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Autosomal Dominant Polycystic Kidney Disease

[*ADPKD. Includes: Polycystic Kidney Disease Type 1 (PKD1), Polycystic Kidney Disease Type 2 (PKD2)*]

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Summary

Disease characteristics. Autosomal dominant polycystic kidney disease (ADPKD) is generally a late-onset, multisystem disorder characterized by bilateral renal cysts; cysts in other organs, such as the liver, seminal vesicles, pancreas, and arachnoid membrane; vascular abnormalities, such as intracranial aneurysms, dilatation of the aortic root, and dissection of the thoracic aorta; mitral valve prolapse; and abdominal wall hernias. The renal manifestations of ADPKD include renal function abnormalities, hypertension, renal pain, and renal insufficiency. Approximately 50% of individuals with ADPKD have end-stage renal disease (ESRD) by age 60 years. Polycystic liver disease is the most common extrarenal manifestation of ADPKD. The prevalence of liver cysts in individuals with ADPKD increases from 20% in the third decade to approximately 75% after the sixth decade. Intracranial aneurysms occur in approximately 10% of individuals with ADPKD. The prevalence is higher in those with a positive family history of aneurysms or subarachnoid hemorrhage (22%) than in those without (6%). Mitral valve prolapse is the most common valvular abnormality and has been demonstrated in up to 25% of affected individuals. Substantial variability of severity of renal disease and other extra-renal manifestations occurs even within the same family.

Diagnosis/testing. The diagnosis of ADPKD is established primarily by imaging studies of the kidneys. Diagnostic criteria for individuals known to be at 50% risk for the disease include: at least two unilateral or bilateral cysts in individuals younger than age 30 years; two cysts in each kidney in individuals age 30-59 years; and four cysts in each kidney in individuals age 60 years or older. The sensitivity of the criteria is nearly 100% for all individuals with ADPKD who are age 30 years or older and for younger individuals with *PKD1* mutations; these criteria are only 67% sensitive for individuals with *PKD2* mutations who are younger than age 30 years. Large echogenic kidneys without distinct macroscopic cysts in an infant/child at 50% risk for ADPKD are diagnostic. In the absence of a family history of ADPKD, the presence of bilateral renal enlargement and cysts, with or without the presence of hepatic cysts, and the absence of other manifestations suggestive of a different renal cystic disease provide presumptive, but not definite, evidence for the diagnosis. In 85% of individuals, ADPKD is caused by mutations in the gene *PKD1*; in 15% of individuals mutations in *PKD2* are causative. Sequence analysis of the *PKD1* and *PKD2* genes is clinically available, with a detection rate for disease-causing mutations of approximately 85%.

Management. Current therapy for ADPKD is directed towards reducing the morbidity and mortality from the renal and extrarenal complications of the disease. Treatment for hypertension may include administration of ACE inhibitors and diet modification. Conservative treatment of flank pain is recommended; options include non-opoid agents, tricyclic antidepressants, narcotic analgesics, splanchnic nerve blockade, and renal denervation. More aggressive treatments include cyst decompression with cyst aspiration and sclerosis. In individuals with many cysts contributing to pain, laparoscopic or surgical cyst fenestration may be of benefit. Episodes of cyst hemorrhage or of gross hematuria are usually self-limited and respond well to conservative management with bed rest, analgesics, and adequate hydration to prevent development of obstructing clots. Treatment of nephrolithiasis is the same as that for individuals without ADPKD. Treatment of cyst infections is difficult - therapeutic agents of choice include trimethoprim-sulfamethoxazole, fluoroquinolones, and chloramphenicol. Therapeutic interventions aimed at slowing the progression of renal failure include control of hypertension and hyperlipidemia, dietary protein restriction, control of acidosis, and prevention of hyperphosphatemia. For ruptured or symptomatic intracranial aneurysm, the mainstay of therapy is surgical clipping of the ruptured aneurysm at its neck. For individuals with high surgical risk or with technically difficult-to-manage lesions, endovascular treatment with detachable platinum coils may be indicated. Surveillance includes MRI screening for intracranial aneurysms.

Genetic counseling. ADPKD is inherited in an autosomal dominant manner. Every child of an affected individual has a 50% chance of inheriting the mutation. The risk to sibs of the proband depends upon the genetic status of the parents; if a parent is affected, the risk to sibs is 50%. The vast majority of individuals with ADPKD have a parent with ADPKD, but *de novo* mutations occur in about 10% of affected individuals. Prenatal testing for ADPKD is clinically available if the mutation has been identified in an affected family member or if linkage has been established in the family. Requests for prenatal testing for adult-onset conditions such as ADPKD that do not affect intellect and have some treatment available are not common.

Diagnosis

Clinical Diagnosis

Autosomal dominant polycystic kidney disease (ADPKD) is a multisystem disorder characterized by the following:

- Bilateral renal cysts [a, b]
- Cysts in other organs, such as the liver, seminal vesicles, pancreas, and arachnoid membrane
- Extrarenal abnormalities, such as intracranial aneurysms and dolichoectasias, dilatation of the aortic root and dissection of the thoracic aorta, mitral valve prolapse, and abdominal wall hernias
- The absence of manifestations suggestive of a different renal cystic disease

a. Diagnostic criteria relying on sonographic findings for individuals known to be at 50% risk for the disease include [Ravine et al 1994]:

- At least two unilateral or bilateral cysts in individuals younger than age 30 years
- Two cysts in each kidney in individuals age 30-59 years
- Four cysts in each kidney in individuals age 60 years or older

The sensitivity of these criteria is nearly 100% [Nicolau et al 1999] for:

- All individuals with ADPKD who are age 30 years or older
- Younger individuals with *PKD1* mutations

The sensitivity of these criteria is 67% for individuals with *PKD2* mutations who are younger than age 30 years [Nicolau et al 1999].

b. Large echogenic kidneys without distinct macroscopic cysts in an infant/child at 50% risk for ADPKD are diagnostic.

Note:
1) In an individual with a positive family history of ADPKD:
--The enlargement of the kidneys or liver on physical examination is highly suggestive for the diagnosis.
--The presence of hypertension, mitral valve prolapse, or abdominal wall hernia is suggestive of the diagnosis. Definite diagnosis, however, relies on imaging or molecular genetic testing.
2) In the absence of a family history of ADPKD, the presence of bilateral renal enlargement and cysts with or without the presence of hepatic cysts, and the absence of other manifestations suggestive of a different renal cystic disease provide presumptive, but not definite, evidence for the diagnosis.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. Two genes are known to be associated with ADPKD:

- *PKD1*, accounting for approximately 85% of affected individuals
- *PKD2*, accounting for approximately 15% of affected individuals

Other loci. At least one further locus representing a small fraction of families not linked to either the *PKD1* or *PKD2* locus is hypothesized.

Molecular genetic testing: Clinical uses

- **Confirmation of diagnosis.** The diagnosis of ADPKD is established primarily by imaging studies of the kidneys; however, in some individuals, molecular genetic testing can be used to confirm or establish the diagnosis when it is uncertain.
- **Presymptomatic diagnosis.** Molecular genetic testing can be used for presymptomatic diagnosis when imaging results are equivocal and/or when a definite diagnosis is required in a younger individual, such as a potential living related kidney donor.
- **Prenatal diagnosis and preimplantation genetic diagnosis.** Molecular testing for prenatal diagnosis or preimplantation diagnosis is not usually requested for ADPKD because the disease usually first occurs in adulthood. A possible exception are rare families in which severe, early-onset disease in one child suggests a significant risk of recurrence of severe disease in a sibling [Zerres et al 1993].

