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# Autosomal Dominant Polycystic Kidney Disease (ADPKD):

## Screening & Differential Diagnosis



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*Otsuka Pharmaceutical Development*
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# Content Overview

- ADPKD Overview
- ADPKD Screening and Diagnosis
  - Clinical Approach and Family History Investigation
  - Imaging Approaches
  - Molecular Diagnosis of ADPKD
  - ADPKD Diagnostic Algorithm
  - ADPKD Differential Diagnosis
  - Risk Assessment
- Summary

ADPKD=autosomal dominant polycystic kidney disease.

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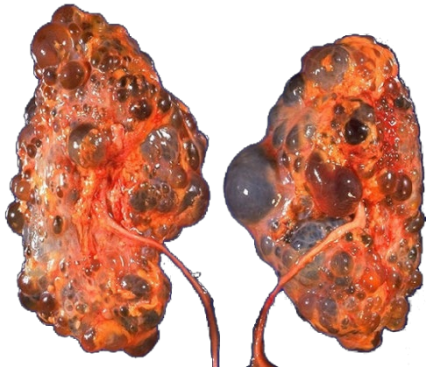
# ADPKD Overview

# What Is PKD?

## Polycystic kidney disease (PKD) is a group of monogenic disorders characterized by the propensity to develop numerous renal cysts[1]



**Syndromic forms**

↓

**Rare, recessively inherited[1,2]**

**Autosomal dominant (ADPKD)[3]**

- ***PKD1*** **(85%)**
- ***PKD2*** **(15%)**

**Autosomal recessive (ARPKD)**

↓

***PKHD1***[1]

ADPKD=autosomal dominant PKD; ARPKD=autosomal recessive PKD; PKD=polycystic kidney disease; *PKDH1*=polycystic kidney and hepatic disease 1.


1. Harris PC, Torres VE. (2009). *Annu Rev Med*. 60: 321–37.
2. Jauregui AR et al. (2005). *Exp Cell Res*. 305(2): 333–42.
3. Rossetti S et al; CRISP Consortium. (2007). *J Am Soc Nephrol*. 18:2143–2160.

# ADPKD Is the Most Common Life-threatening Inherited Renal Disease

**ADPKD does not discriminate on gender, race, ethnicity, or geography[1,2]**

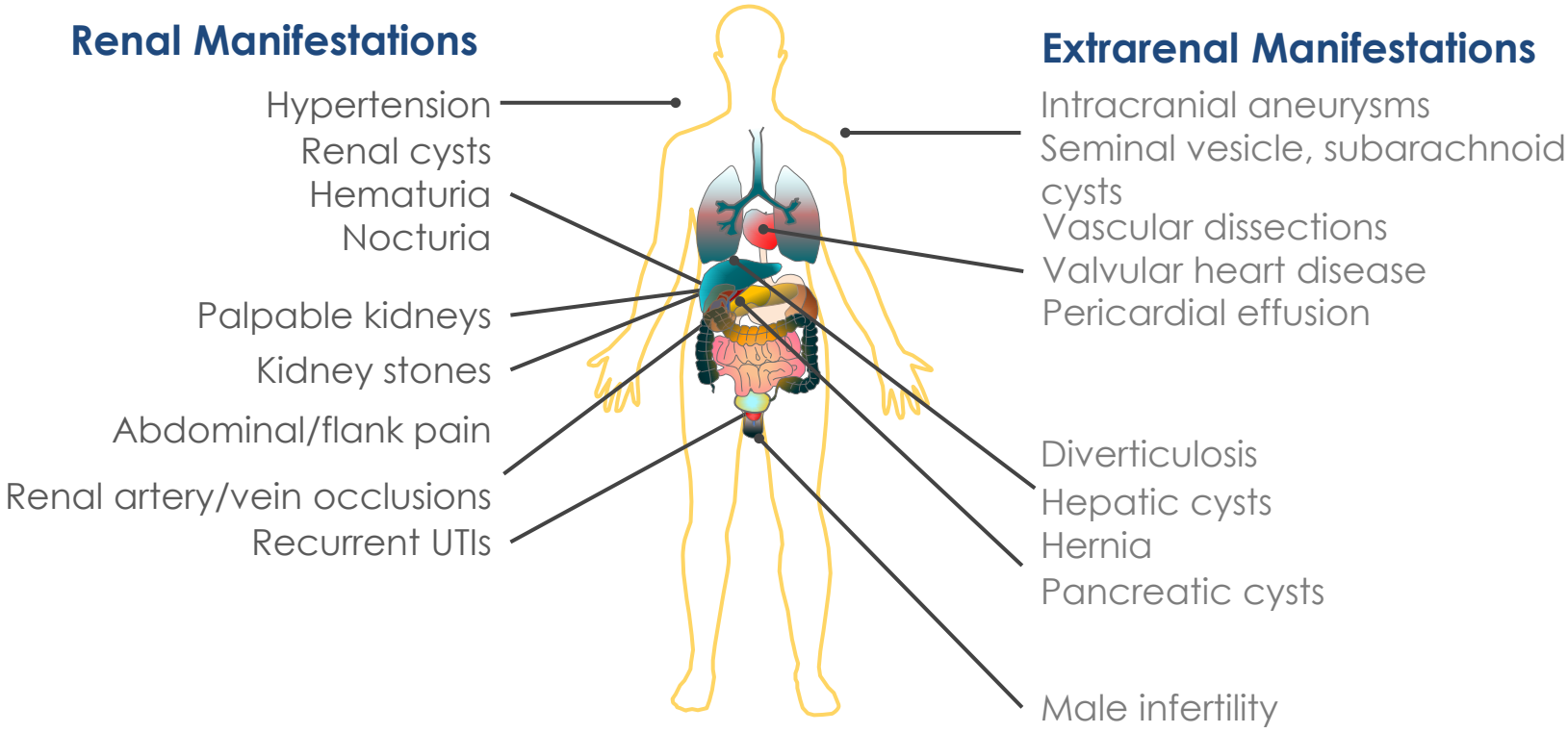
- ADPKD is the most common life-threatening inherited renal disease and accounts for up to ~5% of all patients with ESRD[2]
- ADPKD is the fourth leading cause of ESRD in the United States after diabetes, hypertension and glomerulonephritis[2]
- As many as 1:2,000 people worldwide are currently diagnosed with ADPKD,3 and between 1:400 and 1:1,000* people living today will be diagnosed with ADPKD in their lifetime[1]

*The higher prevalence value of 1:1,000 is believed to be inaccurate as the data are based on a postmortem study and therefore report lifetime morbid risk rather than point prevalence.
ADPKD=autosomal dominant polycystic kidney disease; ESRD=end-stage renal disease.


1. Torres VE, Harris PC. (2009). *Kidney Int*. 76(2): 149–68.
2. United States Renal Data System. 2016 USRDS Annual Data Report Volume 2: ESRD in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2016 (accessed 8 Aug 2017).
3. Willey C. DRAFT: The Descriptive Epidemiology of ADPKD in the U.S. 2017.

# ADPKD Is a Systemic Disease with Renal and Extrarenal Manifestations

**Renal cysts are the first manifestation of ADPKD and precede changes in kidney function by many years[1–3]**




ADPKD=autosomal dominant polycystic kidney disease; UTI=urinary track infection.


1. Halvorson CR et al. (2010). *Int J Nephrol Renovasc Dis*. 3: 69–83.
2. Torres VE, Harris PC. (2009). *Kidney Int*. 76(2): 149–68.
3. Chebib FT, Torres VE. (2016). *Am J Kidney Dis*. 67(5): 792–810.

# ADPKD Is Caused by Genetic Mutations in the *PKD1* or *PKD2* Genes

| ***PKD1*** **Mutation = median age at death or onset of ESRD of 53 years[1]** | ***PKD2*** **Mutation = median age at death or onset of ESRD of 69 years[1]** |
|---|---|
| • Encodes a large, multidomain integral membrane protein, polycystin-1 (PC1)[2] | • Encodes a transient receptor potential (TRP) family cation channel, polycystin-2 (also known as PC2 or TRPP2)[2] |
| • *PKD1* truncation mutations result in rapid progressing phenotype compared with nontruncating mutations[3] | • *PKD2* mutations lead to less severe phenotype due to fewer cysts[4] |

ADPKD=autosomal dominant polycystic kidney disease; ESRD=end-stage renal disease; PKD=polycystic kidney disease.


1. Hateboer N et al. (1999). *Lancet*. 353(9147):103-107.
2. Mochizuki T et al. (1996). *Science*. 272:1339-1342.
3. Cornec–Le Gall E et al. (2016). *J Am Soc Nephrol*. 27:942-951. 4. Harris PC et al. (2006). *J Am Soc Nephrol*. 17:3013-3019.

# ADPKD Is Inherited as an Autosomal Dominant Trait

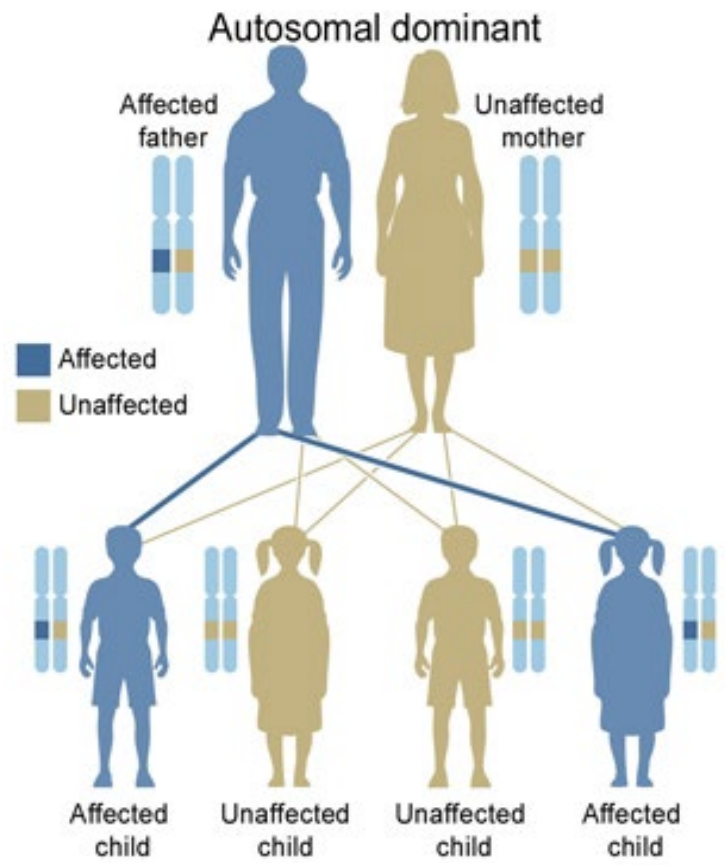



Figure adapted from U.S. National Library of Medicine

Inheritance pattern of autosomal dominant disease[5]

- ADPKD is an autosomal dominant disease with a high degree of penetrance[1]
- A child of an affected parent has a 50% chance of inheriting ADPKD[1]
- In 5% to 10% of cases, ADPKD is caused by a de novo mutation[2,3]
  - In ~10% of newly diagnosed cases, patients report a negative family history[3]
- Disease progression can be highly variable, even among family members with the same mutation[3]
  - Variability suggests a "two-hit" model for ADPKD, in which germ-line and somatic inactivation of both copies of a PKD gene lead to cystogenesis[4]

ADPKD=autosomal dominant polycystic kidney disease.


1. Harris PC, Rossetti S. (2010). *Nat Rev Nephrol.* 6(4):197-206.
2. Grantham JJ. (2009). *Ann Transplant.* 14:86-90.
3. Reed B et al. (2008). *Am J Kidney Dis*. 52(6):1042-1050.
4. Pei Y et al. (1999). *J Am Soc Nephrol*. 10(7):1524-1529.
5. ADPKD. PKD International. http://www.pkdinternational.org/what-is-pkd/ (accessed 13 February 2019).

