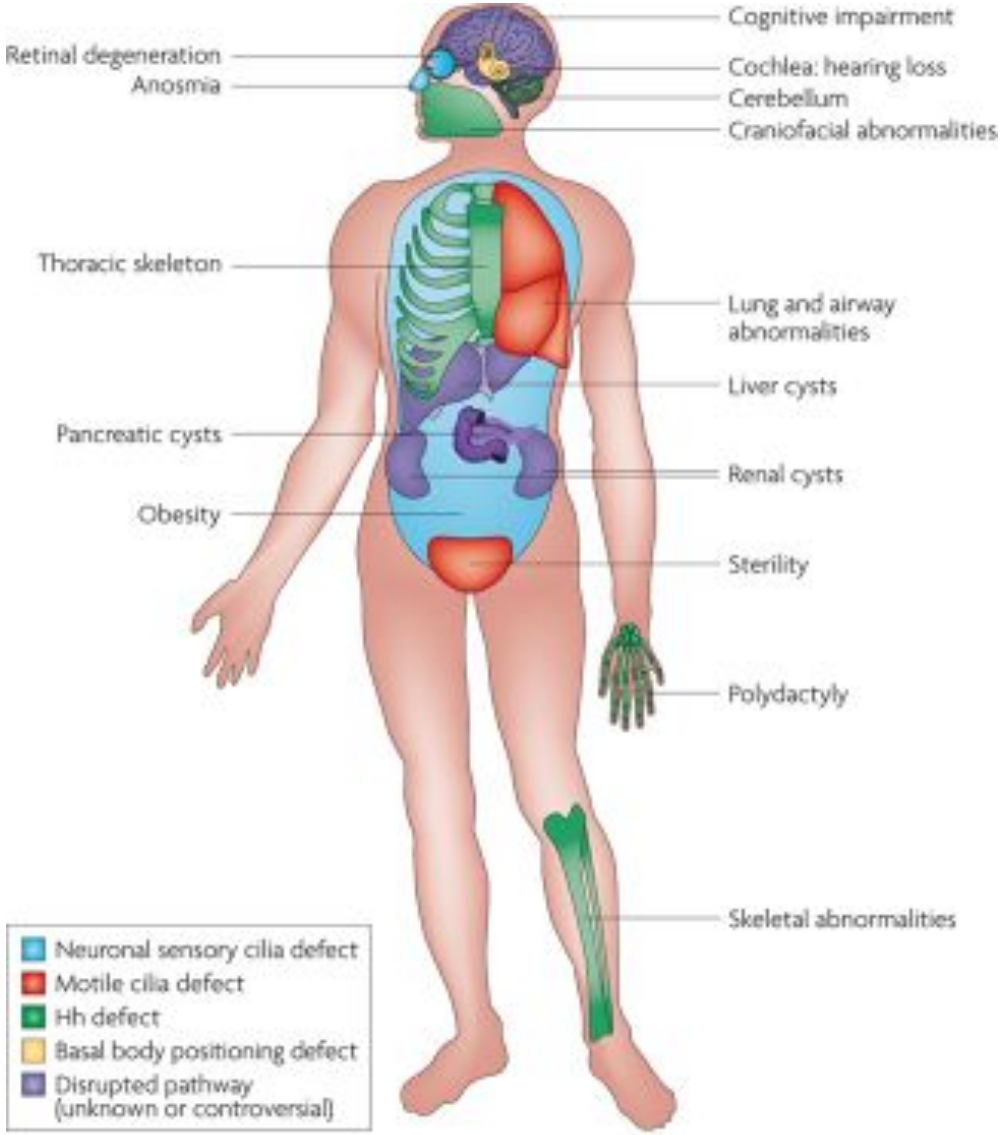

Goetz 2010

Phenotypic overlap in Ciliopathies

- Phenotypic spectrum
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	BBS	JS/JSRD	MKS
Occipital encephalocele	-	+	63-89 %
Pre- or Perinatal death	(+)	(+)	100 %
Liver fibrosis	(+)	+	32-46 % (PF) 100 % (DPM)
Postaxial polydactyly	69 %	+	55-85 %
Renal disease	24-82 %	+ (NPH/MCP)	100 % (MCP)
Retinopathy	93 % (RCD)	+	-
Obesity	72-96 %	(+)	-
Male Hypogonadism	88 %	(+)	-
Cognitive impairment	62 %	100 %	-
Molar tooth sign	-	100 %	-
Ataxia/Hypotonia	50 %	100 %	-
Oculomotor apraxia	-	72-79 %	-
Tachypnea or apnea	-	68-88 %	-

Knopp et al 2015

Diagnostic approach in renal cystic diseases

- Phenotypic spectrum
- Diagnostic genetic testing
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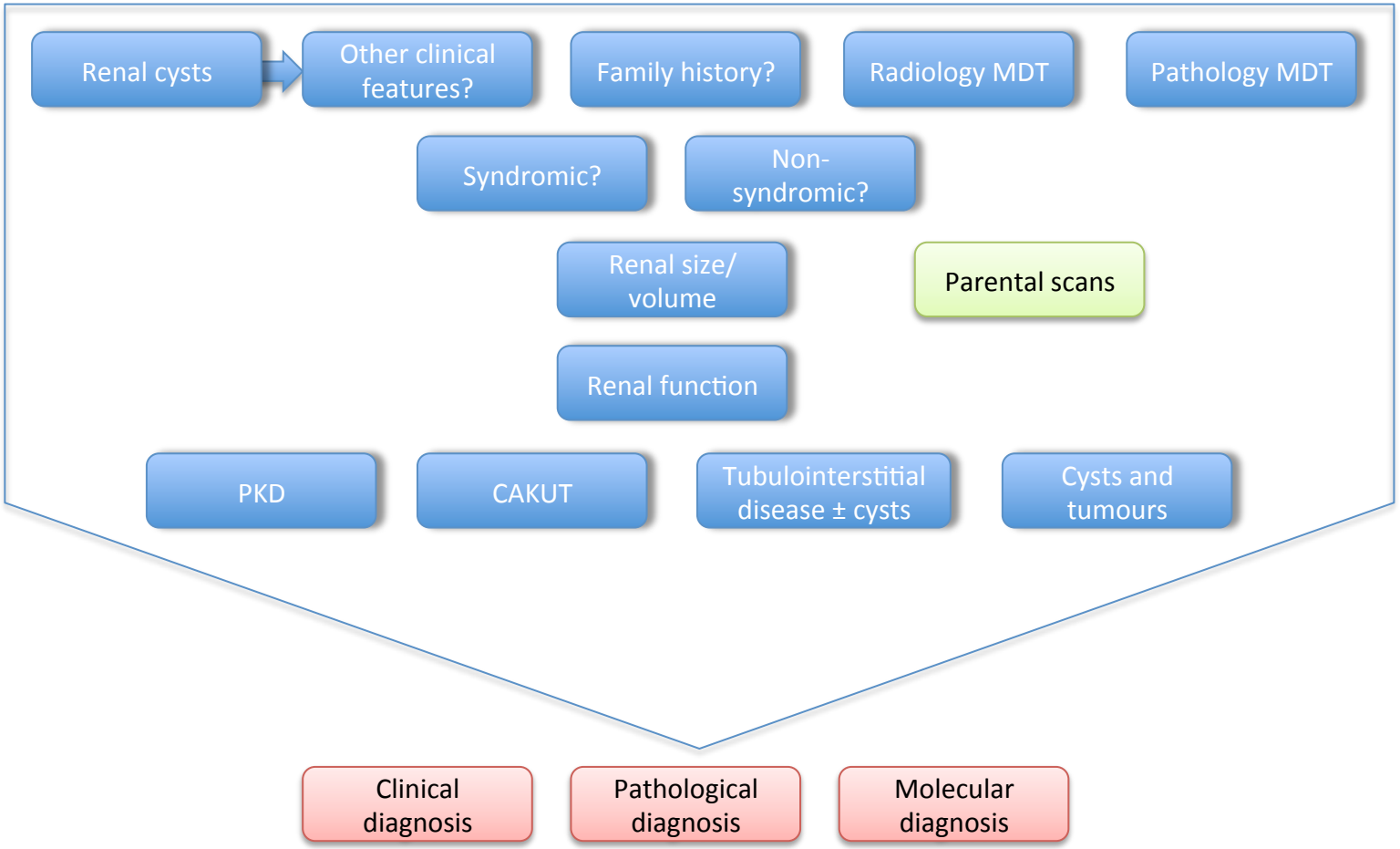

