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Autosomal Recessive Polycystic Kidney Disease – *PKHD1*

Synonym: ARPKD-*PKHD1*

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Summary

Clinical characteristics

Autosomal recessive polycystic kidney disease – *PKHD1* (ARPKD-*PKHD1*) is characterized by primary involvement of the kidneys and liver with mostly secondary effects seen in other organ systems. Of the three ages of initial presentation of kidney disease, the two most common are perinatal (i.e., prenatal/neonatal) and infantile (four weeks to age one year) with the classic finding of enlarged kidneys. The major difference between the perinatal and infantile presentations, which typically have similar kidney and liver findings, is the frequent occurrence of pulmonary involvement in the perinatal presentation, which is a major cause of morbidity and mortality in neonates. The less common initial presentation in childhood (after age one year) to young adulthood can be associated with predominant hepatobiliary manifestations characterized by the clinical consequences of developmental anomalies of biliary ductal plate remodeling (also known as Caroli disease). Although the short-term and long-term mortality rates of ARPKD remain significant, the survival of individuals with ARPKD has improved with modern neonatal respiratory support, kidney replacement therapy (KRT) including dialysis and kidney transplantation (KTx), and liver transplantation (LTx) or combined liver and kidney transplantation (CLKTx).

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Diagnosis/testing

The molecular diagnosis of ARPKD-*PKHD1* is established in a proband with suggestive findings and biallelic pathogenic variants in *PKHD1* identified by molecular genetic testing.

Management

Treatment of manifestations: Multidisciplinary care including (1) kidney disease and nutrition specialists to ensure optimal metabolic control and growth and timely institution of KRT; (2) hepatobiliary disease specialists to assure timely management of complications (that can include ascending cholangitis, cholestasis, and portal hypertension) and LTx/CLKTx; and (3) psychologists and social workers for ongoing family support.

Surveillance: Regularly scheduled follow up as specified by the treating multidisciplinary specialists.

Agents/circumstances to avoid: High-salt diet, smoking, obesity, and sympathomimetic agents (especially individuals who have hypertension). Minimizing use of known nephrotoxic agents including nonsteroidal anti-inflammatory drugs (NSAIDs) and aminoglycosides (unless otherwise advised) and of potentially hepatotoxic agents (e.g., acetaminophen doses >30 mg/kg/day, herbal supplements, and alcohol) is advised.

Evaluation of relatives at risk: Early screening and genetic testing of apparently asymptomatic at-risk sibs can be considered with the goal of identifying those who may benefit from additional examinations and potentially preventive measures. Ultrasonography of the parents of children with ARPKD-*PKHD1* is warranted (1) to confirm the clinical diagnosis and (2) because individuals heterozygous for a *PKHD1* pathogenic variant may, in rare instances, have very mild cystic kidney manifestations or, more frequently, liver cysts.

Genetic counseling

ARPKD-*PKHD1* is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *PKHD1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of being unaffected and not a carrier. Heterozygotes for a *PKHD1* pathogenic variant are not at risk of developing ARPKD-*PKHD1*; however, hyperechogenicity in the kidneys with mild kidney cysts as well as hepatic cysts have been described in individuals with monoallelic *PKHD1* pathogenic variants. Once the *PKHD1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and molecular genetic prenatal testing and preimplantation genetic testing are possible.

GeneReview Scope

The topic of this *GeneReview* is autosomal recessive polycystic kidney disease (ARPKD) caused by biallelic pathogenic variants in *PKHD1* (ARPKD-*PKHD1*). See Differential Diagnosis for other genes known to be associated with ARPKD (the term used when genetic cause has not been specified).

Autosomal Recessive Polycystic Kidney Disease – *PKHD1*: Features by Age at Presentation

Age at Presentation	Features		Comments
	Kidney	Hepatobiliary	
Perinatal (prenatal to age 4 weeks)	• Enlarged hyperechogenic kidneys • Variable CKD	• Inhomogeneous liver parenchyma due to CHF • Hepatomegaly • Bile duct dilatation / cystic changes • Normal biochemical liver function	Oligo- or anhydramnios & related lung disease (i.e., pulmonary hypoplasia, pulmonary hypertension, & pneumothoraces) often cause the most significant complications.

Autosomal Recessive Polycystic continued from previous page.

Age at Presentation	Features		Comments
	Kidney	Hepatobiliary	
Infantile (age 4 weeks to 1 year)	• Enlarged hyperechogenic kidneys • Micro- & macrocysts • Variable CKD	• Inhomogeneous liver parenchyma due to CHF • Hepatomegaly • Bile duct dilatation / cystic changes • Normal biochemical liver function	Caroli disease (CHF & bile duct dilatations) is a variable hepatobiliary finding.
Childhood / young adulthood (age >1 year)	• Enlarged kidneys w/ multiple macrocysts • ↑ echogenicity • ↓ or abrogated cortex-medulla differentiation • Possible variable CKD	Progressive liver fibrosis & portal hypertension as well as bile duct dilatation (incl splenomegaly, esophageal or gastric varices w/risk of bleeding, & cholangitis)	Some persons have predominance of liver disease w/only mild functional & structural kidney disease.

CHF = congenital hepatic fibrosis; CKD = chronic kidney disease

Diagnosis

Consensus expert recommendations for the clinical diagnosis of autosomal recessive polycystic kidney disease (ARPKD) were published in 2014 [Guay-Woodford et al 2014].

Suggestive Findings

Autosomal recessive polycystic kidney disease – *PKHD1* (ARPKD-*PKHD1*) **should be suspected** in probands with the following age-related clinical and ultrasonographic findings at presentation and family history.

Note: (1) Ultrasonography is the imaging method of choice for assessing the kidneys prenatally and in all pediatric age groups because it is cost-effective, painless, widely available, and does not require radiation or sedation. (2) Kidney biopsies **should not be performed** to diagnose ARPKD.

Perinatal Presentation (prenatal to age 4 weeks)

Kidney

- **Prenatal imaging findings.** The following are frequently detected in the second half of pregnancy: enlarged hyperechogenic kidneys with reduced corticomedullary differentiation, microcysts, and few or no macrocysts ("salt-and-pepper appearance").

  With use of modern obstetric ultrasonography, fetuses with severe kidney involvement with oligohydramnios/anhydramnios resulting in a Potter syndrome-like phenotype with pulmonary hypoplasia and characteristic facial and limb findings resulting from fetal compression can be identified.

- **Neonatal period.** Abdominal distention due to massive enlargement of the kidneys and liver can be evident. Enlarged hyperechogenic kidneys with reduced corticomedullary differentiation, microcysts, and few or no macrocysts ("salt-and-pepper appearance") are typical. Kidney function may range from limited impairment to kidney failure requiring dialysis.

Liver

- **Prenatal imaging findings.** Liver anomalies are rarely prominent on prenatal sonography. Changes that may be seen on MRI include the typical findings of hepatomegaly, inhomogeneous liver parenchyma, and dilated bile ducts [Fazecas et al 2022].

- **Neonatal period.** Ultrasonography may detect hepatomegaly, inhomogeneous liver parenchyma, and dilated bile ducts or cystic changes. Magnetic resonance cholangiopancreatography (MRCP), which provides a clear depiction of the biliary duct system, is a sensitive assessment of biliary ductal anatomy. Combined with the imaging findings of the kidney, the biliary duct anomalies (i.e., a developmental defect in which a failure of ductal plate remodeling results in persistence of embryologic bile duct structures that eventually can become massively dilated) are diagnostic of ARPKD and have largely replaced the more invasive analysis of ductal anatomy by liver biopsy [Gunay-Aygun et al 2010a, Gunay-Aygun et al 2013, Burgmaier et al 2021a]. (For more information, click here.)
- **Liver function.** Liver function, as monitored by standard laboratory tests of synthesis and detoxification, is typically normal.

Lungs

- **Prenatal.** When kidney function is reduced, oligo- or anhydramnios resulting in pulmonary hypoplasia is evident. Reduced diaphragmatic movement due to nephromegaly may also contribute to pulmonary hypoplasia.
- **Postnatal.** Pulmonary hypoplasia may be seen on chest radiographs [Liebau 2021]. Respiratory failure and pulmonary hypertension may be severe and require intensive neonatal support especially in premature infants [Guay-Woodford et al 2014, Liebau 2021].

Infantile Presentation (age 4 weeks to 1 year)

Kidney

- **Imaging findings** typically are the following:
  - Bilaterally enlarged kidneys (in relation to age-, height-, or weight-based normal range) that usually retain their typical shape

    Note: (1) Bilaterally enlarged kidneys can be interspersed with macrocysts. (2) During later disease stages relative kidney length may decrease again.
  - Increased echogenicity
  - Poor corticomedullary differentiation
  - High-resolution ultrasonography may demonstrate innumerable very small cysts (rarely exceeding 1-2 mm) in the cortex and medulla.

    Note: In the past this pattern was described by the now-outdated term "salt-and-pepper appearance" (referring to the speckled appearance obtained by older ultrasound transducers).
- **Function** may range from mild impairment to kidney failure.

Liver

- **Imaging findings.** In addition to inhomogeneous liver parenchyma, other findings can include hepatomegaly, bile duct dilatation, and signs of liver fibrosis.
  - Typical liver findings on abdominal ultrasound examination are signs of congenital hepatic fibrosis (CHF) that lead to portal hypertension. Note that MRCP, which provides a clear depiction of the biliary duct system, is a sensitive assessment of biliary ductal anatomy.
  - Signs of portal hypertension include enlarged liver and/or spleen, dilated portal vein, biphasic or retrograde flow in the portal vein, retrograde flow in the splenic vein, portosystemic collateral vessels, and ascites.

