KDIGO 2025 clinical practice guideline for the evaluation, management, and treatment of autosomal dominant polycystic kidney disease (ADPKD): executive summary

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The *Kidney Disease: Improving Global Outcomes (KDIGO) 2025 Clinical Practice Guideline for the Evaluation, Management, and Treatment of Autosomal Dominant Polycystic Kidney Disease* (ADPKD) represents the first KDIGO guideline on this subject. Its scope includes nomenclature, diagnosis, prognosis, and prevalence; kidney manifestations; chronic kidney disease (CKD) management and progression, kidney failure, and kidney replacement therapy; therapies to delay progression of kidney disease; polycystic liver disease; intracranial aneurysms and other extrarenal manifestations; lifestyle and psychosocial aspects; pregnancy and reproductive issues; pediatric issues; and approaches to the management of people with ADPKD. The guideline has been developed with patient partners, clinicians, and researchers around the world, with the goal to generate a useful resource for healthcare providers and patients by providing actionable recommendations. The development of this guideline followed an explicit process of evidence review and appraisal, based on a rigorous, formal systematic literature review. The strength of recommendations follows the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. The guideline also provides practice points serving to direct clinical care or activities relating to areas for which a systematic review was not

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The complete *KDIGO 2025 Clinical Practice Guideline for the Evaluation, Management, and Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD)* is published in *Kidney International*, volume 107, issue 2S, 2025, which is available online at www.kidney-international.org.

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conducted. Limitations of the evidence are discussed. Research recommendations to address gaps in knowledge, and implications for policy and payment, are provided. The guideline targets a broad audience of healthcare providers, people living with ADPKD, and stakeholders involved in the various aspects of ADPKD care.

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KEYWORDS: ADPKD; evidence-based; guideline; monogenic disease; nomenclature

Autosomal dominant polycystic kidney disease (ADPKD) is a major genetic disorder affecting millions of people worldwide, and the fourth most common global cause for kidney replacement therapy. The Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on ADPKD was held in Edinburgh in 2014.[1] Since then, the genetic and clinical landscapes of ADPKD have evolved; distinct imaging patterns and prognostic tools have been identified; results of randomized controlled trials (RCTs) of tolvaptan, somatostatin analogues, levels of blood pressure (BP) targets, renin–angiotensin blockade, and other potential treatments for ADPKD have been published; and tolvaptan has been approved for the treatment of rapidly progressive ADPKD. With the sustained increase in knowledge, and the expansion of the volume of information, a global KDIGO Clinical Practice Guideline for the Evaluation, Management, and Treatment of ADPKD has become timely.

The *KDIGO 2025 Clinical Practice Guideline for the Evaluation, Management, and Treatment of ADPKD* has been developed by an international, multidisciplinary Work Group with expertise in ADPKD, a dedicated Evidence Review Team, and the KDIGO staff. The guideline includes 10 chapters addressing the whole scope of ADPKD diagnosis and management. The focus is on clinical management questions based on high-certainty scientific evidence collected by the Evidence Review Team. The guideline includes graded recommendations, based on the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) criteria and supported by systematic reviews, and ungraded practice points, based on expert opinion or limited evidence serving to direct clinical activities, for which a systematic review was not conducted. Both recommendations and practice points are intended to help guide clinical practice and to aid in decision-making. The KDIGO 2025 ADPKD Guideline has considered disparities in available resources, as well as possible cultural differences in different parts of the world.

This report summarizes the main recommendations and practice points of the guideline (Supplementary Table S1). For more detailed information, the reader is referred to the full guideline, including grading details, a complete reference list, and a research agenda (Supplementary Table S2), available at https://kdigo.org/guidelines/autosomal-dominant-polycystic-kidney-disease-adpkd/.[2]

Chapter 1: Nomenclature, prevalence, diagnosis, and prognosis

Definition and nomenclature. The term ADPKD comprises a group of dominantly inherited disorders associated with kidney cysts and extrarenal manifestations caused by a pathogenic variant in one gene associated with ADPKD. The usual phenotype of ADPKD includes multiple, bilateral kidney cysts causing progressive kidney enlargement, commonly associated with hypertension and liver cysts. Complications may include abdominal fullness and pain, cyst hemorrhage, gross hematuria, nephrolithiasis, cyst infections, and reduced quality of life. Kidney function decline typically occurs in adulthood, resulting in kidney failure (KF), usually after the fourth decade of life.[3,4]

The major ADPKD genes are *PKD1* and *PKD2*, accounting for >90% of diagnosed families. Several minor genes account for a small percentage of affected families. To address the genetic complexity of ADPKD, we suggest a naming format that uses a descriptor of the disease followed by the causal gene (Figure 1). In people with ADPKD and a pathogenic variant in either *PKD1*, *PKD2*, or a minor gene for which pathogenicity is well supported (*IFT140*, *ALG5*, *ALG9*, *GANAB*, *DNAJB11*, *NEK8*), the nomenclature should include ADPKD followed by the gene name (e.g., ADPKD-*PKD1*; Table 1). People who have an ADPKD-spectrum phenotype and have not been genetically tested or had genetic testing, with no pathogenic variant in an ADPKD gene identified, or who have a variant in a minor gene for which pathogenicity remains uncertain (*ALG6*, *ALG8*, *PKHD1*), should continue to be termed as having ADPKD. The designation of ADPKD should not be based on the finding of a likely pathogenic variant in a minor gene when a clinical diagnosis of ADPKD is uncertain. This nomenclature allows maintenance of the familiar disease name and may imply characteristics associated with the specific causal gene (e.g., many minor ADPKD genes confer a very low

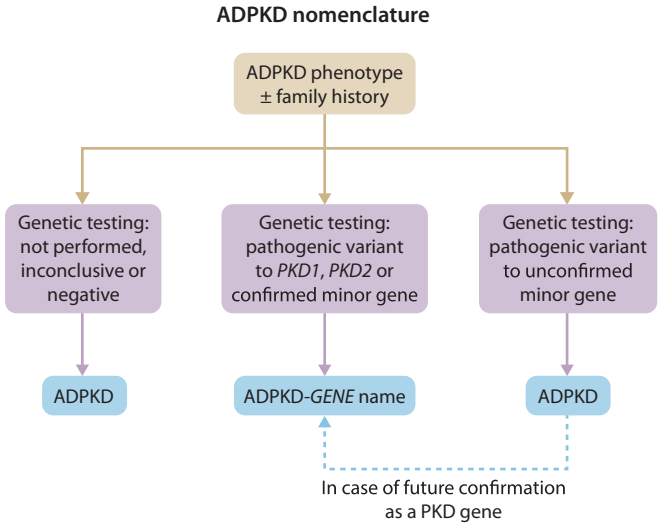


Figure 1 | Nomenclature of autosomal dominant polycystic kidney disease (ADPKD) dependent on phenotype, family history, availability and results of genetic testing. PKD, polycystic kidney disease.

Table 1 | ADPKD genes and proposed nomenclature

Disease designation	Gene	Screened families, %	Kidney phenotype	Extrarenal phenotype	Comments
Major ADPKD genes and nomenclature for unknown, not screened, and unresolved typical cases					
ADPKD	Unknown, not screened, or unresolved	—	Bilateral PKD, kidney enlargement, age-related CKD, may result in KF in adulthood (Chapters 2–3)	Typical presentation (Chapters 5–6)	Wide phenotypic range
Truncating pathogenic variant: ADPKD-*PKD1*	*PKD1*	~48	Bilateral PKD, early kidney enlargement, CKD G3, age around 40 yr, KF in 50s (Chapters 2–3)	Typical presentation (Chapters 5–6)	Often severe, but more benign course possible, sometimes associated with mosaicism
Nontruncating pathogenic variant: ADPKD-*PKD1*		~19	Bilateral PKD, kidney enlargement, age-related CKD, may result in KF (Chapters 2–3)	Typical presentation (Chapters 5–6)	Phenotype ranges from severe (similar to *PKD1* truncating) to mild, partly depending on the degree of residual protein function
ADPKD-*PKD2*	*PKD2*	~15	Bilateral PKD, milder and later kidney enlargement, CKD G3, age around 55 yr, KF in 70s (Chapters 2–3)	Typical presentation (Chapters 5–6)	Includes some disease variability including a more severe or more benign course
Minor ADPKD genes with definitive-to-moderate evidence of disease involvement					
ADPKD-*ALG5*	*ALG5*	<0.5	Low-to-moderate cyst number, limited kidney enlargement and fibrosis; CKD and some KF in older subjects	A few liver cysts in a minority of people	
ADPKD-*ALG9*	*ALG9*	<0.5	Low-to-moderate cyst number, significant CKD in older adults	Frequent liver cysts	Biallelic mutations are associated with the congenital disorder of glycosylation, type IL (CDGIL)
ADPKD-*DNAJB11*	*DNAJB11*	<0.5	Bilateral small cysts, limited or no kidney enlargement, progressive fibrosis, limited CKD G3a age <55 yr, but KF at ages in 70s	Liver cysts, usually mild, possible ICA and vascular risk	Similarities to ADTKD, but visible cysts usually present; biallelic mutations associated with renal-hepatic-pancreatic dysplasia
ADPKD-*GANAB*	*GANAB*	<0.5	Mild PKD, limited CKD, no KF	Liver cysts, sometimes severe PLD, ICA unclear	Can present as ADPLD
ADPKD-*IFT140*	*IFT140*	1–2	Few, large bilateral cysts, kidney enlargement, kidney function usually preserved into old age	Liver cysts rarely, risk of ICA unclear	Biallelic mutations associated with short-rib thoracic dysplasia and retinitis pigmentosa
ADPKD-*NEK8*	*NEK8*	<0.5	Bilateral PKD, kidney enlargement, KF in childhood, occasionally later in cases of specific alleles or mosaicism	Liver cysts rarely	*De novo* occurrence in 75%; biallelic mutations associated with renal-hepatic-pancreatic dysplasia and nephronophthisis

ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; ADTKD, autosomal dominant tubulointerstitial kidney disease; CKD, chronic kidney disease; ICA, intracranial aneurysm; KF, kidney failure; PKD, polycystic kidney disease; PLD, polycystic liver disease.

risk of KF), whereas *PKD1* and *PKD2* (and *DNAJB11*) are associated with a substantial risk of KF.

Polycystic liver disease (PLD) is the most frequent extrarenal manifestation of ADPKD. Autosomal dominant polycystic liver disease (ADPLD) is a different monoallelic disease causing PLD, but with no or few kidney cysts, linked to *PRKCSH* and *SEC63* and a few additional genes.[5] We suggest a naming format similar to that for ADPKD for autosomal dominant polycystic liver disease.

Prevalence. The estimated prevalence of ADPKD in population-based studies, and of pathogenic *PKD1* or *PKD2* mutations in the general population (1 per 1000), is higher than the point prevalence of diagnosed ADPKD in large databases (2–4 per 10,000). Cystic kidneys are the cause of KF in ~5% of people receiving kidney replacement therapy in Europe and North America, whereas very few prevalence studies have been performed in populations from Asia and Africa.

Diagnosis. Appropriate counseling about the possible benefits and risks should be provided to people at risk of ADPKD, before imaging or genetic screening is scheduled, and after screening, to help interpret the results and plan next steps. The values and preferences of the person should be central to these discussions.

We recommend abdominal imaging by ultrasound to screen adults at risk. Age-specific numbers of cysts have been described to diagnose or exclude ADPKD in people with a positive family history (Figure 2; Supplementary Figure S1).