Imaging in Cystic kidney disease

- Phenotypic spectrum
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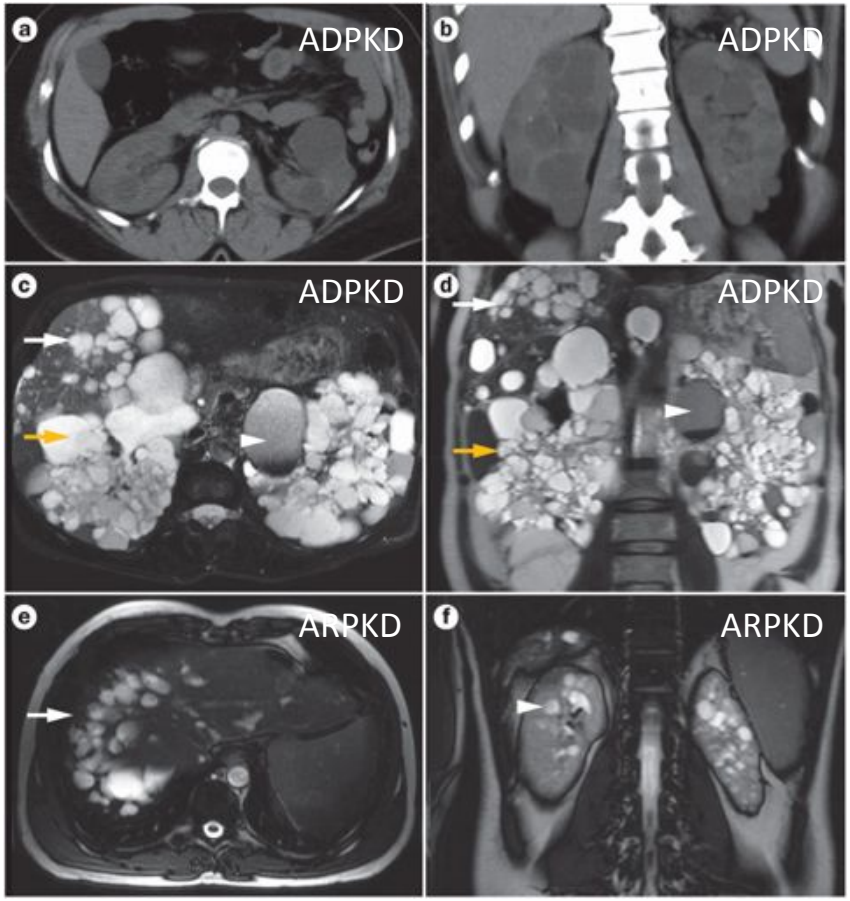

Kurschat, C. E. *et al.* (2014) An approach to cystic kidney diseases: the clinician's view. *Nat. Rev. Nephrol.*

Imaging in Cystic kidney disease

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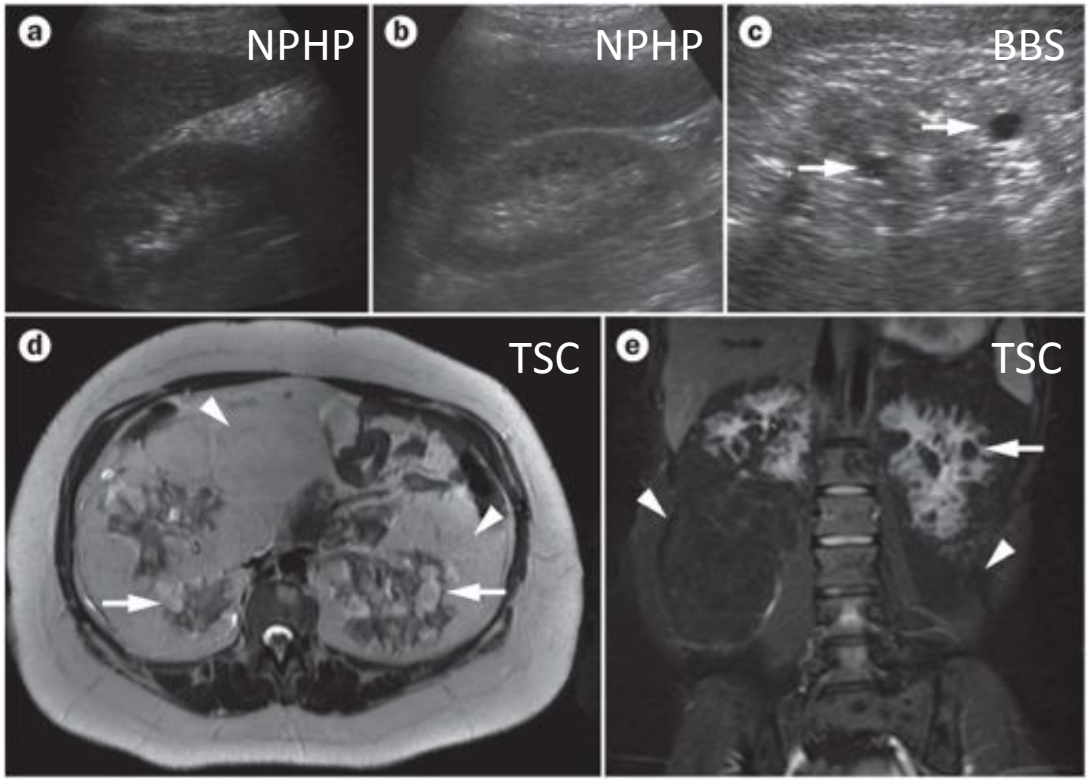
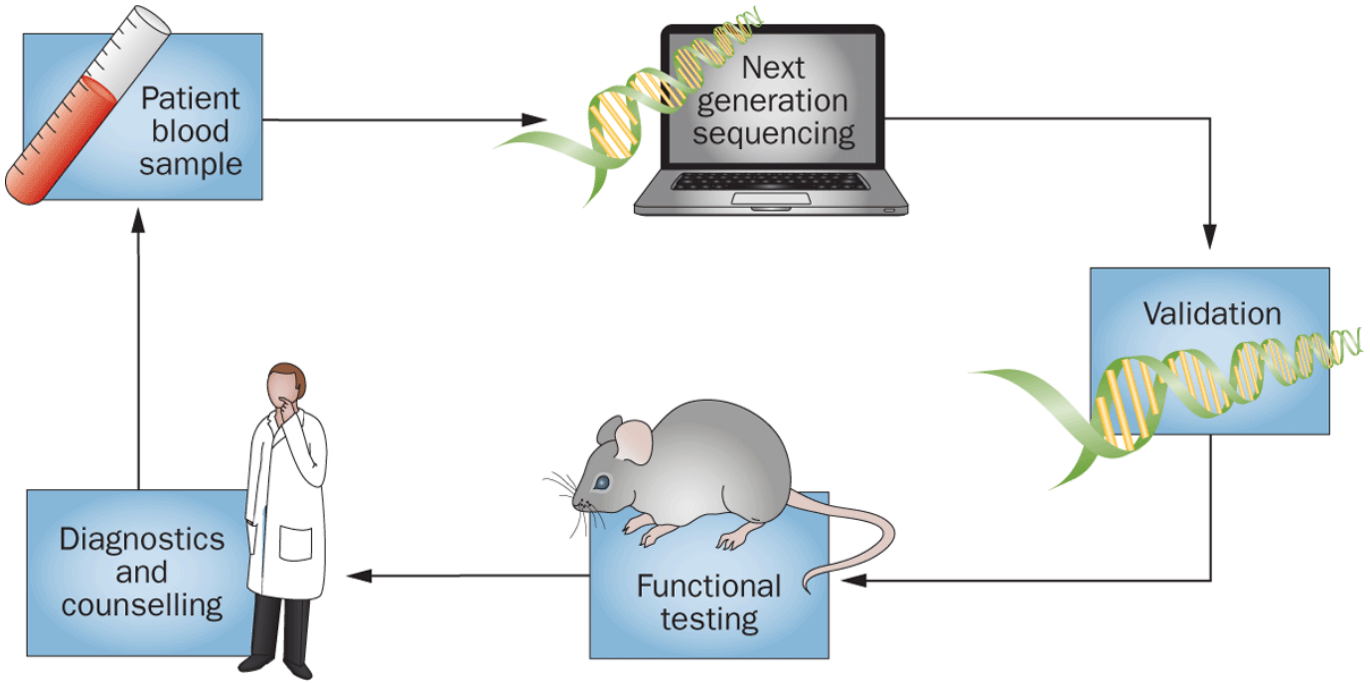


Kurschat, C. E. *et al.* (2014) An approach to cystic kidney diseases: the clinician's view. *Nat. Rev. Nephrol.*

