Polycystic Kidney Disease in Children: The Current Status and the Next Horizon

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Autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD) are inherited disorders that share many features such as kidney cysts, hypertension, urinary concentrating defects, and progressive chronic kidney disease. The underlying pathogenic mechanisms for both include cilia dysfunction and dysregulated intracellular signaling. ADPKD has been traditionally regarded as an adult-onset disease whereas ARPKD has been classically described as an infantile or childhood condition. However, clinicians must recognize that both disorders can present across all age groups, ranging from fetal life and infancy to childhood and adolescence as well as adulthood. Here we highlight the points of overlap and distinct features for these disorders with respect to pathogenesis, diagnostic modalities (radiological and genetic), clinical assessment, and early therapeutic management. In particular, we consider key issues at 2 critical points for transition of care: fetal life to infancy and adolescence to adulthood. These time points are poorly covered in the extant literature. Therefore, we recommend guiding principles for transitions of clinical care at these critical junctures in the life span. Although there is no cure for polycystic kidney disease (PKD), recent insights into pathogenic mechanisms have identified promising therapeutic targets that are currently being evaluated in a growing portfolio of clinical trials. We summarize the key findings from these largely adult-based trials and discuss the implications for designing child-focused studies. Finally, we look forward to the next horizon for childhood PKD, highlighting gaps in our current knowledge and discussing future directions and strategies to attenuate the full burden of disease for children affected with PKD.

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Polycystic kidney disease (PKD) is a set of genetic disorders characterized by bilateral kidney cysts without dysplasia. These disorders can be diagnosed in children as well as adults and are broadly defined in terms of the mode of transmission: autosomal dominant (ADPKD) and autosomal recessive (ARPKD).[1,2] This review highlights the clinical features of childhood PKD, surveys the genetic landscape, reviews issues such as transition of care and the status of pediatric clinical trials, and concludes with key considerations about future research directions.

Clinical Overlap and Distinct Features

ADPKD and ARPKD share multiple common features including kidney cysts, hypertension, urinary concentrating defects, and chronic kidney disease (CKD).[1] Traditionally, these disorders have been considered as distinct entities. Rarer and more "severe," ARPKD has been characterized as an infantile disorder that is associated with oligo/anhydramnios, pulmonary hypoplasia, massively enlarged kidneys, early severe arterial hypertension, and early-onset kidney failure.[3] The complications of concomitant congenital hepatic fibrosis and resultant portal hypertension tend to occur later in life.[4] By comparison, ADPKD has been considered an adult disease with an asymptomatic childhood course due to slower cyst growth.[1]

Arterial hypertension occurs frequently in children with ARPKD and in about 20% of children with ADPKD.[5] Extrarenal manifestations such as liver cysts and cerebral aneurysms have been described in rare cases of childhood ADPKD.[6] By contrast, 60% to 70% of adults with ADPKD have imaging evidence of liver cysts, with the overall prevalence higher in women, particularly after multiple pregnancies. Other risk factors for liver cysts include increased age, severity of cystic kidney disease, and reduced glomerular filtration rate (GFR).[7,8] Histopathologically, cysts in ADPKD are found throughout the nephron, and ARPKD primarily involves dilatation of the collecting ducts.[1]

Recent analyses of clinical cohorts and genotype-phenotype studies indicate that the phenotypic spectrum of ADPKD and ARPKD has multiple points of overlap. For example, a small but significant proportion of patients with ARPKD have preserved corticomedullary differentiation on ultrasound into young adulthood, and they do not progress to CKD until middle age.[9,10] In addition, ARPKD can present in early adulthood with minimal kidney involvement.[9] On the other hand, some children with ADPKD, especially those with very-early-onset (VEO) disease, can progress to kidney failure in childhood.[11,12] Congenital hepatic fibrosis is an invariant feature of ARPKD; however, it can occur rarely in children with ADPKD.[13,14] Decreased kidney concentrating capacity is present in all children with ARPKD[15] and about half of those with ADPKD where it is linked to untreated hypertension.[16] Therefore, decreased kidney concentration

capacity does not exclude ADPKD, but normal concentrating capacity practically excludes ARPKD.

Clinical management is largely dictated by differences in disease severity. For example, hypertension has been reported in about a fifth of children with ADPKD,[5,17] but it is nearly universal in infants/children with ARPKD. The latter often require multidrug antihypertensive therapy and are more likely to develop left ventricular hypertrophy.[18] The utility of nephrectomy to manage massive nephromegaly in infants and toddlers with ARPKD is highly controversial[19] whereas it is very rarely considered in children/adolescents with enlarged kidneys due to ADPKD.

Genetic Landscape

In asymptomatic children with a clear-cut positive family history of ADPKD, the utility of genetic testing in minors needs to be carefully considered.[20] Potential benefits of early diagnosis include (1) the ability to initiate management early in the disease course (including lifestyle modifications), (2) reassurance for unaffected at-risk individuals, (3) resolution of the diagnostic odyssey, and (4) early screening for extrarenal manifestations. These putative benefits need to be weighed against potential complications, including (1) the psychological burden of having a life-altering diagnosis, (2) potential difficulties with employment and insurability (eg, health and/or life insurance), and (3) the possibility of inconclusive test results and the need for interpretation by experts with specialist knowledge. By comparison, genetic testing is commonly performed in children who present with a suspicion of ARPKD or early-onset PKD. This is particularly important for clinical trials given that numerous phenocopy disorders can mimic ARPKD (eg, VEO-ADPKD or infantile nephronophthisis).[21]

ADPKD

Pathogenic variants in *PKD1* (~78% of cases) located on chromosome 16p13.3 or *PKD2* (~15% cases) on chromosome 4q22 encoding 2 integral membrane proteins polycystin-1 and polycystin-2, respectively, are the main cause of ADPKD.[22] Genotype-phenotype correlations associate protein-truncating *PKD1* variants with more severe kidney disease compared with *PKD1* missense and *PKD2* variants.[23-25] However, patients with truncating variants may have mild disease.[26] In addition, there is significant intrafamilial variability and considerable locus heterogeneity with many private variants in both *PKD1* and *PKD2* in ADPKD families.[1]

Several additional genes have more recently been implicated in rare cases of ADPKD (eg, *GANAB* [encoding glucosidase II, α subunit] and *DNAJB11* [encoding DNAJ heat shock protein family {HSP40} member B11]) that are probably less relevant for childhood PKD.[27-29] Monoallelic variants in *IFT140* and *NEK8* (encoding intraflagellar transport 140 and NIMA-related kinase 8, respectively) have been described in pediatric patients with kidney cysts or PKD,[30,31] and monoallelic *PKHD1* variants have been identified in patients with small liver cysts and increased renal medullary echogenicity.[32] The genetic heterogeneity in pediatric PKD has recently been summarized in an excellent review.[2]

