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Autosomal Dominant Polycystic Kidney Disease

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Summary

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of chronic kidney disease resulting in significant morbidity and mortality globally. Advances in molecular genetics and deep-phenotype imaging techniques have refined existing diagnostic and prognostic tools. The strong evidence-base for tolvaptan as a disease-modifying treatment supports its early use in high-risk groups. Screening and management of potentially serious complications including cyst infection, intracranial aneurysms and polycystic liver disease are important components of a comprehensive care plan. This review focuses on current approaches to diagnosis, risk assessment, treatment and specific aspects of clinical management in ADPKD. An updated understanding of the genetic basis of disease, pathobiology with respect to potential therapeutic targets and promising therapies now in clinical trials are summarised. We propose a holistic patient-centered care pathway that emphasizes shared decision-making with a multidisciplinary clinical team to address the varying needs of individual patients throughout their life-long journey.

Word count: 150/150

Literature Search Strategy

We searched PubMed for English language articles published between September 16, 2018 and April 24, 2025 with the following terms: “adpkd” OR “autosomal dominant polycystic kidney” OR “polycystic kidney disease” and cross-referenced them with the following terms: “definition”, “genetics”, “diagnosis”, “prognosis”, “management”, “therapy”, and “clinical trials”. All types of studies, including randomized control trials (RCTs), cohort studies, case-control studies, cross-sectional studies, case reports, systematic reviews, and meta-analyses were considered, but priority was given to studies with high-quality evidence, especially RCTs, systematic reviews, and large observational studies. We also included older publications based on experience and more recent publications based on reviewer feedback.

Glossary:

Protein-truncating (PT) mutations: A specific class of mutation including stop-codon, frameshift and canonical splice-site mutation which is predicted to result in a truncated and putatively inactivated protein missing its 3' tail-end.

Non-truncating (NT) mutations: This class of mutation includes missense mutation (which only change a single amino acid in the protein) and inframe indel (see below). They are thought to have a less deleterious effect on the mutant protein than a PT mutation.

Inframe indels: A specific class of mutation involving insertion or deletion of a multiple of 3 nucleotides of the coding sequence, resulting in addition or deletion of multiple amino acids in the protein without affecting its 3' tail end structure.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic cause of chronic kidney disease (CKD) worldwide imposing a heavy economic burden on healthcare systems.[1,2] The prevalence of ADPKD has been estimated to be ~1 in 1,000 based on *PKD1* and *PKD2* protein-truncating (PT) mutations by population whole exome/genome sequencing and ~4 in 10,000 based on surveys of national clinical registries within the European Union and United States.[3-5] This difference in prevalence estimates indicates that ADPKD is underdiagnosed. The increase in number and size of cysts with age result in a quasi-exponential expansion of total kidney volume (TKV) during adult life,[6] eventually leading to CKD stage 5 (CKD5) in approximately half of all patients by 60 years of age.[7] Although only a handful of cysts may be detectable during the teenage years, bilateral kidney enlargement together with innumerable cysts of different sizes can be detected by ultrasound in most patients by their third to fourth decade of life. Typically, the diagnosis of ADPKD is established during asymptomatic screening in the presence of a positive family history, investigation of abdominal or flank pain, hematuria, or kidney stones, or upon incidental findings by abdominal imaging.[8] Hypertension is highly prevalent in most patients with CKD stage 3 or beyond and may occur in young adults.[7-10] Disease progression is commonly associated with hematuria, urinary tract infections, kidney stones, and kidney failure. Non-kidney manifestations such as liver and pancreatic cysts, seminal megavesicles, bronchiectasis, intracranial aneurysms, abdominal hernias, diverticulosis and cardiovascular abnormalities, may occur variably.[11-19] In this *Seminar,* we present our approach to management of ADPKD with respect to diagnosis, risk assessment, and treatment, and whenever possible, highlight key concepts from the Kidney Disease: Improving Global Outcomes (KDIGO)

2025 Clinical Practice Guideline for ADPKD.[11] We also review pathobiology relevant to therapeutics and discuss promising novel therapeutics currently in clinical trials.

Genetics

Most patients with ADPKD display a dominant inheritance in their family tree; however, ~15% will have a negative family history due to "de novo" disease, and another 10%, an indeterminate family history due to missing parental records or unrecognized mild disease in an affected parent.[20] Mutations of two major genes (i.e. *PKD1* and *PKD2*) and several minor genes (i.e. *GANAB*, *ALG5*, *ALG8*, *ALG9*, *IFT140*, *DNAJB11*) account for the majority of genetically resolved adult patients with ADPKD, with *PKD1* mutations being the most common.[11, 21-32] Polycystin-1 (PC1) and -2 (PC2), localized to the primary cilia and other non-cilia cellular compartments, are proteins encoded by *PKD1* (on chromosome 16) and *PKD2* (on chromosome 4), respectively.[33,34] More than 2,500 different *PKD1* and *PKD2* mutations have been reported to date (www.pkdb.mayo.edu). This high level of genetic heterogeneity requires comprehensive screening of both genes which has been facilitated by recent advances in next-generation sequencing (NGS).[33,34] In genetically enriched cohorts, ~75% of cases are caused by *PKD1* mutations and ~15%, by *PKD2* mutations.[22,23] On average, patients with *PKD1* PT mutations develop a more aggressive phenotype, with larger TKV and earlier progression to CKD5 than those with *PKD1* non-truncating (NT) or *PKD2* mutations.[7, 22-24] For example, a large cohort study from Toronto reported mean ages of onset of CKD5 for *PKD1* PT, *PKD1* inframe indel, *PKD1* missense, and *PKD2* mutations of 53 (95% CI: 51-54), 59 (95% CI: 55-62), 71 (95% CI: 68-74), and 80 (95% CI: 77-83) years, respectively.[24] However, significant intra-familial kidney disease variability is well documented suggesting a strong modifier effect from other genetic and environmental factors.[35,36] Specifically, a deleterious genetic modifier effect is supported by the finding of more

severe disease in a few patients with digenic mutations (i.e. two mutations in each copy of *PKD1* or in one copy of *PKD1* and *PKD2*) compared to their affected relatives carrying a single mutation, including some very early onset (VEO) cases presenting at birth or in early childhood. [20,25, 37-41] In contrast, a protective modifier effect has been suggested by the finding of very mild to mild disease among affected relatives in 18% of families with *PKD1* PT mutations.[42] Thus, *PKD1* and *PKD2* mutation class alone cannot be used for prognostication with high certainty at the level of the individual patient.[34]

Up to 15% of patients with ADPKD have no *PKD1* and *PKD2* mutations detected [24] and many display an atypical kidney imaging pattern associated with good preservation of kidney function and a low risk for advanced kidney failure.[43] A significant proportion of these may have other genetic causes which can be clarified by genetic testing.[33,34] Specifically, mutations in genes known to cause autosomal dominant polycystic liver disease (ADPLD) including *ALG5*, *ALG8*, *ALG9*, *SEC61B*, *SEC63*, *GANAB* and *PRKCSH*, phenocopy mild ADPKD with few to multiple kidney cysts but mild to severe PLD.[11,26-30] Mutations of the ADPLD genes and other minor ADPKD genes [8,30-32] could potentially account for some cases of PKD with no mutations detected when only *PKD1* and *PKD2* are screened. Additionally, somatic mosaicism has been documented in some patients with a negative family, atypical PKD by imaging, and a negative mutation screen.[44,45]

The KDIGO guideline[11] proposes a nomenclature for reporting mutations in clinically diagnosed ADPKD or ADPLD: specifically, for genetically screened patients, ADPKD will be employed as the disease name followed by a major (*PKD1* or *PKD2*) or minor ADPKD gene locus. Similarly, ADPLD will be employed as the disease name followed by a major (*PRKCSH* or *SEC63*) or a minor ADPLD gene locus.[11] For genetically unscreened or screened negative patients, ADPKD or

ADPLD without any gene name will be used for reporting, depending on their clinical phenotype. A list of the major and minor ADPKD genes and their clinical correlates are shown in **Table 1**. This proposal is expected to facilitate more accurate diagnosis and improve genotype-phenotype correlations. However, it also has the potential for harm (i.e. discrimination and refusal of life insurance coverage in some countries) among patients with minor gene mutations. Thus, patients and their families, healthcare providers, insurance companies, and others dealing with the welfare of individuals with ADPKD need to be educated that unlike ADPKD associated with the major genes, patients with ADPKD associated with minor cystic disease genes generally have a benign clinical course and low risk for CKD5.[11]

Pathobiology and Disease Mechanisms

ADPKD is primarily caused by mutations of *PKD1* and *PKD2*, resulting in dysfunction of the PC1-PC2 complex, triggering aberrant regulation of cellular signaling pathways that lead to cyst formation and enlargement.[46] During disease progression, increased cystic volume exerts pressure on surrounding normal kidney tissue, leading to tissue damage from tubular obstruction and decreased blood flow, and eventually kidney failure.[47] A notable feature of ADPKD is focal cyst development along any nephron segment with increasing age.[47,48] Genetic studies of human cystic epithelia and orthologous knock-out mice support a "two-hit" model of cystogenesis in which cyst formation is triggered by the complete loss of PC1 or PC2 within a tubular epithelial cell due to a germline and a somatic mutation of *PKD1* or *PKD2*, respectively.[49-54] However, more recent studies including patients with digenic *PKD1* or *PKD1* and *PKD2* mutations[20,25,37-41] and *Pkd1* knock-out mice with an incomplete mRNA splicing defect[55] suggest that a "threshold model" of

cystogenesis may better explain the cyst initiation process. (i.e. lowering of the normal cellular PC level to ~20% may trigger cyst formation).[46,56,57]

