Classification and Approach to Cystic Kidney Disease in Children

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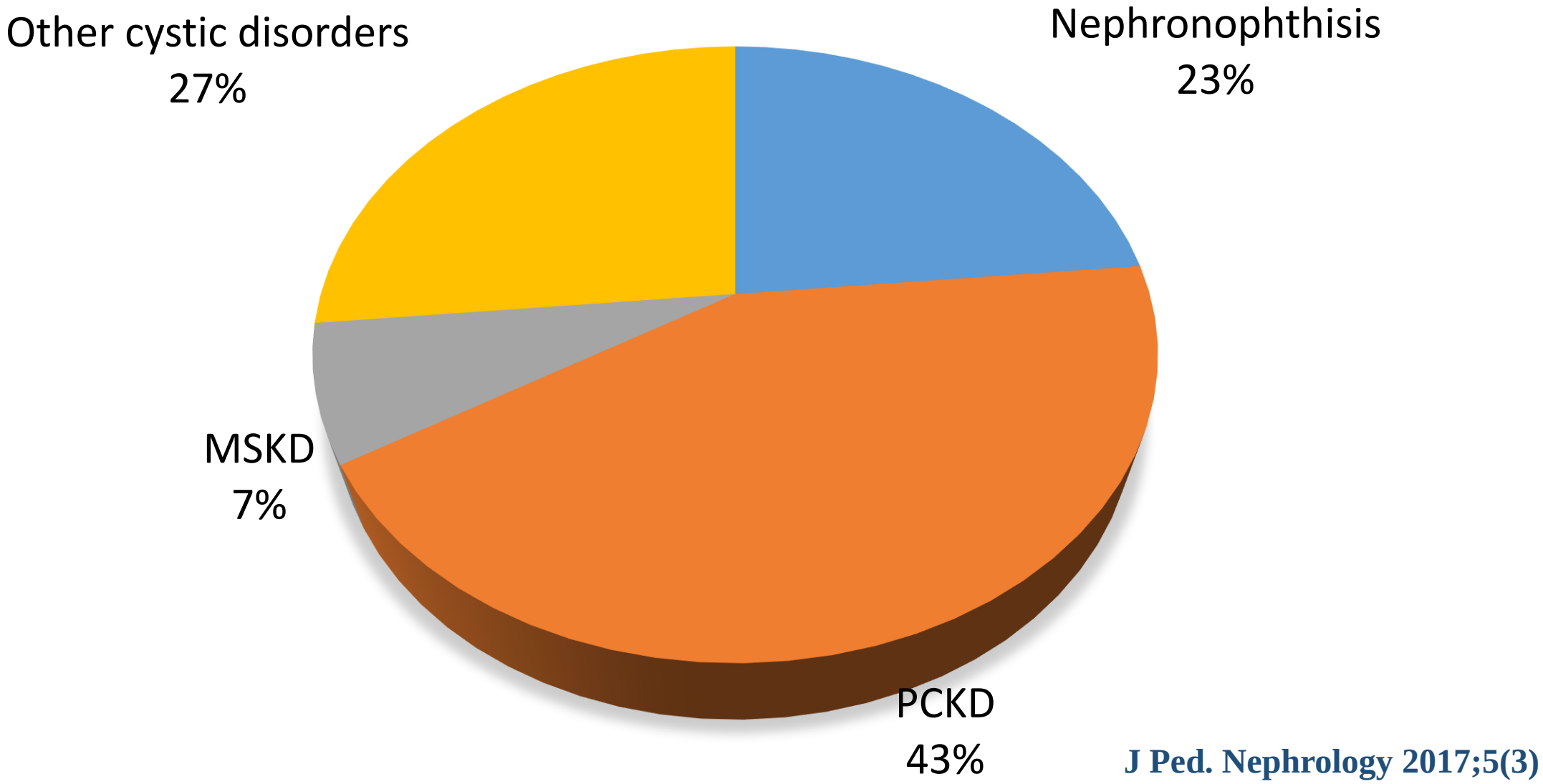
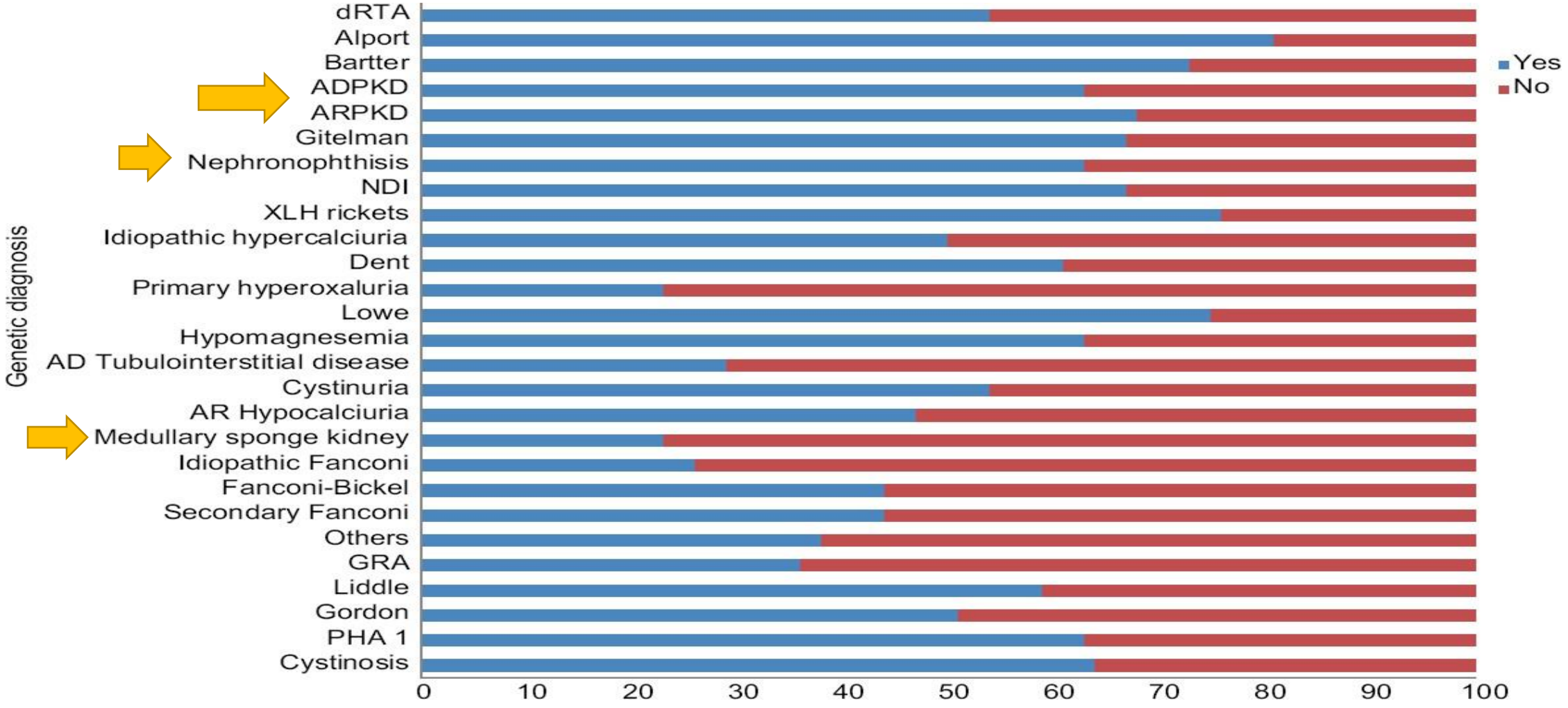
Frequency of inherited cystic disease in Iranian Children
28.8 pmp children <15 yr



J Ped. Nephrology 2017;5(3)

Percentage of Cystic Kidney disease that had genetic diagnosis in Asia



Asian Journal of Pediatric Nephrology 5(1):p 14-20, Jan–Jun 2022. | *DOI:* 10.4103/ajpn.ajpn_2_22

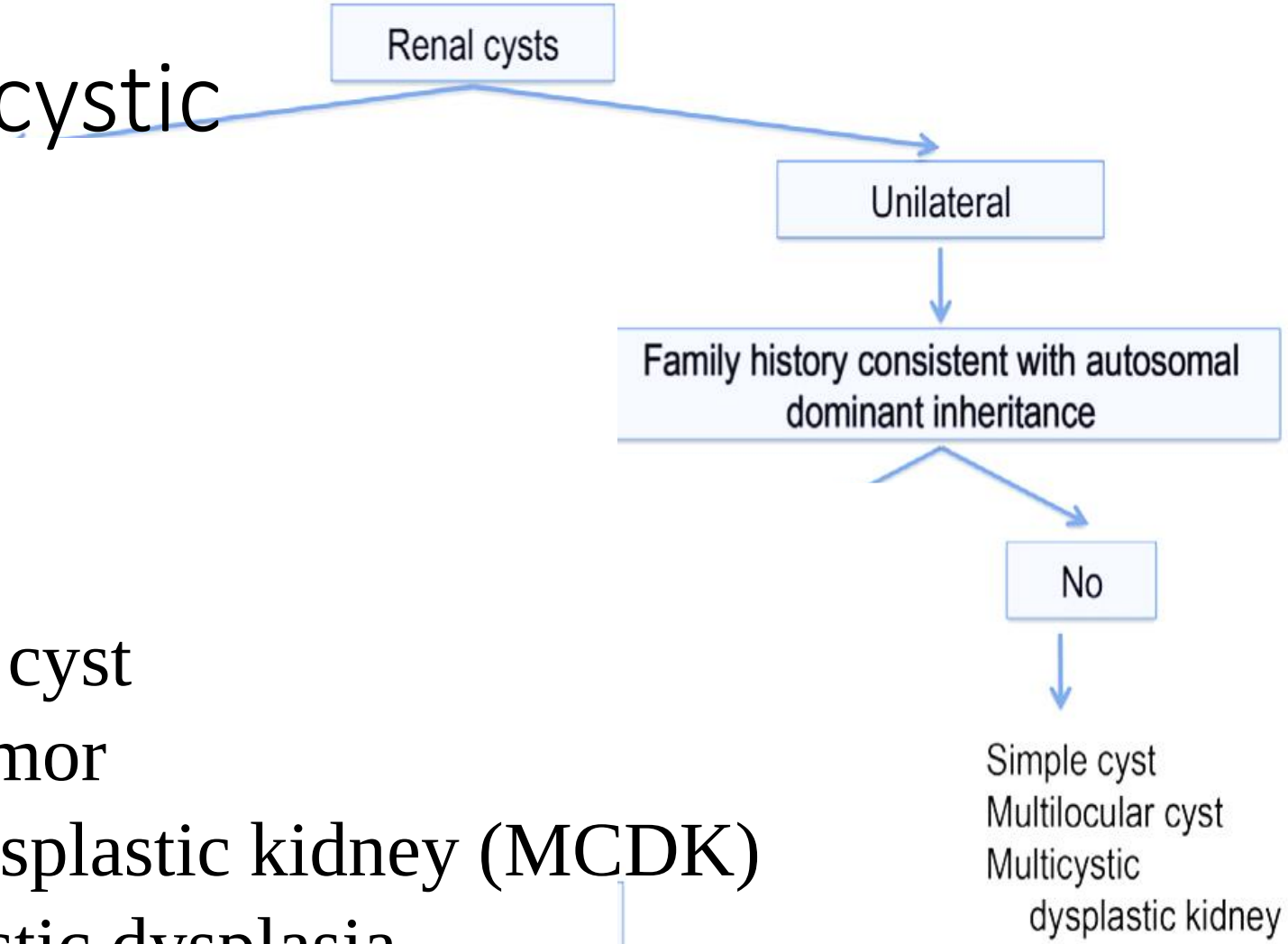
Etiology of CKD in Iran (**N:1247**) compared to other similar studies