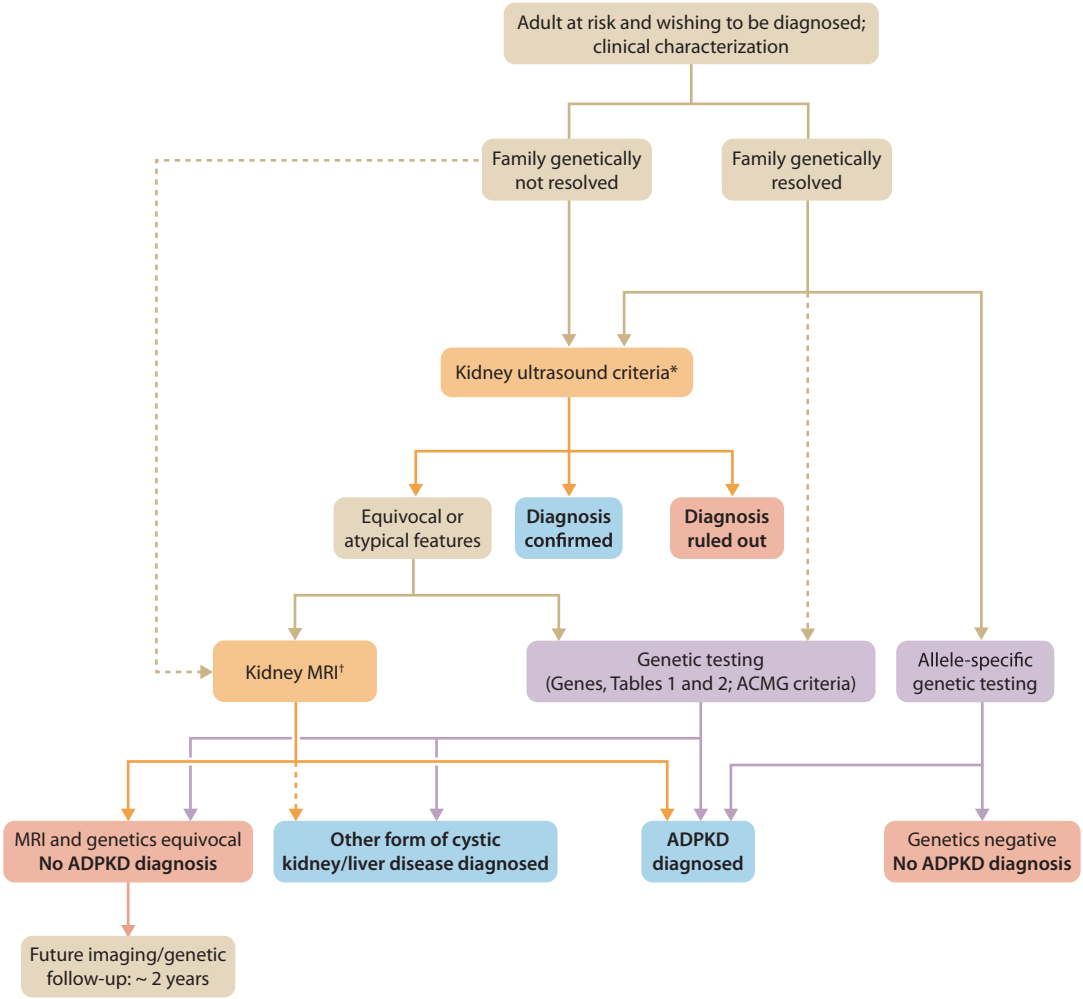


Figure 2 | Diagnosis algorithm in adults at risk (with a positive family history) for autosomal dominant polycystic kidney disease (ADPKD). ACMG, American College of Medical Genetics and Genomics; MRI, magnetic resonance imaging. *ADPKD diagnosis is confirmed by ultrasound if ≥3 total cysts are present (ages 15–39 years), ≥2 cysts are present in each kidney (ages 40–59 years), or ≥4 cysts are present in each kidney (age ≥60 years); the diagnosis is ruled out if ≤1 cyst is present (ages 15–39 years) or ≤2 cysts total are present (ages 40–59 years). ADPKD diagnosis is confirmed by MRI if >10 cysts total are present, and it is ruled out if <5 cysts total are present (ages 16–40 years). †Computed tomography, either with or without contrast, also can be used. Abdominal ultrasound is suggested as the first imaging analysis, with follow-up MRI analysis and/or genetic testing recommended in people with equivocal imaging or atypical extrarenal features or if additional prognostic information is requested. In genetically resolved families, simple testing of the family variant usually provides a diagnosis. Occasionally, if the disease presentation is very different from the family disease, broader genetic testing may be helpful. Solid lines indicate tests that are suggested, and dashed lines indicate tests to consider.

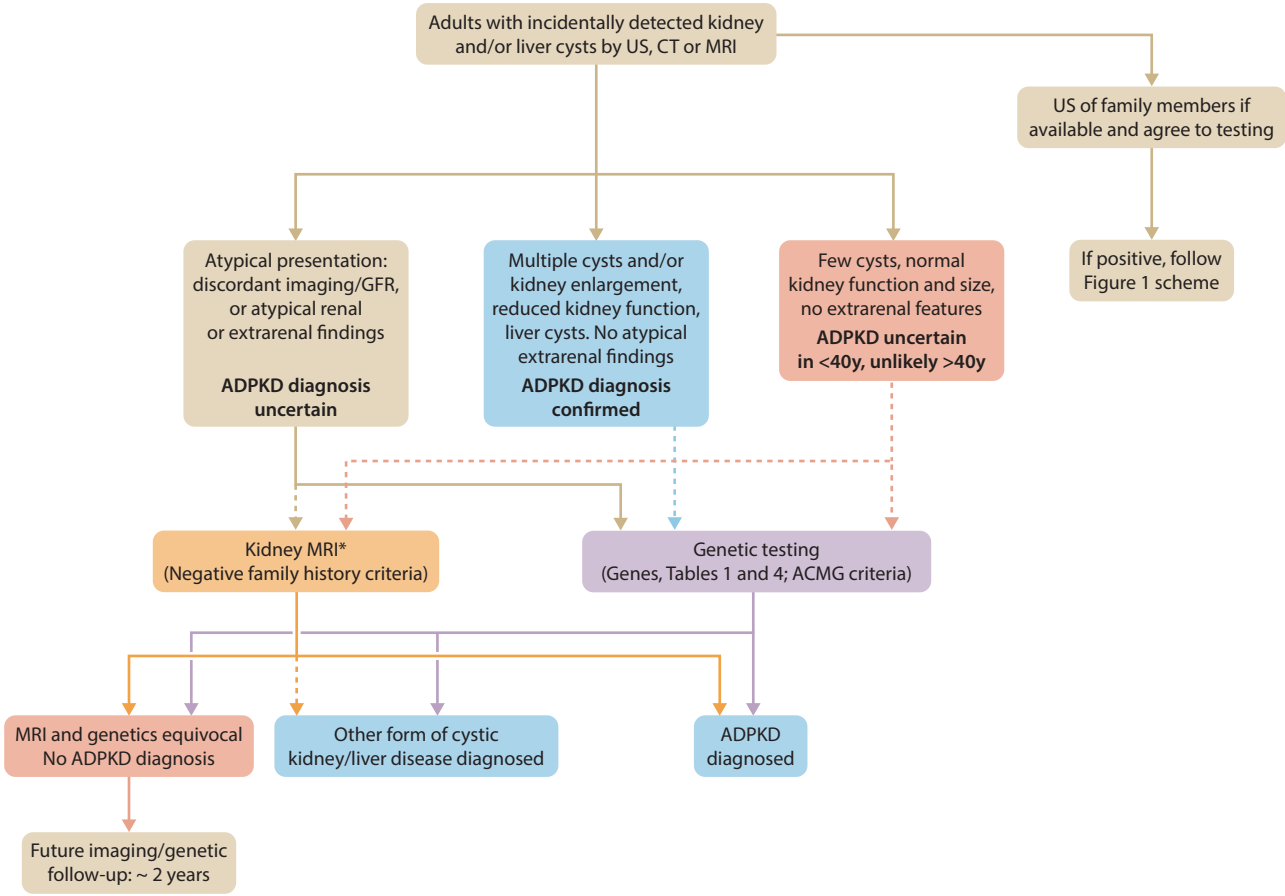


Figure 3 | Diagnosis algorithm in adults with incidentally detected kidney and/or liver cysts in absence of known family history of autosomal dominant polycystic kidney disease (ADPKD). Solid lines indicate tests that are suggested, and dashed lines indicate tests to consider. *CT with or without contrast also can be used. ACMG, American College of Medical Genetics and Genomics; CT, computed tomography; GFR, glomerular filtration rate; MRI, magnetic resonance imaging; US, ultrasound.

For people with a positive family history of ADPKD aged 16–40 years, the cutoff of >10 cysts on magnetic resonance imaging (MRI) has been used to diagnose ADPKD, and the cutoff of <5 cysts has been used to exclude ADPKD. These ultrasound and MRI criteria apply to only families with pathogenic variants of *PKD1* or *PKD2*, and not to those with pathogenic variants to minor genes. In a family with a known pathogenic variant, targeted screening for the specific variant is usually sufficient to diagnose or exclude ADPKD. For people with detected kidney cysts, but no known family history of ADPKD, kidney imaging and genetic testing may help to make a diagnosis (Figure 3).

Genetic testing is particularly helpful in cases involving few kidney cysts; variable intrafamilial disease severity, including very-early-onset ADPKD; discordant imaging and glomerular filtration rate; negative family history; young (aged <30 years) living-related kidney donors at risk of ADPKD, based on family history; and family planning and preimplantation diagnosis.

Several inherited diseases may mimic ADPKD with kidney and/or liver cysts as part of their phenotype (Table 2).[6–8]

Prognosis. The causal gene (*PKD1* > *PKD2* or minor genes), type of *PKD1* mutation (truncating > nontruncating), sex (male > female), and environmental factors (obesity, salt intake) are associated with the severity of ADPKD.