Genes and gene panels

- Phenotypic spectrum
- **Diagnostic genetic testing**
- Disease progression
- Treatment
- Registries



Renkema et al 2014

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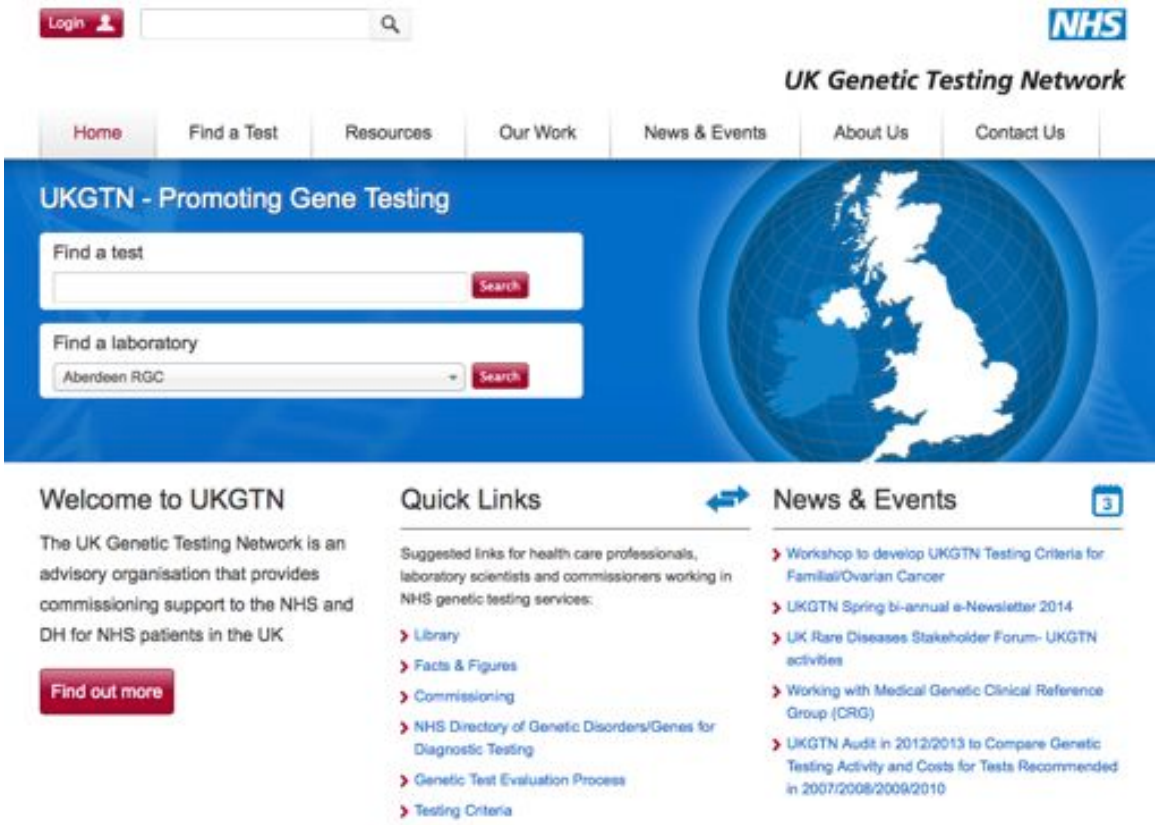

Genes and gene panels

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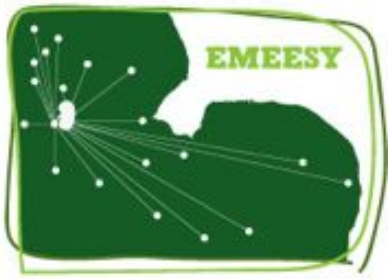
Disease	Genes	Testing available
ADPKD	*PKD1, PKD2*	✓
ARPKD	*PKHD1*	✓
TSC	*TSC1, TSC2*	✓
MCKD	*UMOD, MUC1*	✓ (*UMOD*)

UKGTN Gene Dossiers

- Diagnostic testing
- Predictive testing
- Carrier testing
- PND/PGD



Genes and gene panels

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NPHP	BBS	MKS	JS/JSRD
NPHP1	*CCDC28B*	*MKS1*	*INPP5E*
INVS	*C2orf86*	*TMEM216*	*AHI1*
NPHP3	*BBS5*	*TMEM67*	*ARL13B*
NPHP4	*ARL6*	*CEP290*	*CXORF5*
IQCB1	*BBS7*	*RPGRIP1L*	*TTC21B*
CEP290	*BBS12*	*MKS6*	*KIF7*
GLIS2	*PTHB1*	*NPHP3*	*TCTN1*
RPGRIP1L	*TMEM67*	*TCTN2*	*CEP41*
NEK8	*TRIM32*	*B9D1*	*ZNF423*
SDCCAG8	*BBS1*	*B9D2*	*PDE6D*
TMEM67	*BBS10*	*MKS7*	*EXOC8*
TTC21B	*CEP290*	*CC2D2A*	*POC1B*
WDR19	*TTC8*	*TMEM231*	*ATXN10*
ZNF423	*BBS4*	*TMEM237*	*CEP290*
CEP164	*BBS2*	*TMEM138*	*MKS1*
ANKS6	*MKS1*	*C5ORF42*	*TMEM216*
IFT173	*MKKS*	*TCTN3*	*TMEM67*
	NPHP1	*CSPP1*	*RPGRIP1L*
	IFT27	*BBS2*	*CC2D2A*
	SDCCAG8	*BBS4*	*TMEM231*
	LZTFL1	*BBS6*	*TCTN2*
		BBS10	*B9D1*
			TMEM237
			TMEM138
			C5ORF42
			TCTN3
			CSPP1

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Knopp et al 2015

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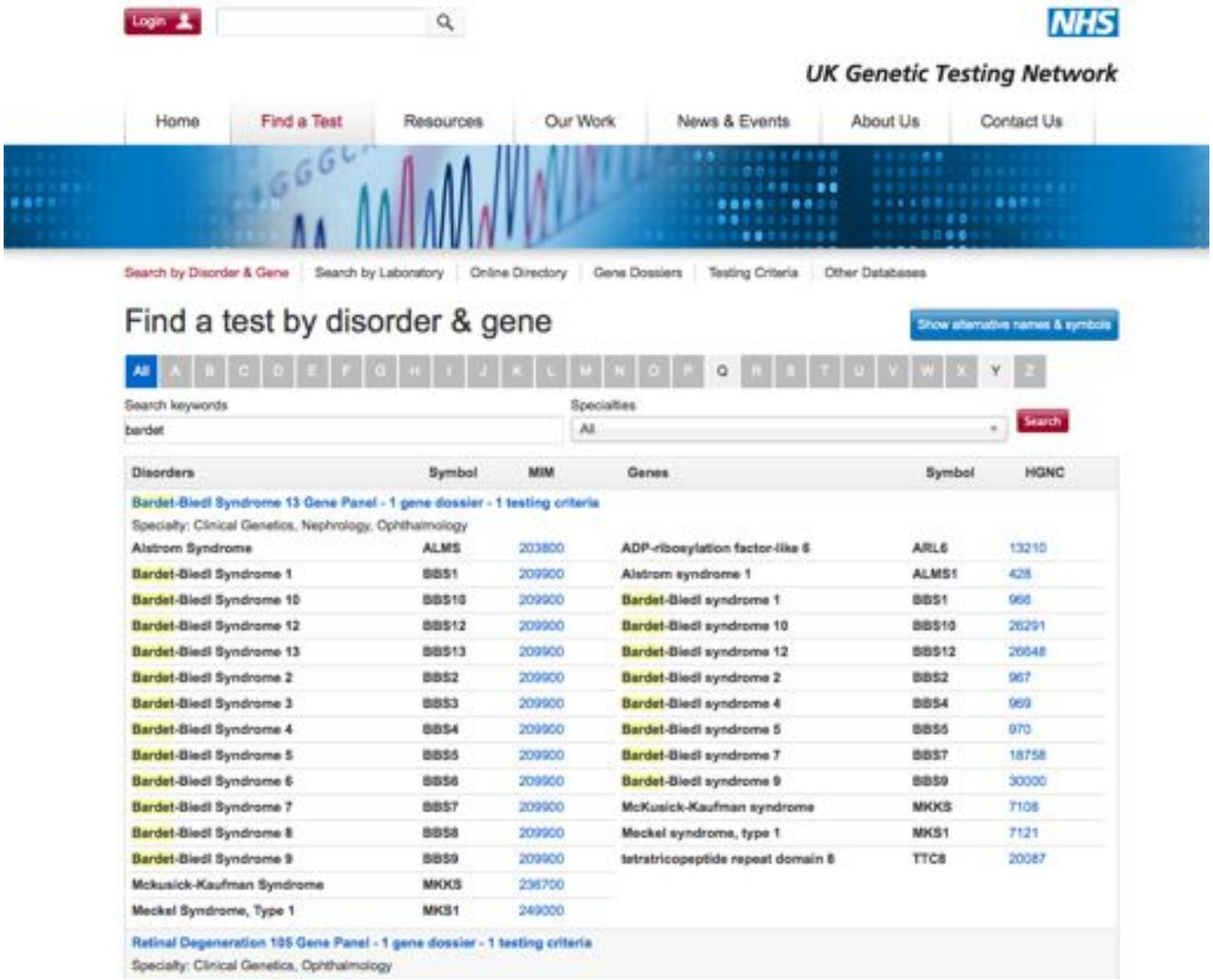

