interactions. PC1 and PC2 also are integral membrane proteins of cilia, including the primary cilia of renal tubular cells. ADPKD is now classified under the new class of diseases called *ciliopathies*.

In the kidney, increases in cyst size and number over time damage adjacent renal architecture and cause renal insufficiency and renin-mediated hypertension. Total kidney volume increases continuously and is associated with progressive decline of renal function. Higher rates of kidney enlargement are associated with a more rapid decrease in renal function.

ADPKD is a multisystem disease. The clinical presentation may range from no symptoms to an array of multiple renal and extrarenal manifestations. In addition to renal tubules, PC1 and PC2 proteins are found in diverse cell types, including bile ducts, endothelial cells, and neurons. ADPKD patients with mutated PC1 or PC2 proteins often have extrarenal manifestations, including polycystic liver disease, which is detected in about 80% of adults. Cardiac valvular abnormalities and cerebral aneurysms are key noncystic features of ADPKD, and familial clustering of cases occurs. Cerebral aneurysms are observed in about 8% of patients with ADPKD, but the incidence increases to 20% among those with a positive family history of cerebral aneurysm or subarachnoid hemorrhage.

Most patients with ADPKD develop cysts before the age of 30, but renal insufficiency can be delayed to beyond the fourth decade. Patients with the *PKD2* mutation have later onset and slower progression of the disease than patients with the *PKD1* mutation. Renal survival associated with *PKD2* mutations is about 20 years longer than that associated with *PKD1* mutations. Twenty percent of patients with ADPKD can develop uric acid and calcium oxalate nephrolithiasis and may have renal colic, obstructive nephropathy, or urinary tract infection.

ADPKD is usually diagnosed by imaging of the kidneys. The finding of three or more cysts (unilateral or bilateral) in those younger than age 30, two or more cysts in each kidney in those between 40 and 59 years of age, and four or more cysts in each kidney in patients older than 60 years is sufficient to make diagnosis of ADPKD. The absence of more than two cysts in individuals older than 40 years of age makes ADPKD very unlikely. Genetic testing is usually not required for an individual with a positive family history if other diagnostic criteria for ADPKD are met, but other family members should be screened.

No specific treatment is available to prevent the growth of renal or liver cysts. Renin-mediated hypertension is a common complication of ADPKD, and it contributes to an increased incidence of cardiovascular mortality and faster progression to ESRD. The main and most effective therapy remains control of hypertension by angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers to achieve a target blood pressure of less than 125/75 mm Hg.

Renal cyst enlargement can cause pain, and cysts can be complicated by infection or bleeding that warrants specific intervention. Surgical decompression is usually reserved for patients who fail conservative management. If ESRD occurs, patients are treated with renal replacement therapy, including dialysis and renal transplantation. Preemptive management of intracranial aneurysms is important but controversial.

The time of onset and rate of progression of ADPKD varies from patient to patient, even within the same family. Risk factors for progressive renal failure include increases in renal cyst volume, a *PKD1* gene mutation, and uncontrolled hypertension. Other risk factors include male gender, diagnosis of ADPKD before 30 years of age, hypertension before 35 years of age, concurrent diabetes mellitus, and hematuria. About 45% of the patients with ADPKD develop ESRD by 60 years of age, but they have a better prognosis than patients with ESRD from other causes.

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY

Autosomal recessive polycystic kidney disease (ARPKD) also is classified under the ciliopathies. ARPKD is characterized by diffused dilation of the collecting ducts and congenital hepatic fibrosis. The estimated incidence of ARPKD is 1 case in 20,000 live births.

Mutations in the polycystic kidney and hepatic disease 1 gene *(PKHD1)* are responsible for ARPKD. *PKHD1* is a large gene located on chromosome 6. More than 300 mutations have been identified at different loci of the *PKHD1* gene. Fibrocystin (i.e., polyductin) is the product of *PKHD1* gene and is expressed in the primary cilia of the thick ascending limb, in cortical and medullary ducts in the kidney, and in hepatic bile ducts. It has an important role in the terminal differentiation of renal and biliary ductules.

Patients with ARPKD may be diagnosed at different ages, but most are identified in utero or at birth because those with more severe phenotypes develop enlarged kidneys, oligohydramnios, pulmonary hypoplasia, Potter's facies, and deformities of the spine and limb. Neonates usually have renal enlargement and renal failure, and older patients have liver disease, including portal hypertension, hepatosplenomegaly, variceal bleeding, and hepatic fibrosis.

The initial diagnosis is usually suspected on the basis of renal imaging with antenatal ultrasound or after birth. Abdominal ultrasound shows bilateral renal cysts and enlarged kidneys. Fetal imaging shows oligohydramnios, pulmonary hypoplasia, and Potter's syndrome.

No treatment is available for ARPKD, and genetic testing is usually not performed outside of research scenarios. Most deaths occur in utero or at the time of birth, and of those with ARPKD who survive birth, 20% to 30% die within the first year of life. Neonates have more renal manifestations, and older patients have more liver disease manifesting as portal hypertension, hepatosplenomegaly, and bleeding esophageal or gastric varices. The likelihood of patients being alive without ESRD increases with older age at presentation due to their more benign phenotypes.

JUVENILE NEPHRONOPHTHISIS–MEDULLARY CYSTIC KIDNEY DISEASE COMPLEX

Nephronophthisis and medullary cystic kidney disease (MCKD) are hereditary forms of renal cystic disease. Both produce bilateral cysts at the corticomedullary junction of the kidney and early-onset ESRD. They are clinically and pathologically indistinguishable, and they are separated only by the age of onset and mode of inheritance.

Nephronophthisis is an autosomal recessive cystic kidney disease, and the median age of onset of renal disease is 11.5 years.