ARPKD

Pathogenic variants in *PKHD1* (chromosome 6p21), which encodes the large transmembrane protein fibrocystin, cause the vast majority of ARPKD cases.[33,34] Most patients have private compound biallelic heterozygous variants in *PKHD1*. The *PKHD1* variant p.Thr36Met has been shown to be the most common variant in European and American cohorts, accounting for 13% to 20% of patients.[35] Patients with 2 truncating (null) *PKHD1* variants express more severe disease than patients carrying at least 1 missense variant, although a severe course can occur in the latter group.[1] Associations of variants in specific regions of the gene with different clinical courses of kidney and liver disease in ARPKD have been described.[35]

Variants in several other genes have more recently been identified in patients with ARPKD, including *DZIP1L*[36] and *CYS1*[37] (encoding DAZ-interacting zinc finger protein 1–like and cystin 1, respectively). In addition, patients with an ARPKD like-phenotype, a negative family history, and biallelic hypomorphic variants in *PKD1* have been identified.[14,38] Variants in additional genes may result in ARPKD-like phenocopies, including *NPHP3* and *HNF1B*[21] (encoding nephrocystin-3 and HNF1 homeobox B, respectively).

Genetic Diagnostics in Pediatric PKD

Identification of the underlying disease-causing variants is important for family counseling and may help guide the evaluation of subtle extrarenal manifestations. For early-onset cystic kidney diseases and atypical presentations, genetic workup with a panel-based approach including the primary genes associated with cystic kidney disease is recommended.[39] The genetic complexity of cystic kidney disease often requires both nephrology and genetics expertise for interpretation of likely disease-causing variants. Lessons from large databases may help to improve counseling of families, such as in the setting of preimplantation genetic diagnostics.[40] Yet prognostic prediction at the level of an individual patient remains a major clinical challenge because our understanding of the complex interplay between genetic and nongenetic factors influencing disease severity is limited. Data demonstrating that many of the genes associated with pediatric cystic kidney diseases are involved in the regulation of cilia-associated intracellular signaling pathways has established a mechanistic framework to begin understanding the cellular events that underpin PKD pathogenesis.[41]

Genetic testing is strongly advised after delivery or at postmortem in severe cases to define the exact genetic diagnosis for subsequent clinical management and

counseling, including discussion of risk for subsequent pregnancies. It should be noted, however, that genetic investigation may be inconclusive even with the most modern clinical or research approaches.[42] A recommended approach to genetic testing in childhood PKD is shown in Table 1.

Transition of Care

Transition of Clinical Care: Fetal Life to Infancy

PKD can be detected at the antenatal anatomic screening scan (~18-20 weeks' gestation) and is typically characterized as bilaterally enlarged, echogenic (bright) kidneys.[39,43] Discrete cysts are not a feature of ARPKD, and in ADPKD cysts are usually too small to visualize at this gestational age. Hence, alternative congenital anomalies of the kidneys and urinary tract (CAKUT), such as urinary tract obstruction or multicystic dysplastic kidneys, should be considered if cysts are detected in the second trimester.[44,45] Prenatal echogenic kidneys with or without discrete cysts may be associated with aneuploidy and syndromic conditions,[43] which, unlike PKD, are often associated with extrarenal structural abnormalities such as cardiac, skeletal, and/or central nervous system defects (Table 2).[43]

Genetic evaluation for fetal echogenic or cystic kidneys should include a detailed family history and parental genetic carrier screening.[46] Microarray analysis is the preferred test to detect copy number variants (CNVs) such as 17q12 deletions (which includes the *HNF1B* gene), which is a relatively common cause of fetal echogenic kidneys.[47] If the microarray is not diagnostic, a multigene panel or whole exome sequencing should be performed.[46] Although noninvasive prenatal testing based on analysis of cell-free DNA in maternal plasma is increasingly used to screen for fetal aneuploidies, this methodology is not currently recommended for clinical analysis of CNVs or single-gene disorders.[48,49]

Table 1. Clinical Contexts in Which Genetic Testing Should Be Offered

Clinical Context for Genetic Testing	Expected Outcomes
Early-onset and/or severe bilateral cystic kidney disease	ARPKD and ARPKD-mimicking phenocopies (including biallelic ADPKD due to hypomorphic PKD1 alleles)
Atypical kidney imaging findings	ADPKD-mimicking phenocopies, involving minor ADPKD genes (*GANAB*, *IFT140*); rare in children
Cystic kidney diseases with negative or unknown family history	De novo ADPKD, ADPKD-mimicking phenocopies

The performance of genetic testing should be predicated on shared decision-making with the patient/family following adequate genetic counseling. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease.

Amniotic fluid is composed predominantly of fetal urine from 14- to 16-weeks' gestation,[50] so oligohydramnios is often considered an important predictor of poor outcomes in fetuses with kidney diseases, particularly because it can lead to pulmonary hypoplasia when severe.[51] Amnioinfusions have been trialed in the management of anhydramnios in fetuses with bilateral renal agenesis and found to mitigate lethal pulmonary hypoplasia, albeit with relatively poor long-term outcomes.[52] However, there is no evidence to support the utility of amnioinfusions in ARPKD, and the potential effectivity may be reduced due to the additional contribution of severe nephromegaly and diaphragmatic displacement to pulmonary hypoplasia.[52]

It is important to note that oligohydramnios alone is an imprecise indicator of kidney function. One retrospective study reviewed 74 live births with renal oligohydramnios from causes including bilateral kidney agenesis, CAKUT, and ARPKD[53]; almost all of the 26 patients with neonatal death had anhydramnios, but more than half of the 48 neonatal survivors also had anhydramnios. Hence, oligohydramnios must be considered with other factors to determine the best estimated prognosis, a point confirmed in a study of 385 patients from the international ARegPKD registry.[54] Prenatal risk factors for early dialysis were (1) oligohydramnios/anhydramnios; (2) enlarged kidneys, and (3) kidney cysts. Infants with all 3 risk factors had an estimated probability of dialysis dependency of 32% by 12 months of life and 35% by 36 months.[54]

Despite potential biases, these studies illustrate the significant prognostic uncertainty that arises when PKD is suspected in utero. Clinicians inexperienced with PKD may therefore err toward a dire prognosis and offer termination (where available) in fetuses with oligohydramnios, enlarged kidneys, and/or kidney cysts. However, in the aforementioned ARegPKD study, the majority of children with these risk factors did not require early dialysis.[54] Families deserve expert support, and many centers now offer multidisciplinary counseling with fetal medicine experts, pediatric nephrologists, neonatologists, and geneticists.[39,55] These teams will rarely formulate a precise prognosis, but they should be able to provide nondirective counseling with a clear range of the possible outcomes.[56] Parent groups report that timely and personalized prenatal counseling can reduce additional distress[57] and may help with ongoing parental anxiety.[58] Counseling should not only discuss the diagnosis, but may include

- Potential issues with pregnancy care.
- Timing and location of delivery to ensure appropriate neonatal intensive care and pediatric nephrology services.
- Family implications of having a child with potentially severe CKD: how it will change their lives and what resources are available to help them.
- Facilitating connections with other families who have volunteered to share their experiences with prenatally diagnosed kidney disease.