- Caroli disease (i.e., multifocal cystic dilatation of intrahepatic bile ducts) is evident as saccular dilatations that may show the "central dot sign" (i.e., portal vein within the dilated bile duct). Dilated extrahepatic bile ducts and choledochal cysts are less common [Turkbey et al 2009].

- **Function**
  - Hepatocellular function is usually preserved early in life [Gunay-Aygun et al 2013].
  - Laboratory markers of portal hypertension include thrombocytopenia and increased prothrombin time, which correlate with splenic volume. Thrombocytopenia may rapidly develop during episodes of infection or sepsis. Although rare, variceal bleeding has been described in young children.

Childhood / Young Adulthood Presentation (age >1 year)

Kidney

- **Imaging findings** typically are the following:
  - Enlarged kidneys with multiple macrocysts, increased echogenicity, and reduced or absent corticomedullary differentiation [Gimpel et al 2019]
  - A relative decrease of kidney length over time [Gunay-Aygun et al 2010a, Abdul Majeed et al 2020, Burgmaier et al 2021b]; however, height-adjusted total kidney volume seems more stable during childhood and adolescence [Burgmaier et al 2021b].
- **Function.** There seems to be an inverse correlation of kidney volume and function in individuals diagnosed early in life [Gunay-Aygun et al 2010a, Burgmaier et al 2021b]. Adults with smaller kidneys resembling medullary cystic kidney disease and good kidney function have been described.

Liver

- **Imaging findings.** Inhomogeneous liver parenchyma, hepatomegaly, bile duct dilatation (e.g., identified on MRCP), and liver fibrosis can become apparent. Signs of portal hypertension and Caroli disease can be present. Liver disease predominance (i.e., liver phenotype but only mild chronic kidney disease) can be observed in individuals with ARPKD-*PKHD1* [Adeva et al 2006, Gunay-Aygun et al 2013, Dorval et al 2021].
- **Function**
  - Thrombocytopenia is the best predictor of portal hypertension and splenomegaly; prothrombin time increases with higher spleen volume [Gunay-Aygun et al 2013].
  - Gamma-glutamyl transferase can be markedly elevated during the disease course, while liver transaminases are only mildly elevated, if at all [Gunay-Aygun et al 2013, Burgmaier et al 2019].

Family History

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs, unaffected parents,* and/or parental consanguinity). Absence of a known family history (e.g., no affected sibs) does not preclude the diagnosis. Note: Pseudodominant inheritance (i.e., an autosomal recessive condition presents in individuals in two or more generations) has been reported in some families (see Genetic Counseling).

* Absence of renal enlargement and/or characteristic imaging findings in both parents, as demonstrated by high-resolution ultrasonography examination.

Establishing the Diagnosis

The molecular diagnosis of ARPKD-*PKHD1* **is established in a proband** with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *PKHD1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can

be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *PKHD1* variants of uncertain significance (or of one known *PKHD1* pathogenic variant and one *PKHD1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Note: Single-gene testing (sequence analysis of *PKHD1*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT currently recommended.

Option 1

A polycystic kidney disease or kidney disease multigene panel that includes *PKHD1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. While the majority of *PKHD1* pathogenic variants reported to date are within the coding or canonical splice site region, several pathogenic variants have been identified that are deep within intronic regions and are therefore likely to be identified by genome sequencing [Michel-Calemard et al 2009, Chen et al 2019, Doreille et al 2022, Liu et al 2022].

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Autosomal Recessive Polycystic Kidney Disease – *PKHD1*

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
PKHD1	Sequence analysis [3]	>95% [4]
	Gene-targeted deletion/duplication analysis [7]	<5% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Bergmann et al [2005], Adeva et al [2006], Burgmaier et al [2021a]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

Autosomal recessive polycystic kidney disease – *PKHD1* (ARPKD-*PKHD1*) is characterized by primary involvement of the kidneys and liver with secondary effects seen in other organ systems [Gunay-Aygun et al 2010b, Burgmaier et al 2019, Burgmaier et al 2021a, Dorval et al 2021, Letavernier et al 2021, Das et al 2023]. Of the three ages of initial presentation of kidney disease, the two most common are perinatal (i.e., prenatal/neonatal) and infantile (four weeks to age one year) with the classic finding of enlarged kidneys. While the perinatal and infantile presentations typically have similar kidney and liver findings, the major difference between the two is the frequent occurrence of pulmonary involvement in the perinatal presentation. The less common initial presentation in childhood (after age one year) to young adulthood can be associated with predominant hepatobiliary manifestations characterized by developmental anomalies of biliary ductal plate remodeling, also known as congenital hepatic fibrosis (CHF). See Table 2 for a comparison of clinical findings at presentation by age at presentation.

Note: (1) Because some data on ARPKD predates the understanding of its heterogeneous genetic causes, information in this section is based on study cohorts with ARPKD in general as well as cohorts with ARPKD-*PKHD1* (see Nomenclature). (2) Although the ARPKD phenotype appears to be clinically similar regardless of the causative gene, the genetic etiology may be relevant for prognosis of kidney survival (i.e., time to onset of kidney replacement therapy) [Lu et al 2017, Halawi et al 2023].

Table 2. Autosomal Recessive Polycystic Kidney Disease: Comparison of Clinical Findings at Presentation by Age at Presentation

Feature		Age at Presentation		
		Perinatal	Infancy (up to age 1 year)	Childhood (>1 year) / young adulthood
Lung	Pulmonary hypoplasia	+/++	(+)	NA
Kidney	Enlarged kidneys	+++	+++	++
	Chronic kidney disease	+++	+++	+++
	Kidney failure	++	+/++	+/++

Table 2. continued from previous page.

Feature		Age at Presentation		
		Perinatal	Infancy (up to age 1 year)	Childhood (>1 year) / young adulthood
Liver	Hepatomegaly	+/++	+/++	++
	Portal hypertension	(+)	+	++
	Splenomegaly	(+)	+	++
	Cholangitis	(+)	+	+

Based on Guay-Woodford & Desmond [2003], Bergmann et al [2005], Adeva et al [2006], Alzarka et al [2017], Burgmaier et al [2018b], Burgmaier et al [2019]; includes cohorts with ARPKD in general and cohorts with a molecular diagnosis of ARPKD-*PKHD1*
+++ = always present; ++ = frequently present; + = rarely present; (+) = very rarely present; NA = not applicable

Perinatal and Infantile Presentation (prenatal to age 1 year)

Pulmonary Involvement

Neonates with perinatal or infantile presentation. Pulmonary hypoplasia of varying degrees resulting from oligo- or anhydramnios is a major cause of morbidity and mortality in neonates. In these infants, massively enlarged kidneys may additionally lead to hypoventilation and respiratory distress because of limitation of diaphragmatic excursion. Persistent pulmonary hypertension may be prominent.

Respiratory support was required in 23% of infants (78/333) in a large retrospective European study [Burgmaier et al 2018b]. Long-term pulmonary function appears to be good unless mechanical ventilation was required in the newborn period [Jahnukainen et al 2015].

Hypertension, often severe and resistant to multidrug therapy, is usually noted within the first few weeks of life and may improve over time [Seeman et al 2022]. Cardiac findings include high rates of left ventricular geometry anomalies with systolic mechanical dysfunction [Chinali et al 2019].

Kidney Involvement

Perinatal presentation. Large bilateral flank masses (nephromegaly) are typically present on physical examination.

Urine output is usually not diminished; rather, polyuria and polydipsia are consistent with a kidney concentrating defect [Seeman et al 2023]. However, oliguria and overt acute kidney injury or kidney failure (KF) may be seen as early as the first weeks of life. Hyponatremia, which is often present in the neonatal period, usually resolves unless severe chronic kidney disease (CKD) or KF is present.

Function (as reflected in serum concentrations of creatinine, cystatin C, and blood urea nitrogen) is often impaired. The time course varies widely. Larger kidneys may be associated with more rapid progression to KF, as kidney function at the end of the first year of life is more severely impaired in individuals with the largest kidneys [Burgmaier et al 2021b].

Improvement in kidney function over the first year of life can occur comparable to that of normal kidney development or other congenital kidney diseases.

Subsequent yearly loss of glomerular filtration rate (GFR) was −1.4 mL/min/1.73m^2 (−6%) in 22 children with ARPKD from the American Chronic Kidney Disease in Children (CKiD) cohort (statepi.jhsph.edu/ckid). Yearly decline was greater in individuals age ≥10 years (−11.5%) [Dell et al 2016]. While details differed, overall comparable findings of changes in estimated GFR (eGFR) were observed in a subset of individuals in two European cohorts [Burgmaier et al 2021b, Dorval et al 2021].

More than 50% of affected individuals progress to KF requiring kidney replacement therapy (KRT; dialysis or kidney transplantation [KTx]) in the first two decades of life [Bergmann et al 2005, Burgmaier et al 2021a] (see Management).

Urinary tract infections are common [Guay-Woodford & Desmond 2003].

Hepatobiliary Involvement

Although histologic hepatic fibrosis is invariably present at birth, clinical, radiographic, or laboratory evidence of liver disease may be absent in newborns and infants [Srinath & Shneider 2012].

In 115 children with ARPKD with a mean age of 29 days at diagnosis, 46% had clinical evidence of liver involvement over a mean observation time of 4.92 years, with positive correlation of detection of clinical signs of hepatic fibrosis with increasing age [Zerres et al 1996].

Other

Premature birth is common. In one international study of 288 children, mean gestational age at birth was 37.5 weeks with a standard deviation of 2.7 weeks. In children requiring dialysis in the first year of life, mean gestational age at birth was 36.1 weeks with a standard deviation of 2.4 weeks [Burgmaier et al 2018b].

