JAMA | Review

Autosomal Dominant Polycystic Kidney Disease
A Review

Fouad T. Chebib, MD; Christian Hanna, MD, MS; Peter C. Harris, PhD; Vicente E. Torres, MD, PhD; Neera K. Dahl, MD, PhD

IMPORTANCE Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive development of kidney cysts and is the most common inherited kidney disorder worldwide. ADPKD accounts for 5% to 10% of kidney failure in the US and Europe, and its prevalence in the US is 9.3 per 10 000 individuals.

OBSERVATIONS ADPKD is typically diagnosed in individuals aged 27 to 42 years and is primarily caused by pathogenic variants in the *PKD1* (78%) or *PKD2* (15%) genes. Most persons with ADPKD have an affected parent, but de novo disease is suggested in 10% to 25% of families. More than 90% of patients older than 35 years have hepatic cysts, which may cause abdominal discomfort and occasionally require medical or surgical intervention. Hypertension affects 70% to 80% of patients with ADPKD, and approximately 9% to 14% develop intracranial aneurysms, which have a rupture rate of 0.57 per 1000 patient-years. Approximately 50% of individuals with ADPKD require kidney replacement therapy by 62 years of age. The severity of kidney disease can be quantified using the Mayo Imaging Classification (MIC), which stratifies patients based on total kidney volume adjusted for height and age and ranges from 1A to 1E. Patients with MIC 1C to MIC 1E have larger kidneys because of more rapid growth (6%-10% per year) compared with those with MIC 1A and 1B (1%-5% per year) and have earlier progression to kidney replacement therapy, which occurs at a mean age of 58.4 years for MIC 1C, 52.5 years for MIC 1D, and 43.4 years for MIC 1E. Optimal management of ADPKD includes systolic blood pressure lower than 120 mm Hg for most patients, but lower than 110/75 mm Hg for patients with MIC 1C to 1E who have an estimated glomerular filtration rate (eGFR) greater than 60 mL/min/1.73 m^2 and are younger than 50 years, dietary sodium restriction (<2000 mg/d), weight management, and adequate hydration (>2.5 L daily). The vasopressin type 2 receptor antagonist tolvaptan reduces the annual rate of eGFR decline by 0.98 to 1.27 mL/min/1.73 m^2 and is indicated for patients with MIC 1C to 1E or an eGFR decline greater than 3 mL/min/1.73 m^2 per year to slow disease progression and delay the onset of kidney failure.

CONCLUSION ADPKD is the most common genetic kidney disease worldwide and is characterized by progressive development of kidney cysts. Patients typically have hypertension and liver cysts, and 9% to 14% develop intracranial aneurysms. First-line treatment includes blood pressure control, dietary and weight management, and adequate hydration. Tolvaptan reduces the rate of eGFR decline for those at high risk of rapid progression to kidney failure.

JAMA. doi:10.1001/jama.2025.0310
Published online March 24, 2025.

Multimedia

CME at jamacmelookup.com

Author Affiliations: Division of Nephrology and Hypertension, Mayo Clinic, Jacksonville, Florida (Chebib); Division of Pediatric Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota (Hanna); Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota (Hanna, Harris, Torres, Dahl); Robert M. and Billie Kelley Pirnie Translational Polycystic Kidney Disease Center, Mayo Clinic, Rochester, Minnesota (Hanna, Harris, Torres, Dahl); Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, Minnesota (Harris).

Corresponding Author: Neera K. Dahl, MD, PhD, Division of Nephrology and Hypertension, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (dahl.neera@mayo.edu).

Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent monogenic kidney disease and the fourth leading cause of kidney failure worldwide. The mean age at diagnosis is typically between 27 and 42 years.[1,2] Across predominantly US sequencing databases (123 136 whole exome and 78 280 whole genome sequences), the prevalence of gene variants causing ADPKD is 9.3 in 10 000.[3] However, the estimated number of persons with clinically recognized ADPKD in the US is 140 000 to 240 000, which is lower than predicted from the genetic variant prevalence.[4,5] Approximately 50% of individuals with ADPKD develop kidney failure requiring kidney replacement therapy by 62 years of age.[6] Patients with ADPKD may also have liver and pancreatic cysts[7]; intracranial[8] and other vascular aneurysms; aortic root dilatation, pericardial effusion, or cardiac valvular abnormalities[9]; abdominal hernias; diverticulosis; and male infertility. This review focuses on the pathophysiology, clinical presentation, diagnosis, treatment, and prognosis of ADPKD diagnosed in adulthood (**Box**).

Methods

A PubMed review was performed for articles about ADPKD published between October 1, 1994, and January 20, 2025. In addition, we reviewed the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for the evaluation, management, and treatment of ADPKD that was published online on January 20, 2025.[10] Of the 193 retrieved articles, 105 were included in this review, comprising 11 randomized clinical trials, 14 prospective and 37 retrospective cohort studies, 6 practice guidelines, 16 narrative reviews, 2 cross-sectional studies, 5 meta-analyses, and 14 genetic or physiology studies.

Genetics and Pathophysiology

ADPKD is caused by a single pathogenic genetic variant in *PKD1* (78% of screened families), *PKD2* (15%),[11] or one of several minor genes including *IFT140*,[12] *GANAB*,[13] *DNAJB11*,[14] *ALG9*,[15] *ALG8*,[16] *ALG5*,[17] and *NEK8*,[18] which affect polycystin maturation or function of primary (nonmobile) cilia. Primary cilia, present on most cells in the body, sense changes in fluid flow or pressure leading to signal transduction.[19] Impaired primary cilia function in renal tubular epithelium, hepatic bile ducts, and vascular endothelial and smooth muscle cells likely lead to the characteristic features of ADPKD: kidney and liver cysts and intracranial aneurysms. The proteins polycystin-1 and polycystin-2 encoded by *PKD1* and *PKD2* genes, respectively, localize to the primary cilium. Loss of polycystin function leads to reduced intracellular calcium, increased cyclic adenosine monophosphate (cAMP) signaling, and activation of protein kinase A, which increases proliferation of cyst cells and cyst fluid secretion and can cause interstitial inflammation and fibrosis that lead to cyst formation, destruction of noncystic kidney parenchyma, and kidney failure (**Figure 1**).[20,21] Enlarging cysts in the kidney compress the renal vasculature, causing ischemia and chronic activation of the renin-angiotensin-aldosterone system[22] resulting in hypertension, an independent risk factor for loss of kidney function.[23] Polycystin-1 also affects mitochondrial function,[24] shifting energy production from oxidative phosphorylation to glycolysis.[25,26]

Box. 3 Commonly Asked Questions About Autosomal Dominant Polycystic Kidney Disease (ADPKD)

What is the role of genetic testing in diagnosing or treating ADPKD?
The diagnosis of ADPKD can be made in patients with bilaterally enlarged kidneys (length >13 cm) and symmetric cyst distribution on kidney imaging (ultrasonography, computed tomographic imaging, or magnetic resonance imaging). However, genetic testing is helpful to diagnose ADPKD in patients with an atypical imaging finding or unusual clinical presentation and in those without a family history of ADPKD. Genetic testing can also help inform prognosis because the risk of progression to kidney failure is associated with the specific gene variant causing ADPKD.

What are appropriate first steps after an initial diagnosis of ADPKD?
Patients diagnosed with ADPKD should undergo blood pressure assessment, blood testing to assess kidney function (serum creatinine), and urinalysis to evaluate for hematuria and/or proteinuria and should be referred to a nephrologist. Family history of kidney failure, hemorrhagic stroke, and intracranial aneurysm rupture should be obtained. If the diagnosis of ADPKD was made using kidney ultrasonography, abdominal magnetic resonance imaging without contrast or a contrast-enhanced abdominal computed tomographic scan may be helpful to provide a more accurate measurement of total kidney volume and evaluate for liver cysts.

What patients are at high risk of early loss of kidney function?
In patients with ADPKD, total kidney volume and genotyping can help inform the predicted rate of progression to kidney failure. Patients with the largest height- and age-adjusted total kidney volume measurements are at highest risk of early kidney failure. Patients with *PKD1* gene variants develop kidney failure at an earlier age than those with *PKD2* gene variants or other pathogenic gene variants associated with ADPKD.