# Role of Genetic Testing in ADPKD

- Genetic mutation is a key determinant of phenotype in ADPKD[1]
  - Genetic and allelic effects determine disease progression[1]
    - *PKD1* protein-truncating mutations are associated with the most severe disease, *PKD1* nontruncating mutations with variable, intermediate disease, and *PKD2* mutations with least severe disease[2]
- Most mutations are unique in ADPKD[2]
  - As such, diagnostic screening of a new patient or family requires complete screening of both genes

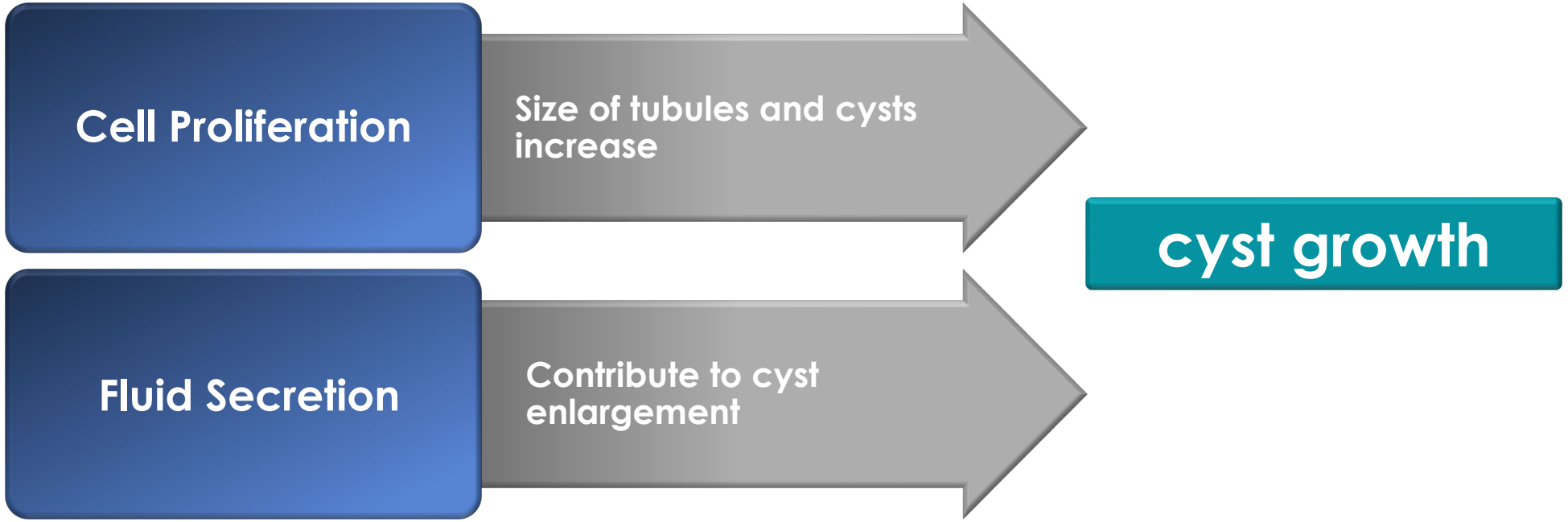
| Indications for Genetic Testing in ADPKD[2] |
|---|
| **Highest impact for clinical genetic testing** |
| Cases where there is doubt regarding diagnosis<br>• *Example*: lack of family history or equivocal imaging findings |
| Cases with high stakes for accurate disease exclusion at an early age<br>• *Examples*: prenatal or preimplantation diagnostics, kidney donation evaluation |
| **Cases in which genetic testing may be appropriate** |
| Risk stratification for initiating disease-modifying therapies |
| Explaining atypical presentations<br>• *Examples*: early and severe disease or discrepancies between imaging findings and decrease in renal function |

ADPKD=autosomal dominant polycystic kidney disease; DNA=deoxyribonucleic acid; PKD=polycystic kidney disease gene.


1. Lee KB. (2016). *Kidney Res Clin Pract*. 35(2):67-68.
2. Lanktree MB, et al. (2018). *Nephrol Dial Transplant*. Aug 27. doi: 10.1093/ndt/gfy261. [Epub ahead of print].

# Pathological Processes That Cause Cyst Growth and Expansion

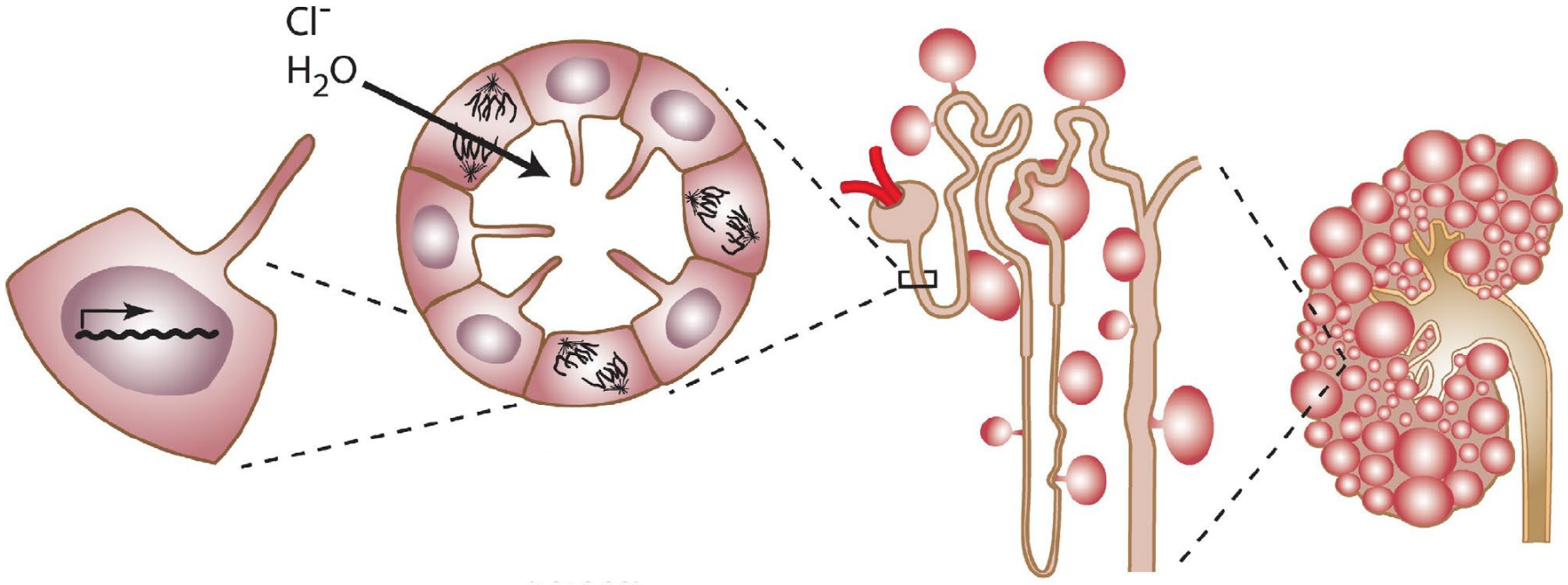
**Two essential cAMP-dependent processes are required for cyst growth: cell proliferation and fluid secretion[1,2]**




cAMP=cyclic adenosine monophosphate.

1. Yamaguchi T et al. (1997). *Am J Kidney Dis.* 30(5): 703–9.
2. Grantham JJ et al. (1987) *Kidney Int*. 31(5): 1145–52.

# Cyst Formation at the Level of the Cell, Nephron, and Kidney




Defective PC1 and PC2, along with second hit mutations, disrupt planar cell polarity and trigger cell division

A cyst is formed in a renal tubule when focal epithelial cell proliferation provokes radial expansion to form a sac-like protrusion out of the tubule

Secretion of chloride and fluid cause cysts to balloon out and pinch off from individual nephrons, normal renal parenchyma is displaced

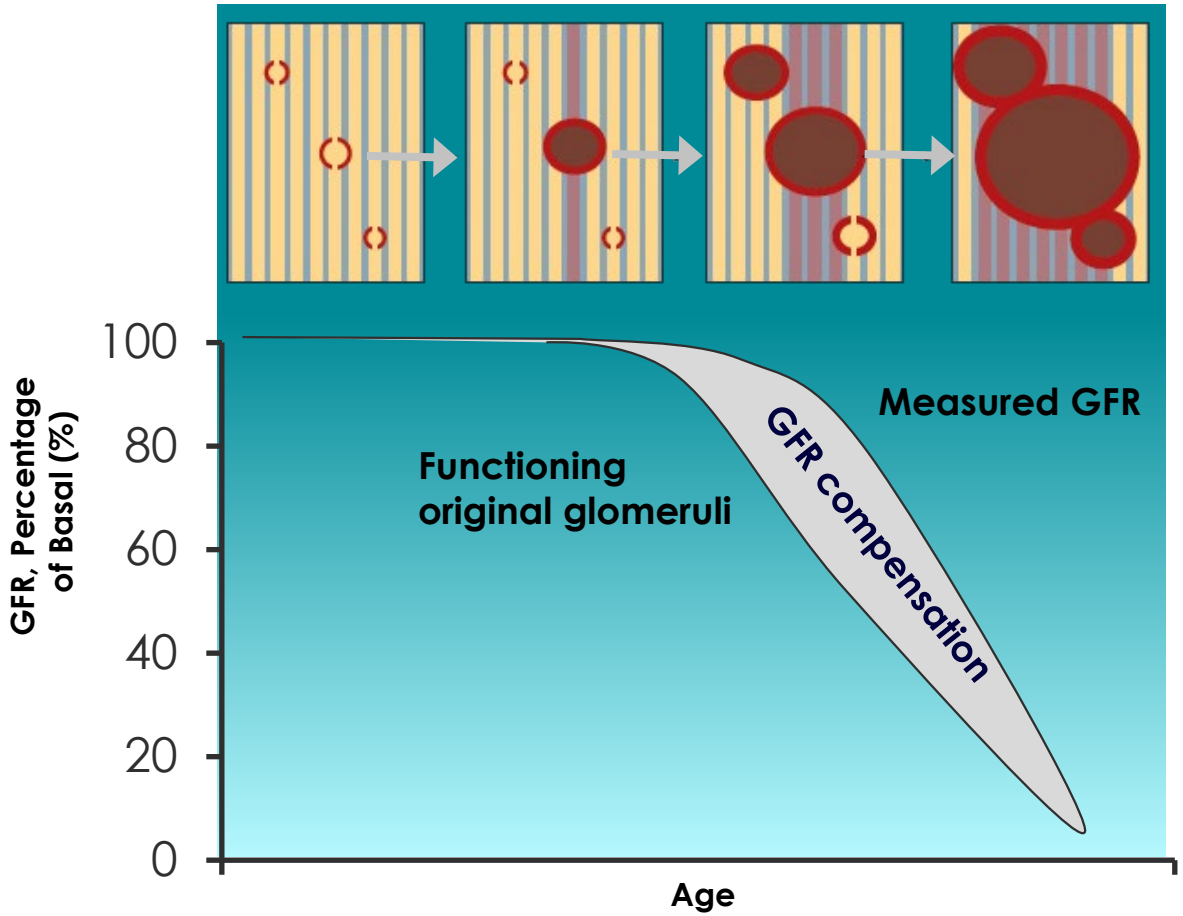
- Only 1 to 3% of nephrons develop cysts
- Significant number are derived from collecting ducts
- Cyst location matters- An inner medullary cyst can potentially diminish urine flow from >16,000 upstream tubules

$Cl^-$=chloride ion; PC1=polycystin-1 protein; PC2=polycystin-2 protein. Figure adapted from Chapin HC et al. (2010). *J Cell Biol.* 191(4): 701–10.

1. Chapin HC et al. (2010). *J Cell Biol.* 191(4): 701–10.
2. Terryn S et al. (2011). *Biochim Biophys Acta*. 1812: 1314–21.
3. Grantham JJ et al. (2011). *Nat Rev Nephrol*. 7(10): 556–66.

# Expansion Destroys Normal Tissue and Causes Loss of Renal Function

- Renal function remains steady
  until kidney volume increases 4–6 times normal size[2]
- Irreversible damage occurs by the time GFR declines[3]
- Disease progression is variable from patient-to-patient[4]




GFR=glomerular filtration rate.


1. Grantham JJ et al. (2011). *Nat Rev Nephrol*. 7(10): 556–66.
2. Braun WE. (2009). *Cleve Clin J Med*. 76(2): 97–104.
3. Grantham JJ et al. (2006). *N Engl J Med*. 354(20): 2122–30.
4. Milutinovic J et al. *Am J Kidney Dis*. 1992;19(5):465–72.

