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Develpments in the diagnosis of ADPKD in adults

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ADPKD prevalence

- ✓ In the past few years, several population studies have estimated the prevalence of ADPKD using various databases in European and the United States . Estimates from these studies vary somewhat with a value *of 3.96/10,000 in the European Union (EU) in 2012,between about 2–4 per 10,000 in various studies in the U.S.*

- ✓ Lanktree et al.42 screened the sequenced gnomAD and BRAVO “normal” populations (total >200,000) for high-confidence pathogenic variants to PKD1 and PKD2 and determined a ADPKD prevalence of ***9.3 cases per 10,000*** sequenced. This estimate likely reflects undercounting of people with asymptomatic ADPKD in population studies, but also possibly that some proposed pathogenic variants do not result in clinically significant disease.

- ✓ ADPKD accounts for ***5%–10% of people with kidney failure*** worldwide

  In the U.S. in 2020, the number of people with cystic kidneys starting kidney replacement therapy (KRT) was 3396, representing ***2.60% of the KRT total***

ADPKD Diagnosis

Possible benefits of early screening	Possible harms of early screening
Resolve diagnosis odyssey.	Psychologic burden of having a life altering diagnosis.
Ability to manage and treat ADPKD.	Possible difficulties with employment and insurability
Initiate screening for extrarenal manifestations	High cost.
Enable enrollment in clinical trials.	Imaging and/or genetic testing results may be inconclusive.
Reassurance of unaffected people	Specialist knowledge to interpret test results may not always be available.
Appropriate family planning	
Appropriate selection of unaffected relatives as possible donors for kidney transplantation.	
Facilitate testing of family members	
Implement lifestyle modifications	

KDIGO 2023 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION, MANAGEMENT, AND TREATMENT OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

Ultrasound

Ultrasound criteria for autosomal dominant polycystic kidney disease (ADPKD) diagnosis in people with a positive family history

Ultrasound criteria by age group to diagnose ADPKD when there is a positive family history							
Age (years)	Number of cysts	PKD1		PKD2		Unknown gene type	
		Predictive value of a negative test (%)	Sn (%)	Predictive value of a negative test (%)	Sn (%)	Predictive value of a negative test (%)	Sn (%)
15–29	≥3 total	100	94	100	70	100	82
30–39	≥3 total	100	97	100	95	100	96
40–59	≥2 in each kidney	100	93	100	89	100	90
60+	≥4 in each kidney	100	100	100	100	ND	ND

Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol 2009; **20:** 205-212.

Ultrasound criteria for autosomal dominant polycystic kidney disease (ADPKD) exclusion in people with a positive family history

Ultrasound criteria by age group to exclude ADPKD when there is a positive family history							
Age (years)	Test criterion (number of cysts)	PKD1		PKD2		Unknown gene type	
		Predictive value of a negative test (%)	Sp (%)	Predictive value of a negative test (%)	Sp (%)	Predictive value of a negative test (%)	Sp (%)
15–29	≥1 total	99	98	84	97	91	97
30–39	≥1 total	100	96	97	94	98	95
40–59	≥2 total	100	98	100	98	100	98

US…

✓Overall, these criteria are still considered to be reliable, supporting this recommendation, but the authors identified that the criteria defined for PKD2 did not perform as well for PKD1 with reduced sensitivity due to more false negatives.

✓the subsequent identification and characterization of additional ADPKD genes and PKD1 hypomorphic alleles mean that these criteria may not be used universally, hence the ***moderate certainty of evidence*** grading.

MRI

✓Ultrasound has traditionally been limited to detection of cysts of 10 mm or greater in diameter;

✓however, high definition ultrasound in the hands of skilled operators can detect cysts as small as 2–3 mm across.

✓ T2-weighted
MRI or CT with contrast readily detects cysts of 2–3 mm in diameter.

Magnetic resonance imaging (MRI) criteria for ages 16-40 years in people with a positive family history.

>10 cysts total	Sufficient for diagnosis (PPV and sensitivity = 100)
<5 cysts total	Sufficient for exclusion (NPV and specificity = 100)

since this study was performed in 2014 before wider ADPKD genetic heterogeneity was described, a minor ADPKD gene as the cause of the cysts was not excluded.

