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CONSENSUS EXPERT RECOMMENDATIONS FOR THE DIAGNOSIS AND MANAGEMENT OF AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE: REPORT OF AN INTERNATIONAL CONFERENCE

Lisa M. Guay-Woodford¹, John J. Bissler², Michael C. Braun³, Detlef Bockenhauer⁴, Melissa A. Cadnapaphornchai⁵, Katherine M. Dell⁶, Larissa Kerecuk⁷, Max C. Liebau⁸, Maria H. Alonso-Peclet⁹, Benjamin Shneider¹⁰, Sukru Emre¹¹, Theo Heller¹², Binita M. Kamath¹³, Karen F. Murray¹⁴, Kenneth Moise¹⁵, Eric E. Eichenwald¹⁶, Jacquelyn Evans¹⁷, Roberta L. Keller¹⁸, Louise Wilkins-Haug¹⁹, Carsten Bergmann^{20,21}, Meral Gunay-Aygun^{22,23}, Stephen R. Hooper²⁴, Kristina K. Hardy²⁵, Erum A. Hartung²⁶, Randi Streisand¹, Ronald Perrone²⁷, and Marva Moxey-Mims²⁸

¹Center for Translational Science, Children's National Health System, Washington, DC, 20010

²Division of Pediatric Nephrology, LeBonheur Children's Hospital and St. Jude Children's Research Hospital, Memphis, TN, 38103

³Renal Section, Texas Children's Hospital, Houston, TX, 77030

⁴UCL Institute of Child Health and Nephrology Department, Great Ormond Street Hospital, London, WC1N 3JH, UK

⁵Division of Pediatric Nephrology, Children's Hospital Colorado, Aurora, CO, 80045

⁶Department of Pediatrics, Case Western Reserve University and Cleveland Clinic Children's Hospital, Cleveland, OH, 44195

⁷Department of Paediatric Nephrology, Birmingham Children's Hospital, NHS Foundation Trust, Birmingham, B4 6NH, UK

⁸Department of Pediatrics and Center for Molecular Medicine, Cologne University Hospital, 50931 Cologne, Germany

⁹Department of Surgery, Cincinnati Children's Hospital, Cincinnati, OH, 45229

¹⁰Division of Pediatric Hepatology, Children's Hospital of Pittsburgh, Pittsburgh, PA, 15224

¹¹Section of Transplantation and Immunology, Department of Surgery, Yale University School of Medicine, New Haven, CT, 06520

Corresponding Author: Lisa M. Guay-Woodford, MD, Center for Translational Science, Children's National Health System, 6th Floor Main Hospital, Center 6, 111 Michigan Ave NW, Washington, DC 20010. Telephone: 202-476-6439. LGuaywoo@childrensnational.org.

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- ¹²Liver Disease Branch, NIDDK, National Institutes of Health, Bethesda, MD, 20814
- ¹³Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, Toronto, Ontario, Canada, M5G 1X8
- ¹⁴Division of Pediatric Gastroenterology and Hepatology, Seattle Children's Hospital, Seattle, WA, 98105
- ¹⁵Department of Obstetrics, Gynecology and Reproductive Sciences, The University of Texas Health Science Center at Houston, Houston, TX, 77030
- ¹⁶Department of Pediatrics, The University of Texas Health Science Center at Houston, Houston, TX, 77030
- ¹⁷Division of Neonatology, Children's Hospital of Philadelphia, Philadelphia, PA, 19104
- ¹⁸Division of Neonatology, University of California at San Francisco Children's Hospital, San Francisco, CA, 94143
- ¹⁹Division of Maternal Fetal Medicine and Reproductive Genetics, Brigham and Women's Hospital, Boston, MA, 02115
- ²⁰Bioscientia, Center for Human Genetics, D-55218 Ingelheim, Germany
- ²¹Department of Nephrology and Center for Clinical Research, University Hospital Freiburg, 79106 Freiburg, Germany
- ²²Department of Pediatrics, Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, 21287
- ²³Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892
- ²⁴Department of Allied Health Sciences and Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill, NC, 2759
- ²⁵Department of Neuropsychology, Children's National Health System, Washington, DC, 20010
- ²⁶Division of Nephrology, Children's Hospital of Philadelphia, Philadelphia, PA, 19104
- ²⁷Division of Nephrology, Tufts Medical Center, Boston, MA, 02111
- ²⁸Division of Kidney, Urologic, and Hematologic Diseases, NIDDK, National Institutes of Health, Bethesda, MD, 20814