# General Management of ADPKD

| Parameter | Goal |
|---|---|
| **Blood Pressure** | • 18 – 50 years: ≤ 110/75 mmHg<br>• Other ages: ≤ 130/85 mmHg |
| **Cholesterol** | • LDL < 100 mg/dL<br>• HDL > 50 mg/dL |
| **Diet** | • Moderate sodium restriction (2.3 – 3 g/day)<br>• Increased hydration (UOsm ≤ 280 mOsm/Kg)<br>• Maintain normal BMI (moderate caloric restriction)<br>• Moderate protein and phosphorus restriction<br>• Maintain serum bicarbonate ≥ 22mEq/L |

ADPKD=autosomal dominant polycystic kidney disease; LDL=low-density lipoprotein; HDL=high density lipoprotein

1. Chebib F et al. (2018). *J Am Soc Nephrol*. 29:2458-2470

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# ADPKD Screening and Diagnosis

# Steps in ADPKD Screening and Diagnosis

- ***Family History***: May include ADPKD, ESRD, intracranial aneurysm, hemorrhagic stroke, or subarachnoid hemorrhage[1]
- ***Physical Examination***: Abdominal examination often reveals a palpable renal or hepatic mass. Hypertension is common and often occurs at a relatively young age[2]
- ***Laboratory Tests***: Serum electrolytes, blood urea, creatinine, and fasting lipid profile. Creatinine can be used to estimate GFR. Urinalysis to detect increased urinary albumin excretion or proteinuria[2]
- ***Renal Imaging:*** US, MRI or CT imaging shows the presence of renal cysts with, or without, hepatic cysts. Appropriate counselling and discussion of potential discrimination before testing[2]
- ***Extrarenal Investigations:*** CT scan may also provide evidence of extrarenal cysts. Hepatic cysts are the most common extrarenal manifestation[2]
- ***Genetic Testing***: Used when imaging results are inconclusive, to confirm a presumed diagnosis in the absence of family history, or when a definite diagnosis is required in a younger patient[1]
- ***Risk Assessment***: Use PROPKD score and Mayo Classification to identify patients as rapid or slow progressors[3,4]

ADPKD=autosomal dominant polycystic kidney disease; CT=computed tomography; ESRD=end-state renal disease; GFR=glomerular filtration rate; MRI=magnetic resonance imaging; US=ultrasonography.


1. Pei Y, Watnick T. (2010). *Adv Chronic Kidney Dis.* 17: 140–52
2. Torra R. (2017). http://emedicine.medscape.com/article/244907-overview (accessed 29 Sept 2017).
3. Irazabal MV et al. (2015). *J Am Soc Nephrol*. 26(1): 160–72.
4. Cornec-Le Gall E et al. (2016). *J Am Soc Nephrol*. 27(3): 942–51.

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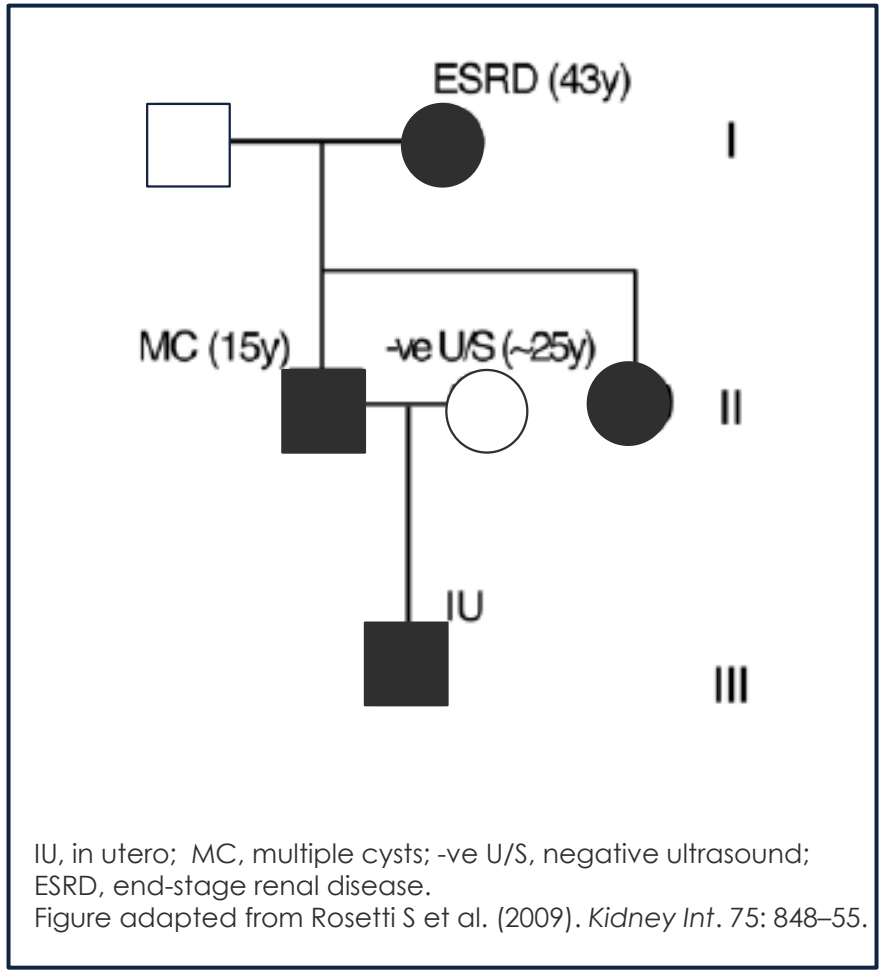
# Obtaining a Detailed Family History Is a Key Step in Diagnosis

- Detailed family history
  - Confirms autosomal dominant pattern of inheritance[1]
  - Renal disease severity may predict mutated gene and prognosis[2]
- However, ~10% of subjects have a negative family history due to mild phenotype segregating in the pedigree or true *de novo* cases[3]
  - In many cases, careful imaging may identify affected individuals with negative clinical findings
  - In some apparently *de novo* cases, mosaicism has been demonstrated in one of the parents




IU, in utero; MC, multiple cysts; -ve U/S, negative ultrasound; ESRD, end-stage renal disease.
Figure adapted from Rosetti S et al. (2009). *Kidney Int*. 75: 848–55.


1. Pei Y, Watnick T. (2010). *Adv Chronic Kidney Dis.* 17: 140–52.
2. Barua M et al. (2009). *J Am Soc Nephrol.* 20: 1833–8.
3. Harris PC, Rossetti S. (2010). *Nat Rev Nephrol.* 6:197–206.

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3. Irazabal MV et al. (2015). *J Am Soc Nephrol*. 26(1): 160–72.
4. Cornec-Le Gall E et al. (2016). *J Am Soc Nephrol*. 27(3): 942–51.

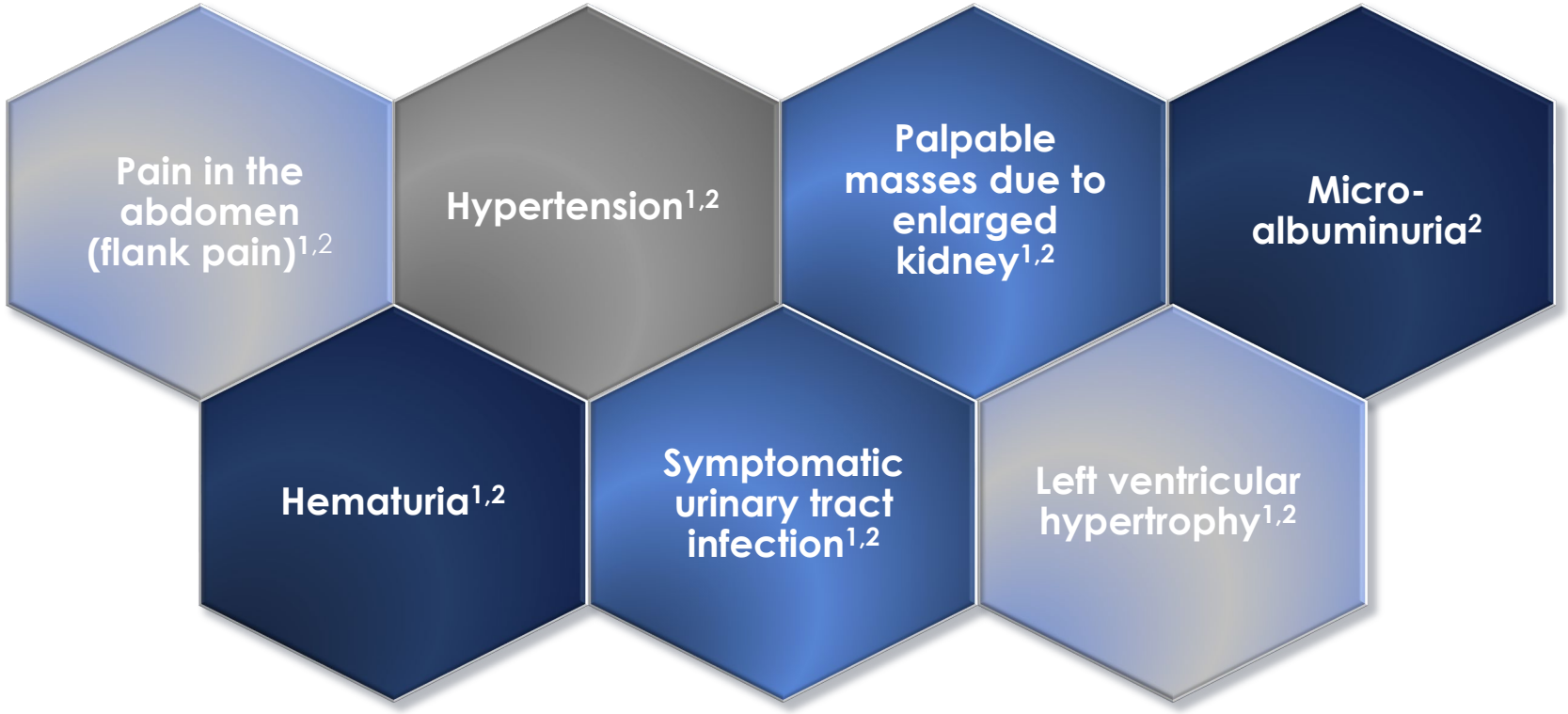
# Presentation of ADPKD Is Highly Variable

- ADPKD is often diagnosed upon:
  - Sudden onset of renal pain or hematuria[1]
  - Discovery of hypertension[1]
  - Finding of nephromegaly or renal cysts on physical or radiologic examinations[2]
- Pain is the most common symptom reported by adult patients[1]
- Other signs/symptoms may include loss of appetite, nausea, weight loss, and pyelonephritis[1]
- Initial awareness of renal dysfunction is typically delayed beyond patient's fourth decade[3]

ADPKD=autosomal dominant polycystic kidney disease.


1. Taylor M et al. (2005). *Am J Kidney Dis.* 46(3): 415-23.
2. Pei Y, Watnick T. (2010). *Adv Chronic Kidney Dis.* 17: 140–52.
3. Franz KA et al. (1993). *Kidney Int.* 23(3): 526-9.

# Presenting Symptoms




- Patients may be asymptomatic and only have a family history of the disease

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1. Halvorson CR et al. (2010). *Int J Nephrol Renovasc Dis.* 3: 69-83.
2. Patient Platform. http://www.patient.co.uk/doctor/autosomal-dominant-polycystic-kidney-disease (accessed 13 Sept 2017).

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- Irazabal MV et al. (2015). *J Am Soc Nephrol*. 26(1): 160–72.
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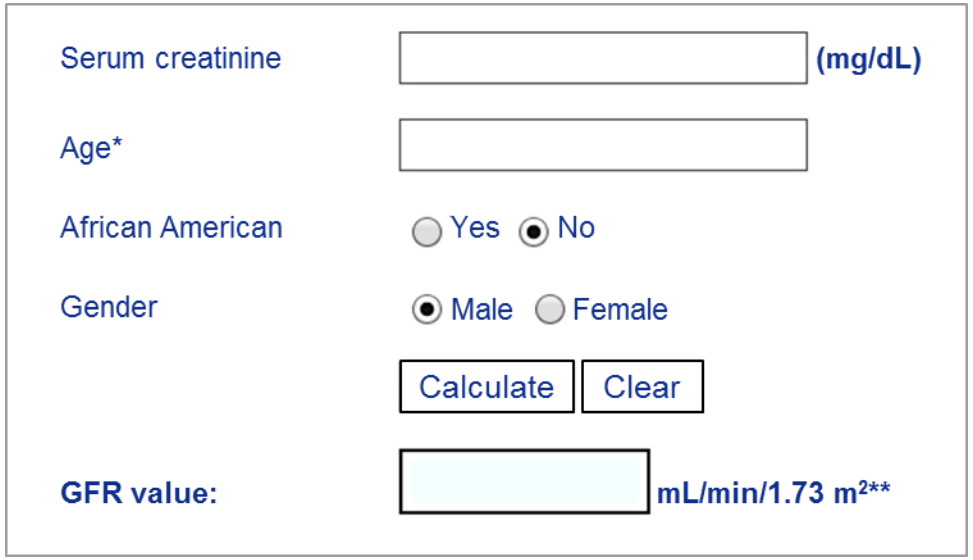
# Estimated Glomerular Filtration Rate (eGFR) Is Typically Used to Assess Kidney Function

- GFR is the best index of kidney function[1]
- Measured GFR assesses the clearance of an exogenous substance such as inulin or 125I-iothalamate[1]
  - Accurate, but cumbersome and expensive
- eGFR utilizes serum Cr levels to assess filtration rates[1]
  - Calculators: Cockcroft-Gault, MDRD, CKD-EPI

## CKD-EPI equation for adults[2]




*This equation should only be used for patients aged 18 and older.

