Evolution of Imaging-Based Diagnosis

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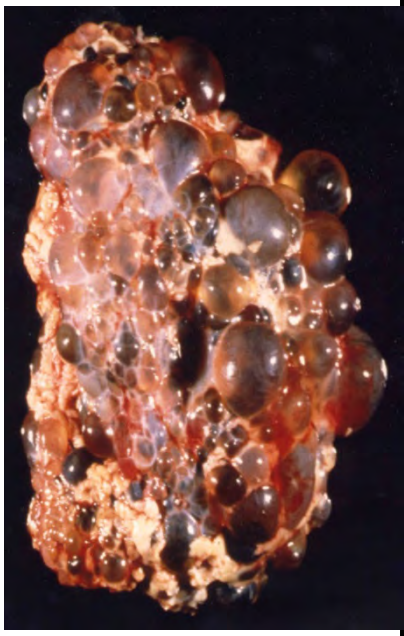

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Disclosure of Interests

Consultancy to:

- Otsuka
- Novartis
- Genzyme/Sanofi

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Background

- Most common hereditary kidney disease (~1/500-1000 births)
- ~70-75% and ~25-30% of cases are due to mutations in *PKD1* and *PKD2*, respectively[1]
- Clinical manifestations of *PKD1* and *PKD2* overlap completely
- *PKD2* is much milder compared to *PKD1* with a delayed onset of ESRD of ~20 years[2]
- Hypomorphic PKD1 mutations are a common cause of mild disease

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1. Adv Chronic Kidney Disease 17: 140-152, 2010
2. Lancet 353: 103-107, 1999

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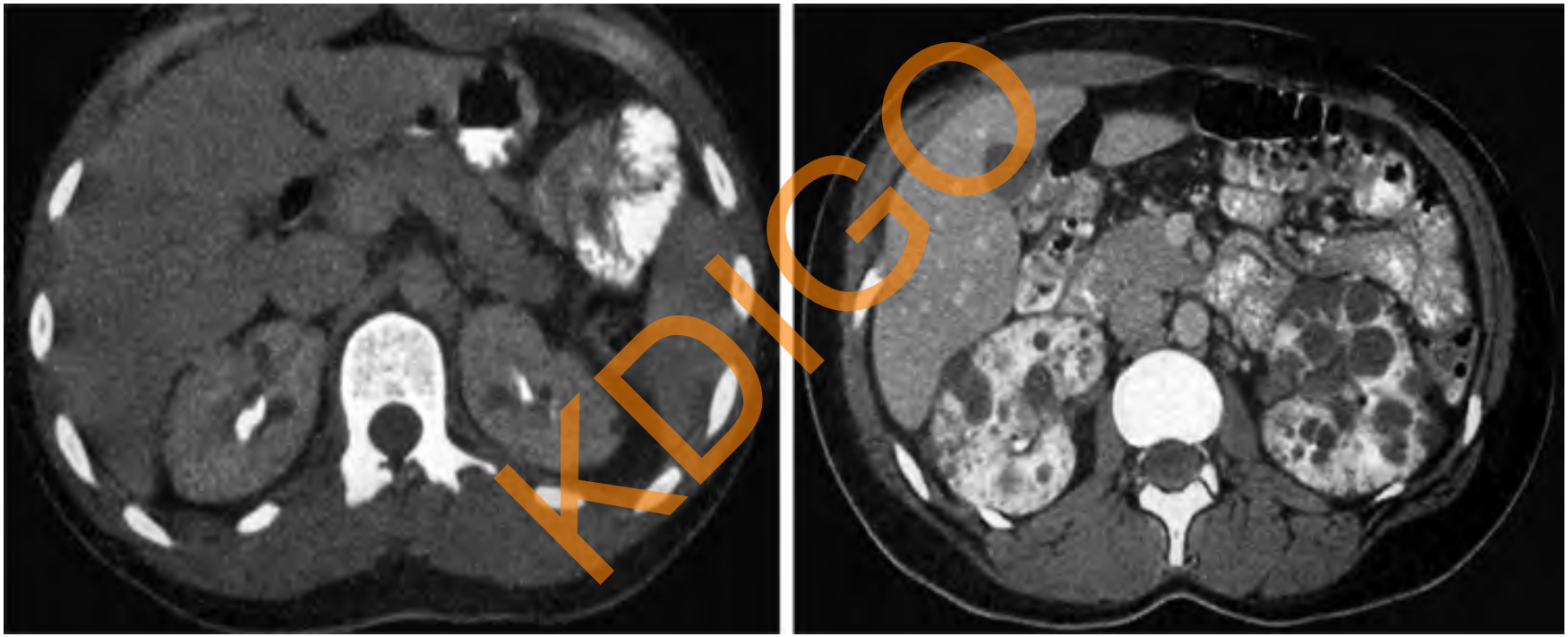
Cyst formation is age-dependent