Reduced PC1 and PC2 levels activate calmodulin-dependent adenylate cyclase by lowering intracellular calcium levels, which increases cAMP, activates protein kinase A and stimulates multiple cellular pathways that mediate cyst fluid secretion and cell proliferation.[46,56] Targeted treatment with a vasopressin V2 receptor antagonist reduced intracellular cAMP and slowed experimental PKD, providing the rationale for subsequent clinical trials that led to the approval of tolvaptan for clinical treatment in ADPKD.[58-61] Multiple other dysregulated signaling pathways including AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), extracellular-signal-regulated kinase (ERK), insulin growth factor (IGF), and Wnt/β-catenin have been shown in preclinical studies to modulate cyst growth through biological processes such as cystic fluid secretion, cellular proliferation and inflammatory responses (**Figure 1**).[46,62] Two current areas of focus for therapeutic development are to target the cilia-dependent cyst activation pathway (**Figure S1A**)[63-66] and metabolic reprogramming (**Figure S1B**).[67-74] Additionally, in a study of mouse models of established ADPKD, regression of cystic disease can be initiated when *Pkd1* or *Pkd2* are re-expressed.[75] Thus, future "precision medicine" approaches that correct the disease allele or protein directly such as by gene editing, gene replacement or corrector molecules could potentially lead to disease regression or stabilization (**Figure 1**). An alternative approach being currently explored is to increase expression of the normal or missense mutant allele (by miR-17 antisense oligonucleotides).[76,77] **Table 2** shows selected recent and ongoing clinical trials of novel therapies in ADPKD.[78]

Diagnosis

The diagnosis of ADPKD relies primarily on clinical phenotype, family history, kidney imaging, and genetic testing. Most patients with ADPKD associated with the two major genes (i.e. *PKD1* or *PKD2)* will typically display bilateral and relatively symmetrical cyst distribution and enlarged cystic kidneys by imaging studies after the second to third decade of life. In new patients or at-risk subjects with a positive family history of ADPKD, kidney ultrasound is the preferred method for initial screening. Among at-risk subjects with a positive family history of ADPKD associated with a major gene, their pre-test probability at birth is 50% and age-specific ultrasound criteria based on kidney cyst number have been established for both diagnosis and disease exclusion (**Table 3**).[79] However, in the absence of a positive family history, the above diagnostic criteria are not valid since the pre-test probability of ADPKD (i.e. at population risk of ~1/1,000) is much lower.[3] Although ultrasound is a useful initial screening test, it has limited capacity for detecting smaller cysts (i.e. <5-7 mm) and does not provide early detection or exclusion of disease. For younger at-risk subjects, magnetic resonance imaging (MRI), with increased sensitivity in detecting cysts >2-3 mm, will enable earlier diagnosis and exclusion of ADPKD associated with the major genes. Specifically, for at-risk subjects aged 16–40 with a positive family history of ADPKD, the presence of >10 cysts in both kidneys is sufficient for diagnosis. while <5 cysts in both kidneys at age >20 years is suggested for disease exclusion. [11,80] For patients with a positive family history and typical kidney imaging pattern, the diagnosis of ADPKD is usually sufficient by ultrasound or MRI using age-dependent criteria. In the absence of a positive family history or typical kidney imaging pattern of ADPKD, the differential diagnosis needs to be broadened to include ADPLD and ADPKD-like phenotype from the minor cystic genes,[11,25-32] autosomal dominant tubulointerstitial kidney disease (ADTKD),[81] recessive forms of PKD,[82] syndromic forms of PKD (e.g. tuberous sclerosis complex, Von Hippel-Lindau disease, and Oro-facial-digital syndrome),

and acquired disorders such as acquired and lithium-associated cystic kidney disease.[83] Age of clinical presentation, kidney imaging patterns and distinct extra-renal features may help to distinguish these phenocopies.[11] Additionally, in patients who present without a family history of ADPKD and an atypical imaging pattern (Mayo Imaging Class 2A) with no *PKD1* and *PKD2* mutation detected, somatic mosaicism should be considered.[44,45]

Genetic testing may be informative for patients suspected to have ADPKD without an apparent family history, and in patients with atypical or equivocal kidney imaging findings, marked variability of cystic disease severity among affected relatives including very-early onset (VEO) disease and syndromic forms of PKD.[84,85] Additionally, genetic testing may also be useful for disease exclusion in younger at-risk subjects being evaluated as a living-related kidney donor, and for selection of unaffected embryo(s) in assisted reproduction to eliminate germline disease transmission.[84] Since mutations of multiple cystic genes may mimic ADPKD, a targeted NGS panel or other clinically accredited genetic or genomic test should be used for genetic testing. Standard sequencing techniques face the challenge of distinguishing the 6 pseudogenes that share 97% sequence similarity with *PKD1*.[86] However, with more specific exome capture probes and advanced bioinformatics, false positive or negative results are generally rare in our experience. Clinical genetic testing should be coupled with genetic counselling. Assignment of pathogenicity in many missense variants may be uncertain and should be classified in accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines.[87] In a patient with typical clinical presentation of ADPKD, negative or uncertain genetic test results do not exclude an inherited form of PKD. **Figure 2** provides a diagnostic algorithm for work up of subjects with kidney cysts suspected to have ADPKD that integrates the use of imaging and mutation-based testing.

Risk Assessment

Clinical risk factors including male sex, early onset hypertension, gross hematuria, kidney stones, overt proteinuria, and *PKD1* PT mutations have been associated with more severe ADPKD.[88] High salt intake, smoking, high blood pressure and possibly high protein intake are other modifiable risk factors.[89,90] More recently, high body mass index (BMI ≥ 25 kg/m^2) have also been shown to be associated with increased TKV growth but inconsistently with eGFR decline or progression to CKD5.[91-94] In clinical practice, three approaches have been used to identify high-risk patients with rapidly progressive disease for possible disease-modifier treatment (**Figure S2**).

Mayo Imaging Classification (MIC):

TKV as measured by MRI increases quasi-exponentially in adult life at ~5%/year on average and is a validated prognostic biomarker for ADPKD.[6,95,96] Adjusted for age, MIC divides patients with a typical imaging pattern (i.e. bilateral kidney enlargement with symmetrical cyst distribution) into five subclasses (1A-1E), based on their annual growth rate of height-adjusted TKV(<1.5%, 1.5%-3.0%, 3.0%-4.5%, 4.5%-6.0%, and >6.0%).[97] Patients with class 1A and 1B experience slow decline in eGFR and are defined as slowly progressing when conservative measures are deemed adequate for management. Patients with class 1C, 1D or 1E experience rapid decline in eGFR and are defined as rapidly progressing when treatment with tolvaptan should be considered. However, transition between adjacent MICs may occur in ~16% of patients and some patients with class 1C near the border zone with 1B may not have rapid disease progression.[97] Inspection of the kidney imaging pattern is mandatory as the prognostic prediction by MIC is not valid in patients with atypical imaging (class 2) patterns.[97] As noted earlier, some patients with MIC 2A (i.e. unilateral,

segmental, asymmetric, or lopsided PKD) may have somatic mosaicism or mutations in the minor ADPKD genes, all generally carry a favorable prognosis.[44,45] Additionally, MIC should not be used in patients with mutations on genes other than *PKD1* or *PKD2*.[11]

Although manual segmentation is the "gold standard" for TKV measurement, it is tedious requiring intensive use of a radiologist's time. Thus, an ellipsoid method, which requires only measurements of three orthogonal kidney axes, is commonly used in clinical practice.[98] Several research teams have recently developed AI-assisted algorithms for TKV measurements by semi- or fully automated segmentations,[99-102] for differentiation of MIC class 1 and 2 patterns,[103] and for second generation kidney volumetric to improve risk prediction beyond TKV.[103-106] However, these approaches need to be validated before they can be used clinically.

When MRI or computed tomography (CT) is unavailable or contraindicated, TKV can be measured by ultrasound using the ellipsoid method. Compared to MRI, ultrasound systematically underestimates TKV by –11%; thus, it provides high accuracy (92%) when classifying MIC 1C-1E, but not 1A and 1B.[98] Additionally, an average kidney length >16.5 cm in patients ≤45 years has been proposed as a cut-off for identifying high-risk patients.[104] Both of these methods are less accurate that MIC; they also require exclusion of the atypical imaging patterns which may be more difficult on ultrasound than MRI.[107]

***Predicting Renal Outcomes in Polycystic Kidney Disease (PROPKD) Score*:**

The presence of a modifier effect in ADPKD makes the use of mutation-based prognostication unreliable at the level of the individual patient.[35-42] By combining mutation class (i.e. *PKD1* PT vs. *PKD1* non-truncating vs. *PKD2* mutations) with clinical risk factors including sex (i.e. male vs. female) and the presence or absence of hypertension or urological events (i.e. gross hematuria, flank pain from large cystic burden, or cyst infection) before 35 years of age, the PROPKD score

may improve risk stratification relative to mutation class alone.[108] A PROPKD score ≤3 indicates low risk, while >6 indicates high risk for ESKD before age 60. This approach requires accurate patient recall of the timing of previous clinical events and may not be helpful for patients <35 years old.

European Renal Association (ERA) Risk Assessment Algorithm:

Annual eGFR decline in patients with ADPKD can range from 0.63 to 4.65 mL/min/1.73m^2. The ERA risk assessment algorithm advocates the use of an upper age limit (i.e. ≤55 years) and rate of eGFR decline (i.e. ≥ 3.0 ml/min/1.73 m^2 over a period of at least 4 years) for identifying high-risk patients for disease-modifier treatment.[109] This approach is simple and inexpensive, but requires the availability of serial serum creatinine measurements for at least 4 years and standardized creatinine measurements if different laboratories are used. Rapid eGFR decline in some patients may be confounded by the presence of a second kidney disease (e.g. renovascular disease, metabolic syndrome) which may not be easily recognized in the absence of kidney imaging (i.e. to identify mild cystic disease as a discordant phenotype).[110] When the eGFR slope is unavailable or unreliable (i.e. CKD1), the ERA algorithm recommends using the MIC or PROPKD for risk assessment.