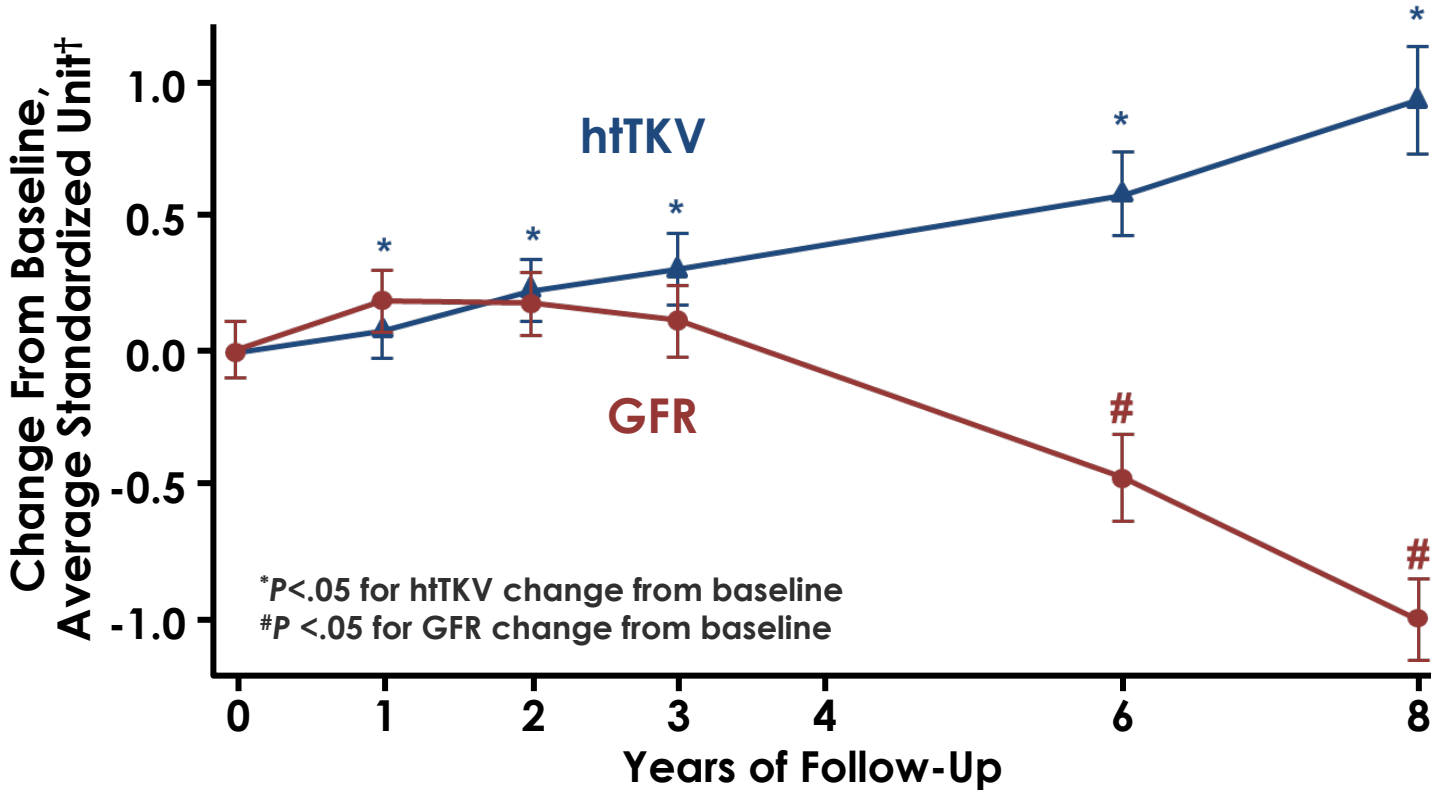
**The NKDEP presently recommends reporting eGFR values ***greater than or equal to 60 mL/min/1.73 m²*** simply as ≥60 mL/min/1.73 $m^2$, not as an exact number.

CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; Cr=creatinine; GFR=glomerular filtration rate; MDRD=Modification of Diet in Renal Disease; NKDEP=National Kidney Disease Education Program.


1. Soares AA et al. (2009). *Clin Chem Lab Med*. 47(9): 1023–32.
2. NIDDK. https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/adults-conventional-unit/Pages/adults-conventional-unit.aspx (accessed 11 Jul 2017).

# Change in Kidney Volume in ADPKD Precedes Changes in Renal Function

**Kidney and cyst volume are determinants of renal outcome and precede changes in renal function by many years[1]**




†% change standardized to common unit.

GFR=glomerular filtration rate; htTKV=height-adjusted total kidney volume.

1. Chapman AB et al. (2012). *Clin J Am Soc Nephrol*. 7(3): 479–86.

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# Ultrasound in ADPKD

# Ultrasound Is the Most Common Method Used for Diagnosis of ADPKD

- Sonographic features confirm diagnosis in the setting of positive family history[1]
- Commonly used due to low cost and safety[2]
- Visualization can be challenging in patients with abundant adipose tissue or bowel gas[3]
- Can be difficult and time-consuming to characterize small cysts[3]

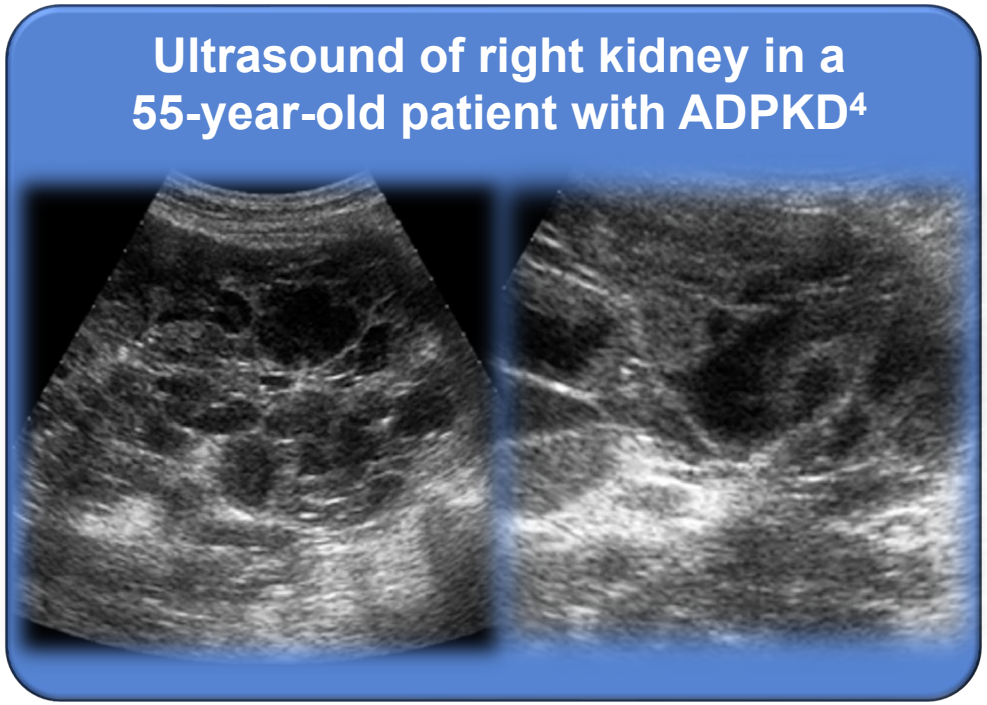



Figure adapted from Saedi D et al. (2009). *Cases J*. 2(66): 1–4.

ADPKD=autosomal dominant polycystic kidney disease.

1. Barua M, Pei Y. (2010). *Semin Nephrol.* 30(4): 356–65.
2. Torres VE, Harris PC. (2009). *Kidney Int*. 76(2): 149–68.
3. Nascimento AB et al. (2001). *Radiology*. 221(3): 628–32.
4. Saedi D et al. (2009). *Cases J*. 2(66): 1–4.

# Pei Criteria for Ultrasound Diagnosis of ADPKD

| Age | Number of Cysts | Cyst Location |
|---|---|---|
| 15–29 years | ≥3 | Unilateral or bilateral renal cysts |
| 30–39 years | ≥3 | Unilateral or bilateral renal cysts |
| 40–59 years | ≥2 | Cysts in each kidney |
| ≥60 years | ≥4 | Cysts in each kidney |

- The Pei criteria are used for testing individuals who are at risk for ADPKD and in whom the gene type (*PKD1* or *PKD2*) is unknown[1]

ADPKD=autosomal dominant polycystic kidney disease.

1. Pei Y et al. (2009). *J Am Soc Nephrol.* 20(1)-205-212.

# Ultrasound Has High Positive Predictive Value and Specificity for ADPKD

## Criteria for Positive Diagnosis[1,2]

| | | Family Genotype* | | |
|---|---|---|---|---|
| | | Unknown | *PKD1* | *PKD2* |
| Age (yr) | | Sen | Sen | Sen |
| 15–29 | ≥3 cysts, unilateral or bilateral | 81.7 | 94.3 | 69.5 |
| 30–39 | ≥3 cysts, unilateral or bilateral | 95.5 | 96.6 | 94.9 |
| 40–59 | ≥2 cysts in each kidney | 90.0 | 92.6 | 88.8 |
| ≥60 | ≥4 cysts in each kidney | 100 | 100 | 100 |

*PPV was 100 for each family genotype.

## Criteria for Diagnosis Exclusion[1,2]

| | | NPV | Spec | NPV | Spec | NPV | Spec |
|---|---|---|---|---|---|---|---|
| 15–29 | ≥1 cyst | 90.8 | 97.1 | 99.1 | 97.6 | 83.5 | 96.6 |
| 30–39 | ≥1 cyst | 98.3 | 94.8 | 100 | 96.0 | 96.8 | 93.8 |
| 40–59 | ≥1 cyst | 100 | 93.9 | 100 | 93.9 | 100 | 93.7 |

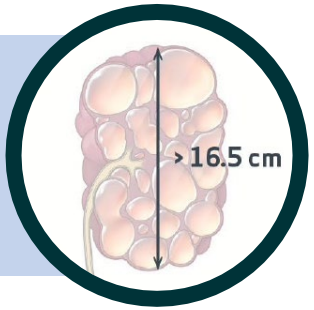
ADPKD=autosomal dominant polycystic kidney disease; NPV=negative predictive value; PPV=positive predictive value; Sen=sensitivity; Spec=specificity.


1. Adapted from Pei Y, Watnick T. (2010). *Adv Chronic Kidney Dis.* 17(2): 140–52.
2. Pei Y et al. (2009). *J Am Soc Nephrol.* 20(1)-205-212.

# Ultrasound for the Measurement of Kidney Length

- MRI is the recommended imaging modality for the most accurate and reproducible measurement of KL, kidney cyst burden, and TKV[1]
- When MRI-calculated TKV is not feasible, US-measured KL has been proposed as a useful surrogate for identifying young ADPKD patients at risk of rapid progression[1]

**US-measured predictor of rapid progression†**
**KL > 16.5 cm**
**htTKV > 650 ml/m**
in patients < 45 years old[1,2]




## Limitations of US-KL in identifying rapid progression

- In data analysis, KL was not normalized for height, which is an important variable*[2]
- Young patients with lengths < 16.5 cm may still have rapidly progressing disease[3]
- Atypical patients with slow progression may have lengths > 16.5 cm[3]
- US-measured KL is less accurate with larger kidneys[1]
- US measurements are operator-dependent and lack precision and accuracy for detecting short-term changes in kidney volume and increase the risk of misclassifying ADPKD progression[1,3,4]

*Based on data analysis comparing US and MRI KL measurements from CRISP.[1] †When rapid progression is defined as CKD 3 development within 8 years.[1,2]
ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; CRISP, Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; htTKV, height-adjusted TKV; KL, kidney length; MRI, magnetic resonance imaging; TKV, total kidney volume; US, ultrasound.


1. Bhutani H et al. *Kidney Int.* 2015; 88:146-151.
2. Gansevoort RT et al. *Nephrol Dial Transplat.* 2016; 31:337-348.
3. Chebib FT et al. *J Am Soc Nephrol.* 2018; 29(10):2458-2470.
4. Magistroni R et al. *Am J Nephrol.* 2018; 48:67-78.