Table 2. Diagnoses in a Study of 316 Fetuses With Prenatally Diagnosed Hyperechogenic Kidneys

Diagnosis	Total (n, % of total 316 fetuses)	Isolated Hyperechogenic Kidneys (n, % of Total With Diagnosis)	Hyperechogenic Kidneys + Other Anomalies of Kidneys/ Urinary Tract (n, % of Total With Diagnosis)	Hyperechogenic Kidneys + Extrarenal Structural Anomalies (n, % of Total With Diagnosis)
ADPKD	12 (4%)	9 (75%)	2 (17%)	1 (8.3%)
ARPKD	10 (3%)	7 (70%)	3 (30%)	—
CAKUT[a]	97 (31%)	37 (38%)	57 (59%)	3 (3%)
Aneuploidy	41 (13%)	3 (7%)	1 (2%)	37 (90%)
Other[b]	15 (5%)	1 (7%)	5 (33%)	9 (60%)
Euploid multiple congenital anomalies	10 (3%)	—	—	10 (100%)

[a]Includes bladder outflow obstruction, unilateral or bilateral cystic dysplasia, multicystic dysplastic kidney, and duplex kidneys.
[b]Includes Bardet-Biedl syndrome, Beckwith-Wiedemann syndrome, variant of hepatocyte nuclear factor (HNF)-1β, mucopolysaccharidosis type I, Roberts syndrome, variant of Wilms tumor gene on X chromosome, preterm premature rupture of membranes, small kidneys, neonatal alloimmune thrombocytopenia, fetal akinesia deformation sequence, congenital pulmonary airway malformation, VACTERL (association of vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, and renal and limb abnormalities), and pentalogy of Cantrell.
Adapted from Yulia et al.[43] Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; CAKUT, congenital abnormalities of the kidneys and urinary tract.

- Involvement of the palliative care team where there is a significant risk of mortality, with minimization of invasive, distressing interventions when appropriate.

Transition of Clinical Care: Adolescence to Adulthood

Transition of clinical care from adolescence to adulthood represents another challenging time for individuals with chronic medical conditions. Previous studies regarding this transition period have been limited by small sample sizes, short follow-up periods, and wide variation in diagnoses and associated medical/psychosocial needs. Current recommendations often remain consensus based. Nonetheless, prior studies consistently identify the high risk of nonadherence and loss to follow-up care during this critical interval.[59,60] Thus, a formal transition process initiated early in adolescence has been recommended for many chronic childhood medical conditions. Key elements are outlined in Box 1.[61]

A key component of preparing adolescents or young adults with PKD for transition to adult provider management is addressing expectations. Specific medical issues of importance for young adults include family planning and the risk of disease in offspring and disease-specific manifestations that occur with aging. This includes but is not limited to the increasing prevalence of hypertension with age in both disorders, the risk of polycystic liver disease and intracranial aneurysms in adults with ADPKD, and appropriate subspecialty follow-up care including hepatology with ARPKD. Individuals who are at risk for ADPKD but have not undergone formal genetic testing or imaging evaluation require counseling regarding evaluation and education about potential disease manifestations.

Education regarding the potential differences in practice between pediatric and adult health care systems is also of value. For example, an academic pediatric center may routinely offer support from social work, nutrition experts, and financial counselors; a private practice adult nephrology center may provide none of these services. Practitioner experience also may vary, with less experience with ARPKD among adult providers due to the rarity of the condition; adult providers may have more experience with ADPKD but perhaps at later stage of disease progression. Providers should be informed about both the medical and psychosocial aspects of chronic disease, encourage medical peer group support through local foundations, and be prepared to discuss novel therapies or research trials with their young adult patients impacted by PKD. In some cases, the transition to adult providers may increase access to research studies for individuals with ADPKD over 18 years of age.

Emerging pediatric and adult centers of excellence in PKD offer the opportunity to collaborate in the education and transition of ARPKD and ADPKD patients. More formal study of transition for these disorders is required.

Status of Clinical Trials

Investigations of children with PKD have focused primarily on natural history registries (databases) and clinical cohort studies. Recently, a limited set of clinical trials in pediatric ARPKD and ADPKD has been performed or proposed, but development of such trials has been hampered by the lack of validated measures for risk stratification or for monitoring response to therapy.

Natural History Studies

ARPKD

Registries. Longitudinal registries have provided important insights into the natural history of ARPKD. The Autosomal Recessive Polycystic Kidney Disease database in North America, a multicenter, longitudinal (retrospective) registry based in the United States,[62] provided the first detailed natural history information on ARPKD patients in North America. ARegPKD is a more recent international multicenter observational registry based in Europe.[63]

Box 1. Key Elements of Transition of Clinical Care From Adolescence to Adulthood

- Ensure developmentally appropriate understanding of:
  - ◇ Clinical features of PKD including self-reporting of concerning symptoms (eg, abdominal pain, gross hematuria, tarry stools).
  - ◇ Necessity and frequency of routine medical monitoring including roles of nephrologist, hepatologist (ARPKD), and primary care provider.
  - ◇ Purpose of prescribed medications and impact of (non) adherence.
  - ◇ Value of routine blood pressure monitoring and appropriate blood pressure goal for long-term cardiovascular and kidney health in PKD.
  - ◇ Potential changes in clinical features through various stages of childhood (eg, increasing risk of hypertension with age).
- Enlist family or other social support to reinforce and assess understanding.
- Introduce plan for transition by 12-14 years of age in a gradual manner with consideration of developmental/intellectual understanding. Emphasize need for lifelong medical monitoring to optimize health.
- Clearly outline goals of transition process to patient and family in context of personal PKD features and complications. Advance independence in self-care over time. Adjust and individualize plan as needed with feedback from patient and family.
- Identify adult and pediatric clinicians (ideally including primary pediatric nephrologist) to serve as transition coordinators for individual patients. Consider combined pediatric-adult PKD transition clinics. Conduct informal visits with adult nephrologist before transfer.
- Coordinate transition and management plans with the individual's other subspecialists (hepatologist in ARPKD).
- Provide access to PKD peer and family support groups when available and appropriate.
- Provide education regarding general and PKD-specific insurance issues related to transfer, including health insurance.
- Provide counseling on genetics of PKD and implications for future children.
- For individuals at risk for ADPKD, discuss impact of screening on health, insurance (medical, disability, life), and future children.
- Do not transfer in times of crisis.
- Follow up to ensure that patient has successfully established care with adult nephrology and other subspecialists, preferably those with specific PKD interest or experience.

