Polycystic Kidney Disease, Autosomal Dominant

**Synonym:** ADPKD

Peter C Harris, PhD  
Division of Nephrology and Hypertension  
Mayo Clinic  
Rochester, Minnesota  
harris.peter@mayo.edu

Vicente E Torres, MD  
Division of Nephrology and Hypertension  
Mayo Clinic  
Rochester, Minnesota  
torres.vicente@mayo.edu

Initial Posting: January 10, 2002; Last Update: June 11, 2015.

**Summary**

**Clinical characteristics.** Autosomal dominant polycystic kidney disease (ADPKD) is generally a late-onset multisystem disorder characterized by: bilateral renal cysts; cysts in other organs including the liver, seminal vesicles, pancreas, and arachnoid membrane; vascular abnormalities including intracranial aneurysms, dilatation of the aortic root, and dissection of the thoracic aorta; mitral valve prolapse; and abdominal wall hernias. Renal manifestations include hypertension, renal pain, and renal insufficiency. Approximately 50% of individuals with ADPKD have end-stage renal disease (ESRD) by age 60 years. The prevalence of liver cysts, the most common extrarenal manifestation of ADPKD, increases with age and may have been underestimated by ultrasound studies. The prevalence of intracranial aneurysms is higher in those with a positive family history of aneurysms or subarachnoid hemorrhage (22%) than in those without such a family history (6%). Mitral valve prolapse, the most common valvular abnormality, occurs in up to 25% of affected individuals. Substantial variability in severity of renal disease and other extrarenal manifestations occurs even within the same family.

**Diagnosis/testing.** The diagnosis of ADPKD is established primarily by imaging studies of the kidneys. In approximately 85% of individuals with ADPKD, pathogenic variants in *PKD1* are causative; in approximately 15% pathogenic variants in *PKD2* are causative.

**Management.** Treatment of manifestations: Treatment for hypertension may include ACE inhibitors or angiotensin II receptor blockers and diet modification. Conservative treatment of flank pain includes nonopioid agents, tricyclic antidepressants, narcotic analgesics, and splanchnic nerve blockade. More aggressive treatments include cyst decompression with cyst aspiration and sclerosis, laparoscopic or surgical cyst fenestration, and renal denervation. Cyst hemorrhage and/or gross hematuria are usually self-limited. Treatment of nephrolithiasis is standard. Treatment of cyst infections is difficult, with a high failure rate. Therapeutic agents of choice may include trimethoprim-sulfamethoxazole, fluoroquinolones, clindamycin, vancomycin, and metronidazole. The diagnosis of malignancy requires a high index of suspicion. Therapeutic interventions aimed at slowing the progression of ESRD in ADPKD include control of hypertension and hyperlipidemia, dietary protein restriction, control of acidosis, and prevention of hyperphosphatemia. Most individuals with polycystic liver disease have no symptoms and require no treatment. The mainstay of therapy for ruptured or symptomatic intracranial aneurysm is surgical clipping of the ruptured aneurysm.
at its neck; however, for some individuals, endovascular treatment with detachable platinum coils may be indicated. Thoracic aortic replacement is indicated when the aortic root diameter exceeds established size.

**Surveillance:** Early blood pressure monitoring starting in childhood; there is insufficient evidence for recommending screening for renal cell carcinoma in asymptomatic individuals; MRI screening for intracranial aneurysms in those determined to be at high risk; screening echocardiography in those with a heart murmur and those with a family history of a first-degree relative with a thoracic aortic dissection.

**Agents/circumstances to avoid:** Long-term administration of nephrotoxic agents, caffeine in large amounts (which may promote renal cyst growth), use of estrogens and possibly progestogens by individuals with severe polycystic liver disease, and smoking.

**Evaluation of relatives at risk:** Testing of adult relatives at risk permits early detection and treatment of complications and associated disorders.

**Pregnancy management:** Pregnant women with ADPKD should be monitored for the development of hypertension, urinary tract infections, oligohydramnios, and preeclampsia; the fetus should be monitored for intrauterine fetal growth restriction and fetal kidney anomalies, including cysts, enlarged size, and atypical echogenicity.

**Genetic counseling.** ADPKD is inherited in an autosomal dominant manner. About 95% of individuals with ADPKD have an affected parent; at least 10% of families can be traced to *de novo* mutation. Each child of an affected individual has a 50% chance of inheriting the pathogenic variant. If the pathogenic variant has been identified in an affected family member prenatal testing for pregnancies at increased risk may be available from a clinical laboratory that offers either testing of this gene or custom prenatal testing. Preimplantation genetic diagnosis (PGD) may be an option for some families in which the pathogenic variant has been identified and is increasing being employed by families at risk for ADPKD

**Diagnosis**

**Clinical Diagnosis**

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

- Bilateral renal cysts (see Renal Cysts)
- Cysts in other organs including the liver, seminal vesicles, pancreas, and arachnoid membrane
- Extrarenal abnormalities including 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

**In an individual with a positive family history of ADPKD**

- Enlargement of the kidneys or liver on physical examination is highly suggestive of the diagnosis.
- The presence of hypertension, mitral valve prolapse, or abdominal wall hernia is suggestive of the diagnosis.