Feeding difficulties may result from mechanical compression of the stomach by enlarged kidneys, liver, and/or spleen, the latter being a complication of portal hypertension. Also, significant kidney impairment may result in feeding difficulties, loss of appetite, and/or impaired gastric motility.

Aggressive nutritional support in the first two years of life has improved growth rates even in children with moderately to severely impaired kidney function and portal hypertension. In one study growth did not seem to differ in children with ARPKD from children with other kidney diseases [Hartung et al 2016]. Children with malnutrition showed a lower eGFR in one study [Tutal et al 2023].

Childhood / Young Adulthood Presentation (age >1 year)

Kidney Involvement

Kidney involvement ranges from enlarged kidneys with multiple macrocysts, increased echogenicity, reduced or abrogated cortex-medulla differentiation, and CKD in some individuals to only mild functional and structural kidney disease in individuals with liver-predominant phenotypes.

In an international cohort of 70 children, Burgmaier et al [2021b] found that those with the largest kidney volumes in the first 18 months of life had the most rapid progression to KF. An earlier study by Adeva et al [2006] had found that the 20-year event-free survival was ~35% in children diagnosed at age <1 year compared to the 20-year event-free survival of 80%-90% in individuals diagnosed between ages one and 20 years children.

Function. Loss of kidney function varies widely in its time course. Larger kidneys may be associated with more rapid progression to KF, as kidney function at the end of the first year of life is more severely impaired in individuals with the largest kidneys [Burgmaier et al 2021b].

Subsequent yearly loss of GFR was −1.4 mL/min/1.73m^2 (−6%) in 22 children with ARPKD from the American CKiD cohort. Decline was greater in individuals age ≥10 years (−11.5%) [Dell et al 2016]. While details differed, overall comparable findings of changes in eGFR were observed in a subset of individuals in two European cohorts [Burgmaier et al 2021b, Dorval et al 2021].

More than 50% of affected individuals progress to KF requiring KRT in the first two decades of life [Guay-Woodford & Desmond 2003, Bergmann et al 2005, Burgmaier et al 2021a] (see Management).

Urinary tract infections are common [Guay-Woodford & Desmond 2003].

Hepatobiliary Involvement

Some individuals with CHF develop progressive portal hypertension with an increased risk of esophageal or gastric varices, enlarged hemorrhoids, splenomegaly, hypersplenism, protein-losing enteropathy, and gastrointestinal bleeding. Bleeding from esophageal varices contributes significantly to morbidity and mortality [Gunay-Aygun et al 2010b, Burgmaier et al 2019, Abdul Majeed et al 2020, Burgmaier et al 2021a, Dorval et al 2021].

In a study that challenged many assumptions about the timing of liver involvement in ARPKD, Adeva et al [2006] found that nearly one third of individuals with hepatic involvement were older than age 20 years at the time of initial presentation. This wide age range in diagnosis was confirmed in a National Institutes of Health (NIH) natural history study of 78 individuals (range: age one to 56 years) [Gunay-Aygun et al 2010a, Gunay-Aygun et al 2010b]. Of note, in an NIH cohort of 73 individuals, Gunay-Aygun et al [2013] found liver-related manifestations in 26% of individuals at the time of diagnosis. Splenomegaly, an early indicator of biliary dysfunction in 60% of children younger than age five years, did not correlate with either kidney function or severity of kidney disease.

In a subset of individuals with ARPKD-*PKHD1* or ARPKD, hepatobiliary disease was the leading clinical feature in this age group, in contrast to kidney disease, which is variable and – when mild – may be discovered incidentally during abdominal imaging studies [Bergmann et al 2005, Adeva et al 2006, Burgmaier et al 2019].

Caroli disease, non-obstructed dilatation of the intrahepatic bile ducts and dilatation of the common bile duct, was observed in more than 60% of individuals with ARPKD [Adeva et al 2006]. The resulting abnormal hepatobiliary drainage contributes to significant risk for recurrent or persistent bacterial ascending cholangitis with sepsis, a significant cause of morbidity and mortality, especially after isolated KTx (i.e., without liver transplantation [LTx]).

Other

Cholangiocarcinoma, a risk for individuals with CHF, has been reported in individuals with ARPKD in adulthood but does not seem to be a major issue during childhood [Fonck et al 2001, Srinath & Shneider 2012].

Cerebral and extracerebral aneurysms were reported in nine individuals with ARPKD [Gately et al 2020]. While a high level of suspicion may be required to identify individuals with this complication, vascular aneurysms seem to be rare in children with ARPKD.

Neurocognitive functioning (including intellectual functioning, academic achievement, attention regulation, executive functioning, and behavior) in children with ARPKD appears to be comparable to that of other children with a similar degree of CKD [Hartung et al 2014]. In contrast, severe neurologic complications have been observed in children following bilateral nephrectomy performed in the first three months of life [Burgmaier et al 2020].

Prognosis

Mortality rate. Although the short-term and long-term mortality rates of ARPKD remain significant, the survival of children with ARPKD has improved with modern neonatal respiratory support and KRT.

Approximately 20%-30% of affected infants die in the neonatal period or within the first year of life, primarily of respiratory insufficiency or superimposed pulmonary infections [Alzarka et al 2017, Liebau 2021].

Of those children with an ARPKD phenotype who survived beyond age one year, subsequent one-year survival was approximately 85%-87%, and ten-year survival was 82% [Guay-Woodford & Desmond 2003, Bergmann et al 2005, Hoyer 2015].

Kidney survival (i.e., time to onset of KRT). About 50% of affected individuals progress to KF during the first two decades of life [Guay-Woodford & Desmond 2003, Bergmann et al 2005, Burgmaier et al 2021a] (see Management).

- **Perinatal kidney disease.** Although as a group individuals with perinatal kidney disease may have a worse outcome than individuals with later clinical presentation, data from different reports are inconclusive [Abdul Majeed et al 2020, Dorval et al 2021]. Perinatal presentation and corticomedullary involvement on high-resolution ultrasound examination were associated with more rapid progression of kidney disease in one prospective study of 60 individuals [Abdul Majeed et al 2020].

  In a large cohort of 164 neonatal survivors, Bergmann et al [2005] reported the following:

  - At age five years, 86% had not progressed to KF requiring KRT or died due to KF;
  - At age ten years, 71% had not progressed to KF requiring KRT or died due to KF;
  - At age 20 years, 42% had not progressed to KF requiring KRT or died due to KF.

  In another large cohort of 304 neonatal survivors, Burgmaier et al [2021a] reported the 15-year kidney survival was 65%-75%.

  Prenatal findings of oligo- or anhydramnios and detection of kidney cysts and kidney enlargement have been associated with a higher likelihood of need for dialysis in the first year of life [Burgmaier et al 2018b].

  Need for respiratory support has been associated with the need for KRT or worse kidney prognosis [Guay-Woodford & Desmond 2003, Burgmaier et al 2018b].

- **Larger kidneys** in the first 18 months of life have been associated with poorer early kidney survival [Burgmaier et al 2021b].

- **In a young adult cohort,** 41% of individuals were on KRT. Importantly, a relevant fraction of individuals had mild-to-moderate CKD at this stage [Burgmaier et al 2019].

Kidney transplantation (KTx). Allograft survival rates for individuals with ARPKD who undergo KTx are comparable to those in individuals with other kidney diseases [Mekahli et al 2016].

Role of hepatobiliary disease in long-term survival. A significant number of individuals with ARPKD or ARPKD-*PKHD1* who require KTx also have significant hepatobiliary disease and progressive portal hypertension [Gunay-Aygun et al 2013, Burgmaier et al 2019, Dorval et al 2021]. In individuals who succumbed after KTx, 64%-80% of deaths occurring after KTx in individuals with ARPKD were attributable to cholangitis and/or sepsis, a consequence of hepatobiliary disease [Khan et al 2002, Davis et al 2003]. Data from a United States study estimated that approximately 7% of affected children surviving the neonatal period required a liver transplantation (LTx) during follow up [Guay-Woodford & Desmond 2003]. A more recent study of young adults with ARPKD by Burgmaier et al [2019] found a higher rate of LTx in this subcohort, suggesting that as advances in KRT (including KTx) improve long-term survival, it is likely that clinical hepatobiliary disease will become a major feature of the natural history of ARPKD [Burgmaier et al 2019].

In a cohort of 304 neonatal survivors, Burgmaier et al [2021a] reported that during an observational period up to age 15 years, 60%-65% developed signs of portal hypertension due to progressive periportal fibrosis during childhood and adolescence, and about 25% developed substantial hepatic complications such as sequelae of portal hypertension (i.e., variceal bleeding, LTx, or interventional/surgical placement of portocaval shunting).

Data from the European Society for Pediatric Nephrology / European Renal Association-European Dialysis and Transplant (ESPN/ERA-EDTA) Registry show very good outcomes after combined liver and kidney transplantation (CLKTx) but suggest a higher peri-interventional mortality with a 6.7-fold age- and sex-adjusted risk for death after CLKTx when compared to KTx [Mekahli et al 2016].

Intrafamilial variability. Historically, when variability of disease severity within a family mainly focused on survival in sibs, up to 20%-42% of affected sibs experienced peri- or neonatal demise in one sib and survival into childhood in another sib [Deget et al 1995, Bergmann et al 2005]. However, with the improvement in neonatal and pediatric intensive care facilities and other aspects of clinical management of ARPKD, a recent report on 70 children with ARPKD from 35 families described only one perinatal demise and only three sib pairs that showed pronounced clinical differences of the kidney and liver phenotype during follow up [Ajiri et al 2022].

Interfamilial variability (referring to phenotypic differences among families with the same two pathogenic *PKHD1* variants) was reported by Burgmaier et al [2021a] and supported by an earlier study of the clinical findings in individuals homozygous for the Afrikaner *PKHD1* founder variant c.1880T>A (p.Met627Lys) [Lambie et al 2015].