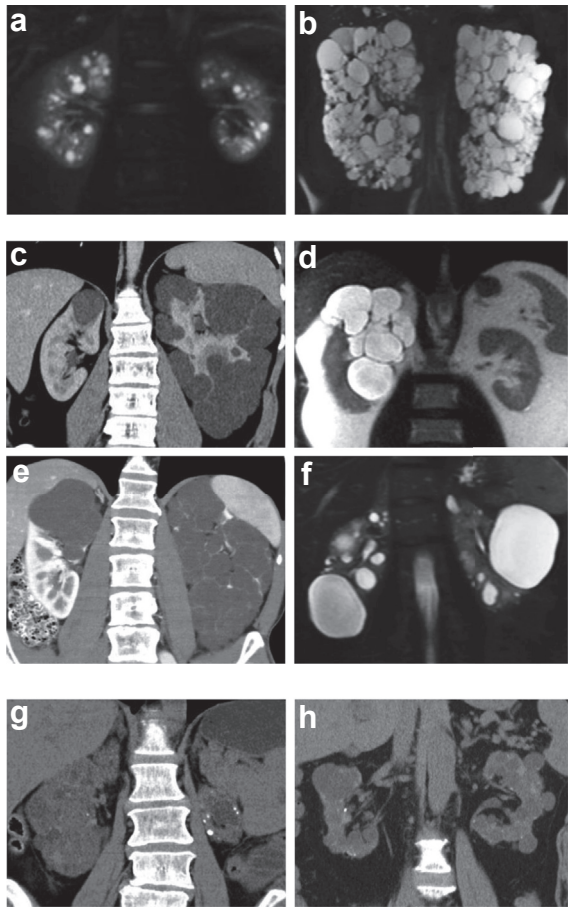
We recommend employing the Mayo Imaging Classification (MIC) to predict future decline in kidney function and the timing of KF. The MIC is divided into typical (class 1) and atypical (class 2) ADPKD. Prognostic information is valid for only class 1 patients with typical imaging findings (Figure 4). The MIC uses height-adjusted total kidney volume, adjusted for age, to stratify people with typical imaging into 5 groups (1A–1E), indicating accelerating decline in kidney function. The height-adjusted total kidney volume is measured most accurately by MRI or computed tomography (CT) scan, using an automated or semiautomated tool, or alternatively, it can be estimated using the ellipsoid equation. Ultrasound-determined total kidney volume and kidney length are less precise but have prognostic value. The MIC should not be used in people with pathogenic variants in genes other than *PKD1* or *PKD2*. The Predicting Renal Outcome in PKD score, and estimated GFR (eGFR) in relation to age and/or

Table 2 | Inherited disorders that present with kidney and/or liver cysts and may mimic ADPKD

Disorders and gene	Disease	Inheritance
Developmental disorders		
HNF1B	*HNF1B*-related kidney disease	AD*
JAG1, NOTCH2	Alagille syndrome	AD
Collagen disorders		
COL4A1	HANAC syndrome	AD
COL4A3, COL4A4, COL4A5	COL4A-related diseases	AD and X-linked
Nephrolithiasis		
CYP24A1, SLC34A3, HOGA1	Kidney stones, nephrocalcinosis	AR (AD)
Autosomal dominant tubulointerstitial kidney disease (ADTKD)		
UMOD, MUC1, REN, SEC61A	ADTKD	AD
Autosomal dominant polycystic liver disease (ADPLD)		
PRKCSH, SEC63, GANAB	ADPLD	AD
Autosomal recessive polycystic kidney disease (ARPKD)		
PKHD1, DZIP1L, CYS1, PKD1	ARPKD	AR
PMM2	HIPKD	AR
Tumorous disorders		
FLCN	Birt-Hogg-Dubé syndrome	AD
TSC1, TSC2	Tuberous sclerosis complex	AD
PKD1/TSC2	*PKD1/TSC2*-CGS	AD
VHL	Von Hippel–Lindau syndrome	AD
FH	HLRCC	AD
Syndromic ciliopathies		
OFD1	Oral-facial-digital syndrome 1	X-linked
NPHP1 and other NPHP genes	Nephronophthisis	AR
Many genes	Syndromic ciliopathies such as Joubert, Bardet Biedl, Meckel syndrome, and short rib thoracic dystrophy	AR
Acquired disorders		
None	Simple cysts	Sporadic
None	ACD	Acquired

ACD, acquired cystic disease; AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; AR, autosomal recessive; CGS, contiguous gene syndrome; COL, collagen; HANAC, hereditary angiopathy with nephropathy, aneurysms, and muscle cramps; HIPKD, hyperinsulinemic hypoglycemia and polycystic kidney disease; HLRCC, hereditary leiomyomatosis and renal cell cancer; NPHP, nephronophthisis.
*Up to 50% of cases appear *de novo*.

Class, subclass, and term	Description
1. Typical ADPKD	Bilateral and diffuse distribution, with mild, moderate, or severe replacement of kidney tissue by cysts, where all cysts contribute similarly to TKV
2. Atypical ADPKD	
A	
Unilateral	Diffuse cystic involvement of one kidney causing marked kidney enlargement with a normal contralateral kidney defined by a normal kidney volume (<275 ml in men; <244 ml in women) and having no or only 1–2 cysts
Segmental	Cystic disease involving only one pole of one or both kidneys and sparing the remaining kidney tissue
Asymmetric	Diffuse cystic involvement of one kidney causing marked kidney enlargement with mild segmental or minimal diffuse involvement of the contralateral kidney defined by a small number of cysts (>2 but <10) and volume accounting for <30% of TKV
Lopsided	Bilateral distribution of kidney cysts with mild replacement of kidney tissue with atypical cysts where ≤5 cysts account for ≥50% TKV (the largest cyst diameter is used to estimate individual cyst volume)
B	
Bilateral presentation with acquired unilateral atrophy	Diffuse cystic involvement of one kidney causing moderate to severe kidney enlargement with contralateral acquired atrophy
Bilateral presentation with bilateral kidney atrophy	Impaired kidney function (serum creatinine ≥1.5 mg/dl [133 μmol/l]) without significant enlargement of the kidneys, defined by an average length <14.5 cm, and replacement of kidney tissue by cysts with atrophy of the parenchyma



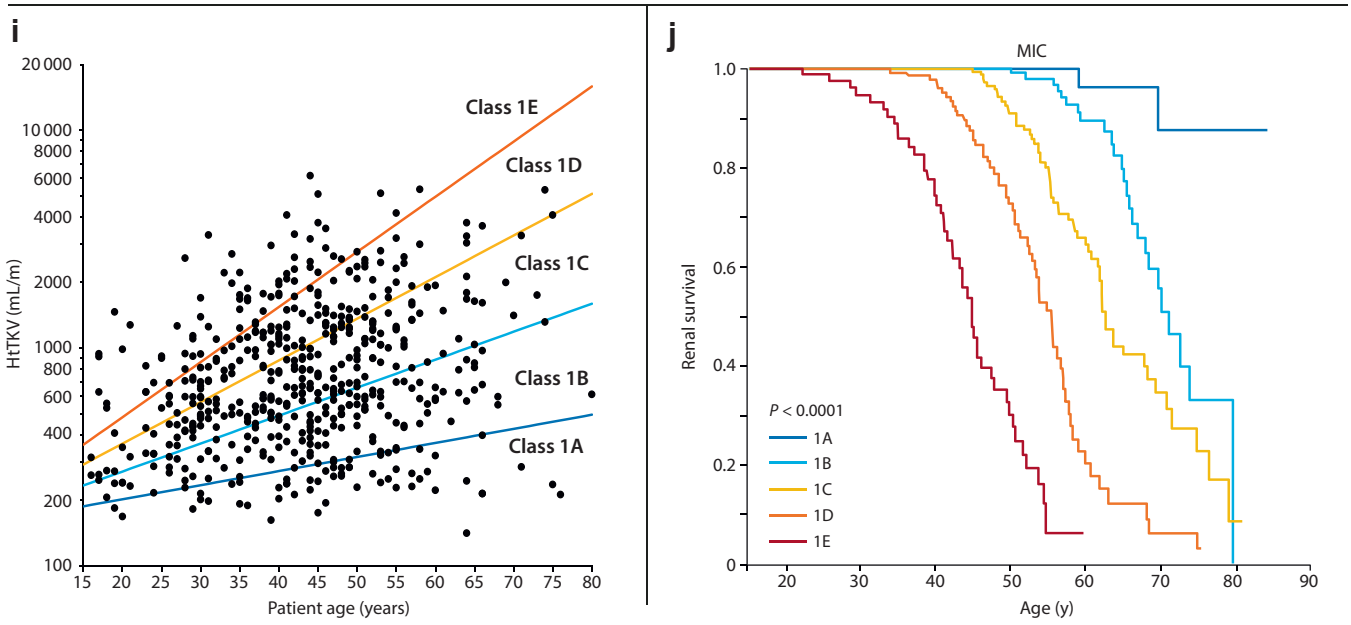


Figure 4 | Mayo Image Classification (MIC) and prognostic of autosomal dominant polycystic kidney disease (ADPKD). TKV, total kidney volume. Top: Principles of the MIC of (left panel) ADPKD, with examples (right panel) of MIC subclass (**a**) 1A and (**b**) 1E for typical ADPKD; and (**c–f**) MIC subclass 2A and (**g,h**) MIC subclass 2B for atypical ADPKD. Only the classification of typical ADPKD (subclass 1) has prognostic value. Bottom panels (**i**) and (**j**) apply to only *typical* ADPKD: (**i,** left panel) The MIC divides height-adjusted total kidney volume (htTKV)/age into 5 different classes. Reproduced from Irazabal *et al.*[9] (**j**) Unadjusted Kaplan-Meier renal survival from birth by MIC (right panel). Reproduced from Lavu *et al.*[10]

longitudinal eGFR slope, can aid in the identification of people who have rapidly progressive ADPKD.[4]

Chapter 2: Kidney manifestations

High blood pressure (BP). Management of high BP in people with ADPKD should include regular BP monitoring, dietary and lifestyle modifications (see Chapter 7), and pharmacotherapy when indicated.

As in all people with chronic kidney disease (CKD), we recommend standardized office BP measurement in people with ADPKD, regardless of kidney function.[11] We suggest that out-of-office BP measurements with home BP-monitoring or ambulatory BP-monitoring be used to complement standardized office BP readings. Use of ambulatory BP-monitoring should be considered with difficult-to-control BP or left ventricular hypertrophy, proteinuria, or declining kidney function but normal office BP readings.

We recommend using renin–angiotensin system inhibitors—that is, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB), as the first-line treatment to achieve the target BP. We recommend avoiding any combination of ACEi, ARB, and direct renin-inhibitor therapy. The appropriate choice of second-line antihypertensive agents will depend on assessing the benefits and risks for individual people.

Based on available RCT results, we recommend a target BP of ≤110/75 mm Hg, as measured by home BP-monitoring, if tolerated, for people aged 18–49 years with CKD G1–G2 and BP >130/85 mm Hg. For those aged 18–49 years with CKD G1–G2 and BP <130/85 mm Hg but >110/75 mm Hg, we suggest using an individualized approach to BP control, incorporating shared decision-making between the healthcare provider(s) and the patient. For those aged ≥50 years and/or with CKD G3–G5, we recommend a target mean systolic blood pressure of <120 mm Hg, if tolerated, assessed using standardized office BP measurement.

Resistant high BP requiring ≥3 drugs should be investigated for patient compliance or other causes of hypertension. High-grade proteinuria should be investigated for a coexisting kidney disease.

Kidney pain. Flank, abdominal, or lumbar pain in people with ADPKD should be investigated, to determine whether it is kidney-related or not. Refractory kidney pain is best managed by a multidisciplinary team, and pain-management strategies guided by shared decision-making. Nonpharmacologic, noninvasive interventions generally should be considered initially, followed by pharmacologic treatment if they do not relieve pain. Referral to a center of expertise should be made when invasive intervention is considered. Cyst aspiration or aspiration sclerotherapy may be considered when pain can be attributed to a single or several dominant cysts. Celiac plexus block, either in isolation or followed by major splanchnic nerve block, and percutaneous renal denervation, may be effective in the treatment of selected people with refractory chronic visceral pain caused by cyst enlargement. Spinal-cord stimulation may provide significant pain relief in specific cases of moderate-to-severe refractory mechanical or visceral pain. Nephrectomy is reserved for severe intractable pain, typically with advanced kidney disease or after KF, in those who have failed to respond to other modalities.

Nephrolithiasis. Medical treatment of nephrolithiasis in people with ADPKD should be the same as that used in the general population. Obstructing kidney stones should be managed by centers of expertise, as they are more challenging in ADPKD.