Age: 29 years **vs** **40 years**

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Current Diagnosis of ADPKD

- Pre-symptomatic Dx of at-risk family members is most commonly made by renal U/S which is:
  - based on age-dependent criteria
  - inexpensive and widely available
- CT/MRI are also used for disease exclusion in at-risk potential LRTx donors. However, the validity of this approach is unclear
- Gene-based testing reserved for atypical cases, de novo disease, equivocal imaging results, and disease exclusion in younger at-risk subjects

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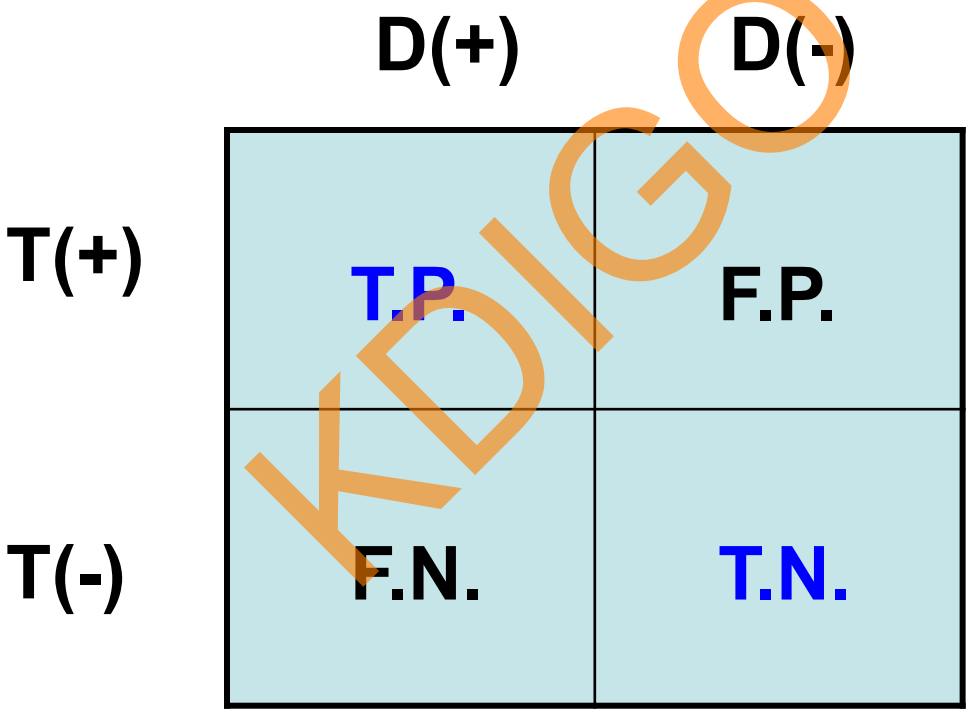
Diagnostic Testing (I)