Therefore, a more conservative level of <5 cysts is suggested here.

Imaging-based diagnosis of autosomal dominant polycystic kidney disease. J Am Soc Nephrol 2015; **26:** 746-753.

Genetic testing

- ✓Increasingly, genetic testing is being employed to provide a firm diagnosis and prognostic information in ADPKD (Section 1.4). However, it is not necessary to make a diagnosis by genetics in people with a typical presentation, including those with an uncertain family history.

- ✓It is also essential for some family planning situations, such as preimplantation genetic diagnosis

- ✓*Genetic testing does not always identify the causative gene, even in people with typical ADPKD. Therefore, negative or equivocal genetic results in a person with typical ADPKD should not be interpreted as the person not having ADPKD, and management, treatment options, and enrollment in clinical trials should not be changed based on the lack of a genetic diagnosis.*

Situation	Genetic findings
Limited number of cysts	Positive result can show a genetic origin (minor gene or hypomorphic allele)
Variable disease severity in a family	Mosaicism or biallelic/digenic disease can explain some extreme variability
Atypical imaging, including asymmetric or unilateral disease	Positive result can show a genetic origin (mosaicism or minor gene involvement)
Discordance between structural (MIC) and functional (GFR) ADPKD severity*	Genetic testing may reveal an atypical form of the disease or additional genetic or contributory factors. Non-genetic factors may also be important.
Negative family history	Positive result can show a genetic origin (*de novo* mutation can be proven)
VEO-ADPKD	Biallelic disease may be found (Chapter 9)
Related living transplant donor (<30 years and/or a few cysts detected)	Genetic testing can exclude the familial variant and test for other genetic causes
Family planning and PGD	Obtaining a genetic diagnosis can aid family planning and enable PGD (Chapter 8)
All people	Genetics can confirm the diagnosis, identify the responsible gene and variant, and provide prognostic information

Situations where genetic testing can clarify the diagnosis and aid prognosis

Genetic testing can be useful for selection of a living related donor for transplantation

- If the potential donor is ≥40 years old and no cysts are detected by MRI or CT, the imaging analysis alone is sufficient to exclude ADPKD and genetic testing is not required.

- if the imaging data of the prospective donor show some cysts and exclusion of ADPKD is equivocal based on the cyst number criteria and/or if the person is <30 years old, genetic testing can determine if the potential donor has the familial pathogenic variant in genetically resolved families.

	Sequencing method			
Factors compared between method	**Targeted next generation sequencing (tNGS) gene panel** Exons and flanking intronic regions of candidate PKD genes captured and screened by NGS	**Sanger sequencing** All genes (exons) screened separately Long range (LR)-PCR needed to screen the duplicated region of PKD1	**Whole exome sequencing (WES) slicea** Exons and flanking intronic regions of all genes captured and screened by NGS and candidate (PKD or nephrology) genes analyzed	**Whole genome sequencing (WGS) slice** The whole genomic is screened and candidate (PKD or nephrology) genes analyzed
Guidance	**Best method for primary screening**	**Method of choice for variant confirmation**	**Possible for primary screening, with flexibility of the genes screened**	**Follow-up for high probability cases not resolved by tNGS**

Genetic testing methods for screening for autosomal dominant polycystic kidney disease (ADPKD)

Genetic testing is not always definitive in a person with ADPKD caused by mutations in PKD1 or PKD2 because screening methods do not detect all pathogenic variants and some variants are not classed as pathogenic using ACMG guidelines.

In a person with ADPKD and with a typical presentation, negative or uncertain genetic results *do not exclude* an inherited form of ADPKD.

In a person with ADPKD and atypical imaging or another unusual presentation, negative or uncertain genetic results *do not exclude* an inherited form of PKD.