Gout. No evidence shows that gout is more common in ADPKD than in other forms of CKD. We agree with the recommendations from the *2020 American College of Rheumatology Guideline for the Management of Gout*.[12] People with ADPKD should not receive routine pharmacologic treatment for asymptomatic hyperuricemia. People with ADPKD and gout should be evaluated and treated taking into account their level of kidney function. People with onset of hyperuricemia and gout in childhood or adolescence should receive genetic testing for autosomal dominant tubulointerstitial kidney disease.[8]

Hematuria. Healthcare providers should discuss the possibility of, causes of, and natural history of gross hematuria with patients at the time of diagnosis of ADPKD, to avoid unnecessary worry when it happens.

Urinary tract infections. We agree that the recommendations for the general population from the *American Urological Association, the Canadian Urological Association, and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction*, for female pelvic medicine and urogenital reconstruction, also apply to people with ADPKD.[13] Healthcare providers should do the following: not treat asymptomatic bacteriuria; use first-line therapy (i.e., nitrofurantoin, trimethoprim-sulfamethoxazole, fosfomycin), dependent on the local antimicrobial susceptibility profiles, for the treatment of uncomplicated, symptomatic urinary tract infections (UTIs) in women; obtain a urine culture before antibiotics are started; and treat people with recurrent UTIs experiencing acute cystitis episodes with as short a duration of antibiotics as is reasonable, generally no longer than 7 days. Following discussion with patients of risks, benefits, and alternatives, healthcare providers may prescribe antibiotic prophylaxis to decrease the risk of future UTIs in women previously diagnosed with UTIs.

Recurrent UTIs in people with ADPKD should be investigated for an underlying predisposition. Blood cultures should be obtained if an upper UTI or kidney cyst infection is suspected. UTIs in people with ADPKD should be differentiated from cyst hemorrhage or kidney stone. People with ADPKD who present with fever, acute abdominal or flank pain, and an increased white blood cell count and/or C-reactive protein level should undergo workup for kidney cyst infection (Figure 5).[14] We recommend 4–6 weeks of

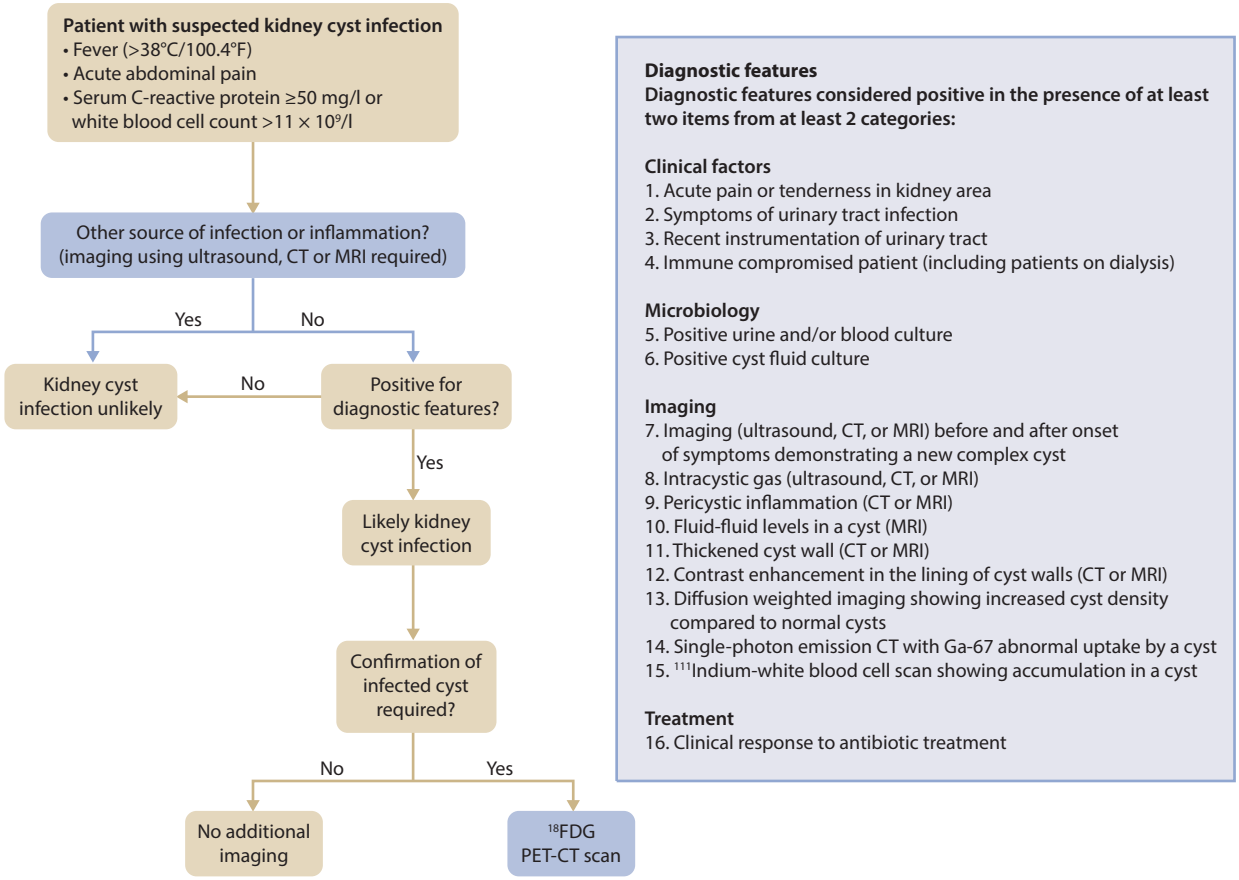


Figure 5 | Diagnostic algorithm for an infected kidney cyst in autosomal dominant polycystic kidney disease. CT, computed tomography; ^{18}FDG PET-CT, positron emission tomography with ^{18}F-fluorodeoxyglucose integrated with computed tomography; Ga-67, Gallium-67; MRI, magnetic resonance imaging. Adapted from Lantinga *et al.*[15]

antibiotic therapy in people with ADPKD and kidney cyst infection. A lipid-soluble antibiotic (e.g., trimethoprim-sulfamethoxazole, fluoroquinolone) may have better penetration into the cysts, and should be used if possible. However, the use of fluoroquinolones has been associated with an increased risk for tendinopathies and aortic aneurysms and dissections.

Renal cell carcinoma. No clear association exists between ADPKD and an increased risk of renal cell carcinoma. However, healthcare providers should be aware of atypical presentation of renal cell carcinoma in people with ADPKD.

Chapter 3: CKD management and progression, KF, and kidney replacement therapy

CKD management and progression. In general, the management of CKD in ADPKD is similar to that in other kidney diseases.[16–19] People with ADPKD tend to have a higher hemoglobin level, compared to that of people with other forms of CKD, due to regional hypoxia driving production of hypoxia-inducible transcription factors. Erythrocytosis (hematocrit level >51% or hemoglobin level >17 g/dl [170 g/l]) may occur in people with ADPKD, rarely before KF, and more frequently following kidney transplantation. Administration of an ACEi or an ARB is usually the initial treatment for post-transplant erythrocytosis, with hematocrit and hemoglobin targets of <51% and <17 g/dl [170 g/l], respectively. Therapeutic phlebotomy is indicated when an ACEi or an ARB is contraindicated or is ineffective at a maximal-tolerated dose.

Management of diabetes in people with ADPKD should be the same as that for people with other forms of CKD. Due to lack of evidence, use of sodium-glucose cotransporter-2 inhibitors is not advised at this time. Preferred glycemic management strategies are use of metformin when eGFR is ≥30 ml/min per 1.73 m^2, or a glucagon-like peptide-1 receptor agonist when eGFR is <30 ml/min per 1.73 m^2, when metformin is not tolerated, or when treatment with metformin alone is not sufficient for optimal glycemic control.

For the primary prevention of cardiovascular disease, lipid-lowering therapy should be initiated, in line with the *KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease*.[19]

Kidney transplantation. Kidney transplantation, preferably preemptive, living-donor kidney transplantation, is the preferred treatment for KF for people with ADPKD. During the pretransplantation workup, estimated total kidney and liver weights derived from total kidney and liver volumes

should be subtracted from the body weight, for an accurate assessment of body mass index. Pretransplant evaluation should consider performing imaging of the kidneys within 1 year prior to the anticipated timing of transplantation, to rule out solid or complex cystic lesions. Immunosuppressive protocols should be the same as those used for other transplant recipients.

Native nephrectomy should be performed only for specific indications and when the benefit outweighs the risk. Potential indications include severe symptoms from massively enlarged kidneys, recurrent or severe kidney infection or bleeding, complicated nephrolithiasis, intractable pain, suspicion of renal cell carcinoma, insufficient space for the kidney graft, and severe ventral hernia. Nephrectomy should occur either at the time of or after transplantation, but not before, due to the potential need for transfusion, preventing preemptive transplantation, and the increased risk of complications. The type of nephrectomy should be hand-operated laparoscopic nephrectomy, rather than open nephrectomy. The choice between unilateral versus bilateral native nephrectomy will depend on providers' clinical judgment and the availability of local expertise.

New-onset diabetes, erythrocytosis, worsening aortic, tricuspid, or mitral regurgitation, aortic root dilatation, subarachnoid hemorrhage, thromboembolic events, skin cancers, kidney or liver cyst infections, and colon diverticulitis were more common in some studies of kidney transplant recipients with ADPKD than they were in the general kidney transplant population.

Chronic dialysis. Shared decision-making, prescription of hemodialysis, and supportive therapies, such as anticoagulation, should be the same as those for people without ADPKD.[20] Peritoneal dialysis should be considered as a viable option, with caution used when massive kidney and/or liver enlargement or abdominal wall hernias are present.

Chapter 4: Therapies to delay the progression of ADPKD

Interventions targeting the action of the antidiuretic hormone arginine vasopressin on the vasopressin-2 receptor in the kidney cystic epithelium are presently the cornerstone of treatment in people with ADPKD at risk of rapid kidney disease progression.

Tolvaptan. Our systematic review found 3 RCTs of tolvaptan, an antagonist of the vasopressin-2 receptor, together with 2 extension studies; a pooled, matched comparison of long-term tolvaptan-treated and untreated groups; and a post marketing analysis of harms. Overall, the evidence review found a net difference in eGFR decline of 1.3 ml/min per 1.73 m^2 per year (95% confidence interval: 1.0–1.7) and in total kidney volume growth of −2.7% (95% confidence interval: –3.3% to –2.1%), both favoring tolvaptan use. The incidences of UTI, kidney stones, hematuria, and kidney pain events were significantly reduced in the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial. The effect of tolvaptan on the rate of eGFR decline is accepted as a reliable surrogate for delaying the onset of KF.[21,22]

We recommend initiating tolvaptan treatment in adults with ADPKD with an eGFR ≥25 ml/min/1.73 m^2 who are at risk for rapidly progressive disease.

The definition of risk of rapidly progressing ADPKD was determined largely by clinical consensus. We advise using the MIC, ideally based on MRI, as the primary method for risk prediction and consideration of tolvaptan use in clinical care. Low-dose CT is an alternative to determine the MIC. When MRI and CT are not available or are contraindicated, employing ultrasound using the ellipsoid formula is acceptable. The historical decline in eGFR also can be used in the absence of advanced imaging. An annual eGFR decline ≥3 ml/min per 1.73 m^2, as determined by multiple measurements of eGFR over 3–5 years, or a Predicting Renal Outcome in PKD score >6, may provide evidence for risk for rapid progression.