	Registry [reference]	NAPRTCS[6]	Italy[10]	Belgium[29]	Iran	ANZDATA[34]	ESPN/ERA-EDTA [37]	UK [36]	Japan [32]
	Inclusion criteria	CKD(eGFR <75)	CKD(eGFR <75)	CKD(eGFR <60)	CKD(eGFR <75)	ESRD (RRT)	ESRD (RRT)	ESRD (RRT)	ESRD (RRT)
	Age (years)	0-20	0-19	0-19	0-19	0-19	0-15	0-15	0-19
	Period	1994 - 2007	1990 - 2000	2001-2005	1991-2009	2003-2008	2008	2004-2008	1998
	Study sample size	7,037	1,197	143	1247	369	499	428	582
	CAKUT	3,361 (48%)	689 (58.0%)	84 (59%)	499 (40%)	127 (34%)	182 (36.0%)	184(43%)	208 (36%)
	Hypodyspalasia±	1,907(27%)	516(43.1%)	66 (46.1%)	309 (24.7%)	95 (25.7%)	-	135(31.5%)	198 (34%)
Etiology	reflux nephropathy								
	Obstructive uropathy	1,454(20.6%)	173 (14.4%)	18 (12.6%)	190 (15.2%)	32 (8.7%)	-	49(11.4%)	10 (1.7%)
	Glomerulopathies	993 (14%)	55 (5%)	10 (7%)	237 (19.0%)	108 (29%)	76 (15%)	78(18%)	130 (22%)
	HUS	141 (2.0%)	43 (4%)	9 (6%)	40 (3.2%)	9 (2.0%)	29 (6%)	-	13 (2%)
	Hereditary nephropathies	717 (10%)	186 (15%)	27 (19%)	21 (1.7%)	-	112 (22%)	-	69 (12%)
	Congenital NS	75 (1%)	13 (1%)	5 (3.5%)	22 (1.8%)	7 (1.9%)	-	15(3.5%)	34 (5.8%)
	Metabolic disease	-	-	5 (3.5%)	-	-	17 (3.4%)	18(4.2%)	-
	Cystic kidney disease	368 (5.2%)	101 (8.4%)	13 (9%)	**43 (3.4%)**	25 (6.7%)	59 (11.8%)	49(11.4%)	35 (6%)
	Ischemic renal failure	158 (2%)	49 (4%)	3 (2%)	4 (0.3%)	8 (2%)	11 (2%)	-	11(1.9%)
	Miscellaneous conditions	1,485 (21.1%)	122 (10.2%)	10 (7%)	47 (3.8%)	65 (17.6%)	52 (10.4%)	19(4.4%)	83 (14.3%)
	Missing / unknown	182 (2.6%)	40 (3.3%)	-	228 (18.3%)	16 (4.3%)	37 (7.4%)	65 (15.2%)	34 (5.8%)

Urology Journal/Vol 18 No. 1/ 2021/ 122-130. [DOI: 10.22037/uj.v16i7.5759]

Non-hereditary cystic renal diseases

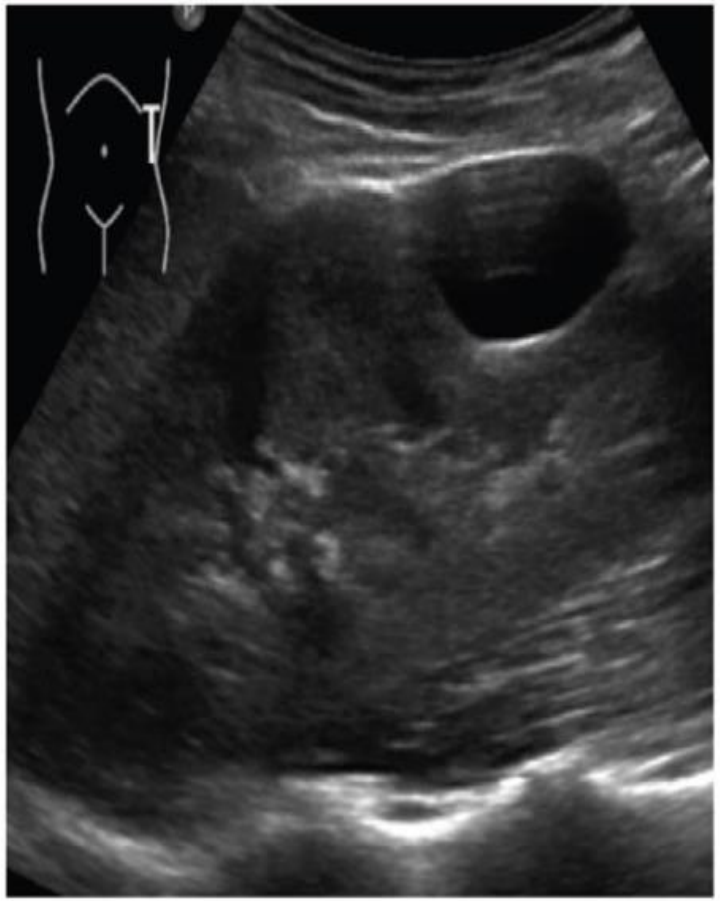
- Simple renal cyst
  - Congenital
  - Acquired
- Complex renal cyst
- Cystic renal tumor
- Multicystic dysplastic kidney (MCDK)
- Obstructive cystic dysplasia
- Medullary sponge kidney



Journal of Ultrasound (2019) 22:381–393
https://doi.org/10.1007/s40477-018-0347-9

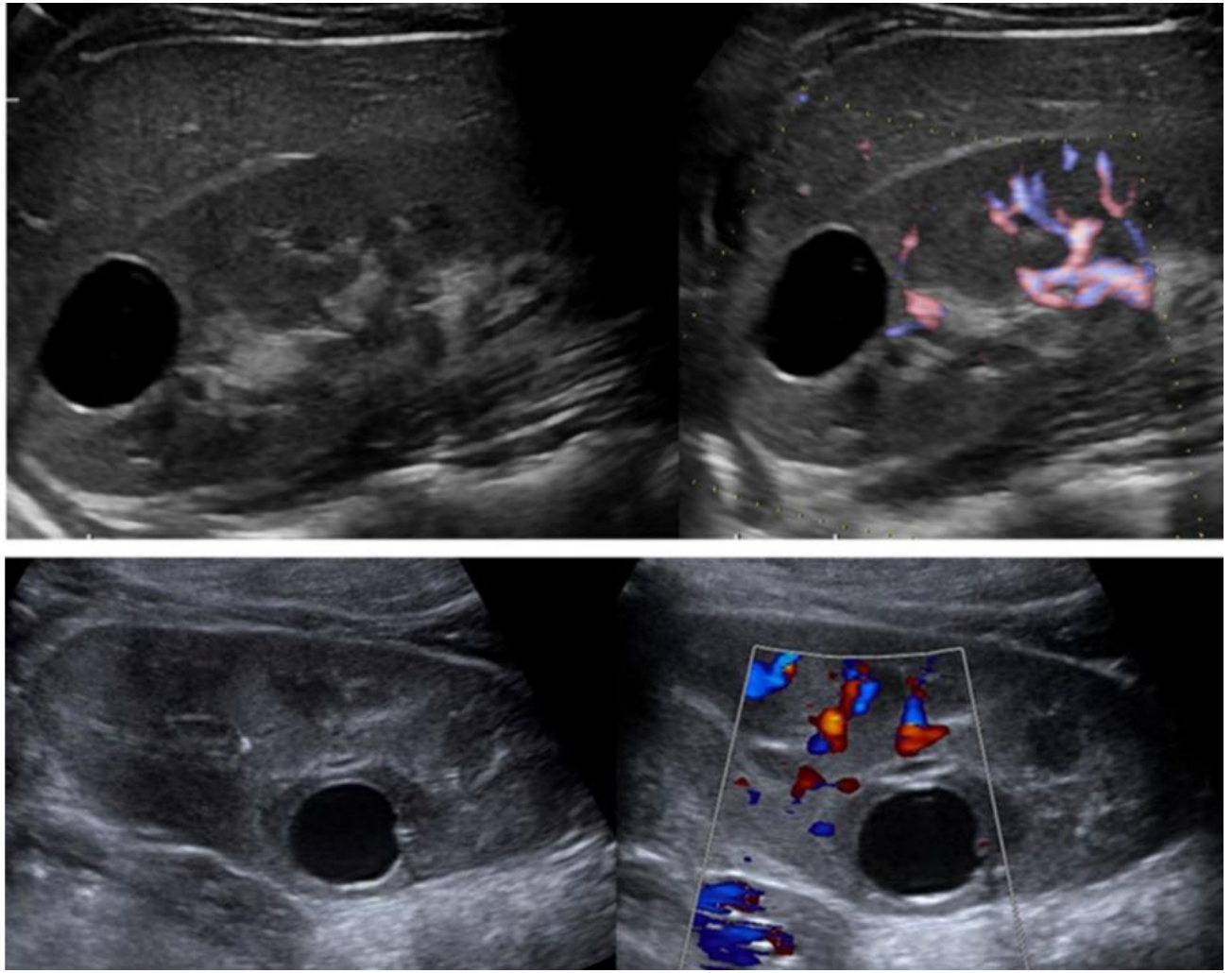
Advances in Chronic Kidney Disease, Vol 22, No 4 (July), 2015: pp 297-305

Simple cyst

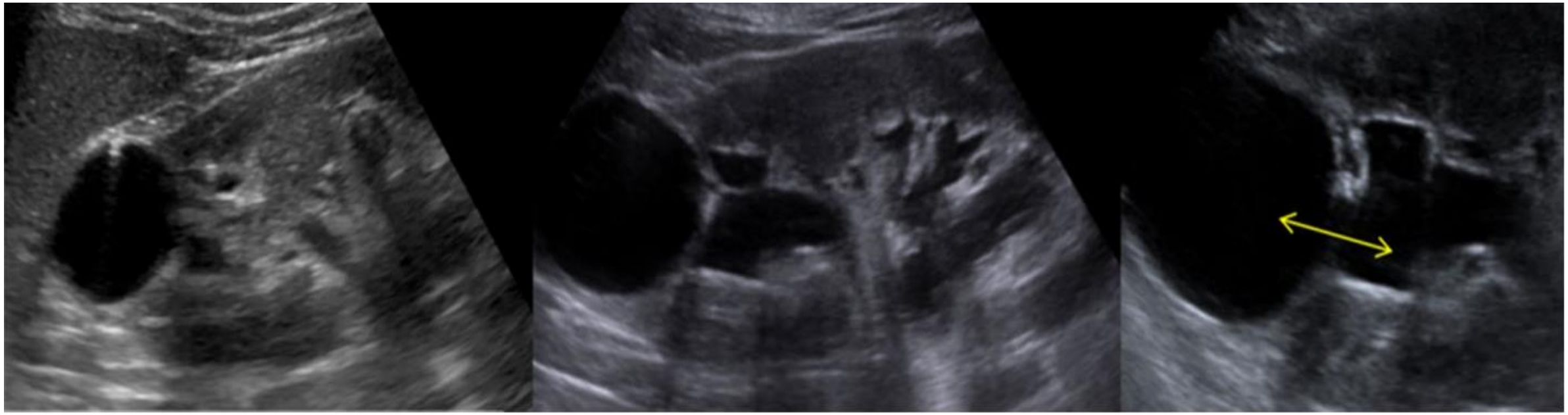
US Diagnosis	Image	Comment	Additional Imaging/ Follow-up
Simple cyst • single • round • thin-walled • anechoic • nonseptated • separate from collecting system • no Doppler flow • normal renal parenchyma		Diagnosis of exclusion in children	Clinical work-up and at least one follow-up US to rule out development of another cystic kidney disease. No need for contrast-enhanced US, MRI or CT.