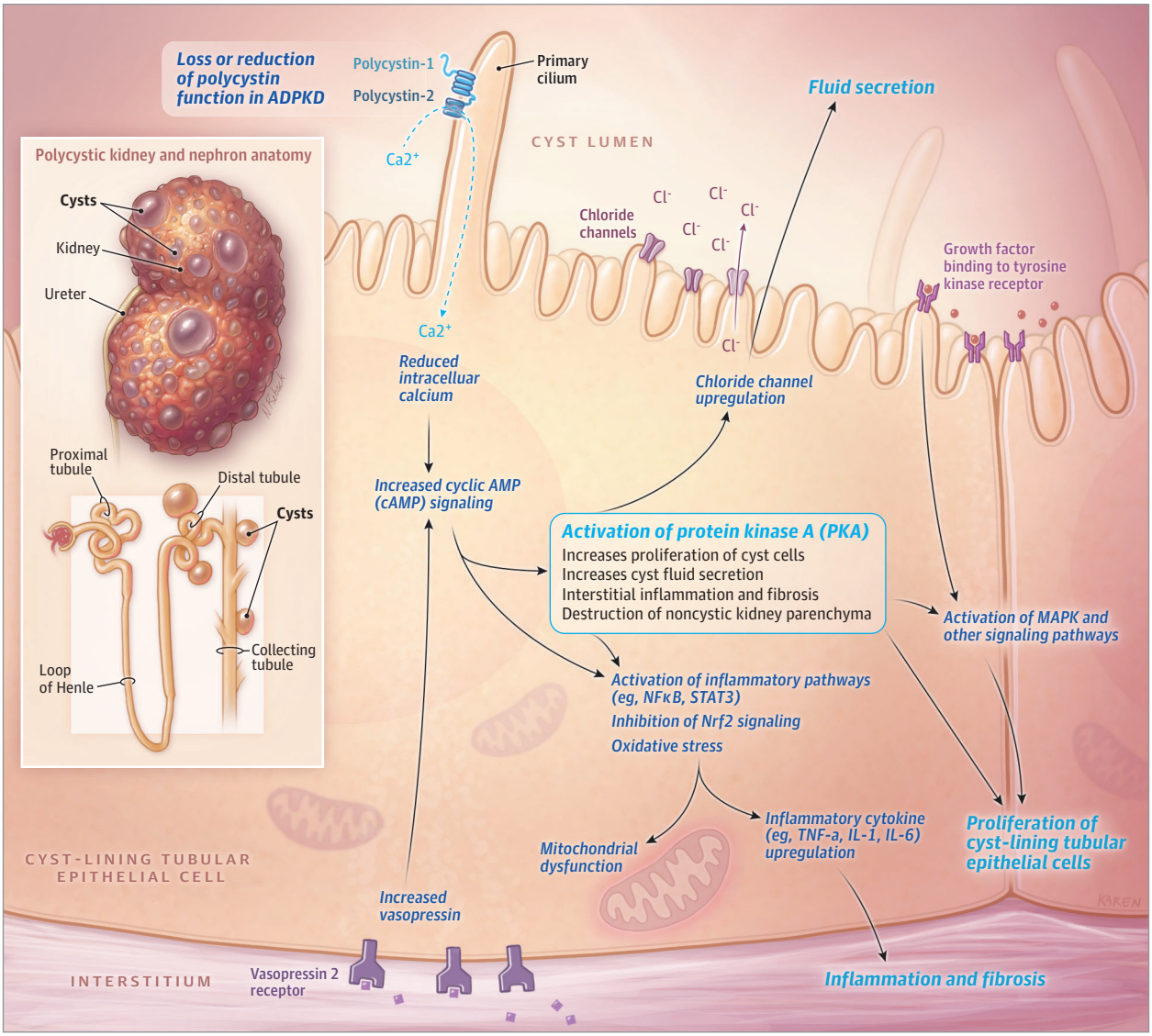
Kidney Cysts

ADPKD is characterized by numerous bilateral kidney cysts (>10 per kidney) and kidney enlargement (kidney length >13 cm; reference range, 10-12 cm in adults) and is distinct from acquired cystic kidney disease, which typically occurs after onset of kidney failure and is associated with small or atrophic kidneys (<10 cm).[27] A study of a cohort of 1948 potential living kidney donors[28] found that the presence of bilateral kidney cysts in healthy individuals without kidney disease increased with age, from 2.3% (age 18-49 years) to 11% (age 50-75 years). However, abdominal imaging with incidental findings of multiple bilateral kidney cysts should raise suspicion for ADPKD (**Figure 2**).

Liver Cysts

Approximately 90% of patients with ADPKD older than 35 years have liver cysts. Polycystic liver disease, defined as 10 or more hepatic fluid-filled cysts,[29] is typically associated with preserved liver synthetic function and leads to moderate liver enlargement, with height-adjusted total liver volume of 1000 to 1800 mL/m (reference, 900 mL/m) in 50% of cases and severe enlargement (exceeding 1800 mL/m) in 5.3% of 558 patients.[30] In a study of 558 patients with ADPKD, more than 80% of patients with severe PLD were female[30]; women 16 years and older were more likely than men to have more than 15 liver cysts.[31] Postmenopausal hormone replacement may be associated with increased liver cyst growth in persons with ADPKD. In a study of 19 women with ADPKD, 1 year of

Figure 1. Cellular Pathways in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Pathogenesis



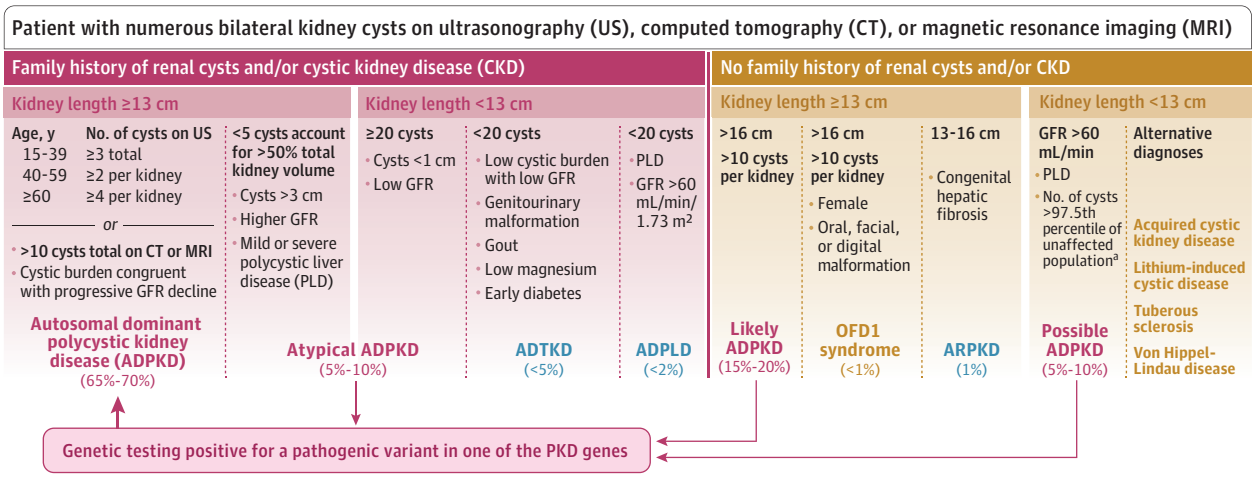
This figure illustrates the molecular mechanisms implicated in ADPKD that contribute to various cellular phenomena. Key processes include cell proliferation, facilitated through various signaling pathways including mitogen-activated protein kinase (MAPK) activation and fluid secretion via chloride (Cl^-) channels. Additional mechanisms include mitochondrial dysfunction and interstitial inflammation. A possible central pathway involves the augmented production of cyclic adenosine monophosphate (cAMP), primarily due to increased vasopressin activity that stimulates vasopressin 2 receptors, subsequently activating protein kinase A (PKA). Nrf2, nuclear factor erythroid 2–related factor 2; TNF, tumor necrosis factor.

estrogen treatment was associated with a mean (SD) increase of 7% (12%) in liver volume, compared with a mean (SD) decrease of 2% (8%) among 8 women not treated with estrogen ($P < .03$).[32]

Intracranial Aneurysms

The prevalence of intracranial aneurysms is 9% to 14%[33] in individuals with ADPKD, with higher prevalence rates (21% to 27%) in those with a family history of intracranial aneurysm or subarachnoid hemmorhage,[33] compared with 3.2%[8] in an age-matched general population. In ADPKD, most intracranial aneurysms are small (<5 mm) and predominantly located in the anterior circulation, with 15% to 25% of affected individuals having multiple aneurysms.[34] A study that performed systematic screening brain magnetic resonance angiography (MRA) for 83 patients with ADPKD revealed the prevalence of intracranial aneurysms was 16.9%, and 6% of patients required neurosurgical intervention.[35] In a cross-sectional study of a multicenter cohort of 2449 patients in Europe, 44 were identified as having aneurysms prior to enrollment and an additional 66 were identified after enrollment through screening those with a family history of aneurysms, those with at-risk occupations, or those requesting screening after comprehensive information; risk factors for an aneurysm were female sex (1.47 fold higher in females vs males; $P = .01$), older age (cumulative probability at age 40 years vs 70 years, 1.3% [95% CI, CI, 0.9%-1.7%] vs 8.1% [95% CI, 6.5-9.7]),[34] and a family history of intracranial aneurysm or subarachnoid hemorrhage. The risk of intracranial aneurysms

Figure 2. Diagnostic Algorithm for Evaluating Individuals With Numerous Bilateral Renal Cysts to Guide the Differentiation of ADPKD From Other Cystic Kidney Diseases



The thresholds for the minimum number of kidney cysts (each ≥ 5 mm in diameter) necessary for considering a possible autosomal dominant polycystic kidney disease (ADPKD) diagnosis are based on surpassing the 97.5th percentile for each age and sex demographic. For males: 2 cysts (ages 18-29 y), 3 cysts (30-39 y), 4 cysts (40-49 y), 6 cysts (50-59 y), and 11 cysts (≥60 y with at least 5 in each kidney). For females: 2 cysts (ages 18-29 y), 3 cysts (30-49 y), 4 cysts (50-59 y), 5 cysts (60-69), and 10 cysts (≥70 y with at least 5 in each kidney). These criteria, derived from contrast-enhanced abdominal computed tomographic scans of healthy potential kidney donors, are helpful for identifying possible ADPKD. ADPLD indicates autosomal dominant polycystic liver disease; ADTKD, autosomal dominant tubulointerstitial kidney disease; GFR, glomerular filtration rate; OFD1 syndrome, orofaciodigital syndrome type 1.

also increases with higher total kidney volume (TKV; ≥1000 mL; odds ratio [OR], 2.81) or Mayo Imaging Class (MIC) 1C, 1D, or 1E (OR, 2.52) and advanced chronic kidney disease (CKD) (CKD stages G3-G5; OR, 2.31), as described in a series with 94 intracranial aneurysms diagnosed in 519 patients with ADPKD.[36]

Epidemiology and Clinical Presentation

ADPKD is an autosomal-dominant disease, so children of a parent with ADPKD have a 50% risk of ADPKD. Although most patients have a parent with ADPKD, 10% to 25% of families have possible de novo disease.[37] In a cohort of 1044 patients, mean age at diagnosis of ADPKD was 27 to 33 years and the diagnosis was established in 39.8% of patients during screening of asymptomatic individuals with a known family history, 14.8% during evaluation for abdominal or flank pain, 13% were incidentally detected on imaging, 12.7% were identified during work-up of hypertension, and 7.1% during evaluation of hematuria or urinary tract infection.[1] In an international prospective cohort study[38] of 3400 patients aged 2 to 70 years with ADPKD of unknown genotype, mean (SD) ages were 34.2 (10.8) years for patients with estimated glomerular filtration rate (eGFR) greater than 90 mL/min/1.73 m^2, 45.6 (10.7) years for eGFR of 60 to 90 mL/min/1.73 m^2, and 55.3 (9.7) years for eGFR less than 30 mL/min/1.73 m^2. By the mean age of 45 years, 67% had hypertension, 23% had proteinuria, and 29% had hematuria. Other associated conditions included nephrolithiasis (17.7%),[39] urinary tract infection (27.5%), and abdominal wall hernias (12%).[38]