Based on information in Watson et al.[61] Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; PKD, polycystic kidney disease.

ARegPKD studies have identified risk factors for early dialysis,[64] described genotype-phenotype correlations[35] and the clinical disease course in young adults,[9] examined height-adjusted total kidney volume (htTKV) to identify very young children (<18 months old) at risk for early kidney failure,[65] and validated phenotypic variability within sibships.[66]

Cohort Studies. Two relatively small longitudinal cohort studies have provided key information on ARPKD kidney disease progression. Both studies found highly variable rates of kidney function decline with relatively slow overall progression.[67,68] These findings highlight a major barrier for implementing clinical trials in ARPKD and emphasize the need for additional methods to identify patients at high risk for kidney disease progression, including validated imaging biomarkers.

ADPKD

Registries. Several clinical registries enrolling children with ADPKD, including those supported by the National Health Service in the United Kingdom, the National Institutes of Health in the United States, and the global pediatric ADPKD registry (ADPedKD), have been established with the potential to identify early prognostic biomarkers of high risk for rapid kidney disease progression.[69]

Cohort Studies. A longitudinal pediatric and young adult cohort based in the United States has provided key insights into clinical risk factors for kidney disease progression (eg, hyperfiltration or rapidly growing kidneys)[70] and cardiovascular morbidities.[71] The characterization of the interrelationship between hypertension, which is common in pediatric ADPKD,[5,17] and left ventricular hypertrophy has informed clinical management of these patients. Subcohort analysis has defined kidney disease progression in children with VEO-ADPKD.[22]

Biomarker Development

In adults, measurement of htTKV is well-established as a predictor of progression to kidney failure in ADPKD.[72] In children with ADPKD, TKV on 3-dimensional ultrasound with adequate age-adjustments may predict progression risk,[29] but specific age-related htTKV thresholds for predicting progression have not been established. In ARPKD, maximal htTKV in the first 18 months of life is inversely correlated with 10-year kidney survival.[65] However, beyond that age htTKV appears not to be a useful biomarker because kidney size stabilizes with progressive disease.

Recent studies have used imaging biomarkers beyond htTKV to risk stratify PKD and monitor progression. These include developing novel quantitative magnetic resonance imaging methodologies in ARPKD[73,74] and examining rates of kidney growth in children with ADPKD.[75] Several recent studies have examined the use of blood and/or urinary biomarkers to predict disease progression in ADPKD,[76,77] including the development of a urinary biomarker score based on urinary monocyte chemoattraction protein 1 (MCP-1) and β_2-microglobulin for adults with ADPKD.[78] Similar studies have not yet been conducted in children with ADPKD or patients with ARPKD.

Clinical Trials

ARPKD and ADPKD have overlapping kidney phenotypes.[79] A therapy that targets a disease-specific pathway in one disease could be effective in the other. A case in

point is tolvaptan, which targets vasopressin-2 (V2) receptor–mediated cyclic adenosine monophosphate production. In clinical trials, tolvaptan attenuated kidney disease progression in ADPKD adults.[80] In ARPKD rat models, V2 receptor antagonists were effective in attenuating kidney disease progression,[81] an observation that must be formally tested in clinical trials of infants/children with ARPKD.

The current status of ARPKD and ADPKD clinical trials in children (from clinicaltrials.gov) is provided in Table 3.

Gaps in Knowledge and Future Directions

There are currently no clinically available, disease-specific treatments for children with ARPKD or ADPKD. Various targeted approaches have been studied in clinical trials for adult patients with ADPKD, but only one disease-modifying therapy (tolvaptan) has been approved by the regulatory agencies for adults with rapid progression of ADPKD.[82] Limited safety data regarding the use of this medication for children with ADPKD are available, and 2 trials are ongoing for children with ARPKD (Table 3). There remains an urgent need to develop and study novel, disease-modulating medications in children with ARPKD and ADPKD.

Many challenges, however, need to be overcome to accelerate drug development and the design of clinical trials for children with ARPKD and ADPKD including:

1. Identification and validation of primary end points for renal and extrarenal disease. While initiation of kidney replacement therapy may be a valid end point for ARPKD-related kidney disease, it is not relevant for ADPKD in children. Moreover, kidney biomarkers may have no or limited relevance for ARPKD-related liver disease.
2. Identification and validation of potential prognostic and predictive biomarkers for children with PKD. Patient numbers in pediatric PKD trials will most likely remain small. Given the clinical variability of ARPKD and ADPKD, it is particularly important to ensure that patients included in a clinical trial have comparable clinical starting points. For ARPKD trials in particular, alternative study designs and enrichment strategies will need to be considered.[83]
3. Exploration of the childhood-specific prognostic value of validated or novel biomarkers as a surrogate end point for progression. Although htTKV is validated for adults with ADPKD, emerging pediatric data require validation. For example, in children it is unclear whether TKV correction for height alone (vs body surface area) is the optimal biomarker to establish risk for disease progression. In addition, emerging data in animal and human studies suggest that dysregulated metabolism, such as alterations in fatty acid oxidation, is a feature of both ADPKD and ARPKD.[84,85]

There are also substantial knowledge limitations in terms of genetic diagnosis, clinical management, and prognostic considerations for affected patients. The value and timing of genetic testing is currently considered on a case-by-case basis, and there is no widely accepted diagnostic algorithm. In general, clinicians have a limited ability to accurately predict the rate of kidney disease progression except in the most severely affected fetuses and children, and this limitation contributes to uncertainty in counseling parents. Optimal hypertension management is not fully defined, despite advances in overall pediatric hypertension management, such as increased use of ambulatory blood pressure monitoring and recognition that lower blood pressure targets slow disease progression in all-cause CKD.[86] In addition, patient perspectives and