# Use of Ultrasound Imaging to Exclude ADPKD in Kidney Donors at Risk of Disease

- In most moderate to advanced cases, US easily detects classic findings of ADPKD,* however in younger patients with early-stage PKD, diagnosis may not be obvious
  - Smaller cysts are more likely to escape sonographic detection, especially for those with milder *PKD2* disease
- Age-graded US criteria for disease exclusion have been used for evaluating potential living-related kidney donors who are at risk for ADPKD

## Utility of US for disease exclusion improves with age

For patients aged 15–29 years with no cysts, ADPKD can **NOT** be excluded, regardless of genotype (NPV 99.1%, 83.5%, and 90.8% for *PKD1*, *PKD2*, and unknown genotypes, respectively)

For patients aged 30–39 years with no cysts, ADPKD can **ONLY** be excluded in those with a family genotype of *PKD1* (NPV 96.8% and 98.3% for *PKD2* and unknown genotypes, respectively)

For patients aged 40–59 years with no cysts, ADPKD **CAN** be excluded, regardless of genotype (NPV 100% for all genotypes)

*Classic findings include multiple, bilateral renal cysts and liver cysts.

ADPKD=autosomal dominant polycystic kidney disease; PKD=polycystic kidney disease; PKD1 or PKD2= PKD gene 1 or 2; US=ultrasound.

1. Pei Y and Watnick T. (2010). *Adv Chronic Kidney Dis*. 17(2):140-52.

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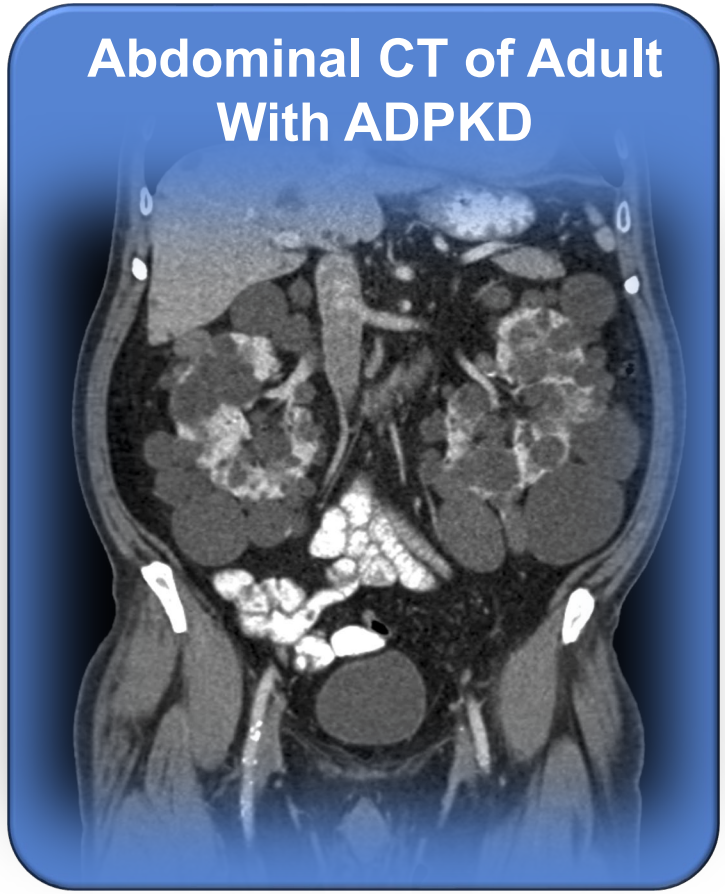
# CT and MRI Imaging

# CT and MRI for ADPKD Diagnosis

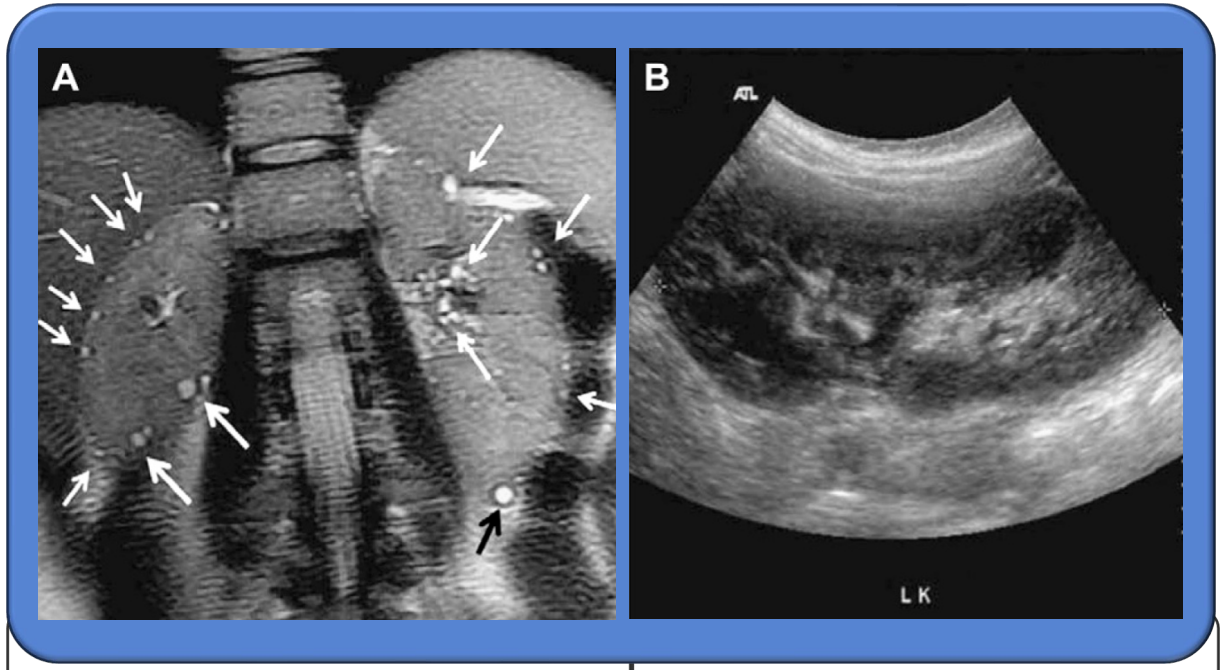
- CT and MRI may be useful when ultrasound results are equivocal or indeterminate[1]
  - Both techniques can detect smaller cysts than ultrasound[2,3]
- A dose-minimizing ultra low dose CT protocol has been established as an alternative to MRI[4]
  - In a recent trial, ultra low dose CT provided accurate and timely TKV measurements similar to the MRI protocol[4]
- Limitations
  - Predictive utility in ADPKD not validated[1]
  - Ultrasound criteria cannot be extrapolated[1]
  - Risks of CT include radiation exposure and allergy to contrast medium[3]




ADPKD=autosomal dominant polycystic kidney disease; CT=computed tomography; MRI=magnetic resonance imaging.

1. Pei Y, Watnick T. (2010). *Adv Chronic Kidney Dis*. 17(2): 140–52.
2. Nascimento AB et al. (2001). *Radiology*. 221: 628–32.
3. Pei Y. (2006). *Clin J Am Soc Nephrol*. 1(5): 1108–14.
4. Bevilacqua, M. U., et al. (2019). Radiology, 291(3), 660-667.

# MRI and Ultrasound From 28-Year-Old at Risk of ADPKD




**T2-weighted breath-held MRI** performed without contrast injection in 1 breath-hold shows multiple tiny cysts (white arrows) in both kidneys (>10/kidney)[1]

**Ultrasound of left kidney**
Ultrasound through both kidneys was normal[1]

*DNA testing subsequently detected a truncating PKD2 mutation in this patient and other affected family members*

ADPKD=autosomal dominant polycystic kidney disease; MRI=magnetic resonance imaging.

1. Pei Y, Watnick T. (2010). *Adv Chronic Kidney Dis*. 17: 140–152.

# Limitations of Family History and Imaging for Diagnosis

- Diagnosis based on imaging/family history may be ambiguous in young patients, where renal sonography may not be conclusive[1]
- Diagnosis may also be challenging when the family history is unknown[1]
  - Significant issue when renal donation is being considered before age 30 years, when the sensitivity of these criteria is only 67% in patients with a PKD2 mutation
- In these and other cases, molecular diagnostic methods may be valuable[1]

1. Tan YC et al. (2011). Biochim Biophys Acta. 1812: 1202–12.

# Steps in ADPKD Screening and Diagnosis

***Family History***: May include ADPKD, ESRD, intracranial aneurysm, hemorrhagic stroke, or subarachnoid hemorrhage[1]

***Physical Examination***: Abdominal examination often reveals a palpable renal or hepatic mass. Hypertension is common and often occurs at a relatively young age[2]

***Laboratory Tests***: Serum electrolytes, blood urea, creatinine, and fasting lipid profile. Creatinine can be used to estimate GFR. Urinalysis to detect increased urinary albumin excretion or proteinuria[2]

***Renal Imaging:*** US, MRI or CT imaging shows the presence of renal cysts with, or without, hepatic cysts. Appropriate counselling and discussion of potential discrimination before testing[2]

***Extrarenal Investigations:*** CT scan may also provide evidence of extrarenal cysts. Hepatic cysts are the most common extrarenal manifestation[2]

***Genetic Testing:*** Used when imaging results are inconclusive, to confirm a presumed diagnosis in the absence of family history, or when a definite diagnosis is required in a younger patient[1]

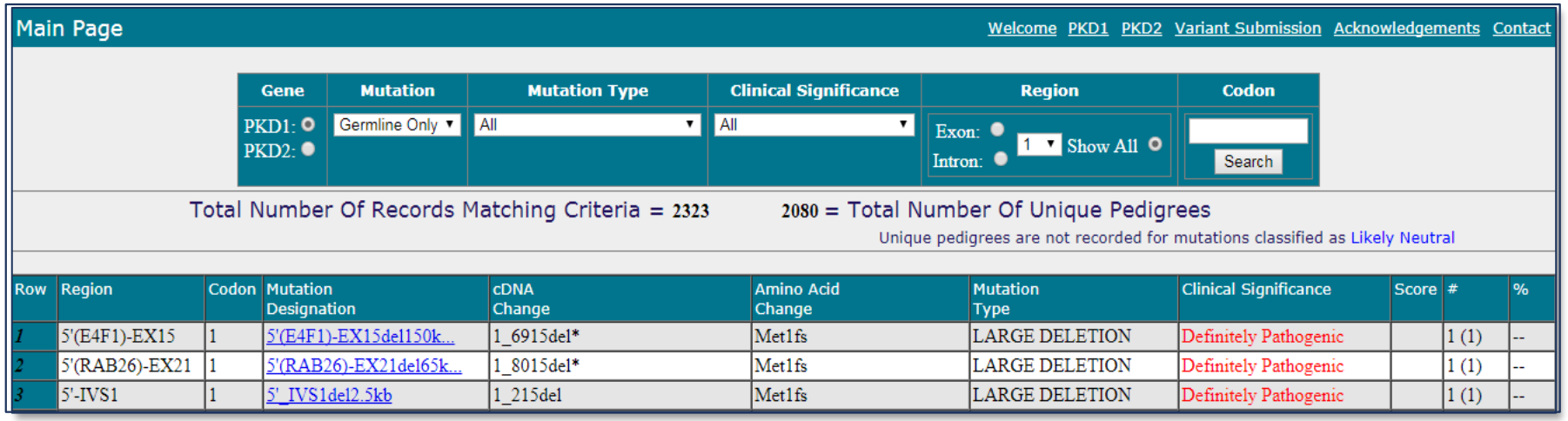
***Risk Assessment***: Use PROPKD score and Mayo Classification to identify patients as rapid or slow progressors[3,4]

ADPKD=autosomal dominant polycystic kidney disease; CT=computed tomography; ESRD=end-state renal disease; GFR=glomerular filtration rate; MRI=magnetic resonance imaging; US=ultrasonography.


1. Pei Y, Watnick T. (2010). *Adv Chronic Kidney Dis.* 17: 140–52
2. Torra R. (2017). http://emedicine.medscape.com/article/244907-overview (accessed 29 Sept 2017).
3. Irazabal MV et al. (2015). *J Am Soc Nephrol*. 26(1): 160–72.
4. Cornec-Le Gall E et al. (2016). *J Am Soc Nephrol*. 27(3): 942–51.