In a study of 230 patients with ADPKD, hepatic cysts were present on abdominal MR imaging (MRI) in 57% to 60% of patients at age 15 to 24 years and 93% to 95% at age 35 to 46 years.[40] Although many patients with ADPKD do not experience symptoms related to liver cysts, 38 of 49 patients (77.6%) with polycystic liver disease had abdominal distention, fullness and discomfort, early satiety, back pain, or dyspnea.[41] Patients with ADPKD and polycystic liver disease typically have more symptoms associated with increasing liver volume due to cyst growth.[42] In a study of 137 patients, complications of polycystic liver disease included liver cyst hemorrhage (14%), cyst infection (6%), cyst rupture (4%), ascites (4%), portal hypertension (5%), inferior vena cava compression (3%), and esophageal varices (1.5%).[29]

Additional extrarenal manifestations of ADPKD include pancreatic cysts (19%),[43] bronchiectasis (up to 37%),[44] seminal vesicle cysts (up to 40%),[7] and abdominal wall hernias (10%).[7] Less commonly, ADPKD is associated with aortic root or thoracic aortic aneurysms (0.92%),[45] coronary artery dissection (rare),[46] mitral valve prolapse (0%-26%),[9] mitral regurgitation (7.45%),[47] primary cardiomyopathy (8.3%),[48] and pericardial effusion (35%).[49]

Assessment and Diagnosis

The diagnosis of ADPKD is usually made by evaluation of kidney imaging, often in consultation with a nephrologist (Figure 2). Bilaterally enlarged kidneys (>13 cm or 97.5th percentile for age and sex) with more than 10 cysts per kidney are diagnostic of likely ADPKD,[50] even in patients without a family history. Age-stratified cyst number criteria in those with a family history of ADPKD allow a clinical diagnosis without genotyping (Figure 2). For example, an ultrasonography-based total kidney cyst count of more than 3 in a 31-year-old individual with a family history of ADPKD has a positive predictive value of 94.7% for the diagnosis of ADPKD, compared with the criterion standard of genotyping. For patients 30 years or younger with a family history of ADPKD who are being evaluated for ADPKD, MRI is preferred over ultrasonography due to its superior resolution for detecting smaller cysts. In patients with family history of ADPKD aged 16 to 40 years, detection of a total of 10 kidney cysts or more on MRI has a sensitivity and specificity of 100% to diagnose

ADPKD, compared with a confirmed genetic diagnosis. Conversely, presence of 5 or fewer cysts on MRI in patients aged 16 to 40 years with a family history of ADPKD effectively rules out the disease.[51] Genetic testing of the familial disease-causing variant in a young (<40 y) at-risk individual can also provide a definitive diagnosis.[52]

Individuals with incidentally detected multiple kidney cysts who have atypical imaging findings, such as unilateral, asymmetric, segmental, lopsided cysts or bilateral cysts with unilateral or bilateral kidney atrophy[53] or other features inconsistent with ADPKD, such as liver fibrosis, benefit from genetic testing to obtain a definitive diagnosis (Figure 2).[54] Although genetic testing is not necessary to diagnose ADPKD, particularly in a patient with a family history and classic imaging findings, it is now more commonly offered because genetic testing has become more affordable and reliable. A targeted polycystic kidney disease or kidney gene panel or analysis of these genes in whole exome or whole genome sequencing are common testing approaches.[54]

Risk of Decline in Kidney Function

From 30 to 40 years of age, the annual decline in eGFR among patients with ADPKD ranges from 0.63 to 4.65 mL/min/1.73 m^2.[55] Kidney growth in ADPKD also varies widely, with annual TKV growth rates ranging from 1.5% to more than 20%.[53] Kidney enlargement due to cyst development and growth starts at birth. However, kidney function typically remains stable until the TKV is greater than 1500 mL,[56] at which point kidney function declines. TKV continues to increase until kidney replacement therapy is required.[57] For individuals with ADPKD younger than 45 years and a creatinine clearance greater than 70 mL/min/1.73 m^2, kidney length on ultrasonography of 16.5 cm or greater predicts the development of stage 3 CKD within 8 years.[58]

Overweight and obesity are also associated with increased TKV growth and eGFR decline. In a phase 3 study of patients with ADPKD, 670 with a BMI of 18.5 to 24.9 (healthy weight), 429 with a BMI of 25 to 29.9 (overweight), and 213 with a BMI of 30 or greater (obese), overweight and obesity were associated with 1.52- and 2.91-fold greater TKV growth over 3 years, respectively.[59] A cohort study of 441 patients with early ADPKD reported each 5-unit increase in BMI was associated with an eGFR decline of 1.71 mL/min/1.73 m^2 over 60 months (P = .03).[60]

Preferred imaging for TKV includes abdominal MRI with or without intravenous gadolinium or contrast-enhanced abdominal computed tomographic imaging. Ultrasonography measurements underestimate TKV by 9% to 11% compared with MRI measurements.[61] MIC stratifies patients with ADPKD who have symmetric, bilaterally enlarged kidneys with uniform distribution of cysts into 5 imaging classes based on age- and height-adjusted TKV. Each class is defined by a theoretical growth rate from a baseline height-adjusted volume of 150 mL/m: 1A (<1.5% growth/y), 1B (1.5%-3%), 1C (3%-4.5%), 1D (4.5%-6%), and 1E (>6%). Transitions between adjacent MICs were observed in 11.5% to 15.6% of 538 patients over a 7-year follow-up period.[53] A single imaging scan is typically sufficient to establish the MIC class, unless the patient's height-adjusted TKV is between MIC 1B and 1C, which is the threshold for specific medical therapies such as tolvaptan (see below).

Approximately 50% of patients with ADPKD require kidney replacement therapy by 62 years of age.[6] Persons with MIC 1C, 1D, and 1E are at high risk of early kidney failure, with mean (SD) ages of kidney replacement therapy of 58.4 (7.9) years, 52.5 (8.6) years, and 43.4 (7.0) years, respectively.[62] Presence of the *PKD1* gene is associated with more severe kidney disease than *PKD2* (mean age requiring kidney replacement therapy, 58.0 vs 74.8 years).[6] The Prognosis of Polycystic Kidney Disease (PROPKD) score incorporates APKD genotype, sex, and 2 clinical risk factors (hypertension and a urologic complication, such as gross hematuria, flank pain, or kidney cyst infection, before 35 years of age). The median age of kidney failure onset for those with a PROPKD score of more than 6 is 49 years and those with a score of more than 6 have a 91% probability of kidney failure by 60 years of age.[63]

Approximately 30% to 36% of patients with ADPKD are classified at low risk of progression,[53] including those with MIC 1A or 1B,[53] those with atypical features (focal cystic disease, MIC 2A),[64] and those with a PROPKD score less than 4.[63] The median age of development of kidney failure in patients with MIC 1B is 71.2 years.[6] Patients predicted to have slow progression based on MIC or PROPKD score who develop rapid or early loss of kidney function should be evaluated for other causes of kidney disease.[2]

Treatment

All patients with ADPKD benefit from dietary modifications,[65] adequate hydration, and weight and blood pressure control to preserve kidney function (**Table 1**). Patients should follow a low-salt diet (2.0 g or 90 mEq of sodium daily).[69] In an observational cohort of 589 patients with baseline mean salt intake of 9.1 g per day, each 1-g of salt intake increase correlated with an annual eGFR decrease of 0.11 mL/min/m^2.[71] Because ADPKD is associated with uric acid and calcium oxalate kidney stones, daily water intake of 2.5 L is recommended.[10] A randomized clinical trial of 184 patients with ADPKD did not demonstrate additional benefit in slowing TKV growth in those randomized to receive increased oral fluid intake to maintain a urine osmolarity of 270 mL/kg vs ad libitum water intake.[72]

Hypertension Treatment

Angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists were recommended as first-line treatment for hypertension in ADPKD by KDIGO guidelines in 2025.[10] The recommendation for a systolic BP less than 120 mm Hg for patients with ADPKD older than 50 years or with an eGFR less than 60 mL/min/1.73 m^2 was based on CKD management guidelines.[69] The recommendation of a BP goal of less than or equal to 110/75 mm Hg for patients with ADPKD younger than 50 years with eGFR greater than 60 mL/min was based on the HALT-PKD study, which included 558 patients with early-stage ADPKD (mean age, 36 years; mean baseline BP, 125/79 mm Hg; mean eGFR, 90-93 mL/min/1.73 m^2).[73] Patients randomized to a lower BP target (95/60 to 110/75 mm Hg) vs a higher BP target (120/70 to 130/80 mm Hg) with either lisinopril and telmisartan or lisinopril and placebo had smaller increases in TKV (5.6% vs 6.6%; P = .006) and significant decreases in urinary albumin (3.77% vs 2.43%; P < .001).[73] However, symptoms of dizziness and lightheadedness were more common in the low BP group (80.7% vs 69.4%; P = .002).[73]

Tolvaptan

Patients at high risk for rapid eGFR decline (MIC 1C, 1D, or 1E or PROPKD score >6) may benefit from tolvaptan, a vasopressin (V2)-receptor antagonist that reduces cAMP-mediated cyst