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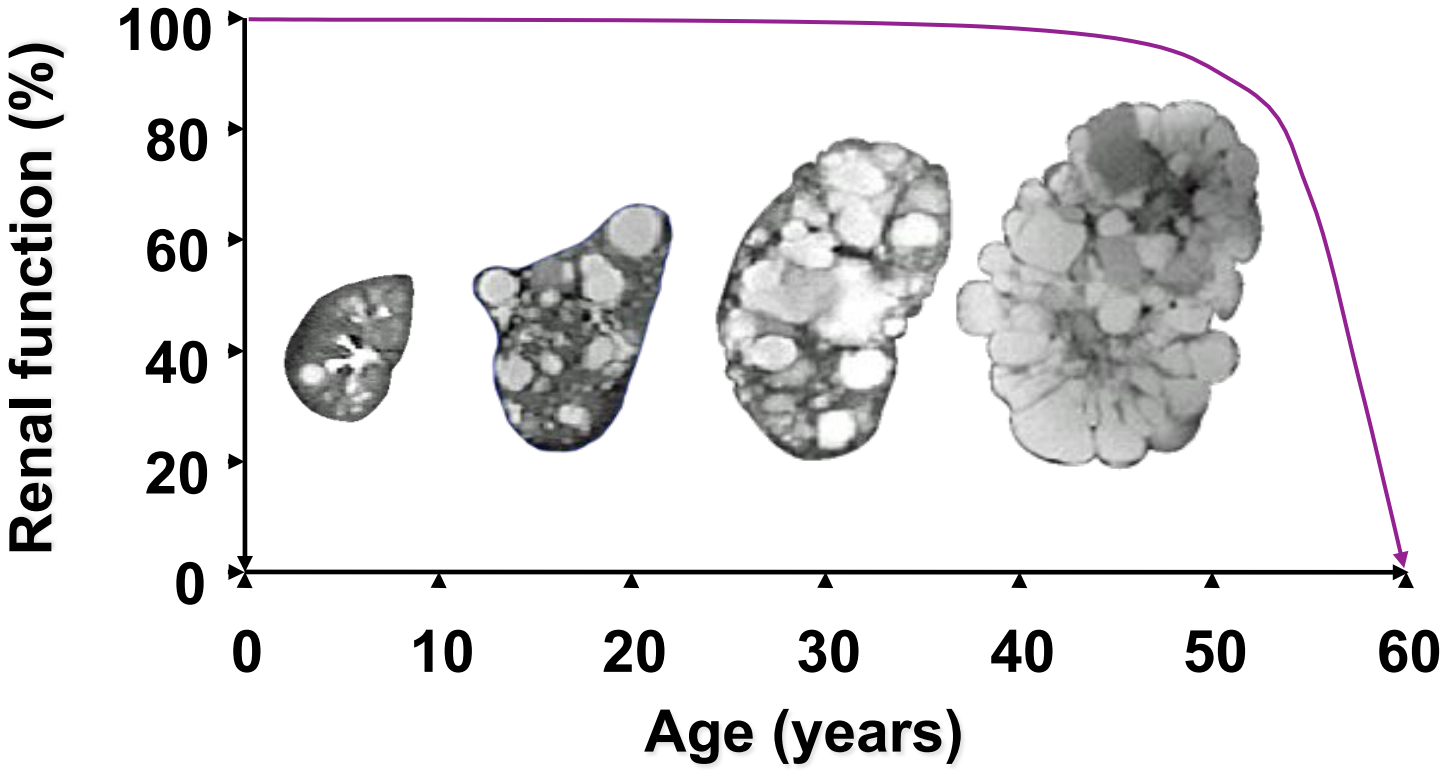
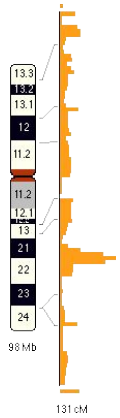
Disease progression-ADPKD



Family planning, genetics, fetal medicine	Paediatrics: Ix Incidental finding screening (FH) Symptoms HT	Symptoms HT Abdo pain Macro haematuria Screening 'Normal eGFR'	HT CKD (eGFR) (annual review)	LCC and RRT LRD

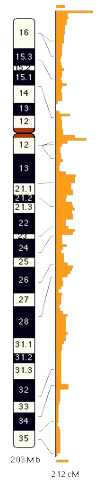
Long-term follow-up (1° to 2° to 3°)