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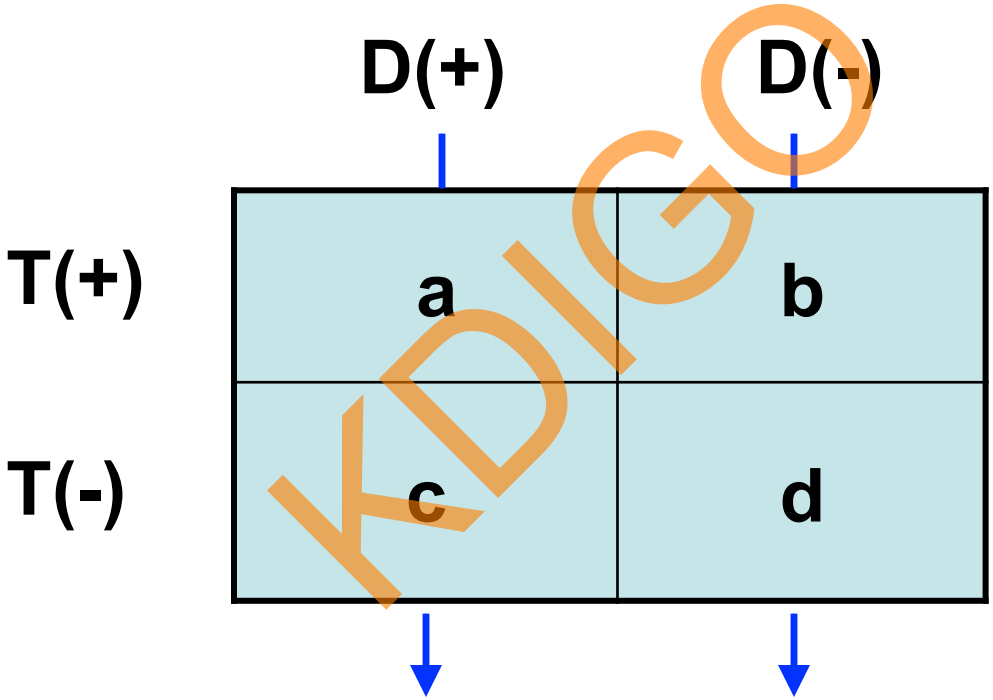
Diagnostic Testing (II)



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SEN = a/(a+c) FNR = 1-SEN = c/(a+c)

SPEC = d/(b+d) FPR = 1-SPEC = b/(b+d)

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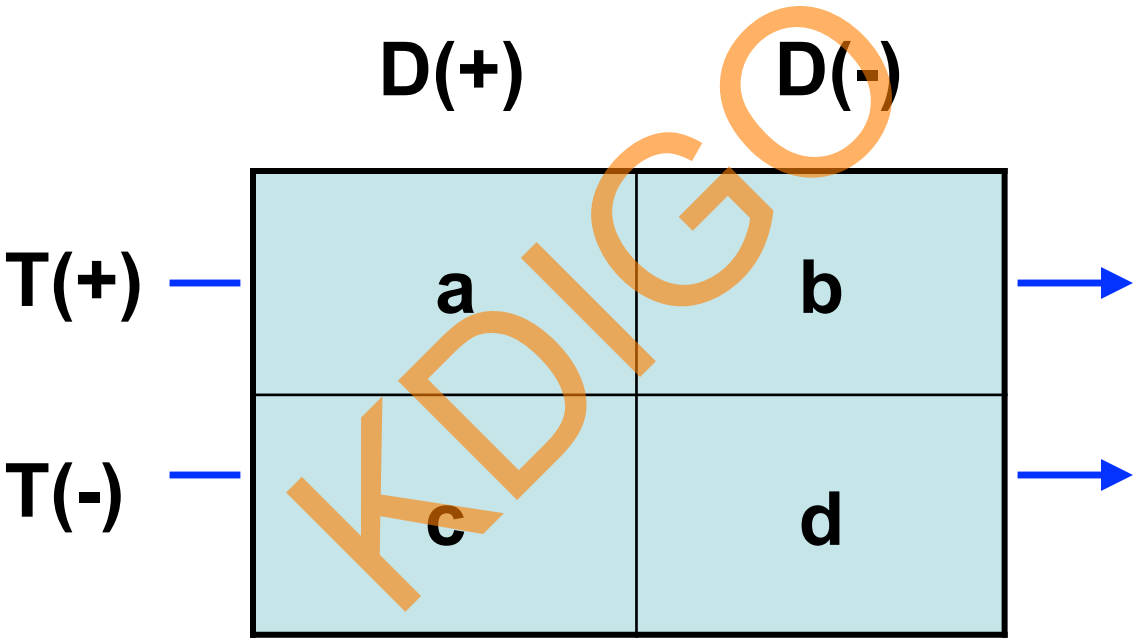
Diagnostic Testing (III)



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PPV = a/(a+b)
NPV = d/(c+d)

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U/S Diagnostic Criteria for PKD1

Age	SEN (%)	SPEC (%)	PPV (%)	NPV (%)
< 30 yrs[1]	88.5	100	100	96.6
30-59 yrs[2]	100	100	100	100
≥ 60 yrs[3]	100	100	100	100

Ravine criteria:

1. A total of 2 cysts in both kidneys
2. 2 or more cysts in each kidney
3. 4 or more cysts in each kidney

- Do these criteria perform equally well in PKD2?