# Molecular Diagnosis of ADPKD

- DNA linkage analysis[1,2]
  - Indirect analysis based on genetic markers located in the regions of the PKD1 and PKD2 genes
  - Requires characterization of multiple affected and unaffected family members
- Direct mutation screening[1,2]
  - Genetic sequencing of all *PKD1* and *PKD2* exons and flanking introns
  - The ADPKD Database (curated by Mayo Clinic) was established to facilitate the characterization of variants in *PKD1* and *PKD2* (http://pkdb.mayo.edu)
  - Expensive




| Row | Region | Codon | Mutation Designation | cDNA Change | Amino Acid Change | Mutation Type | Clinical Significance | Score | # | % |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 5'(E4F1)-EX15 | 1 | 5'(E4F1)-EX15del150k... | 1_6915del* | Met1fs | LARGE DELETION | Definitely Pathogenic | | 1 (1) | -- |
| 2 | 5'(RAB26)-EX21 | 1 | 5'(RAB26)-EX21del65k... | 1_8015del* | Met1fs | LARGE DELETION | Definitely Pathogenic | | 1 (1) | -- |
| 3 | 5'-IVS1 | 1 | 5'_IVS1del2.5kb | 1_215del | Met1fs | LARGE DELETION | Definitely Pathogenic | | 1 (1) | -- |

Figure adapted from ADPKD Mutation Database. http://pkdb.mayo.edu.
ADPKD=autosomal dominant polycystic kidney disease.


1. Harris PC, Rossetti S. (2010). *Nat Rev Nephrol*. 6(4): 197-206.
2. Torra Balcells R, Ars Criach E. (2011). *Nefrologia*. 31(1): 35-43.

# Other Situations in Which to Consider Molecular Testing in ADPKD

## Other situations where molecular testing may be valuable[1]

### Individuals with no family history of ADPKD

- Atypical radiological presentation, for example
  - Disease more severe in one kidney
  - Patient with multiple small cysts
- Patients with mild renal disease
- Patients with extrarenal manifestations atypical of ADPKD
- Provide prognostic information where guidance from other family members is not available

### Families affected by early-onset disease

- In a family with otherwise typical ADPKD to identify variants that may be associated with severe disease
- In individuals with a negative family history of ADPKD, but who have negative PKHD1 mutation test results and/or who have ADPKD radiological features
- For pre-implantation genetic diagnostics in families with a history of early-onset disease

### Patients requesting a definite diagnosis

- For prognostic value
- To aid informed family planning choices

ADPKD=autosomal dominant polycystic kidney disease; PKDH1=polycystic kidney and hepatic disease 1.

1. Harris PC, Rossetti S. (2010). *Nat Rev Nephrol.* 6:197-206.

# Benefits and Limitations of Early Testing for ADPKD

| Early Diagnosis of ADPKD | |
|---|---|
| **Benefits[1–3]** | **Limitations[4,5]** |
| Allows for selection of unaffected family members for living donor transplantation | Restricts access to health and life insurance |
| Allows for informed family planning decisions | May restrict access to employment |
| Allows for early detection and treatment of complications | Negative psychological impact |
| Potential for receiving early preventative therapies that are currently being investigated in clinical trials | May impact social and sexual relationships |
| May allow implementation of lifestyle measures to preserve kidney function | |

ADPKD=autosomal dominant polycystic kidney disease.


1. Pei Y. (2011). *Nephron Clin Pract*. 118(1): c19–30.
2. Pei Y, Watnick T. (2010). *Adv Chronic Kidney Dis.* 17(2): 140–52.
3. Search Results National Institute of Diabetes and Digestive and Kidney Diseases. file:///C:/Users/simpsonk/Downloads/PKD_508%20(1).pdf (accessed 29 Sept 2017).
4. PKD Foundation. http://www.pkdcure.org/research/making-a-clinical-diagnosis-of-pkd-pros-and-cons (accessed 2 Dec 2014).
5. Kidney health Australia. http://www.cari.org.au/Patient%20and%20Carers/3.%20ADPKD_GeneticTesting_Draft_25Jan2017.pdf (accessed 29 Sept 2017).

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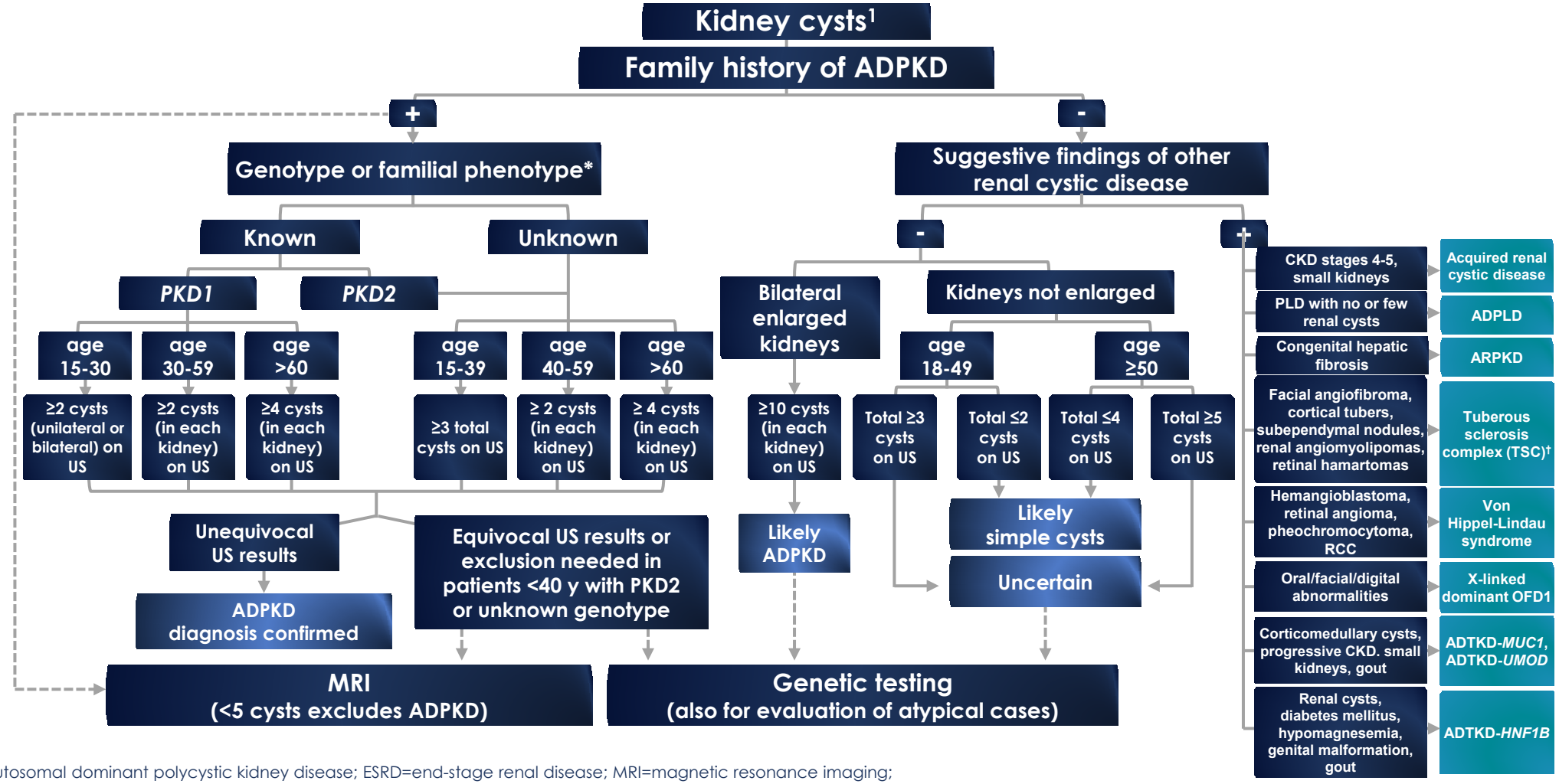
# ADPKD Diagnostic Algorithm

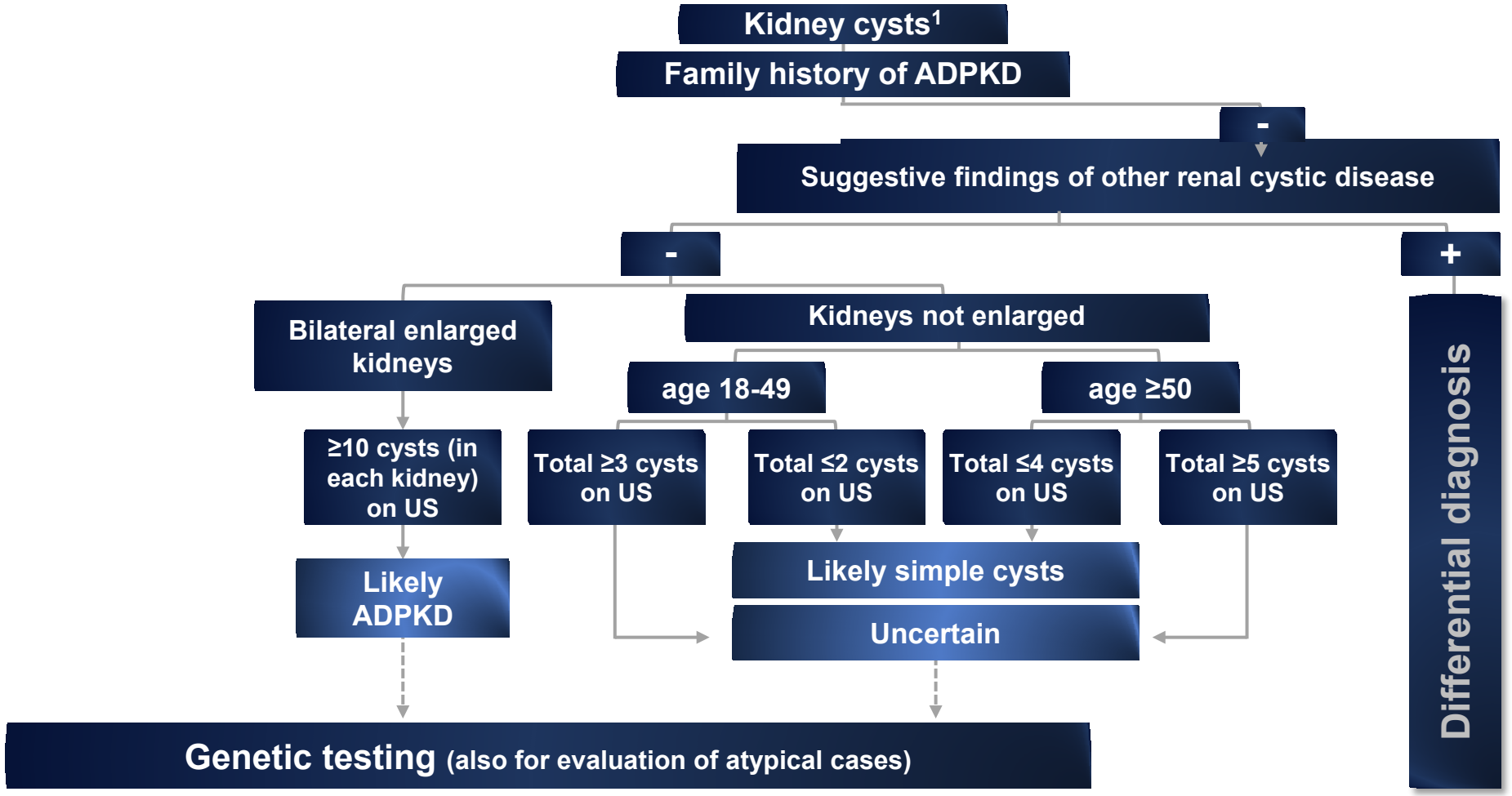
# Diagnostic Algorithm for ADPKD




ADPKD=autosomal dominant polycystic kidney disease; ESRD=end-stage renal disease; MRI=magnetic resonance imaging; *PKD1*=polycystic kidney disease gene 1; *PKD2*=polycystic kidney disease gene 2; RCC=renal cell carcinoma; US=ultrasound.

1. figure adapted from Chebib FT, Torres VE. (2016). *Am J Kidney Dis.* 67(5): 792–810.

# Diagnostic Algorithm for ADPKD (Negative Family History)




ADPKD=autosomal dominant polycystic kidney disease; US=ultrasound.