Molecular genetic testing: Clinical methods

- **Linkage analysis.** Presymptomatic testing is possible in larger families by linkage analysis using highly informative microsatellite markers flanking the *PKD1* and

PKD2 genes. A significant drawback with linkage analysis is the need for a relatively large number of affected family members in order to establish which of the two possible genes is the responsible one within each family. Linkage studies are based upon accurate clinical diagnosis of ADPKD in the affected family members, understanding of the genetic relationships in the family, and the availability and willingness of family members to be tested. Because of these constraints, linkage analysis is probably suitable in fewer than 50% of families, but is accurate if all the provisos outlined above are met. Linkage testing is not available to families with a single affected individual and linkage testing may be complicated if a *de novo* mutation has occurred recently in the family.

- **Sequence analysis.** The large size and complexity of the *PKD1* gene, as well as marked allelic heterogeneity, have presented obstacles to molecular testing by direct DNA analysis. Detection rates by direct sequencing are now approximately 85% [Rossetti, manuscript in preparation].
- **FISH/genomic microarray analysis.** These methods are of limited diagnostic value in ADPKD because of the genomic duplication of much of the gene and because only approximately 3% of *PKD1* mutations are large deletions [European Polycystic Kidney Disease Consortium 1994, Ariyurek et al 2004].

Molecular genetic testing: Research. Use of mutation scanning by methods such as DHPLC in research settings has yielded mutation detection rates of approximately 65-70% for *PKD1* and *PKD2*.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in ADPKD

Gene	Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
PKD1	FISH/genomic microarray analysis	*PKD1* deletions	Very low [1]	Clinical Testing
	Sequence analysis	*PKD1* sequence alterations	~85% [2]	
PKD2		*PKD2* sequence alterations		Clinical Testing

1. Communication with laboratories performing the analysis [Rossetti, in preparation]
2. Veldhuisen et al 1997; Rossetti et al 2001; Rossetti, Chauveau et al 2002

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

As most mutations are unique and up to one-third of *PKD1* changes are missense, the pathogenicity of some changes is difficult to prove.

Testing Strategy for a Proband

1. Kidney imaging methods such as abdominal ultrasound, CT, or MR should be considered first for diagnosis.
2. Molecular genetic testing by sequence analysis can be helpful when the imaging results are equivocal and/or when a definite diagnosis is required in a younger adult.
3. Screening for larger rearrangements using FISH/genomic microarray analysis in a proband with ADPKD detects only a few mutations.

Genetically Related (Allelic) Disorders

No other disorders are known to be associated with mutations in the *PKD1* or *PKD2* genes.

A contiguous gene syndrome in which *PKD1* and the adjacent tuberous sclerosis complex gene, *TSC2*, are disrupted by deletion has been described [Sampson et al 1997]. In individuals with this syndrome, the phenotype of tuberous sclerosis and severe polycystic kidney disease is usually evident in utero or is diagnosed in infancy.

Clinical Description

Natural History

Renal Manifestations —Although all individuals with ADPKD develop cysts within the kidneys, substantial variability occurs in severity of renal disease and other manifestations of this disease even within the same family. Genetic heterogeneity, mutation position in *PKD1* modifier genes and environmental factors account for this variability. The renal manifestations of ADPKD include renal function abnormalities, hypertension, renal pain, and renal insufficiency.

Renal function abnormalities. Reduction in urinary concentrating capacity and excretion of ammonia occur early and may result from the disruption of the renal architecture by the cysts, interference with the countercurrent exchange and multiplication mechanisms, and defective trapping of solutes and ammonia in the renal medulla. In the early stages of the disease, these defects are moderate and significant overlap exists between affected and unaffected individuals. Although the concentrating defect may not have clinical consequences, the reduction of urinary excretion of ammonia in the presence of metabolic stresses, such as dietary indiscretions, may contribute to the development of uric acid and calcium oxalate stones, which, in association with low urine pH values and hypocitric aciduria, occur with increased frequency in individuals with ADPKD [Torres, Keith et al 1994]. Glomerular hyperfiltration has also been described early in the course of ADPKD [Wong et al 2004].

Hypertension. Another early functional abnormality is a reduction in renal blood flow, which can be detected in young individuals, when systolic and diastolic blood pressures are still normal, and precedes the development of hypertension [Chapman et al 1990; Torres et al 1991; Torres, personal observation]. Hypertension usually develops before any decline in glomerular filtration rate (GFR). It is characterized by the following:

- An increase in renal vascular resistance and filtration fraction
- Normal or high peripheral plasma renin activity
- Resetting of the pressure-natriuresis relationship
- Salt sensitivity
- Normal or increased extracellular fluid volume, plasma volume, and cardiac output
- Partial correction of renal hemodynamics and sodium handling by converting-enzyme inhibition

Hypertension in individuals with ADPKD may lead to end-organ damage, increase the morbidity and mortality from associated vascular and cardiac defects, and cause fetal and maternal complications during pregnancy [Chapman et al 1994].

Renal pain. Pain is a common manifestation of ADPKD [Segura et al 1996]. Potential etiologies include cyst hemorrhage, nephrolithiasis, cyst infection, and rarely, tumor. Discomfort, ranging from a sensation of fullness to severe pain, can also result from renal enlargement and distortion by the cysts. Gross hematuria can occur in association with complications such as cyst hemorrhage and nephrolithiasis or as an isolated event. Passage of clots can also be a source of pain. A cyst hemorrhage can be accompanied by fever, possibly

caused by cyst infection. Most often the pain is self-limited and resolves within two to seven days. Rarely, pain may be caused by retroperitoneal bleeding, which may be severe and require transfusion.

Nephrolithiasis. The prevalence of renal stone disease in individuals with ADPKD is approximately 20% [Torres et al 1993]. The majority of stones are composed of uric acid and/or calcium oxalate. Urinary stasis thought to be secondary to distorted renal anatomy and metabolic factors plays a role in the pathogenesis.

Predisposing factors to the development of renal stone disease in ADPKD include decreased ammonia excretion, low urinary pH, and low urinary citrate concentration.

Urinary tract infection and cyst infection. In the past, the incidence of urinary tract infection may have been overestimated in individuals with ADPKD because of the frequent occurrence of sterile pyuria. As in the general population, females experience urinary tract infection more frequently than males and the majority of infections are caused by E. coli and other enterobacteriaceae [Elzinga & Bennett 1996]. Retrograde infection from the bladder may lead to pyelonephritis or cyst infection.

Renal cell carcinoma (RCC). RCC does not occur more frequently in individuals with ADPKD than in the general population. Nevertheless, when RCC develops in individuals with ADPKD, it has a different biologic behavior, including earlier age of presentation, frequent constitutional symptoms, and a higher proportion of sarcomatoid, bilateral, multicentric, and metastatic tumors; males with ADPKD are not more likely to develop RCC than are females with ADPKD [Keith et al 1994].

Other. Massive renal enlargement can cause complications resulting from compression of local structures, such as inferior vena cava compression and gastric outlet obstruction (mainly by cysts of the right kidney).