Lancet 343: 824-827, 1994

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Unified Ultrasound Diagnostic Criteria for ADPKD

Y. Pei[1], A. Dupuis[2], A. Paterson[2], R. Magistroni[1,3], E. Dicks[4], P. Parfrey[4], B. Cramer[4], E. Coto[5], R. Torra[6], J.L. SanMillan[7], M. Breuning[8], D. Peters[8], D. Ravine[9]

[1]University Health Network, Toronto, Canada; [2]Hospital for Sick Children, Toronto, Canada; [3]University of Modena, Modena, Italy; [4]Memorial University, St. Johns, Newfoundland, Canada; [5]Hospital Central de Asturias, Oviedo, Spain; [6]Fundacio Puigvert, Barcelona, Spain; [7]Unidad de Genetica Molecular, Hospital Ramon y Cajal, Madrid, Spain; [8]Leiden University Medical Center, Leiden, Netherlands, [9]University of Western Australia, Perth, Australia

JASN 20: 205-212, 2009

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Study Design

- Retrospective study of 58 PKD1 and 39 PKD2 families from 8 international PKD research centers
  - 577 subjects borne with 50% risk of PKD1
  - 371 subjects borne with 50% risk of PKD2
- U/S performed using a 3 or 5 MHz sector probe with scanners from >10 years ago
- Molecular Dx ("gold standard") by either linkage or gene-based mutation screen of PKD1 and PKD2
- U/S and molecular studies collated to evaluate the performance of different age-specific diagnostic criteria for PKD1, PKD2, and unknown gene type

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Unified Ultrasound Diagnostic Criteria

Age (yrs)	PKD1	PKD2	Unknown Gene Type
15-30[1]	PPV=100% SEN=94.3%	PPV=100% SEN=69.5%	PPV=100% SEN=81.7%
30-39[1]	PPV=100% SEN=96.6%	PPV=100% SEN=94.9%	PPV=100% SEN=95.5%
40-59[2]	PPV=100% SEN=92.6%	PPV=100% SEN=88.8%	PPV=100% SEN=90%

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1. A total of 3 cysts in both kidneys
2. 2 or more cysts in each kidney

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Exclusion of ADPKD

by absence of renal cyst

Age (yrs)	PKD1	PKD2	Unknown Gene Type
15-30	NPV=99.1% SPEC=97.6%	NPV=83.5% SPEC=96.6%	NPV=90.8% SPEC=97.1%
30-39	NPV=100% SPEC=96%	NPV=96.8% SPEC=93.8%	NPV=98.3% SPEC=94.8%
40-59[2]	NPV=100% SPEC=93.9%	NPV=100% SPEC=93.7%	NPV=100% SPEC=93.9%

JASN 20: 205-212, 2009

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Unified Ultrasound Diagnostic Criteria

Limitations

- Applies only to at-risk subjects with +ve family Hx (i.e. borne with 50% risk)
- Disease exclusion is not possible in younger at-risk subjects (<40 years of age)
- Results may not be generalizable to new generations of U/S scanners