Contraindications to tolvaptan use should be considered before initiating such treatment.[21,22] Absolute contraindications include the following: a planned pregnancy; pregnancy; breastfeeding; medical conditions associated with a high risk of volume depletion; inability to respond to or perceive thirst; hypernatremia; urinary tract obstruction; strong cytochrome P450, family 3, subfamily A inhibitors; and significant liver disease, unless due to PLD. Relative contraindications to be considered include the following: an eGFR at initiation of <25 ml/min per 1.73 m^2; a history of gout or hyperuricemia; cytochrome P450, family 3, subfamily A inhibitors; P-glycoprotein inhibitors; grapefruit and Seville orange consumption; and urinary incontinence.[21,22]

We suggest using shared decision-making when deciding to initiate tolvaptan use in people aged >55 years who have rapid kidney disease progression.

Physicians should be educated on the adverse effects, contraindications, and drug interactions of tolvaptan.[21,22] The aquaretic effects of tolvaptan require the need to drink enough water to replace urinary losses, to ensure long-term tolerability. Tolvaptan treatment should be interrupted in situations causing volume depletion or an inability to compensate for the aquaresis. Tolvaptan causes a small, reversible reduction in eGFR, likely reflecting its impact on compensatory hyperfiltration.

People with ADPKD should have a "sick-day plan" and be advised to skip doses of tolvaptan in situations in which they are at risk of volume depletion, such as those with limited access to water, those with increased fluid losses, and activities in warm weather. Individual adjustments should include adapting the schedule, timing, and doses of tolvaptan to the person's activities. Patients should be counseled to drink liquids without sugar or fat, and to adopt a low-sodium intake, because low osmolar intake reduces polyuria.

Tolvaptan should be initiated with a daily dose of 45 mg upon waking, and of 15 mg 8 hours later; this should be titrated gradually by the treating physician to permit adequate

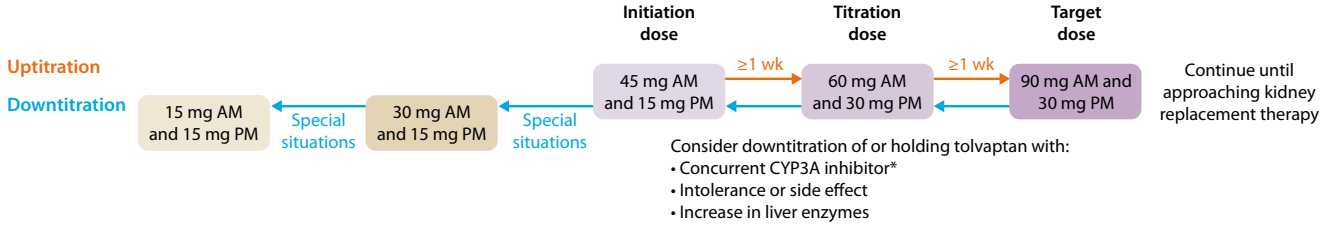


Figure 6 | Commencement of and titration approach to tolvaptan use in autosomal dominant polycystic kidney disease. *Examples of strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitors (reduce clearance by >80%) are as follows: antifungals (itraconazole, ketoconazole); antibiotics (clarithromycin); and protease inhibitors (saquinavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir). Examples of moderate CYP3A inhibitors (reduce clearance by 50%–80%) are as follows: antiarrhythmics (amiodarone); antifungals (fluconazole); antibiotics (erythromycin); calcium-channel blockers (diltiazem, verapamil); protease inhibitors (amprenavir, fosamprenavir); and complementary and/or dietary agents, such as grapefruit juice (240 ml coadministration).

adaptation to the aquaresis (Figure 6).[21,22] Monitoring through uptitration should include kidney function, blood electrolyte (sodium), and liver function test (LFT) levels in morning blood samples should be obtained before the dose of tolvaptan is taken. Serum sodium levels provide insight into the adequacy of water intake. Tolvaptan use can be continued in people aged >55 years and/or when the eGFR falls below 25 ml/min/1.73 m^2, if it is well tolerated.

Tolvaptan use is associated with an increased risk for idiosyncratic drug-induced liver injury. Approximately 5% of people with ADPKD treated with tolvaptan, compared to 1% of people receiving placebo, in RCTs displayed an increase in transaminase levels that was above 3-fold the upper limit of normal. The increases in alanine transaminase level occurred most often during the first 18 months of treatment and resolved within 1–4 months after tolvaptan cessation.

Frequent monitoring (monthly for the first 18 months, and then every 3 months until drug discontinuation) of LFTs is mandatory in people treated with tolvaptan for ADPKD. Following regulatory approval by the United States (U.S.) Food and Drug Adminstration, all physicians prescribing tolvaptan for ADPKD in the U.S. must be trained and certified to appropriately apply the Risk Evaluation and Mitigation Strategies (REMS) program, whereas the European Medicines Agency has implemented a risk-management plan that includes education of both prescribing physicians and people with ADPKD.

The management of abnormal LFTs detected during tolvaptan treatment should be conducted according to local regulatory guidelines and product information (Figure 7). The administration of tolvaptan should be held, other possible etiologies considered, and LFTs rechecked within

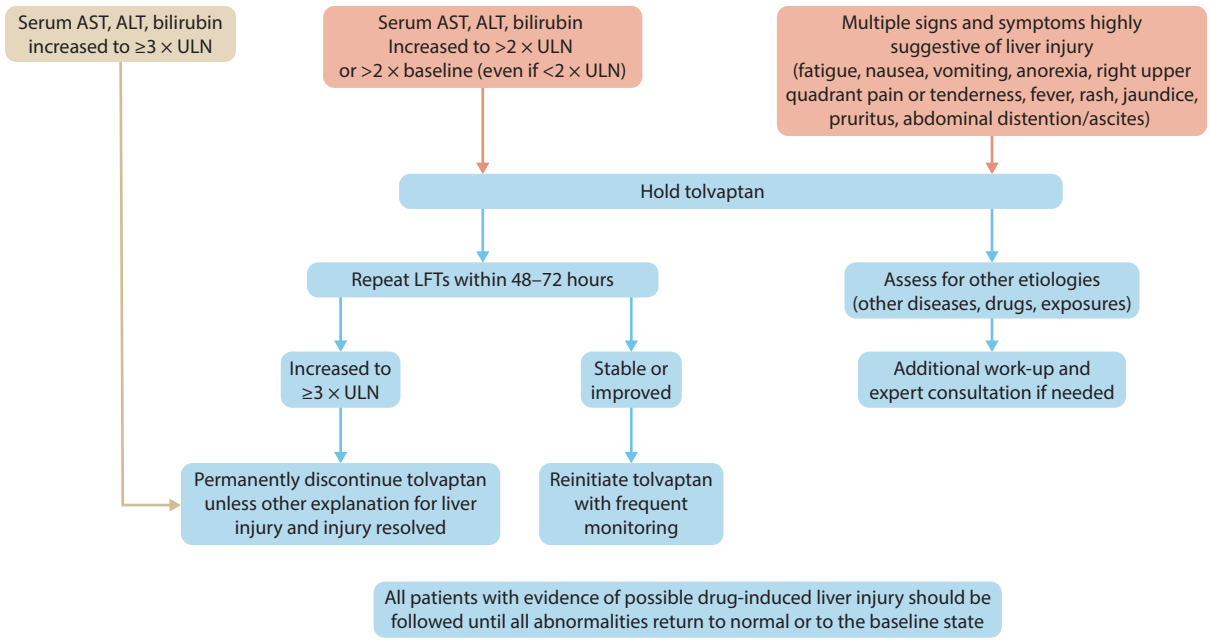


Figure 7 | Algorithm summarizing recommendations for evaluation and management of potential tolvaptan-induced liver injury. ALT, alanine transaminase; AST, aspartate aminotransferase; LFT, liver function test; ULN, upper limit of normal. Reproduced from Chebib *et al.*[21]

48–72 hours if an elevation occurs in alanine transaminase or aspartate aminotransferase levels to >2× the upper limit of normal or >2× baseline values. Rechallenge after the LFTs return to normal can be considered, with increased monitoring in people who had mild transaminase-levels elevations. Per the U.S. label, tolvaptan should not be restarted in people who have had signs or symptoms consistent with hepatic injury or an alanine transaminase or aspartate aminotransferase level that is >3× the upper limit of normal, unless another explanation accounts for the liver injury.

Additional side effects of tolvaptan include hyperuricemia, and rarely gout.

Water intake in the absence of tolvaptan. We suggest adapting water intake, spread throughout the day, to achieve an intake of at least 2–3 liters of water per day in people with ADPKD, and an eGFR ≥30 ml/min per 1.73 m^2, without contraindications, such as medication use that may increase the risk of hyponatremia (e.g., serotonin reuptake inhibitors, tricyclic antidepressants, thiazide diuretics).[21,22]

Other pharmacologic interventions. We recommend not using mammalian target of rapamycin inhibitors, or metformin (in people who do not have diabetes), to slow the rate of disease progression in ADPKD. We recommend not using statins specifically to slow kidney disease progression. Somatostatin analogues should not be prescribed for the sole purpose of slowing eGFR decline, but their use can be considered in people with severe symptoms due to massively enlarged kidneys, to lower the growth rate of kidney cysts when no better options are available. We suggest not using sodium-glucose cotransporter-2 inhibitors or glucagon-like peptide-1 receptor agonists to slow the rate of eGFR decline, until further research determines their efficacy and safety. We suggest not using ketogenic interventions to slow the progression of ADPKD, without further evidence of their efficacy and safety in long-term trials. Complementary medicines or supplements should not replace standard medical treatments in people with ADPKD and should be discussed with the healthcare team.

Chapter 5: Polycystic liver disease

Although in the majority of people with ADPKD, the number of liver cysts increases with age, most people will not develop clinically symptomatic PLD. Liver cysts, even in advanced PLD, do not usually impact the synthetic or secretory capacity of the liver. However, symptoms can ensue due to the mass effect of a large cystic liver exerting pressure on the diaphragm and abdominal wall, compressing other abdominal organs and vascular structures. Multiple classification and staging systems based on liver volume (LV) and cyst characteristics have been proposed to plan management and monitor severity of PLD.[4,6,23]

Diagnosis and staging of PLD. The liver should be included in abdominal imaging, using MRI, CT scan, or if these are not available, ultrasonography, to obtain LV and characterize the severity of PLD. People should be advised of the likely outcomes and possible symptoms of PLD. Symptoms of PLD should be captured with specific questionnaires.

Risk factors. PLD occurs at earlier ages and with more-aggressive cyst growth in women than in men. Women with ADPKD, particularly those with PLD, should be counseled about the benefits and potential harms of receiving sex hormone therapy. Exposure to estrogen-containing oral contraceptives, as well as estrogen-replacement therapy, was associated with a greater LV, and an annual increase in LV, in several studies of women with ADPKD.

Nutrition and lifestyle. People with symptomatic PLD should be assessed for sarcopenia and malnutrition. People with sarcopenia or malnutrition should be provided with intensive nutrition counseling and exercise rehabilitation.

Management of PLD. Treatment for PLD should be performed in centers of expertise. People with cyst-related symptoms or complications that impact their quality of life should be treated. The type of treatment should be based on symptoms, liver cyst characteristics, total LV, and available expertise (Table 3).[4,23]

We recommend prescribing long-acting somatostatin analogues in people with marked cystic hepatomegaly in PLD with severe volume-related symptoms. Long-acting somatostatin analogues (e.g., octreotide, lanreotide, pasireotide) reduced 3′,5′-cyclic adenosine monophosphate levels in cystic cholangiocytes, and inhibited cholangiocyte cell proliferation and fluid secretion. Four RCTs assessed the effect of somatostatin analogues on PLD, with a follow-up period of ≥1 year. They all reported a significant reduction in the rate of LV growth. The effect on symptom burden and/or volume of polycystic liver and kidneys should be evaluated after 6–12 months. When beneficial effects of therapy are not observed, use of somatostatin analogues should be discontinued.