Simple cyst

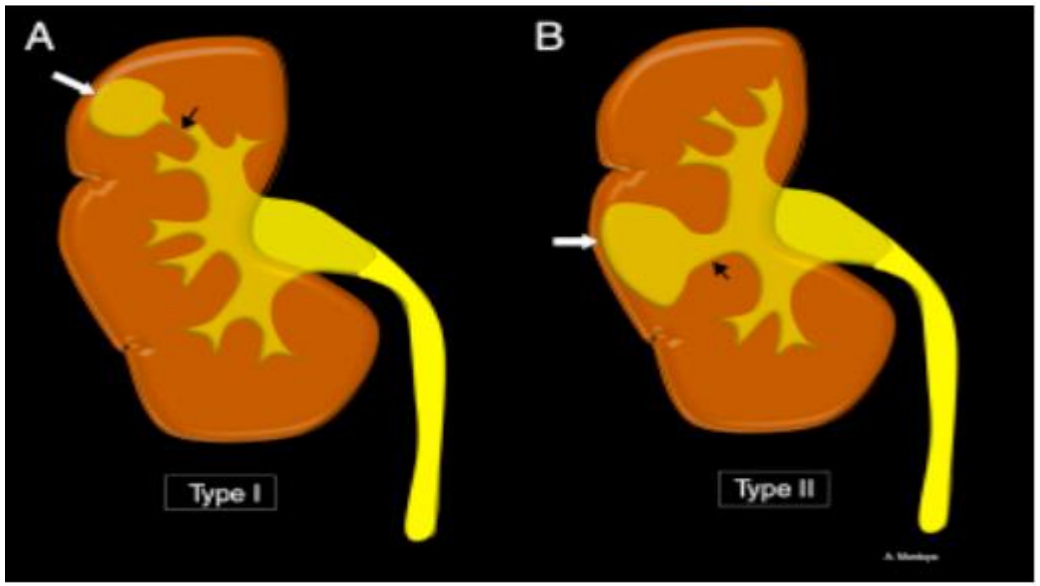
- 0.2–2% prevalence, 0.2–0.5% incidence
- Asymptomatic and symptomatic forms (abdominal pain, hematuria etc.)
- biannual clinical/ultrasound checks during the first year from diagnosis and annual checks for the following 10 years
- Cysts may disappear or show slight dimensional increase, approximately 0.3–1.6 mm/year in about 1–4% of the cases



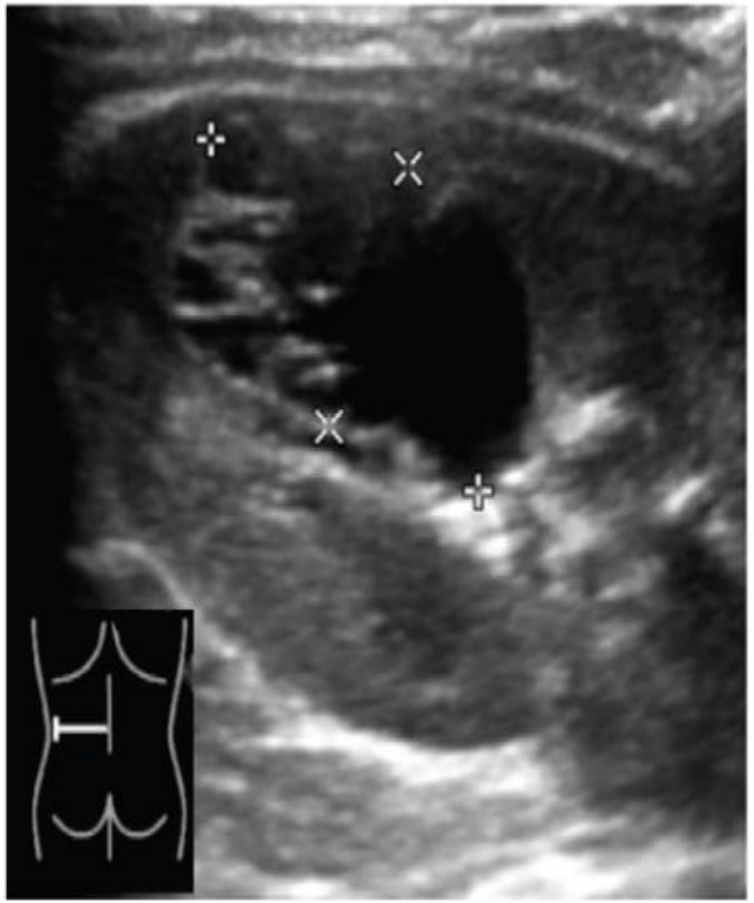
Caliceal diverticulum



Initially appear as a simple cyst suspicion of a diverticulum should arise when calculi are found in the ‘cyst’ or when scans show progressive abnormal increase in its size.

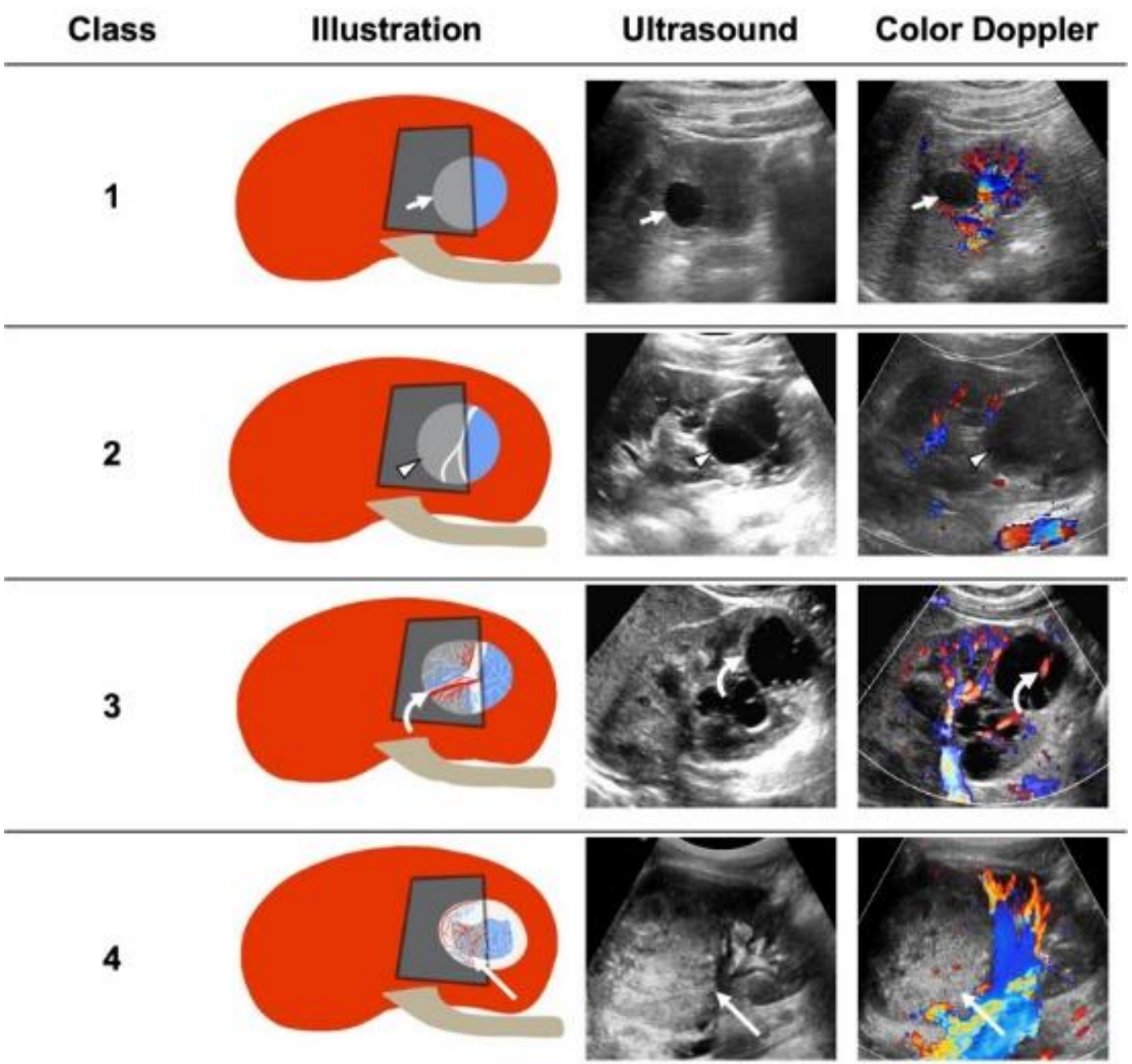


Complex cysts

Complex cysts Cyst with any of: • thickened wall • septations • calcifications • enhanced perfusion on color Doppler		Limited evidence in children suggests modified US Bosniak classification can be used to decide on need to biopsy.	Contrast-enhanced MRI if malignancy is suspected. Contrast-enhanced US in experienced centers.

Complex cysts and cystic tumors

- US has proven to be more sensitive than CT in the detection of septa and small nodules.
- US follow-up in children with class II cysts at 3–6- month intervals for the first year and then annually once the cysts are deemed to be stable.
- Contrast-enhanced CT or MR should be reserved for cystic lesions showing thickened wall, parietal nodules or irregular septa. If the report is positive, surgical excision is required.