Renal failure. Approximately 50% of individuals with ADPKD have end-stage renal disease (ESRD) by age 60 years [Gabow 1996]. Once renal insufficiency has begun, the average yearly rate of decline in GFR is approximately 5 mL/min [Klahr et al 1995]. Compression of the normal renal parenchyma by expanding cysts, vascular sclerosis, interstitial inflammation and fibrosis, and apoptosis of the tubular epithelial cells are the causative mechanisms.

Genetic background and environmental factors account for significant intrafamilial variability in disease severity. *PKD1* mutations are associated with a 20-year earlier onset of ESRD than *PKD2* mutations [Hateboer et al 1999]. In PKD2, males progress to ESRD more rapidly than females [Magistroni et al 2003], but no gender difference is seen in PKD1 [Hateboer et al 1999; Rossetti, Burton et al 2002]. Other risk factors include diagnosis before age 30 years, first episode of hematuria before age 30 years, onset of hypertension before age 35 years, hyperlipidemia, low concentration of high-density lipoprotein (HDL) cholesterol, and presence of sickle cell trait [Gabow 1996]. Whether African-Americans or individuals with specific genotypes of the *ACE* or *ENOS* genes are at an increased risk for disease progression is controversial.

Extrarenal Manifestations—Polycystic liver disease is the most common extrarenal manifestation of ADPKD. The severity of polycystic liver disease usually parallels that of polycystic kidney disease, but exceptions are common.

The prevalence of liver cysts in individuals with ADPKD increases from 20% in the third decade to approximately 75% after the sixth decade [Torres 1996]. Polycystic liver disease develops at a younger age in women and is more severe in women who have had multiple

pregnancies. After menopause, the size of the liver cysts increases in those women who receive estrogen replacement therapy, suggesting that estrogens have an important effect on the progression of polycystic liver disease [Sherstha et al 1997].

Liver cysts are usually asymptomatic and never cause liver failure. Symptoms, when they occur, are caused by the mass effect of the cysts, the development of complications, or rare associations. Mass effects include abdominal distention and pain, early satiety, dyspnea, and low back pain. Liver cysts can also cause extrinsic compression of the inferior vena cava (IVC), hepatic veins, or bile ducts [Torres, Rastogi et al 1994].

Complications of polycystic liver disease include cyst hemorrhage, infection, or rupture. Hemorrhagic cysts may cause fever and masquerade as cholecystitis or cyst infection. Infected cysts cause localized pain or tenderness, fever, leukocytosis, elevated erythrocyte sedimentation rate, and high serum concentration of alkaline phosphatase. CT scan and MRI are helpful in the diagnosis of cyst infection but have low specificity. White blood cell scans are more specific but not always conclusive [Telenti et al 1990]. The rupture of a hepatic cyst can cause acute abdominal pain and ascites.

Other liver disease

- Dilatation of biliary ducts may be associated with episodes of cholangitis.
- Congenital hepatic fibrosis is very rare in individuals with ADPKD.
- Cholangiocarcinoma is infrequently associated with ADPKD.

Pancreatic lesions. Pancreatic cysts occur in approximately 8% of individuals with ADPKD. They are usually less prominent than those observed in von Hippel-Lindau disease. Some authors have reported an association between ADPKD and pancreatic neoplasms [Naitoh et al 2005]; however, these cases may represent chance associations of two common disorders.

Vascular and cardiac manifestations. The most important non-cystic manifestations of ADPKD include intracranial and other arterial aneurysms, and more rarely, dolichoectasias, dilatation of the aortic root, dissection of the thoracic aorta and cervicocephalic arteries, abnormalities of the cardiac valves, and possibly coronary artery aneurysms [Pirson et al 2002]. Evidence also exists of familial clustering of thoracic aortic dissections in ADPKD.

Intracranial aneurysms occur in approximately 10% of individuals with ADPKD [Pirson et al 2002]. The prevalence is higher in those with a positive family history of intracranial or subarachnoid hemorrhage (22%) than in those without (6%). The majority of intracranial aneurysms are asymptomatic. Focal findings such as cranial nerve palsy or seizure may result from compression of local structures by an enlarging aneurysm.

The mean age of rupture of intracranial aneurysms is lower in individuals with ADPKD than in the general population (age 39 years versus age 51 years).

The risk of rupture of asymptomatic intracranial aneurysms depends on whether there is a history of rupture from a different site [International Study of Unruptured Intracranial Aneurysms Investigators 1998]. In the absence of such history, the risk is 0.05% per year for aneurysms smaller than 10 mm in diameter, about 1% per year from aneurysms measuring 10-24 mm, and 6% within one year for those measuring 25 mm or larger. When a previous history of rupture from a different site exists, the risk of rupture is 0.5-1% per year regardless of size.

The risk of rupture of symptomatic aneurysms is higher, approximately 4% per year.

Intracranial aneurysm rupture carries a 35-55% risk of combined severe morbidity and mortality at three months [Inagawa 2001]. At the time of rupture of an aneurysm, most individuals have normal renal function and up to 30% have normal blood pressure.

Follow-up studies of individuals with ADPKD with intracranial aneurysms found a moderate risk for the development of new aneurysms or enlargement of an existing one in previously symptomatic individuals and a low risk of enlargement of asymptomatic aneurysms detected by presymptomatic screening [Belz et al 2003, Gibbs et al 2004].

Mitral valve prolapse is the most common valvular abnormality and has been demonstrated by echocardiography in up to 25% of individuals with ADPKD.

Several studies have shown increased left ventricular mass, left ventricular diastolic dysfunction, endothelial dysfunction, increased carotid intima-media thickness, and exaggerated blood pressure response during exercise even in young normotensive individuals with ADPKD with well-preserved renal function. Even normotensive individuals with ADPKD may show significant biventricular diastolic dysfunction, suggesting cardiac involvement early in the course of the disease [Martinez-Vea et al 2004, Oflaz et al 2005]. The clinical significance of this finding remains to be determined.

Genotype-Phenotype Correlations

Heterozygotes. A clear association exists between the severity of renal disease and the gene involved *(PKD1* or *PKD2*).

Mutations in *PKD1* are associated with more severe disease with an earlier age at diagnosis and mean age of onset of end-stage renal disease (ESRD) (54.3 years for *PKD1*; 74.0 years for *PKD2*) [Hateboer et al 1999]. Therefore, while most individuals with mutations associated with *PKD1* experience renal failure by age 70 years, more than 50% of individuals with mutations in *PKD2* have adequate renal function at that age.

Two individuals in one family who were double heterozygotes for both a *PKD1* and a *PKD2* mutation had more severe renal disease, but lived into adulthood [Pei et al 2001].

The extrarenal manifestations of ADPKD are associated with both genes. Evidence has shown that mutations in both *PKD1* and *PKD2* are associated with increased risk for intracranial aneurysms [Rossetti et al 2003].

Studies have analyzed whether the type or position of the mutation within the *PKD1* or *PKD2* gene correlates with the resulting phenotype. Significant intrafamilial phenotypic variability is seen, both in the severity of renal disease and the array of extrarenal manifestations, indicating that genetic modifiers and the environment significantly influence the disease presentation and course.

Analysis of the phenotypic variability in renal function between monozygotic twins and siblings supports the role of genetic modifying factors [Persu et al 2004]. Recent studies estimate that 18-59% of the variance in age to ESRD may result from heritable modifying factors [Fain et al 2005, Paterson et al 2005].