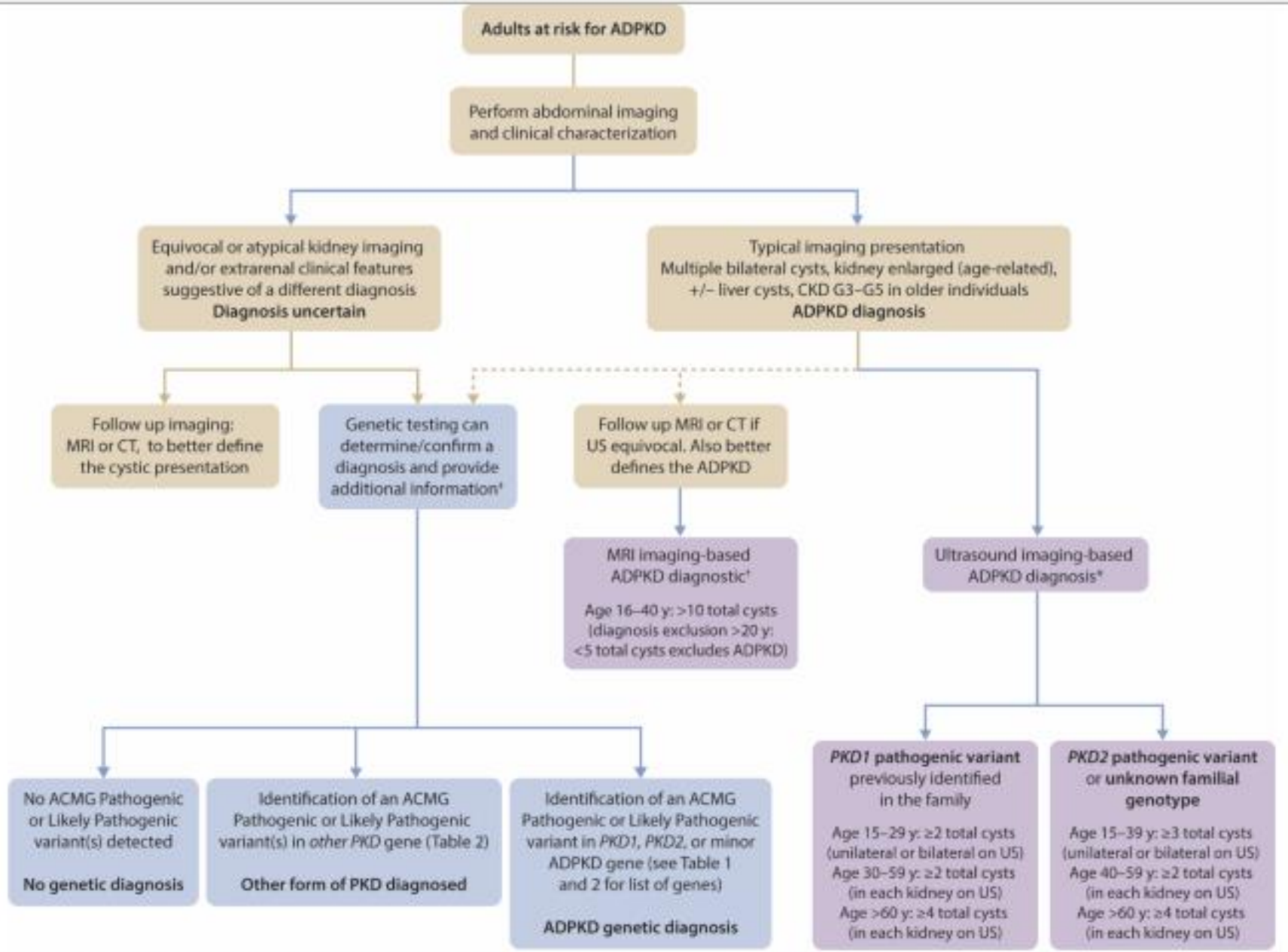

Figure 3. Diagnosis algorithm in at risk adults (positive family history) for autosomal dominant polycystic kidney disease (ADPKD). *Ultrasound and †MRI diagnostic criteria as described. MRI criteria relevant in