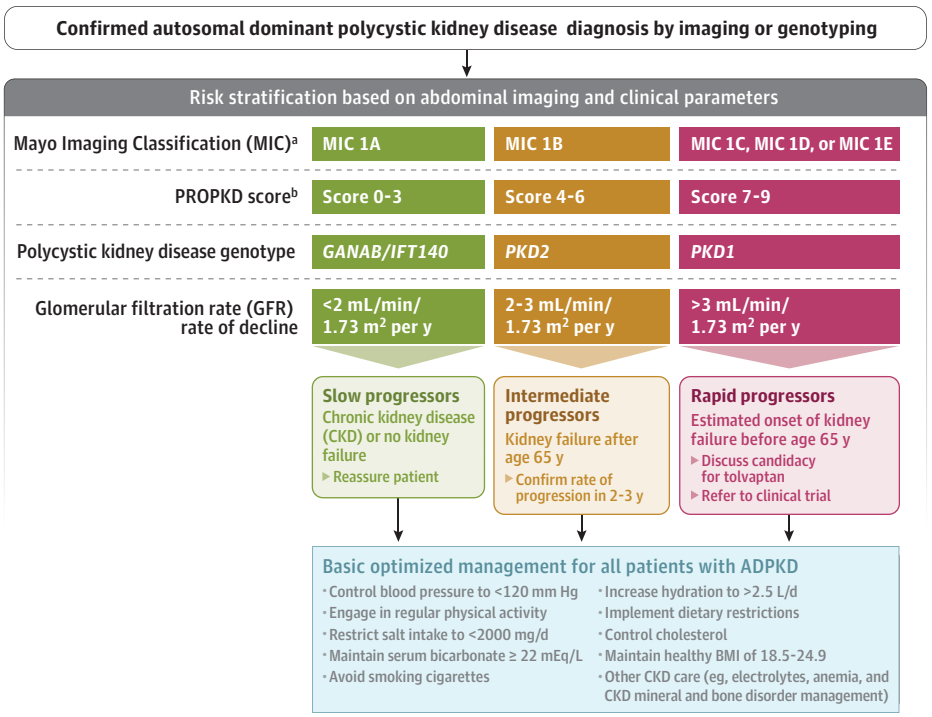
Table 1. Current Clinical Practice Recommendations and Available Therapies for Kidney-Related Manifestations in ADPKD

Treatment	Indication, benefits, and risks	Recommended practice guidance	Adverse effects
Disease-modifying treatment			
Tolvaptan[66]	Adults with ADPKD at risk of rapid progression (MIC 1C, 1D, or, 1E or eGFR decline ≥3 mL/min/y) Benefits: reduces GFR decline by 30% and may delay kidney failure onset Risks: aquaresis, potential liver injury (requires LFT monitoring)	Age 18-55 y: GFR ≥25 mL/min/1.73 m^2, with MIC 1C-1E Age 56-65 y[67]: CKD G3 or G4, eGFR decline ≥3 mL/min/y, and MIC 1C-1E Starting dose: 45 mg in the morning, 15 mg in the afternoon, titrate to tolerability Monitor liver function monthly (first 18 mo), then quarterly Long-term treatment until kidney failure[68]	Thirst: 4%-55% Polyuria: 5%-38% Nocturia: 5%-29% Polydipsia: 2%-10% Hypernatremia: 1%-4% Increased liver enzymes (alanine transaminase >2.5-fold ULN): 1%-6%; reversible after stopping tolvaptan
Optimized basic management			
Blood pressure control[10]	All patients with BP >130/85 mm Hg Benefits: decrease cardiovascular complications, prevent worsening kidney function Risks: dizziness, adverse effects related to antihypertensives, increased pill burden	Target BP ≤110/75 mm Hg for patients 18-49 y with CKD G1-G2 SBP target of <120 mm Hg if ≥50 y First-line treatment option: ACEIs or ARBs; second-line options: α and β dual blocker, β-blockers, diuretics (if not on tolvaptan), dihydropyridine calcium channel blockers Reduce dietary sodium (<2.0 g/d)	ACEI: hyperkalemia (1.8%); angioedema (<1%), cough (up to 11%) ARB: hyperkalemia (4%) Dihydropyridine calcium channel blockers: limb edema (10%) Dual α/β blockers: bradycardia, bronchospasm, diarrhea (2%-12%), fatigue (24%), hyperglycemia (5%-12%)
Weight management[65]	Patients with BMI >25 Patients with overweight or obesity have faster TKV growth and eGFR decline Benefit: weight loss associated with slower TKV rate of growth Risks/safety: requires medical supervision and dietitian consultation	Target or maintain BMI ≤25 Restrict caloric intake by 30% or intermittent fasting and time-restricted eating (long-term efficacy and safety to be determined)	Caloric restriction: no major concerns; monitor for anemia, bone loss Intermittent fasting: fatigue, cold intolerance, irritability, insomnia Ketogenic diet: hypercholesteremia (17%), increased risk of uric acid stones
Lifestyle, dietary changes, and other CKD management[65,69]	All patients with ADPKD Benefit: reducing osmolar intake and increased hydration can suppress vasopressin, which plays a central role in ADPKD pathophysiology	Sodium restriction <2.0 g/d (<5 g salt/d) Hydration: target morning urine osmolality ≤280 mOsm/kg by drinking >2.5 L of water/d Physical activity: >150 min per wk Lifestyle: avoid tobacco, limit alcohol to <1 drink/d for women and <2/d for men Phosphate restriction: moderate (800 mg/d) Bicarbonate levels: target >22 mEq/L Protein intake: 0.8-1.0 g/kg of ideal body weight, not exceeding 1.3 g/kg/d Assess for other kidney processes if acute drop in GFR	
Severe flank pain[70]	Evaluate pain in all patients: assess eligibility for interventions; refer to centers of expertise Benefits of interventions: pain control Risks: failure to reduce pain; intervention-specific risks	Cyst aspiration with sclerosing agent, surgical fenestration, spinal cord stimulation, celiac plexus block, renal denervation, nephrectomy	Cyst aspiration with sodium tetradecyl sulfate sclerotherapy: hematoma (<1%), hematuria (1%), pain (6%), infection (3%) Nephrectomy complications: hemorrhage, infection, pneumonia, wound infection, bowel perforation
Urinary stone disease[39]	Evaluate risk factors and complications, particularly if acute pain or recurrent stones	Hydration: fluid intake >2.5 L/d unless contraindicated Medications: potassium citrate if hypocitraturia or uric acid stones Lifestyle: control weight, diabetes, and metabolic syndrome Urology referral	Hydration: risk of hyponatremia if excessive Potassium citrate: gastrointestinal upset, hyperkalemia, particularly if combined with amiloride

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ADPKD, autosomal dominant polycystic kidney disease; ARB, angiotensin II receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LFT, liver function test; LDL, low-density lipoprotein; MIC, Mayo Imaging Classification; SBP, systolic blood pressure; ULN, upper limit of normal.

fluid secretion and cell proliferation (**Figure 3**).[74] A study of 1445 patients with ADPKD aged 18 to 50 years with a TKV greater than 750 mL and an estimated creatinine clearance greater than 60 mL/min reported that, compared with placebo, those randomized to receive tolvaptan at the highest tolerable dose (45 mg/15 mg, 60 mg/30 mg, or 90 mg/30 mg) for 3 years had lower TKV yearly growth (2.8% vs 5.5% in the placebo group; $P < .001$) and a slower decline in kidney function (difference of 0.98 ml/min/1.73 m^2 per year compared with placebo; $P < .001$).[75] Another trial of 1370 patients with ADPKD aged 18 to 55 years with an eGFR of 25 to 65 mL/min/1.73 m^2 or aged 56 to 65 years with an eGFR of 25 to 44 mL/min/1.73 m^2 reported that those treated with tolvaptan for 1 year had a 1.27 mL/min/1.73 m^2 slower decrease of eGFR compared with placebo ($P < .001$).[76]

Figure 3. Risk Stratification for Patients With Autosomal Dominant Polycystic Kidney Disease (ADPKD)



[a]The Mayo Imaging Classification (MIC), which adjusts total kidney volume based on age and height.

[b]The PROPKD score, a scoring system that incorporates the PKD genotype, sex, and clinical complications—assigning 1 point for males, 2 points for hypertension onset before age 35 years, 2 points for cyst bleeding or infection before age 35 years, 2 points if a nontruncating pathogenic variant of *PKD1* is present, and 4 points for a truncating pathogenic variant of *PKD1*. Additional risk stratification approaches include analysis based on the PKD genotype alone or the annual rate of glomerular filtration rate (GFR) decline. BMI indicates body mass index.

Pooled analyses of 8 clinical trials of tolvaptan and 5 cohort studies in which patients did not receive tolvaptan showed a sustained benefit of tolvaptan over 5.5 years of treatment,[77] with an extrapolated cumulative delay in the onset of end-stage kidney disease of 1.5 to 7 years,[66] depending on kidney function at treatment initiation. Tolvaptan may benefit patients aged 56 to 65 years with CKD stage G3 or G4 and eGFR decline greater than 3 mL/min/1.73 m^2 per year.[67] Benefit continues for patients with an eGFR of 15 to 29 to mL/min/1.73 m^2.[68] Excessive thirst (55%), polyuria (38%), nocturia (29%), and increased urinary frequency (23%) are common adverse effects of tolvaptan,[75] leading to a discontinuation rate of 15.4% vs 5.0% in the placebo group. Because approximately 5% of patients treated with tolvaptan develop abnormalities on liver function test results,[75] a Risk Evaluation and Mitigation Strategy is mandated in the US, consisting of routine monitoring of liver function tests prior to initiation of tolvaptan, at 2 and 4 weeks, monthly for 18 months, and then every 3 months while taking tolvaptan. This monitoring has resulted in a low risk (0.9%) of severe liver injury with tolvaptan.[78] Chronic use of a diuretic was not permitted in the tolvaptan trials,[75,76] thus diuretics should be avoided in patients taking tolvaptan. The role of hydrochlorothiazide in decreasing treatment-associated polyuria in patients with ADPKD taking tolvaptan is currently being investigated.[79]