Among individuals with *PKD1* mutations, interfamilial phenotypic differences have been documented and data indicates that the position of the mutation may correlate with the severity of the disease [Rossetti, Burton et al 2002]. Familial clustering of intracranial aneurysms has also been recorded and a recent study showed that mutations in the 5' half of *PKD1* are more likely to result in the development of intracranial aneurysms than 3' changes [Rossetti et al 2003]. These associations with mutation position may result from the cleavage of polycystin-1

into more than one protein product [Qian et al 2002]. No clear correlations with mutation type or position were found in *PKD2* [Magistroni et al 2003].

Homozygotes. The embryonic lethal phenotype (with cystic kidneys) of homozygous *Pkd1* or *Pkd2* knockout mice [Lu et al 1997, Wu et al 2000] suggests that the corresponding homozygous or compound heterozygous genotype in humans would be incompatible with live birth. Consistent with this, a consanguineous family in which both parents were affected with PKD1 had two spontaneous miscarriages at four and six months' gestation, although fetal tissue for histologic analysis was not available [Paterson et al 2002].

Penetrance

Cyst development. Penetrance of ADPKD is very high with practically all older adults with a *PKD1* or *PKD2* mutation developing multiple bilateral cysts. Because the disease is progressive, few cysts may be evident during childhood or young adulthood, especially for PKD2.

ESRD. Penetrance is reduced for ESRD. While the majority of individuals with PKD1 experience ESRD during their lifetime, many individuals with PKD2 (especially females) have adequate renal function into old age.

Anticipation

Anticipation has been suggested in ADPKD; however, natural history studies reveal that despite considerable intrafamilial phenotypic variability, parent-child pairs are as likely to show more severe disease in the parent as in the child [Geberth et al 1995].

Nomenclature

A term for ADPKD that is no longer in use is adult polycystic kidney disease (APKD).

Prevalence

ADPKD is the most common potentially lethal single-gene disorder. Its prevalence at birth is between 1:400 and 1:1,000 and it affects approximately 400,000 persons in the United States [Iglesias et al 1983]. Approximately 1,800 individuals start renal replacement therapy every year.

ADPKD occurs worldwide and in all races consistent with a significant level of *de novo* mutation [Rossetti et al 2001]. In the United States, the percentage of end-stage renal disease (ESRD) attributable to ADPKD is less among African-Americans than among Caucasians, but this reflects a higher incidence of other causes of ESRD among African-Americans.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

In the absence of a family history of the disease or in the presence of atypical presentations, benign simple cysts and other cystic diseases should be considered in the differential diagnosis.

The prevalence of simple renal cysts (at least one renal cyst) in disease-free individuals studied by ultrasound examination is 0% in those age 15-29 years, 1.7% in those age 30-49 years, 11.5% in those age 50-70 years, and 22.1% in those age 70 years or older. The prevalence of bilateral renal cysts (at least one in each kidney) is 1% in those age 30-49 years, 4% in those age 50-69 years, and 9% in those age 70 years or older [Ravine et al 1993].

Simple hepatic cysts occur in 2.5% to 4.6% of individuals referred for abdominal ultrasound examination. They are more common among women than men and increase in frequency with age. The majority of simple hepatic cysts are solitary and no more than three cysts are present in those with multiple cysts [Gaines & Sampson 1989].

Renal cystic diseases that are occasionally confused with ADPKD include autosomal recessive polycystic kidney disease, tuberous sclerosis complex (TSC), von Hippel-Lindau (VHL) syndrome, oral-facial-digital syndrome type 1, glomerulocystic kidney disease, Hajdu-Cheney syndrome, other malformation or disruption syndromes, localized renal cystic disease, and acquired renal cystic disease. In many individuals affected with one of these disorders, the establishment of the correct diagnosis depends on the appropriate identification of characteristic extrarenal manifestations.

Autosomal recessive polycystic kidney disease (ARPKD) is characterized by various combinations of bilateral renal cystic disease resulting from the fusiform dilatation of the collecting tubules and congenital hepatic fibrosis. Congenital hepatic fibrosis or biliary dysgenesis is a developmental abnormality that leads to portal hypertension and is characterized by enlarged and fibrotic portal areas with apparent proliferation of bile ducts, absence of central bile ducts, hypoplasia of the portal vein branches, and sometimes prominent fibrosis around the central veins. Individuals with ARPKD have unaffected parents, whereas individuals with ADPKD usually have an affected parent. In a minority of individuals, ARPKD can present later in childhood or adulthood with significant liver disease and focal cystic renal disease similar to ADPKD [Adeva et al 2006].

Tuberous sclerosis complex is an autosomal dominant disorder often associated with abnormalities of the skin, brain, heart and kidneys. Renal findings include renal angiomyolipomas, renal cysts, and less frequently, renal cell carcinoma. The coexistence of renal cysts and angiomyolipomas is pathognomonic for tuberous sclerosis complex. However, renal cysts can occur in the absence of angiomyolipomas, particularly in the first year of life. In these cases, the radiographic findings mimic those of ADPKD.

Von Hippel-Lindau syndrome is an autosomal dominant disorder that manifests with retinal and/or central nervous system hemangioblastomas, renal cysts, renal cell carcinoma, pancreatic cysts, pheochromocytomas, and papillary cystadenomas of the epididymis. Renal cysts are usually multiple and bilateral and often associated with multiple solid tumors. In the absence of solid tumors, the appearance of the kidneys in von Hippel-Lindau disease may mimic that of ADPKD.

Oral-facial-digital syndrome type 1 is a rare X-linked dominant disorder that is lethal in males. Affected females may have kidneys that are indistinguishable from those seen in ADPKD. Liver cysts may also be present. The correct diagnosis should be suggested by the extrarenal manifestations, including oral abnormalities, such as hyperplastic frenula, cleft tongue, cleft palate or lip, and malposed teeth; facial abnormalities, such as broad nasal root with hypoplasia of nasal alae and malar bone; and digital abnormalities.

Glomerulocystic kidney disease is a term used to describe a poorly defined disease or group of diseases characterized by the predominance of glomerular cysts, absence of or minimal tubular involvement and lack of urinary tract obstruction, renal dysplasia, or evidence of a recognizable cystic disease or malformation syndrome. Most of the individuals initially described who met this definition were infants or young children without a family history of renal disease presenting with enlarged kidneys or variable degrees of renal insufficiency. More recently, this disease has been described in children and adults from families with an autosomal dominant pattern of inheritance. Linkage analysis in two of these families has shown that it is not PKD1 or PKD2 [Sharp et al 1997].

Hajdu-Cheney syndrome. Renal enlargement with cortical and medullary cysts with or without impairment of renal function can occur in individuals with Hajdu-Cheney syndrome. This rare autosomal dominant disorder is characterized by short stature, midfacial flattening with proptosis, receding chin, hirsutism, acro-osteolysis of terminal phalanges, and basilar invagination of the skull.

Localized renal cystic disease is characterized by the cystic degeneration of a portion of one kidney with a histologic appearance that strongly resembles that of advanced ADPKD, but that is neither progressive nor familial. This entity should be differentiated from asymmetric presentation of ADPKD as well as from other lesions such as multilocular cystic nephroma, cystic renal cell carcinoma, and segmental multicystic renal dysplasia.