Cureus. 2023 Apr; 15(4): e37331

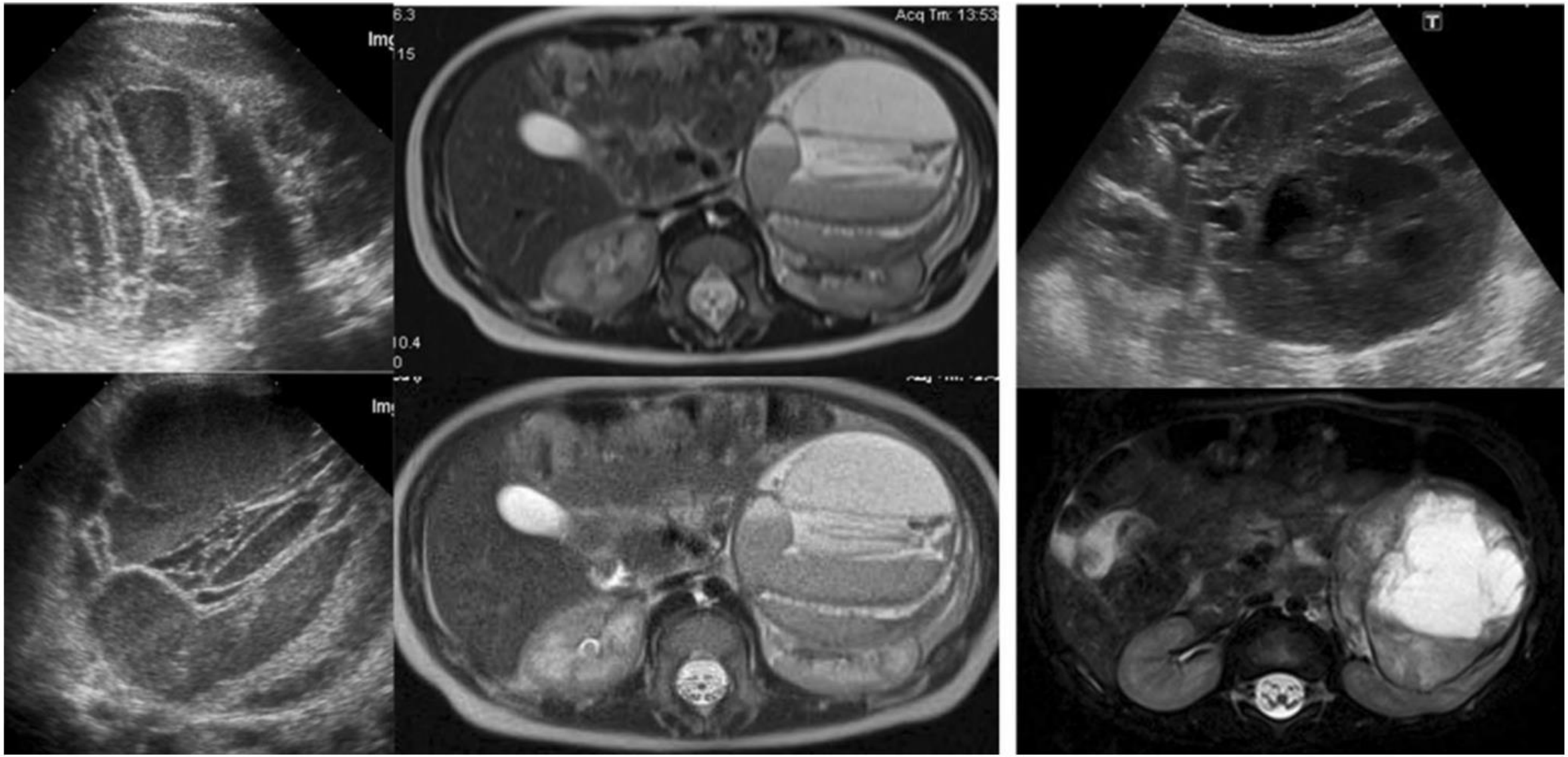
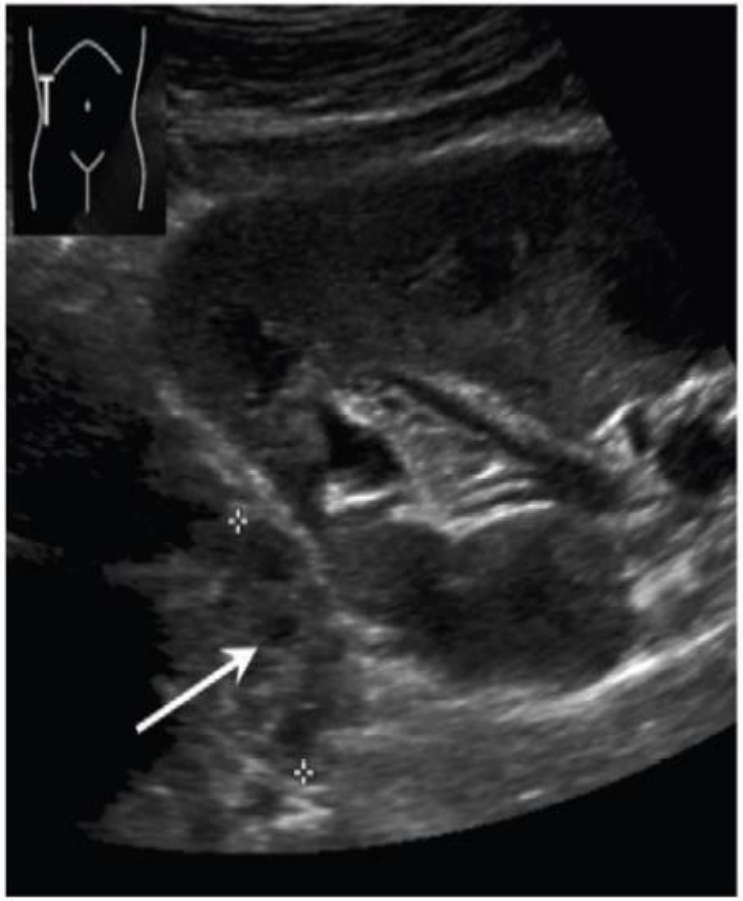
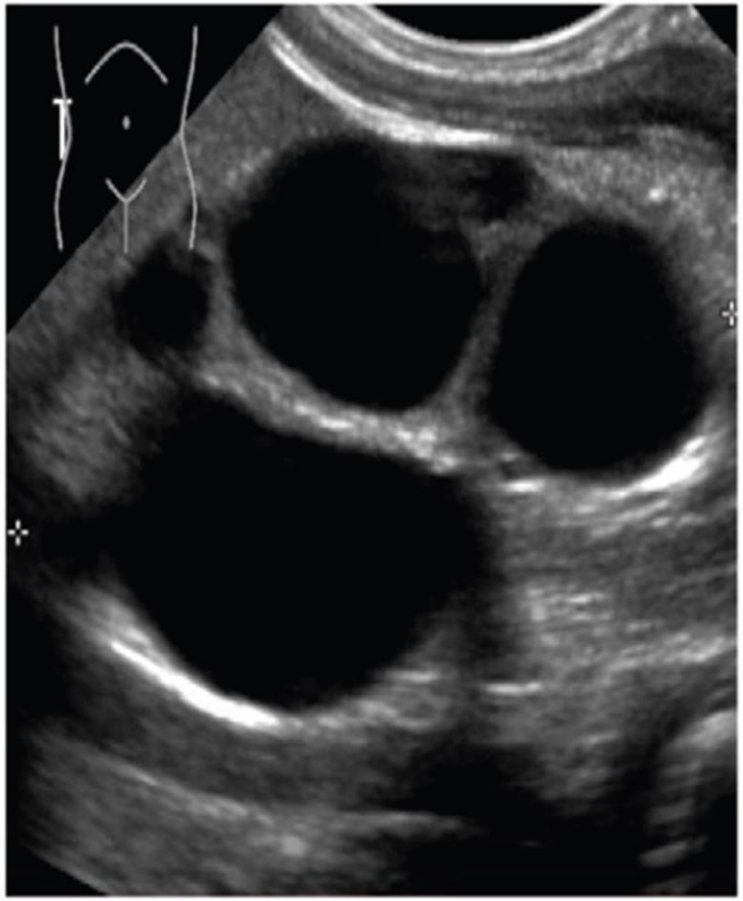


Fig. 9 Two examples of cystic pediatric renal tumors: US and MR appearance

Acquired cystic kidney disease

Acquired cystic kidney disease In patients with end-stage renal disease, after kidney or liver transplantation • multiple small cysts • bilaterally small kidneys		Increased risk of malignancy. **White arrow**: cyst in native kidney adjacent to kidney transplant.	Yearly US of native kidneys in at-risk individuals

MCKD

• normal renal parenchyma			
Multicystic Dysplastic Kidney (MCDK) • Multiple, disorganized cysts • No normal parenchyma		30% have abnormal contralateral kidney. 15% have extrarenal anomalies. Atypical presentation in duplex, horseshoe, or ectopic kidney.	Functional imaging unnecessary. US follow-up to ensure adequate compensatory hypertrophy of contra-lateral kidney (refer to pediatric nephrologist if inadequate).

MCDK

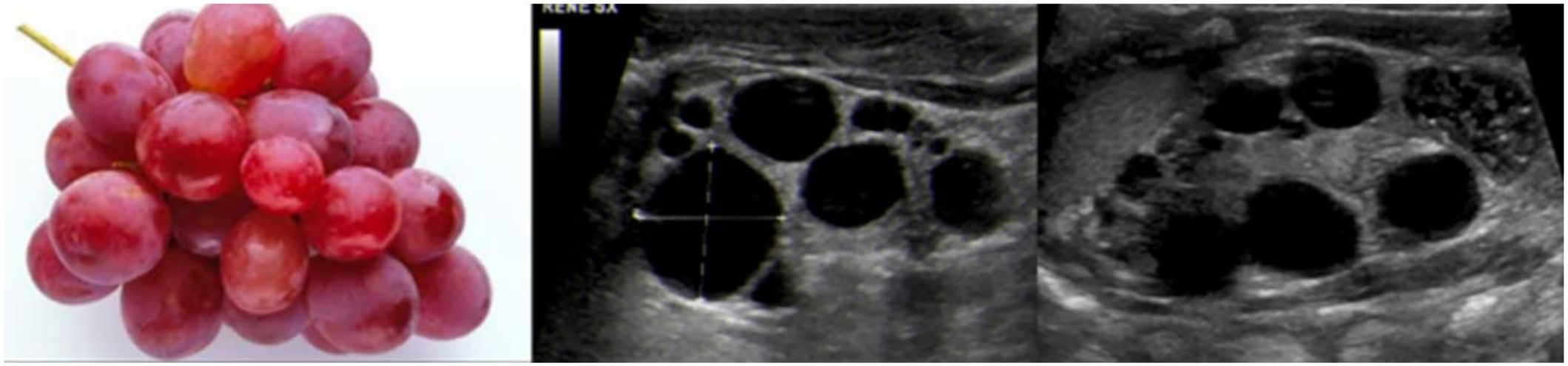
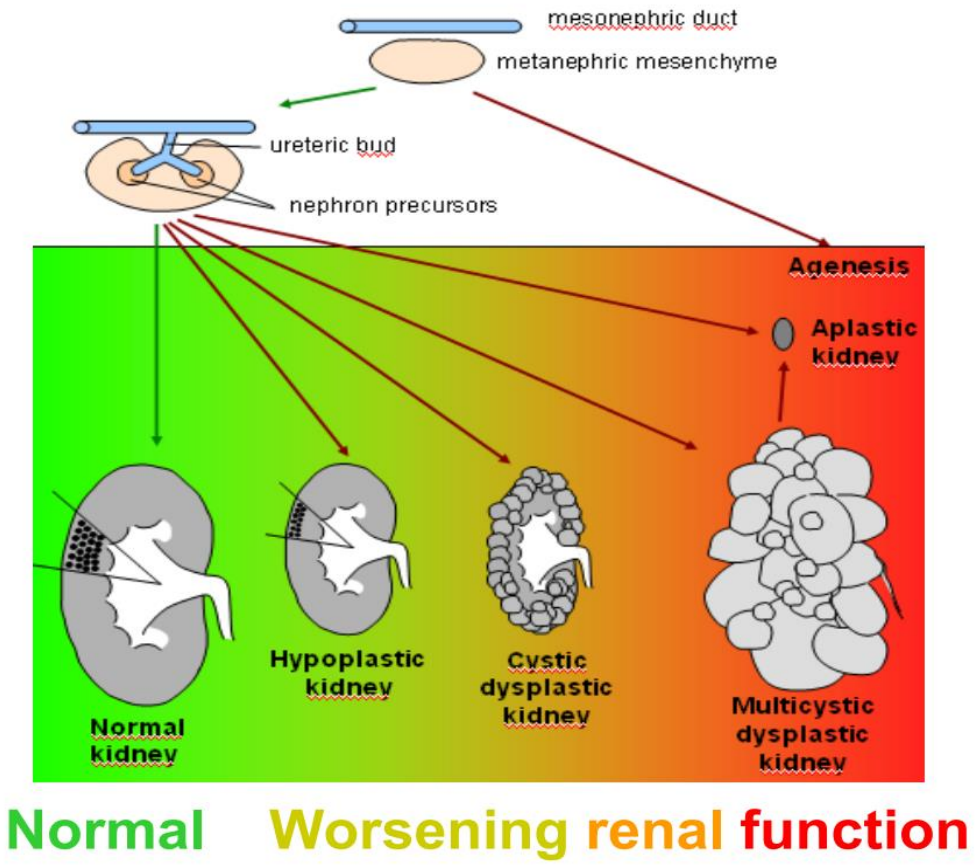