1. Figure adapted from Chebib FT, Torres VE. (2016). Am J Kidney Dis. 67(5): 792–810.

# Differential Diagnosis of ADPKD

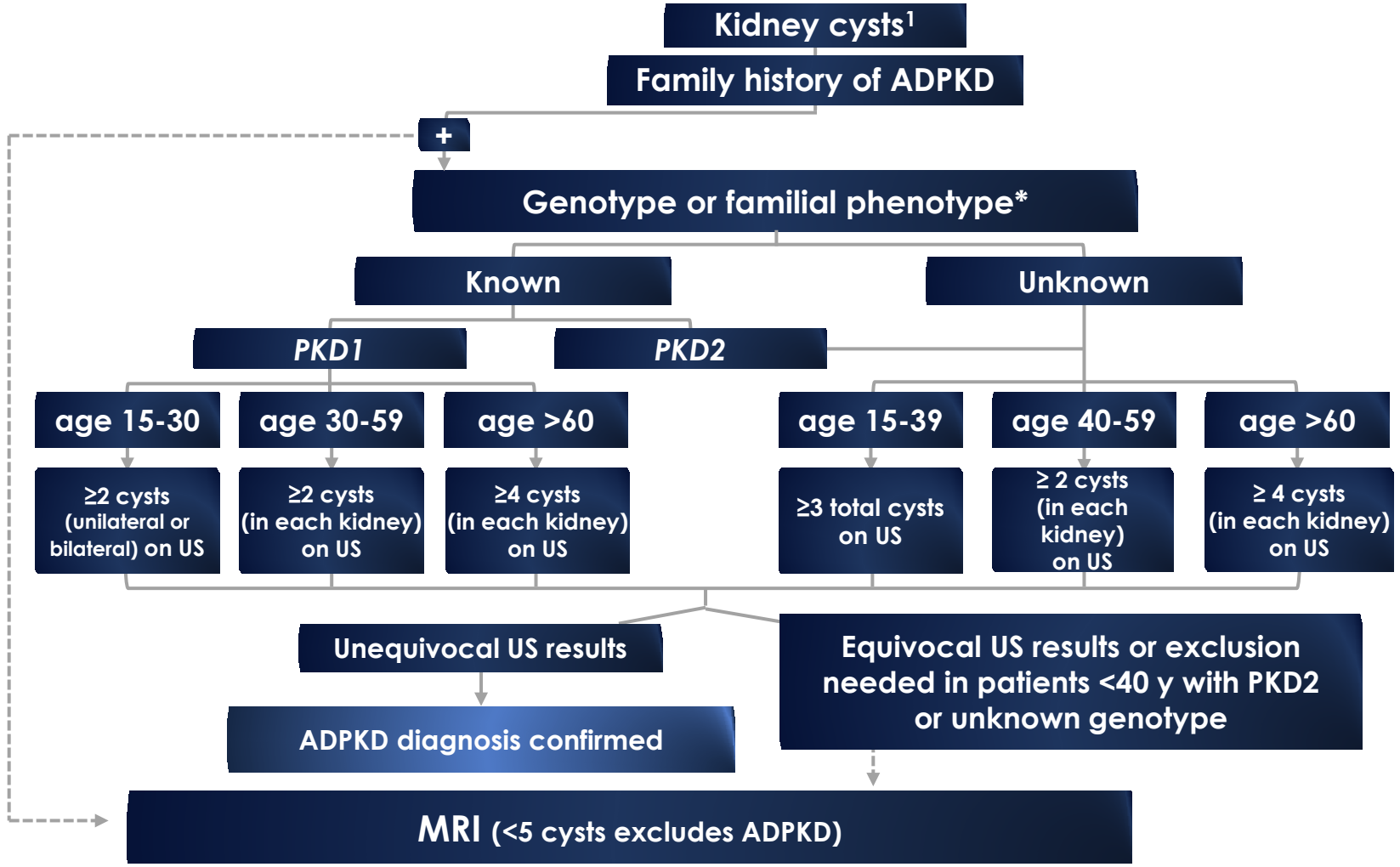
**Renal cysts can be a manifestation of both hereditary and acquired disorders other than ADPKD[1]**

- **Acquired renal cystic disease[1]**
  Associated with chronic renal insufficiency or ESRD; multiple renal cysts
- **Polycystic liver disease[1]**
  Small number of renal cysts
- **ARPKD[1]**
  Early in life; kidneys cystic, enlarged, and echogenic
- **Tuberous sclerosis[1]**
  Angiomyolipoma; severe early-onset PKD with ESRD in first two decades of life
- **von Hippel-Lindau syndrome[1]**
  High risk of renal cell carcinomas
- **Orofaciodigital syndrome I[1]**
  X-linked, dominant; cleft palate, bifid tongue, hyperplastic frenula, hypertelorism, broadened nasal ridge, digital abnormalities, CNS malformations
- **Medullary sponge kidney[1]**
  Interstitial fibrosis; small to normal-sized kidneys
- **Renal cysts and diabetes syndrome[2]**
  Kidney cysts or malformation in 90%; diabetes mellitus in 45%; hypomagnesemia in 40%; genital tract abnormalities in 20%; hyperuricemia in 20%; elevated liver enzymes in 15%
- **Glomerulocystic disease[1]**
  May have hyperechogenic kidneys, renal hypoplasia/dysplasia, multiple renal cysts, or glomerulocystic disease
- **Simple renal cysts[1]**
  Increasing number with age; normal renal function and normal-sized kidneys

ADPKD=autosomal dominant polycystic kidney disease; ARPKD=autosomal recessive polycystic kidney disease; CNS=central nervous system; ESRD=end-stage renal disease; PKD=polycystic kidney disease.


1. Pei Y, Watnick T. (2010). *Adv Chronic Kidney Dis*. 17(2): 140–52.
2. Chebib FT, Torres VE. (2016). *Am J Kidney Dis*. 67(5): 792–810.

# Diagnostic Algorithm for ADPKD (Positive Family History)




ADPKD=autosomal dominant polycystic kidney disease; ESRD=end-stage renal disease; MRI=magnetic resonance imaging; *PKD1*=polycystic kidney disease gene 1; *PKD2*=polycystic kidney disease gene 2; US=ultrasound.

1. Figure adapted from Chebib FT, Torres VE. (2016). *Am J Kidney Dis.* 67(5): 792–810.

# Steps in ADPKD Screening and Diagnosis

***Family History***: May include ADPKD, ESRD, intracranial aneurysm, hemorrhagic stroke, or subarachnoid hemorrhage[1]

***Physical Examination***: Abdominal examination often reveals a palpable renal or hepatic mass. Hypertension is common and often occurs at a relatively young age[2]

***Laboratory Tests***: Serum electrolytes, blood urea, creatinine, and fasting lipid profile. Creatinine can be used to estimate GFR. Urinalysis to detect increased urinary albumin excretion or proteinuria[2]

***Renal Imaging:*** US, MRI or CT imaging shows the presence of renal cysts with, or without, hepatic cysts. Appropriate counselling and discussion of potential discrimination before testing[2]

***Extrarenal Investigations:*** CT scan may also provide evidence of extrarenal cysts. Hepatic cysts are the most common extrarenal manifestation[2]

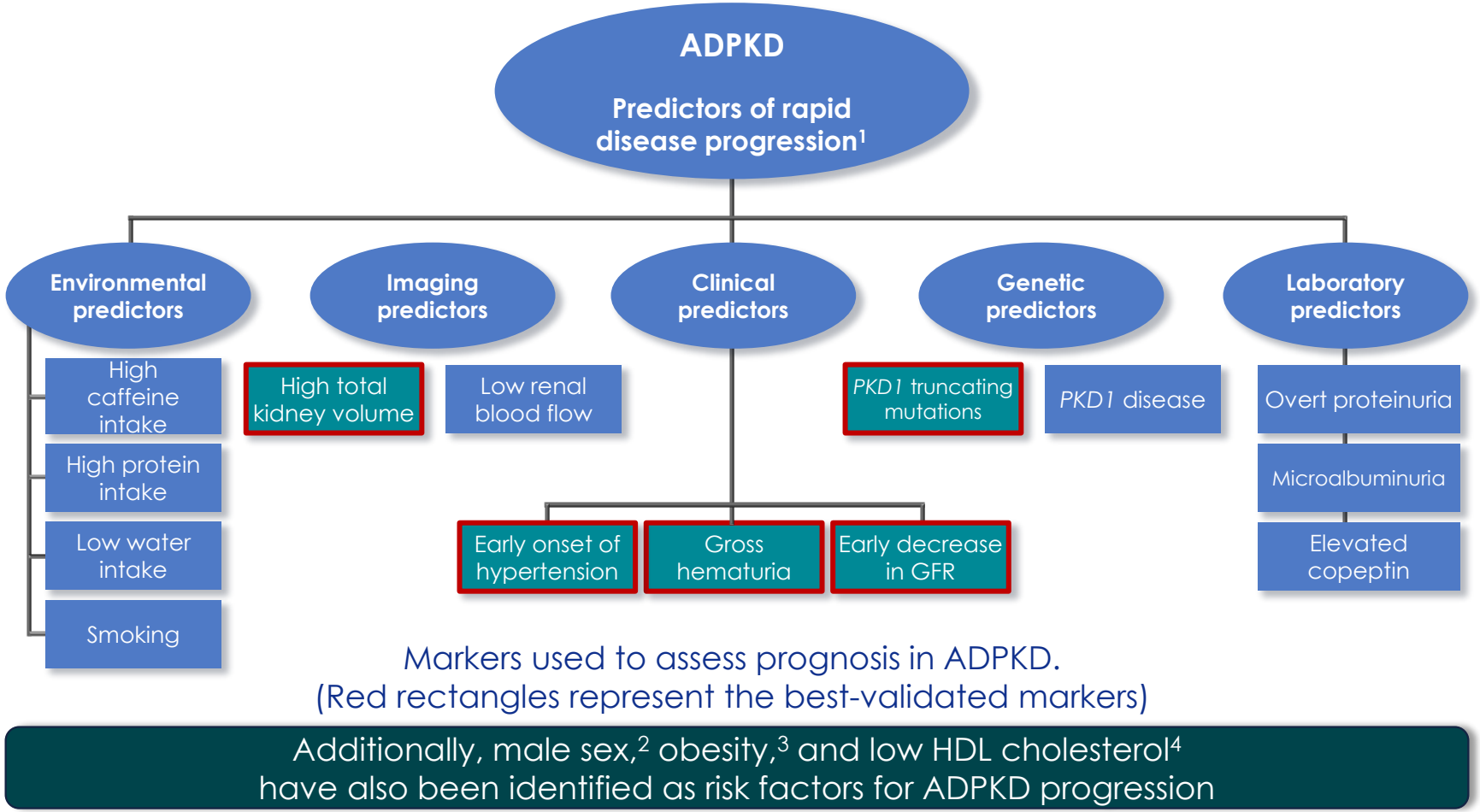
***Genetic Testing***: Used when imaging results are inconclusive, to confirm a presumed diagnosis in the absence of family history, or when a definite diagnosis is required in a younger patient[1]

***Risk Assessment:*** Use PROPKD score and Mayo Classification to identify patients as rapid or slow progressors[3,4]

ADPKD=autosomal dominant polycystic kidney disease; CT=computed tomography; ESRD=end-state renal disease; GFR=glomerular filtration rate; MRI=magnetic resonance imaging; US=ultrasonography.


1. Pei Y, Watnick T. (2010). *Adv Chronic Kidney Dis.* 17: 140–52.
2. Torra R. (2017). http://emedicine.medscape.com/article/244907-overview (accessed 29 Sept 2017).
3. Irazabal MV et al. (2015). *J Am Soc Nephrol*. 26(1): 160–72.
4. Cornec-Le Gall E et al. (2016). *J Am Soc Nephrol*. 27(3): 942–51.

# Predictors of Rapid Disease Progression in ADPKD




Markers used to assess prognosis in ADPKD.
(Red rectangles represent the best-validated markers)

Additionally, male sex,[2] obesity,[3] and low HDL cholesterol[4] have also been identified as risk factors for ADPKD progression

ADPKD=autosomal dominant polycystic kidney disease; GFR=glomerular filtration rate; HDL=high-density lipoprotein; *PKD1*=polycystic kidney disease gene 1.


1. Figure adapted from Gansevoort RT et al. (2016). *Nephrol Dial Transplant*. 31(3):337-348.
2. Schrier RW et al. (2014). *J Am Soc Nephrol*. 25(11):2399-2418.
3. Nowak KL, et al. (2018). *J Am Soc Nephrol*. 29(2):571-578.
4. Torres VE, et al. (2011). *Clin J Am Soc Nephrol*. 6(3):640-647.