Acquired renal cystic disease refers to the cystic degeneration of the renal parenchyma that occurs in ESRD. Affected individuals are often asymptomatic; occasionally, complications such as hematuria, hemorrhage into cysts, cyst rupture with retroperitoneal hemorrhage, cyst infection, and development of adenomas or carcinomas can occur.

Autosomal dominant polycystic liver disease (ADPLD) without kidney involvement, an inherited disorder distinct from ADPKD, appears to be genetically heterogenous [Reynolds et al 2000, Qian et al 2003, Tahvanainen et al 2003]. Two genes, *PRKCSH* and *SEC63* (6q21) have been identified [Drenth et al 2003, Li et al 2003, Davila et al 2004].

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- **Renal ultrasound examination,** helpful in screening all individuals except those with a *PKD2* mutation who are younger than age 30 years. In those individuals, CT or MRI is preferable because of the low sensitivity of renal ultrasound examination.
- **CT of the abdomen without and with contrast enhancement** to help determine the extent of cystic disease in the kidneys and liver and estimating the prognosis. CT, but not MRI, can detect stones and parenchymal calcifications. CT or MR angiography can be used when visualization of the renal arteries is necessary. MRI can be used when administration of iodinated contrast material is contraindicated.
- **Standardized blood pressure screening** per the recommendations of the American Heart Association to detect early stages of hypertension. When "white coat" hypertension (i.e., blood pressure that is elevated when measured in the clinic, but normal when measured outside of the clinic) is suspected, two-hour ambulatory blood pressure monitoring is appropriate.
- **Measurement of blood lipid concentrations** because hyperlipidemia is a correctable risk factor for progressive renal disease, including ADPKD
- **Urine studies** to detect the presence of microalbuminuria or proteinuria, which in the presence of severe renal cystic disease indicates a worse prognosis and mandates strict control of the blood pressure
- **Echocardiography** in persons with heart murmurs or systolic clicks possibly resulting from valvular heart disease, mitral valve prolapse or congenital cardiac abnormalities
- **Echocardiography or cardiac MRI** to screen persons at high risk because of a family history of thoracic aortic dissections

- **Head MRA or CT angiography** to screen persons at high risk because of a family history of intracranial aneurysms (Screening for intracranial aneurysms in individuals without a family history of intracranial aneurysms is not recommended.)

Treatment of Manifestations

Current therapy for ADPKD is directed towards reducing the morbidity and mortality from the renal and extrarenal complications of the disease.

Hypertension. The antihypertensive agent(s) of choice in ADPKD has not been clearly established. Because of the role of the renin angiotensin system in the pathogenesis of hypertension in ADPKD, ACE inhibitors and angiotensin II receptor antagonists may be superior to other agents in individuals with preserved renal function. ACE inhibitors and angiotensin II receptor blockers increase renal blood flow, have a low side-effect profile, and may reduce vascular smooth muscle proliferation and development of atherosclerosis.

- The administration of ACE inhibitors, but not the administration of calcium channel blockers, has been shown to reduce microalbuminuria in individuals with ADPKD [Ecder & Schrier 2001].
- In a historic non-randomized study, the administration of ACE inhibitors without diuretics was found to result in a lower rate of decline in glomerular filtration rate (GFR) and less proteinuria than the administration of a diuretic without an ACE inhibitor for similar control of blood pressure [Ecder & Schrier 2001].
- A recent study found no renal protective effect of an ACE inhibitor over a β-blocker [van Dijk et al 2003], while another found that more rigorous blood pressure control did not preserve renal function, although it did lead to a greater decrease in left ventricular mass [Schrier et al 2002].
- A long-term follow-up of the Modification of Diet in Renal Disease (MDRD) study showed that individuals with ADPKD randomized to a low blood pressure target (MAP <92 mmHg) experienced significantly less ESRD and combined ESRD/death than those randomized to the usual blood pressure target (MAP <107 mmHg) [Sarnak et al 2005].

Flank pain. After excluding causes of flank pain that may require intervention, such as infection, stone, or tumor, an initial conservative approach to pain management is best.

- **Nonopioid agents** are preferred and care should be taken to avoid long-term administration of nephrotoxic agents such as combination analgesic and nonsteroidal anti-inflammatory drugs.
- **Tricyclic antidepressants** are helpful, as in all chronic pain syndromes, and are well tolerated.
- **Narcotic analgesics** should be reserved for the management of acute episodes, as chronic use can lead to physical and psychologic dependence.
- **Splanchnic nerve blockade** with local anesthetics or steroids can result in pain relief beyond the duration of the local anesthetic.
- **Renal denervation** via a thoracoscopic approach was successful in one affected individual [Chapuis et al 2004].

When conservative measures fail, therapy can be directed toward cyst decompression with cyst aspiration and sclerosis.

- **Cyst aspiration,** under ultrasound or CT guidance, is a relatively simple procedure carried out routinely by interventional radiologists. Complications from aspiration of centrally located cysts are more common, and the morbidity of the procedure is proportional to the number of cysts treated.
- **Sclerosing agents** such as 95% ethanol or acidic solutions of minocycline are commonly used to prevent the reaccumulation of cyst fluid. Excellent results have been obtained with 95% ethanol, achieving a success rate of 90% in benign renal cysts. Minor complications include microhematuria, localized pain, transient fever, and systemic absorption of the alcohol. More serious complications such as pneumothorax, perirenal hematoma, arteriovenous fistula, urinoma, and infection are rare [Segura et al 1996].

In individuals with many cysts contributing to pain, laparoscopic or surgical cyst fenestration through lumbotomy or flank incision may be of benefit.

- **Surgical decompression** was effective in 80-90% of individuals for one year and 62-77% had sustained pain relief for longer than two years [Elzinga et al 1992]. Surgical intervention does not accelerate the decline in renal function, but neither does it appear to preserve declining renal function.
- **Laparoscopic fenestration** has been shown to be as effective as open surgical fenestration in short-term follow-up for individuals with limited disease, and has a shorter, less complicated recovery period.
- **Laparoscopic and retroperitonoscopic nephrectomy and arterial embolization** have been used to treat symptomatic polycystic kidneys in individuals with ADPKD who have ESRD [Ubara et al 1999, Dunn et al 2000].
- **Hand-assisted laparoscopic nephrectomy** may be preferable to standard laparoscopic nephrectomy because of shorter operating time and lower morbidity [Lee & Clayman 2004].

Cyst hemorrhage and gross hematuria. Episodes of cyst hemorrhage or of gross hematuria are usually self-limited and respond well to conservative management with bed rest, analgesics, and adequate hydration to prevent development of obstructing clots.

Rarely, episodes of bleeding are more severe with extensive subcapsular or retroperitoneal hematoma, significant drop in hematocrit, and hemodynamic instability. In such cases, individuals require hospitalization, transfusion, and investigation by CT or angiography. In cases of unusually severe or persistent hemorrhage, segmental arterial embolization can be successful. If not, surgery may be required to control bleeding.

Gross hematuria persisting more than one week or developing for the first time in an individual older than age 50 years requires thorough investigation.

Nephrolithiasis. Small uric acid stones can be missed on nephrotomography and are best detected by computed tomography (CT). CT should be obtained before and after the administration of contrast material to confirm the localization within the collecting system and to differentiate calculi from parenchymal calcifications.

Excretory urography detects precaliceal tubular ectasia in 15% of individuals with ADPKD.