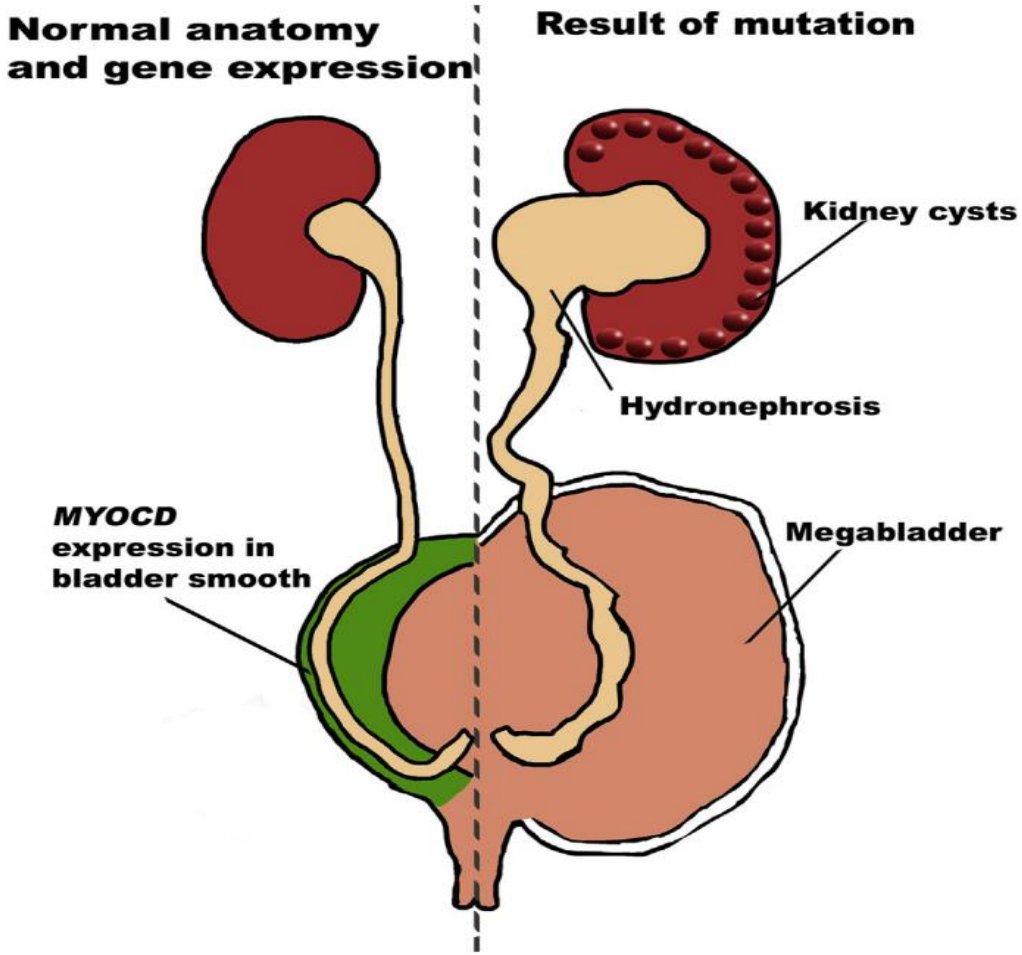
Fig. 10 MCDK: multiple cysts of variable size and dysplastic residual parenchyma in a central position

Dysplastic kidney

MCDK

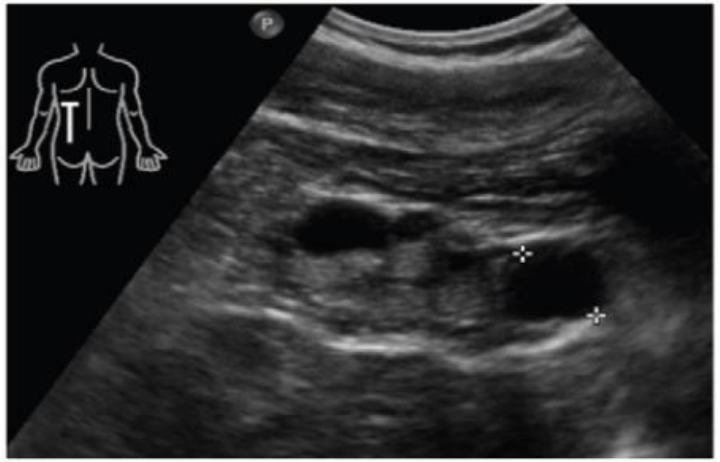
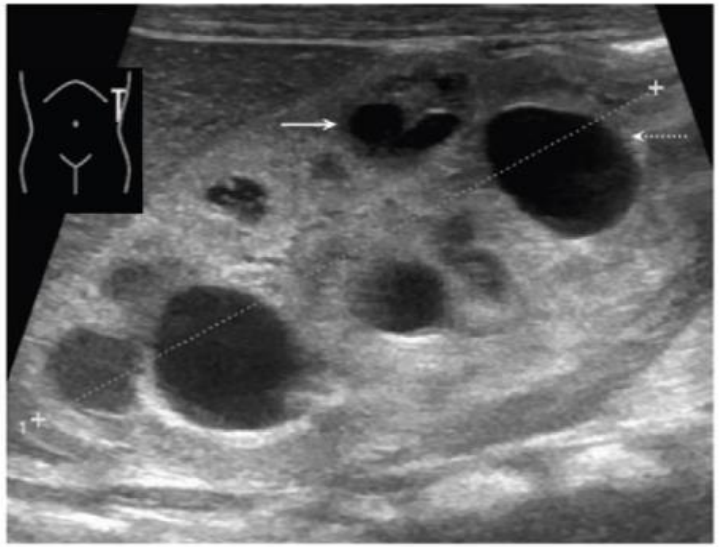


Obstructive



J Pediatr Urol. 2021 Oct;17(5):610-620. doi: 10.1016/j.jpurol.2021.07.002.

Cystic dysplasia

US Diagnosis	Image	Comment	Additional Imaging/ Follow-up
Cystic dysplasia • Abnormal renal parenchyma o Hyperechogenic o Loss of corticomedullary differentiation • Single or multiple cysts		Isolated or as part of a large number of syndromes. **Image a**: cystic dysplasia with hypoplasia.	Risk of confusion with high-grade urinary obstruction. Examine for urinary flow impairment if in doubt. Refer to pediatric nephrologist for evaluation of kidney function, proteinuria, and hypertension.
		**Image b**: cystic dysplasia with obstruction (pelvic dilatation = dashed arrow, cyst = solid arrow)	

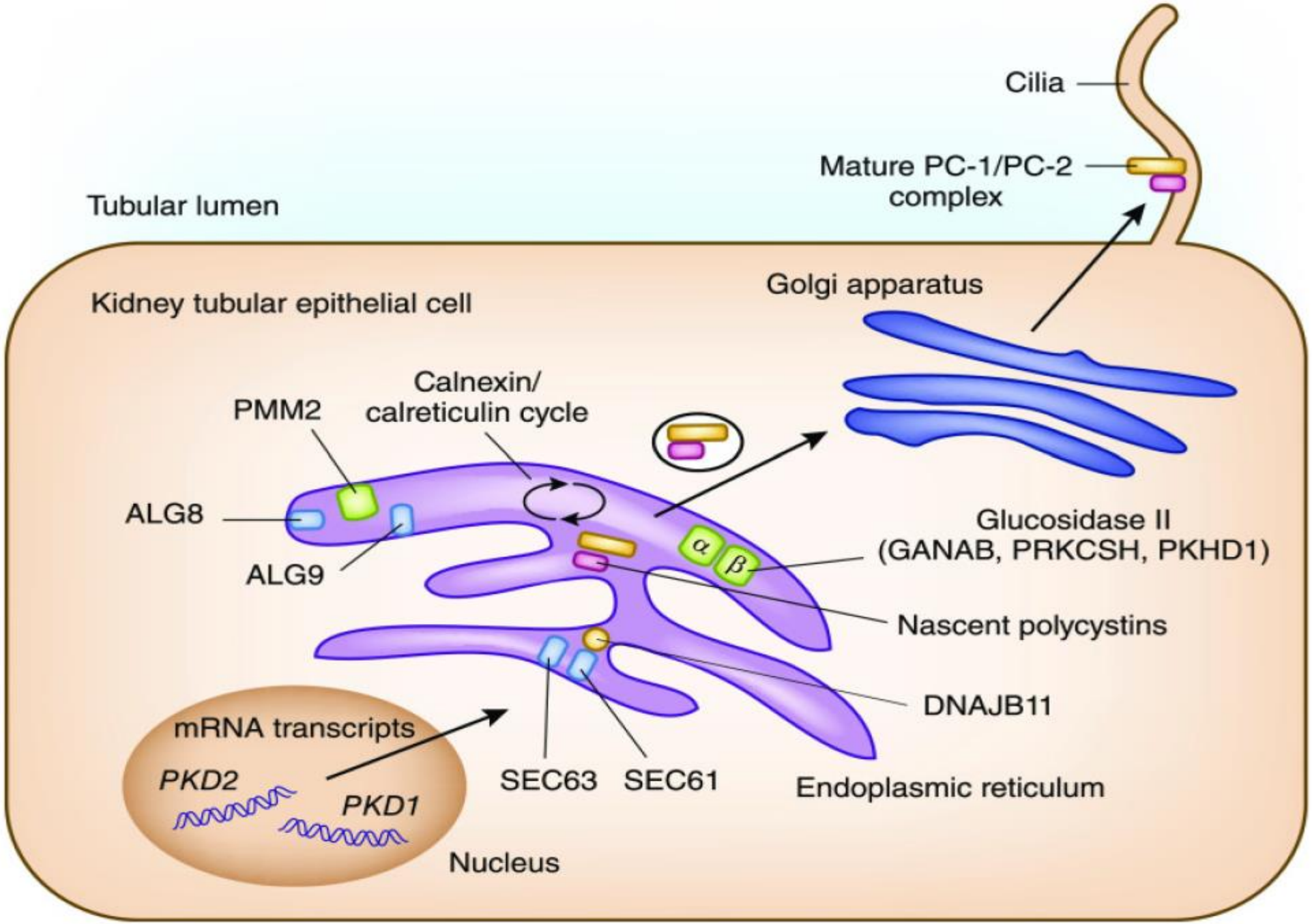
Hereditary cystic renal diseases

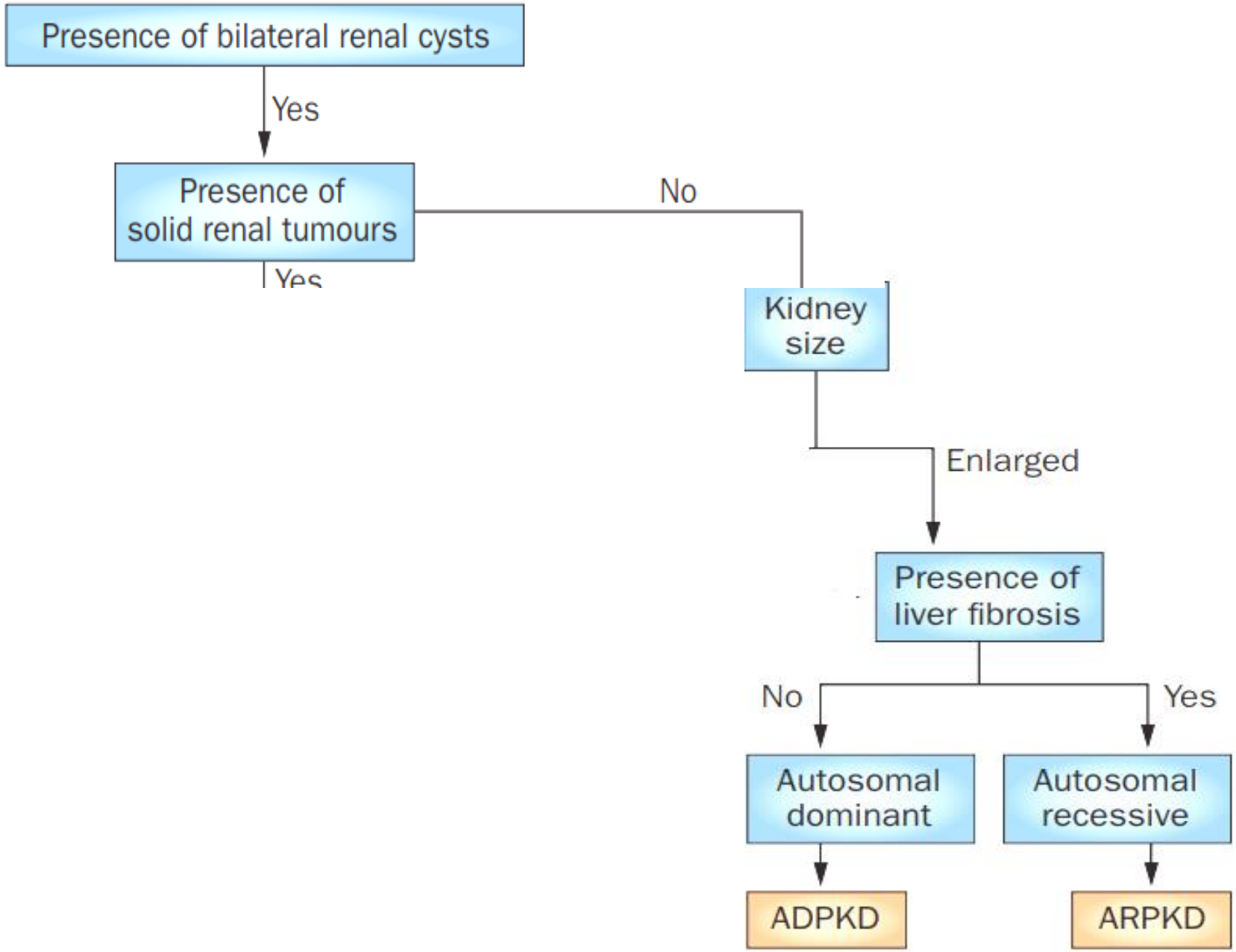
Ciliopathies

- Autosomal recessive polycystic kidney disease (ARPKD)
- Autosomal dominant polycystic kidney disease (ADPKD)
- Nephronophthisis
- Glomerulocystic kidney disease (GCKD)
- HNF1B/TCF2-associated disease