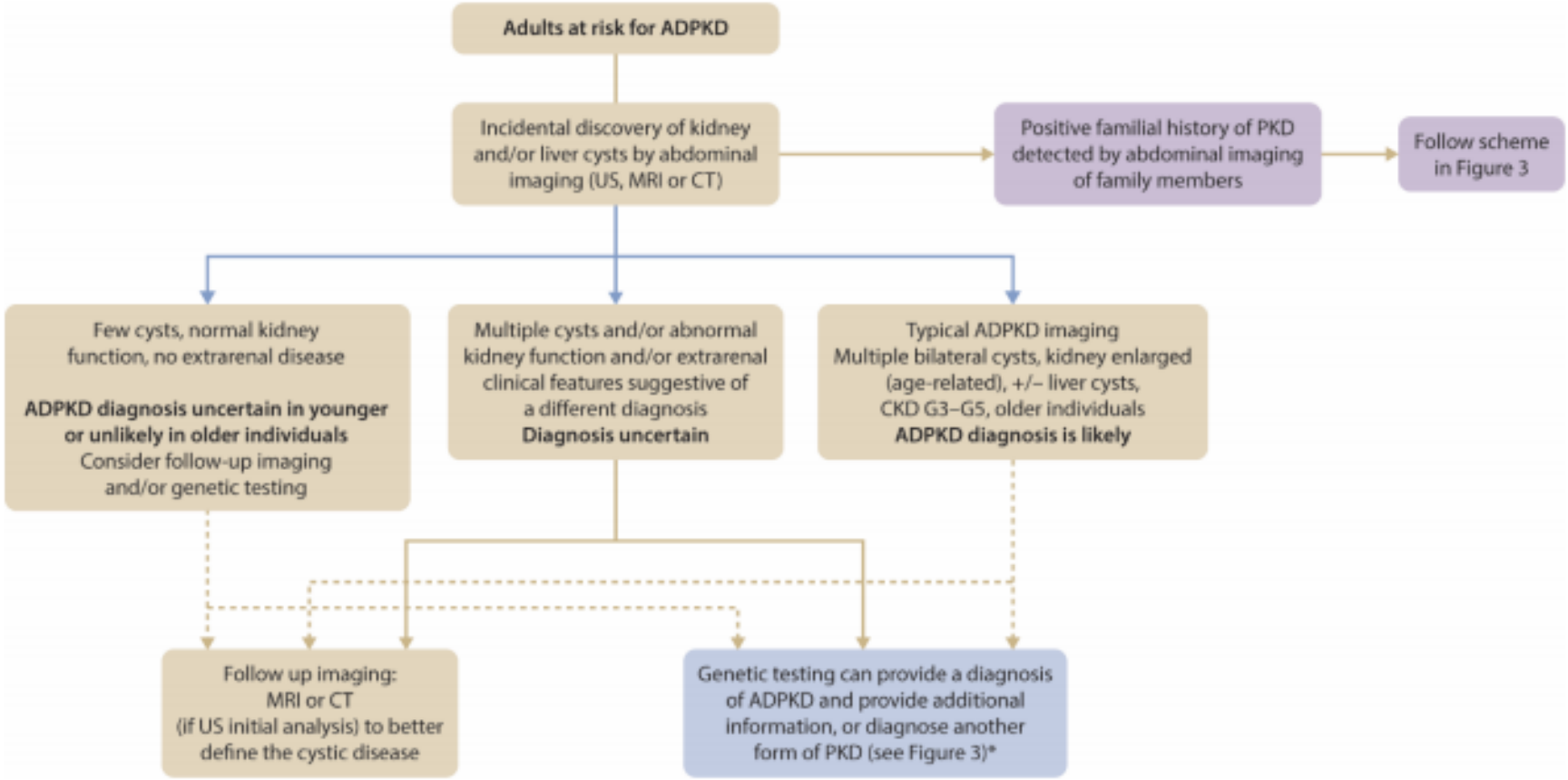

Figure 4. Diagnosis algorithm in adults with incidentally detected kidney and/or liver cysts (no known family history of ADPKD). *Genetic testing of genes shown in Tables 1 & 2. Reasons for genetic testing are

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Imaging-Based Diagnosis of Autosomal Dominant Polycystic Kidney Disease

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ABSTRACT

The clinical use of conventional ultrasonography (US) in autosomal dominant polycystic kidney disease (ADPKD) is currently limited by reduced diagnostic sensitivity, especially in at-risk subjects younger than 30 years of age. In this single-center prospective study, we compared the diagnostic performance of MRI with that of high-resolution (HR) US in 126 subjects ages 16–40 years born with a 50% risk of ADPKD who