Management of ADPKD

General Measures

All patients should be educated regarding conservative measures including hydration, diet, blood pressure and weight control (**Figure 3**). High water intake has a theoretical benefit of suppressing arginine vasopressin release to reduce kidney cyst growth, but the evidence supporting this practice is inconclusive. A randomized controlled trial of 184 adults with ADPKD showed that water intake

of ~3 L/day to maintain a urine osmolality of 270 mOsmol/kg vs. ad lib intake of ~2.2 L/day did not slow TKV growth over 3 years.[111] However, this study was limited by a relatively small sample size and a high rate (52.3%) of patients in the prescribed water intake group unable to achieve the physiological measures of treatment adherence based on urinary osmolality. The KDIGO guideline currently recommends daily water intake of 2-3 L in patients with an eGFR ≥ 30 mL/min/1.73m^2 to reduce their risk of kidney stones.[11] Patients should also limit their salt intake to ≤ 5 g of sodium chloride or ~90 mmol of sodium per day as high salt intake is associated with more rapid eGFR decline and suboptimal blood pressure control in ADPKD.[112,113]

The use of renin-angiotensin-system inhibitors (RASi) as the first-line antihypertensive in ADPKD is supported by their kidney-protective, cardio-protective effect and overall safety profile.[11] The KDIGO ADPKD guideline recommends intensive blood pressure control ≤110/75 mmHg using RASi for patients younger than 50 years with eGFR >60 ml/min.[11] This recommendation is based on the HALT-PKD RCT of 558 patients (aged 18-49 years with CKD G1-G2) showing that a lower BP target (95/60 to 110/75 mm Hg) using home BP monitoring was associated with a smaller increase in TKV (5.6% vs. 6.6%; p=0.006), decrease in urinary albumin (3.8% vs. 2.4%; p<0.001), but more frequent lightheadedness (81% vs. 69%; p=0.02) compared to a higher BP target (120/70 to 130/80 mm Hg).[114]

Post hoc analysis of HALT-PKD trials showed that only patients with severe disease (MIC 1D, 1E) randomized to rigorous BP control had slower TKV increase, and slower decline in eGFR after 4 months of treatment compared to standard BP group, raising the question whether other patients (MIC 1A-1C) should also have such a strict BP target.[115] For patients 50 years or older or with an eGFR <60 ml/min, a systolic BP target <120 mm Hg by standardized office BP measurements is recommended based on the 2021 KDIGO CKD guideline.[116] Dual RASi and

angiotensin receptor blockade should be avoided due to a lack of additional benefit compared to monotherapy and potentially increased side-effects. [114,117] While striving for optimal control, all BP treatment should avoid symptoms of orthostatic hypotension.[11]

Overweight and obesity should be avoided in ADPKD given their association with higher risk of progression. Assessment of these conditions using body mass index (BMI) needs to be adjusted for the cystic kidney and liver weights which can be approximated from MRI.[11] Although multiple interventions such as ketogenic diet, metformin, sodium-glucose cotransporter-2 inhibitors, and glucagon-like peptide-1 receptor agonists have been used to treat diabetes, obesity and metabolic syndrome, their efficacy for slowing progression in ADPKD is currently unknown. Therefore, these interventions should not be used for this purpose until results from adequately powered and long-term clinical trials become available (Table 2). [11,78] Finally, systematic screening for extrarenal manifestations such as liver cysts, intracranial aneurysms, cardiac valve abnormalities, among others, as well as routine psychological assessment is also key for the comprehensive management of ADPKD.[11]

Kidney Replacement Therapy (KRT)

Kidney replacement therapy KRT is the primary treatment for CKD5 and includes hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation.[118] Despite concerns about limited abdominal space and increased pressure due to enlarged kidneys in ADPKD, the mortality rate is similar between both dialysis techniques, with overall low certainty of evidence. ADPKD patients using PD generally face fewer complications.[119,120] An individualized approach with careful attention for potential risks such as hernia and leakage is recommended. Kidney transplantation is generally preferred for quality of life, especially since ADPKD patients have better mean long-

term post-transplant survival rates compared to other ESRD causes.[11] After transplantation, native kidneys may diminish in size, hence, reducing "mass effect" symptoms.[121] Native nephrectomy in patients with ADPKD receiving kidney transplantation should only be performed after shared-decision making with multidisciplinary consultation, preferably during or after transplantation. Potential indications of nephrectomy include severe "mass effect" symptoms, recurrent kidney infection or bleeding, complicated kidney stones, intractable pain, suspicion of renal cell carcinoma, and insufficient space for the kidney allograft.[118] Whenever possible, laparoscopic surgery is preferred to open surgery, and the decision between unilateral or bilateral nephrectomy should be made based on individual clinical circumstances.[11,122]

Disease Modifyng Treatment

Two large RCTs have shown that tolvaptan reduced kidney growth by 45% and eGFR decline by 26% in patients with early to mid-stages of ADPKD over a 3-year period (TEMPO 3:4)[60] and eGFR decline of 35% in patients with later disease stages over 1 year (REPRISE).[61] Collectively, these data have led to the regulatory approval of tolvaptan for treatment of ADPKD in many countries.[11] Tolvaptan is indicated for the treatment of ADPKD patients who are deemed to be at high-risk for progression to CKD5 generally by MIC, PROPKD score or ERA eGFR slope algorithms (**Figure S2**). Extrapolations of the results of TEMPO 3:4 and REPRISE have given estimates that tolvaptan could delay progression to CKD5 by 7.3, 4.4, 2.9, and 1.5 years if pre-treatment eGFR was 90, 60, 45, and 30 ml/min, respectively.[11] The KDIGO ADPKD guideline recommends the MIC as the preferred tool to identify "high-risk" patients for tolvaptan therapy. Non-contrast CT for TKV measurement may be used for patients in whom MRI is contraindicated (e.g. claustrophobia, non-removable metal part in body). Initiation of tolvaptan is a joint decision with the patient after discussion of its potential risks and benefits. Tolvaptan should be initiated

with a daily dose of 45 mg upon waking and 15 mg 8 hours later, titrated gradually to a maximum dose of 90 + 30 mg, according to individual tolerance. Regular monitoring should include kidney function, serum sodium, uric acid, and liver function tests (LFTs). Patients should be educated to stop the drug during any acute illness associated with fluid loss or reduced fluid intake. Common side-effects of tolvaptan include thirst, polyuria, nocturia, and LFT elevation.[123] Real life experience with tolvaptan usage in ADPKD indicates that polyuria up to 6-9 L/day may limit long-term treatment adherence in some patients..[124-127] Tolvaptan-induced polyuria is influenced by urinary osmolar load; thiazide diuretics can reduce urine volume by lowering osmolality and improve tolerance.[128,129] However, more studies are needed to evaluate the long-term effects of thiazide diuretics on GFR decline and overall kidney protection. Idiosyncratic drug-induced liver injury can occur with tolvaptan in up to 5% of patients; therefore, monthly liver monitoring during the first 18 months, followed by quarterly assessments, is necessary to detect LFT changes early.[130,131] Other side-effects of tolvaptan include hyperuricemia and rarely gout.[11]

Management of Other Selected Complications

Patients may experience various complications during their lifetime, among which kidney and liver cyst infections, pain, intracranial aneurysms (ICAs), and polycystic liver disease are potentially the most clinically important.

Kidney and liver cyst infections

Cyst infection is a common complication that can lead to acute pain and sepsis in ADPKD. Patients diagnosed with suspected kidney or liver cyst infection should be promptly investigated based on history, clinical and laboratory investigations including abdominal imaging (**Figure S3**).[132] Suspected or confirmed kidney or liver cyst infection should be treated with a lipid-soluble

antibiotic (i.e. fluoroquinolone, trimethoprim-sulfamethoxazole) which has better cystic penetration and for 4-6 weeks to ensure a high treatment success rate. If fever persists for more than 48-72 hours, imaging tests should be repeated to rule out possible complications (such as a perirenal abscess or urinary obstruction). In difficult cases, ^{111}indium WBC scan or ^{18}FDG PET-CT may be useful for confirming and locating the infection. Infected cysts >5 cm unresponsive to antibiotic treatment could require percutaneous or surgical drainage. In severe cases, surgical intervention, such as nephrectomy may be necessary.[11] Empirical antibiotic treatment should not be prescribed for patient with acute kidney or liver pain without fever, elevated white cell counts and CRP levels. In such cases, other causes such as cyst hemorrhage should be considered.[11]

Pain Management

Pain is a major burden in patients with ADPKD, with acute episodes often triggered by infections, kidney stones, or cyst rupture, and chronic pain originating from kidney or liver capsule distension or pressure on surrounding organs and may be best managed by an interdisciplinary team. Therapeutic strategies should follow a stepwise approach starting with non-pharmacologic measures, followed by oral medications (e.g. non-opioid and opioids) and minimally invasive therapies (e.g. foam sclerotherapy). For refractory cases, more invasive options (e.g celiac plexus block, nephrectomy, and hepatectomy) may be considered. [133,134]

Intracranial Aneurysms (ICA)

The prevalence of ICAs is four times higher in people with a family history of ICA/SAH than those without such a family history; most are small (<5mm), predominantly located in large caliber arteries in the anterior circulation.[135,136] Although the majority of ICA are asymptomatic and may not rupture,[137] ICA rupture can result in significant morbidity and mortality. It is vital to educate patients on the increased ICA risk and modifiable risk factors such as smoking cessation and

stringent blood pressure control (**Figure S4**).[138,139] Patients with ADPKD should be educated to recognize the clinical significance of a "thunderclap headache", characterized by a sudden onset, typically unilateral headache that reaches maximal intensity within seconds to minutes; this unusual headache is typically due to a minor bleed preceding ICA rupture and should alert the patient to seek emergency assessment immediately.[11] Headache in ADPKD patients can also be due to spinal meningeal diverticula or spontaneous spinal cerebrospinal fluid leak resulting in spontaneous intracranial hypotension.[140] Screening by time-of-flight magnetic resonance angiography (MRA) or high-resolution computed tomography angiography (CTA) is recommended in high-risk individuals with a positive personal history of ICA/ SAH or a family history of ICA/SAH/unexplained sudden death who are eligible for treatment and have a reasonable life expectancy.[11,138] Comprehensive discussion of the option of screening, and its advantages and limitations is important to facilitate informed decision-making. Screened positive cases should be referred to the neurosurgical team for assessment and discussion of management options, including observation, coiling, clipping and flow-diverter therapy. Rescreening every 5-10 years should be individualized for those initially screened negative but at high-risk of ICA.[11]

Polycystic liver disease (PLD)