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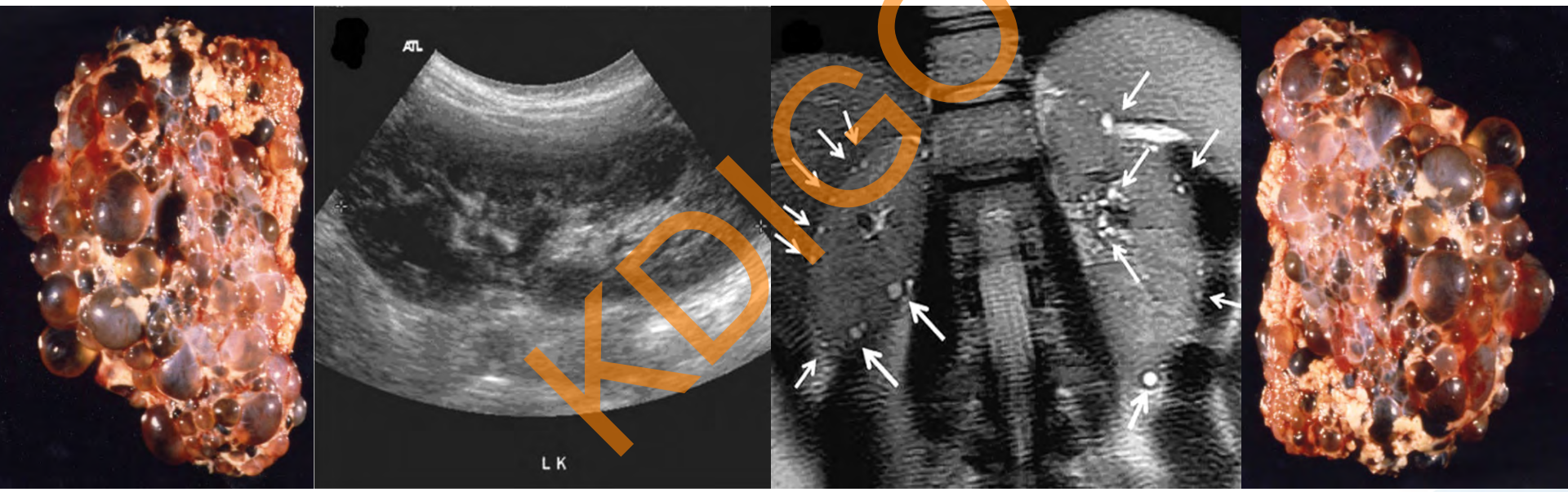
Evolution of Imaging-Based Diagnosis of ADPKD



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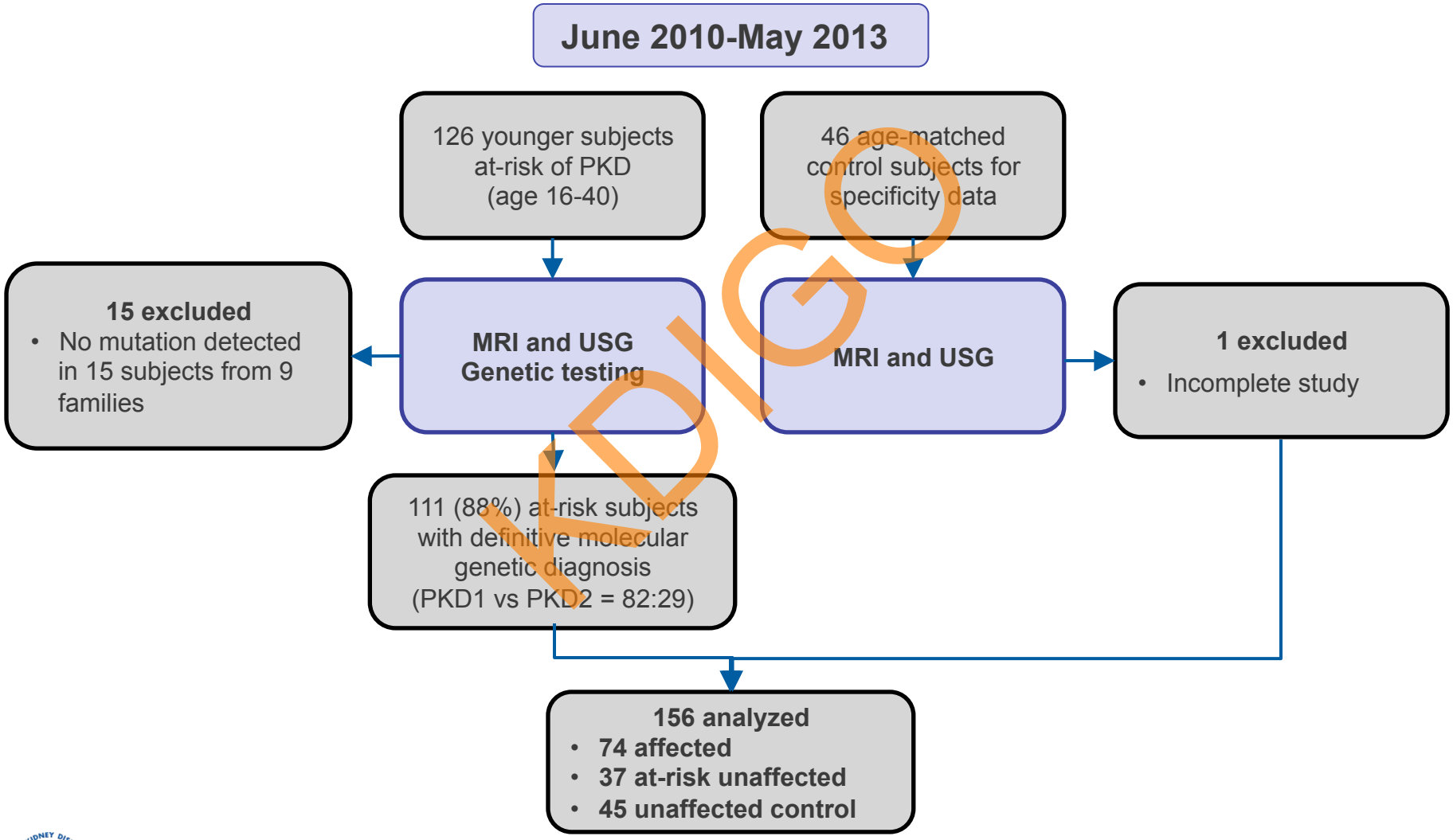
Toronto Radiologic Imaging Studies of Polycystic Kidney Disease (TRISP)