Genotype-Phenotype Correlations

In ARPKD-*PKHD1* several genotype-phenotype correlations have been observed based on class of the pathogenic variant and location within the fibrocystin protein (see Tables 3a and 3b, respectively) [Burgmaier et al 2021a]. Importantly, no statistically significant differences for kidney survival (i.e., time to onset of KRT) were found during childhood and adolescence when comparing subgroups of individuals stratified according to their molecular diagnosis [Burgmaier et al 2021a].

Table 3a. Autosomal Recessive Polycystic Kidney Disease – *PKHD1*: Genotype-Phenotype Correlations by Variant Class

PKHD1 Variant Class	Genotype-Phenotype Correlation	Comment
Biallelic truncating variants	• Most truncating variants expected to result in complete loss of protein function ("null variants") & assoc w/most severe phenotypes (compared to persons w/at least 1 missense variant) [1] • Assoc w/poorer kidney & liver outcomes w/early/perinatal demise in most persons [1, 2, 3]	15-year survival rate w/o: • KRT = 34% • Signs of portal hypertension = 42% • Substantial hepatic complications = 78% [1] Survival beyond neonatal period documented in some persons [4]
Biallelic missense variants [5] vs missense [5]/ null variants	• No major difference in kidney & liver outcomes between these groups in several studies [1, 2] • Typically, mild-to-moderate phenotypes in persons w/at least 1 missense variant [5] in previous studies [2, 3, 6] (but severe phenotypes not precluded)	15-year survival rate w/o: • KRT = 64%-82% • Signs of portal hypertension = 36%-46% • Substantial hepatic complications = 77%-80% [1]

KRT= kidney replacement therapy

1. Burgmaier et al [2021a]. This study is based on analysis of 304 individuals of mostly European ancestry surviving the neonatal period (largely with missense variants). Additional detailed analyses are available in the same publication.

2. Bergmann et al [2005]

3. Furu et al [2003]

4. Frank et al [2014], Ebner et al [2017a]

5. Includes pathogenic variants, likely pathogenic variants, and variants of uncertain significance

6. Rossetti et al [2003], Adeva et al [2006], Gunay-Aygun et al [2010b]

Table 3b. Autosomal Recessive Polycystic Kidney Disease – *PKHD1*: Genotype-Phenotype Correlations by Variant Location within the Fibrocystin Region

PKHD1 Variant Location [1]	Genotype-Phenotype Correlation	Comment
Amino acids 709-1837	• Less frequently assoc w/KF [2] • In 35 persons w/1 null variant & 1 missense variant in this region, substantial hepatic complications were absent during observation period in childhood.	15-year survival rate w/o: • KRT = 95% • Signs of portal hypertension = 51% • Substantial hepatic complications = 94%
Amino acids 1000-2000	• Milder presentation • Observed in children surviving neonatal period [3]	
Amino acids 1838-2624	Better liver outcomes [2]	15-year survival rate w/o: • KRT = 30%-59% • Signs of portal hypertension = 53% • Substantial hepatic complications = 86%
Amino acids 2625-4074	• Poorer liver outcomes [2] • Predominant liver phenotype in persons w/variants around amino acids 2831-2840 & 3051-3209 [4]	15-year survival rate w/o: • KRT = 72% • Signs of portal hypertension = 13% • Substantial hepatic complications = 48%

KF = kidney failure; KRT = kidney replacement therapy

1. Variant location referrs specifically to the location of the corresponding missense variant(s) in individuals with either null/missense or biallelic missense variants. For biallelic missense variants to be included in this table, both had to be within the same region to be assigned to a specific group.

2. Burgmaier et al [2021a]

3. Furu et al [2003]

4. Bergmann et al [2005]

Nomenclature

Autosomal recessive polycystic kidney disease (ARPKD) – a broad term referring to all individuals with a clinical diagnosis of ARPKD – encompasses individuals with a molecular diagnosis (e.g., ARPKD-*PKHD1*) as well as individuals in whom a molecular diagnosis has not been established.

When ARPKD was first described, it was assumed that pathogenic variants in a single gene were causative and that ARPKD study cohorts were genetically homogeneous. However, the *PKHD1* variant detection rate was ~85% in larger study cohorts, and advances in gene discovery revealed genetic heterogeneity underlying the ARPKD phenotype. While the vast majority of ARPKD is caused by biallelic *PKHD1* pathogenic variants, some individuals with ARPKD have the disorder as the result of biallelic hypomorphic variants in *PKD1*, biallelic pathogenic variants in *CYS1* or *DZIP1L*, or pathogenic variants in other as-yet-unidentified genes (see Differential Diagnosis).

Current proposed polycystic kidney disease (PKD) nomenclature is based on phenotype and mode of inheritance, with the recent addition of genetic etiology; for example, the title of this *GeneReview* – ARPKD-*PKHD1* – refers to PKD inherited in an autosomal recessive manner (i.e., neither biological parent has PKD) and caused by biallelic pathogenic variants in *PKHD1*. Likewise, the terms ARPKD-*PKD1*, ARPKD-*CYS1*, and ARPKD-*DZIP1L* may be used to refer to PKD caused by biallelic pathogenic variants in the respective genes.

Designations used previously to refer to ARPKD include the following:

- "Infantile polycystic kidney disease" and "Potter syndrome I"

- Perinatal, neonatal, infantile, and juvenile polycystic kidney disease (based on clinical and histologic findings in the kidneys and liver) [Blyth & Ockenden 1971]

Prevalence

The incidence of ARPKD in live births in Europe was proposed to be about 1:20,000 with a corresponding carrier frequency of 1:70 [Zerres et al 1998] and a higher incidence in isolated populations [Kääriäinen et al 1988, Lombard et al 1989].

Based on an electronic health record system, Alzarka et al [2017] calculated an annualized incidence of 1:26,485 live births in the United States.

The *PKHD1* pathogenic variant c.107C>T (p.Thr36Met) is found in the heterozygous state in an estimated 13%-20% of individuals in European cohorts [Bergmann et al 2005, Burgmaier et al 2021a]. Haplotype analysis indicates that this *PKHD1* variant occurs at a mutational hot spot [Bergmann et al 2004] and suggests that the variant may have a single European origin [Consugar et al 2005].

The Afrikaner pathogenic founder variant c.1880T>A (p.Met627Lys) was present in the homozygous state in 67% of Afrikaner individuals with ARPKD-*PKHD1* [Lambie et al 2015].

Pathogenic founder variants in the Ashkenazi Jewish population are c.107C>T (p.Thr36Met) and c.3761_3762delCCinsG (p.Ala1254GlyfsTer49) [Shi et al 2017].

Genetically Related (Allelic) Disorders

Monoallelic *PKHD1*. Increased medullary echogenicity in the kidneys consistent with nephrocalcinosis and/or multiple small liver cysts without functional deterioration have been detected in a small subgroup of individuals with heterozygous *PKHD1* pathogenic variants [Gunay-Aygun et al 2011, de Fallois et al 2021, Van Buren et al 2023]. More data are needed to better assess the risk of kidney manifestations in individuals with heterozygous *PKHD1* pathogenic variants (see Autosomal Dominant Polycystic Kidney Disease).

Differential Diagnosis

Autosomal recessive polycystic kidney disease (ARPKD) belongs to a group of congenital hepatorenal fibrocystic syndromes and is a cause of significant kidney- and liver-related morbidity and mortality in children.

Among individuals with ARPKD, *PKHD1* is the most commonly involved gene. ARPKD caused by pathogenic variants in *PKHD1* (i.e., ARPKD-*PKHD1*) must be distinguished from the following (see Table 4):

- ARPKD caused by biallelic pathogenic variants in less commonly involved genes (e.g., *PKD1*, *CYS1*, or *DZIP1L*). Of note, although the ARPKD phenotype can appear clinically similar regardless of the causative gene, the genetic etiology may be relevant for prognosis of kidney survival [Lu et al 2017, Halawi et al 2023].
- Phenocopies of ARPKD associated with pathogenic variants in *NPHP3*, *PMM2*, or *TMEM67*
- Autosomal dominant polycystic kidney disease (ADPKD), which may resemble ARPKD in some individuals, such as individuals with very early-onset ADPKD [Cornec-Le Gall et al 2018, Gimpel et al 2018, Gimpel et al 2019, Halawi et al 2023]. Severe and early-onset polycystic kidney disease has been documented in individuals with pathogenic variants in *PKD1* and other ADPKD-related genes [Bergmann et al 2011, Halawi et al 2023]. Note: Multigene panels using next-generation sequencing should be carefully designed to maximize identification of a *PKD1* pathogenic variant, which is complicated by several highly homologous pseudogenes.
- Pathogenic *HNF1B* variants and *HNF1B* deletions

It is important to note that not all individuals with prenatal detection of enlarged and/or hyperechogenic kidneys have ARPKD [Erger et al 2017, Gimpel et al 2018, Yulia et al 2021, Botero-Calderon et al 2023].