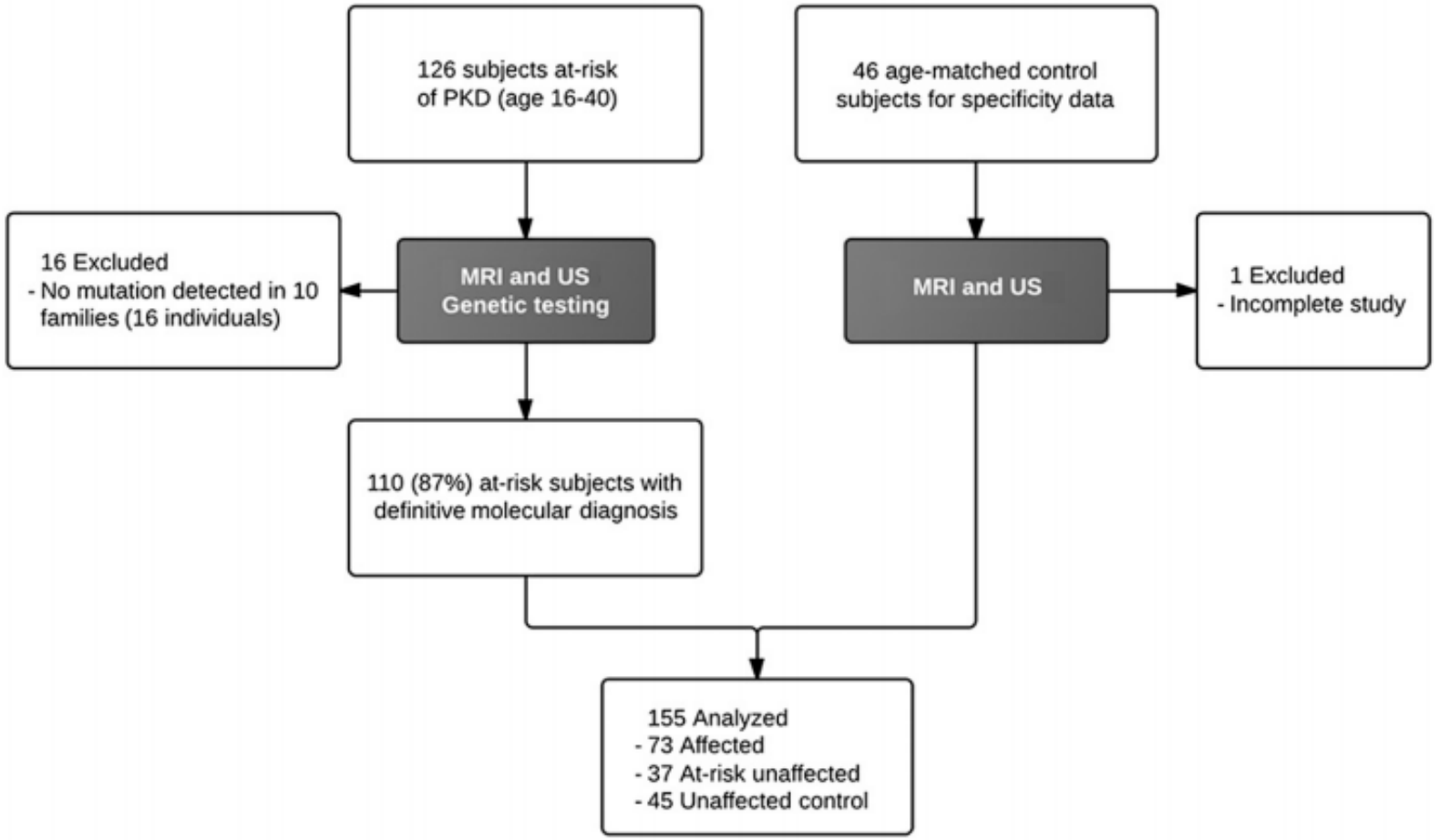


Figure 1. Study subject recruitment and exclusion. Flow diagram detailing the number of at-risk and age-matched control subjects recruited, excluded, and analyzed in the study.

Results

- the presence of a total of >10 renal cysts by MRI provides a clear separation of the unaffected from affected subjects.
- Interobserver agreement for MRI renal cyst counts was excellent with k-values of 0.96–0.97for the three reader pairs
- complete separation of the unaffected from affected subjects by US was not possible.