People with PLD should be referred for liver transplantation in the event of massive PLD, in the absence of contraindications or alternative treatment options. People with PLD should be referred for combined kidney–liver transplantation when an indication is present for liver transplantation and the kidney function is severely impaired (eGFR <30 ml/min per 1.73 m^2).

Liver cyst infections. Diagnosis of liver cyst infections should utilize clinical signs and symptoms, microbiology, and advanced imaging such as MRI or 2-deoxy-2-fluorine-18-fluoro-D-glucose positron emission tomography–computed tomography. Pain and tenderness over the liver, and history of biliary instrumentation, help to differentiate it from kidney cyst infection (Figure 8). Imaging studies should be performed to determine the severity and location of a liver cyst infection. Fever >38 °C, abdominal pain, an

Table 3 | Treatment options for PLD

Treatment option	Liver phenotype indication	Efficacy	Morbidity and mortality
Aspiration sclerotherapy	One or few large dominant cysts, symptomatic or causing compression of veins or bile ducts	Symptomatic improvement: 72%–100% Individual cyst volume reduction: 76%–100%	Minor complications: 5%–90% Mortality: <1.0% (none reported)
Transarterial embolization	Diffuse symptomatic cysts, at least one segment of functioning liver, no alternative treatment options	Symptomatic improvement: 72%–93% Need for reintervention: 15% Reduction in TLV: 13% at 3 mo; 28% at 51 mo	Postembolization syndrome: 100% Complications: 7.5%
Laparoscopic cyst fenestration	Large symptomatic liver cysts located anteriorly and caudally	Symptomatic recurrence: 34% Need for reintervention: 26%	Complications: 29% Clavien III-IV[a] perioperative complications: 7.2% Mortality: 2.3%
Combined partial hepatectomy and/or cyst fenestration	Massive, highly symptomatic PLD, at least one hepatic sector relatively spared, patent afferent and efferent sectoral vasculature	Reduction in TLV: 61% postoperative and at 8 yr Symptomatic improvement: 94%	Clavien III-IV perioperative complications: 21% Mortality: 2.7% Survival: 96%, 93%, 86%, and 78% at 1, 5, 10, and 15 yr
Liver transplantation	Massive PLD and high symptom burden or sarcopenia or PLD-related complications, contraindication or failure of alternative treatment options	Only curative treatment option	Postoperative complications: 46% Mortality: 9% 1-yr patient survival: 85%–95% 5-yr patient survival: 77%–92%
Somatostatin analogues	Severe, symptomatic hepatomegaly	Reduction in annual liver growth rate of 6%–15% after 1–3 yr of follow-up	Dose adjustments for side effects (e.g., GI complaints or hyperglycemia) Gallstones Bradycardia Rarely cyst infections Pasireotide has high hyperglycemia risk

GI, gastrointestinal; PLD, polycystic liver disease; TLV, total liver volume.
[a]Clavien grade III complications require surgical, endoscopic, or radiologic intervention. Clavien grade IV complications are life-threatening and require intensive-care management.

elevated serum C-reactive protein level of ≥50 mg/l, and elevated white blood cell counts are highly suggestive of a liver cyst infection. Empiric antibiotics should not be used to treat people with localized liver pain without fever who have normal white blood cell counts and C-reactive protein levels. Other causes of pain, such as cyst hemorrhage, should be considered.

Empiric antibiotic treatment of liver cyst infections should target gram-negative *Enterobacteriaceae* bacteria, using a third-generation i.v. cephalosporin, with or without a fluoroquinolone. After clinical stabilization, i.v. therapy can be switched to an oral fluoroquinolone, with adjustment according to culture results when available. Duration of antibiotic therapy should be ≥4 weeks for liver cyst infection, and longer treatment periods may be required based on the response to therapy. An approach that may be reasonable is to perform percutaneous drainage of infected liver cysts when pathogens unresponsive to antibiotic therapy are isolated from a cyst aspirate, in cases of the following: isolation from a cyst aspirate of pathogens that are unresponsive to antibiotic therapy; immunocompromise; large infected hepatic cysts (>8 cm); hemodynamic instability, and/or signs of sepsis. The percutaneous drain should be kept in place until drainage stops. In the case of deep cysts for which percutaneous drainage is not feasible, surgical drainage may be necessary. Infected liver cysts that do not respond to 48–72 hours of antibiotic treatment should be evaluated further.

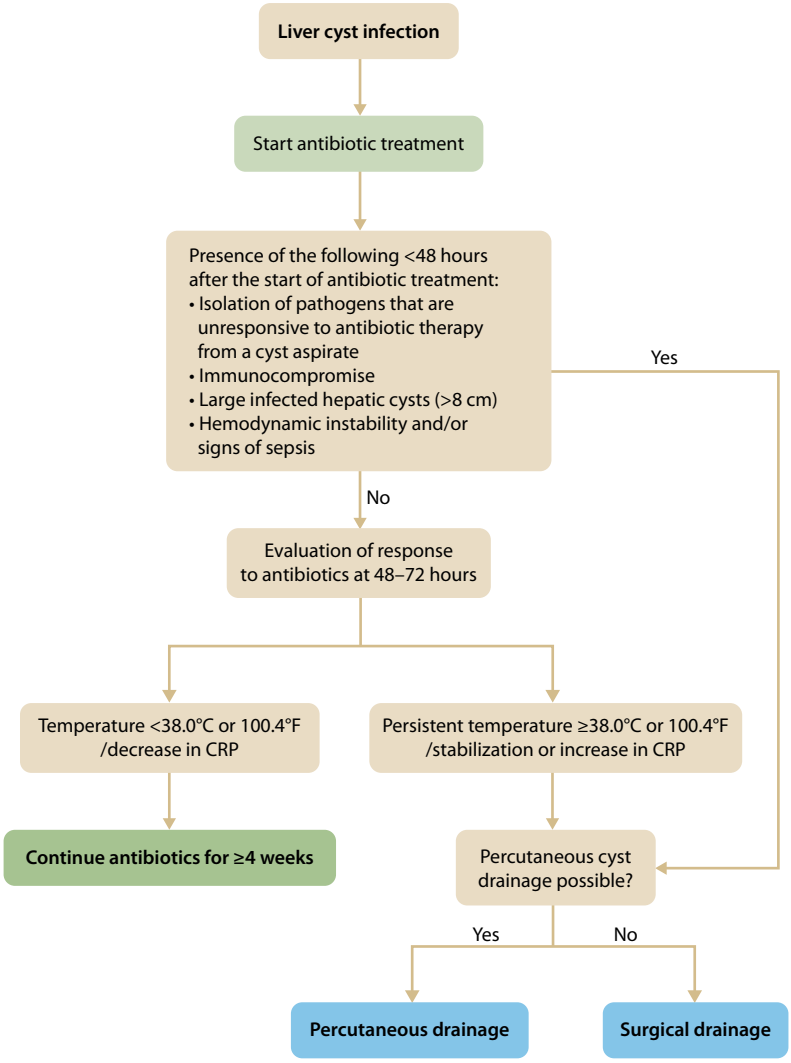


Figure 8 | Management of liver cyst infections in autosomal dominant polycystic kidney disease. CRP, C-reactive protein.

Chapter 6: Intracranial aneurysms (ICAs) and other extrarenal manifestations

ICAs. People with ADPKD have an increased risk for ICAs and aneurysmal subarachnoid hemorrhage (SAH), compared to the general population.[24] The vast majority of aneurysms in people with ADPKD do not rupture. The potential benefit of presymptomatic screening and preemptive intervention to prevent aneurysmal rupture depends on the following: the prevalence of ICA; the risk of rupture with medical therapy alone; the yield and risk of the screening technique; the rate of complications associated with strategies employed for preventive occlusion, as well as their technical success rate; and the risk of aneurysm recurrence and *de novo* aneurysm development and rupture. Potential implications of detecting an intracranial vascular abnormality on imaging (e.g., eligibility for life insurance), as well as anxiety, notably when preventive occlusion is not indicated, should be considered. Ethnic and local differences and possible effects of improved BP control and reduction in smoking on the declining incidence of SAH in the general population also need to be considered.

We recommend informing adults with ADPKD about the increased risk for ICA and SAH, including risk factors, screening, preventive measures, and symptoms that should trigger immediate medical attention. All people with ADPKD should be educated to recognize thunderclap headache, characterized by a sudden onset of severe headache that reaches its maximum intensity within seconds to a minute. Signs of an aneurysmal rupture should prompt immediate medical attention. Because smoking is a strong modifiable factor for ICA development and rupture, healthcare providers should ask all people with ADPKD about their tobacco use, advise them to stop using tobacco, and provide behavioral interventions and approved

pharmacotherapy for cessation, if needed. Because uncontrolled hypertension is a modifiable risk factor for ICA development and rupture, hypertension should be diagnosed early and treated adequately in people at risk of or diagnosed with ADPKD.

We recommend screening for ICA in people with ADPKD and a personal history of SAH or a positive family history of ICA, SAH, or unexplained sudden death if the person will be eligible for treatment and has a reasonable life expectancy. Screening for unruptured ICA should be discussed in people with *de novo* ADPKD, those with unknown or unclear familial history, and those with personal or familial history of extracerebral vascular phenotype. Screening also may be considered in specific clinical settings, such as during evaluation for kidney and/or liver transplantation, or before major elective surgery. People with ADPKD who are not considered at increased risk for ICA and who, after being given comprehensive information, prefer being screened for ICA, should be given access to screening. In women in whom screening is indicated or considered for the reasons stated above, screening for ICA should be discussed before pregnancy.

Time-of-flight magnetic resonance angiography without gadolinium enhancement should be the method of screening for ICA in people with ADPKD. High-resolution CT angiography can be an alternative. If the screening is negative in people with a high risk of ICA, the timing of rescreening should be individualized to every 5–10 years, based on risk factors, age, and life expectancy. When one or several ICAs are identified, treatment options, such as conservative management and microvascular or endovascular repair, should be assessed within a multidisciplinary setting at centers of expertise that have high volumes of ICA cases.

Other vascular associations. Routine screening of vascular abnormalities of nonintracranial large arteries has no role in people with ADPKD and no familial history of vascular aneurysms or dissections. In cases of familial history of aortic root or thoracic aortic aneurysms in people with ADPKD, screening of first-degree relatives should be performed. In people with ADPKD and dilatation of the aortic root or thoracic aortic aneurysm, therapeutic measures to limit aortic expansion should include smoking cessation, statin therapy, and antihypertensive therapy, including a beta-blocker and/or an ACEi or ARB.

Cardiac associations. Echocardiography at baseline and/or during follow-up should be considered in people with ADPKD who have the following: a history of severe or uncontrolled hypertension; heart murmur, signs or symptoms of cardiac dysfunction, or other cardiovascular manifestations; or a familial history of thoracic aortic aneurysm or nonischemic cardiomyopathy.

Abdominal wall hernia. In people with asymptomatic abdominal wall hernias and severe kidney enlargement and/or KF, nonsurgical management should be discussed, because of the increased risk for complications associated with repair and because of potential hernia recurrence. People with ADPKD managed expectantly for abdominal wall hernia should be educated to recognize symptoms of hernia incarceration or strangulation, which should lead to prompt surgical evaluation. Surgical repair of abdominal wall hernias should be considered in people with ADPKD who elect peritoneal dialysis as a mode of kidney replacement therapy.