Note: Definitive diagnosis relies on imaging and/or molecular genetic testing.

**In the absence of a family history of ADPKD.** The (1) presence of bilateral renal enlargement and cysts with or
without the presence of hepatic cysts and (2) absence of other manifestations suggestive of a different renal cystic disease provide presumptive (though not definite) evidence for the diagnosis. Molecular testing may provide a definitive diagnosis (see Testing Strategy).

**Renal Cysts**

**Age-specific ultrasound criteria** to confirm a diagnosis of ADPKD have been proposed for individuals who are at 50% risk for ADPKD because they have an affected first-degree relative [Pei et al 2009].

Note: The positive predictive value of these criteria is 100%, regardless of (1) which form of the disorder (PKD1 or PKD2) is present and (2) the age of the individual at the time of initial evaluation. However, the sensitivity of the criteria depends on the underlying genotype and the age of the individual at the time of evaluation (see Table 1).

Criteria:

- The presence of three or more (unilateral or bilateral) renal cysts in an individual age 15-39 years
- The presence of two or more cysts in each kidney in an individual age 40-59 years

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

Note: Although the ultrasound criteria listed above are appropriate to establish a diagnosis of ADPKD in an individual at risk, their sensitivity is low (Table 1, 81.7%-95.5%), particularly in families who have a *PKD2* or a mild *PKD1* pathogenic variant (69.5%-94.9%). In this situation, a significant number of affected individuals may not be diagnosed, which may pose a problem when exclusion of the diagnosis is critical (see Testing Strategy, Presymptomatic diagnosis).

**Table 1.**

Ultrasound Criteria for Diagnosis of ADPKD in Individuals at 50% Risk for ADPKD Based on Family History

<table>
<thead>
<tr>
<th>Age</th>
<th>PKD1</th>
<th>PKD2</th>
<th>Unknown ADPKD Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-30 years</td>
<td>≥3 cysts 1 PPV = 100% SEN = 94.3%</td>
<td>≥3 cysts 1 PPV = 100% SEN = 69.5%</td>
<td>≥3 cysts 1 PPV = 100% SEN = 81.7%</td>
</tr>
<tr>
<td>30-39 years</td>
<td>≥3 cysts 1 PPV = 100% SEN = 96.6%</td>
<td>≥3 cysts 1 PPV = 100% SEN = 94.9%</td>
<td>≥3 cysts 1 PPV = 100% SEN = 95.5%</td>
</tr>
<tr>
<td>40-59 years</td>
<td>≥2 cysts in each kidney PPV = 100% SEN = 92.6%</td>
<td>≥2 cysts in each kidney PPV = 100% SEN = 88.8%</td>
<td>≥2 cysts in each kidney PPV = 100% SEN = 90%</td>
</tr>
</tbody>
</table>

Derived from Pei et al [2009]. All values presented are mean estimates.

PPV = positive predictive value

SEN = sensitivity

1. Unilateral or bilateral
Age-specific MRI criteria that are particularly useful when ultrasound results are equivocal have been established [Pei et al 2015]:

- For individuals ages 16-40 years who are at 50% risk for ADPKD because they have an affected first-degree relative, the presence of a total of more than ten cysts is sufficient for a diagnosis of ADPKD.

- When evaluating at-risk individuals in the same age group as living related donors, a total of fewer than five cysts is considered sufficient for disease exclusion.

Note: These criteria may also be more appropriate to use when employing a modern, high-resolution ultrasound scanner that can detect cysts as small as 1-2 mm.

Molecular Genetic Testing

Genes. The two genes in which pathogenic variants are known to cause ADPKD are \(PKD1\) and \(PKD2\) (see Table 2).

Table 2.

Summary of Molecular Genetic Testing Used in ADPKD

<table>
<thead>
<tr>
<th>Gene</th>
<th>Test Method</th>
<th>Proportion of ADPKD Attributed to Pathogenic Variants in This Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>(PKD1)</td>
<td>Sequence analysis (^3, 4)</td>
<td>~85%</td>
</tr>
<tr>
<td></td>
<td>Deletion/duplication analysis (^5)</td>
<td></td>
</tr>
<tr>
<td>(PKD2)</td>
<td>Sequence analysis (^3, 4)</td>
<td>~15%</td>
</tr>
<tr>
<td></td>
<td>Deletion/duplication analysis (^5)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

1. See Table A. Genes and Databases for chromosome locus and protein. See Molecular Genetics for information on allelic variants detected in this gene.