Table 3. Diagnostic performance of US

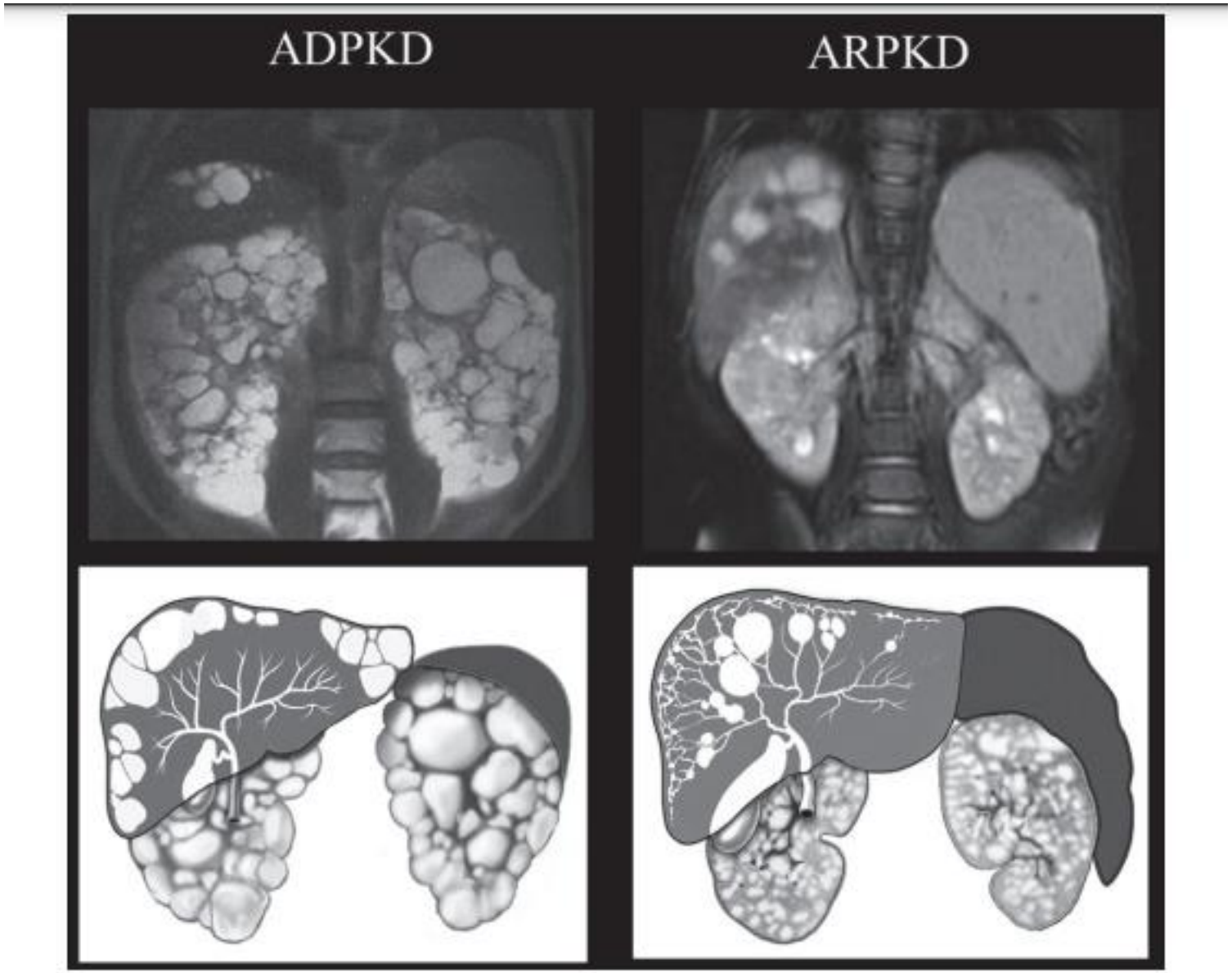
Diagnostic Criterion/Study Cohort	Affected	Unaffected	SEN	SPEC	PPV	NPV
16–29 yr	37	58				
≥1 renal cyst[a]						
Present	36	9	0.973	0.845	0.800	0.980
ref. 19			0.893	0.971	0.966	0.908
≥2 renal cysts[a]						
Present	36	3	0.973	0.948	0.923	0.982
ref. 19			0.848	0.994	0.992	0.877
≥3 renal cysts[a,b]						
Present	36	1	0.973	0.983	0.973	0.983
ref. 19			0.817	1.000	1.000	0.855
≥4 renal cysts[a]						
Present	36	1	0.973	0.983	0.973	0.983
≥2 cysts in each kidney						
Present	36	0	0.973	1.000	1.000	0.983
30–40 yr	36	24				
≥1 renal cyst[a]						
Present	36	4	1.000	0.833	0.900	1.000
ref. 19			0.980	0.948	0.940	0.983
≥2 renal cysts[a]						
Present	36	2	1.000	0.917	0.947	1.000
ref. 19			0.964	0.983	0.979	0.970
≥3 renal cysts[a,b]						
Present	36	2	1.000	0.917	0.947	1.000
ref. 19			0.955	1.000	1.000	0.964
≥4 renal cysts[a]						
Present	36	0	1.000	1.000	1.000	1.000
≥2 cysts in each kidney						
Present	36	0	1.000	1.000	1.000	1.000
ref. 19			0.828	1.000	1.000	0.875