Other extrarenal manifestations. ADPKD is a systemic disorder with additional manifestations in multiple tissues (Table 4).

Table 4 | Extrarenal manifestations associated with ADPKD

Extrarenal manifestations	Estimation of people with ADPKD affected, %	Details and/or notes
Intracranial aneurysm	12.9	Prevalence in ADPKD population is difficult to assess because systematic screening usually is not performed.
Subarachnoid hemorrhage	Incidence rate 0.57 per 1000 patients/yr	Thunderclap headache should lead to immediate medical attention.
Intracranial arterial dolichoectasia	~0.7–5	Dolichoectasia (dilatative arteriopathy) is usually asymptomatic, but may cause stroke, and may mimic ICA on imaging studies.
Arachnoid cyst	8–15	Usually asymptomatic, incidental diagnosis Possible increased risk of spontaneous subdural hematoma
Meningeal cyst	Rare	Usually asymptomatic, incidental diagnosis May very rarely cause spontaneous intracranial hypotension
Mitral valve prolapse and regurgitation	3–26	Usually asymptomatic MVP was formerly reported to be present in 20%–30% of people with ADPKD, but more recent studies using current definition of MVP reported prevalence of 1% in pediatric and 3.4% in adult cohorts, similar to prevalence in the general population.
Pericardial effusion	~20	Usually asymptomatic, incidental diagnosis
Cardiomyopathy	Rare	Hypertrophic cardiomyopathy: 2.5%[a] Dilated cardiomyopathy: 5.8%[a] Left ventricular noncompaction: 0.3%
Congenital heart malformation	Rare	Very rare case-series and case reports Left-to-right shunt, obstructive cardiomyopathies, and other complex malformations reported
Situs inversus and large vessels transposition	Rare	Laterality defects including dextrocardia and situs inversus totalis have been reported in a small number of people with ADPKD, mostly *PKD2*.
Thoracic aortic aneurysm	~1.5	
Thoracic aortic dissection	Rare	Acute chest/upper back/abdominal pain is present in >90% of the cases.
Coronary arteries dissection	Rare	Symptoms of acute myocardial infarction Usually more frequent in young women
Carotid and vertebral artery dissection	Rare	Often result in ischemic stroke or transient ischemic attack, often associated with neck pain or headaches. Occasional Horner syndrome in cases of carotid dissections
Retinal artery and vein occlusion	Rare	Single case-series of 8 people with ADPKD
Symptomatic polycystic liver disease	<5, predominant in females	Liver cysts are present in >80% by age 30 yr.
Congenital hepatic fibrosis	Rare	More common in ARPKD
Pancreatic cysts and IPMN	Pancreatic cysts ~10	Complex or multiple pancreatic cysts should be followed and evaluated to exclude malignancy, particularly Von Hippel–Lindau syndrome.
Splenic cysts	~7	Like general population; usually asymptomatic, incidental diagnosis
Abdominal wall hernia	Common	Published evidence from a small cohort in Wales, but very common clinical finding
Dilated extrahepatic bile duct	~40	Small cohort single study
Colonic diverticulosis	1.5	Single, large national database
Duodenal or small-bowel diverticula	Rare	Rarely, periampullary duodenal diverticula may be associated with obstructive jaundice or ascending cholangitis.
Bronchiectasis	19–37	Incidental radiologic finding, typically of no clinical significance
Pleural effusion	21 vs. 8 in controls	Incidental radiologic finding, more frequent in females, not clinically significant
Sperm abnormality	Abnormal semen parameters reported	May be associated with male infertility, although no large study has demonstrated that male infertility was more common in ADPKD
Seminal vesicle cysts	20–40	Although commonly identified, seminal vesicle cysts do not result in male infertility.
Seminal vesicle ectasia	Ectasia >10 mm: 23	Although commonly identified, seminal vesicle ectasia does not result in male infertility.

ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; CKD, chronic kidney disease; ICA, intracranial aneurysm; IPMN, intraductal papillary mucinous neoplasms; MVP, mitral valve prolapse.
[a]Likely referral bias, estimates taken from a single study and should be intepreted with caution.

Chapter 7: Lifestyle and psychosocial aspects

Healthcare providers need to provide people with ADPKD with advice and guidance regarding nutrition, lifestyle, physical activity, and management of psychosocial issues. Care can be provided by the core multidisciplinary team or by referral to dedicated services.

Nutrition. People with ADPKD should follow the general advice for a healthy diet, consistent with World Health Organization and CKD guidelines, and should work with accredited nutrition providers or registered dietitians to receive individualized counseling, particularly people with CKD G4–G5, those at high risk of urinary stones, those who are overweight (body mass index, 25–29.9 kg/m^2) or obese (body mass index, $>$30 kg/m^2), and those with malnutrition or sarcopenia.[25] The estimated weight of cystic kidneys should be taken into consideration when calculating the body mass index.

Physical activity. Adults with ADPKD should be encouraged to undertake moderate-intensity physical activity, for a cumulative duration of at least 150 minutes per week or to a level compatible with their cardiovascular and physical tolerance, and strength training at least 2 sessions per week. People with large kidneys and/or liver should be advised of the possibility of direct injury during physical activity and exercise. Expert consultation is advisable in prescribing exercise for people with cardiovascular disease, frailty or risk of falling, bone disease, or who are on dialysis or are post-transplantation.

Lifestyle management. All people with ADPKD should be asked about the following: their use of tobacco products, all of which should be avoided; their use of alcohol, with the recommendation that they consume $\leq$1 alcoholic drink per day, for females, and $\leq$2 drinks per day, for males; caffeine intake, with advice to avoid excessive caffeine intake, particularly during pregnancy; cannabis products, with counseling about the potential dangers of acute kidney injury related to product contamination and synthetic versions; and recreational drugs and anabolic steroids, with advice to refrain from these drugs.

Psychosocial care. Healthcare providers should screen for and conduct periodic assessment of psychosocial issues. Key stressors related to ADPKD include those that are physical, social, related to family members, and related to the inherited nature of the disease. Education programs to promote self-management should be implemented to provide comprehensive and practical information to people and their families. People should be informed about patient organizations dealing with PKD or kidney disease in general, and other support and advice services. The healthcare team should discuss with patients and their caregivers the financial impacts of having ADPKD and try to help patients avoid unnecessary medical expenses.

Chapter 8: Pregnancy and reproductive issues

Healthcare for women with ADPKD of childbearing age includes management of hormonal therapies, contraceptive measures, preconception counseling, and pregnancy management.

Contraceptive measures in women. Given that estrogen, and possibly progesterone, exposure may be associated with an increased risk of PLD progression, women with ADPKD and liver cysts should be educated regarding their contraceptive choices.[26] When hormone therapy is being considered in women with ADPKD, liver imaging should be made available to inform discussion. Estrogen oral contraceptives may aggravate PLD, whereas the impact of combined estrogen and/or progestin oral contraceptives, patches, and vaginal rings on PLD is not known. The impact of progestin-only methods (pills, injections, implants, and intrauterine devices) on PLD is not known, but the level of systemic exposure with levonorgestrel-releasing intrauterine devices is low (4%–13% of that with use of combined oral contraceptives). People without or with mild PLD can use combined low estrogen and/or progestin contraceptives. Progestin-only intrauterine devices are likely safe for people with moderately severe PLD. Nonhormonal methods (barrier-based and copper intrauterine devices) are safest for people with severe PLD. Contraception in adolescents or young adults with ADPKD should not be restricted.

Preconception counseling. Preconception counseling should be offered to both men and women with ADPKD, to discuss options to prevent transmitting ADPKD to future children.[23] The counseling should be provided by a multidisciplinary team in an ADPKD referral center when possible and should include all available reproductive options (Figure 9). Use of renin–angiotensin system inhibitors, tolvaptan, and any other teratogenic drug should be stopped prior to the start of pregnancy and not restarted until the mother has completed breastfeeding. Although men with ADPKD show an increased prevalence of seminal tract cysts and sperm abnormalities, these do not appear to impact fertility.

Pregnant women with ADPKD. Pregnant women with ADPKD should be followed by a multidisciplinary team in an expert center.[27] During pregnancy, BP, kidney function, the soluble fms-like tyrosine kinase-1-to-placental growth factor ratio (if available), and proteinuria should be monitored. Pregnant women with ADPKD should undergo monthly urinalysis; in the case of a positive urine culture, even when patients are asymptomatic, they should be treated with appropriate antibiotics, as used during pregnancy in the general population. Women with ADPKD can safely perform vaginal delivery. When a pregnant woman with ADPKD experiences acute abdominal pain, imaging can be performed safely with either ultrasound or MRI.

More frequent BP monitoring, preferably weekly home BP monitoring, should be advised, particularly in cases of pre-existing hypertension or hypertension diagnosed during pregnancy. Antihypertensive medications to control BP during pregnancy (i.e., labetalol, nifedipine long-release, hydralazine, clonidine, or methyldopa) can be used when indicated in women with ADPKD. The BP target in pregnant women with ADPKD is $\leq$130/85 mm Hg.

Pregnant women with ADPKD should be monitored, because of an increased risk of preeclampsia and preterm

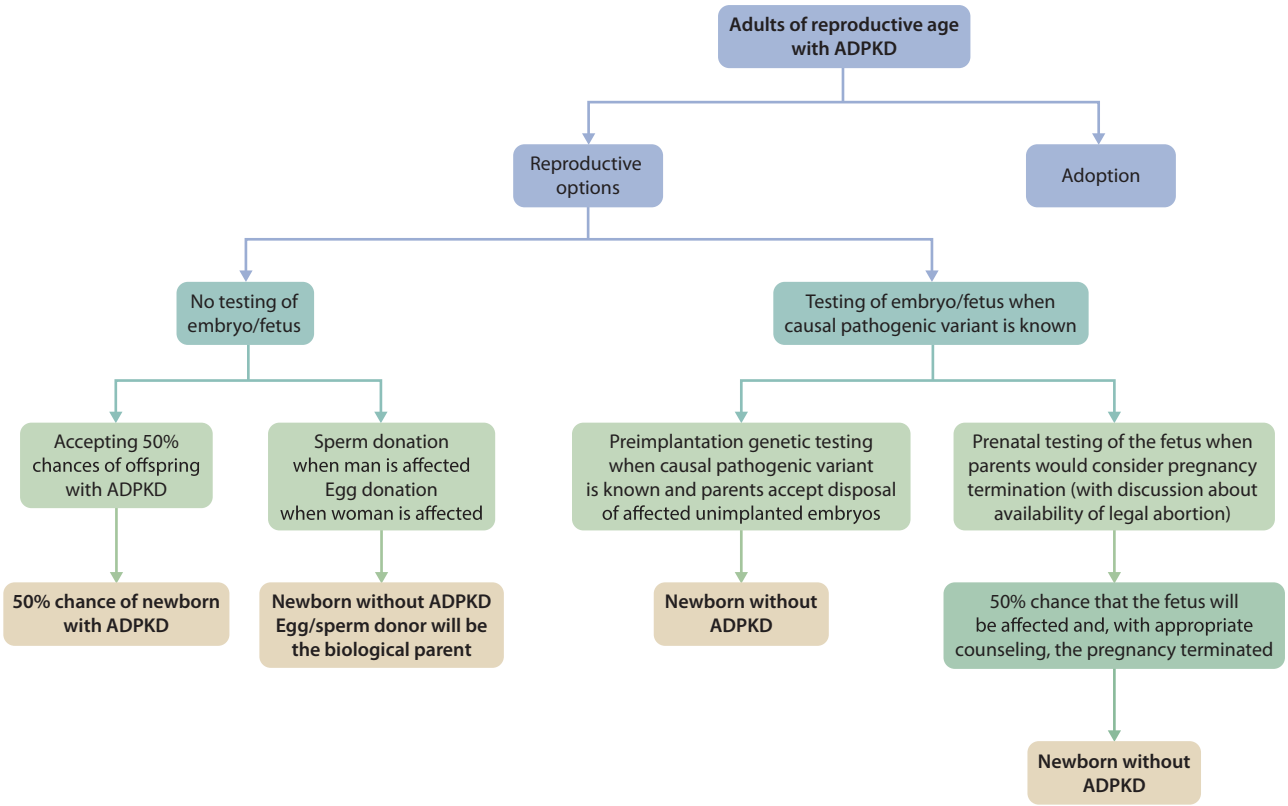


Figure 9 | Reproductive options for men and women with autosomal dominant polycystic kidney disease (ADPKD).

delivery.[28] Assessment of the soluble fms-like tyrosine kinase-1-to-placental growth factor ratio in plasma, from 24 weeks of gestation (earlier in patients with history of early pre-eclampsia in a previous pregnancy), and every 4–6 weeks, should be done for prediction of and to rule out pre-eclampsia. Low-dose aspirin should be prescribed from week 12 to week 36 in pregnant women with ADPKD.