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Methods: Imaging Techniques

- **MRI:** Performed at TGH using a respiratory triggered T2 weighted axial fat suppressed fast spin echo sequence on a 1.5T scanner. Cyst number was enumerated (by J.C. and M.H.) if cyst count/kidney was <10. For a kidney with >10 cysts, enumeration was not performed.

- **USG:** Performed at TGH by experienced technicians (supervised by M.A.) using a Toshiba Aplio (with L6 MHz and C3.5MHz probes) or Philips IU22 (with C1-5 MHz and L4-8 MHz probes). Cyst number <10/kidney was enumerated for each kidney. For a kidney with >10 cysts, enumeration was not performed.

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Methods: Molecular Diagnosis

- Direct sequencing of all coding regions and splice sites of *PKD1* and *PKD2* in an affected family member of the proband. In any mutation-negative case, MLPA was performed to detect large gene rearrangements
- For hypomorphic *PKD1* mutations, segregation analysis was performed with additional affected and older (>40 years) unaffected family members, whenever possible
- DNA samples of test subjects were then screened for their family-specific mutation by sequencing or MLPA to define the disease status

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Characteristics of Study Subjects

	PKD1 Truncating Mutations	PKD1 Hypomorphic Mutations	PKD2 Mutations	Control
Total, N (%)	57 (52)	25 (21)	29 (27)	45
Age, 16-29, N (%) 30-40, N (%)	37 (65) 20 (35)	13 (48) 12 (52)	14 (48) 15 (52)	32 (71) 13 (29)
Male, N (%)	25 (44)	13 (52)	10 (35)	23 (51)
Disease status Affected, N (%) Unaffected, N (%)	 35 (61) 22 (39)	 21 (87) 4 (13)	 18 (62) 11 (38)	 45
TKV (ml) (median) Affected Unaffected	 806* 304	 476 279	 424 310	 N/A 307
S-[Cr] (μM)	79 [50-120]	79 [56-98]	66 [50-85]	

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*P=0.001 (Kruskal-Wallis test)