While ~80% of patients with ADPKD will have liver cysts by 40 years of age, only 5-10% develop symptomatic PLD.[141,142] Symptomatic PLD is more common in women, generally associated with a liver volume >1800 mL or 2x normal, and typically presents with "mass effect" symptoms (e.g. bloating, early satiety, acid reflux, abdominal fullness and pain) but not liver failure.[141,142] Massive liver enlargement can severely affect quality of life, body image, physical activities, sexual life, and even nutritional intake. When abdominal MRI or CT is performed for ADPKD, kidney and liver images should be included to assess both kidney and liver cystic burden.[11] Early screening

may identify individuals at increased risk of progressive PLD, particularly young women with multiple liver cysts in whom estrogen exposure should be avoided. Patients with symptomatic PLD[143,144] should be assessed for sarcopenia and malnutrition, and referred to a center of expertise for consultation and management.[11] For symptomatic PLD, treatment with a long-acting somatostatin analogue can reduce liver volume by 2-8% over 6-36 months.[145,146] Somatostatin analogues also slow the total kidney volume growth but have no effect on kidney function decline.[147] Depending on the size and distribution of the liver cysts, different radiological or surgical treatments can be used, including foam sclerotherapy, cyst fenestration, segmental hepatic resection, and liver transplantation (**Figure S5**).[11] For patients with ADPKD, liver transplantation is considered when there is a massively enlarged liver combined with at least one of the following: severe portal hypertension, hepatic decompensation, malnutrition, or severe sarcopenia.[148] For patients with an eGFR below 30 mL/min, a combined kidney and liver transplant is recommended. Treatment options should also take into consideration that liver volume growth tends to plateau after menopause in females.[149,150]

The impact of PLD on female reproductive health is considerable. Hormonal therapies, including oral contraceptives, hormone replacement therapy during menopause, estrogens and gestagens for in vitro fertilization should be used with caution in patients with significant PLD, as higher estrogen exposure has been associated with increased cyst growth. If hormonal agents are used, estrogen-free or low-estrogen preparation are preferred. .In women with enlarged liver considering reproductive options, referral to an expert center for consultation is recommended.[151]

Patient-Centered Care

There is increasing interest in developing multidisciplinary care pathways,[152] identifying future research priorities,[153] and defining clinical trial outcomes[154] for ADPKD that are truly patient-centred through patient-initiated or patient-embedded studies. Clear advantages include addressing major patient priorities, patient perceptions and the most relevant research questions, thus promoting patient engagement in self-management and research.[155,156] Of relevance, the top research priority was to develop treatments to slow or prevent kidney function decline.[153] A second common issue was the importance of kidney pain as a neglected symptom which has a major impact on quality of life.[157] The optimal organization of medical care was identified by a systematic review and ranked as the third highest priority by a patient-initiated research priority setting partnership.[153] **Figure S6** summarizes a patient-centred care pathway model for comprehensive management of ADPKD.

Current Challenges and Future Directions

Recent advances in kidney imaging and NGS-based genetic technologies have provided clinicians with better diagnostic and prognostication tools to improve clinical management. Recognition of milder ADPKD-like phenotypes associated with several minor cystic genes requires minor modification of the established imaging-based diagnostic criteria. While tolvaptan is currently the only approved disease-modifying treatment for patients with rapidly progressive disease, new concepts of disease mechanisms are leading testing of promising new therapies. Looking ahead, a patient-centred model of care together with implementation and refinement of these new clinical tools and continued development of disease mechanism-based therapeutics have the exciting potential to delay or arrest kidney failure, reduce symptom burden and improve quality of life for patients with ADPKD.

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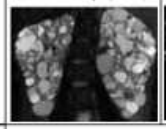
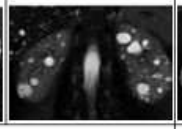
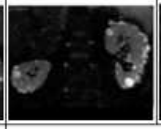
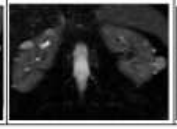
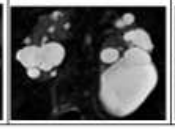
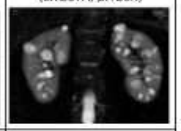
Figure 1. Clinical features of major and minor cystic genes for adult patients with ADPKD

	Major Genes		Minor Genes					
	PKD1	***PKD2***	***ALG5***	***ALG8***	***ALG9***	***GANAB***	***IFT140***	***DNAJB11***
Contribution to all genetic diagnosis	~70-80%	~15-20%	<0.5%	<0.5%	<0.5%	<0.5%	~1-2%	<0.5%
Imaging pattern	Typical ADPKD		Atypical ADPKD					
Imaging case example	37 yo male eGFR: 70 ml/min/1.73m² *PKD1* mutation (c.2113C>T; p.Q705X) 	39 yo male eGFR: 95 ml/min/1.73m² *PKD2* mutation (c.1973delC, p.P658fs) 	57 yo female eGFR: 59 ml/min/1.73m² *ALG5* mutation (c.919C>T; p.Arg307X) 	52 yo female eGFR: 96 ml/min/1.73m² *ALG8* mutation (c.446T>G;p.L149R) 	29 yo male eGFR: 95 ml/min/1.73m² *ALG9* mutation (c.A302G; p.Y101C) 	59 yo male eGFR: 91 ml/min/1.73m² *GANAB* mutation (c.1321delC; p.H441fs) 	58 yo female eGFR: 93 ml/min/1.73m² *IFT140* mutation (c.1432+1G>A) 	39 yo female eGFR: 110 ml/min/1.73m² *DNAJB11* mutation (c.T267A; p.Y89X) 
Kidney phenotype	• Mild to severe bilateral kidney enlargement with numerous to innumerable cysts in a relatively symmetrical distribution • On average, most severe disease associated with *PKD1* PT mutations, followed by *PKD1* IF indels, *PKD1* NT, and *PKD2* mutations		Normal to mild kidney enlargement with a few to numerous cysts and occasionally lopsided distribution pattern				Normal to mild kidney enlargement with a few large, predominantly exophytic cysts	Normal to small kidneys with few to numerous cysts, similar to ADTKD
Kidney prognosis	Mean ages of ESKD onset for *PKD1* PT, *PKD1* IF indel, *PKD1* NT, and *PKD2* mutations were 53, 59, 71, and 80 years, respectively		Some develop ESKD in elderly	Preserved kidney function in elderly	Significant CKD in elderly	Limited CKD No ESKD	Preserved kidney function in elderly	ESKD in ~70s yr
Liver cysts	Most patients have few to numerous liver cysts by age 40 years		Uncommon	Common			Uncommon	
Symptomatic PLD	Less than 5% of patients, mostly female and independent of genotype		Rare, likely due to low prevalence of the cystic disease	Possible in a small percentage of patients	Rare, likely due to low prevalence of the cystic disease		Not well defined, but unlikely	
Risk of ICA	Increased		Unclear					Possibly increased

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ADTKD, autosomal dominant tubulointerstitial kidney disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; ICA, intracranial aneurysm; IF, in-frame; NT, non-truncating; PLD, polycystic liver disease; PT, protein-truncating.

Figure 2

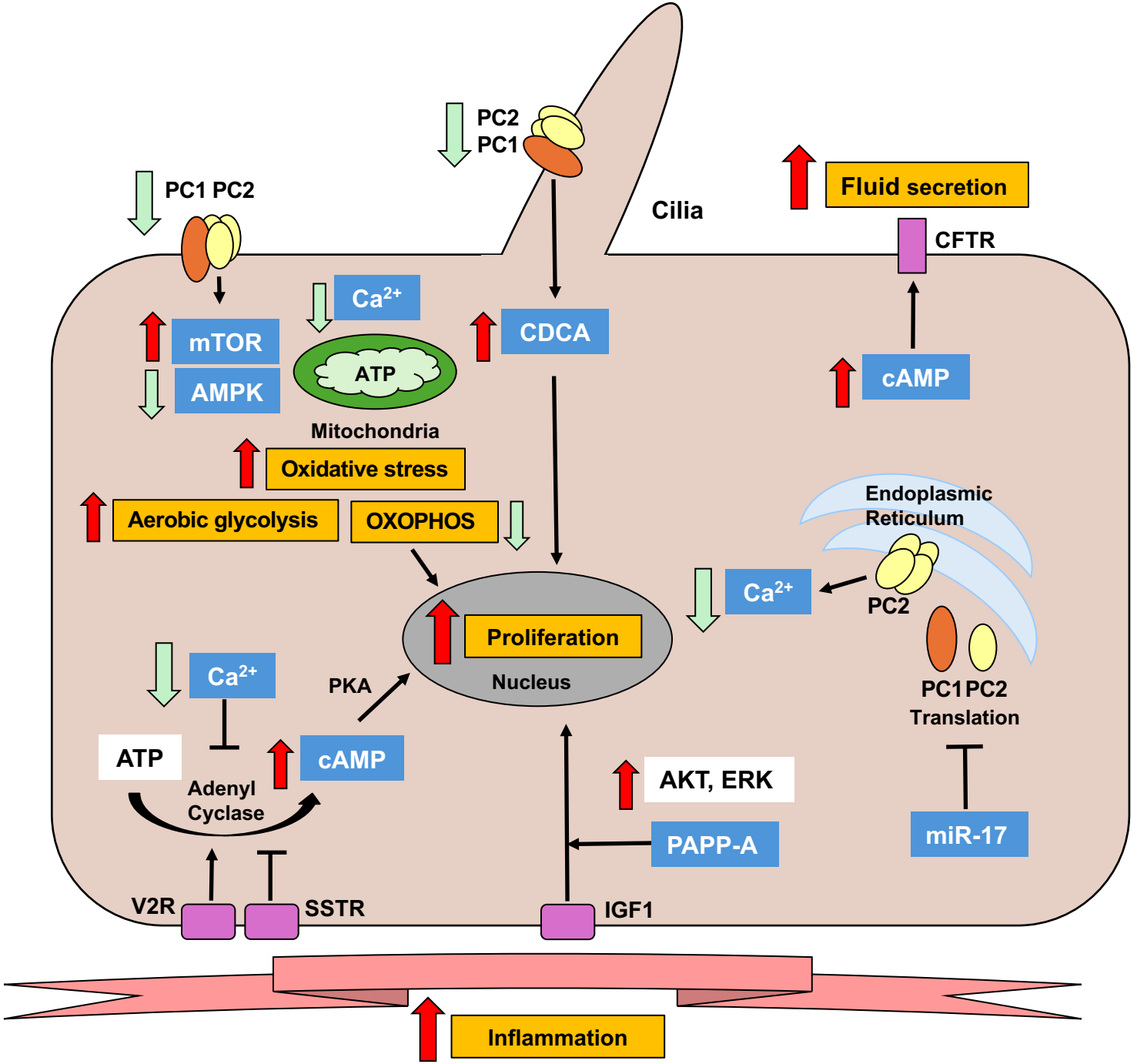

PC2
PC1
PC1 PC2
Cilia
Fluid secretion
CFTR
Ca2+
mTOR
AMPK
ATP
Mitochondria
CDCA
cAMP
Oxidative stress
Aerobic glycolysis
OXOPHOS
Endoplasmic
Reticulum
Ca2+
PC2
Proliferation
Nucleus
PC1 PC2
Translation
Ca2+
PKA
ATP
cAMP
Adenyl
Cyclase
AKT, ERK
PAPP-A
miR-17
V2R
SSTR
IGF1
Inflammation