Table 4. Genes of Interest in the Differential Diagnosis of Autosomal Recessive Polycystic Kidney Disease – *PKHD1*

Gene	Disorder	MOI	Selected Features	Comment
PKD1 *PKD2* *ALG5* *ALG9* *DNAJB11* *GANAB* *IFT140* *NEK8*	ADPKD	AD	• Progressive cyst development & bilaterally enlarged polycystic kidneys • Systemic disease w/cysts in other organs (e.g., liver, seminal vesicles, pancreas, arachnoid membrane) & non-cystic anomalies (e.g., intracranial aneurysms & dolichoectasias, dilatation of the aortic root & dissection of the thoracic aorta, mitral valve prolapse, colonic diverticulae, abdominal wall hernias) • Cerebral & extracerebral aneurysms, a common & potentially severe complication of ADPKD, have only been reported in 9 persons w/ ARPKD.	• ADPKD usually presents in adulthood; however, 1%-2% of affected persons present as newborns, often with features indistinguishable from those of ARPKD-*PKHD1*. [1] Early & severe ADPKD phenotypes primarily involve *PKD1*. • Specific heterozygous *NEK8* pathogenic variants are assoc w/an early PKD phenotype mimicking ARPKD-*PKHD1*. [2] • CHF – an invariable finding in ARPKD-*PKHD1* – is rarely observed in ADPKD. [3] • Kidney ultrasonography may often distinguish ADPKD & ARPKD-*PKHD1*: bilateral macrocysts are typical of ADPKD. Early in the course of ADPKD, esp in younger children, renal involvement may be unilateral. As ADPKD progresses involvement becomes bilateral; cysts can become massive.
PKD1	ARPKD-*PKD1* [4, 5,6, 7]	AR	• Bilaterally enlarged hyperechogenic kidneys pre- & perinatally • Liver: no cysts; no CHF in early childhood; [6] isolated cases of ductal plate malformations have been described; [4, 5] frequently, normal liver imaging in young adulthood [7]	• Biallelic hypomorphic pathogenic variants in *PKD1* have been reported in persons with an early phenotype resembling ARPKD-*PKHD1*. [4, 5, 6] • KF at age 8.5 yrs in 1 person w/compound homozygosity for 2 *PKD1* pathogenic variants: Val1045Met & Thr1570Met [6]
DZIP1L	ARPKD-*DZIP1L* (OMIM 617610)	AR	• Bilaterally enlarged hyperechogenic kidneys: multiple small cysts, some macrocysts, poor corticomedullary differentiation • Liver: no cysts, liver elasticity (FibroScan®) normal, [8] hepatosplenomegaly in 1 person [9]	• 7 persons from 4 families: KF at age 12, 18, 20, & 26 yrs [9] • 4 children from 3 consanguineous families: KF at age 9 yrs; homozygous for c.193T>C (p.Cys65Arg) [8]
CYS1	ARPKD-*CYS1* [10]	AR	• Multiple bilateral medullary & cortical cysts • Liver: mild CHF	Reported in child age 5 yrs w/ homozygous splice site pathogenic variant c.318+5G>A [10]

Table 4. continued from previous page.

Gene	Disorder	MOI	Selected Features	Comment
PMM2	Hyperinsulinemic hypoglycemia / polycystic kidney disease (HIPKD) [11]	AR	• Enlarged kidneys w/multiple cysts • Liver cysts • CHF in 1/17 persons • Hyperinsulinemia: often w/ hypoglycemic seizures, mostly in 1st yr of life	• ARPKD-like kidney disease & hyperinsulinemia in childhood • 17 persons from 11 families w/ cysts of various sizes in enlarged kidneys; predominantly glomerulocystic disease; 1 person w/prenatal polyhydramnios [11]
>20 NPH-related genes incl: *NPHP2* *NPHP3* *TMEM67* [12]	Nephronophthisis-related ciliopathies	AR [12]	• Infantile NPH: moderately enlarged cystic kidneys w/ cortical hyperechogenicity • Prenatal manifestation w/oligo- & anhydramnios, postnatal hypertension, & CKD • Liver: possible CHF • Possible situs inversus, tapetoretinal degeneration	ARPKD-like disease manifestations w/KF in early childhood is possible. [5]
HNF1B	*HNF1B*-related kidney disease [13]	AD	• Kidney cysts are the most frequently detected feature, although other renal phenotypes (single kidney, renal hypoplasia/dysplasia) can also occur. • Extrakidney phenotypes are common & incl MODY, genital malformations, autism, epilepsy, gout, hypomagnesemia, hyperthyroidism, liver & intestinal anomalies, & a rare form of kidney cancer (chromophobe renal carcinoma). [13]	Pathogenic variants in *HNF1B* represent the most common known monogenic cause of developmental kidney disease & are the leading cause of hyperechoic enlarged or normal-sized fetal kidneys, which often leads to a misdiagnosis of ARPKD.

Table 4. continued from previous page.

Gene	Disorder	MOI	Selected Features	Comment
>25 BBS-related genes incl: *BBS10* *CEP290* [14]	Bardet-Biedl syndrome	AR	• Primary criteria: retinal degeneration (cone-rod dystrophy), central obesity, postaxial polydactyly, learning disabilities, hypogonadism &/or genitourinary malformations, & kidney malformations (e.g., ranging from single unilateral & multiple bilateral cysts) • Additional secondary criteria incl cataract, speech disorders, behavioral disorders, polyuria, or craniofacial dysmorphism	• Highly variable kidney phenotype w/structural anomalies & parenchymal disease incl PKD-mimicking phenotypes & kidney dysplasia phenotypes • CKD in 31% of children & 42% of adults [15]

AD = autosomal dominant; ADPKD = autosomal dominant polycystic kidney disease; AR = autosomal recessive; ARPKD = autosomal recessive polycystic kidney disease; BBS = Bardet-Biedl syndrome; CHF = congenital hepatic fibrosis; CKD = chronic kidney disease; KF = kidney failure; MODY = maturity-onset diabetes of the young; MOI = mode of inheritance; NPH = nephronophthisis; PKD = polycystic kidney disease

1. Kääriäinen et al [1988]
2. Claus et al [2023]
3. O'Brien et al [2012]
4. Durkie et al [2021]
5. Halawi et al [2023]
6. Vujic et al [2010]
7. de Fallois et al [2021]
8. Hertz et al [2022]
9. Lu et al [2017]
10. Yang et al [2021]
11. Cabezas et al [2017]
12. More than 20 genes are known to be associated with nephronophthisis (NPH); the NPH-related genes of primary interest in the differential diagnosis of ARPKD-*PKHD1* are *NPHP2*, *NPHP3*, and *TMEM67*. Nephronophthisis-related ciliopathies are typically inherited in an autosomal recessive manner (see Nephronophthisis-Related Ciliopathies, Genetic Counseling).
13. Clissold et al [2015], Bockenhauer & Jaureguiberry [2016]
14. More than 25 genes are known to be associated with Bardet-Biedl syndrome (BBS); the BBS-related genes of primary interest in the differential diagnosis of ARPKD-*PKHD1* include *BBS10* and *CEP290*.
15. Forsythe et al [2017]

Other disorders with kidney involvement that may mimic ARPKD in the neonatal period include malignancies such as leukemia or Wilms tumor (see Wilms Tumor Predisposition), kidney dysplasia with cysts, bilateral renal vein thrombosis, and inherited metabolic disorders, such as disorders of fatty acid oxidation like glutaric acidemia type II (see Multiple Acyl-CoA Dehydrogenase Deficiency) and carnitine palmitoyltransferase II deficiency (Guay-Woodford et al 2014, Bergmann et al 2018, Gimpel et al 2018, Gimpel et al 2019].

Calcifications that can occur in ARPKD-*PKHD1* may hamper differentiation from medullary sponge disease in young adults [Gunay-Aygun et al 2010a, Burgmaier et al 2019, Letavernier et al 2021, Das et al 2023].

Management

Consensus expert recommendations for the management of autosomal recessive polycystic kidney disease (ARPKD) [Guay-Woodford et al 2014] and clinical practice recommendations for perinatal cystic kidney diseases have been published [Gimpel et al 2018]. The following recommendations are based on these published practice guidelines, additional data, and the authors' personal experience managing individuals with this disorder.

Note: Because some data on ARPKD predates the understanding of its heterogeneous genetic causes, information in this section is based on both study cohorts with ARPKD in general and cohorts with ARPKD-*PKHD1* (see Nomenclature).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with ARPKD-*PKHD1*, the following evaluations are recommended (if not already performed as part of the evaluation that led to the diagnosis).

Perinatal and infantile presentation (prenatal to age 1 year)

- If possible, delivery should take place at a center with ample experience in intensive care neonatology and pediatric nephrology that can offer multidisciplinary postnatal treatment.
- Assess postnatal respiratory status, including physical examination, pulse oximetry, blood gas analysis, chest radiographs, and echocardiography (as clinically indicated).
- Measure blood pressure regularly (and train parents in home measurements if elevated).
- Assess:
  - Kidney function, including serum concentrations of blood urea nitrogen (BUN), creatinine, and cystatin C;
  - Serum electrolyte concentrations and blood gases to identify electrolyte and acid-base anomalies (e.g., hyponatremia, hyperkalemia, acidosis).
- Perform urinalysis:
  - To assess urinary concentration and detect proteinuria;
  - In case of fever or biochemical signs of infection to identify potential urinary tract infections.
- Perform clinical and sonographic assessment of intravascular volume status for possible volume depletion or overload.
- Perform kidney ultrasonography to determine kidney volumes and height-adjusted total kidney volumes.
- Further abdominal ultrasound should be performed to evaluate anomalies of the liver (signs of congenital hepatic fibrosis, hepatomegaly, periportal fibrosis, liver cysts, bile duct cysts), signs of portal hypertension (diminished portal blood flow, collateral vessels, splenomegaly, ascites), and the potential need for further diagnostics (including liver elastography and magnetic resonance cholangiopancreatography [MRCP]).
- Assess feeding, weight gain, and linear growth accompanied by consultation with nutritional experts as appropriate. Aggressive nutritional support in the first two years of life may improve growth rates even in children with moderately to severely impaired kidney function and portal hypertension.
- Measure liver transaminases, serum bile acids, hepatic synthetic function (e.g., by assessing serum albumin concentration, coagulation studies), 25-hydroxyvitamin D levels and potentially other fat-soluble vitamin levels, and complete blood counts.
- Perform physical examination of the liver to assess for hepatomegaly/splenomegaly.
- Perform echocardiography as clinically indicated, such as in case of arterial hypertension.
- Perform cranial sonography to assess for structural brain defects and intraventricular hemorrhage at initial examination.
- Set up evaluation by interdisciplinary team including psychologists and social workers to assess type of support needed by the family.
- Set up consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of ARPKD-*PKHD1* to facilitate medical and personal decision making.
- Consider initiating interdisciplinary and interprofessional shared decision-making processes early in challenging clinical situations potentially requiring decisions on palliative treatment approaches or restrictions on specific treatment modes.