The treatment of nephrolithiasis in individuals with ADPKD is the same as that for individuals without ADPKD.

- Potassium citrate is the treatment of choice in uric acid lithiasis, hypocitric calcium oxalate nephrolithiasis, and distal acidification defects [Torres et al 1993].
- Extracorporeal shock-wave lithotripsy and percutaneous nephrostolithotomy can be successful in individuals with ADPKD without excessive complications.

Cyst infection. If cyst infection is suspected, diagnostic imaging should be undertaken to assist in the diagnosis.

- CT and magnetic resonance imaging (MRI) are sensitive for detecting complicated cysts and provide anatomic definition, but the findings are not specific for infection.
- Nuclear imaging, especially indium-labeled white cell scanning, is useful, but false-negative and false-positive results are possible.

In the appropriate clinical setting of fever, flank pain, and suggestive diagnostic imaging, cyst aspiration under ultrasound or CT guidance should be undertaken to culture the organism and assist in selection of antimicrobial therapy.

Cyst infection is often difficult to treat. It has a high treatment failure rate despite prolonged therapy with an antibiotic to which the organism is susceptible. Treatment failure results from the inability of certain antibiotics to penetrate the cyst epithelium successfully and achieve therapeutic concentrations within the cysts [Elzinga & Bennett 1996]. The epithelium that lines gradient cysts has functional and ultrastructural characteristics of the distal tubule epithelium. Penetration is via tight junctions, allowing only lipid-soluble agent access. Non-gradient cysts, which are more common, allow solute access via diffusion. However, kinetic studies indicate that water-soluble agents penetrate non-gradient cysts slowly and irregularly, resulting in unreliable drug concentrations within the cysts. Lipophilic agents have been shown to penetrate both gradient and non-gradient cysts equally and reliably and have a pKa that allows for favorable electrochemical gradients into acidic cyst fluids.

Therapeutic agents of choice include trimethoprim-sulfamethoxazole and fluoroquinolones. Chloramphenicol has shown therapeutic efficacy in otherwise refractory disease.

If fever persists after one to two weeks of appropriate antimicrobial therapy, percutaneous or surgical drainage of infected cysts should be undertaken. If fever recurs after discontinuation of antibiotics, complicating features, such as obstruction, perinephric abscess, or stones should be considered and treated appropriately. If complicating features are not identified, the course of previously effective therapy should be extended and several months may be required to completely eradicate the infection.

Malignancy. The diagnosis of **renal cell carcinoma** (RCC) in a polycystic kidney requires a high index of suspicion. Magnetic resonance imaging (MRI) with gadolinium enhancement is particularly helpful to detect atypical solid or cystic masses, tumor thrombi, and regional lymphadenopathy.

The diagnosis of **transitional cell carcinoma** in a polycystic kidney is equally challenging and usually requires retrograde pyelography.

Renal failure. Therapeutic interventions aimed at slowing the progression of renal failure in ADPKD include control of hypertension and hyperlipidemia, dietary protein restriction, control of acidosis, and prevention of hyperphosphatemia.

Animal data support the role of dietary protein restriction and careful control of hypertension in slowing the rate of renal failure in PKD [Qian et al 2001]. However, the Modification of Diet in Renal Disease (MDRD) trial showed no beneficial effect on renal function of strict —

compared with standard — blood pressure control and only a slight (borderline significant) beneficial effect of a very low protein diet [Klahr et al 1995]. Since these interventions were introduced at a late state of the disease (GFR 13-55 mL/min per 1.73^2), these results do not exclude a beneficial effect of interventions introduced at an earlier stage of the disease.

Actuarial data indicate that individuals with ADPKD do better on dialysis than individuals with renal failure from other causes. Females appear to do better than males. The reason for this improved outcome is unclear but may relate to better-maintained hemoglobin levels through higher endogenous erythropoietin production. Rarely, hemodialysis can be complicated by intradialytic hypotension if the inferior vena cava is compressed by a medially located renal cyst. Despite renal size, peritoneal dialysis can usually be performed in individuals with ADPKD, although these individuals are at increased risk for inguinal and umbilical hernias, which require surgical repair.

Polycystic liver disease. Most individuals with polycystic liver disease have no symptoms and require no treatment [Torres 1996].

The treatment of symptomatic disease includes the avoidance of estrogens and the use of H2 blockers or proton pump inhibitors for symptomatic relief.

Severe symptoms may require percutaneous aspiration and sclerosis, laparoscopic fenestration, combined hepatic resection and cyst fenestration, or liver transplantation. Any of these interventions should be tailored to the individual.

Cyst aspiration and sclerosis with alcohol or minocyline is the treatment of choice for symptoms caused by one or a small number of dominant cysts. Before instillation of the sclerosing agent, a contrast medium is injected into the cyst to rule out communication with the bile ducts. The success rate of this procedure (70% after a single treatment and an additional 20% after repeated treatment) is inversely correlated with the size of the cyst(s).

Laparoscopic fenestration of hepatic cysts, a less commonly performed procedure, is complicated by transient ascites in 40% of individuals, and the results are often short-lived. Thus, laparoscopic cyst fenestration is indicated only for the treatment of disproportionally large cysts as an alternative to percutaneous sclerosis. Neither percutaneous sclerosis nor laparoscopic fenestration is helpful in individuals with large polycystic livers with many small- and medium-sized cysts. In most individuals, part of the liver is spared, allowing treatment by combined hepatic resection and cyst fenestration. Because the surgery and recovery can be difficult, with complications such as transient ascites and bile leaks and a perioperative mortality of 2.5%, it should be performed only in specialized centers. The surgery has good long-term results in individuals with severe polycystic liver disease and is often preferable to liver transplantation, which is reserved for those rare individuals with severely affected liver parenchyma and hepatic insufficiency [Que et al 1995].

Intracranial aneurysms

Ruptured or symptomatic intracranial aneurysm. The mainstay of therapy is surgical clipping of the ruptured aneurysm at its neck.

Asymptomatic aneurysms

- Those measuring 5.0 mm or smaller in diameter, diagnosed by presymptomatic screening, can be observed and followed initially at yearly intervals. If the size increases, surgery is indicated.
- The management of aneurysms 6.0-9.0 mm in size remains controversial.

- Surgical intervention is usually indicated for unruptured aneurysms measuring larger than 10.0 mm in diameter.

For individuals with high surgical risk or with technically difficult-to-manage lesions, endovascular treatment with detachable platinum coils may be indicated. Endovascular treatment seems to be associated with fewer complications than clipping, but the long-term efficacy of this method is as yet unproven [Pirson et al 2002].

Aortic dissection. When the aortic root diameter reaches 55 mm to 60 mm, replacement of the aorta is indicated.

Surveillance

Intracranial aneurysms. Widespread screening is not cost effective or indicated because most intracranial aneurysms found by screening asymptomatic individuals are small, have a low risk of rupture, and require no treatment [Gibbs et al 2004].

Indications for screening in 20- to 50-year-old individuals with a good life expectancy include family history of intracranial aneurysms or subarachnoid hemorrhage, previous aneurysmal rupture, preparation for elective surgery with potential hemodynamic instability, high-risk occupations such as airplane pilots, significant anxiety on the part of the individual despite adequate risk information, and, possibly, mutation position in PKD1 [Rossetti et al 2003].