Figure 3

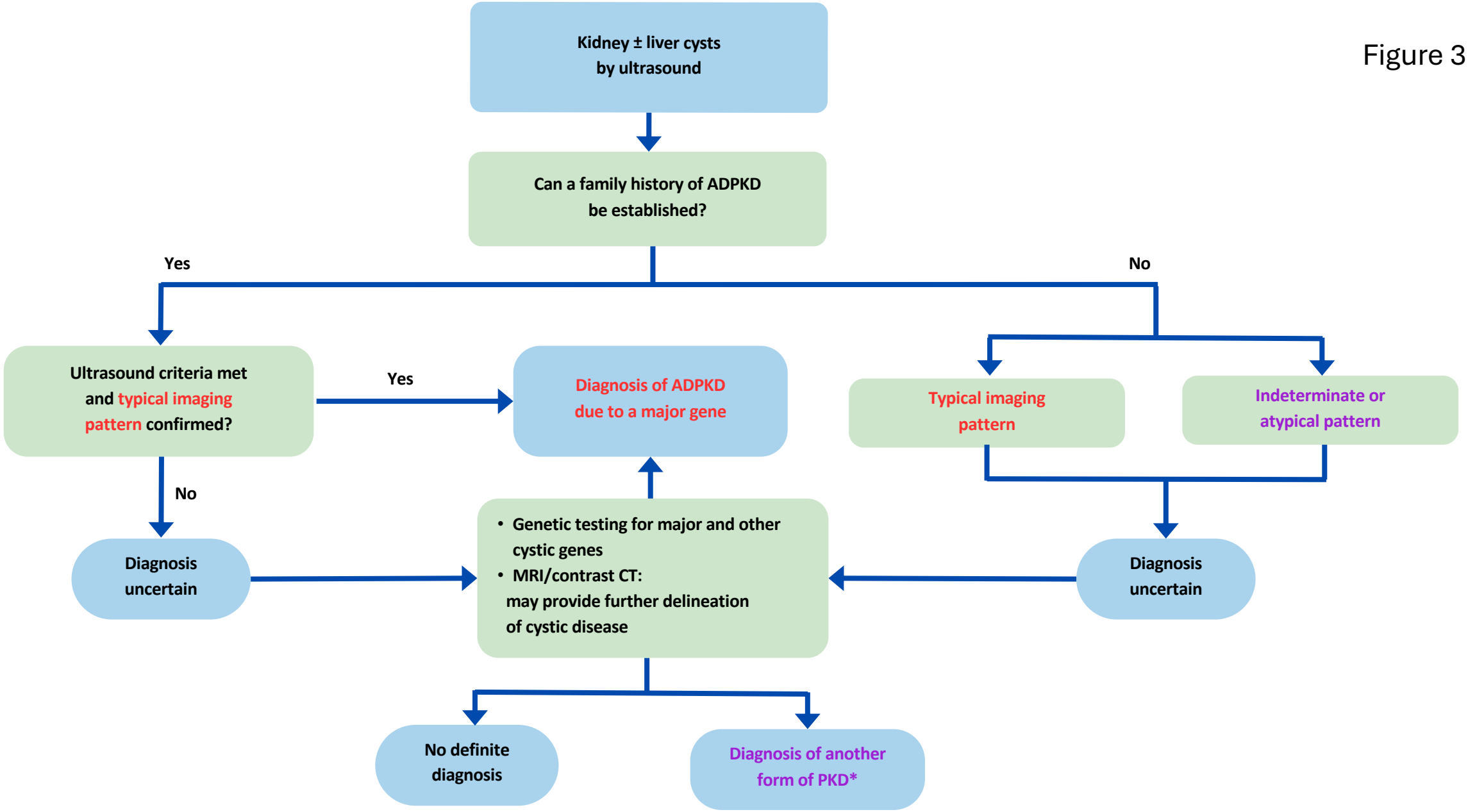

Kidney ± liver cysts by ultrasound
Can a family history of ADPKD be established?
Yes
No
Ultrasound criteria met and typical imaging pattern confirmed?
Yes
Diagnosis of ADPKD due to a major gene
No
Diagnosis uncertain
Typical imaging pattern
Indeterminate or atypical pattern
Diagnosis uncertain
• Genetic testing for major and other cystic genes
• MRI/contrast CT: may provide further delineation of cystic disease
No definite diagnosis
Diagnosis of another form of PKD*

Figure 4

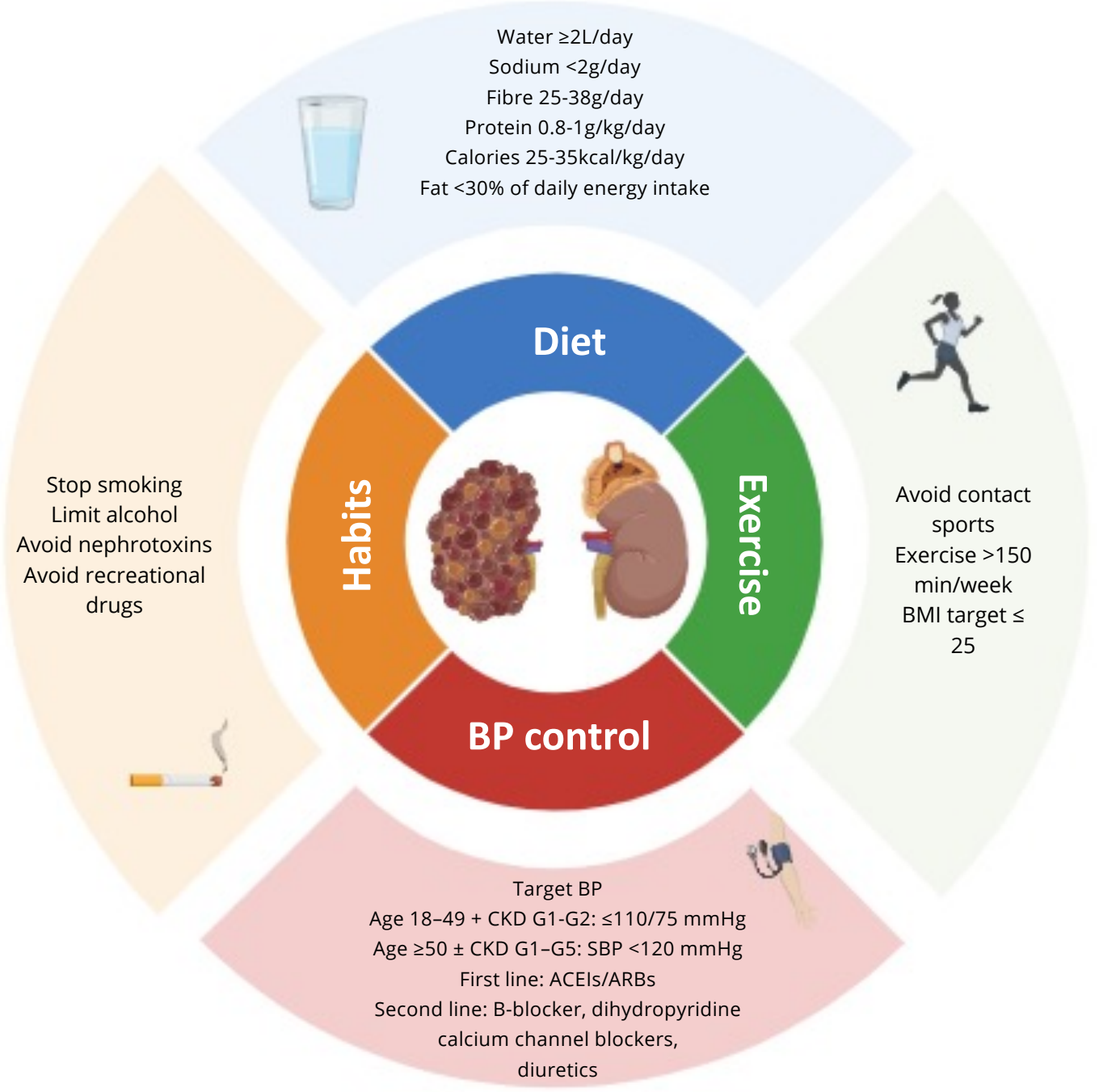

Water ≥2L/day
Sodium <2g/day
Fibre 25-38g/day
Protein 0.8-1g/kg/day
Calories 25-35kcal/kg/day
Fat <30% of daily energy intake
Diet
Exercise
BP control
Habits
Stop smoking
Limit alcohol
Avoid nephrotoxins
Avoid recreational drugs
Avoid contact sports
Exercise >150 min/week
BMI target ≤ 25
Target BP
Age 18–49 + CKD G1-G2: ≤110/75 mmHg
Age ≥50 ± CKD G1–G5: SBP <120 mmHg
First line: ACEIs/ARBs
Second line: B-blocker, dihydropyridine calcium channel blockers, diuretics