- Assess need for family support and resources including community or online resources such as Parent to Parent, social work involvement for parental support, and home nursing referral.

Childhood / young adulthood presentation (age >1 year)

- Assess kidney function, including serum concentrations of BUN, creatinine, and cystatin C.
- Assess serum electrolyte concentrations and perform blood gas analysis to identify electrolyte and acid-base anomalies (e.g., hyponatremia, hyperkalemia, acidosis).
- Measure blood pressure. If elevated, home blood pressure monitoring during follow up can be helpful in distinguishing fixed hypertension from "white coat" hypertension (i.e., high blood pressure that occurs during medical examinations).
- Perform urinalysis:
  - To assess urinary concentration and detect proteinuria;
  - In case of fever or biochemical signs of infection to identify potential urinary tract infections.
- Perform clinical and sonographic assessment of intravascular volume status for possible volume depletion or overload.
- Perform kidney ultrasonography to determine kidney volumes and height-adjusted total kidney volumes.
- Further abdominal ultrasound should be performed to evaluate anomalies of the liver (signs of congenital hepatic fibrosis, hepatomegaly, periportal fibrosis, liver cysts, bile duct cysts), signs of portal hypertension (diminished portal blood flow, collateral vessels, splenomegaly, ascites), and the potential need for further diagnostics (including liver elastography and MRCP).
- Assess feeding, weight gain, and linear growth accompanied by consultation with nutritional experts as appropriate. Aggressive nutritional support in the first two years of life may improve growth rates even in children with moderately to severely impaired kidney function and portal hypertension.
- Measure liver transaminases, serum bile acids, hepatic synthetic function (e.g., by assessing serum albumin concentration, coagulation studies), 25-hydroxyvitamin D levels and potentially other fat-soluble vitamin levels, and complete blood counts.
- Perform physical examination of the liver to assess for hepatomegaly/splenomegaly.
- Perform echocardiography as clinically indicated, such as in case of arterial hypertension.
- Perform neurodevelopmental examination, EEG, head sonography, and/or cranial MRT (if clinically indicated).
- Perform lung function tests (if clinically indicated).
- Set up an interdisciplinary and interprofessional team including psychologists and social workers for family support.
- Set up a consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of ARPKD-*PKHD1* to facilitate medical and personal decision making.
- Assess need for family support and resources including community or online resources such as Parent to Parent, social work involvement for parental support, and home nursing referral.

Treatment of Manifestations

There is currently no cure for autosomal recessive polycystic kidney disease – *PKHD1* (ARPKD-*PKHD1*). Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves interdisciplinary and interprofessional care by specialists in relevant fields.

Perinatal and Infantile Presentation (prenatal to age 1 year)

Initial management of affected infants focuses on stabilization of pulmonary and kidney function.

Pulmonary disease. In severely affected infants, oligo- or anhydramnios may result in pulmonary hypoplasia. Non-invasive and/or invasive respiratory support may be required to treat hypoxic and/or hypercapnic respiratory insufficiency. In individual cases extracorporal membrane oxygenation (ECMO) may be considered. Pulmonary hypertension, uni- or bilateral pneumothoraces, and massively enlarged kidneys hampering diaphragmatic excursion may complicate respiration and may require treatment as clinically indicated.

When massively enlarged kidneys are considered to prevent diaphragmatic excursion and/or cause severe feeding intolerance and/or massive arterial hypertension, some have advocated unilateral or bilateral nephrectomy; however, evidence supporting this approach is limited and mainly focused on nutritional aspects [Bean et al 1995, Shukla et al 2004, Beaunoyer et al 2007, Overman et al 2021].

- Unilateral nephrectomy may be of value, but the contralateral kidney may show marked rapid enlargement following unilateral nephrectomy [Burgmaier et al 2020, Overman et al 2021].
- Bilateral nephrectomies with placement of a peritoneal dialysis catheter have been suggested as a strategy for early management of critically ill infants. The expected benefits regarding nutrition or arterial hypertension must be weighed against the following risks:
    - Maturation of native kidney function is no longer possible and life-long kidney replacement therapy (KRT) is necessary after bilateral nephrectomies.
    - There are reports of arterial hypotension after bilateral nephrectomies possibly associated with neurologic damage in young children who are on peritoneal dialysis [van Lieburg & Monnens 2001, Hassinger & Garimella 2013, Dufek et al 2014, Al-Kaabi et al 2016].
    - Very early bilateral nephrectomies (i.e., age ≤3 months) and hypotensive episodes were identified as independent risk factors for severe neurologic complications in a study of a mostly European cohort of individuals with ARPKD [Burgmaier et al 2020].

  A very cautious approach to bilateral nephrectomies, especially in the first months of life during which maturation processes of autonomic cardiovascular control occur, is recommended.

Kidney disease. Children with significant chronic kidney disease (CKD) can be treated with all modalities of modern pediatric kidney failure (KF) therapy, including dialysis and kidney transplantation (KTx) as well as standard recommendations for treatment of CKD-associated anemia, acidosis, and mineral bone disease. KF is not the leading cause of neonatal demise. Importantly, kidney function may improve during the first months of life [Cole et al 1987, Liebau 2021].

- Neonates with oliguria or anuria may require dialysis within the first days of life. Peritoneal dialysis is the modality of choice [Zurowska et al 2013, Guay-Woodford et al 2014, Gimpel et al 2018]. Maintenance peritoneal dialysis has been successful even in young children with ARPKD [Akarkach et al 2020].
- Hyponatremia is common and should be treated according to standard recommendations depending on the individual's volume status [Guay-Woodford et al 2014].
- Early recognition and treatment of dehydration, insufficient weight gain, and/or poor growth is critical. Supplemental feedings or fluid therapy via nasogastric or gastrostomy tube placement may be required. As caloric intake relies on fluid intake in the early months of life, sufficient caloric intake should be monitored and modified as needed by a nutrition specialist.
- Early recognition of arterial hypertension is essential. In many individuals, hypertension is so severe that it requires multiple antihypertensive medications. Following general CKD recommendations targeting blood pressure values in the 50th percentile seems reasonable [Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group 2021].
- Early recognition and treatment of urinary tract infections is important. Nephrotoxic agents like aminoglycosides should be avoided when possible.

- With severe portal hypertension and splenic dysfunction, immunization against encapsulated bacteria (e.g., pneumococcus, *H influenza* type B, meningococcus) is indicated. In addition, general recommendations for routine immunizations for healthy children and premature children apply.

Hepatobiliary disease. Clinical consequences of liver involvement usually evolve later in life; details are discussed in Childhood / Young Adulthood Presentation.

Feeding and growth

- Feeding intolerance and growth failure can be significant even in the absence of KF, especially in young infants. Nutritional support, which may include supplemental feedings via nasogastric or gastrostomy tube, is often required to optimize weight gain and growth.
- Concerns about the potential risk of bleeding after gastrostomy tube placement in individuals with ARPKD and portal hypertension were addressed in a global survey (in which respondents were mainly European pediatric nephrologists) that identified very few complications and support by most respondents for gastrostomy tube placement in these children [Burgmaier et al 2018a].
- A subanalysis from the American Chronic Kidney Disease in Children (CKiD) cohort did not find evidence for an ARPKD-specific effect on growth when comparing children with a mean age of 7.9 years to age-matched control groups with other underlying congenital kidney diseases [Hartung et al 2016].
- Aggressive nutritional support in the first two years of life may improve growth rates even in children with moderately to severely impaired kidney function and portal hypertension.
- Treatment with growth hormone should be guided by standard recommendations for pediatric CKD.

Childhood / Young Adulthood Presentation (age >1 year)

In addition to the treatments listed in Perinatal and Infantile Presentation, aspects of liver involvement and dual organ transplantation are discussed in detail due to the evolving hepatic phenotype at these age stages.

Kidney disease

- KTx is the treatment of choice for children with KF, as graft survival is good. Previous or simultaneous nephrectomy of native ARPKD kidney(s) may be required.
- Peritoneal dialysis is the method of choice for chronic dialysis in children. In young children with ARPKD, maintenance peritoneal dialysis can be performed with only minor modifications compared to children with other early-onset kidney diseases [Akarkach et al 2020].

Hepatobiliary disease. Treatment of biliary dysfunction focuses on (1) the risk for ascending cholangitis and (2) the risk of portal hypertension resulting from hepatic fibrosis.

- **Bacterial cholangitis,** an underdiagnosed complication in those with hepatic involvement, may present as recurrent bacteremia with enteric pathogens without typical clinical features of cholangitis.
    - Persistent fevers, particularly with right upper-quadrant pain, should be evaluated and treated aggressively.
    - Alkaline phosphatase and gamma-glutamyl transferase may be elevated during episodes of acute ascending cholangitis and may be helpful in establishing a diagnosis, but normal liver enzymes do not exclude cholangitis.
    - Imaging studies may be supportive.
    - Recurrent cholangitis can contribute to bile duct damage with resulting cholestasis and the need for liver transplantation (LTx).
    - The role of chronic antibiotic prophylaxis in all children with ARPKD remains controversial. Antibiotic prophylaxis may be considered for six to 12 weeks after an episode of ascending

cholangitis, in the post-transplant period, or in states of enhanced immunosuppression; however, there are no general recommendations for antibiotic prophylaxis [Guay-Woodford et al 2014].