Magnetic resonance angiography is the diagnostic imaging modality of choice for presymptomatic screening, as it is noninvasive and does not require intravenous contrast material. Because only one of 76 individuals with an initial negative study had a new intracranial aneurysm after a mean follow-up of 9.8 years, re-screening after an interval of ten years has been suggested as a reasonable approach [Schrier et al 2004].

Agents/Circumstances to Avoid

- Long-term administration of nephrotoxic agents such as combination analgesics and NSAIDs
- Caffeine because it interferes with the breakdown of cAMP and hence may promote renal cyst growth
- Use of estrogens in individuals with severe polycystic liver disease
- Smoking

Testing of Relatives at Risk

ADPKD

- Testing of adult relatives at risk:
  - Allows those found to be affected to become better educated on the disease;
  - Permits early detection and treatment of complications and associated disorders;
  - Reassures those found to be unaffected.
- Appropriate counseling prior to screening, including a discussion of the possible impact on insurability and employability, is most important.
- At present, there is no indication for testing of asymptomatic children. This may change in the future if and when effective therapies are found.

Aortic dissection. Until more information becomes available, it is reasonable to screen first-degree adult relatives of individuals with thoracic aortic dissection using either echocardiography or MRI. If aortic root dilatation is found, yearly follow-up and strict blood pressure control with beta blockers should be recommended.

Therapies Under Investigation

Significant advances in the understanding of the genetics of ADPKD and the mechanisms of cyst growth have revealed likely targets for therapeutic intervention.

Of particular interest are recent studies that have shown that modulation of cAMP levels by targeting the vasopressin V2 receptor can dramatically inhibit cyst development in animal models of nephronophthisis, autosomal recessive polycystic kidney disease (ARPKD), and ADPKD [Gattone et al 2003, Torres et al 2004, Wang et al 2005]. A clinical trial with a vasopressin V2 receptor antagonist is currently in progress.

Octreotide, a long-acting form of somatostatin has been shown to slow the enlargement of polycystic kidneys in a small randomized, placebo-controlled, crossover study [Ruggenenti et al 2005].

Antagonists of the epidermal growth factor receptor [Sweeney et al 2000] and rapamycin [Tao et al 2005, Shillingford et al 2006, Wahl et al 2006] have been effective in animal models of polycystic kidney disease.

Search ClinicalTrials.gov 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

ADPKD is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most affected individuals have one parent who has ADPKD.
- The incidence of *de novo* mutations is significant, occurring in about 10% of affected families.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include adequate screening by imaging methods, especially in the case of PKD2.

Note: The family history may also appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

Sibs of a proband

- The risk to sibs of the proband depends upon the genetic status of the parents.
- If a parent is affected, the risk to sibs is 50%.
- When renal image analysis suggests that the parents are unaffected and the disease-causing mutation found in the proband cannot be detected in the DNA of the either parent, the disease in the proband is likely caused by a *de novo* mutation and the risk to sibs is small. Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Every child of an individual with ADPKD has a 50% chance of inheriting the mutation.

Other family members of the proband. The risk to other family members depends upon the genetic status of the proband's parents. If a parent is found to be affected or to have a disease-causing mutation, his or her relatives are at risk.

Related kidney donor. Relatives being considered as kidney donors need to be evaluated to determine if they have ADPKD. Evaluation usually consists of comprehensive renal image analysis by ultrasound, CT, and/or MRI. If a disease-causing mutation has been identified in the affected relative or if studies have established linkage in the family, molecular genetic testing is appropriate to establish the genetic status of the potential donor.

Related Genetic Counseling Issues

Testing of at-risk asymptomatic adults. Testing of at-risk asymptomatic adults for ADPKD should first involve renal image analysis. Molecular genetic testing is also possible (as described), but this is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals.

Testing for the disease in the absence of definite symptoms of the disease is predictive testing. Renal imaging should be considered as the first means to test for ADPKD. Molecular genetic testing should only be considered if the imaging results are equivocal or if a definite diagnosis in a young person (<30 years of age) is required, as for a potential renal transplant donor. At-risk asymptomatic adult family members may seek testing in order to make personal decisions. Others may have different motivations including simply the "need to know." Testing of asymptomatic at-risk adult family members usually involves pre-test interviews in which the motives for requesting the test, the individual's knowledge of ADPKD, and the possible impact of positive and negative test results are assessed. Those seeking testing should be counseled about possible problems that they may encounter with regard to health, life, and disability insurance coverage, employment discrimination, and changes in social and family interaction. Other issues to consider are implications for the at-risk status of other family members. Informed consent should be procured and records kept confidential. Individuals with a positive test result need arrangements for long term follow-up and evaluations.

Testing of at-risk asymptomatic individuals during childhood. In general, the consensus holds that whereas clinical monitoring for early disease presentations in individuals at risk for adult-onset disorder is important, such individuals should not have testing during childhood in the absence of symptoms. The principal arguments against testing asymptomatic individuals during childhood are that it removes their choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings, and it could have serious educational and career implications [Bloch & Hayden 1990, Harper & Clarke 1990]. Individuals who become symptomatic during childhood usually benefit from having a specific diagnosis established (See also the National Society of Genetic Counselors resolution on

genetic testing of children and the American Society of Human Genetics and American College of Medical Genetics points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents).

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and availability of prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The disease-causing allele of an affected family member must be identified or linkage established in the family before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for adult-onset conditions such as ADPKD that do not affect intellect and have some treatment available are not common. The possible exception is in rare families in which a severely affected family member may present with perinatal lethality or with grossly enlarged kidneys during infancy. As such families are thought to be at high risk for a subsequent severely affected child, ultrasound monitoring for early evidence of renal enlargement is appropriate and prenatal testing may be considered in these families [Zerres et al 1993]. Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Surveys of families with ADPKD suggest that only 4-8% of family members would terminate a pregnancy for ADPKD [Sujansky et al 1990]. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) has been reported [De Rycke et al 2005] and may be available for families in which the disease-causing mutation has been identified in an affected family member or linkage established in the family in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Polycystic Kidney Disease, Autosomal Dominant

Gene Symbol	Chromosomal Locus	Protein Name
PKD1	16p13.3-p13.1	Polycystin-1
PKD2	4q21-q23	Polycystin-2

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Polycystic Kidney Disease, Autosomal Dominant

173900	POLYCYSTIC KIDNEYS
173910	POLYCYSTIC KIDNEY DISEASE 2; PKD2
601313	POLYCYSTIC KIDNEY DISEASE 1; PKD1

Table C. Genomic Databases for Polycystic Kidney Disease, Autosomal Dominant

Gene Symbol	Entrez Gene	HGMD	GeneCards	GDB	GenAtlas
PKD1	5310 (MIM No. 601313)	PKD1	*PKD1*	120293	PKD1
PKD2	5311 (MIM No. 173910)	PKD2	*PKD2*	118851	PKD2

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

ADPKD is caused by mutation to the *PKD1* (~85% of individuals) or *PKD2* genes (~15% of individuals) with the probability of at least one further locus representing a small fraction of unlinked families [Peters & Sandkuijl 1992, Daoust et al 1995]. The *PKD1* gene was identified in 1994 [European Polycystic Kidney Disease Consortium 1994] and fully sequenced in 1995 [Hughes et al 1995, International Polycystic Kidney Disease Consortium 1995]. The *PKD2* gene was cloned in 1996 [Mochizuki et al 1996].