Abstract

Autosomal recessive polycystic kidney disease (ARPKD; MIM 263200) is a severe, typically early onset form of cystic disease that primarily involves the kidneys and biliary tract. Phenotypic expression and age at presentation can be quite variable¹. The incidence of ARPKD is 1 in 20,000 live births², and its pleotropic manifestations are potentially life-threatening. Optimal care requires proper surveillance to limit morbidity and mortality, knowledgeable approaches to diagnosis and treatment, and informed strategies to optimize quality of life. Clinical management therefore is ideally directed by multidisciplinary care teams consisting of perinatologists, neonatologists, nephrologists, hepatologists, geneticists, and behavioral specialists to coordinate patient care from

the perinatal period to adulthood. In May 2013, an international team of 25 multidisciplinary specialists from the US, Canada, Germany, and the United Kingdom convened in Washington, DC, to review the literature published from 1990 to 2013 and to develop recommendations for diagnosis, surveillance, and clinical management. Identification of the gene *PKHD1*, and the significant advances in perinatal care, imaging, medical management, and behavioral therapies over the past decade, provide the foundational elements to define diagnostic criteria and establish clinical management guidelines as the first steps towards standardizing the clinical care for ARPKD patients. The key issues discussed included recommendations regarding perinatal interventions, diagnostic criteria, genetic testing, management of renal and biliary-associated morbidities, and behavioral assessment. The meeting was funded by the National Institutes of Health and an educational grant from the Polycystic Kidney Disease Foundation. Here we summarize the discussions and provide an updated set of diagnostic, surveillance, and management recommendations for optimizing the pediatric care of patients with ARPKD. Specialist care of ARPKD-related complications including dialysis, transplantation, and management of severe portal hypertension will be addressed in a subsequent report. Given the paucity of information regarding targeted therapies in ARPKD, this topic was not addressed in this conference.”

Keywords

ARPKD; hepatorenal fibrocystic diseases; congenital hepatic fibrosis; oligohydramnios; *PKHD1*; neurocognition

GENETICS WORK GROUP

ARPKD Genetics

As an autosomal recessive trait, ARPKD has a recurrence risk of 25%, regardless of sex.

***PKHD1* gene and fibrocystin/polyductin (FPC) protein**—*PKHD1* is a large gene extending over a ~500-kb genomic segment on chromosome 6p12³. The longest open reading frame comprises 66 exons that encode fibrocystin/polyductin complex (FPC). There is evidence for extensive alternative splicing; whether all the predicted alternative *PKHD1* transcripts are translated into proteins and what their biological functions may be it remains unknown. Overall, a critical amount of full-length protein seems to be required for sufficient biological function.

DNA-based diagnostic testing—The large size of *PKHD1* poses significant challenges to current DNA sequencing methods. Other diagnostic challenges relate to the high frequency of missense mutations and private mutations in ‘non-isolate’ populations³. “In cases with strong clinical and/or histopathological evidence for ARPKD, mutation detection rates of about 80–85% have been demonstrated for the patients across the entire clinical spectrum^{1, 4}. Several other cilia-related disease genes may mimic (“phenocopy”) ARPKD. For instance, 2% of all ADPKD patients express an early onset, severe phenotype that is clinically indistinguishable from ARPKD⁵. Finally, the phenotype of ARPKD can also be mimicked by mutations in the *HNF1B* gene, which encodes the transcription factor,

hepatocyte nuclear factor-1beta (HNF1B), as well as by other gene defects that cause the hepatorenal fibrocystic diseases (HRFD; Table).

Expert opinion

- Given the high number of phenocopy disorders, mutational analysis of *PKHD1* using current single-gene testing methodologies should not be considered as a first-line diagnostic approach for infants and children presenting with an ARPKD-like phenotype.
- Pathogenicity predictions for missense variants represent another diagnostic challenge; caution is required when only novel or rare missense changes are detected.
- More robust next generation sequencing methods that allow simultaneous investigation of multiple cystic kidney disease genes will increasingly become available.

Prenatal genetic diagnosis

Prenatal US detection of ARPKD is often not early enough for pregnancy termination.

Expert opinion

- At present, early and reliable prenatal diagnosis is only feasible by molecular genetic analysis using single-gene testing methodologies.
- Indirect, haplotype-based linkage analysis was performed for ARPKD before complete gene sequencing was widely available. Given the possibility of misdiagnosis, linkage analysis is no longer a diagnostic method of choice.

Genotype-phenotype correlations

Genotype-phenotype correlation for *PKHD1* is hampered by a wide range of mutations, with children typically inheriting a different ARPKD mutation from each parent (compound heterozygotes)⁶. Practically all patients carrying two truncating mutations display a severe phenotype with peri- or neonatal demise, although exceptions have been reported⁷. In comparison, patients surviving the neonatal period usually bear at least one missense mutation; although the converse does not seem to apply and some missense changes can be as devastating as truncating mutations.

Expert opinion

- Caution must be exercised when predicting the clinical course from the genotype.