Table 1. Recent and current clinical trials of novel therapies for ADPKD*

Treatments	Design	Intervention	Study Outcomes	Duration (months)	Sample size	NCT number
Phase 3						
DAPA-PKD	RCT	Oral SGLT2 inhibitor (Dapagliflozin 10mg) vs. placebo	Safety, tolerability, and efficacy (changes in eGFR slope and TKV)	24	400 (Multi-center)	
Empagliflozin (EMPA-PKD) +/- Tolvaptan	RCT	Oral SGLT2 inhibitor (Empagliflozin 10mg/d) vs. placebo	Safety, tolerability, and efficacy (changes in TKV and eGFR slope). Stratification by Tolvaptan use	18	44 (Single center)	NCT06391450
Metformin XR (IMPEDE-PKD)	RCT	Oral Metformin XR (AMPK activator) vs. placebo at 0.5-2 g/day	Safety, tolerability, and efficacy (changes in eGFR slope and composite outcome)	24	1174 (Multi- center)	NCT04939935
Hydrochlorothiazide (HYDRO-PROTECT) with Tolvaptan	RCT	Oral hydrochlorothiazide vs. placebo at 25 mg/day in patients treated with Tolvaptan	Safety, tolerability, and efficacy (changes in eGFR slope and reduction of 24-hour urine volume)	39	300 (Multi- center)	NCT05373264
Phase 2						
ABBV-CLS-628	RCT	Intravenous monoclonal anti-PAPP-A antibody (inhibition of IGF-1 signaling) vs. placebo every 4 weeks	Safety, tolerability, and efficacy (changes in eGFR slope and TKV)	23	240 (Multi- center)	NCT06902558
AGAINST-PLD	RCT	Subcutaneous leuprorelin (3.75mg once monthly for 3 months followed by 3-monthly injections of 11.25mg) vs. standard of care for 18 months followed by intervention	Safety and efficacy (changes in liver volumes)	36	36 (Multi-center)	NCT05478083
Empagliflozin	RCT	Oral SGLT2 inhibitor (to improve ~~renal~~ kidney hemodynamic and metabolism) vs. placebo at 10 or 25 mg/day	Safety and tolerability; exploratory outcome (changes in TKV)	12	50 (Single center)	NCT05510115

~~Empagliflozin (EMPA-PKD) +/- Tolvaptan~~	~~RCT~~	~~Oral SGLT2 inhibitor (10mg/d vs. placebo)~~	~~Safety, tolerability, and efficacy (changes in TKV and eGFR slope). Stratification by Tolvaptan use~~	~~18~~	~~44 (Single center)~~	~~NCT06391450~~
Dapagliflozin	RCT	Oral SGLT2 inhibitor (Dapagliflozin 10mg) vs usual care among patients receiving Tolvaptan	- Slope of eGFR determined by linear regression from 1 to 6 months Interim result at 6-month: -$eGFR_{cr\text{-}cys}$ and $eGFR_{cys}$ slopes were significantly attenuated in the Dapagliflozin group compared to the one without Dapagliflozin (2.57 ± 7.88 vs. −5.65 ± 9.57 ml/min per 1.73 m^2 per year, P = 0.002; 3.91 ± 11.40 vs. −8.43 ± 13.44 ml/min per 1.73 m^2 per year, P = 0.003, respectively) -TKV change was significantly attenuated in the Dapagliflozin group compared to the one without Dapagliflozin (−0.44 ± 4.91% vs. 5.04 ± 8.09%, P = 0.01)	180	27 (Multicenter)	UMIN-CTR number: UMIN000046275; 6/12/2021
GLP1RA (tirzepatide)	RCT	Oral GLP1R agonist (to improve metabolism) vs. placebo titrated to 10 mg/day	Safety and tolerability; exploratory outcome (changes in TKV)	12	126 (Single center)	NCT06582875
VX407 (AGLOW)		PC1 corrector (for subset PKD1 variants)	Safety and tolerability; exploratory outcome (changes in TKV)	12	24	NCT07161037
Phase 1						

RGLS8429		Subcutaneous injection of miR-17 inhibitor every two weeks	Safety, tolerability, pharmacokinetics; exploratory outcome with biomarkers	4	68 (completed)	NCT05521191
GSK4771261		Intravenous/ subcutaneous monoclonal anti-PAPP-A antibody	Safety, tolerability, and pharmacokinetics	6	84	NCT06734234
PYC-003		Single intravenous dose of a PKD1 activator; anti-sense oligonucleotide	Safety, tolerability, and pharmacokinetics	6	24	NCT06714006
VX407		PC1 corrector (for subset PKD1 variants)	Safety, tolerability, pharmacokinetics	<1 (24 days)	159 (completed)	NCT06345755

*Only trials with sufficient details on the treatment were included.
Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; AMPK, AMP-activated protein kinase; eGFR, estimated glomerular filtration rate; $eGFR_{cr\text{-}cys}$, eGFR based on mean of $eGFR_{cr}$ and $eGFR_{cys}$; $eGFR_{cys}$, eGFR based on cystatin C levels; GLP1RA, glucagon-like peptide-1 receptor agonist; IGF-1, insulin growth factor 1; miR-17, microRNA-17; PAPP-A, pregnancy-associated plasma protein-A; PC1, polycystin 1; RCT, randomized controlled trial; SGLT2, sodium-glucose co-transporter 2; TKV, total kidney volume.

Table 2. Age-dependent ultrasound criteria for diagnosis or exclusion of typical ADPKD associated with PKD1 or PKD2 variants*

Ultrasound criteria for diagnosis of ADPKD in the presence of a positive family history				
Age (years)	**Test criterion:**	**Diagnosis confirmed if test criterion is met in a family with**		
		known *PKD1* mutation	**known *PKD2* mutation**	**unknown genotype**
15-39	**>3 cysts in both kidneys**	**100%**	**100%**	**100%**
40-59	**>2 cysts in both kidneys**	**100%**	**100%**	**100%**
60+	**>4 in each kidney**	**100%**	**100%**	**100%**
Ultrasound criteria for exclusion of ADPKD in the presence of a positive family history				
Age (years)	**Test criterion:**	**Disease excluded if test criterion is met in a family with**		
		known *PKD1* mutation	**known *PKD2* mutation**	**unknown genotype**
15-29	**No cyst**	**99%**	**84%**	**91%**
30-39	**No cyst**	**100%**	**97%**	**98%**
40-59	**≤1 cyst in both kidneys**	**100%**	**100%**	**100%**

*Also requires documentation of typical imaging pattern (i.e. bilaterally enlarged kidneys with relatively symmetrical cyst distribution) in the test subject or an older affected relative.

Appendix

Figure S1. Novel mechanisms for disease progression in ADPKD

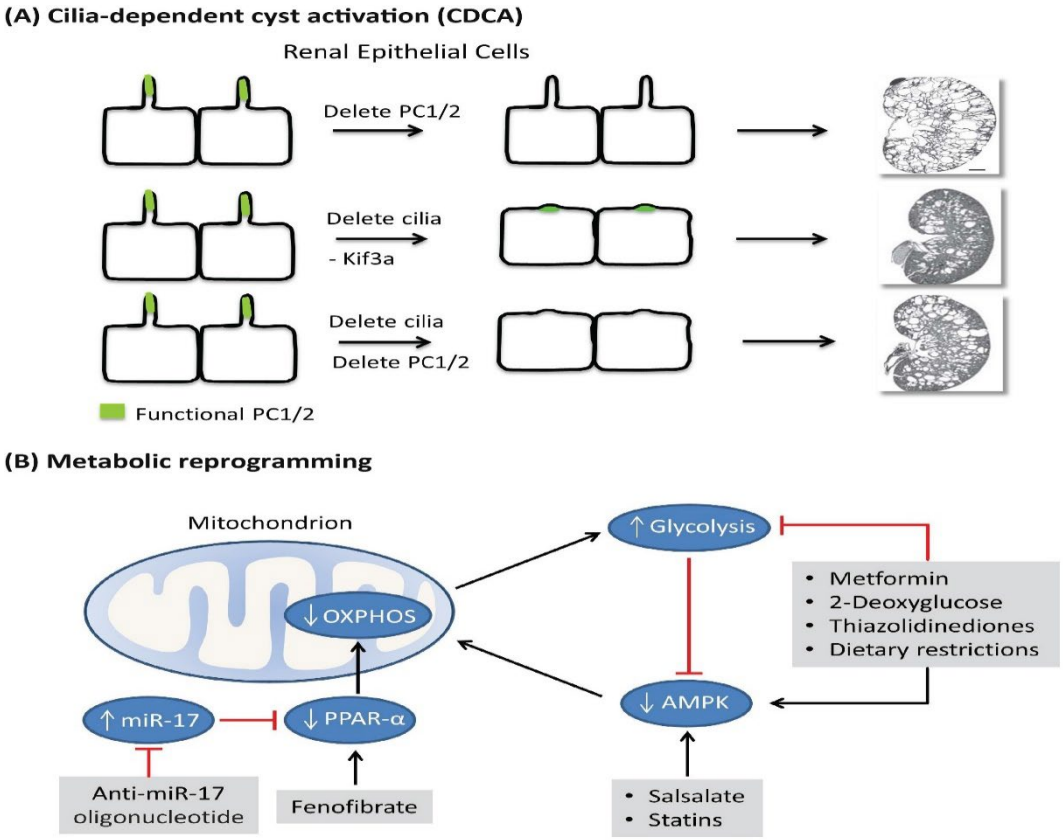
Figure S2. Risk assessment to identify high risk patients in ADPKD