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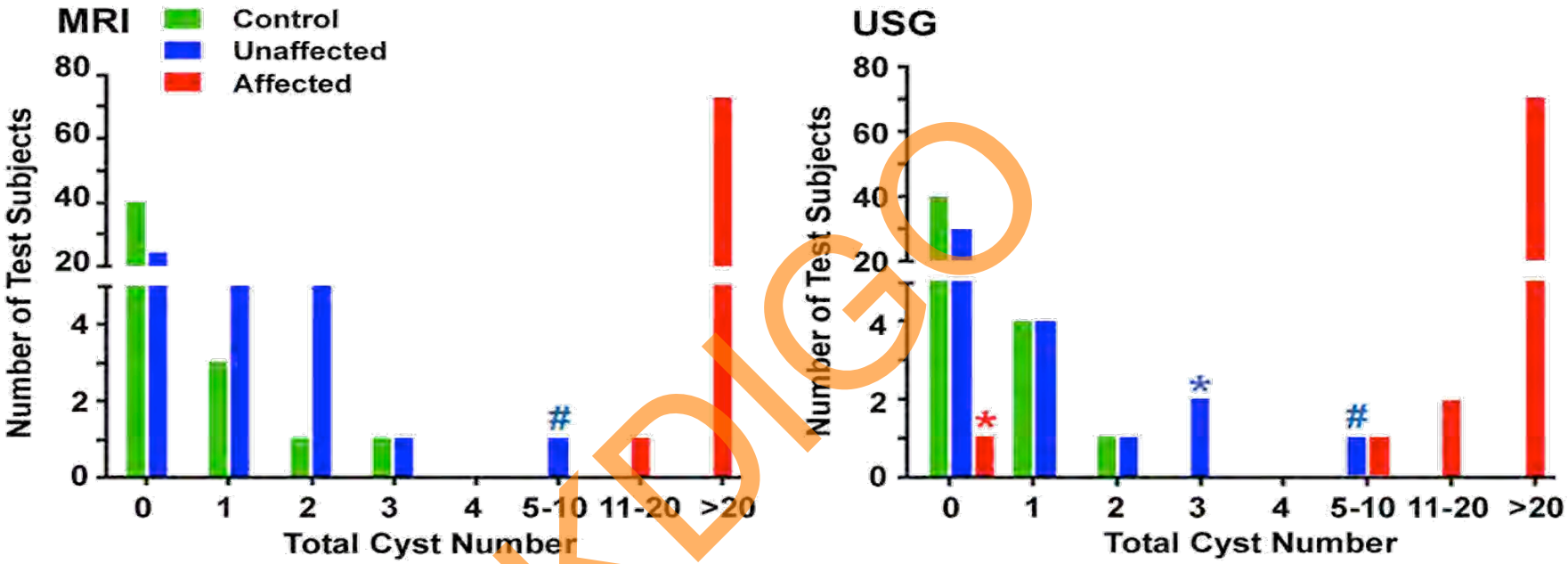
Total Cyst Count by Disease Status



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*25 y.o. male with 15 and 18 cysts in each kidney by MRI (max diameter 5-6 mm), but no cyst on USG. He carried a hypomorphic *PKD1* mutation (i.e. A2752P) which segregated in a family of 4 affected with mild ADPKD. His BMI was 35.6

*USG detected 3 cysts in each of 2 male subjects (36 & 40y). However, MRI showed ≤2 cysts in these subjects and their molecular diagnosis was negative.

#30 y.o. male with 6 cysts in his right kidney by USG, a total of 10 renal cysts (6 in RK and 4 in LK) by MRI, but negative for a *PKD2* (IVS5+1G>A) mutation identified in his family.

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Total Cyst number by USG vs MRI

At-Risk Subjects

MRI \ USG	0	1	2	3	4	5-10	11-20	>20	
0	19	3	1	1*					24
1	6								6
2	3	1		1*					5
3	1								1
4									0
5-10						1*			1
11-20							1		1
>20	1#					1	1	70	73
	30	4	1	2	0	2	2	70	111

Controls

MRI \ USG	0	1	2	3	4	5~10	11~20	>20	
0	37	3							40
1	2	1							3
2	1								1
3			1						1
4									0
5~10									0
11~20									0
>20									0
	40	4	1	0	0	0	0	0	45

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Blue and red color denote affected and unaffected subjects, respectively