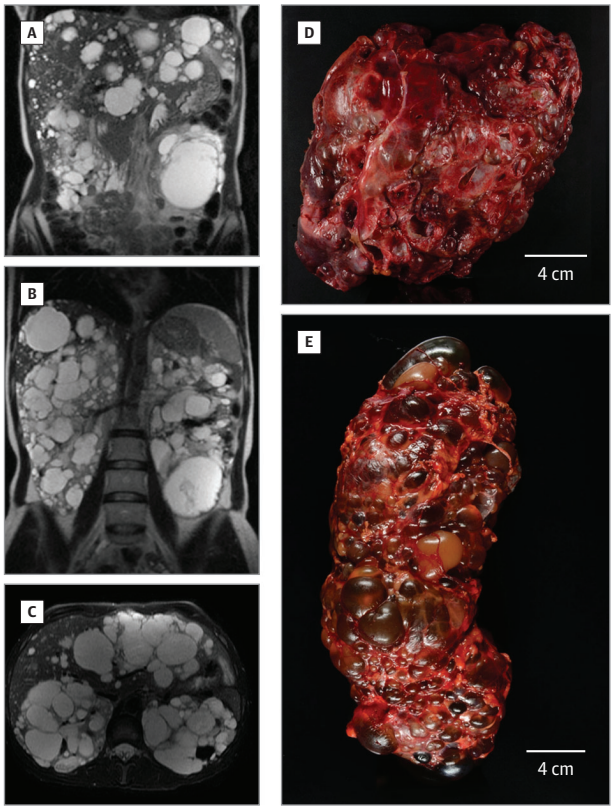
Dialysis, Nephrectomy, and Kidney Transplant

Patients with ADPKD who have stage 45 CKD (eGFR of 15-20 mL/min/1.73 m^2) should be referred for dialysis and/or kidney transplant evaluation, with transplant prior to dialysis initiation preferred if feasible, consistent with guidelines for CKD.[69] A study from 2000-2018 that included 41 485 patients in the US with ADPKD reported that at the time of the first need for kidney replacement therapy, 63% to 80% of patients started hemodialysis, 15% to 18% started peritoneal dialysis, and 5% to 19% underwent transplant.[80] ADPKD does not recur in transplanted kidneys. In a retrospective study from a large single transplant center in the UK, among 126 patients with ADPKD, median dialysis-free survival was 18.2 years and the rate of transplant failure or death was 2.5% per year.[81] After kidney transplant, ongoing surveillance of patients with ADPKD for intracranial aneurysm, symptomatic liver enlargement and cardiac complications is necessary. Unilateral or bilateral nephrectomy may be performed for patients with ADPKD and kidney failure who have recurrent kidney infections, bleeding from ruptured cysts, intractable abdominal pain, or massively enlarged kidneys that do not allow space for placement of a donor kidney.[82]

Hepatic Cyst Aspiration, Sclerotherapy, Somatostatins, and Liver Transplant

Treatment options for symptomatic ADPKD-associated hepatomegaly include cyst aspiration and sclerotherapy (17%-19% reduction in liver volume),[83] partial liver resection[84] (**Figure 4**), and treatment with somatostatin analogs[85-87] (**Table 2**). Somatostatin analogs, such as long-acting octreotide, inhibit secretin-induced cAMP-mediated fluid secretion in cholangiocytes[89] and lower insulin-like growth factor levels.[90] A meta-analysis of 7 randomized clinical trials including 652 patients with polycystic kidney and liver disease reported that long-acting octreotide or lanreotide decreased the TLV growth rate by 6.37% compared with control (mean difference, −3.66% [95% CI, −5.35% to −1.97%]; $P < .001$), without reducing eGFR decline.[87] Liver transplant for patients with ADPKD and polycystic liver disease is reserved for those with severe portal hypertension, hepatic decompensation, malnutrition, or severe sarcopenia,[91] and accounted for 1.4% (51/3560) of liver transplants

Figure 4. Radiological Images of ADPKD With Severe Polycystic Kidney and Liver Disease



This figure displays radiological images from a 49-year-old female diagnosed with autosomal dominant polycystic kidney disease (ADPKD) and severe polycystic liver disease, attributed to a *PKD1*-truncating pathogenic variant. The patient's estimated glomerular filtration rate (eGFR) is 19 mL/min/1.73 m^2. Magnetic resonance imaging (A, B, C) demonstrate a total kidney volume of 3220 mL and a Mayo Imaging Classification of 1D. The total liver volume measures 5581 mL. Gross images of the excised cystic liver (D) and kidney (E) show a kidney length of 30 cm. Images courtesy of Fouad Chebib, MD (Mayo Clinic).

at 2 large transplant centers in Canada.[92] Although there are currently no published randomized clinical trials of hormonal treatments on liver cyst growth, a study of antiestrogen therapy and liver cyst growth is ongoing.[93] Use of hormone-containing birth control or hormone replacement therapy should be avoided in women at high risk of developing symptomatic hepatomegaly due to rapid liver cyst growth[94] or established hepatomegaly (height-adjusted TLV >1000 mL/m).[30]

Treatment of Intracranial Aneurysms

Management options for identified intracranial aneurysms include observation, endovascular coiling, microsurgical clipping, stent-supported coiling, and flow-diverter therapy. Treatment decisions should be individualized based on aneurysm size, location, and likelihood of rupture[95] (Table 2). The complication rate for endovascular repair of intracranial aneurysms is low (4%-6%); however, this rate may exceed the likelihood of rupture of an untreated aneurysm, particularly for small asymptomatic intracranial aneurysms that tend to have slow or no growth.[88]

Symptom Management

Some patients with ADPKD have substantial abdominal or flank pain and discomfort from enlarging kidney or liver cysts. In a 2-round Delphi survey involving 1014 participants (60% were patients or caregivers), kidney cyst–related pain was identified as the most important patient-reported outcome, with almost all patients considering it critically important or important.[96] Consensus-based KDIGO recommendations for conservative pain management include nonpharmacologic approaches, such as heat, light exercise, ice massage, and medications including acetaminophen (no increased risk of toxicity with liver cysts), tricyclic antidepressants, and gabapentin, and avoidance of NSAIDs.[10] In select patients with severe pain, celiac plexus nerve block or renal denervation may be considered.[70]

For some patients with ADPKD and large cysts, aspiration coupled with injection of a foaming and sclerosing agent, such as sodium tetradecyl sulfate,[97] or surgical cyst fenestration may provide pain relief. In a prospective cohort study of 66 patients with ADPKD, foam sclerotherapy was associated with reduced pain in 70% of patients and a decrease in TKV of 21.8% (median [IQR] TKV, 1138 [801-1582] mL before sclerotherapy vs 891 [548-1450] mL after sclerotherapy; $P < .001$) in the treated kidney vs a 3.4% increase the untreated kidney at 13 months of follow-up.[97] Cyst fenestration, which involves combined surgical deroofing and aspiration, provided symptom relief in 92% (286/311) of patients, but was associated with adverse effects including ascites, pleural effusion, bleeding, bile leak (23%), and mortality (2%).[84]

Screening for Intracranial Aneurysms

The American Heart Association/American Stroke Association recommends screening with brain MRA or computed tomography angiography for adults with ADPKD, particularly those with a family history of intracranial aneurysms. However, negative screening by computed tomography angiography or MRA does not exclude development and rupture of a subsequent de novo aneurysm. KDIGO suggests tailoring screening recommendations to individual patients with ADPKD, considering factors such as family history, timing relative to major surgery such as a kidney transplant, patient occupation, and personal preferences.[10]

Prognosis

A study using US Renal Data System data from 2014 to 2016 reported that all-cause mortality among 1936 patients with ADPKD and non-ESRD CKD was approximately 18.4 deaths per 1000 patient-years, compared with 37.4 deaths per 1000 patient-years among 37 461 patients with ADPKD and ESRD.[98] However, ADPKD-related ESRD mortality in patients 65 years and older (99.8 per 1000 patient-years) was lower than the general ESRD mortality in the US (216 per 1000 patient-years).[98]

In a retrospective analysis of 812 participants, among 75 (9%) with ADPKD with an intracranial aneurysm detected on presymptomatic screening over a median follow-up of 9 years, intracranial aneurysms remained stable in 83% (62/75), increased in size without rupturing in 10.6% (8/75), and new aneurysms formed in 6.7% (5/75) or ruptured after prior negative imaging in 0.27% (2/737).[99] Intracranial aneurysm rupture in patients with ADPKD occurs at a median age of 41 years, which is 11 years younger than in the general population.[34]

Table 2. Current Clinical Practice Recommendations and Available Therapies for Extrarenal Manifestations in ADPKD

	Indication, benefits, and risks	Recommended practice guidance	Adverse effects
Management of extrarenal manifestations			
Intracranial aneurysm (IA)[33]	Inform patients about IA prevalence and the risks/benefits of screening Screening: every 5 y for high-risk patients (family history of subarachnoid hemorrhage, IA, or sudden death)	If IA detected, refer to multidisciplinary team Immediate emergency department visit if thunderclap headache Strict BP control (<100/75 mm Hg), smoking cessation, limit alcohol, avoid stimulant medications	Surgical vs endovascular treatment (no prior subarachnoid hemorrhage): morbidity and mortality: 10.1% vs 7.1%[88]
Mild-moderate polycystic liver disease (PLD)[30]	Evaluate liver cysts and symptoms PLD defined as >10 liver cysts	Asymptomatic PLD: usually no treatment is needed Symptomatic PLD: treatment to improve quality of life Aspiration sclerotherapy: reduce liver volume by 17%-19%[83]; 41% of patients achieve partial/full regression and 36% experience recurrence[84]	Cyst aspiration and sclerotherapy: pain with procedure, cyst regrowth, variable symptom improvement
Severe PLD	Defined as height-adjusted total liver volume >1800 mL/m with severe symptoms	Somatostatin analogue (eg, long-acting octreotide): reduce liver growth and symptoms[85] Partial hepatectomy with cyst fenestration Liver or combined liver-kidney transplant Transarterial embolization	Somatostatin analogue: hyperglycemia (pasireotide), abdominal cramping, diarrhea, bradycardia, cholelithiasis Hepatic resection: ascites, pleural effusion, bile leak, hemorrhage[84] Liver transplant: 30 d mortality, 3%; 1-y survival, 93%; 5-y survival, 92%[84]