Figure S3. Diagnostic algorithm for suspected kidney or liver cyst infection

Figure S4. Screening and management of intracranial aneurysms

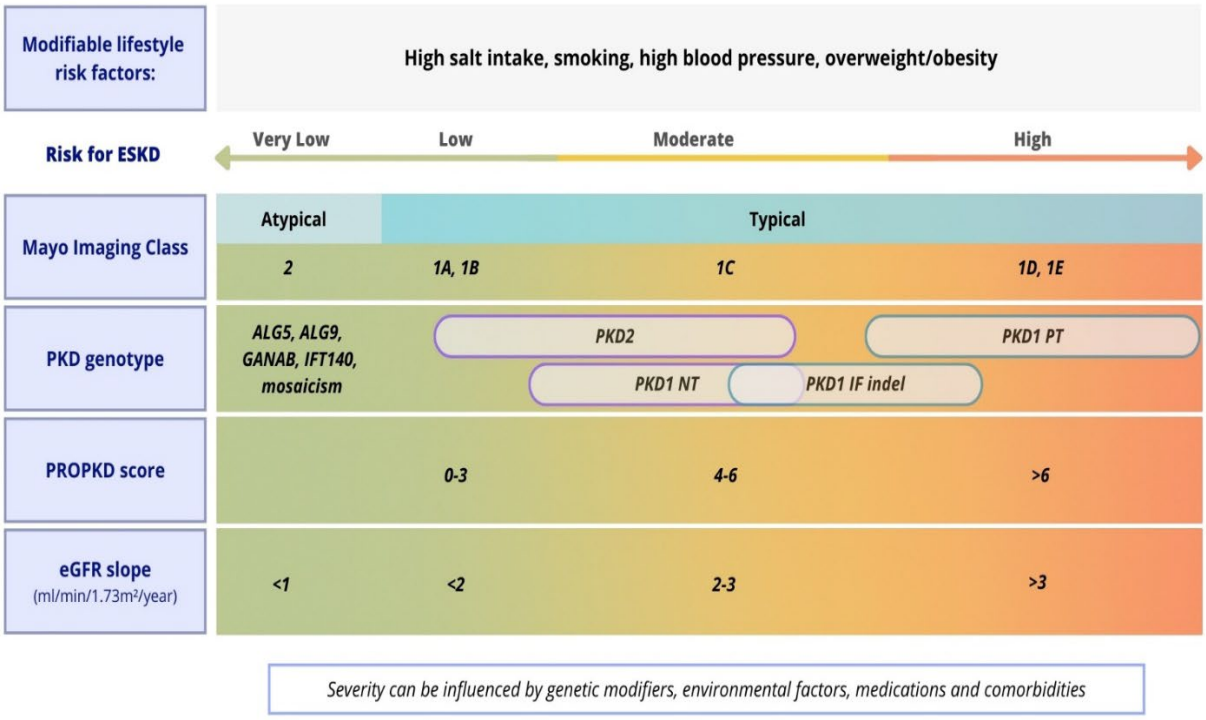
Figure S5. An algorithm for management of polycystic liver disease

Figure S6. A patient-centered care pathway for ADPKD



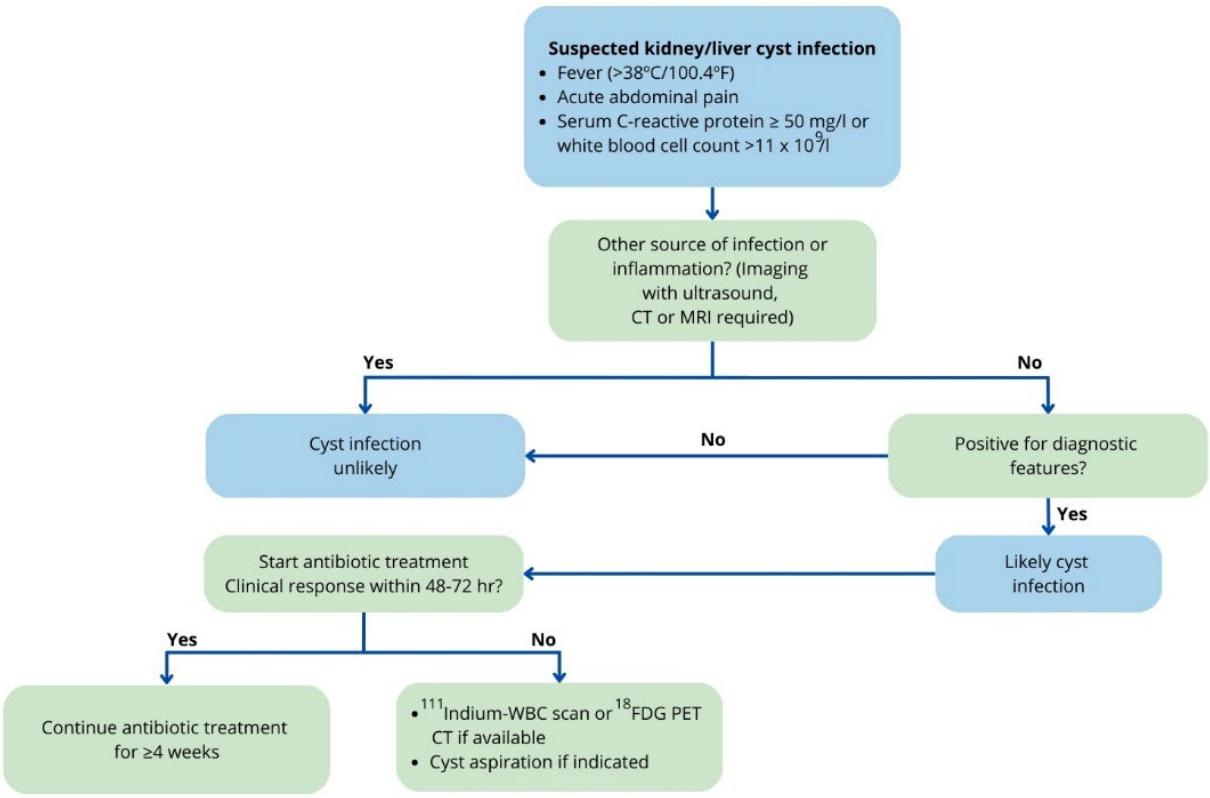
Abbreviations: PC1, polycystin 1; PC2, polycystin 2; Kif3A, kinesin family member 3A; OXOPHOS, oxidative phosphorylation; miR-17, microRNA-17; PPAR-α, peroxisome proliferation-activated receptor alpha.

Figure S1A. Cilia-dependent cyst activation pathway in ADPKD. Loss of PC1 or PC2, or primary cilia by Kif3a deletion can individually result in cystic kidney disease. However, double knock-out of PC1 or PC2 and Kif3a did not result in more severe, but rather attenuated cystic kidney disease. Thus, loss of intact primary cilia suppresses rapid cyst growth following polycystin inactivation indicating the existence of a cilia-dependent cyst activation (CDCA) pathway with suppressive effects on the loss of polycystin function.[58] A recent study, using translating ribosome affinity purification RNASeq on mouse kidneys with PC1 and cilia inactivation before cyst formation, has identified Glis2 as a candidate functional effector of the CDCA. Since genetic inactivation of Glis2 and Glis2 antisense oligonucleotides slowed disease progression in mouse models of ADPKD, Glis2 may be a potential therapeutic target for ADPKD.[59] **Figure S1B. Metabolic reprogramming in ADPKD**. Cystic epithelial cells are characterized by increased aerobic glycolysis, decreased AMPK activity, and globally depressed mitochondrial oxidative metabolism, including branched-chain amino acid degradation, fatty acid degradation, the Krebs cycle, and oxidative phosphorylation. Targeting these metabolic defects offers potential therapeutic strategies for ADPKD. Black arrows indicate activation, and red blocked arrows indicate inhibition.[66]



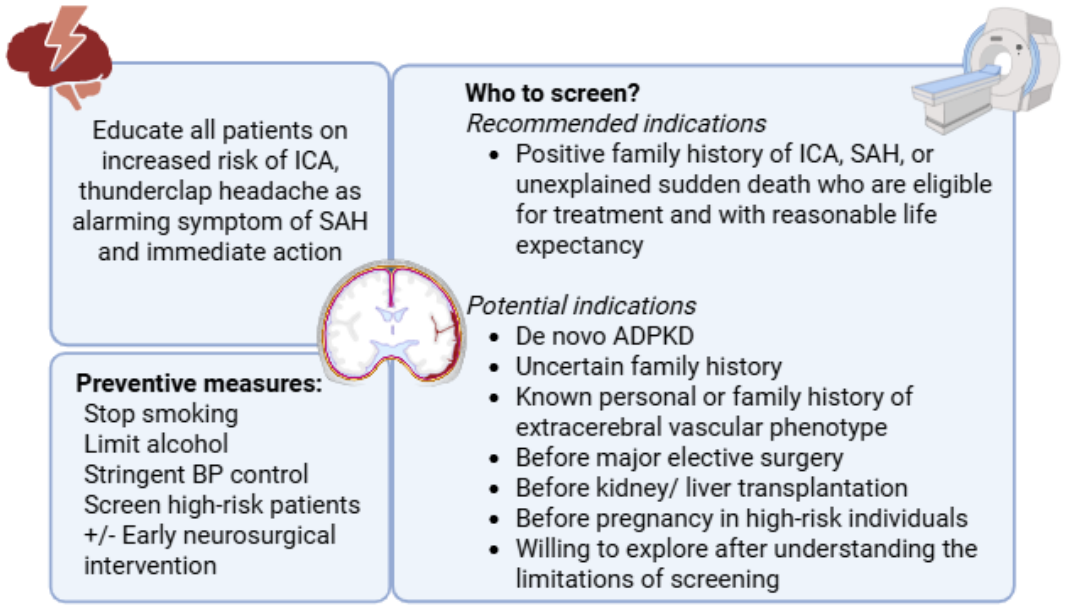
Abbreviations: ESKD; end stage kidney disease; PKD, polycystic kidney disease; PROPKD, Predicting Renal Outcome in Polycystic Kidney Disease; eGFR, estimated glomerular filtration rate; PT, protein truncating; NT, non-truncating; IF, in-frame.

Figure S2. Risk assessment to identify high risk patients in ADPKD. Due to a wide overlap of disease severity between the *PKD1* and *PKD2* mutation classes, mutation class alone should not be used for risk prediction in individual patients. The Mayo Imaging Class 1C-1E, PROPKD score >6; or eGFR slope >3 ml/min/1.73m^2/year have been used to select high-risk patients for disease-modifying therapy.