*False +ve Dx by USG using the criterion of 3 cysts in both kidneys

#False -ve Dx by USG in a subject with poor body habitus

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Discordant Cases

ID	Age	Disease status	Mutation	MRI, RK	MRI, LK	USG, RK	USG, LK	Comment
AC[#]	25	*PKD1* (A)	p.Ala2752Asp	15	18	0	0	Cyst size 2-6 mm on MRI; BMI 35.6 (suboptimal USG)
CW*	30	*PKD2* (ARUA)	IVS5+1G>A	6	4	6	0	Cyst size 2-10 mm on MRI and USG
CW*	40	*PKD1* (ARUA)	p.Pro3551fs111X	1	1	2	1	Cyst size 2-6 mm on MRI and USG
PF*	36	*PKD2* (ARUA)	p.Val569fs3X	0	0	3	0	Cyst size 2-5 mm on USG

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Performance Characteristics of USG

Age group (yr)	Diagnostic criterion	Study subjects	SEN	SPEC	PPV	NPV
15-29		**(Affected, n=38; Unaffected, n=58)**				
	≥1 renal cyst	Present study	0.97	0.85	0.80	0.98
		Pei et al (2009)	0.89	0.97	0.97	0.91
	≥2 renal cysts	Present study	0.97	0.95	0.93	0.98
		Pei et al (2009)	0.99	0.88	0.99	0.88
	≥3 renal cysts	**Present study**	**0.97**	**0.98**	**0.97**	**0.98**
		Pei et al (2009)	**0.82**	**1.00**	**0.86**	**1.00**
	≥2 cysts in each kidney	Present study	0.97	1.00	1.00	0.98
		Pei et al (2009)	NA	NA	NA	NA
30-40		**(Affected, n=36; Unaffected=24)**				
	≥1 renal cyst	Present study	1.00	0.83	0.90	1.00
		Pei et al (2009)	0.98	0.95	0.94	0.98
	≥2 renal cysts	Present study	1.00	0.92	0.95	1.00
		Pei et al (2009)	0.96	0.98	0.98	0.97
	≥3 renal cysts	**Present study**	**1.00**	**0.92**	**0.95**	**1.00**
		Pei et al (2009)	**0.96**	**1.00**	**1.00**	**0.96**
	≥2 cysts in each kidney	Present study	1.00	1.00	1.00	1.00
		Pei et al (2009)	0.83	1.00	0.88	1.00

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Performance Characteristics of MRI

Age group (yr)	Diagnostic criterion	No. of Affected	No. of Unaffected	SEN	SPEC	PPV	NPV
15-29		N=38	N=58				
	≥1 renal cyst	38	11	1.00	0.81	0.78	1.00
	≥2 renal cysts	38	4	1.00	0.93	0.91	1.00
	≥3 renal cysts	38	2	1.00	0.97	0.95	1.00
	≥5 renal cysts	38	1	1.00	0.98	0.97	1.00
	>10 renal cysts	**38**	**0**	**1.00**	**1.00**	**1.00**	**1.00**
	≥2 cysts in each kidney	38	1	1.00	0.98	0.97	1.00
30-40		N=36	N=24				
	≥1 renal cyst	36	7	1.00	0.71	0.84	1.00
	≥2 renal cysts	36	5	1.00	0.79	0.88	1.00
	≥3 renal cysts	36	1	1.00	0.96	0.97	1.00
	≥5 renal cysts	36	0	1.00	1.00	1.00	1.00
	>10 renal cysts	**36**	**0**	**1.00**	**1.00**	**1.00**	**1.00**
	≥2 cysts in each kidney	36	0	1.00	1.00	1.00	1.00

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Imaging-Based Diagnosis of ADPKD

Concluding Remarks

- MRI is highly sensitive and specific for early Dx and exclusion of ADPKD
- USG using modern scanners performed better than expected with results rivaling those by MRI. However, it is both operator and center-dependent and may be influenced by body habitus of test subjects
- Revision of current USG Dx criteria is needed to reflect improved imaging resolution of new scanners. Pending replication, our USG results should not be generalized to other centers at this time

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Evolution of Imaging-based diagnosis of ADPKD

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Evolution of Imaging-Based Diagnosis

- How and when should ultrasound, CT (contrast-enhanced) or MRI be used to diagnose ADPKD?
- Are the current US-based criteria for diagnosis and disease exclusion appropriate?
- Specific evaluation of ADPKD living-related donors?
- What criteria should be used for high-resolution US and what are its potential barriers?
- Is there any role for imaging-based diagnosis of ADPKD in subjects without a family history?

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