Table 3. Completed and Ongoing Clinical Trials in ARPKD and ADPKD

Drug	NCT	Trial Phase/Status	Key Findings
ARPKD			
Tesevatinib	03096080	Phase 1, completed	No results reported
Tolvaptan	04782258	Phase 3b (open label, nonrandomized), enrolling	n/a
Tolvaptan	04786574	Phase 3b (open label, nonrandomized), enrolling	n/a
ADPKD			
Pravastatin	00456365	Phase 3 RCT, completed	Pravastatin diminished the increase of cyclooxygenase- and lipoxygenase-derived plasma lipid mediators, which are components of inflammation and endothelial dysfunction pathways.[64]
Curcumin	02494141	Phase 4 RCT, completed	Curcumin supplementation does not improve vascular function or slow kidney growth in children/young adults with ADPKD.[88]
Enalapril	—	Phase 3 RCT, completed	No significant effect of ACE inhibitor on renal growth in young patients with ADPKD, but ACE inhibitor treatment may prevent the development of increased LVMI and deterioration in renal function in normotensive or borderline hypertensive children with ADPKD.[89]
Tolvaptan	02964273	Phase 3 RCT, completed	Tolvaptan exhibited pharmacodynamic activity in pediatric ADPKD.[90]

Abbreviations: ACE, angiotensin-converting enzyme; ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; LVMI, left ventricular mass index; RCT, randomized clinical trial.

patient-reported outcome (PRO) measures have gained recognition as important considerations in clinical trial design. The value of PROs would be strengthened by clinician- and/or observer-reported outcomes, where applicable.[87]

Summary

ARPKD and ADPKD are important causes of CKD across all age groups. Though the magnitude of their clinical impact may vary across the age spectrum, PKD-related, clinically significant complications may become apparent at any time, ranging from fetal life to adulthood. Recent advancements of specific relevance to children, adolescents, and young adults affected by PKD have included recognition of age-related clinical spectra, varied clinically significant presentations, advancement in molecular diagnosis, ongoing efforts to advance mechanistic insights, and the design of meaningful and promising clinical trials. Despite this progress, there are still challenges that require further work and urgent progress, including specialized multidisciplinary counseling and care of families (including during the in utero period), patient-centered counseling and transition models of care, and identification and validation of age-group specific clinical trial outcome measures to empower future trial efforts. With increasing momentum in these domains, there are expanding opportunities for those affected by PKD and their families to receive and benefit from dedicated, evidence-based clinical care. In addition to improving morbidity and quality of life, addressing these challenges also promises a future in which effective therapies mitigate the likelihood that affected children will suffer the full impact of PKD during their lifetime.

Article Information

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References

1. Bergmann C, Guay-Woodford LM, Harris PC, Horie S, Peters DJM, Torres VE. Polycystic kidney disease. *Nat Rev Dis Primers*. 2018;4(1):50. doi:10.1038/s41572-018-0047-y
2. Hanna C, Iliuta IA, Besse W, Mekahli D, Chebib FT. Cystic kidney diseases in children and adults: differences and gaps in clinical management. *Semin Nephrol*. 2023;43(4):151434. doi:10.1016/j.semnephrol.2023.151434
3. Burgmaier K, Broekaert IJ, Liebau MC. Autosomal recessive polycystic kidney disease: diagnosis, prognosis, and management. *Adv Kidney Dis Health*. 2023;30(5):468-476. doi:10.1053/j.akdh.2023.01.005
4. Lasagni A, Cadamuro M, Morana G, Fabris L, Strazzabosco M. Fibrocystic liver disease: novel concepts and translational perspectives. *Transl Gastroenterol Hepatol*. 2021;6:26. doi:10.21037/tgh-2020-04
5. Marlais M, Cuthell O, Langan D, Dudley J, Sinha MD, Winyard PJ. Hypertension in autosomal dominant polycystic kidney disease: a meta-analysis. *Arch Dis Child*. 2016;101(12):1142-1147. doi:10.1136/archdischild-2015-310221
6. Walker EYX, Marlais M. Should we screen for intracranial aneurysms in children with autosomal dominant polycystic kidney disease? *Pediatr Nephrol*. 2023;38(1):77-85. doi:10.1007/s00467-022-05432-5
7. Gabow PA, Johnson AM, Kaehny WD, Manco-Johnson ML, Duley IT, Everson GT. Risk factors for the development of hepatic cysts in autosomal dominant polycystic kidney disease. *Hepatology*. 1990;11(6):1033-1037. doi:10.1002/hep.1840110619
8. Nicolau C, Torra R, Bianchi L, et al. Abdominal sonographic study of autosomal dominant polycystic kidney disease.