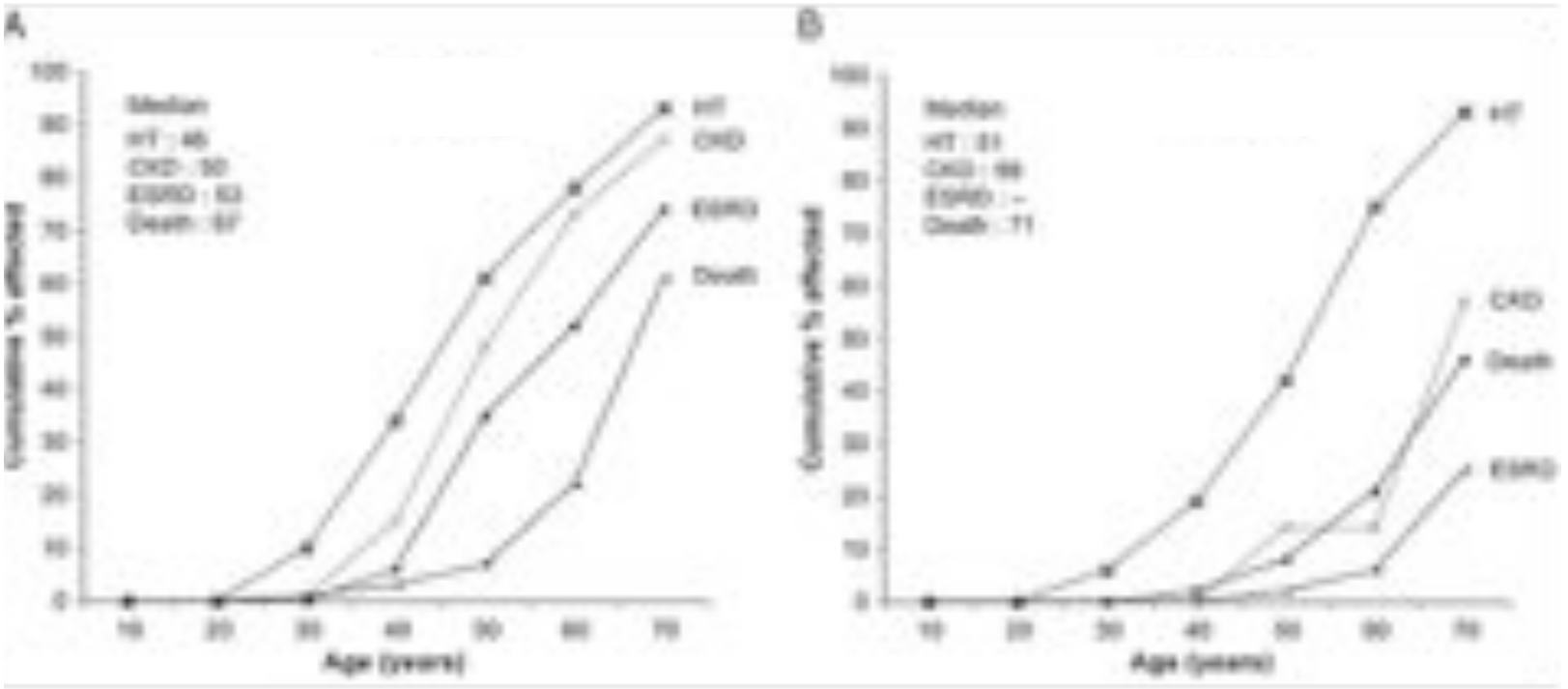
The natural history of ADPKD



PKD1
Chromosome 16
80%

PKD2
Chromosome 4
20%





Dicks et al 2006

Genetic predictors of disease progression

- Phenotypic spectrum
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Ref./Findings	*PKD1*	*PKD2*	*P* Value
5			
Patients, *n*	392	95	
Mean age at hypertension diagnosis, yr	39	49	<0.001
Median age at ESRD onset, yr	58	79	<0.001
6			
Patients, *n*	146	20	
Mean age at diagnosis of ADPKD, yr	27	41	<0.001
Mean age at diagnosis of hypertension, yr	35	50	0.001
Mean age at onset of ESRD, yr	54	73	<0.001
7			
Patients, *n*	287	34	
Median age at onset of ESRD, yr	53	68	<0.001
8			
Patients, *n*	333	291	
Median age at diagnosis of ADPKD caused by symptoms, yr	42	56	NA
Median age at death/ESRD, yr	53	69	<0.001
Median age at ESRD, yr	54	74	
9			
Patients, *n*	136	60	
Median age at hypertension treatment, yr	46	51	NA
Median age at stage 3 CKD onset, yr	50	66	NA
Median age at ESRD onset, yr	53	Only 21% had ESRD by age 70 yr	NA
Median age at death, yr	67	71	NA
10			
Patients, *n*	185	34	
Findings	Patients with *PKD1* had significantly larger kidneys and more cysts versus patients with *PKD2* mutations; they also had significantly higher frequency of hypertension/higher urinary albumin excretion		
11			
Patients, *n*	50	10	
Findings	Children with *PKD1* had significantly larger kidneys with more and larger cysts than children with *PKD2* (mean age of 8.6 versus 8.9 yr); they also had significantly higher daytime/nighttime systolic BP by ambulatory monitoring over 24 h		

Schrier et al *JASN* 2014

Genic and allelic effects are strong in ADPKD:

- Phenotypic spectrum
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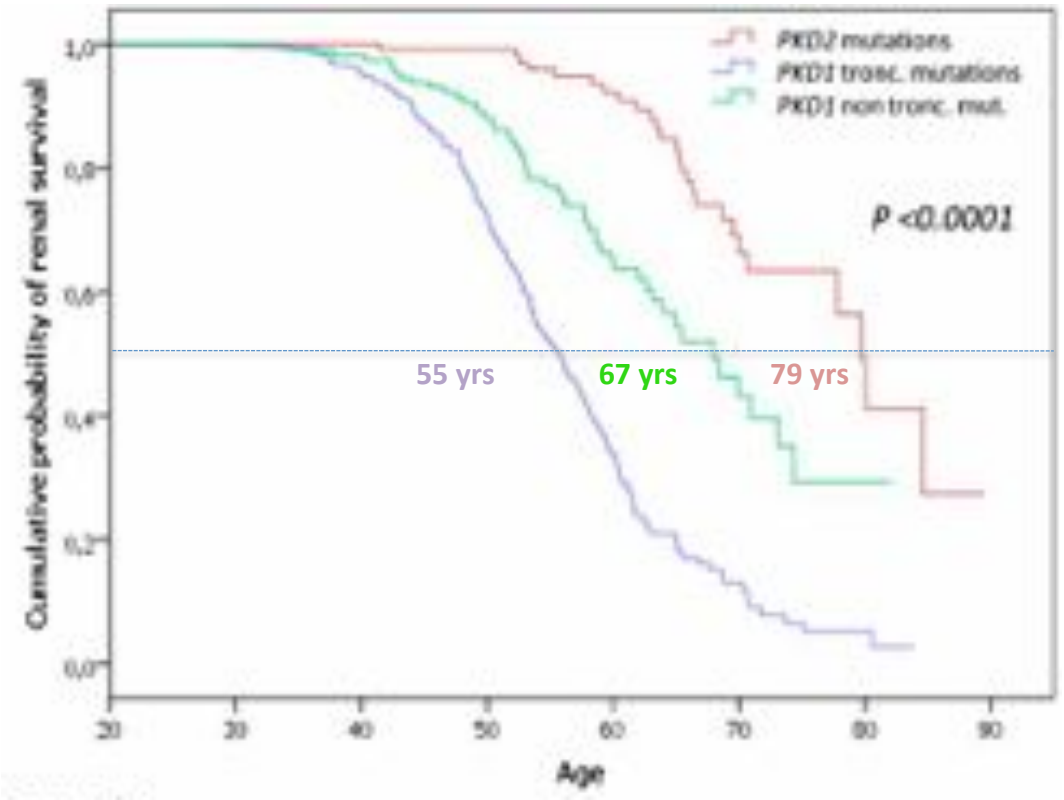

Cornec-Le Gall et al 2013

The PROPKD Score in ADPKD:

- Phenotypic spectrum
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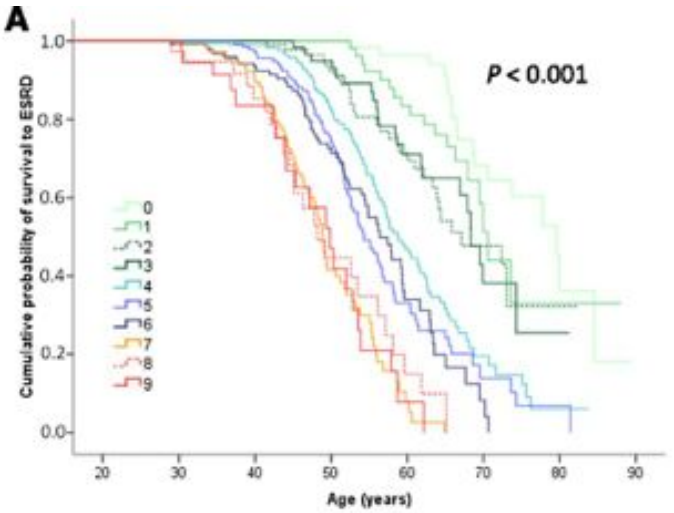
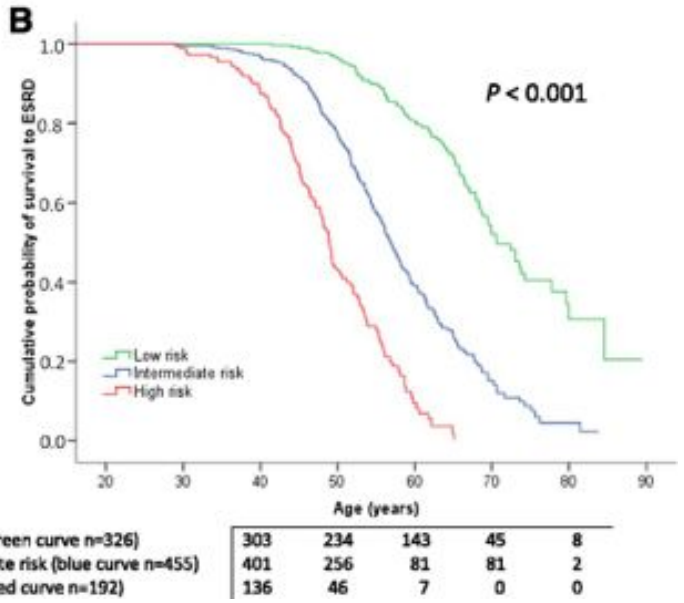
Points	
1	Male gender
2	HT before age 35
2	First urologic event before age 35
0	PKD2 mutation
2	Non-truncating PKD1 mutation
4	Truncating PKD1 mutation





Cornec-Le Gall et al 2015

Total Kidney Volume in Relation to Age in the 185 Patients with Identified *PKD1* (Red) or *PKD2* (Blue) Mutations