# PROPKD Score

**PROPKD Score[1]:** Multivariate survival analysis identified four variables that were significantly associated with age at ESRD onset, and scoring system from 0 to 9 was developed as follows:

| PROPKD Calculator | |
|---|---|
| Variable | Points |
| Being male | 1 |
| Hypertension before 35 years of age | 2 |
| First urologic event* before 35 years of age† | 2 |
| Mutation | |
| *PKD2* mutation | 0 |
| Non truncating *PKD1* mutation | 2 |
| Truncating *PKD1* mutation | 4 |
| PROPKD Score = | SUM |

**Sample PROPKD Score Calculation**

ADPKD patient info: 29-year-old male with hypertension and a truncating *PKD1* mutation

1 point for being male
2 points for hypertension before 35 years of age
\+ 4 points for a truncating *PKD1* mutation

**PROPKD Score** = 7 points

**HIGH** Risk of Progression to ESRD

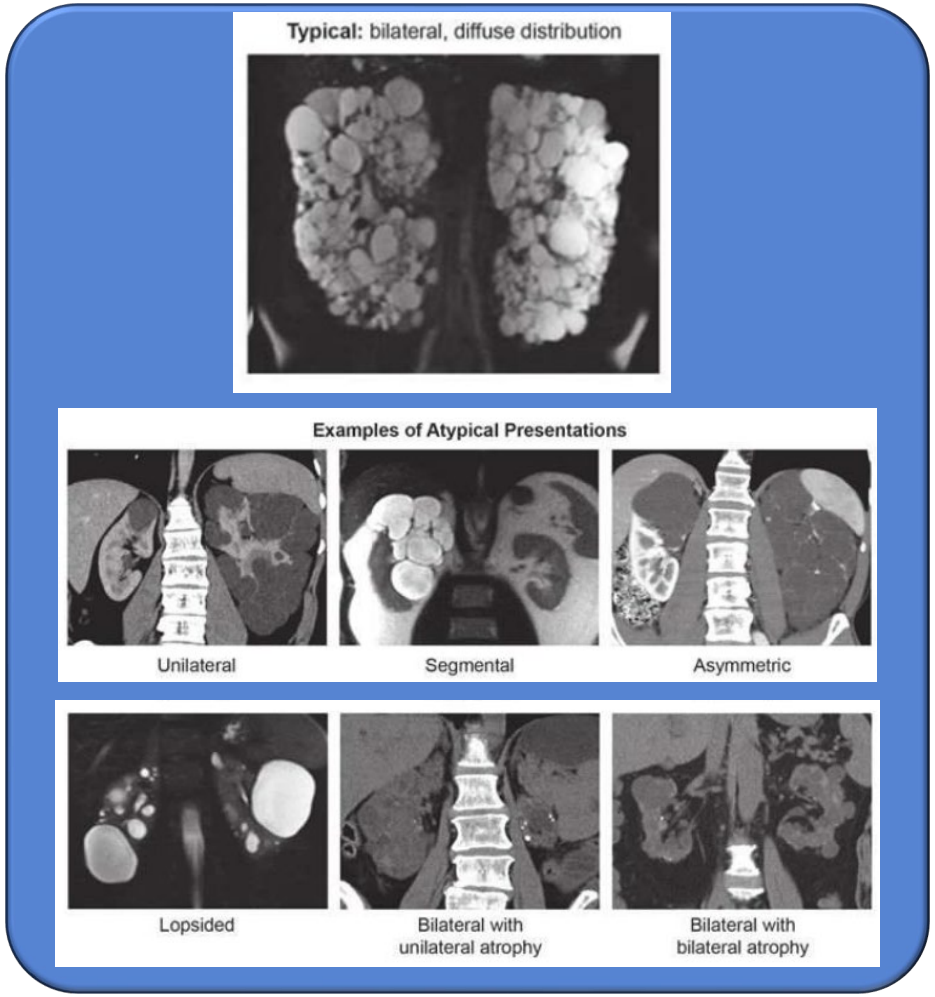
| PROPKD Score | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| **Risk of Progression to ESRD** | **LOW**<br>**70.6 median age for ESRD onset**<br>• Eliminates evolution to ESRD before age 60‡ | | | **INTERMEDIATE**<br>**56.9 median age for ESRD onset** | | | **HIGH**<br>**49 median age for ESRD onset**<br>• Forecasts ESRD onset before age 60§ | | |

*Previous urological events defined as gross hematuria, cyst infections, and flank pain related to cysts. †PROPKD score may not be helpful identifying rapid progression in patients < 35 years old unless they are already hypertensive and have experienced urological complications.[2] ‡Negative predictive value of 81.4%. §Positive predictive value of 90.9%.
ADPKD, autosomal dominant polycystic kidney disease; ESRD, end-stage renal disease; *PKD1/2*, polycystic kidney disease gene 1/2; PROPKD, Predicting Renal Outcomes in autosomal dominant polycystic kidney disease; ADPKD, autosomal dominant polycystic kidney disease.

1. Cornec-Le Gall E et al. *J Am Soc Nephrol.* 2016; 27(3): 942–51.
2. Chebib FT et al. *J Am Soc Nephrol*. 2018; 29(10):2458-2470.

# Mayo Clinic Imaging Classification: Typical vs Atypical Cyst Presentation

- Patients were classified as Typical (Class I) or Atypical (Class II) based on cyst presentation[1]
  - Most PKD patients are expected to be Class I-/Class II-specific
- Typical (n=538) patients were subclassifed according to htTKV[1]
- Atypical patients were excluded from the study

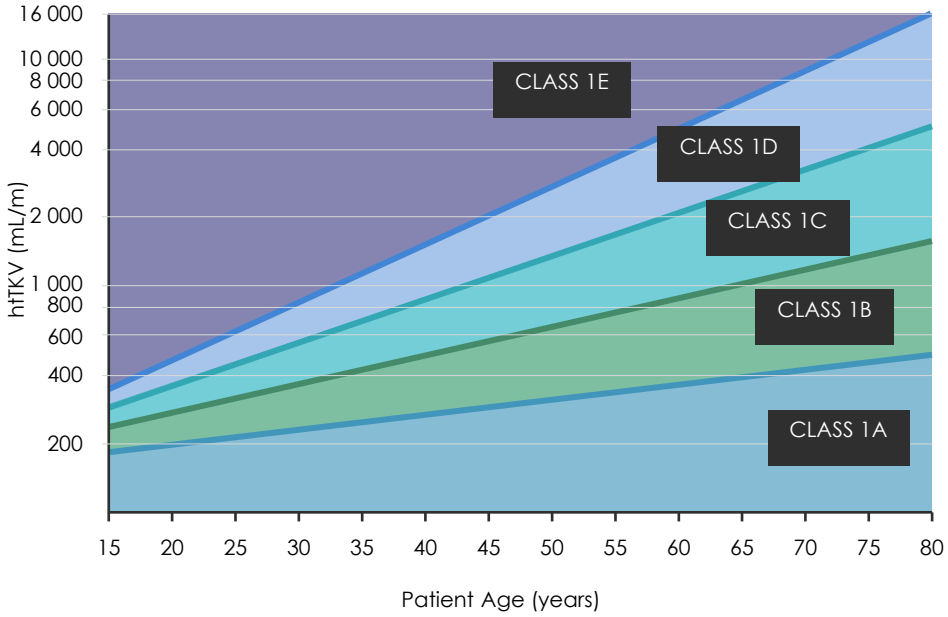



htTKV=height-adjusted total kidney volume; PKD=polycystic kidney disease.

1. Irazabal MV et al. (2015). *J Am Soc Nephrol.* 26(1): 160–72.

# TKV-based Classification of ADPKD

## Age and htTKV predicts decline in eGFR over time in patients with typical* presentation of ADPKD




| Class | Estimated kidney growth rate: yearly percentage increase | Male Estimated slope (ml/min per 1.73m$^2$ per year) | Female Estimated slope (ml/min per 1.73m$^2$ per year) | Risk for eGFR decline |
|---|---|---|---|---|
| 1E | >6.0% | -4.78 | -4.58 | High risk |
| 1D | 4.5 – 6.0% | -3.48 | -3.29 | High risk |
| 1C | 3.0 – 4.5% | -2.63 | -2.43 | High risk |
| 1B | 1.5 - 3.0% | -1.33 | -1.13 | Intermediate risk |
| 1A | <1.5% | -0.23 | 0.03 | Low risk |

*Typical presentation refers to patients with a bilateral and diffuse cyst distribution in both kidneys with mild to severe replacement of kidney tissue by cysts, with all cysts contributing similarly to TKV.
ADPKD, autosomal dominant polycystic kidney disease; eGFR, estimated glomerular filtration rate; htTKV, height-adjusted TKV; TKV, total kidney volume.

1. Irazabal MV et al. *J Am Soc Nephrol.* 2015; 26: 160-172.

# Summary

- Family history, age, number of cysts and type of mutation are key factors in ADPKD diagnosis[1]
- Ultrasound is the most common method used for diagnosis of ADPKD and may confirm diagnosis in the setting of positive family history[1,2]
- CT and MRI are more sensitive than ultrasound and can be used to determine TKV, which is informative for prognosis[3,4]
- Molecular testing may be appropriate in some situations, such as negative family history or equivocal imaging data[3]
- Recently published risk assessment tools (PROPKD score and Mayo Classification) use genetic, clinical and imaging data to assess disease progression[5,6]

ADPKD=autosomal dominant polycystic kidney disease; CT=computed tomography; MRI=magnetic resonance imagine; TKV=total kidney volume.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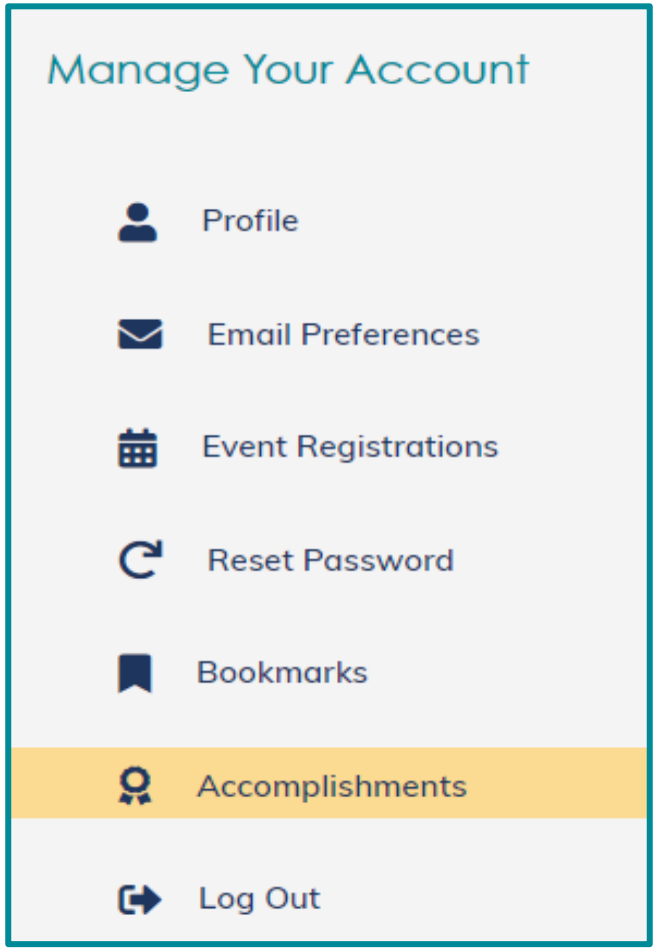


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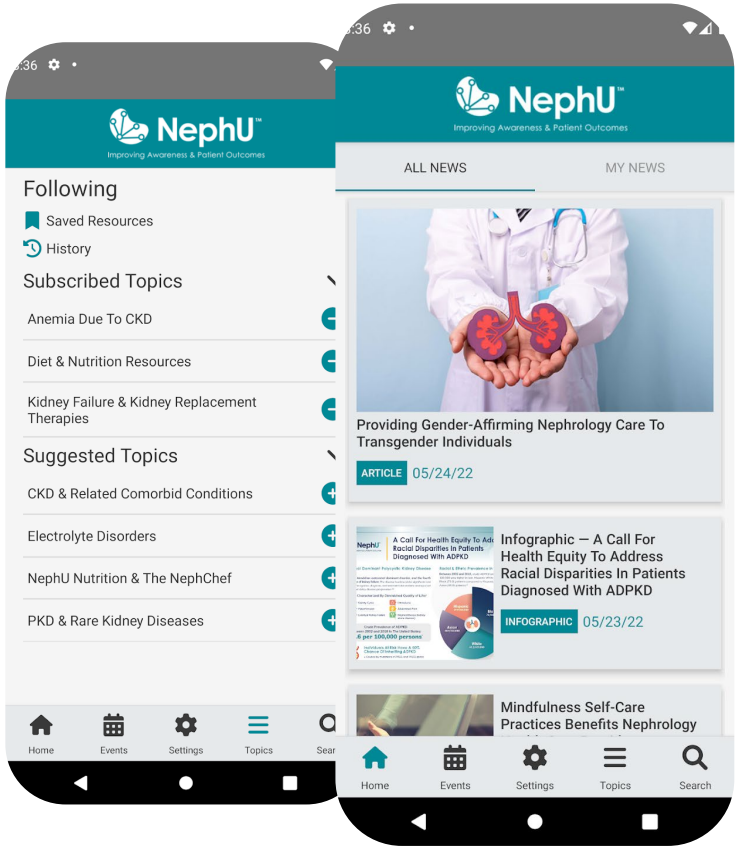


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# Autosomal Dominant Polycystic Kidney Disease (ADPKD):

## Screening & Differential Diagnosis



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