PERINATAL/NEONATAL WORK GROUP

Fetal Diagnostic Considerations

Expert opinion

- Standard second trimester ultrasound (US) imaging is usually sufficient to suggest the diagnosis of ARPKD, especially if findings include bilateral changes of large hyperechogenic kidneys with poor cortico-medullary differentiation.
- Macrocysts (>10 mm) in the fetal ARPKD kidney are unusual and suggest multicystic dysplasia; whereas bilateral cysts of 5–7 mm are reported in 29% of ARPKD cases⁸.
- A systematic evaluation should be undertaken for extra-renal anomalies, as other fetal conditions have been associated with renal hyperechogenicity. Of particular note, mutations in *HNF1B* have been shown in some studies to be the most common cause of fetal hyperechogenic kidneys⁹. Other associations include: Turner syndrome; Trisomies 8, 13, or 18; congenital cytomegalovirus infection; acyl-CoA dehydrogenase defects (glutaric aciduria type II); and the hepatorenal fibrocystic disorders (Table).
- In the context of severe oligohydramnios, fetal magnetic resonance imaging may better delineate the renal anatomy¹⁰.
- Amniocentesis should be considered for fetal karyotype and polymerase chain reaction for cytomegalovirus (CMV). Following transplacental passage, CMV typically infects the fetal kidney, which can result in sonographic evidence of increased renal echogenicity and oligohydramnios in CMV-infected fetuses¹¹.
- A complete three-generation family pedigree should be documented, particularly adult onset renal diseases and neonatal death related to pulmonary insufficiency or renal failure.
- Ultrasonography of the parents is recommended to screen for pre-symptomatic, dominant cystic kidney diseases, such as ADPKD or *HNF1B*-related disease.

Fetal monitoring

Once a presumptive diagnosis of ARPKD is made, US should be performed every 2 – 3 weeks for serial assessment of the renal size and amniotic fluid volume. The gestational age (GA) at onset of oligohydramnios is variable in ARPKD. Onset of oligohydramnios in the second trimester may be associated with pulmonary hypoplasia and in one series, renal size >4 SD in association with oligohydramnios was associated with 100% perinatal mortality¹². A study of 46 fetuses with severe genitourinary anomalies¹³ demonstrated that after 26 weeks GA, a total lung volume value of <0.90 by magnetic resonance imaging has a sensitivity of 77.8% and specificity of 95% for predicting non-survival. A 3D US study showed that total fetal lung volume <5 %ile corrected for GA yielded a positive predictive value of 80% and a negative predictive value of 94% for lethal pulmonary hypoplasia.

Expert opinion

- Prenatal imaging does not provide precise prediction for the development of lethal neonatal pulmonary hypoplasia.

Perinatal management

After delivery, neonatal pulmonary status will usually dictate early management. When there has been a presumptive diagnosis of ARPKD, a mortality of 30–40% due to pulmonary hypoplasia has been reported¹⁴. Some infants with milder forms of pulmonary hypoplasia may respond well to high frequency ventilation. Persistent pulmonary hypertension (HTN) may be a prominent, but potentially reversible, component of the lung disease in the first days after birth that may respond to inhaled nitric oxide. In some cases, even extracorporeal membrane oxygenation may be appropriate if respiratory failure and/or pulmonary hypertension is not thought to be due to lethal lung hypoplasia. The potential need for dialysis in severely affected ARPKD neonates raises complex issues. Although survival of infants who initiate dialysis has improved significantly, mortality and morbidity remain concerning¹⁵.

Expert opinion

- Patients with a presumptive diagnosis of ARPKD should be referred for delivery at a facility with a level IV NICU¹⁶.
- Multidisciplinary prenatal consultation with input from maternal-fetal medicine, neonatology, and pediatric nephrology addressing delivery plans, neonatal respiratory illness, and short- and longer-term renal function should be arranged.
- A delivery plan should include the possibility of cesarean delivery for fetal abdominal dystocia due to renal enlargement.
- Given the lack of definitive fetal predictors of postnatal survival, decisions regarding aggressiveness of intervention both in labor and at delivery must take into account family preferences and all clinical information available at the time.
- The decision to offer (or withhold) dialysis should be made jointly by the treating physicians and the infant's parents. Peritoneal dialysis is the preferred modality¹⁷.

RENAL WORK GROUP**General Considerations**

Diagnostics—ARPKD is suggested by characteristic hepatorenal involvement and a pedigree consistent with autosomal-recessive inheritance¹.

Expert opinion

- Finding large echogenic kidneys with poor cortico-medullary differentiation bilaterally, and coexisting liver disease on standard diagnostic US imaging is usually sufficient for the diagnosis of ARPKD.