- Phenotypic spectrum
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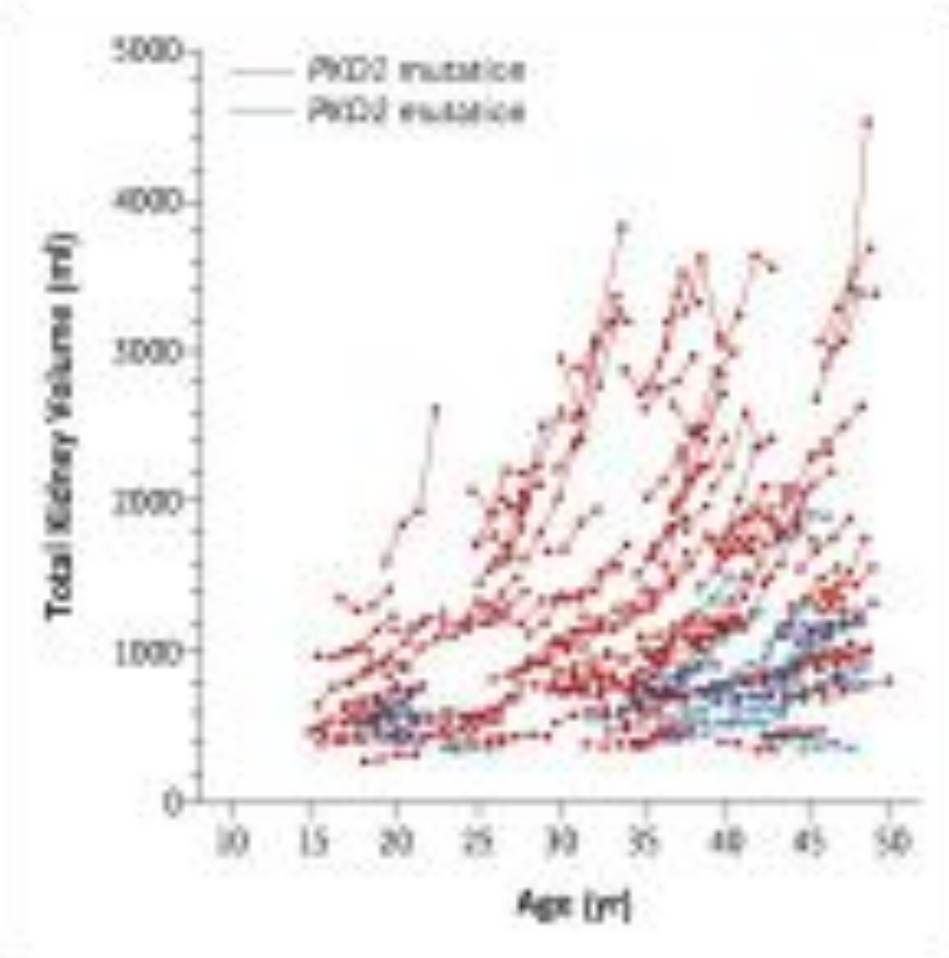
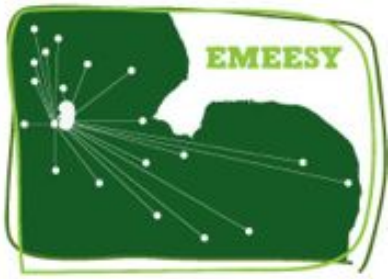


Harris *et al*. JASN 2006



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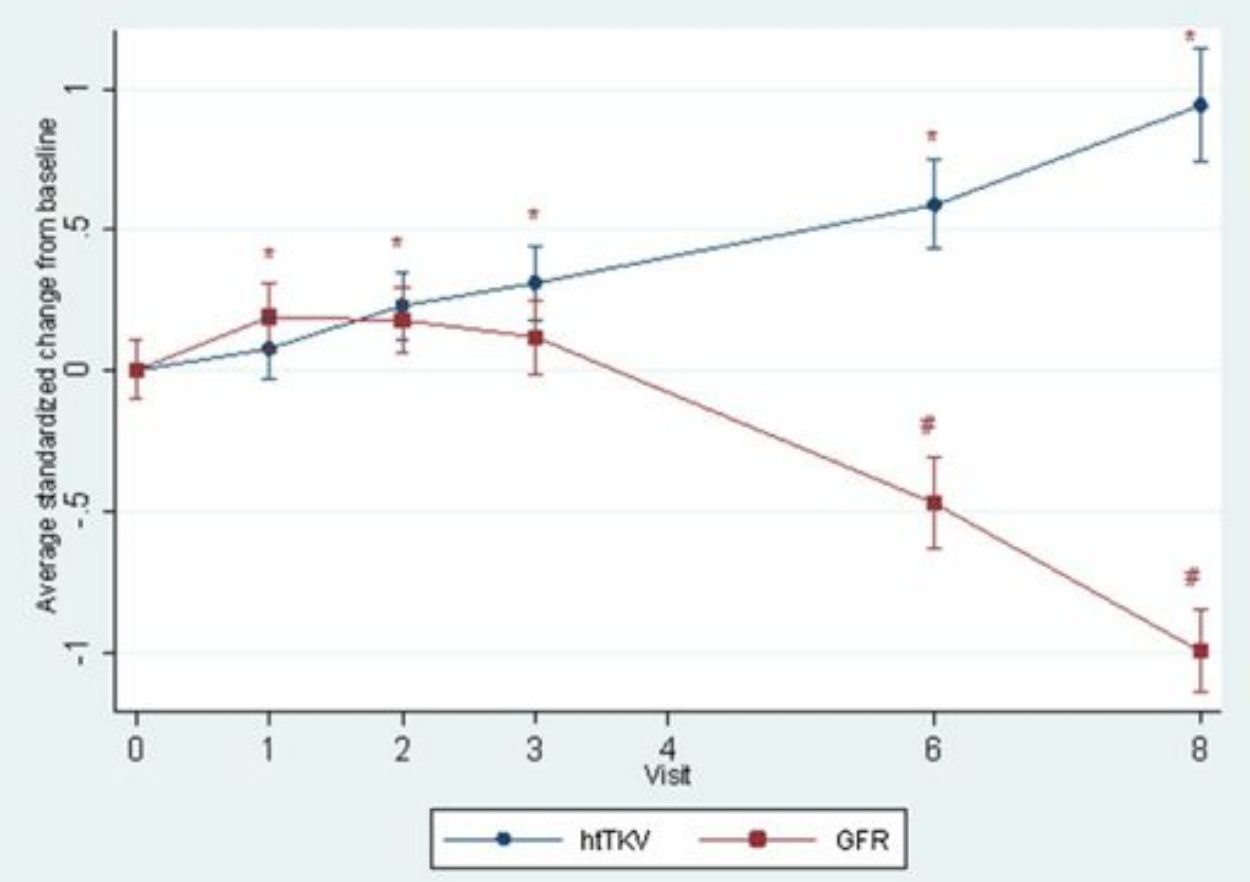
Average standardized change in htTKV and iothalamate GFR. htTKV determined at baseline and iothalamate GFR at baseline and five subsequent visits until year 8 (n=93 with complete data).



a htTKV value of 600 cc/m forecasts stage 3 CKD within 8 years

Chapman A B et al. 2012

Relationship between TKV and Clinical Variables

- Phenotypic spectrum
- Diagnostic genetic testing
- Disease progression
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Variable	Number Studied	Volume Method	Mean Kidney Volume[a]			
			With variable	Without variable	*P* Value	Reference
Proteinuria	270	US	1190 ± 93	578 ± 32	<0.0001	8
Microalbuminuria	49	US	853 ± 87	535 ± 52	<0.01	8
Hypertension		US				5
males	76		624 ± 47	390 ± 43	<0.0005	
females	89		446 ± 32	338 ± 24	<0.002	
Hypertension	43	CT	976 ± 472	739 ± 311	<0.05	84
	241	MR	628 ± 48	352 ± 33	<0.0001	80
Hypertension children	62	US	2.7 ± 2.3[b]	1.2 ± 2.5[b]	<0.05	85
Hypertension children	70	US	125 ± 7	83 ± 6	<0.0001	42, 43
Gross hematuria	191	US	820 ± 87	588 ± 52	<0.03	3
Progressive loss of renal function	43	CT	895[c]	606[c]		84
	220	US	598 ± 368	366 ± 168	<0.0001	77