J Clin Ultrasound. 2000;28(6):277-282. doi:10.1002/1097-0096(200007/08)28:6<277::aid-jcu2>3.0.co;2-l
9. Burgmaier K, Kilian S, Bammens B, et al. Clinical courses and complications of young adults with autosomal recessive polycystic kidney disease (ARPKD). *Sci Rep*. 2019;9(1):7919. doi:10.1038/s41598-019-43488-w
10. Adeva M, El-Youssef M, Rossetti S, et al. Clinical and molecular characterization defines a broadened spectrum of autosomal recessive polycystic kidney disease (ARPKD). *Medicine (Baltimore)*. 2006;85(1):1-21. doi:10.1097/01.md.0000200165.90373.9a
11. Nowak KL, Cadnapaphornchai MA, Chonchol MB, Schrier RW, Gitomer B. Long-term outcomes in patients with very-early onset autosomal dominant polycystic kidney disease. *Am J Nephrol*. 2016;44(3):171-178. doi:10.1159/000448695
12. Selistre L, de Souza V, Ranchin B, Hadj-Aissa A, Cochat P, Dubourg L. Early renal abnormalities in children with postnatally diagnosed autosomal dominant polycystic kidney disease. *Pediatr Nephrol*. 2012;27(9):1589-1593. doi:10.1007/s00467-012-2192-y
13. O'Brien K, Font-Montgomery E, Lukose L, et al. Congenital hepatic fibrosis and portal hypertension in autosomal dominant polycystic kidney disease. *J Pediatr Gastroenterol Nutr*. 2012;54(1):83-89. doi:10.1097/MPG.0b013e318228330c
14. Gulati A, Dahl NK, Hartung EA, et al. Hypomorphic PKD1 alleles impact disease variability in autosomal dominant polycystic kidney disease. *Kidney360*. 2023;4(3):387-392. doi:10.34067/KID.0000000000000064
15. Seeman T, Blahova K, Fencl F, et al. Kidney concentrating capacity in children with autosomal recessive polycystic kidney disease is linked to glomerular filtration and hypertension. *Pediatr Nephrol*. 2023;38(7):2093-2100. doi:10.1007/s00467-022-05834-5
16. Seeman T, Dusek J, Vondrak K, et al. Renal concentrating capacity is linked to blood pressure in children with autosomal dominant polycystic kidney disease. *Physiol Res*. 2004;53(6):629-634.
17. Massella L, Mekahli D, Paripovic D, et al. Prevalence of hypertension in children with early-stage ADPKD. *Clin J Am Soc Nephrol*. 2018;13(6):874-883. doi:10.2215/CJN.11401017
18. Lucchetti L, Chinali M, Emma F, Massella L. Autosomal dominant and autosomal recessive polycystic kidney disease: hypertension and secondary cardiovascular effect in children. *Front Mol Biosci*. 2023;10:1112727. doi:10.3389/fmolb.2023.1112727
19. Burgmaier K, Ariceta G, Bald M, et al. Severe neurological outcomes after very early bilateral nephrectomies in patients with autosomal recessive polycystic kidney disease (ARPKD). *Sci Rep*. 2020;10(1):16025. doi:10.1038/s41598-020-71956-1
20. Gimpel C, Bergmann C, Bockenhauer D, et al. International consensus statement on the diagnosis and management of autosomal dominant polycystic kidney disease in children and young people. *Nat Rev Nephrol*. 2019;15(11):713-726. doi:10.1038/s41581-019-0155-2
21. Halawi AA, Burgmaier K, Buescher AK, et al. Clinical characteristics and courses of patients with autosomal recessive polycystic kidney disease-mimicking phenocopies. *Kidney Int Rep*. 2023;8(7):1449-1454. doi:10.1016/j.ekir.2023.04.006
22. Cornec-Le Gall E, Torres VE, Harris PC. Genetic complexity of autosomal dominant polycystic kidney and liver diseases. *J Am Soc Nephrol*. 2018;29(1):13-23. doi:10.1681/ASN.2017050483
23. Hateboer N, v Dijk MA, Bogdanova N, et al. Comparison of phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. *Lancet*. 1999;353(9147):103-107. doi:10.1016/s0140-6736(98)03495-3
24. Cornec-Le Gall E, Audrezet MP, Chen JM, et al. Type of PKD1 mutation influences renal outcome in ADPKD. *J Am Soc Nephrol*. 2013;24(6):1006-1013. doi:10.1681/ASN.2012070650
25. Lavu S, Vaughan LE, Senum SR, et al. The value of genotypic and imaging information to predict functional and structural outcomes in ADPKD. *JCI Insight*. 2020;5(15):e138724. doi:10.1172/jci.insight.138724
26. Lanktree MB, Guiard E, Akbari P, et al. Patients with protein-truncating PKD1 mutations and mild ADPKD. *Clin J Am Soc Nephrol*. 2021;16(3):374-383. doi:10.2215/CJN.11100720
27. Porath B, Gainullin VG, Cornec-Le Gall E, et al. Mutations in GANAB, encoding the glucosidase II alpha subunit, cause autosomal-dominant polycystic kidney and liver disease. *Am J Hum Genet*. 2016;98(6):1193-1207. doi:10.1016/j.ajhg.2016.05.004
28. Cornec-Le Gall E, Olson RJ, Besse W, et al. Monoallelic mutations to DNAJB11 cause atypical autosomal-dominant polycystic kidney disease. *Am J Hum Genet*. 2018;102(5):832-844. doi:10.1016/j.ajhg.2018.03.013
29. Breysem L, De Keyzer F, Schellekens P, et al. Risk severity model for pediatric autosomal dominant polycystic kidney disease using 3D ultrasound volumetry. *Clin J Am Soc Nephrol*. 2023;18(5):581-591. doi:10.2215/CJN.0000000000000122
30. Claus LR, Chen C, Stallworth J, et al. Certain heterozygous variants in the kinase domain of the serine/threonine kinase NEK8 can cause an autosomal dominant form of polycystic kidney disease. *Kidney Int*. 2023;104(5):995-1007. doi:10.1016/j.kint.2023.07.021
31. Seeman T, Sulakova T, Bosakova A, Indrakova J, Grecmalova D. The first pediatric case of an IFT140 heterozygous deletion causing autosomal dominant polycystic kidney disease: case report. *Case Rep Nephrol Dial*. 2024;14(1):104-109. doi:10.1159/000539176
32. Gunay-Aygun M, Turkbey BI, Bryant J, et al. Hepatorenal findings in obligate heterozygotes for autosomal recessive polycystic kidney disease. *Mol Genet Metab*. 2011;104(4):677-681. doi:10.1016/j.ymgme.2011.09.001
33. Ward CJ, Hogan MC, Rossetti S, et al. The gene mutated in autosomal recessive polycystic kidney disease encodes a large, receptor-like protein. *Nat Genet*. 2002;30(3):259-269. doi:10.1038/ng833
34. Onuchic LF, Furu L, Nagasawa Y, et al. PKHD1, the polycystic kidney and hepatic disease 1 gene, encodes a novel large protein containing multiple immunoglobulin-like plexin-transcription-factor domains and parallel beta-helix 1 repeats. *Am J Hum Genet*. 2002;70(5):1305-1317. doi:10.1086/340448
35. Burgmaier K, Brinker L, Erger F, et al. Refining genotype-phenotype correlations in 304 patients with autosomal recessive polycystic kidney disease and PKHD1 gene variants. *Kidney Int*. 2021;100(3):650-659. doi:10.1016/j.kint.2021.04.019
36. Lu H, Galeano MCR, Ott E, et al. Mutations in DZIP1L, which encodes a ciliary-transition-zone protein, cause autosomal recessive polycystic kidney disease. *Nat Genet*. 2017;49(7):1025-1034. doi:10.1038/ng.3871
37. Yang C, Harafuji N, O'Connor AK, et al. Cystin genetic variants cause autosomal recessive polycystic kidney disease associated with altered Myc expression. *Sci Rep*. 2021;11(1):18274. doi:10.1038/s41598-021-97046-4
38. Vujic M, Heyer CM, Ars E, et al. Incompletely penetrant PKD1 alleles mimic the renal manifestations of ARPKD. *J Am Soc Nephrol*. 2010;21(7):1097-1102. doi:10.1681/ASN.2009101070
39. Gimpel C, Avni FE, Bergmann C, et al. Perinatal diagnosis, management, and follow-up of cystic renal diseases: a clinical