- High resolution US may improve diagnostic sensitivity, particularly in mild disease⁶. Unlike in ADPKD, kidney size/volume do not correlate with renal function in ARPKD⁶.
- There may be phenotypic overlay with ADPKD and other HRFD (Table).
- In some patients, serial observation may be required to make the correct diagnosis.
- Genetic testing may facilitate the diagnosis in patients with suspected ARPKD.

Screening of siblings

Expert opinion

- ARPKD expression can be highly variable within sibships^{1, 18}.
- Abdominal imaging of siblings into adulthood may be appropriate¹⁹. Genetic testing may be helpful in defining the affection status of even apparently asymptomatic siblings if two pathogenic *PKHD1* mutations have been identified in the index case.

Hypertension (HTN)—The prevalence of systemic HTN in children with ARPKD is 33–75%^{1, 6, 18, 20}. Marked HTN is often observed in the first months of life, and neonates with systemic HTN are statistically more likely to require mechanical ventilation ($p < 0.0001$)¹. The pathogenic mechanism remains poorly understood. Limited studies in humans and animal models suggest that activation of the intra-renal renin-angiotensin-aldosterone system, without concurrent elevation in systemic angiotensin I and II levels, may play a role^{21, 22}. In addition, impaired urinary dilution with associated fluid retention and dysregulation of the collecting duct epithelial sodium channel may be contributing factors to ARPKD-related systemic HTN^{23, 24}.

Expert opinion

- “The mainstays of current therapy are angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). Combination ACEI/ARB therapy is not recommended due to increased risk of side effects, without clear added benefit. Therapy should be directed towards optimizing blood pressure control, while minimizing further reduction in GFR in the context of chronic kidney disease (CKD)²⁰.
- The recent multicenter ESCAPE trial in children with Chronic Kidney Disease stages 2–4 indicated that aggressive blood pressure control (target 24-hour mean arterial blood pressure below the 50th percentile for age, height and sex) may slow progression to end-stage renal disease²⁵; the specific target for ARPKD has not been established.

Intracranial aneurysms—In contrast to ADPKD, intracranial aneurysms are rarely described with ARPKD²⁶.

Expert opinion

- There is no evidence-based association between ARPKD and intracranial aneurysms.
- Routine screening of asymptomatic patients is not warranted.

Hyponatremia—Hyponatremia is common in ARPKD, with a reported incidence of 6–26%^{1, 27}. The mechanism likely involves impaired urinary dilution (rather than sodium wasting) leading to water overload, at a time when caloric and fluid intake is coupled and nutrition has a low osmotic load.

Expert opinion

- Standard treatment principles apply: in euvoemia or hypervolemia, fluid intake should be minimized without compromising nutrition, e.g. by concentrating feeds.
- Supplementation with sodium is likely to worsen HTN and should be avoided, unless there is evidence of hypovolemia.
- It is not known whether the hyponatremia is due to excessive vasopressin or tubulointerstitial dysfunction. Thus, vasopressin receptor blockers (Vaptans) are currently not recommended.

Postnatal Management/Recommendations—Even in newborns with massively enlarged kidneys, some renal function may be preserved and may transiently improve during the first months of life²⁸. Given the often difficult issues with respiratory and nutritional support, unilateral or bilateral nephrectomy has been suggested to improve respiratory status or feeding. However, the risk of accelerating renal function loss and the consequent need for renal replacement therapy early in life must be carefully weighed. Dialysis recommendations for infants are addressed above.

Expert opinion

- The rationale for unilateral nephrectomy is based on few small nutrition studies^{29–31}.
- There is no evidence that nephrectomy results in respiratory improvement.
- There is no evidence to support nephrectomy for severe HTN in early ARPKD.

LIVER WORK GROUP**General Considerations**

Diagnostics—The primary liver disease in ARPKD is often referred to as congenital hepatic fibrosis (CHF) or ductal plate malformation and is manifest primarily by portal HTN and/or bile duct disease³². Portal HTN can cause splenomegaly with hypersplenism, and varices at risk for hemorrhage. Biliary disease may be very subtle, may not be appreciated by liver biochemistries or imaging studies, but can result in cholangitis. CHF is not typically associated with significant hepatobiliary inflammation or hepatic dysfunction; serum amino transferases and laboratory findings reflective of synthetic liver function (e.g. coagulation

profile) are normal or near normal. Therefore, a high index of suspicion is required to recognize advancing liver disease in children with ARPKD.

Expert opinion

- In the context of known ARPKD, CHF is presumed when portal HTN is present (see below) and biochemical evidence of liver disease is minimal (i.e. serum amino transferases $<2 \times$ upper limit of normal (ULN)), liver biopsy is not indicated and extensive investigation for other causes of liver disease is not necessary. However, portal vein thrombosis should be excluded by US.
- Portal HTN is defined by splenomegaly (i.e. spleen palpable >2 cm below the left costal margin or >1 cm larger than the ULN for age³³) and thrombocytopenia with a value <150 mm³, or known varices, ascites, or hepatopulmonary syndrome.
- Cholangiopathy is defined by noninvasive radiologic demonstration of intra- or extra-hepatic biliary abnormalities. Of note, CHF-cholangiopathy with cholangitis may exist despite normal radiologic findings.