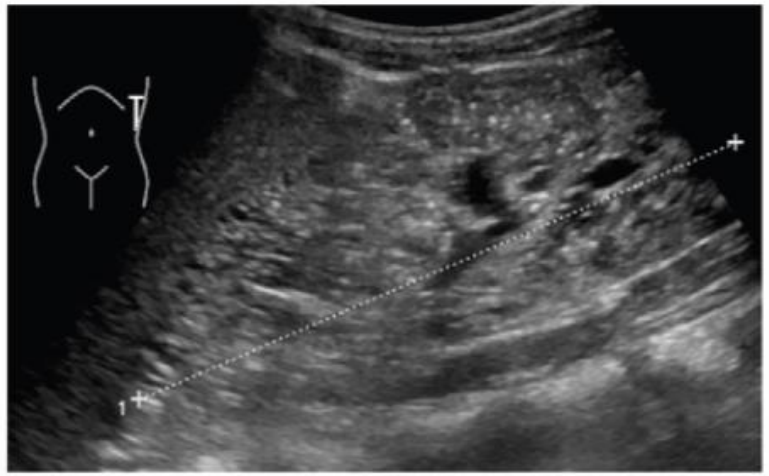
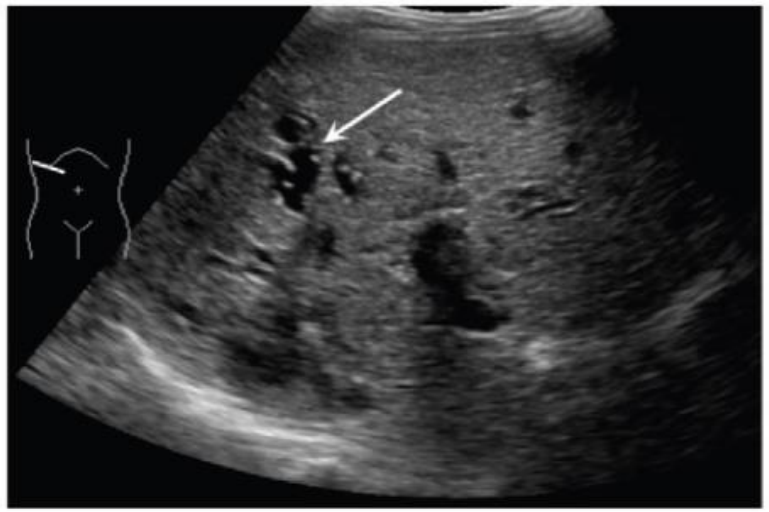
Syndromic diseases

- Tuberous sclerosis
- Von Hippel–Lindau syndrome

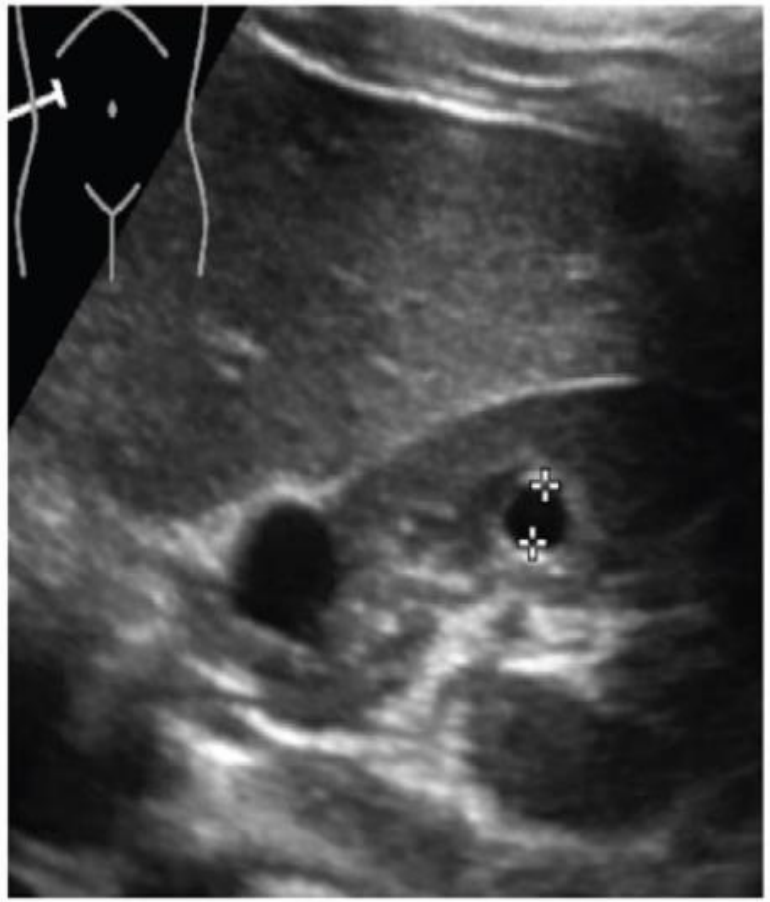

Cilia
Mature PC-1/PC-2 complex
Tubular lumen
Kidney tubular epithelial cell
Golgi apparatus
Calnexin/ calreticulin cycle
PMM2
ALG8
ALG9
Glucosidase II (GANAB, PRKCSH, PKHD1)
α
β
Nascent polycystins
DNAJB11
mRNA transcripts
PKD2
PKD1
SEC63
SEC61
Endoplasmic reticulum
Nucleus

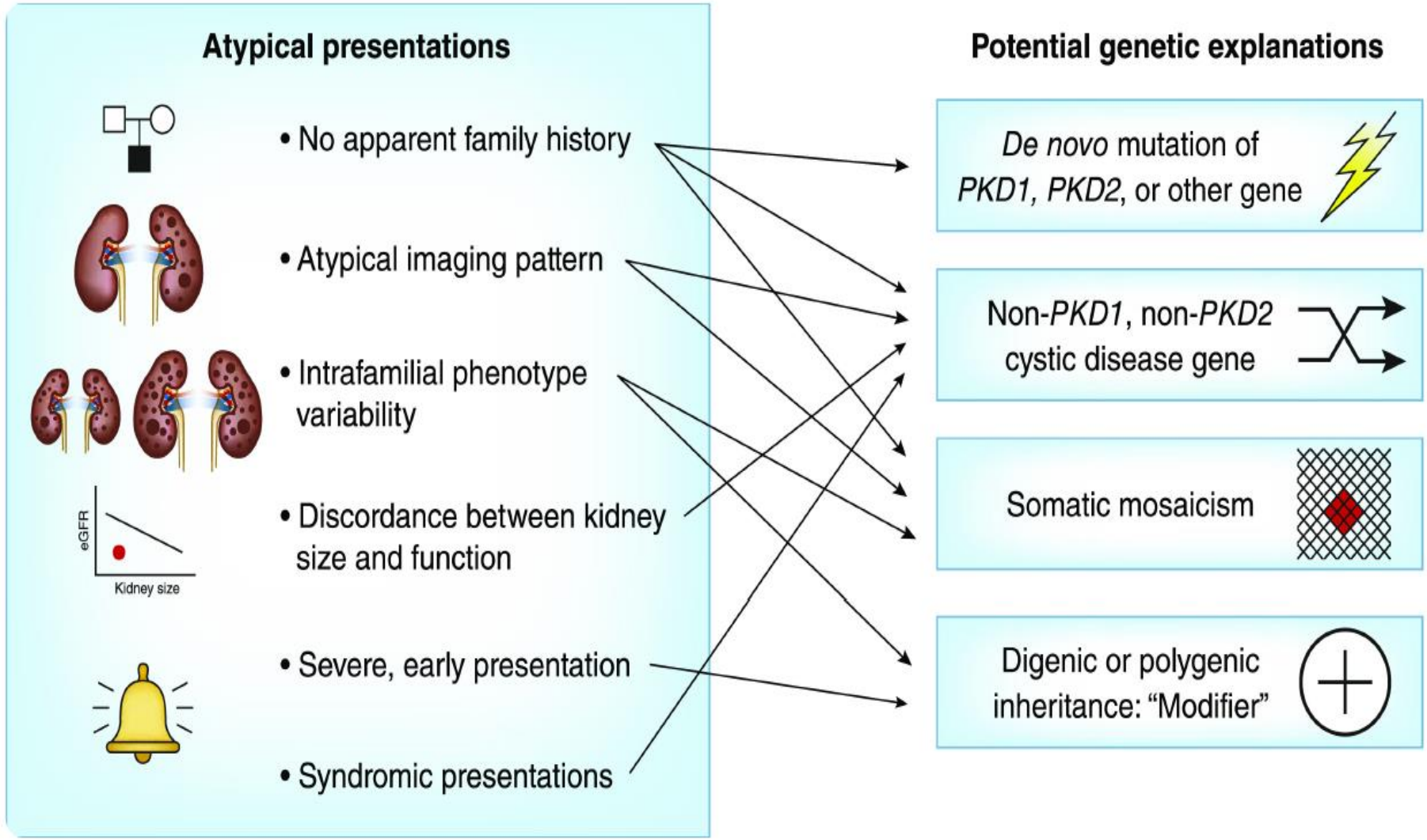

Presence of bilateral renal cysts
Yes
Presence of solid renal tumours
Yes
No
Kidney size
Enlarged
Presence of liver fibrosis
No
Yes
Autosomal dominant
Autosomal recessive
ADPKD
ARPKD

ARPKD

US Diagnosis	Image	Comment	Additional Imaging/ Follow-up
Autosomal recessive polycystic kidney disease (ARPKD) • Heterogeneous parenchymal echogenicity ("salt and pepper" pattern) • Enlarged kidneys Unusual presentations: • normal size kidney • medulla-limited hyperechogenicity • macrocysts		Kidney cysts may be visible only with high-resolution imaging.	Regular abdominal US for congenital hepatic fibrosis, signs of portal hypertension, and/or Caroli syndrome. Refer to pediatric nephrologist.
		**Image b**: Caroli syndrome of the liver. Arrow: dilated bile duct with hepatic artery "central dot"	