Cystic Kidney Diseases That Require a Differential Diagnosis from ADPKD

J. Clin. Med. **2022**, *11*, 6528.
https://doi.org/10.3390/jcm11216528

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

- ✓ Prevalence is 1/8000–1/40,000
- ✓ Renal cystic lesions reflecting the expansion of the collecting duct with kidney function impairment
- ✓ congenital hepatic fibrosis characterized by bile duct dysplasia and intrahepatic periportal fibrogenesis. Thrombocytopenia, splenomegaly, and portal hypertension.
- ✓ can manifest at any age, including well into adulthood.
- ✓ Typically, CT imaging reflects kidney enlargement with small embedded cysts or a striated appearance with collecting duct enlargement


ADPKD
ARPKD

Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD)

- ✓ Tubulointerstitial fibrogenesis and progressive kidney function impairment.
- ✓ Poor urinary findings, slow decline in kidney function. Small renal cysts without kidney enlargement.
- ✓ has previously been referred to by various terms, such as familial juvenile hyperuricemic nephropathy and medullary cystic kidney disease
- ✓ For patients with kidney failure (adolescence through to old age), with a family history of kidney function impairment, who show few findings on urinary examination, and experience a slow decline in kidney function, ADTKD should be considered.
- ✓ Hyperuricemia is observed from childhood or early adulthood in almost all of disease variants.
- ✓ Some extrarenal abnormalities in some variants

Nephronophthisis (NPH)

- ✓Impaired urinary concentration, chronic tubulointerstitial nephritis, renal cystic lesions and accompanying kidney function impairment and progress to ESKD by the age of 30 years.

- ✓Extrarenal lesions are reportedly found in 10–20% of patients, retinitis pigmentosa, cerebellar vermis hypoplasia, gaze palsy, hepatic fibrosis, and skeletal abnormalities.

- ✓Prevalance is 1/50,000– 1/100,000

OFD type1

- ✓Progress to kidney failure in adulthood with PKD with a variety of morphological abnormalities in the oral, facial, and finger and toe.
- ✓Normal to large-sized kidneys.
- ✓ *The rate of kidney function decline in OFD-1 is faster than ADPKD, with the mean age at ESRD in patients with OFD-1 being approximately 36 years (range:11 to 64 years)*
- ✓ *the typical complications of kidney cysts in ADPKD, including lumbar pain, lithiasis, and hematuria are not common in OFD-I*