Screening of Family Members

Asymptomatic at-risk family members, such as children of an affected parent, can delay screening for ADPKD until early adulthood even if affected relatives have high-risk features such as early-onset kidney failure. However, individuals at risk of ADPKD, including those younger than 18 years, should have regular blood pressure screening because hypertension occurs in 20%[100] to 31%[101] of affected children and adolescents. Although a new diagnosis of a genetic condition does not currently affect medical insurance eligibility in the US, it may affect future employment, life insurance, and disability insurance coverage[102]; therefore, screening is sometimes deferred. Screening may also be performed in a young asymptomatic family member who is considering donating a kidney to an affected relative. Screening for ADPKD may be performed by abdominal ultrasonography for those older than 40 years. Abdominal MRI or genetic testing may be used in younger individuals.[52]

Pregnancy

Pregnant individuals with ADPKD have similar live birth rates as the general population,[103] but higher rates of new-onset hypertension (16% vs 6%), worsening of preexisting hypertension (7% vs 1%), increased peripheral edema (25% vs 15%), and higher rates of preeclampsia (11% vs 4%) during pregnancy compared with individuals without ADPKD.[104] Individuals with ADPKD can undergo preimplant genetic testing performed after in vitro fertilization to select embryos for implantation that do not carry the ADPKD genetic variant.[105]

Practical Considerations and Application of Evidence

All patients with ADPKD should be treated by a kidney specialist and engage in shared decision-making about genetic testing, disease-modifying treatments, frequency of eGFR measurements and imaging, and intracranial aneurysm screening. Persons with ADPKD should be informed that ruptured intracranial aneurysms may present with thunderclap headaches, characterized by sudden, severe onset that reach maximum intensity within seconds to a minute and require emergency medical attention.[10]

Limitations

This review has limitations. First, the quality of the literature included was not formally evaluated. Second, some relevant studies may have been missed. Third, due to the limited number of randomized clinical studies on ADPKD, data were often derived from pooled results of clinical practice instead of clinical trials.

Conclusions

ADPKD is the most common genetic kidney disease worldwide and is characterized by progressive development of kidney cysts. Patients typically have hypertension and liver cysts, and 9% to 14% develop intracranial aneurysms. First-line treatment includes blood pressure control, dietary and weight management, and adequate hydration. Tolvaptan reduces the rate of eGFR decline for those at high risk of rapid progression to kidney failure.

ARTICLE INFORMATION

Accepted for Publication: January 9, 2025.

Published Online: March 24, 2025. doi:10.1001/jama.2025.0310

Conflict of Interest Disclosures: Dr Chebib reported receiving grants from Natera Inc, Otsuka Pharmaceuticals, Regulus, and Vertex outside the submitted work and having a patent 11547685 issued. Dr Harris reported receiving grants to the institution from Espervita, Navitor, Acceleron, Jemincare, and Regulus; licenses from Bayer, Sanofi, Vertex, Mitobridge, Maze Therapeutics, Calico Life Sciences; and personal fees paid to the institution from Otsuka, Janssen, Caraway Therapeutics, Renasant, Sen Therapeutics, PYC Therapeutics, Regulus, Vertex, Mitobridge, and Maze Therapeutics outside the submitted work. Dr Dahl reported personal fees paid to the institution from Regulus and Vertex during the conduct of the study and personal fees from the American Society of Nephrology for serving an associate editor role and personal fees from Natera paid to the institution outside the submitted work. No other disclosures were reported.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

REFERENCES

1. Torres VE, Chapman AB, Perrone RD, et al; HALT PKD Study Group. Analysis of baseline parameters

in the HALT polycystic kidney disease trials. *Kidney Int*. 2012;81(6):577-585. doi:10.1038/ki.2011.411

2. Cornec-Le Gall E, Audrézet MP, Renaudineau E, et al. PKD2-related autosomal dominant polycystic kidney disease: prevalence, clinical presentation, mutation spectrum, and prognosis. *Am J Kidney Dis*. 2017;70(4):476-485. doi:10.1053/j.ajkd.2017.01.046

3. Lanktree MB, Haghighi A, Guiard E, et al. Prevalence estimates of polycystic kidney and liver disease by population sequencing. *J Am Soc Nephrol*. 2018;29(10):2593-2600. doi:10.1681/ASN.2018050493

4. Willey C, Kamat S, Stellhorn R, Blais J. Analysis of nationwide data to determine the incidence and diagnosed prevalence of autosomal dominant polycystic kidney disease in the USA: 2013-2015. *Kidney diseases (Basel)*. 2019;5(2):107-117. doi:10.1159/000494923

5. Suwabe T, Shukoor S, Chamberlain AM, et al. Epidemiology of autosomal dominant polycystic kidney disease in Olmsted County. *Clin J Am Soc Nephrol*. 2020;15(1):69-79. doi:10.2215/CJN.05900519

6. Lavu S, Vaughan LE, Senum SR, et al; HALT PKD and CRISP Study Investigators. The value of genotypic and imaging information to predict functional and structural outcomes in ADPKD. *JCI Insight*. 2020;5(15):e138724. doi:10.1172/jci.insight.138724

7. Pirson Y. Extrarenal manifestations of autosomal dominant polycystic kidney disease. *Adv Chronic Kidney Dis*. 2010;17(2):173-180. doi:10.1053/j.ackd.2010.01.003

8. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol*. 2011;10(7):626-636. doi:10.1016/S1474-4422(11)70109-0

9. Sagar PS, Rangan GK. Cardiovascular manifestations and management in ADPKD. *Kidney Int Rep*. 2023;8(10):1924-1940. doi:10.1016/j.ekir.2023.07.017

10. KDIGO Workgroup. KDIGO 2025 clinical practice guideline for the evaluation, management and treatment of autosomal dominant polycystic kidney disease (ADPKD). *Kidney Int*. 2025;107(S2):234-254. doi:10.1016/j.kint.2024.07.009

11. Heyer CM, Sundsbak JL, Abebe KZ, et al; HALT PKD and CRISP Investigators. Predicted mutation strength of nontruncating PKD1 mutations aids genotype-phenotype correlations in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2016;27(9):2872-2884. doi:10.1681/ASN.2015050583

12. Senum SR, Li YSM, Benson KA, et al; Genomics England Research Consortium, the HALT PKD, CRISP, DIPAK, ADPKD Modifier, and TAME PKD studies. Monoallelic IFT140 pathogenic variants are an important cause of the autosomal dominant polycystic kidney-spectrum phenotype. *Am J Hum Genet*. 2022;109(1):136-156. doi:10.1016/j.ajhg.2021.11.016

13. Besse W, Dong K, Choi J, et al. Isolated polycystic liver disease genes define effectors of polycystin-1 function. *J Clin Invest*. 2017;127(5):1772-1785. doi:10.1172/JCI90129

14. Cornec-Le Gall E, Olson RJ, Besse W, et al; Genkyst Study Group; HALT Progression of Polycystic Kidney Disease Group; Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease. Monoallelic mutations to DNAJB11 cause atypical autosomal-dominant polycystic kidney disease. *Am J Hum Genet*. 2018;102(5):832-844. doi:10.1016/j.ajhg.2018.03.013

15. Besse W, Chang AR, Luo JZ, et al; Regeneron Genetics Center. *ALG9* mutation carriers develop kidney and liver cysts. *J Am Soc Nephrol*. 2019;30(11):2091-2102. doi:10.1681/ASN.2019030298

16. Apple B, Sartori G, Moore B, et al. Individuals heterozygous for ALG8 protein-truncating variants are at increased risk of a mild cystic kidney disease. *Kidney Int*. 2023;103(3):607-615. doi:10.1016/j.kint.2022.11.025

17. Lemoine H, Raud L, Foulquier F, et al; Genomics England Research Consortium; Genkyst Study Group. Monoallelic pathogenic ALG5 variants cause atypical polycystic kidney disease and interstitial fibrosis. *Am J Hum Genet*. 2022;109(8):1484-1499. doi:10.1016/j.ajhg.2022.06.013

18. Claus LR, Chen C, Stallworth J, et al; Genomics England Research Consortium. Certain heterozygous variants in the kinase domain of the serine/threonine kinase NEK8 can cause an autosomal dominant form of polycystic kidney disease. *Kidney Int*. 2023;104(5):995-1007. doi:10.1016/j.kint.2023.07.021

19. Ma M, Tian X, Igarashi P, Pazour GJ, Somlo S. Loss of cilia suppresses cyst growth in genetic models of autosomal dominant polycystic kidney disease. *Nat Genet*. 2013;45(9):1004-1012. doi:10.1038/ng.2715

20. Grantham JJ, Mulamalla S, Swenson-Fields KI. Why kidneys fail in autosomal dominant polycystic kidney disease. *Nat Rev Nephrol*. 2011;7(10):556-566. doi:10.1038/nrneph.2011.109

21. Harris PC, Torres VE. Genetic mechanisms and signaling pathways in autosomal dominant polycystic kidney disease. *J Clin Invest*. 2014;124(6):2315-2324. doi:10.1172/JCI72272

22. Barrett BJ, Foley R, Morgan J, Hefferton D, Parfrey P. Differences in hormonal and renal vascular responses between normotensive patients with autosomal dominant polycystic kidney disease and unaffected family members. *Kidney Int*. 1994;46(4):1118-1123. doi:10.1038/ki.1994.374

23. Gabow PA, Johnson AM, Kaehny WD, et al. Factors affecting the progression of renal disease in autosomal-dominant polycystic kidney disease. *Kidney Int*. 1992;41(5):1311-1319. doi:10.1038/ki.1992.195

24. Padovano V, Kuo IY, Stavola LK, et al. The polycystins are modulated by cellular oxygen-sensing pathways and regulate mitochondrial function. *Mol Biol Cell*. 2017;28(2):261-269. doi:10.1091/mbc.e16-08-0597