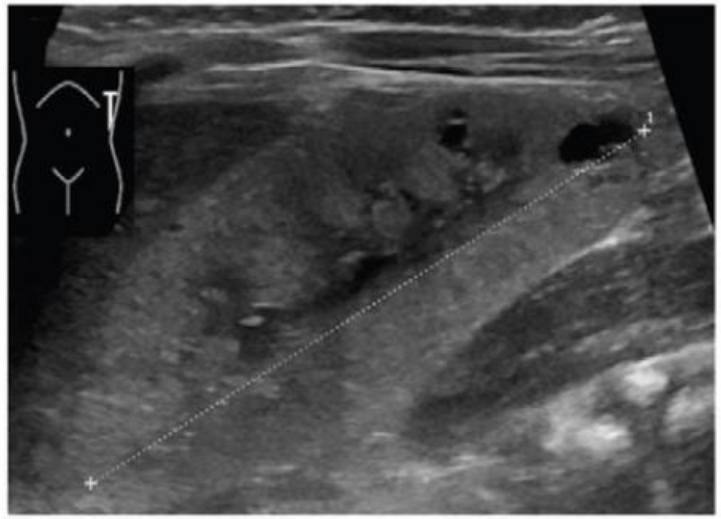
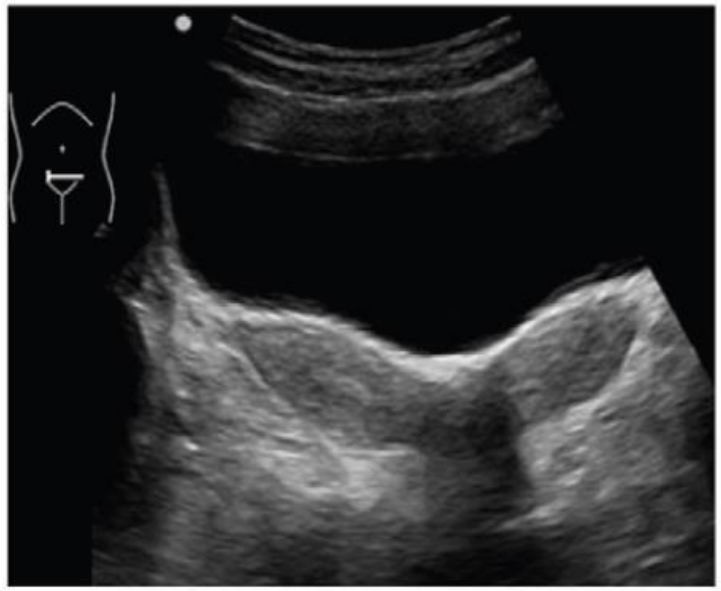
ADPKD

Autosomal dominant polycystic kidney disease (ADPKD) • Multiple cortical and medullary cysts • Number of cysts increase with age • Fetus/neonate may present with isolated hyperechogenic kidneys		Over 15 years ≥ 3 uni- or bilateral cysts required for diagnosis. Under 15 years with positive family history ≥ 1 cyst is highly suggestive. Very-early onset and unusually severe forms in childhood exist. In clinical trials with cooperative children MRI total kidney volume may be a good disease marker.	Before screening asymptomatic minors with positive family history, ensure family understands implications. Monitoring for hypertension and proteinuria is more important than imaging follow-up.

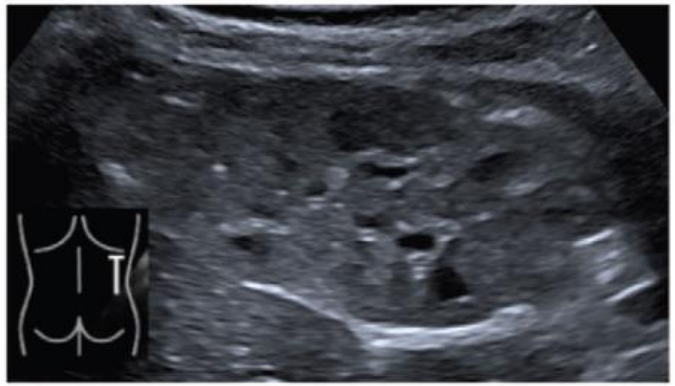
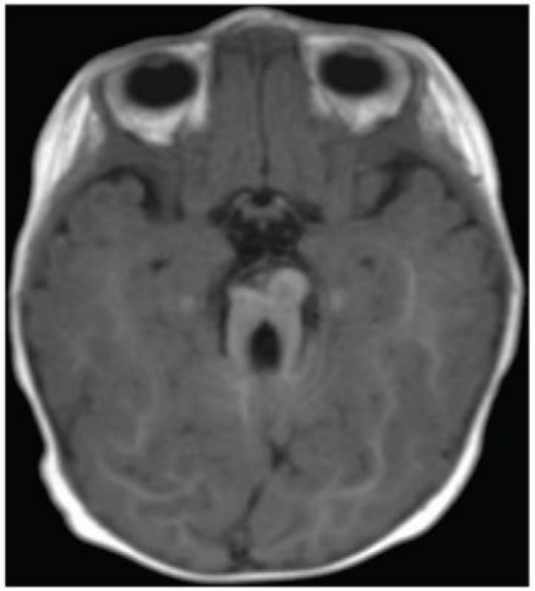


Clinical scenarios of atypical ADPKD presentations and potential genetic explanations.

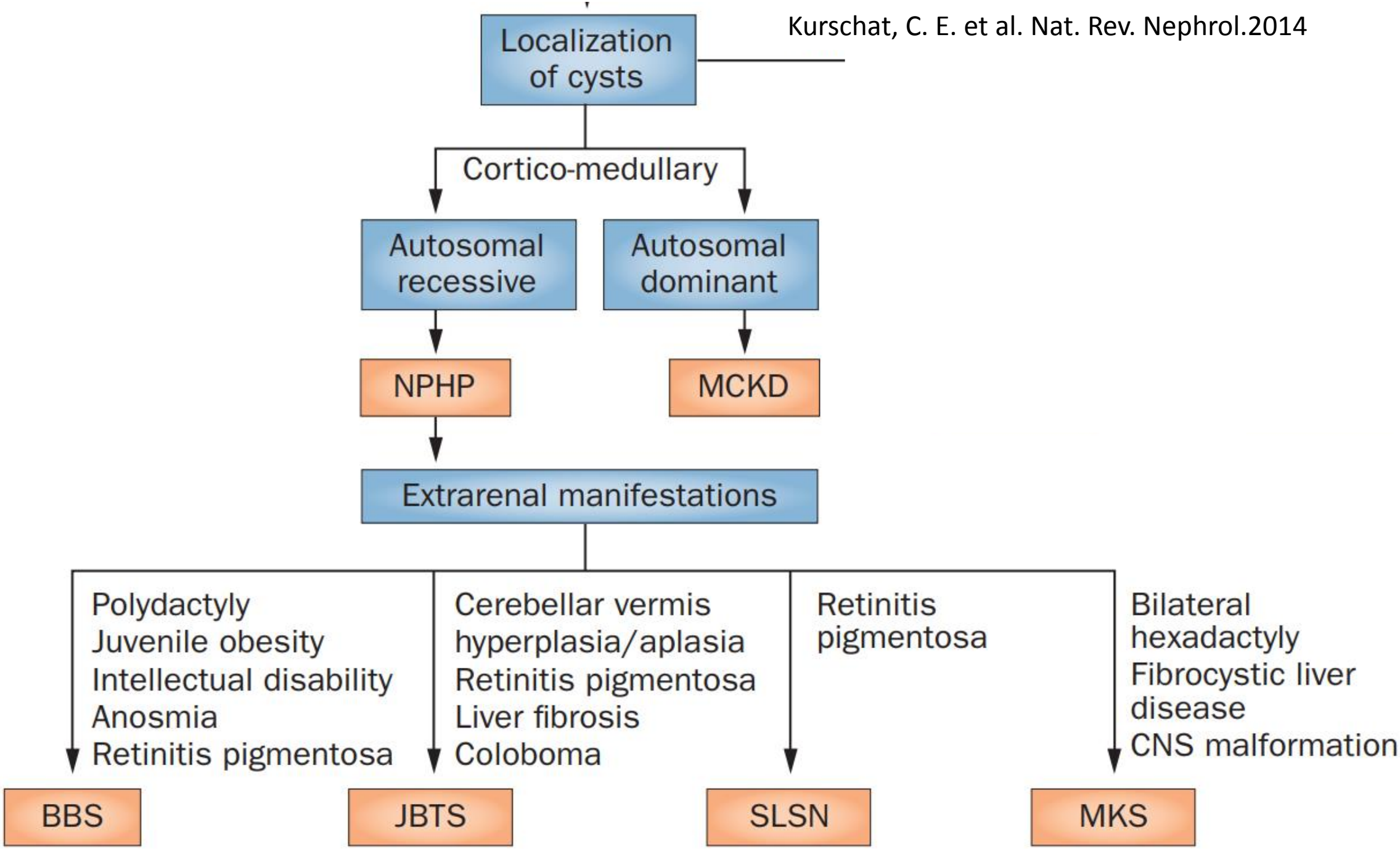
HNF1B disease

***HNF1B* disease** Variable findings • eg, uni- or bilateral cysts, hypo/dysplasia, agenesis, or normal kidney		Multiple nonimaging complications (eg, diabetes, hyperuricaemia, hypomagnesemia)	Genital US in girls for Müllerian duct anomalies and abdominal US for pancreatic anomalies
		Image b: uterus bicornus	

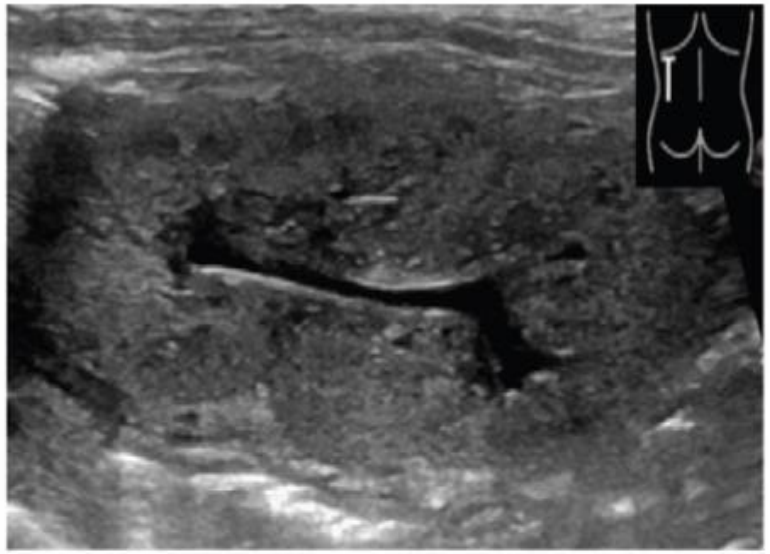
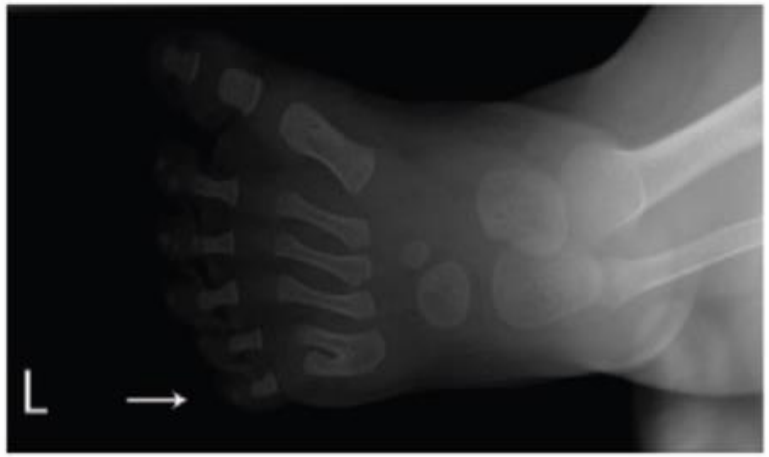
Nephronophthisis