Anticipatory Guidance—Although uncommon, clinical manifestations of CHF (e.g. variceal hemorrhage and/or cholangitis) can be life-threatening³⁴, requiring a heightened awareness and anticipatory guidance for possible complications. Even though still relatively low, the risk of mortality increases if treatment is delayed. Cholangitis, in particular, may be difficult to diagnose definitively; the classical triad of fever, jaundice, and right upper quadrant pain is rarely observed in children, and other more common causes of fever in childhood are often invoked. Although there is an increased risk of hepatobiliary cancer (e.g. cholangiocarcinoma and hepatocellular carcinoma) in individuals with CHF, this dreadful complication has not been described in individuals younger than 40 years of age³⁴.

Expert opinion

- Hematemesis, hemochezia and/or melena require **immediate** medical attention (e.g. in an emergency facility with capacity for red blood cell transfusion).
- A high index of suspicion for cholangitis is required of those caring for ARPKD children.
- Hepatobiliary cancer is not a feature of ARPKD in childhood.

Screening—Screening for liver disease, especially complications of CHF, are warranted in children who have ARPKD. Features of portal HTN are the most frequent early manifestation of CHF and their identification permits anticipation of further complications. Liver biochemistries are not typically informative. Splenomegaly on physical examination is useful, but may be difficult to appreciate in a child with significant nephromegaly. Absence of splenomegaly does not exclude portal hypertension, however, so one should monitor for associated neutropenia or thrombocytopenia. There is no clear correlation between the severity of biliary abnormalities and the risk of cholangitis.

Expert opinion

- Care should be taken to identify splenomegaly on physical examination, with further evaluation by US (e.g. Doppler of the portal and splenic veins; measurement of maximal dimension of the spleen; and surveillance for intra- or extra-hepatic biliary dilatation).
- Annual complete blood and platelet count should be performed, with attention to the absolute counts, as well as the trends in these measurements.
- At 5 years of age, abdominal US should be performed, with attention to both intra- and extra-hepatic bile ducts and the maximal linear dimension of the spleen. If the initial studies are negative, follow up is recommended at least every 2 to 3 years.
- Suspicion for portal hypertension or biliary abnormalities should prompt a referral to a pediatric gastroenterologist/hepatologist. Once portal hypertension is verified, screening for associated complications follows standard guidelines³⁵.

Prophylaxis—The utility of antibiotic prophylaxis for complications of CHF is not clearly established. Ursodeoxycholic acid (UDCA), with its choleric effect, is theoretically useful in chronic cholestasis, but this does not apply to in most cases of CHF. Furthermore, randomized, placebo-controlled studies in adults with sclerosing cholangitis have identified a previously unknown **potential** toxicity of UDCA³⁶; the relevance to CHF is unknown.

Expert opinion

- Routine antibiotic prophylaxis for cholangitis is not indicated.
- Antibiotic prophylaxis for 6 to 12 weeks after a cholangitis episode, immediately following transplantation, or in the context of enhanced immunosuppression may be considered.
- Approaches to prevention and treatment of varices are similar, if not identical, to approaches used in children with portal HTN from other causes and are typically decided upon by the subspecialist.
- The use of UCDA as a choleric cannot be recommended.

Cholangitis and Hypersplenism—Complications of biliary disease and portal hypertension in ARPKD raise important considerations for the pediatrician. A diagnosis of cholangitis often necessitates a prolonged course of intravenous antibiotics and potentially worsens the prognosis of the CHF. Recurrent cholangitis is sometimes an indication for liver transplantation. Cytopenia in the context of portal HTN may unnecessarily raise concerns, as these blood count abnormalities are not typically associated with the same morbidities as cytopenias observed with bone marrow failure or related disorders. Similarly, symptoms like abdominal pain and anorexia are sometimes attributed to pronounced splenomegaly, although a causal relationship is difficult to prove. Perhaps the most vexing issue relates to splenomegaly and concerns about splenic injury when a portion of the spleen is unprotected by the rib cage.

Expert opinion on cholangitis

- Cholangitis is a clinical diagnosis that can be difficult to definitively establish.
- Cholangitis should be considered in any ARPKD child with unexplained fever.
- An especially high index of suspicion is warranted in the first months after renal transplantation or when immunosuppression is high.
- Liver biopsy rarely yields a diagnosis of cholangitis and may represent a significant risk in the setting of biliary dilatation.