Mild radiographic kidney abnormalities in the fetal kidneys do not necessarily predict a severe outcome. Shared decision-making regarding the value and implications of confirmatory genetic testing is advised. Severe fetal bilateral structural kidney cystic disease and/or oligohydramnios portend a higher risk of a poor neonatal outcome or early-onset childhood kidney dysfunction. A normal fetal ultrasound does not exclude the diagnosis of ADPKD in an at-risk child.

Women with ADPKD should be seen by a nephrologist early (at 6 weeks) and within 6 months after delivery, for a postpartum kidney review. Women with ADPKD may have bladder instability or urinary incontinence after delivery and should be offered pelvic-floor physical therapy.

Chapter 9: Pediatric issues

Currently, no validated stratification models have been developed to identify children at risk of rapid progression, and no approved therapies are available for specifically this population.

Diagnosis of ADPKD in children. ADPKD may begin antenatally or in early childhood. Diagnoses of very early-onset ADPKD (clinical abnormalities due to ADPKD before age 18 months) and early-onset forms of ADPKD (between ages 18 months and 15 years) are rare and are distinct subentities of ADPKD.

Shared decision-making should be undertaken when discussing the benefits and harms related to the screening and/or diagnosis of at-risk children in families with ADPKD, including the parents and/or legal guardians and the mature child.[26] Expert counseling about diagnostic options, delivered by a team that includes a pediatric nephrologist and a geneticist, should be offered. Ultrasound should be the preferred imaging method. People and families should be informed that the presence of a single kidney cyst in an at-risk child (aged <15 years) is highly suspicious for the diagnosis of ADPKD, but that the absence of cysts does not rule out ADPKD.

Ultrasound of the parents (or the grandparents, if the parents are aged <40 years) should be considered when seeking a diagnosis in children with incidentally detected kidney cysts and negative family history for ADPKD, with the goal of detecting an unknown family history. The possibility of a benign simple cyst should be included in the differential diagnosis of children with an isolated cyst, a negative family history, and a negative workup of the parents or grandparents. Genetic testing should be offered for children with very-early-onset ADPKD or an atypical presentation of ADPKD, or with cystic kidneys and a negative familial history of ADPKD, or in the context of screening at-risk children after a shared decision has been made.

BP control in children and adolescents with ADPKD. Standardized office BP measurement should be performed annually in

children (aged ≥5 years) and adolescents with or at risk for ADPKD. Annual 24-hour ambulatory BP-monitoring should be performed in children and adolescents (aged ≥5 years; height ≥120 cm) with very-early-onset ADPKD or early-onset ADPKD, and in children and adolescents with or at risk for ADPKD with BP at ≥75th percentile.[29] If ambulatory BP-monitoring is not available, routine in-office or home BP-monitoring are acceptable alternatives. Evaluation of high BP in children and adolescents with or at risk for ADPKD should include consideration of the possibility of primary or other secondary causes of hypertension. Echocardiography to exclude left ventricular hypertrophy should be performed in children and adolescents with ADPKD and high BP. High BP should be managed by a pediatric nephrologist.

We recommend targeting BP to be at ≤50th percentile for age, sex, and height, or ≤110/70 mm Hg in adolescents in the setting of ADPKD and high BP, and using renin–angiotensin system inhibitors (i.e., ACEi or ARBs) as the first-line therapy for high BP in children and adolescents with ADPKD.

Follow-up assessment in children with ADPKD. Monitoring of kidney disease progression in children with ADPKD should be tailored based on clinical indications, BP, kidney function, urine studies, and ultrasound findings. Routine screening for extrarenal manifestations is not advised, but screening should be performed when concerning symptoms are present. UTI in children with ADPKD should be managed the same as UTI in children without ADPKD. Ultrasound examination should be performed with atypical courses of UTIs, to rule out cyst infection. Abdominal pain, nephrolithiasis, and proteinuria in children with ADPKD should be managed the same as those in children without ADPKD. Vasopressin analogues should not be used to treat nocturnal enuresis in children with or at risk of ADPKD.

Diet and lifestyle in children with ADPKD. Children with ADPKD should follow general recommendations for a healthy diet, consistent with World Health Organization guidelines, and should maintain a healthy body weight and levels of physical activity. Children with ADPKD and hypertension or CKD should follow the same recommendations for diets and physical activities as those for all children with hypertension or CKD.

Optimal models of care for children with ADPKD. Currently, the evidence is insufficient to support use of disease-modifying therapies for ADPKD in children, beyond antihypertensive treatment.[30] A formal transition process for entering young adulthood should be developed for all children diagnosed with or at risk for ADPKD.

Chapter 10: Approaches to the management of people with ADPKD

Shared decision-making should be the cornerstone of patient-centered management in people with ADPKD. The lifelong management of people with ADPKD should follow a comprehensive, multidisciplinary, and holistic care pathway (Figure 10).[31,32]

People with ADPKD should be encouraged and enabled to participate in registries, cohort studies, and clinical trials testing novel diagnostic or therapeutic approaches (including novel agents, repurposed drugs, or combinations of agents). Healthcare systems should provide care coordination and/or patient navigation for people with ADPKD along their care pathways. Healthcare systems should implement a self-management program for people with ADPKD, taking into consideration the local and cultural context, and the

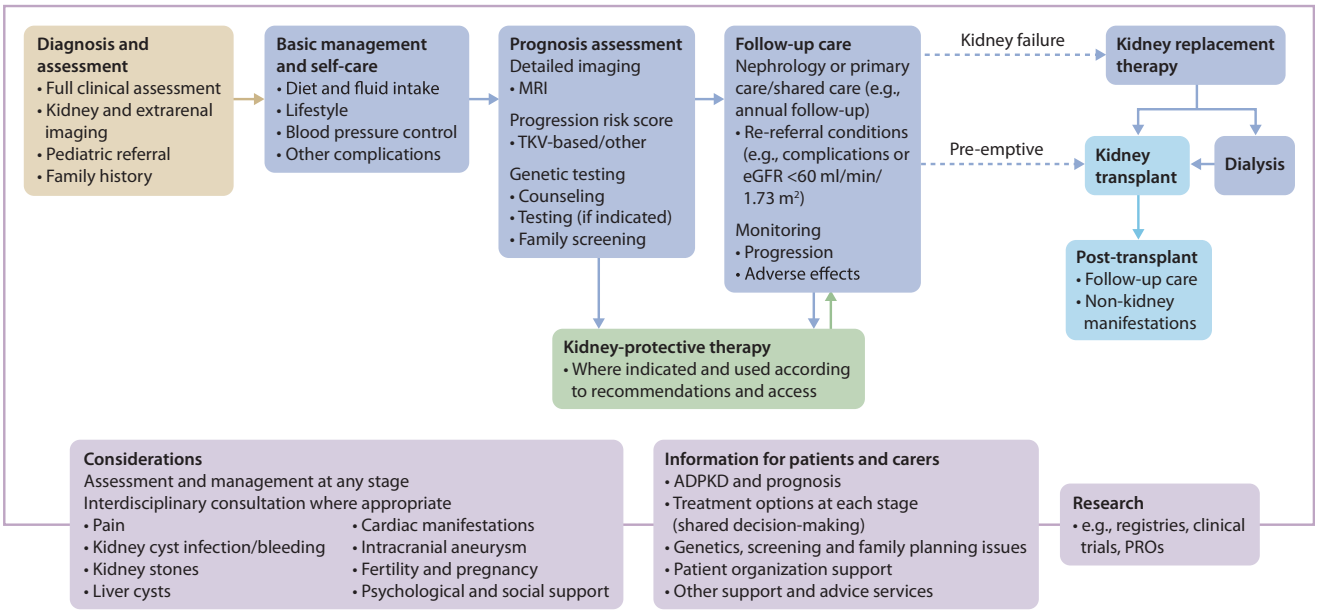


Figure 10 | A proposed autosomal dominant polycystic kidney disease (ADPKD) care pathway. Ultrasound-based kidney imaging, including kidney length measurements, could be considered if MRI or computed tomography are not routinely available. eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; PRO, patient-reported outcome; TKV, total kidney volume. Adapted from EAF Co-chairs *et al.*[31]; Mao *et al.*[32]; Ong *et al.*[33]

availability of resources. Healthcare systems should promote participation in registries for people with ADPKD, so that outcome data using standardized data definitions can be gathered. ADPKD-focused patient organizations, national kidney federations, and patient-support groups can help enhance the care of people with ADPKD and their families, through provision of general information and peer support (Supplementary Table S3).

Conclusions

The *KDIGO 2025 Clinical Practice Guideline for the Evaluation, Management, and Treatment of ADPKD* represents the first KDIGO guideline that focuses on a genetic disorder that affects millions of people worldwide and is a major cause of KF. Recent developments impacting all aspects of ADPKD, and the emergence of local guidelines and recommendations, justified the need for a global guidance document. The comprehensive KDIGO guideline, developed with clinicians, researchers, and patients from around the world, points to important aspects of living with ADPKD, for people at all ages, relating to diagnosis, definition, staging, management, and treatment, and taking into account the availability of resources. Specific aspects linked to the dominant mode of transmission of ADPKD are addressed. Our systematic review identified gaps in the knowledge base, and remaining controversies, which are integrated into a comprehensive research agenda. Together, these recommendations and practice points offer a strong basis to implement new approaches and therapies for people living with ADPKD and their families, following a comprehensive, multidisciplinary, and holistic care pathway.

DISCLOSURE

The development and publication of this guideline were supported by Kidney Disease: Improving Global Outcomes (KDIGO). The opinions or views expressed in this summary are those of the authors and do not necessarily reflect the opinions or recommendations of the International Society of Nephrology or Elsevier. Dosages, indications, and methods of use for products that are referred to in the supplement by the authors may reflect their clinical experience or may be derived from the professional literature or other clinical sources. Because of the differences between *in vitro* and *in vivo* systems and between laboratory animal models and clinical data in humans, *in vitro* and animal data do not necessarily correlate with clinical results.

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ADDITIONAL INFORMATION

Only key references, including major reviews, guidelines, and those supporting the figures, have been included. Please refer to the full guideline for detailed references.

Supplementary material is available online at www.kidney-international.org.

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