Abbreviations: CT, computed tomography; ^{18}FDG PET-CT, positron emission tomography with 18F-2-deoxy-2-fluoro-glucose integrated with computed tomography; WBC, white blood cell; MRI, magnetic resonance imaging.

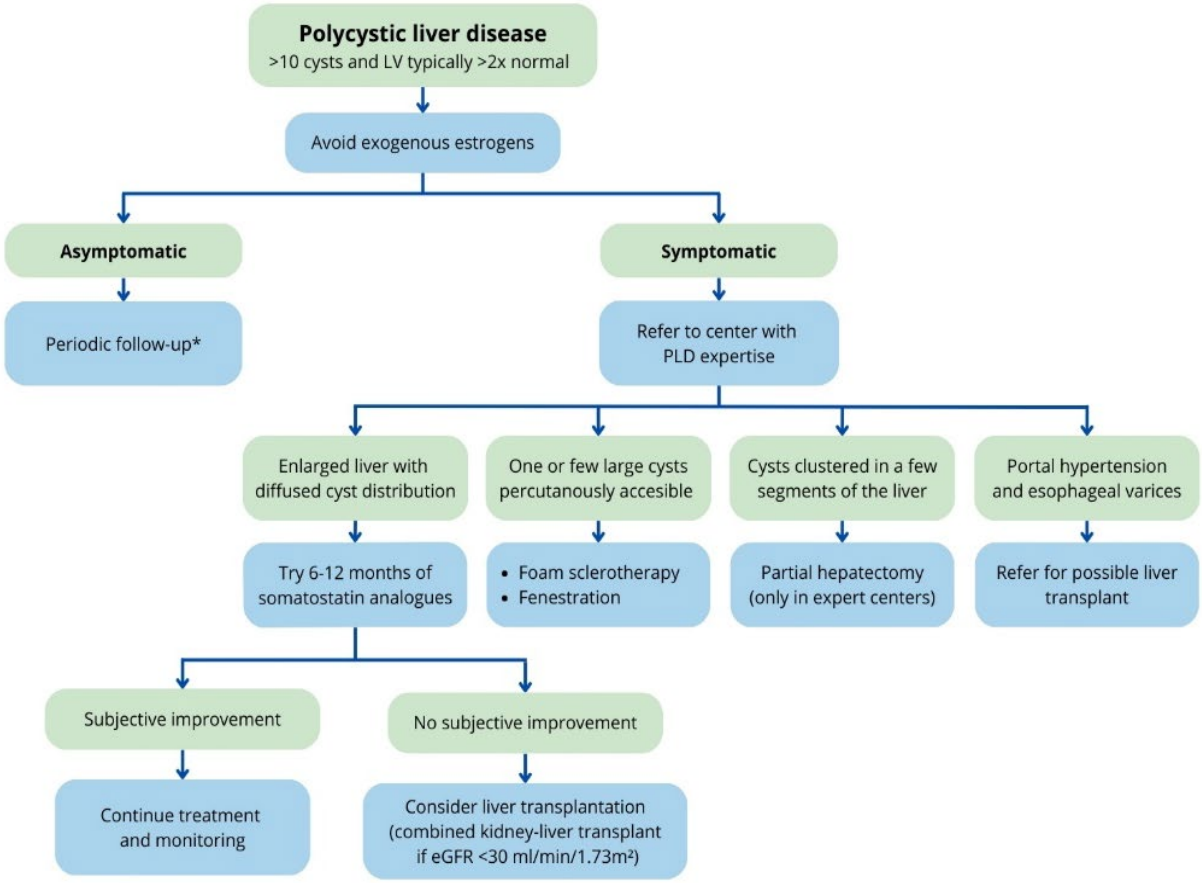
Figure S3. Diagnostic algorithm for suspected kidney or liver cyst infection.[11] The presence of fever and elevated inflammatory markers (i.e. WBCs and C-reactive protein) but no obvious source in a patient with ADPKD should raise the suspicion of a kidney or liver cyst infection. Additional findings such as abdominal pain and tenderness, and/or imaging diagnostic features (e.g. identification of a new complex cyst compared to a recent scan before the onset of symptoms, intracystic fluid level or gas, contrast enhancement or thickening of cystic wall) may further help to localize the cyst infection. Failure to respond to antibiotic treatment after 48-72 hours should prompt further investigations including ^{111}indium WBC scan or ^{18}FDG PET-CT, and/or cystic aspiration.[116]



Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; BP, blood pressure; ICA, intra-cranial aneurysm; SAH, subarachnoid hemorrhage.

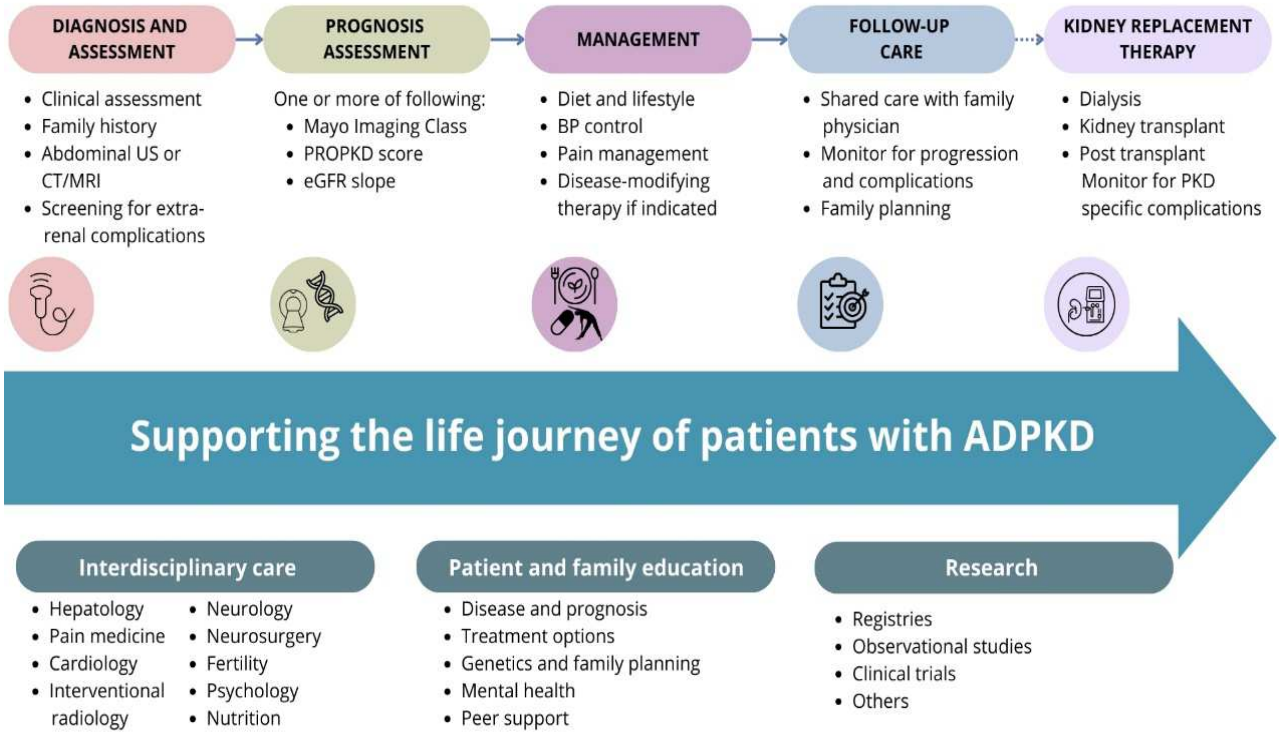
Figure S4. Screening and management of intracranial aneurysms. Compared to the general population, patients with ADPKD have a 4-5 fold increased risk of developing ICA and ~7 times higher risk of subarachnoid hemorrhage. A detailed family history is needed to identify ADPKD patients at increased risk of ICA/SAH. Patients should be educated to recognize the clinical significance of a "thunderclap headache" characterized by a sudden onset, unilateral headache that reaches maximal intensity within minutes and to seek emergency assessment immediately.

Screening by time-of-flight magnetic resonance angiography (MRA) or high-resolution computed tomography angiography (CTA) is recommended in high-risk individuals with a positive personal history of ICA/ SAH or a family history of ICA/SAH/unexplained sudden death. The advantages and limitations of ICA screening should be discussed with individual patient.



Abbreviations: LV, liver volume; MRI, magnetic resonance imaging; CT, computed tomography; PLD, polycystic liver disease; eGFR, estimated glomerular filtration rate.

Figure S5. An algorithm for management of polycystic liver disease (PLD). PLD, defined as >10 liver cysts, is frequently associated with ADPKD. While ~80% of patients with ADPKD will have liver cysts by 40 years of age, only 5-10% develop symptomatic PLD generally associated with a liver volume at least 2x normal (or ~1.8 L) and clinically manifested by "mass effect" symptoms (e.g. bloating, early satiety, acid reflux, abdominal fullness and pain). *Younger women <30 years with significant PLD (i.e. numerous small liver cysts but minimal or no gross hepatomegaly) should be monitored preferably by MRI every one-two years, while those without significant PLD can be monitored periodically (e.g. every 3-5 years) based on clinical judgement. All women with significant liver cyst burden should be educated to avoid estrogen containing medication and symptomatic patients should be referred early to a PLD Centre of expertise to explore potential treatment options. During treatment planning it should be made aware that liver volume growth tends to plateau after menopause in females and some experience liver volume regression.



Abbreviations: PROPKD, Predicting Renal Outcome in Polycystic Kidney Disease; eGFR, estimated glomerular filtration rate.

Figure S6. A patient-centered care pathway for ADPKD. Transitioning to a more comprehensive patient-centered approach is recommended in the management of ADPKD. Current KDIGO guideline emphasizes the importance of structured patient education, shared decision-making, and multidisciplinary care, involving nephrology, mental health, genetics, nutrition, reproductive specialists and other specialists, particularly for individuals facing complex decision such as a family planning, pain interventions, evaluation for nephrectomy, etc. Including these patient-centered strategies into clinical practice can substantially improve the quality of care and align therapeutic decisions with patient preferences and values.