Expert opinion on cholangitis

- Hypersplenism-associated leukopenia does not typically increase infection risk.
- Splenectomy is rarely indicated as an isolated procedure.
- Limiting contact activities in individuals with a palpable spleen is highly controversial and not guided by evidence, but more by common sense.

NEUROCOGNITIVE/BEHAVIORAL WORK GROUP

In children and adolescents with ARPKD clinical features such as HTN and CKD predispose them to neurocognitive and social-behavioral challenges^{37, 38}. In addition hepatic encephalopathy is well-described in individuals with renal dysfunction following portosystemic shunting (PSS) to relieve severe portal hypertension³⁴; however, it is unknown whether this association occurs in patients with milder CKD. The only available pediatric study showed that children with mild to moderate ARPKD had neurocognitive functioning comparable with children with other causes of CKD across IQ, academic achievement, attention/executive functioning, and behavior³⁹. To date, there is limited literature to explicitly guide clinical practice around neurodevelopmental and socialbehavioral issues in ARPKD children.

Expert opinion

- An interdisciplinary team model is suggested, that ideally would include a consulting psychologist or neuropsychologist with specialized knowledge of CKD and the associated co-morbid conditions.
- The team should engage in systematic developmental surveillance, (e.g. brief annual or biannual screenings), to track cognitive, social, and behavioral functioning over time, as well as track parent and child quality of life and adherence to medical treatment.
- Neuropsychological assessment may be indicated for those children with signs of learning/attention problems and for those who manifest behavioral/emotional difficulties.

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REFERENCES

1. Guay-Woodford LM, Desmond RA. Autosomal recessive polycystic kidney disease: the clinical experience in North America. *Pediatrics*. 2003; 111:1072–1080. [PubMed: 12728091]
2. Zerres K, Rudnik-Schoneborn S, Steinkamm C, Becker J, Mucher G. Autosomal recessive polycystic kidney disease. *J Mol Med (Berl)*. 1998; 76:303–309. [PubMed: 9587064]
3. Rossetti S, Harris PC. Genotype-phenotype correlations in autosomal dominant and autosomal recessive polycystic kidney disease. *J Am Soc Nephrol*. 2007; 18:1374–1380. [PubMed: 17429049]
4. Bergmann C, Senderek J, Schneider F, Dornia C, Küpper F, Eggermann T, et al. PKHD1 mutations in families requesting prenatal diagnosis for autosomal recessive polycystic kidney disease (ARPKD). *Human mutation*. 2004; 23:487–495. [PubMed: 15108281]
5. Bergmann C, Bothmer JV, Bru NO, Frank V, Fehrenbach H, Hampel T, et al. Mutations in multiple PKD genes may explain early and severe polycystic kidney disease. *J Am Soc Nephrol*. 2011; 22:2047–2056. [PubMed: 22034641]
6. Gunay-Aygun M, Font-Montgomery E, Lukose L, Tuchman M, Graf J, Bryant JC, et al. Correlation of kidney function, volume and imaging findings, and PKHD1 mutations in 73 patients with autosomal recessive polycystic kidney disease. *Clinical journal of the American Society of Nephrology : CJASN*. 2010; 5:972–984. [PubMed: 20413436]
7. Zvereff V, Yao S, Ramsey J, Mikhail FM, Vijzelaar R, Messiaen L. Identification of PKHD1 multiexon deletions using multiplex ligation-dependent probe amplification and quantitative polymerase chain reaction. *Genetic testing and molecular biomarkers*. 2010; 14:505–510. [PubMed: 20575693]
8. Chaumoitre K, Brun M, Cassart M, Maugey-Laulom B, Eurin D, Didier F, et al. Differential diagnosis of fetal hyperechogenic cystic kidneys unrelated to renal tract anomalies: A multicenter study. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2006; 28:911–917.
9. Decramer S, Parant O, Beaufils S, Clauin S, Guillou C, Kessler S, et al. Anomalies of the TCF2 gene are the main cause of fetal bilateral hyperechogenic kidneys. *J Am Soc Nephrol*. 2007; 18:923–933. [PubMed: 17267738]
10. Hawkins JS, Dashe JS, Twickler DM. Magnetic resonance imaging diagnosis of severe fetal renal anomalies. *American journal of obstetrics and gynecology*. 2008; 198:328 e1–328 e5. [PubMed: 18036507]
11. Choong KK, Gruenewald SM, Hodson EM. Echogenic fetal kidneys in cytomegalovirus infection. *Journal of clinical ultrasound : JCU*. 1993; 21:128–132. [PubMed: 8381133]
12. Tsatsaris V, Gagnadoux MF, Aubry MC, Gubler MC, Dumez Y, Dommergues M. Prenatal diagnosis of bilateral isolated fetal hyperechogenic kidneys. Is it possible to predict long term outcome? *BJOG : an international journal of obstetrics and gynaecology*. 2002; 109:1388–1393. [PubMed: 12504976]
13. Zaretsky M, Ramus R, McIntire D, Magee K, Twickler DM. MRI calculation of lung volumes to predict outcome in fetuses with genitourinary abnormalities. *AJR American journal of roentgenology*. 2005; 185:1328–1334. [PubMed: 16247158]
14. Guay-Woodford, L. Other cystic diseases. In: Feehally, RJA, editor. *Comprehensive Clinical Nephrology*. 4th ed.. London: Mosby; 2010. p. 543-559.
15. Rheault MN, Rajpal J, Chavers B, Nevins TE. Outcomes of infants <28 days old treated with peritoneal dialysis for end-stage renal disease. *Pediatric nephrology (Berlin, Germany)*. 2009; 24:2035–2039.
16. Levels of neonatal care. American Academy of Pediatrics Committee on Fetus and Newborn. *Pediatrics*. 2012:587–597. (2012). [PubMed: 22926177]
17. Zurowska AM, Fischbach M, Watson AR, Edefonti A, Stefanidis CJ. Clinical practice recommendations for the care of infants with stage 5 chronic kidney disease (CKD5). *Pediatric nephrology (Berlin, Germany)*. 2013; 28:1739–1748.