practice recommendation with systematic literature reviews. *JAMA Pediatr*. 2018;172(1):74-86. doi:10.1001/jamapediatrics.2017.3938
40. Thompson WS, Babayev SN, McGowan ML, et al. State of the science and ethical considerations for preimplantation genetic testing for monogenic cystic kidney diseases and ciliopathies. *J Am Soc Nephrol*. 2024;35(2):235-248. doi:10.1681/ASN.0000000000000253
41. McConnachie DJ, Stow JL, Mallett AJ. Ciliopathies and the kidney: a review. *Am J Kidney Dis*. 2021;77(3):410-419. doi:10.1053/j.ajkd.2020.08.012
42. Deng L, Liu Y, Yuan M, Meng M, Yang Y, Sun L. Prenatal diagnosis and outcome of fetal hyperechogenic kidneys in the era of antenatal next-generation sequencing. *Clin Chim Acta*. 2022;528:16-28. doi:10.1016/j.cca.2022.01.012
43. Yulia A, Napolitano R, Aiman A, et al. Perinatal and infant outcome of fetuses with prenatally diagnosed hyperechogenic kidneys. *Ultrasound Obstet Gynecol*. 2021;57(6):953-958. doi:10.1002/uog.22121
44. Al Naimi A, Baumuller JE, Spahn S, Bahlmann F. Prenatal diagnosis of multicystic dysplastic kidney disease in the second trimester screening. *Prenat Diagn*. 2013;33(8):726-731. doi:10.1002/pd.4112
45. Wiesel A, Queisser-Luft A, Clementi M, Bianca S, Stoll C, Group ES. Prenatal detection of congenital renal malformations by fetal ultrasonographic examination: an analysis of 709,030 births in 12 European countries. *Eur J Med Genet*. 2005;48(2):131-144. doi:10.1016/j.ejmg.2005.02.003
46. Hertenstein CB, Miller KA, Estroff JA, Blakemore KJ. Fetal hyperechoic kidneys: Diagnostic considerations and genetic testing strategies. *Prenat Diagn*. 2024;44(2):222-236. doi:10.1002/pd.6517
47. Verscaj CP, Velez-Bartolomei F, Bodle E, et al. Characterization of the prenatal renal phenotype associated with 17q12, HNF1B, microdeletions. *Prenat Diagn*. 2024;44(2):237-246. doi:10.1002/pd.6424
48. Koumbaris G, Achilleos A, Nicolaou M, et al. Targeted capture enrichment followed by NGS: development and validation of a single comprehensive NIPT for chromosomal aneuploidies, microdeletion syndromes and monogenic diseases. *Mol Cytogenet*. 2019;12:48. doi:10.1186/s13039-019-0459-8
49. Luong TLA, Nguyen DA, Dao TT, et al. Combined cell-free DNA screening for aneuploidies and selected single-gene disorders for pregnancies with sonographically detected fetal anomalies: detection rate and residual risk. *Prenat Diagn*. 2025;45(1):70-76. doi:10.1002/pd.6720
50. Beall MH, van den Wijngaard JP, van Gemert MJ, Ross MG. Amniotic fluid water dynamics. *Placenta*. 2007;28(8-9):816-823. doi:10.1016/j.placenta.2006.11.009
51. Wu CS, Chen CM, Chou HC. Pulmonary hypoplasia induced by oligohydramnios: findings from animal models and a population-based study. *Pediatr Neonatol*. 2017;58(1):3-7. doi:10.1016/j.pedneo.2016.04.001
52. Miller JL, Baschat AA, Atkinson MA. Fetal therapy for renal anhydramnios. *Clin Perinatol*. 2022;49(4):849-862. doi:10.1016/j.clp.2022.08.001
53. Nishi K, Ozawa K, Kamei K, et al. Long-term outcomes, including fetal and neonatal prognosis, of renal oligohydramnios: a retrospective study over 22 years. *J Pediatr*. 2024:114151. doi:10.1016/j.jpeds.2024.114151
54. Burgmaier K, Kunzmann K, Ariceta G, et al. Risk factors for early dialysis dependency in autosomal recessive polycystic kidney disease. *J Pediatr*. 2018;199:22-28.e6. doi:10.1016/j.jpeds.2018.03.052
55. Sanderson KR, Shih WV, Warady BA, Claes DJ. Severe fetal CAKUT (congenital anomalies of the kidneys and urinary tract), prenatal consultations, and initiation of neonatal dialysis. *Am J Perinatol*. 2024;41(S1):e156-e162. doi:10.1055/a-1850-4429
56. Walker EYX, Winyard P, Marlais M. Congenital anomalies of the kidney and urinary tract: antenatal diagnosis, management and counselling of families. *Pediatr Nephrol*. 2024;39(4):1065-1075. doi:10.1007/s00467-023-06137-z
57. Fisher J. Termination of pregnancy for fetal abnormality: the perspective of a parent support organisation. *Reprod Health Matters*. 2008;16(31)(suppl):57-65. doi:10.1016/S0968-8080(08)31382-2
58. Marokakis S, Kasparian NA, Kennedy SE. Prenatal counselling for congenital anomalies: a systematic review. *Prenat Diagn*. 2016;36(7):662-671. doi:10.1002/pd.4836
59. Watson AR. Non-compliance and transfer from paediatric to adult transplant unit. *Pediatr Nephrol*. 2000;14(6):469-472. doi:10.1007/s004670050794
60. Dobbels F, Ruppar T, De Geest S, Decorte A, Van Damme-Lombaerts R, Fine RN. Adherence to the immunosuppressive regimen in pediatric kidney transplant recipients: a systematic review. *Pediatr Transplant*. 2010;14(5):603-613. doi:10.1111/j.1399-3046.2010.01299.x
61. Watson AR, Harden P, Ferris M, Kerr PG, Mahan J, Ramzy MF. Transition from pediatric to adult renal services: a consensus statement by the International Society of Nephrology (ISN) and the International Pediatric Nephrology Association (IPNA). *Pediatr Nephrol*. 2011;26(10):1753-1757. doi:10.1007/s00467-011-1981-z
62. Guay-Woodford LM, Desmond RA. Autosomal recessive polycystic kidney disease: the clinical experience in North America. *Pediatrics*. 2003;111(5):1072-1080. doi:10.1542/peds.111.5.1072
63. Ebner K, Feldkoetter M, Ariceta G, et al. Rationale, design and objectives of ARegPKD, a European ARPKD registry study. *BMC Nephrol*. 2015;16:22. doi:10.1186/s12882-015-0002-z
64. Klawitter J, McFann K, Pennington AT, et al. Pravastatin therapy and biomarker changes in children and young adults with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2015;10(9):1534-1541. doi:10.2215/CJN.11331114
65. Burgmaier K, Kilian S, Arbeiter K, et al. Early childhood height-adjusted total kidney volume as a risk marker of kidney survival in ARPKD. *Sci Rep*. 2021;11(1):21677. doi:10.1038/s41598-021-00523-z
66. Ajiri R, Burgmaier K, Akinci N, et al. Phenotypic variability in siblings with autosomal recessive polycystic kidney disease. *Kidney Int Rep*. 2022;7(7):1643-1652. doi:10.1016/j.ekir.2022.04.095
67. Dell KM, Matheson M, Hartung EA, Warady BA, Furth SL; Chronic Kidney Disease in Children (CKiD) Study. Kidney disease progression in autosomal recessive polycystic kidney disease. *J Pediatr*. 2016;171:196-201.e1. doi:10.1016/j.jpeds.2015.12.079
68. Abdul Majeed N, Font-Montgomery E, Lukose L, et al. Prospective evaluation of kidney and liver disease in autosomal recessive polycystic kidney disease-congenital hepatic fibrosis. *Mol Genet Metab*. 2020;131(1-2):267-276. doi:10.1016/j.ymgme.2020.08.006
69. De Rechter S, Bockenhauer D, Guay-Woodford LM, et al. ADPedKD: a global online platform on the management of children with ADPKD. *Kidney Int Rep*. 2019;4(9):1271-1284. doi:10.1016/j.ekir.2019.05.015
70. Helal I, Reed B, McFann K, et al. Glomerular hyperfiltration and renal progression in children with autosomal dominant