25. Torres JA, Kruger SL, Broderick C, et al. Ketosis ameliorates renal cyst growth in polycystic kidney disease. *Cell Metab*. 2019;30(6):1007-1023.e5. doi:10.1016/j.cmet.2019.09.012

26. Nowak KL, Hopp K. Metabolic reprogramming in autosomal dominant polycystic kidney disease: evidence and therapeutic potential. *Clin J Am Soc Nephrol*. 2020;15(4):577-584. doi:10.2215/CJN.13291019

27. Grantham JJ. Clinical practice: autosomal dominant polycystic kidney disease. *N Engl J Med*. 2008;359(14):1477-1485. doi:10.1056/NEJMcp0804458

28. Rule AD, Sasiwimonphan K, Lieske JC, Keddis MT, Torres VE, Vrtiska TJ. Characteristics of renal cystic and solid lesions based on contrast-enhanced computed tomography of potential kidney donors. *Am J Kidney Dis*. 2012;59(5):611-618. doi:10.1053/j.ajkd.2011.12.022

29. Van Keimpema L, De Koning DB, Van Hoek B, et al. Patients with isolated polycystic liver disease referred to liver centres: clinical characterization of 137 cases. *Liver Int*. 2011;31(1):92-98. doi:10.1111/j.1478-3231.2010.02247.x

30. Hogan MC, Abebe K, Torres VE, et al. Liver involvement in early autosomal-dominant polycystic kidney disease. *Clin Gastroenterol Hepatol*. 2015;13(1):155-64.e6. doi:10.1016/j.cgh.2014.07.051

31. Gabow PA, Johnson AM, Kaehny WD, Manco-Johnson ML, Duley IT, Everson GT. Risk factors for the development of hepatic cysts in autosomal dominant polycystic kidney disease. *Hepatology*. 1990;11(6):1033-1037. doi:10.1002/hep.1840110619

32. Sherstha R, McKinley C, Russ P, et al. Postmenopausal estrogen therapy selectively stimulates hepatic enlargement in women with autosomal dominant polycystic kidney disease. *Hepatology*. 1997;26(5):1282-1286.

33. Perrone RD, Malek AM, Watnick T. Vascular complications in autosomal dominant polycystic kidney disease. *Nat Rev Nephrol*. 2015;11(10):589-598. doi:10.1038/nrneph.2015.128

34. Lefèvre S, Audrézet MP, Halimi JM, et al; Genkyst Study Group. Diagnosis and risk factors for intracranial aneurysms in autosomal polycystic kidney disease: a cross-sectional study from the Genkyst cohort. *Nephrol Dial Transplant*. 2022;37(11):2223-2233. doi:10.1093/ndt/gfac027

35. Niemczyk M, Gradzik M, Niemczyk S, Bujko M, Gołębiowski M, Pączek L. Intracranial aneurysms in autosomal dominant polycystic kidney disease. *AJNR Am J Neuroradiol*. 2013;34(8):1556-1559. doi:10.3174/ajnr.A3456

36. Kataoka H, Akagawa H, Yoshida R, et al. Impact of kidney function and kidney volume on intracranial aneurysms in patients with autosomal dominant polycystic kidney disease. *Sci Rep*. 2022;12(1):18056. doi:10.1038/s41598-022-22884-9

37. Iliuta IA, Kalatharan V, Wang K, et al. Polycystic kidney disease without an apparent family history. *J Am Soc Nephrol*. 2017;28(9):2768-2776. doi:10.1681/ASN.2016090938

38. Perrone RD, Oberdhan D, Ouyang J, et al. OVERTURE: a worldwide, prospective, observational study of disease characteristics in patients with ADPKD. *Kidney Int Rep*. 2023;8(5):989-1001. doi:10.1016/j.ekir.2023.02.1073

39. Torres VE, Wilson DM, Hattery RR, Segura JW. Renal stone disease in autosomal dominant polycystic kidney disease. *Am J Kidney Dis*. 1993;22(4):513-519. doi:10.1016/S0272-6386(12)80922-X

40. Bae KT, Zhu F, Chapman AB, et al; Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP). Magnetic resonance imaging evaluation of hepatic cysts in early autosomal-dominant polycystic kidney disease: the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease cohort. *Clin J Am Soc*

Nephrol. 2006;1(1):64-69. doi:10.2215/CJN.00080605

41. Qian Q, Li A, King BF, et al. Clinical profile of autosomal dominant polycystic liver disease. *Hepatology*. 2003;37(1):164-171. doi:10.1053/jhep.2003.50006

42. Neijenhuis MK, Kievit W, Verheesen SM, D'Agnolo HM, Gevers TJ, Drenth JP. Impact of liver volume on polycystic liver disease-related symptoms and quality of life. *United European Gastroenterol J*. 2018;6(1):81-88. doi:10.1177/2050640617705577

43. McNicholas BA, Kotaro Y, Martin W, et al. Pancreatic cysts and intraductal papillary mucinous neoplasm in autosomal dominant polycystic kidney disease. *Pancreas*. 2019;48(5):698-705. doi:10.1097/MPA.0000000000001306

44. Driscoll JA, Bhalla S, Liapis H, Ibricevic A, Brody SL. Autosomal dominant polycystic kidney disease is associated with an increased prevalence of radiographic bronchiectasis. *Chest*. 2008;133(5):1181-1188. doi:10.1378/chest.07-2147

45. Sung PH, Yang YH, Chiang HJ, et al. Risk of aortic aneurysm and dissection in patients with autosomal-dominant polycystic kidney disease: a nationwide population-based cohort study. *Oncotarget*. 2017;8(34):57594-57604. doi:10.18632/oncotarget.16338

46. Hadimeri H, Lamm C, Nyberg G. Coronary aneurysms in patients with autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 1998;9(5):837-841. doi:10.1681/ASN.V95837

47. Chedid M, Kaidbay HD, Wigerinck S, et al. Cardiovascular outcomes in kidney transplant recipients with ADPKD. *Kidney Int Rep*. 2022;7(9):1991-2005. doi:10.1016/j.ekir.2022.06.006

48. Chebib FT, Hogan MC, El-Zoghby ZM, et al. Autosomal dominant polycystic kidney patients may be predisposed to various cardiomyopathies. *Kidney Int Rep*. 2017;2(5):913-923. doi:10.1016/j.ekir.2017.05.014

49. Qian Q, Hartman RP, King BF, Torres VE. Increased occurrence of pericardial effusion in patients with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2007;2(6):1223-1227. doi:10.2215/CJN.01920507

50. Chapman AB, Devuyst O, Eckardt KU, et al; Conference Participants. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2015;88(1):17-27. doi:10.1038/ki.2015.59

51. Pei Y, Hwang YH, Conklin J, et al. Imaging-based diagnosis of autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2015;26(3):746-753. doi:10.1681/ASN.2014030297

52. Cornec-Le Gall E, Alam A, Perrone RD. Autosomal dominant polycystic kidney disease. *Lancet*. 2019;393(10174):919-935. doi:10.1016/S0140-6736(18)32782-X

53. Irazabal MV, Rangel LJ, Bergstralh EJ, et al; CRISP Investigators. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. *J Am Soc Nephrol*. 2015;26(1):160-172. doi:10.1681/ASN.2013101138

54. Franceschini N, Feldman DL, Berg JS, et al; NKF Genetic Testing Working Group. Advancing genetic testing in kidney diseases: report from a National Kidney Foundation Working Group. *Am J Kidney Dis*. 2024;84(6):751-766. doi:10.1053/j.ajkd.2024.05.010

55. Yu ASL, Shen C, Landsittel DP, et al; Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP). Long-term trajectory of kidney function in autosomal-dominant polycystic kidney disease. *Kidney Int*. 2019;95(5):1253-1261. doi:10.1016/j.kint.2018.12.023

56. Grantham JJ, Torres VE, Chapman AB, et al; CRISP Investigators. Volume progression in polycystic kidney disease. *N Engl J Med*. 2006;354(20):2122-2130. doi:10.1056/NEJMoa054341

57. Suwabe T, Ubara Y, Oba Y, et al. Changes in kidney and liver volumes in patients with autosomal dominant polycystic kidney disease before and after dialysis initiation. *Mayo Clin Proc Innov Qual Outcomes*. 2023;7(1):69-80. doi:10.1016/j.mayocpiqo.2022.12.005

58. Bhutani H, Smith V, Rahbari-Oskoui F, et al; CRISP Investigators. A comparison of ultrasound and magnetic resonance imaging shows that kidney length predicts chronic kidney disease in autosomal dominant polycystic kidney disease. *Kidney Int*. 2015;88(1):146-151. doi:10.1038/ki.2015.71

59. Nowak KL, Steele C, Gitomer B, Wang W, Ouyang J, Chonchol MB. Overweight and obesity and progression of ADPKD. *Clin J Am Soc Nephrol*. 2021;16(6):908-915. doi:10.2215/CJN.16871020

60. Nowak KL, You Z, Gitomer B, et al. Overweight and obesity are predictors of progression in early autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2018;29(2):571-578. doi:10.1681/ASN.2017070819

61. Akbari P, Nasri F, Deng SX, et al. Total kidney volume measurements in ADPKD by 3D and ellipsoid ultrasound in comparison with magnetic resonance imaging. *Clin J Am Soc Nephrol*. 2022;17(6):827-834. doi:10.2215/CJN.14931121

62. Shukoor SS, Vaughan LE, Edwards ME, et al. Characteristics of patients with end-stage kidney disease in ADPKD. *Kidney Int Rep*. 2020;6(3):755-767. doi:10.1016/j.ekir.2020.12.016

63. Cornec-Le Gall E, Audrézet MP, Rousseau A, et al. The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2016;27(3):942-951. doi:10.1681/ASN.2015010016

64. Iliuta IA, Win AZ, Lanktree MB, et al. Atypical polycystic kidney disease as defined by imaging. *Sci Rep*. 2023;13(1):2952. doi:10.1038/s41598-022-24104-w

65. Chebib FT, Nowak KL, Chonchol MB, et al. Polycystic kidney disease diet: what is known and what is safe. *Clin J Am Soc Nephrol*. 2024;19(5):664-682.