- **Cholestasis** due to bile duct anomalies may be associated with fat malabsorption and reduced absorption of fat-soluble vitamins that should be treated according to the individual's clinical and biochemical findings.

  Note: The use of ursodeoxycholic acid (UDCA) as choleretic agent generally cannot be recommended [Guay-Woodford et al 2014].

- **Esophageal varices** should be treated with endoscopic banding or sclerotherapy according to local standard procedures as for children with other causes of portal hypertension [Guay-Woodford et al 2014, Jeanniard-Malet et al 2017]. Measures to prevent varices follow general approaches applying to other causes of portal hypertension in children and adults.

- **Interventional or surgical portosystemic shunting** may be necessary to treat progressive portal hypertension; successful placement of transjugular intrahepatic portosystemic shunt (TIPS) has been reported [Verbeeck et al 2018] and may be an option especially in individuals with good residual kidney function. Tsimaratos et al [2000] reported recurrent hepatic encephalopathy and death following portocaval shunting in two individuals with KF.

- In severe instances of intractable portal hypertension or severe dual renal and hepatobiliary disease, LTx or simultaneous/combined liver and kidney transplantation (CLKTx) is a viable option.

Dual-organ transplantation. Successful CLKTx has been reported in several case series [Brinkert et al 2013, Telega et al 2013, Büscher et al 2015, Loos et al 2023] and in an analysis from the European Society for Pediatric Nephrology / European Renal Association-European Dialysis and Transplant (ESPN/ERA-EDTA) Registry [Mekahli et al 2016]. It can be considered when an individual has relevant CKD and substantial liver involvement, notably severe portal hypertension and/or recurrent cholangitis. As both liver and kidney derive from the same donor, immunoprotective effects of the liver allograft in CLKTx have been described. The molecular basis is not fully understood, but among other factors neutralization of circulating autoantibodies by the transplanted liver has been considered [Knechtle & Kwun 2009, Key et al 2010, Ranawaka et al 2020].

A study from the United Network for Organ Sharing (UNOS) database reported superior five-year kidney transplant organ survival in individuals starting from six months after CLKTx compared to individuals after isolated KTx [de la Cerda et al 2010]. Possible benefits must be critically weighed against possible risks: CLKTx is a complex surgical procedure with relevant postoperative complications leading to a 6.7-fold age- and sex-adjusted risk for death after CLKTx when compared to isolated KTx [Mekahli et al 2016]. An algorithm for management and evaluation of the risks vs benefits of dual-organ transplantation in individuals with ARPKD who have both severe kidney and liver disease has been proposed to assist clinicians in the decision-making process [Brinkert et al 2013, Telega et al 2013]; however, more data are required.

In summary, individual decision making regarding single or combined transplantation is indispensable because clear-cut criteria evaluating risks and benefits for decision making in individuals with ARPKD remain to be defined.

Surveillance

To monitor existing manifestations in all individuals regardless of age of initial presentation, the individual's response to supportive care, and the emergence of new manifestations, the following evaluations are recommended.

- Blood pressure. Monitor at regular physician's visits as well as at home if indicated (see Evaluations Following Initial Diagnosis), according to standard recommendations for individuals with CKD with a blood pressure target in the 50th percentile for children.
- Kidney function. Close monitoring for the complications of CKD should be undertaken by the treating pediatric nephrologist according to standard practices.
- Electrolyte balance. Monitor via serum concentrations of sodium, potassium, chloride, and hydrogen bicarbonate.
- Mineral balance. Monitor via serum concentrations of calcium, phosphorous, magnesium, and 25-hydroxyvitamin D.
- Hydration status. Monitor at periodic physician's visits as well as at home if indicated.
- Nutritional status. Plot growth on standard growth charts. Set up nutrition consultation as indicated.
- Hepatoportal involvement. Perform physical examination; obtain complete blood counts, prothrombin time, and serum concentrations of albumin, 25-hydroxyvitamin D, and other fat-soluble vitamins.
- Abdominal ultrasound, liver elastography, and MRCP
    - For signs of portal hypertension (such as splenomegaly or abnormal portal Doppler flow), abdominal ultrasound is suggested in regular intervals tailored according to individual disease course and previous imaging findings (e.g., every 1-3 years) [Guay-Woodford et al 2014, Gimpel et al 2019].
    - Increased liver and spleen shear wave speed in ultrasound elastography with acoustic radiation force impulse can detect liver fibrosis and portal hypertension [Hartung et al 2019]. Liver magnetic resonance elastography may quantify liver stiffness [Hartung et al 2021].
    - If liver involvement is confirmed, it may be advisable to search for aggravation (i.e., check portal vessels and possible development of collateral circulation via color and duplex Doppler ultrasound) at shorter intervals [Gimpel et al 2018, Gimpel et al 2019].
    - MRI and MRCP, a more sensitive measurement for biliary ectasia, should be considered in individuals with clinical complications of liver disease and/or during detailed liver assessment prior to KTx [Gimpel et al 2018]. MRCP is well suited to identify Caroli disease as hypointense (T_1) or hyperintense (T_2) dilatation of intrahepatic bile ducts. Contrast agents may enhance visualization of the central portal radicles within the dilated bile ducts but should be used with caution in individuals with reduced renal function.

Agents/Circumstances to Avoid

Individuals with hypertension should avoid sympathomimetic agents.

In general, unless the clinical situation warrants their use, avoid known nephrotoxic agents including nonsteroidal anti-inflammatory drugs (NSAIDs) and aminoglycosides.

High-salt diet, smoking, and obesity should be avoided.

Minimize use of potentially hepatotoxic agents (e.g., acetaminophen doses >30 mg/kg/day, herbal supplements, and alcohol).

While work in cell and animal models suggests that caffeine, theophylline-like agents, and calcium channel blockers may exacerbate the formation and growth of renal cysts, this hypothesis has not been rigorously studied in individuals with ARPKD. Thus, the clinical relevance of these observations remains unclear.

Evaluation of Relatives at Risk

Sibs of a proband. Early screening and genetic testing of apparently asymptomatic at-risk sibs can be considered with the goal of identifying those who may benefit from additional examinations and potentially preventive measures. Prior to screening/testing, families should be offered clinical education regarding potential evaluations

and the capabilities and limitations of predictive genetic testing; possible socioeconomic and medical care issues should be discussed in the context of formal genetic counseling. Abdominal ultrasound and blood pressure measurement of sibs may provide relevant clinical information.

Parents of a proband. It is important to perform kidney ultrasonography in parents of children with ARPKD-*PKHD1*, as individuals who are heterozygous for a *PKHD1* pathogenic variant may, in rare cases, have very mild cystic kidney manifestations or, more frequently, liver cysts. Increased medullary echogenicity in the kidneys consistent with nephrocalcinosis and/or multiple small liver cysts without functional deterioration have been detected in small subgroups of heterozygous mothers and fathers [Gunay-Aygun et al 2011, Besse et al 2017].

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Very little is known about pregnancy outcomes for women with ARPKD. As both kidney and liver phenotypes show clinical variability, comprehensive recommendations cannot currently be given. In general, women with CKD face an increased risk of pregnancy-related decline in renal function, preeclampsia, and impaired fetal outcomes [Vellanki 2013, Rao & Brewster 2023]. Although women with portal hypertension might have an increased risk of variceal bleeding, data on noncirrhotic portal hypertension are sparse [Sumana et al 2008, Joshi et al 2010].

In a small case series of four pregnant women with ARPKD and live birth deliveries, three had uncomplicated pregnancies (in two of three the diagnosis of ARPKD was established after delivery) and one had transient worsening of kidney function [Banks et al 2015]. Until more data are available, individual counseling regarding both kidney- and liver-related aspects of ARPKD-*PKHD1* with respect to pregnancy is strongly recommended. Furthermore, women with ARPKD-*PKHD1* considering pregnancy or who are pregnant might benefit from more frequent appointments with their nephrologist or hepatologist and consultation with a high-risk prenatal clinic.

Therapies Under Investigation

Recent studies in two animal models of ARPKD suggest that tesevatinib (TSV), a unique multikinase inhibitor, markedly slows the progression of both renal cystic disease and hepatobiliary disease [Sweeney et al 2017]. These data, in addition to safety data generated by a Phase I/II multicenter clinical trial of TSV (also called KD-019) in ADPKD (NCT01559363), have led to an initial Phase I/II multicenter clinical trial of TSV in infants and children with ARPKD. To date, results have not been published.

Two multinational open-label Phase III trials on the effects of tolvaptan in ARPKD-*PKHD1* have been initiated [Mekahli et al 2023]. One trial focuses on children with a high risk for KRT in the first year of life based on recently established risk patterns for dialysis dependency. The trial studies if tolvaptan can reduce this risk relative to a historical control. A second trial mainly studies safety and tolerability.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

By definition, autosomal recessive polycystic kidney disease – *PKHD1* (ARPKD-*PKHD1*) is inherited in an autosomal recessive manner.

Note: In rare families, pseudodominant inheritance (i.e., an autosomal recessive condition present in individuals in two or more generations) has been reported [de Fallois et al 2021].