Polycystin-1 and polycystin-2 are thought to interact to form a functional complex. Recent evidence indicates that, in common with many other PKD proteins, polycystin-1 and polycystin-2 are localized on primary cilia and the polycystin complex may play a role in the detection of fluid flow within the tubule [Pazour et al 2002, Yoder et al 2002, Nauli et al 2003]. According to this hypothesis, flow within tubules of the normal kidney results in bending of cilia and activation of the polycystin flow sensor that results in a Ca^{2+} influx into the cell [Praetorius & Spring 2001, Nauli et al 2003]. Inactivation of the polycystin complex as a result of mutations in *PKD1* or *PKD2* (plus somatic events) results in altered Ca^{2+} homeostasis that may be associated with the multiple cellular changes (such as increased proliferation and apoptosis and altered polarity and secretory properties) that are characteristic of ADPKD cells [Torres & Harris 2006; Harris & Torres, in press].

Common to the vascular and cardiac lesions is the disruption of the connective tissue framework responsible for their mechanical properties. Abnormalities of the internal elastic lamina, which is responsible for most of the tensile strength of the wall of the intracranial arteries, cause intracranial aneurysms and dolichoectasias. Dissection of the thoracic aorta and cervicocephalic arteries is characterized by disruption of the normal myoelastic lamellar structure of the arterial wall. It seems likely that the *PKD1* and *PKD2* mutations are directly responsible for the vascular and cardiac manifestations of ADPKD, since polycystin-1 and polycystin-2 are strongly expressed in the medial myocytes of elastic and large distributive arteries, as well as in the cardiac myocytes and valvular myofibroblasts [Griffin et al 1997, Torres et al 2001].

PKD1

Normal allelic variants: *PKD1* encodes an approximately 14-kb transcript and is divided into 46 exons within 50 kb of genomic DNA [Hughes et al 1995]. The genomic region encoding *PKD1* has undergone a complex duplication, such that several reiterated copies of the 5' three-quarters of the gene are present as pseudogenes elsewhere on chromosome 16 [European Polycystic Kidney Disease Consortium 1994]. The similarity of these pseudogenes to *PKD1* has complicated molecular genetic testing at this locus. Several alternatively spliced forms of *PKD1* have also been described, but the functional significance of any of these is not known [Hughes et al 1995, International Polycystic Kidney Disease Consortium 1995].

PKD1 orthologs have been sequenced from a wide range of mammalian species and from amphibians and fish. No true orthologs are found in more primitive species, but homologous proteins in *C. elegans* and sea urchins have provided insights into the function of polycystin-1-like proteins [Moy et al 1996, Barr & Sternberg 1999, Mengerink et al 2002].

Pathologic allelic variants: *PKD1* is characterized by extreme allelic variability, with most mutations unique to a single family [Rossetti et al 2001; Rossetti, Chauveau et al 2002; Rossetti et al, manuscript in preparation]. The mutations are spread throughout the gene and the majority are predicted to truncate the product. The pattern is consistent with the mutations inactivating the allele and it has been suggested that a somatic mutation disrupting the normal allele is required for cyst development [Qian et al 1996]. About 270 different *PKD1* mutations have been described (see HGMD, Genomic Databases Table above).

Normal gene product: The *PKD1* gene product, polycystin, is a 4303 amino-acid (aa) protein with a calculated molecular mass of 460 kd [Hughes et al 1995, International Polycystic Kidney Disease Consortium 1995, Sandford et al 1997]. The protein is membrane-associated with a large extracellular region and short cytoplasmic tail. The extracellular area contains several characterized domains that are generally involved in interactions with proteins or carbohydrates. The function of the protein is not known. It may be a receptor, although the ligand has not been identified [Ong & Harris 2005].

Polycystin-1 is expressed in the epithelia of maturing tubules in the kidney and epithelial cells in many other organs, with the highest expression in the embryo and down-regulation in the adult. Expression is also found in smooth, skeletal, and cardiac muscle, suggesting that polycystin has a direct role in many of the extrarenal manifestations of the disease.

Abnormal gene product: The wide array of truncating mutations in *PKD1* that cause ADPKD suggests that they inactivate the gene with no functional protein produced. However, evidence of genotype/phenotype correlations associated with mutation position and the fact that polycystin-1 may be cleaved into more than one protein product indicate that all mutations may not simply inactivate all products [Qian et al 2002; Rossetti, Burton et al 2002; Rossetti et al 2003; Chauvet et al 2004, Low et al 2006]. Recent evidence indicates that a reduction in the level of polycystin-1 protein may be sufficient for cyst development and that cyst expansion may be a complex process [Lantinga-van Leeuwen et al 2004, Nishio et al 2005, Jiang et al 2006].

PKD2

Normal allelic variants: *PKD2* encodes an approximately 3-kb open reading frame that is encoded by 15 exons in a genomic area of approximately 70 kb [Hayashi et al 1997].

PKD2 orthologs or homologs have been characterized in many mammalian species, frog, fish, and many invertebrates including *C. elegans* and *Drosophila.* Polycystin-2-like proteins in

these species have a range of roles from influencing mating behavior to defects in sperm motility [Barr & Sternberg 1999, Gao et al 2003].

Pathologic allelic variants: *PKD2* is characterized by extreme allelic variability, with most mutations unique to a single family [Veldhuisen et al 1997]. As in *PKD1*, the mutations are spread throughout the gene and the majority are predicted to truncate the protein, consistent with inactivation of the allele. Approximately 75 different *PKD2* mutations have been described (see HGMD, Genomic Databases Table above).

Normal gene product: Polycystin-2 is predicted to have six transmembrane domains with cytoplasmic N- and C-termini. It shares a region of homology with polycystin-1 in the transmembrane region and also has sequence similarity to TRP and voltage-activated channel subunits. Polycystin-2 acts as a Ca^{2+} permeable cation channel and the basic defect in ADPKD may be in aberrant regulation of intracellular Ca^{2+} [Hanaoka et al 2000, Gonzalez-Perrett et al 2001, Vassilev et al 2001, Koulen et al 2002]. A recent focus has been the role of polycystin-2 on the primary cilia and its function in the influx of Ca^{2+} associated with flow, although it may also be associated with intracellular Ca^{2+} stores in the ER. Polycystin-2 expression is similar to that of polycystin-1, but it continues at a more consistent level in the adult.

Abnormal gene product: The wide array of truncating mutations in *PKD2* suggests that they inactivate the gene with no functional protein produced.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Polycystic kidney disease

NCBI Genes and Disease
APKD

The PKD Charity
PO Box 141
Bishop Auckland
County Durham
United Kingdom
Phone: (+44) 01388 665004
Email: support@pkdcharity.org.uk
www.pkdcharity.co.uk

PKD Foundation
9221 Ward Parkway Suite 400
Kansas City MO 64114-3367
Phone: 800-PKD-CURE
Fax: 816-931-8655
Email: pkdcure@pkdcure.org
www.pkdcure.org

National Kidney Foundation
30 East 33rd Street Suite 1100
New York NY 10016
Phone: 800-622-9010; 212-889-2210
Fax: 212-689-9261
Email: info@kidney.org
www.kidney.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

American Society of Human Genetics and American College of Medical Genetics (1995) Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents

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Suggested Readings

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Chapter Notes

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