18. Bergmann C, Senderek J, Windelen E, Kupper F, Middeldorf I, Schneider F, et al. Clinical consequences of PKHD1 mutations in 164 patients with autosomal-recessive polycystic kidney disease (ARPKD). *Kidney international*. 2005; 67:829–848. [PubMed: 15698423]
19. Gunay-Aygun M, Font-Montgomery E, Lukose L, Tuchman Gerstein M, Piwnica-Worms K, Choyke P, et al. Characteristics of congenital hepatic fibrosis in a large cohort of patients with autosomal recessive polycystic kidney disease. *Gastroenterology*. 2013; 144:112–121. e2. [PubMed: 23041322]
20. Dias NF, Lanzarini V, Onuchic LF, Koch VH. Clinical aspects of autosomal recessive polycystic kidney disease. *Jornal brasileiro de nefrologia : orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia*. 2010; 32:263–267. [PubMed: 21103689]
21. Loghman-Adham M, Soto CE, Inagami T, Sotelo-Avila C. Expression of components of the renin-angiotensin system in autosomal recessive polycystic kidney disease. *The journal of histochemistry and cytochemistry : official journal of the Histochemistry Society*. 2005; 53:979–988. [PubMed: 15879580]
22. Goto M, Hoxha N, Osman R, Dell KM. The renin-angiotensin system and hypertension in autosomal recessive polycystic kidney disease. *Pediatric nephrology (Berlin, Germany)*. 2010; 25:2449–2457.
23. Rohatgi R, Greenberg A, Burrow CR, Wilson PD, Satlin LM. Na transport in autosomal recessive polycystic kidney disease (ARPKD) cyst lining epithelial cells. *J Am Soc Nephrol*. 2003; 14:827–836. [PubMed: 12660316]
24. Veizis IE, Cotton CU. Abnormal EGF-dependent regulation of sodium absorption in ARPKD collecting duct cells. *American journal of physiology Renal physiology*. 2005; 288:F474–F482. [PubMed: 15522985]
25. Group ET, Wuhl E, Trivelli A, Picca S, Litwin M, Peco-Antic A, et al. Strict blood-pressure control and progression of renal failure in children. *The New England journal of medicine*. 2009; 361:1639–1650. [PubMed: 19846849]
26. Chalhoub V, Abi-Rafeh L, Hachem K, Ayoub E, Yazbeck P. Intracranial aneurysm and recessive polycystic kidney disease: the third reported case. *JAMA neurology*. 2013; 70:114–116. [PubMed: 23318517]
27. Zerres K, Rudnik-Schoneborn S, Deget F, Holtkamp U, Brodehl J, Geisert J, et al. Autosomal recessive polycystic kidney disease in 115 children: clinical presentation, course and influence of gender. *Arbeitsgemeinschaft fur Padiatrische, Nephrologie. Acta Paediatrica (Oslo, Norway: 1992)*. 1996; 85:437–445.
28. Cole BR, Conley SB, Stapleton FB. Polycystic kidney disease in the first year of life. *The Journal of pediatrics*. 1987; 111:693–699. [PubMed: 3668738]
29. Bean SA, Bednarek FJ, Primack WA. Aggressive respiratory support and unilateral nephrectomy for infants with severe perinatal autosomal recessive polycystic kidney disease. *The Journal of pediatrics*. 1995; 127:311–313. [PubMed: 7636663]
30. Shukla AR, Kiddoo DA, Canning DA. Unilateral Nephrectomy as Palliative Therapy in an Infant with Autosomal Recessive Polycystic Kidney Disease. *The Journal of urology*. 2004; 172:2000–2001. [PubMed: 15540776]
31. Beauoyer M, Snehal M, Li L, Concepcion W, Salvatierra O Jr, Sarwal M. Optimizing outcomes for neonatal ARPKD. *Pediatric transplantation*. 2007; 11:267–271. [PubMed: 17430481]
32. Shneider BL, Magid MS. Liver disease in autosomal recessive polycystic kidney disease. *Pediatric transplantation*. 2005; 9:634–639. [PubMed: 16176423]
33. Megremis SD, Vlachonikolis IG, Tsilimigaki AM. Spleen length in childhood with US: normal values based on age, sex, and somatometric parameters. *Radiology*. 2004; 231:129–134. [PubMed: 14990814]
34. Srinath A, Shneider BL. Congenital hepatic fibrosis and autosomal recessive polycystic kidney disease. *Journal of pediatric gastroenterology and nutrition*. 2012; 54:580–587. [PubMed: 22197937]
35. Shneider BL, Bosch J, de Franchis R, Emre SH, Groszmann RJ, Ling SC, et al. Portal hypertension in children: expert pediatric opinion on the report of the Baveno v Consensus Workshop on

