next-generation sequencing with multiplexing individually bar-coded long-range polymerase chain reaction libraries, may reduce the costs and improve the sensitivity for clinical genetic testing.

TREATMENT AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

No specific treatment to prevent cyst growth or the decline of renal function has been approved by U.S. Food and Drug Administration. Blood pressure control to a target of 140/90 mmHg is recommended according to the guidelines from the eighth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VIII report) for reducing cardiovascular complications in ADPKD and renal disease progression. More rigorous blood pressure control does not equal greater clinical benefits. Maintaining a target systolic blood pressure to 110 mmHg in patients with moderate or advanced disease may increase the risk of renal disease progression by reducing renal blood flow. Lipid-soluble antibiotics against common gram-negative enteric organisms, such as trimethoprim-sulfamethoxazole, quinolones, and chloramphenicol, are preferred for cyst infection because most renal cysts are not connected to glomerular filtration and antibiotics that are capable of penetrating the cyst walls are likely to be more effective. Treatment often requires 4–6 weeks. The treatment of kidney stones in ADPKD includes standard measures such as analgesics for pain relief and hydration to ensure adequate urine flow. Management of chronic flank, back, or abdominal pain due to renal enlargement may include both pharmacologic (nonnarcotic and narcotic analgesics) and nonpharmacologic measures (transcutaneous electrical nerve stimulation, acupuncture, and biofeedback). Occasionally, surgical decompression of cysts may be necessary. More than half of ADPKD patients eventually require peritoneal dialysis, hemodialysis, or kidney transplantation. Peritoneal dialysis may not be suitable for some patients with massively enlarged polycystic kidneys due to the small intraabdominal space for efficient peritoneal exchange of fluid and solutes and increased chance of abdominal hernia and back pain. Patients with very large polycystic kidneys and recurrent renal cyst infection may require pretransplant nephrectomy or bilateral nephrectomy to accommodate the allograft and reduce the pain.

Specific treatment strategies for ADPKD have focused on slowing renal disease progression and lowering cardiovascular risk. For the latter, the main approach is to control blood pressure by inhibiting the renin-angiotensin-aldosterone system. The ongoing HALT PKD trial was set to evaluate the impact of intensive blockade of the renin-angiotensin-aldosterone system and levels of blood pressure control on progressive renal disease. Most approaches target the slowing of renal disease progression by inhibiting cell proliferation and fluid secretion. Several clinical trials have been conducted targeting cell proliferation, including studies on sirolimus and everolimus, inhibitors of the mTOR pathway; OPC31260 and tolvaptan, which inhibit cAMP pathways by antagonizing the activation of vasopressin V2 receptor (V2R) in collecting ducts and reduce cell proliferation by decreasing renal cAMP levels; and somatostatin analogues, which reduce cAMP levels by binding to several GPCRs. Both the V2R antagonists and somatostatin analogues appear to slow the decline of renal function, although with some side effects such as liver function impairment, polydipsia, and diarrhea. A combination of different growth inhibitors may enhance efficacy and reduce side effects. Additional preclinical studies in animal models include the use of inhibitors to nonreceptor tyrosine kinase Src, B-raf, cyclin-dependent kinase (CDK), transcription factors STAT3 and STAT6 (pyrimethamine and leflunomide), purinergic receptors, hepatocyte growth factor receptor, and glucosylceramide, and agonists to peroxisome proliferator activated receptor-γ (PPARγ receptors (thiazolidodinediones).

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

Genetic Considerations ARPKD is a significant hereditary renal disease in childhood, with an estimated prevalence of 1 in 20,000 live births. A carrier frequency of up to 1:70 has been reported. Mutations in a single gene, *PKHD1*, are responsible for all the clinical presentations of ARPKD. *PKHD1*, localized on human chromosome region 6p21.1-6p12.2, is one of the largest genes in the genome, occupies ~450 kb of DNA, and contains at least 86 exons. It produces multiple alternatively spliced transcripts. The largest transcript encodes fibrocystin/polyductin (FPC), which is a large receptor-like integral membrane protein of 4074 amino acids. FPC has a single transmembrane, a large N-terminal extracellular region, and a short intracellular cytoplasmic domain. FPC is localized on the primary cilia of epithelia cells of cortical and medullary collecting ducts and cholangiocytes of bile ducts, similar to polycystins and several other ciliopathy proteins. FPC is also expressed on the basal body and plasma membrane. The large extracellular domain of FPC is presumed to bind to an as yet unknown ligand(s) and is involved in cell-cell and cell-matrix interactions. FPC interacts with ADPKD protein PC2 and may also participate in regulation of the mechanosensory function of the primary cilia, calcium signaling, and PCP, suggesting a common mechanism underlying cystogenesis between ADPKD and ARPKD. FPC is also found on the centrosomes and mitotic spindle and may regulate centrosome duplication and mitotic spindle assembly during cell division. A large number of various mutations have been found throughout *PKHD1* and are unique to individual families. Most patients are compound heterozygotes for *PKHD1* mutations. Patients with two truncation mutations appear to have an earlier onset of the disease.

Clinical Features Classic ARPKD is generally diagnosed in utero or within the neonatal period and characterized by greatly enlarged echogenic kidneys in diseased fetuses. Reduced fetal urine production may contribute to oligohydramnios and pulmonary hypoplasia. About 30% of affected neonates die shortly after birth due to respiratory insufficiency. Close to 60% of mortality occurs within the first month of life. In the classic group, most patients are born with renal insufficiency and ESRD. However, infants often have a transient improvement in their GFR; death from renal insufficiency at this stage is rare. Some patients are diagnosed after the neonatal stage and form the older group. Morbidity and mortality in this group often involve systemic hypertension, progressive renal insufficiency, and liver manifestations. The hallmarks of ARPKD liver disease are biliary dysgenesis due to a primary ductal plate malformation with associated periportal fibrosis, namely congenital hepatic fibrosis (CHF) and dilatation of intrahepatic bile ducts (Caroli's disease). CHF and Caroli's disease can then lead to portal hypertension exhibiting hepatosplenomegaly, variceal bleeding, and cholangitis. Some patients with the diagnosis of ARPKD at 1 year of age with nephromegaly exhibit slowly declining renal function over 20 years with only minimally enlarged kidneys at ESRD and markedly atrophic kidneys following renal transplantation. The slow progression of renal disease is likely due to increasing fibrosis rather than the development of cysts. Systemic hypertension is common in all ARPKD patients, even those with normal renal function.

Diagnosis Ultrasonography, CT, and MRI all can be used for diagnosis. Ultrasonography reveals large, echogenic kidneys with poor corticomedullary differentiation. The diagnosis can be made in utero after 24 weeks of gestation in severe cases. Macrocysts generally are not common at birth in ARPKD patients. The absence of renal cysts in either parent, particularly if they are more than 40 years of age on ultrasonography, helps distinguish ARPKD from ADPKD in older patients. Clinical, laboratory, or radiographic evidence of hepatic fibrosis, hepatic pathology demonstrating characteristic ductal plate abnormalities, family history of affected siblings, or parental consanguinity suggestive of autosomal recessive inheritance is helpful. The lack of mutational hotspots and the large and complex genomic structure of *PKHD1* make molecular diagnosis difficult; however, presymptomatic screening of other at-risk members in a family with already identified ARPKD mutations is straightforward and inexpensive.