polycystic kidney disease. *Clin J Am Soc Nephrol*. 2011;6(10):2439-2443. doi:10.2215/CJN.01010211
71. Fick-Brosnahan GM, Tran ZV, Johnson AM, Strain JD, Gabow PA. Progression of autosomal-dominant polycystic kidney disease in children. *Kidney Int*. 2001;59(5):1654-1662. doi:10.1046/j.1523-1755.2001.0590051654.x
72. Irazabal MV, Rangel LJ, Bergstralh EJ, et al. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. *J Am Soc Nephrol*. 2015;26(1):160-172. doi:10.1681/ASN.2013101138
73. MacAskill CJ, Markley M, Farr S, et al. Rapid B(1)-insensitive MR fingerprinting for quantitative kidney imaging. *Radiology*. 2021;300(2):380-387. doi:10.1148/radiol.2021202302
74. MacAskill CJ, Kretzler ME, Parsons A, et al. Multimodal magnetic resonance imaging assessments of kidney disease severity in autosomal recessive polycystic kidney disease. *Kidney Int Rep*. 2024;9(12):3592-3595. doi:10.1016/j.ekir.2024.09.006
75. Yang X, Wang W, Gitomer B, Cadnapaphornchai MA, Xing F, Chonchol M. Imaging biomarkers in young patients with ADPKD. *Kidney Int Rep*. 2023;8(10):2153-2155. doi:10.1016/j.ekir.2023.07.004
76. Ghanem A, Borghol AH, Munairdjy Debeh FG, et al. Biomarkers of kidney disease progression in ADPKD. *Kidney Int Rep*. 2024;9(10):2860-2882. doi:10.1016/j.ekir.2024.07.012
77. Liebau MC, Mekahli D, Perrone R, Soyfer B, Fedeles S. Polycystic kidney disease drug development: a conference report. *Kidney Med*. 2023;5(3):100596. doi:10.1016/j.xkme.2022.100596
78. Messchendorp AL, Meijer E, Visser FW, et al. Rapid progression of autosomal dominant polycystic kidney disease: urinary biomarkers as predictors. *Am J Nephrol*. 2019;50(5):375-385. doi:10.1159/000502999
79. Liebau MC, Mekahli D. Translational research approaches to study pediatric polycystic kidney disease. *Mol Cell Pediatr*. 2021;8(1):20. doi:10.1186/s40348-021-00131-x
80. Torres VE, Chapman AB, Devuyst O, et al. Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease: the TEMPO 4:4 Trial. *Nephrol Dial Transplant*. 2018;33(3):477-489. doi:10.1093/ndt/gfx043
81. Gattone VH, 2nd, Wang X, Harris PC, Torres VE. Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. *Nat Med*. 2003;9(10):1323-1326. doi:10.1038/nm935
82. Muller RU, Messchendorp AL, Birn H, et al. An update on the use of tolvaptan for autosomal dominant polycystic kidney disease: consensus statement on behalf of the ERA Working Group on Inherited Kidney Disorders, the European Rare Kidney Disease Reference Network and Polycystic Kidney Disease International. *Nephrol Dial Transplant*. 2022;37(5):825-839. doi:10.1093/ndt/gfab312
83. Liebau MC, Hartung EA, Perrone RD. Perspectives on drug development in autosomal recessive polycystic kidney disease. *Clin J Am Soc Nephrol*. 2022;17(10):1551-1554. doi:10.2215/CJN.04870422
84. Podrini C, Cassina L, Boletta A. Metabolic reprogramming and the role of mitochondria in polycystic kidney disease. *Cell Signal*. 2020;67:109495. doi:10.1016/j.cellsig.2019.109495
85. Liebau MC. Is there a functional role of mitochondrial dysfunction in the pathogenesis of ARPKD? *Front Med (Lausanne)*. 2021;8:739534. doi:10.3389/fmed.2021.739534
86. Flynn JT. What level of blood pressure is concerning in childhood? *Circ Res*. 2022;130(5):800-808. doi:10.1161/CIRCRESAHA.121.319819
87. Gimpel C, Liebau MC, Schaefer F. Systematic review on outcomes used in clinical research on autosomal recessive polycystic kidney disease-are patient-centered outcomes our blind spot? *Pediatr Nephrol*. 2021;36(12):3841-3851. doi:10.1007/s00467-021-05192-8
88. Nowak KL, Farmer-Bailey H, Wang W, et al. Curcumin therapy to treat vascular dysfunction in children and young adults with ADPKD: a randomized controlled trial. *Clin J Am Soc Nephrol*. 2022;17(2):240-250. doi:10.2215/CJN.08950621
89. Cadnapaphornchai MA, McFann K, Strain JD, Masoumi A, Schrier RW. Prospective change in renal volume and function in children with ADPKD. *Clin J Am Soc Nephrol*. 2009;4(4):820-829. doi:10.2215/CJN.02810608
90. Mekahli D, Guay-Woodford LM, Cadnapaphornchai MA, et al. Tolvaptan for children and adolescents with autosomal dominant polycystic kidney disease: randomized controlled trial. *Clin J Am Soc Nephrol*. 2023;18(1):36-46. doi:10.2215/CJN.0000000000000022