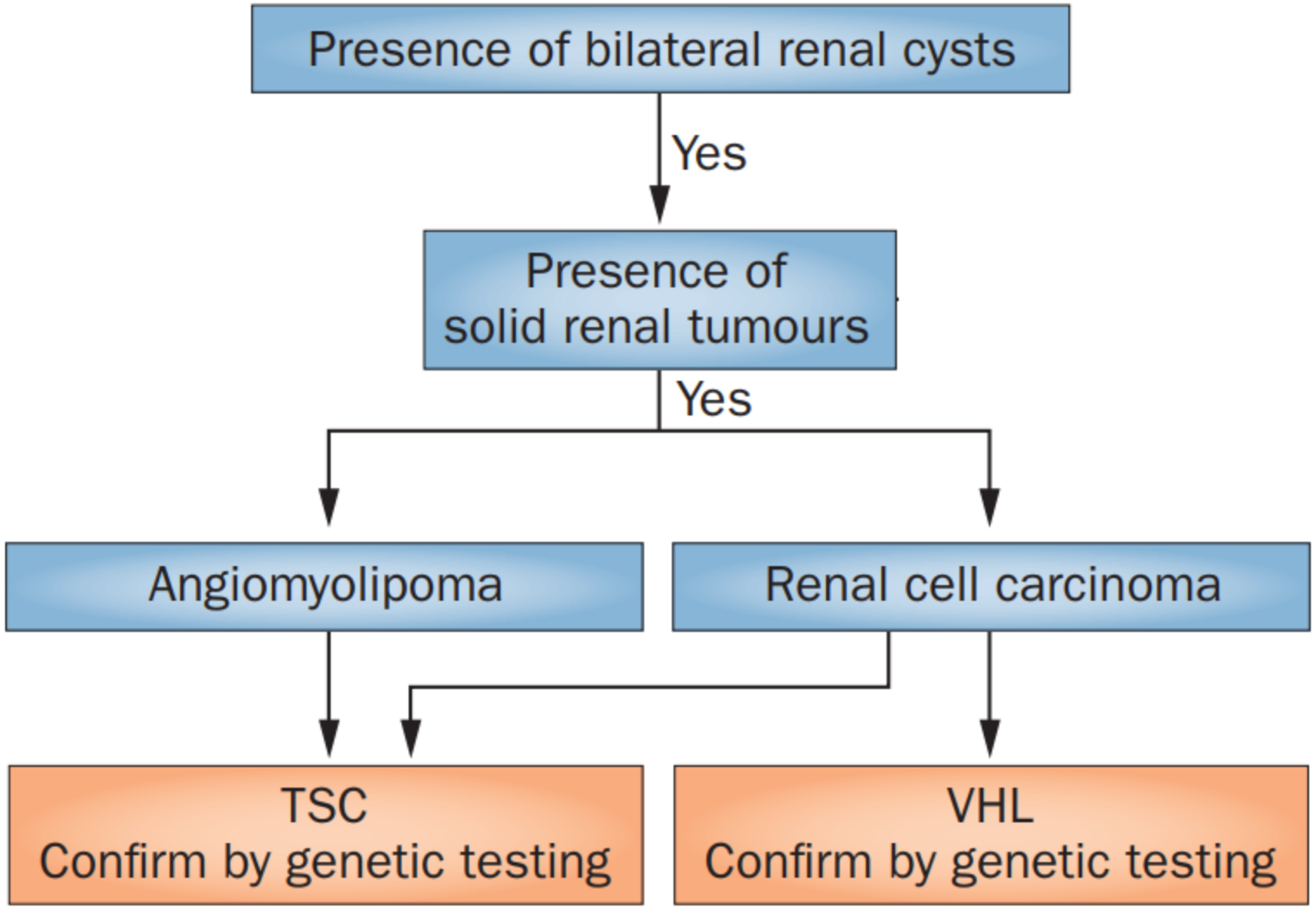
US Diagnosis	Image	Comment	Additional Imaging/ Follow-up
Nephronophthisis Variable picture • Kidney size small to normal • Bilateral increased echogenicity • ± cysts (especially at the corticomedullary border)		Can be part of a number of syndromes.	Abdominal US for liver fibrosis and signs of portal hypertension.
		**Image b**: Cerebllar vermis hypoplasia ("Molar tooth sign") in Joubert syndrome	

Kurschat, C. E. et al. Nat. Rev. Nephrol.2014



Bardet-Biedl syndrome

Bardet-Biedl syndrome Very variable picture, eg • single or multiple uni- or bilateral cysts • loss of corticomedullary differentiation • persistent fetal lobulation • ectopic, duplex, horseshoe, or absent kidneys • urinary tract malformations		Multiple nonimaging compli-cations (eg, obesity, retinal degeneration, cognitive impairment).	Genital US for uterine malformations. Follow-up monitoring dependent on type or renal/urinary tract involvement.
		**Image b**: postaxial polydatyly (common).	

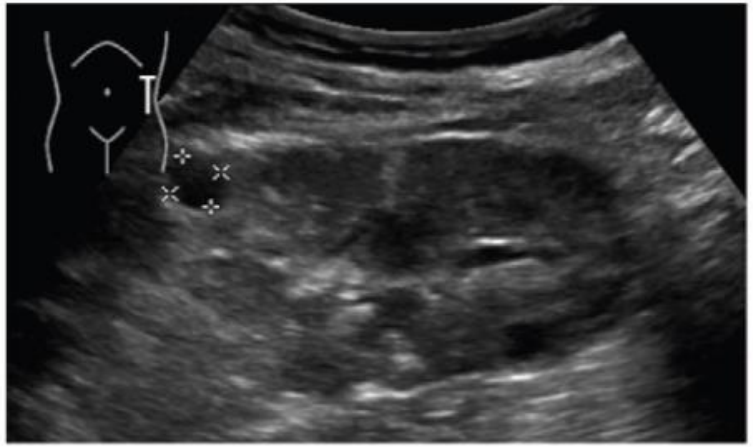
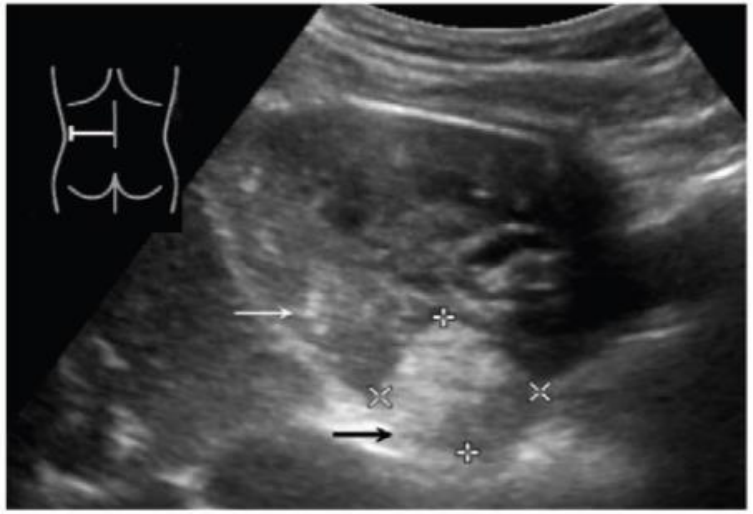


N:51
AML:60%
CysKD:19.6%
CysKD+AML:16%

Acta Neurologica Belgica https://doi.org/10.1007/s13760-021-01635-z

NATURE REVIEWS | NEPHROLOGY
2014; doi:10.1038/nrneph.2014.173

TSC

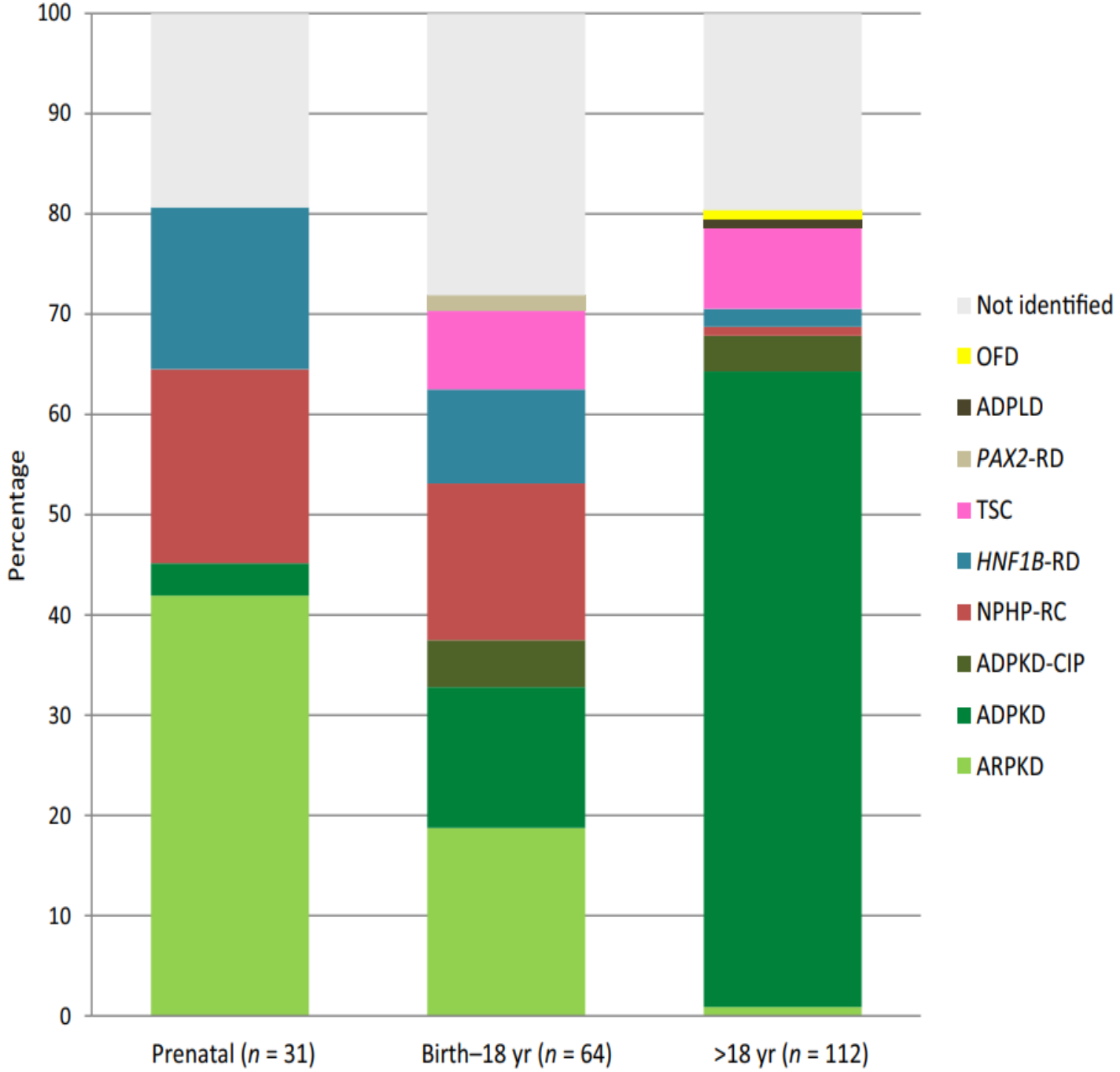
US Diagnosis	Image	Comment	Additional Imaging/ Follow-up
Tuberous sclerosis complex (TSC) • single or multiple cysts • usually also with angiomyolipomas (AML) • increase with age		US can miss fat-poor angiomyolipomas. **Image a**: small cyst in kidney with small angiomyolipomas.	Cerebral imaging usually required. MRI for follow-up of AML ≥ 3 cm. Yearly kidney US in patients < 12 years without AML on first MRI.
		**Image b**: small, parenchymal (white arrow) and larger, exophytic (black arrow) angiomyolipomas.	

www.kidney-international.org

A kidney-disease gene panel allows a comprehensive genetic diagnosis of cystic and glomerular inherited kidney diseases

Gemma Bullich[1,2], Andrea Domingo-Gallego[1,2], Iván Vargas[3], Patricia Ruiz[1]

Distribution of cystic inherited kidney diseases according to the age at diagnosis



Kidney International (2018) 94, 363–371;
https://doi.org/10.1016/ j.kint.2018.02.027

Summary

- Cystic kidney diseases are important causes of ESRD in children and adults.
- Various important subtypes of cystic kidney diseases exist. Genetic testing may be required to confirm a specific diagnosis but widely available markers can help to rapidly establish a clinical diagnosis. Extrarenal manifestations should actively be sought.
- Cystic kidney diseases are currently considered to be ciliopathies and, as such, are systemic disorders.
- For pediatric patients the definition of primary end points for clinical trials is challenging as there is ample phenotypic variability.