Tuberus sclerosis and VHL syndrome

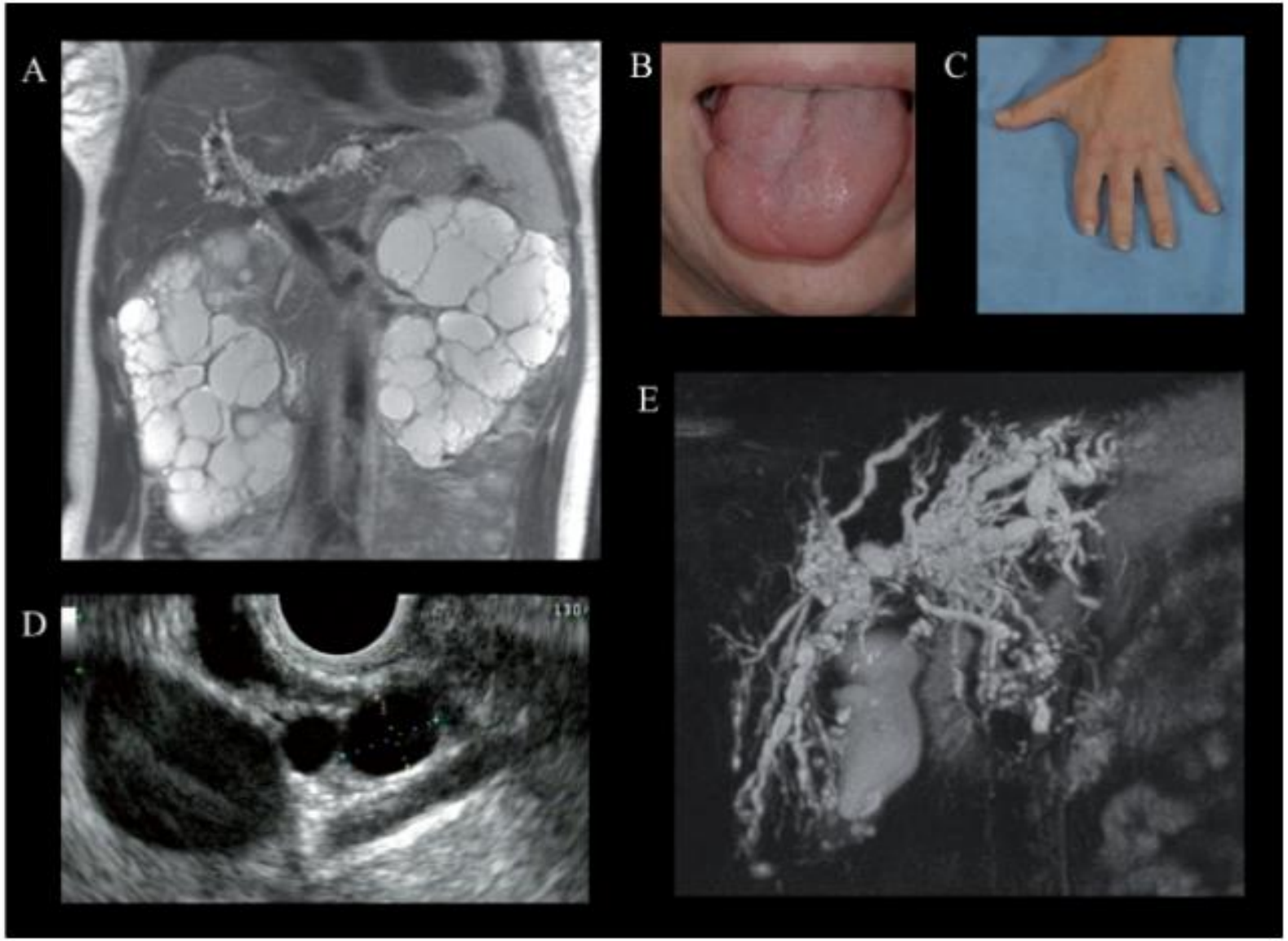
✓**Prevalence:** 1/10,000 and 1/50,000 respectively

✓**TS**: Hamartoma in the skin, nervous system, kidney, lung, bone, and elsewhere.

Renal lesions; angiomyolipoma (AML), renal cysts,renal cell carcinoma.

✓**VHL**: Renal cell carcinoma, pancreatic cysts, central nervous system and

retinal hemangioblastoma, and pheochromocytoma. Kidney function impairment is rare.


A
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E

Take home message

- ✓US sensitivity is lower for diagnosis in PKD2 .
- ✓MRI is more sensitive for small cysts.
- ✓*Genetic testing does not always identify the causative gene, even in people with typical ADPKD.*


ISNA PHOTO
Morteza Zangene