66. Chebib FT, Perrone RD, Chapman AB, et al. A practical guide for treatment of rapidly progressive ADPKD with tolvaptan. *J Am Soc Nephrol*. 2018;29(10):2458-2470. doi:10.1681/ASN.2018060590

67. Chebib FT, Zhou X, Garbinsky D, et al. Tolvaptan and kidney function decline in older individuals with autosomal dominant polycystic kidney disease: a pooled analysis of randomized clinical trials and observational studies. *Kidney Med*. 2023;5(6):100639. doi:10.1016/j.xkme.2023.100639

68. Torres VE, Gansevoort RT, Perrone RD, et al. Tolvaptan in ADPKD patients with very low kidney function. *Kidney Int Rep*. 2021;6(8):2171-2178. doi:10.1016/j.ekir.2021.05.037

69. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*. 2024;105(4S):S117-S314.

70. Casteleijn NF, van Gastel MDA, Blankestijn PJ, et al; DIPAK Consortium. Novel treatment protocol for ameliorating refractory, chronic pain in patients with autosomal dominant polycystic kidney disease. *Kidney Int*. 2017;91(4):972-981. doi:10.1016/j.kint.2016.12.007

71. Kramers BJ, Koorevaar IW, Drenth JPH, et al. Salt, but not protein intake, is associated with accelerated disease progression in autosomal dominant polycystic kidney disease. *Kidney Int*. 2020;98(4):989-998. doi:10.1016/j.kint.2020.04.053

72. Rangan GK, Wong ATY, Munt A, et al. Prescribed water intake in autosomal dominant polycystic kidney disease. *NEJM Evid*. 2022;1(1):EVIDoa2100021. doi:10.1056/EVIDoa2100021

73. Schrier RW, Abebe KZ, Perrone RD, et al; HALT-PKD Trial Investigators. Blood pressure in early autosomal dominant polycystic kidney disease. *N Engl J Med*. 2014;371(24):2255-2266. doi:10.1056/NEJMoa1402685

74. Torres VE, Meijer E, Bae KT, et al. Rationale and design of the TEMPO (tolvaptan efficacy and safety in management of autosomal dominant polycystic kidney disease and its outcomes) 3-4 study. *Am J Kidney Dis*. 2011;57(5):692-699. doi:10.1053/j.ajkd.2010.11.029

75. Torres VE, Chapman AB, Devuyst O, et al; TEMPO 3:4 Trial Investigators. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med*. 2012;367(25):2407-2418. doi:10.1056/NEJMoa1205511

76. Torres VE, Chapman AB, Devuyst O, et al; REPRISE Trial Investigators. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med*. 2017;377(20):1930-1942. doi:10.1056/NEJMoa1710030

77. Zhou X, Davenport E, Ouyang J, et al. Pooled data analysis of the long-term treatment effects of tolvaptan in ADPKD. *Kidney Int Rep*. 2022;7(5):1037-1048. doi:10.1016/j.ekir.2022.02.009

78. Estilo A, Tracy L, Matthews C, et al. Evaluating the impact of a risk evaluation and mitigation strategy with tolvaptan to monitor liver safety in patients with autosomal dominant polycystic kidney disease. *Clin Kidney J*. 2022;15(8):1553-1561. doi:10.1093/ckj/sfac076

79. Bais T, Meijer E, Kramers BJ, et al. Hydrochlorothiazide versus placebo to protect polycystic kidney disease patients and improve their quality of life: study protocol and rationale for the HYDRO-PROTECT randomized controlled trial. *Trials*. 2024;25(1):120. doi:10.1186/s13063-024-07952-x

80. McGill RL, Saunders MR, Hayward AL, Chapman AB. Health disparities in autosomal dominant polycystic kidney disease (ADPKD) in the United States. *Clin J Am Soc Nephrol*. 2022;17(7):976-985. doi:10.2215/CJN.00840122

81. Garland S, Pullerits K, Chukwu CA, Chinnadurai R, Middleton R, Kalra PA. The effect of primary renal disease upon outcomes after renal transplant.

Clin Transplant. 2024;38(3):e15216. doi:10.1111/ctr.15216

82. Kanaan N, Devuyst O, Pirson Y. Renal transplantation in autosomal dominant polycystic kidney disease. *Nat Rev Nephrol*. 2014;10(8):455-465. doi:10.1038/nrneph.2014.104

83. van Keimpema L, de Koning DB, Strijk SP, Drenth JP. Aspiration-sclerotherapy results in effective control of liver volume in patients with liver cysts. *Dig Dis Sci*. 2008;53(8):2251-2257. doi:10.1007/s10620-007-0121-x

84. Drenth JP, Chrispijn M, Nagorney DM, Kamath PS, Torres VE. Medical and surgical treatment options for polycystic liver disease. *Hepatology*. 2010;52(6):2223-2230. doi:10.1002/hep.24036

85. Hogan MC, Masyuk TV, Page LJ, et al. Randomized clinical trial of long-acting somatostatin for autosomal dominant polycystic kidney and liver disease. *J Am Soc Nephrol*. 2010;21(6):1052-1061. doi:10.1681/ASN.2009121291

86. Gevers TJ, Inthout J, Caroli A, et al. Young women with polycystic liver disease respond best to somatostatin analogues: a pooled analysis of individual patient data. *Gastroenterology*. 2013;145(2):357-365. doi:10.1053/j.gastro.2013.04.055

87. Suwabe T, Barrera FJ, Rodriguez-Gutierrez R, Ubara Y, Hogan MC. Somatostatin analog therapy effectiveness on the progression of polycystic kidney and liver disease: a systematic review and meta-analysis of randomized clinical trials. *PLoS One*. 2021;16(9):e0257606. doi:10.1371/journal.pone.0257606

88. Wiebers DO, Whisnant JP, Huston J III, et al; International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet*. 2003;362(9378):103-110. doi:10.1016/S0140-6736(03)13860-3

89. Messchendorp AL, Casteleijn NF, Meijer E, Gansevoort RT. Somatostatin in renal physiology and autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2020;35(8):1306-1316. doi:10.1093/ndt/gfz054

90. Kashyap S, Zeidler JD, Chini CCS, Chini EN. Implications of the PAPP-A-IGFBP-IGF-1 pathway in the pathogenesis and treatment of polycystic kidney disease. *Cell Signal*. 2020;73:109698. doi:10.1016/j.cellsig.2020.109698

91. Mehta S, Rosenstengle CA. Policy Corner: polycystic liver disease MELD exception update. *Liver Transpl*. 2024;30(9):960-961. doi:10.1097/LVT.0000000000000414

92. Alsager M, Neong SF, Gandhi R, et al. Liver transplantation in adult polycystic liver disease: the Ontario experience. *BMC Gastroenterol*. 2021;21(1):115. doi:10.1186/s12876-021-01703-x

93. Aapkes SE, Bernts LHP, Barten TRM, van den Berg M, Gansevoort RT, Drenth JPH. Estrogens in polycystic liver disease: a target for future therapies? *Liver Int*. 2021;41(9):2009-2019. doi:10.1111/liv.14986

94. Bae KT, Tao C, Feldman R, et al; CRISP and HALT PKD Consortium. Volume progression and imaging classification of polycystic liver in early autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2022;17(3):374-384. doi:10.2215/CJN.08660621

95. Thompson BG, Brown RD Jr, Amin-Hanjani S, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention; American Heart Association; American Stroke Association. Guidelines for the management of patients with unruptured intracranial aneurysms: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46(8):2368-2400. doi:10.1161/STR.0000000000000070

96. Cho Y, Rangan G, Logeman C, et al. Core outcome domains for trials in autosomal dominant polycystic kidney disease: an international delphi survey. *Am J Kidney Dis*. 2020;76(3):361-373. doi:10.1053/j.ajkd.2020.01.005

97. Iliuta IA, Shi B, Pourafkari M, et al. Foam sclerotherapy for cyst volume reduction in autosomal dominant polycystic kidney disease: a prospective cohort study. *Kidney Med*. 2019;1(6):366-375. doi:10.1016/j.xkme.2019.07.015

98. Mladsi D, Zhou X, Mader G, et al. Mortality risk in patients with autosomal dominant polycystic kidney disease. *BMC Nephrol*. 2024;25(1):56. doi:10.1186/s12882-024-03484-3

99. Sanchis IM, Shukoor S, Irazabal MV, et al. Presymptomatic screening for intracranial aneurysms in patients with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2019;14(8):1151-1160. doi:10.2215/CJN.14691218

100. Marlais M, Cuthell O, Langan D, Dudley J, Sinha MD, Winyard PJ. Hypertension in autosomal dominant polycystic kidney disease: a meta-analysis. *Arch Dis Child*. 2016;101(12):1142-1147. doi:10.1136/archdischild-2015-310221

101. Massella L, Mekahli D, Paripović D, et al. Prevalence of hypertension in children with early-stage ADPKD. *Clin J Am Soc Nephrol*. 2018;13(6):874-883. doi:10.2215/CJN.11401017

102. Bélisle-Pipon JC, Vayena E, Green RC, Cohen IG. Genetic testing, insurance discrimination and medical research: what the United States can learn from peer countries. *Nat Med*. 2019;25(8):1198-1204. doi:10.1038/s41591-019-0534-z

103. Al Sayyab M, Chapman A. Pregnancy in autosomal dominant polycystic kidney disease. *Adv Kidney Dis Health*. 2023;30(5):454-460. doi:10.1053/j.akdh.2023.10.006

104. Chapman AB, Johnson AM, Gabow PA. Pregnancy outcome and its relationship to progression of renal failure in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 1994;5(5):1178-1185. doi:10.1681/ASN.V551178

105. Thompson WS, Babayev SN, McGowan ML, et al. State of the science and ethical considerations for preimplantation genetic testing for monogenic cystic kidney diseases and ciliopathies. *J Am Soc Nephrol*. 2024;35(2):235-248. doi:10.1681/ASN.0000000000000253