Grantham J J et al. CJASN 2006;1:148-157

Classification by HtTKV0 and age at HtTKV0 predicts the change in eGFR over time

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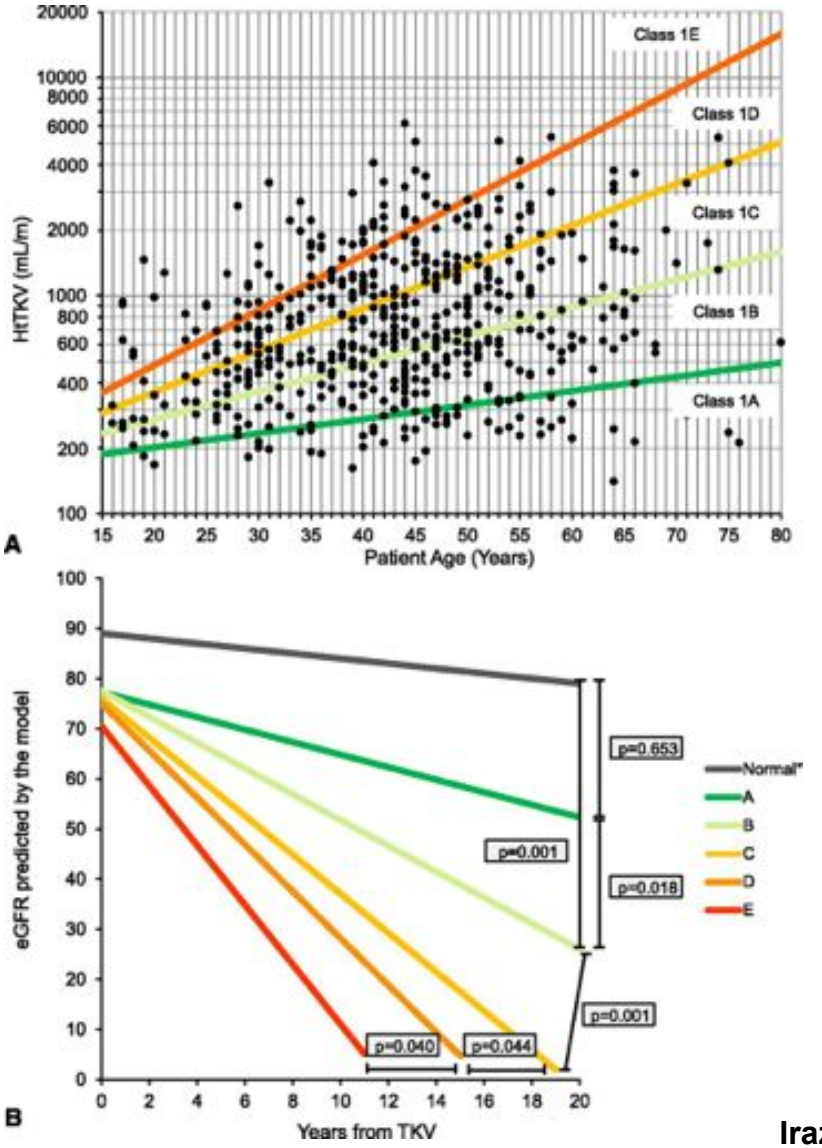

Irazabal M V et al. JASN 2014

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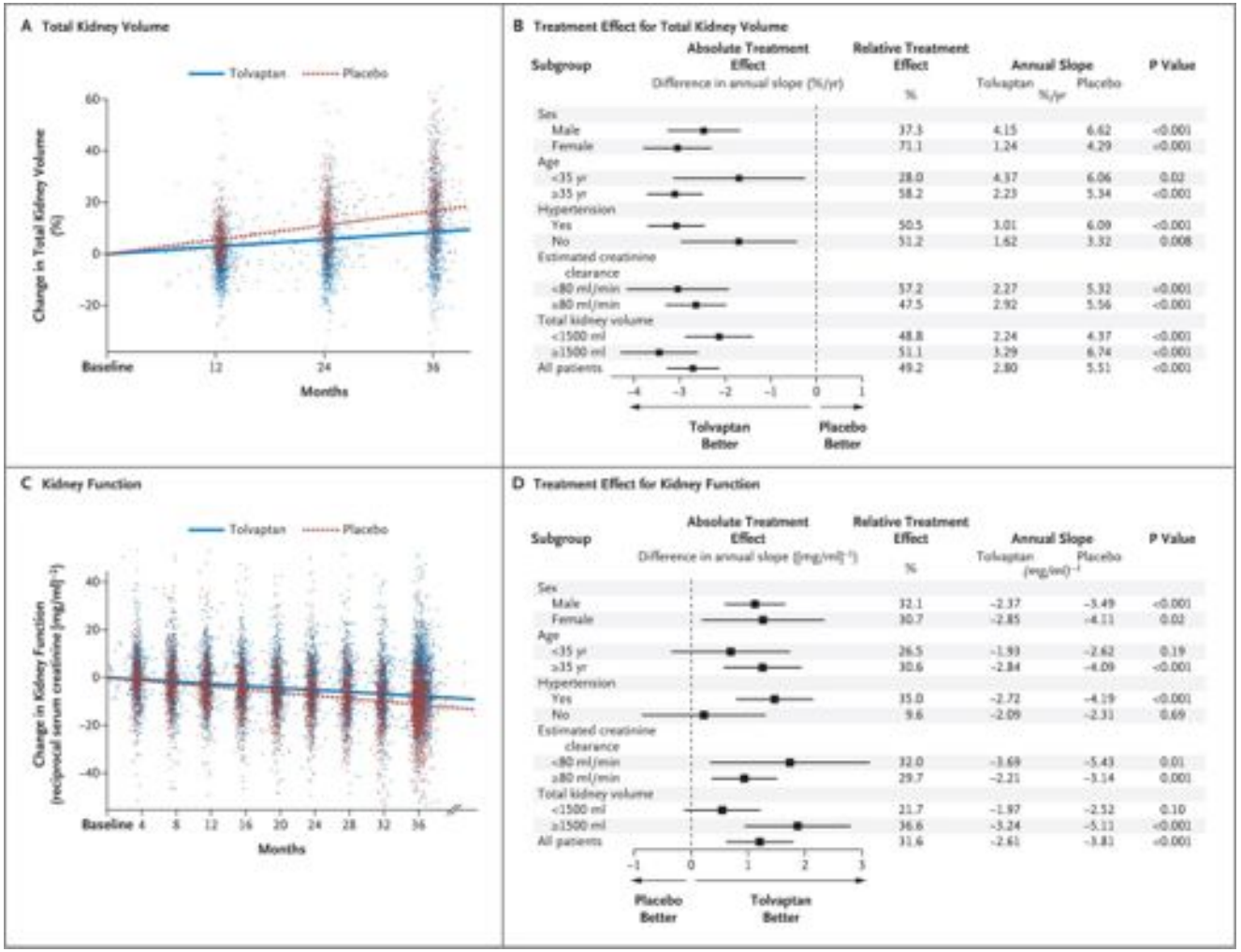
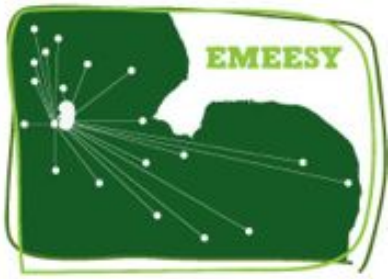
Effect of Tolvaptan on the Annual Slopes of Total Kidney Volume and Kidney Function.



Torres VE et al. N Engl J Med 2012;367:2407-2418.



- Phenotypic spectrum
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- Monitoring disease
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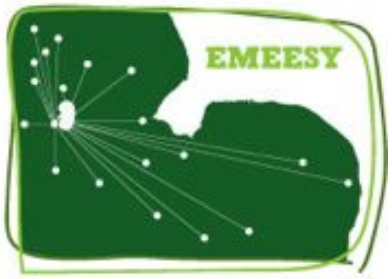
In 10 years?



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http://www.kidney-international.org