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *PKHD1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *PKHD1* pathogenic variant and to allow reliable assessment of recurrence risk.
- If a *PKHD1* pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the *PKHD1* pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a parent [Jónsson et al 2017]. If the proband appears to have homozygous *PKHD1* pathogenic variants (i.e., the same two *PKHD1* pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon *PKHD1* deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the *PKHD1* pathogenic variant that resulted in homozygosity for the *PKHD1* pathogenic variant in the proband.
- Individuals who are heterozygous for a *PKHD1* pathogenic variant are not at risk of developing ARPKD-*PKHD1* but may in rare cases have cystic kidney disease manifestations. Increased medullary echogenicity in the kidneys consistent with nephrocalcinosis and/or multiple small liver cysts without functional deterioration have been detected in a small subgroup of mothers and fathers heterozygous for a *PKHD1* pathogenic variant [Gunay-Aygun et al 2011, Besse et al 2017]. As such, it is important to perform kidney ultrasonography on parents of children with ARPKD-*PKHD1*.

Sibs of a proband

- If both parents are known to be heterozygous for a *PKHD1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of being unaffected and not a carrier.
- While previous data described pronounced intrafamilial variability in survival among affected sibs, a more recent study of 70 sibs surviving the neonatal period found comparable clinical courses of kidney and hepatobiliary disease during follow up, suggesting a strong effect of the underlying genotype [Ajiri et al 2022].
- Heterozygotes for a *PKHD1* pathogenic variant are not at risk of developing ARPKD-*PKHD1*. However, hyperechogenicity in the kidneys and mild courses of kidney cysts as well as hepatic cysts have been described in individuals with monoallelic *PKHD1* pathogenic variants [Gunay-Aygun et al 2011, de Fallois et al 2021, Van Buren et al 2023]. Abdominal ultrasound and blood pressure measurement of sibs may provide relevant clinical information. Options for the evaluation of sibs, including the capabilities and limitations of early screening as well as socioeconomic considerations, should be discussed with families.

Offspring of a proband. Unless an affected individual's reproductive partner also has ARPKD-*PKHD1* or is a carrier (see Prevalence), offspring will be obligate heterozygotes (carriers) for a *PKHD1* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for a *PKHD1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *PKHD1* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Carrier testing should be considered for the reproductive partners of known heterozygotes for an *PKHD1* pathogenic variant and for the reproductive partners of individuals affected with ARPKD-*PKHD1*, particularly if both partners are of the same ancestral background. Pathogenic founder variants have been identified in individuals of Afrikaner and Ashkenazi Jewish descent (see Table 5).

Prenatal Testing and Preimplantation Genetic Testing

High-risk pregnancies (i.e., those at 25% risk based on family history). Once the *PKHD1* pathogenic variants have been identified in an affected family member, molecular genetic prenatal and preimplantation genetic testing are possible.

No systematic data are available on the sensitivity and specificity of prenatal ultrasound examination in diagnosis of ARPKD in pregnancies at 25% risk.

Low-risk pregnancies (i.e., those not known to be at increased risk but in which routine prenatal ultrasound examination reveals enlarged cystic kidneys)

- Karyotype or array comparative genomic hybridization (CGH) and detailed fetal ultrasonography can be performed to evaluate for the presence of a chromosomal anomaly and/or other congenital anomalies in a fetus not known to be at increased risk for ARPKD-*PKHD1*.
- Molecular genetic testing of *PKHD1* may be appropriate. Failure to detect two *PKHD1* pathogenic variants, however, does not exclude the diagnosis of ARPKD-*PKHD1*, as a second *PKHD1* pathogenic variant may have been missed by current testing techniques. If molecular genetic testing is performed, a polycystic kidney disease or kidney disease multigene panel that includes *PKHD1* and other cystic nephropathy genes (e.g., *HNF1B*, *PKD1*, *PKD2*) (see Differential Diagnosis) is preferable.
- Kidney and liver ultrasound examinations of both parents of fetuses with ARPKD-*PKHD1* should be considered to evaluate for the possibility of monoallelic *PKHD1*-related kidney and liver manifestations (see Genetically Related Disorders).
- Prenatal hyperechogenicity and enlargement of the fetal kidneys alone are not sufficient to definitively diagnose ARPKD-*PKHD1* prenatally.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Delivery considerations for infants with prenatally suspected/confirmed ARPKD-*PKHD1*

- If possible, delivery should occur at a center with ample experience in intensive care neonatology and pediatric nephrology that can offer multidisciplinary postnatal treatment. Prenatal assessment of the lungs

remains challenging. Early oligohydramnios seems to be associated with more severe outcomes. Data on serial amnioinfusions are insufficient to support a general recommendation [Gimpel et al 2018]. Prenatal steroids may be helpful for lung maturation in late preterm fetuses.
- There is a potential risk of abdominal dystocia with vaginal delivery [Belin et al 2019].

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **ARPKD/CHF Alliance**
  Phone: 800-708-8892 ; 717-529-5555
  Fax: 800-807-9110
  Email: info@arpkdchf.org
  www.arpkdchf.org
- **MedlinePlus**
  Polycystic kidney disease
- **PKD Foundation**
  Phone: 816-931-2600
  Email: pkdcure@pkdcure.org
  www.pkdcure.org
- **Ciliopathy Alliance**
  United Kingdom
  ciliopathyalliance.org
- **ERKNet: The European Rare Kidney Disease Reference Network**
  Phone: 49 0 6221 56-34191
  Email: contact@erknet.org
  erknet.org
- **Kidney Foundation of Canada**
  Canada
  Phone: 514-369-4806
  Email: info@kidney.ca
  kidney.ca
- **National Kidney Foundation**
  Phone: 855-NKF-CARES; 855-653-2273
  Email: nkfcares@kidney.org
  kidney.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Autosomal Recessive Polycystic Kidney Disease – PKHD1: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

PKHD1	6p12.3-p12.2	Fibrocystin	PKHD1 database	PKHD1	PKHD1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Autosomal Recessive Polycystic Kidney Disease – PKHD1 (View All in OMIM)

263200	POLYCYSTIC KIDNEY DISEASE 4 WITH OR WITHOUT POLYCYSTIC LIVER DISEASE; PKD4
606702	PKHD1 CILIARY IPT DOMAIN-CONTAINING FIBROCYSTIN/POLYDUCTIN; PKHD1

Molecular Pathogenesis

PKHD1 encodes fibrocystin (or polyductin), a large protein with a single transmembrane domain comprising an extracellular domain and a short cytoplasmic tail expressed in the kidneys, bile ducts, and pancreas. Biallelic *PKHD1* pathogenic variants are predicted to result in either reduced or complete loss of fibrocystin function. The function of fibrocystin is poorly understood. It can be found in multiple subcellular localizations including primary cilia [Bergmann et al 2018], membrane-associated organelles that have been associated with many forms of cystic kidney disease. Multiple polycystic kidney disease-associated proteins are localized to cilia and influence ciliary function. Ciliary dysfunction has been associated with the development of cystic kidney phenotypes [McConnachie et al 2021].

In addition to localization in cilia, fibrocystin also localizes to cell junctions, and fragments of the fibrocystin cytoplasmic tail have been found in the cell nucleus and in mitochondria [Bergmann et al 2018]. Fibrocystin has been identified in extracellular vesicles in a joint complex with the autosomal dominant polycystic kidney disease (ADPKD) proteins polycystin-1 (encoded by *PKD1*) and polycystin-2 (encoded by *PKD2*) [Hogan et al 2009].

Data from multiple preclinical models suggest that fibrocystin regulates intracellular signaling cascades (also involved in the development of ADPKD [Bergmann et al 2018, Liebau & Mekahli 2021]) including the regulation of intracellular concentrations of cyclic AMP, signaling cascades involving protein kinase A, SRC-STAT3, or Myc [Wang et al 2005, Banales et al 2009, Olson et al 2019, Dafinger et al 2020, Harafuji et al 2023]. Cell metabolic changes may also be regulated through fibrocystin [Li et al 2012, Walker et al 2023]. These mechanisms seem to jointly regulate cellular proliferation and epithelial morphogenesis and function.

Deficiency of fibrocystin in the liver may promote fibrosis through recruitment of macrophages [Locatelli et al 2016].

Mechanism of disease causation. Loss of function.

***PKHD1*-specific laboratory technical considerations.** *PKHD1* is a large gene – comprising 86 exons – that undergoes complex splicing. While the majority of *PKHD1* pathogenic variants reported to date are within the coding or canonical splice site region, several *PKHD1* pathogenic variants have been identified that are deeper within intronic regions and are therefore likely to be identified by genome sequencing [Michel-Calemard et al 2009, Chen et al 2019, Doreille et al 2022, Liu et al 2022].

Because private *PKHD1* variants are identified in many families, variants of uncertain significance are commonly observed throughout the gene [Ebner et al 2017b, Burgmaier et al 2021a]. To date, there are no standardized laboratory tests to assess the pathogenicity of such variants.

Table 5. *PKHD1* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_138694.4 NP_619639.3	c.107C>T	p.Thr36Met	• Most frequent *PKHD1* pathogenic variant (identified in 13%-20% of affected persons) in European cohorts [2, 3] • Possibly occurs at a mutational hot spot & may have a single European origin [3, 4] • Founder variant in Ashkenazi Jewish population [5]
	c.3761_3762delCCinsG	p.Ala1254GlyfsTer49	Founder variant in Ashkenazi Jewish population [5]
	c.1880T>A	p.Met627Lys	Founder variant in Afrikaner population [6]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
2. Bergmann et al [2005]
3. Burgmaier et al [2021a]
4. Consugar et al [2005]
5. Shi et al [2017]
6. Lambie et al [2015]

Chapter Notes

Author Notes

Max Liebau and Kathrin Burgmaier are actively involved in clinical research regarding individuals with ARPKD or ARPKD-*PKHD1*. They would be happy to communicate with persons who have any questions regarding diagnosis of ARPKD-*PKHD1* or other considerations.

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