Methodology of Diagnosis and Therapy in Portal Hypertension. *Pediatric transplantation*. 2012; 16:426–437. [PubMed: 22409296]

36. Lindor KD, Kowdley KV, Luketic VA, Harrison ME, McCashland T, Befeler AS, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Hepatology (Baltimore, Md)*. 2009; 50:808–814.
37. Hooper SR, Gerson AC, Butler RW, Gipson DS, Mendley SR, Lande MB, et al. Neurocognitive functioning of children and adolescents with mild-to-moderate chronic kidney disease. *Clinical journal of the American Society of Nephrology*. 2011; 6:1824–1830. [PubMed: 21737850]
38. Adams HR, Szilagyi PG, Gebhardt L, Lande MB. Learning and attention problems among children with pediatric primary hypertension. *Pediatrics*. 2010; 126:e1425–e1429. [PubMed: 21059718]
39. Hartung E, Matheson M, Lande M, Dell K, Guay-Woodford L, Gerson A, et al. Neurocognition in children with Autosomal Recessive Polycystic Kidney Disease in the CKiD Cohort Study. *Pediatric nephrology (Berlin, Germany)*. in press.

Table 1

ARPKD and hepatorenal fibrocystic disease phenocopies

Disease	Gene(s)	Renal disease	Hepatic disease	Systemic features	Prevalence
ARPKD	<i>PKHD1</i>	Collecting duct dilatation	CHF; Caroli disease	no	~1 in 20,000
ADPKD	<i>PKD1</i> ; <i>PKD2</i>	Cysts along entire nephron	Biliary cysts; CHF (rare)	yes -adults	~1 in 1,000
Nephronophthisis (NPHP)	<i>NPHP1-NPHP16</i>	Cysts at the cortico-medullary junction	CHF	+/-	~1 in 50,000
Joubert syndrome and related disorders (JBRD)	<i>JBTS1-JBTS20</i>	Cystic dysplasia; NPHP	CHF; Caroli disease	yes	~1 in 100,000
Bardet-Biedel syndrome (BBS)	<i>BBS1-BBS18</i>	Cystic dysplasia; NPHP	CHF	yes	~1 in 100,000
Meckel-Gruber syndrome (MKS)	<i>MKS1-MKS10</i>	Cystic dysplasia	CHF	yes	~1 in 140,000
Oral-facial-digital syndrome, Type I	<i>OFD1</i>	Glomerular cysts	CHF (rare)	yes	~1 in 250,000
Glomerulocystic disease	<i>PKD1</i> ; <i>HNF1B</i> ; <i>UMOD</i>	Enlarged; normal or hypoplastic kidneys	CHF (with <i>PKD1</i> mutations)	+/-	rare
Jeune syndrome (asphyxiating thoracic dystrophy (ATD))	<i>IFT80 (ATD2)</i> ; <i>DYNC2H1 (ADT3)</i> ; <i>ADT1</i> , <i>ADT4</i> , <i>ADT5</i>	Cystic dysplasia	CHF; Caroli disease	yes	rare
Renal-hepatic-pancreatic dysplasia (Ivemark II)	<i>NPHP3</i> , <i>NEK8</i>	Cystic dysplasia	Intrahepatic biliary dysgenesis	yes	rare
Zellweger syndrome	<i>PEX1-3,5-6;10-11;13;14;16;19;26</i>	Renal cortical microcysts	Intrahepatic biliary dysgenesis	yes	rare

AD – autosomal dominant; AR – autosomal recessive; CHF – congenital hepatic fibrosis