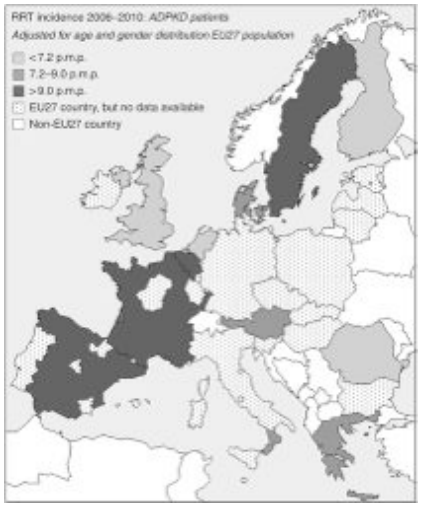
meeting report

Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

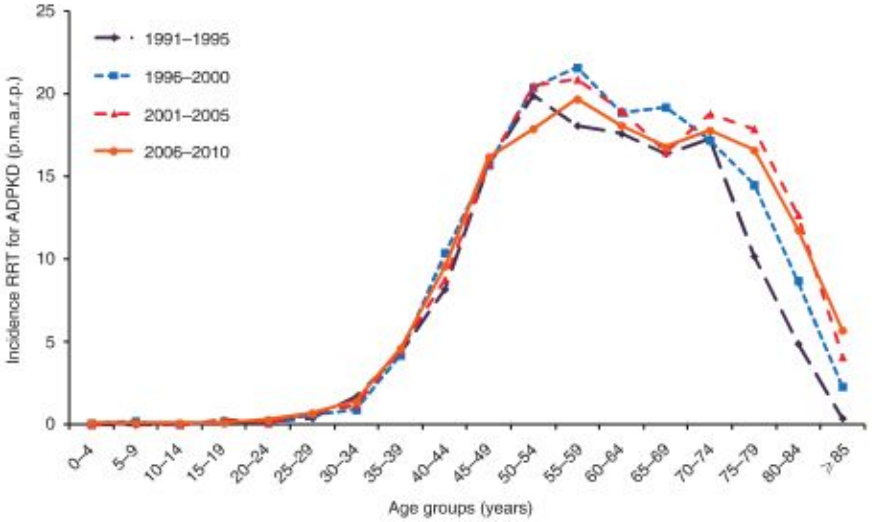
Arlene B. Chapman[1], Olivier Devuyst[2], Kai-Uwe Eckardt[3], Ron T. Gansevoort[4], Tess Harris[5], Shigeo Horie[6], Bertram L. Kasiske[7], Dwight Odland[8], York Pei[9], Ronald D. Perrone[10], Yves Pirson[11], Robert W. Schrier[12], Roser Torra[13], Vicente E. Torres[14], Terry Watnick[15] and David C. Wheeler[16] for Conference Participants[17]

Registered Charity No. 1060134

Mean age at ESRD in ADPKD: ERA-EDTA Registry

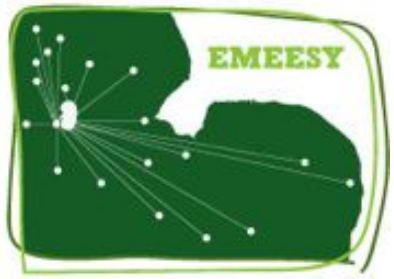


	1991–1995	1996–2000	2001–2005	2006–2010
All RRT for ADPKD				
Austria	57.4	59.1	58.6	59.5
Belgium[a]	58.1	58.2	59.5	58.9
Denmark	55.6	58.1	60.0	59.9
Finland	54.0	57.3	57.3	58.3
France				58.9
Greece	55.1	56.7	58.1	58.9
Italy, Calabria		61.5	59.8	60.2
Romania				55.9
Spain[a]	56.8	57.6	58.0	57.6
Sweden	58.7	57.9	60.6	58.2
The Netherlands	56.5	56.2	56.7	58.4
United Kingdom[a]	54.9	55.5	56.5	55.5
All countries[b]	56.6	57.4	58.2	58.0
Female	57.1	58.4	58.7	58.6
Male	56.1	56.5	57.7	57.5
All RRT for non-ADPKD				
All countries[b]	57.6	60.8	63.5	64.7
Female	57.9	61.4	64.1	62.5
Male	57.3	60.4	63.1	64.5



"conventional treatments for chronic kidney disease do not reduce the need for renal replacement therapy in autosomal dominant polycystic kidney disease"

Spithoven et al 2014



- Phenotypic spectrum
- Diagnostic genetic testing
- Disease progression
- Monitoring disease
- Treatment
- Registries

DNA/FH/Clinical

Lab

Imaging/biomarkers

Registry: International

Registry: National

- Registry: Single Centre
- Research study
- Clinical Trial

Case series

Case reports

100,000

10,000

1,000

100

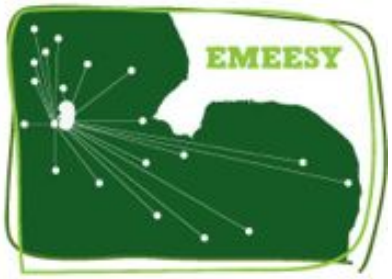
10

1

Cases

Population

RenalRadar.org



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Genomics england

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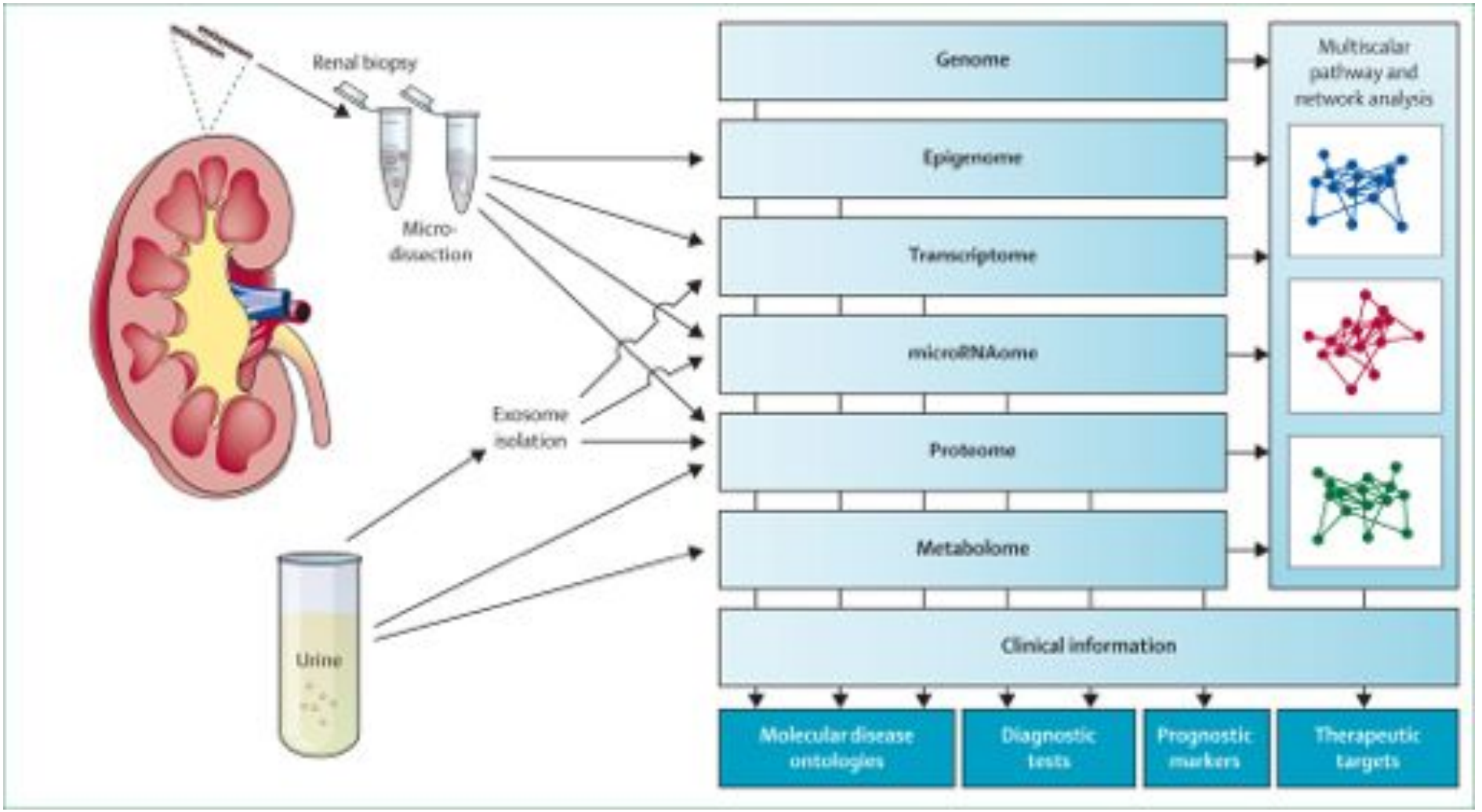
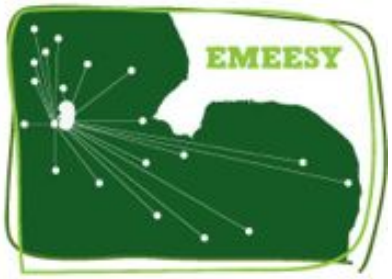
Genomics England is delivering the **100,000 Genomes Project.**

We are creating a new genomic medicine service with the NHS – to support **better diagnosis and better treatments** for patients. We are also enabling medical research.

Find out more...



Devuyst 2014



ClinicalTrials.gov

- Phenotypic spectrum
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- Lists 106 trials for ‘polycystic kidney disease’
- From water to curcumin!

Summary

- Considerable progress has been made in the clinical and molecular characterisation of renal cystic diseases
- Molecular diagnostics are becoming more widely available
- Assessing disease severity and prognosis remains a major clinical challenge
- RCTs have identified novel therapies for ADPKD; however progress remains slow for other rare diseases
- An ‘Omics approach based on disease registries holds considerable promise