2. This proportion refers to individuals with ADPKD caused by a known pathogenic variant in either \(PKD1\) or \(PKD2\). It does not include those with ADPKD in whom no pathogenic variant has been found.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

4. Rossetti et al [2007], Audrézet et al [2012].

5. Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Due to the segmental duplication of \(PKD1\), such analysis requires methods that detect large rearrangements, such as multiplex ligation-dependent probe amplification (MLPA) [Consugar et al 2008] or chromosomal...
6. Approximately 9% of individuals who undergo comprehensive mutation screening of \(PKD1\) and \(PKD2\) have no pathogenic variant identified [Rossetti et al 2007, Consugar et al 2008, Audrézet et al 2012]. It is unclear if this finding is the result of missed pathogenic variants at the known loci or further genetic heterogeneity. A recent study of families described as not linked to \(PKD1\) or \(PKD2\) identified pathogenic variants in \(PKD1\) or \(PKD2\) in four of the five families, and the phenotype in the fifth was atypical for ADPKD, questioning whether there is further genetic heterogeneity in ADPKD [Paul et al 2014].

**Interpretation of test results.** In the most recent studies, 50%-70% of pathogenic variants are unique to a family and approximately 30% of \(PKD1\) changes and approximately 15% of \(PKD2\) changes are in-frame; therefore, the pathogenicity of some allelic variants is difficult to prove [Rossetti et al 2007, Audrézet et al 2012]. In addition, it is now clear that a significant proportion of in-frame \(PKD1\) changes are incompletely penetrant (hypomorphic) [Cornec-Le Gall et al 2013], adding to the complexity of test interpretation. The development of specific algorithms to score missense variants has helped to assess likely pathogenicity [Rossetti et al 2007, Rossetti et al 2009, Vujic et al 2010, Audrézet et al 2012]. The ADPKD Mutation Database (see Table A. Genes and Databases) also contains scored information on published variants for research use.

**Testing Strategy**

To **confirm/establish the diagnosis in a proband.** 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, particularly in individuals who represent simplex cases (i.e., a single occurrence in a family), in individuals with unusually severe or unusually mild disease, or in individuals with other atypical presentations.

- **Kidney imaging methods** including abdominal ultrasound, CT, or MRI should be considered first for diagnosis.
  
  Note: A small number of cysts can be detected by these imaging methods in the general population.

- **Single-gene testing.** Serial molecular genetic testing of \(PKD1\) followed by \(PKD2\) is available; however, due to interpretation issues [Rossetti et al 2009, Vujic et al 2010, Bergmann et al 2011] a strategy that employs simultaneous sequence analysis and deletion/duplication analysis of both genes is more informative [Authors, personal observation].

- **Multigene panels.** Approaches that screen a panel of genes, such as multigene panels or whole-exome sequencing, can be problematic, particularly for evaluation of exons 1-33 of \(PKD1\). Such methods can generate both false positive and false negative results. Therefore, these approaches are not suitable for molecular confirmation of a diagnosis of ADPKD.

**Presymptomatic diagnosis.** If the family-specific pathogenic variant is known, molecular genetic testing can be used for presymptomatic diagnosis when imaging results are equivocal and/or when a definitive diagnosis is required in a younger individual.

- Exclusion of the diagnosis is of great importance for evaluating potential living-related kidney donors at risk for ADPKD. The absence of renal cysts by ultrasound examination virtually excludes a diagnosis of ADPKD caused by mutation of \(PKD1\) in an at-risk person age 15-30 years (NPV = 99.1%) or older (NPV = 100%), but not in persons younger than age 40 years who are at risk for ADPKD caused by pathogenic variants.
associated with milder disease or ADPKD of unknown genotype.

- A normal renal ultrasound does not exclude ADPKD with certainty in an at-risk individual younger than age 30 years (see below for information on other imaging modalities).

- Ultrasound criteria used to exclude an at-risk relative as a potential living-related kidney donor are shown in Table 3.

- MRI or contrast-enhanced CT, which has much higher sensitivity than ultrasound to detect cysts and is routinely performed in most transplantation centers to define the donor kidney anatomy, provides further assurance for the exclusion of the diagnosis if cysts are absent (see Clinical Diagnosis, Renal Cysts, Age-specific MRI criteria).

- When the family-specific pathogenic variant has not been identified:
  - An ultrasound scan finding of normal kidneys in an individual age 30-39 years or of normal kidneys or only one renal cyst in an individual age 40 years or older has a negative predictive value of 100%.
  - The family history of renal disease severity can be used as a rough guide to predict the severity of disease in other family members (see Genotype-Phenotype Correlations).

Table 3.

Ultrasound Criteria that Exclude an Individual at 50% Risk for ADPKD from Being a Kidney Donor

<table>
<thead>
<tr>
<th>Age</th>
<th>PKD1</th>
<th>PKD2</th>
<th>Unknown ADPKD Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-30 years</td>
<td>≥1 cyst NPV = 99.1% SPEC = 97.6%</td>
<td>≥1 cyst NPV = 83.5% SPEC = 96.6%</td>
<td>≥1 cyst NPV = 90.8% SPEC = 97%</td>
</tr>
<tr>
<td>30-39 years</td>
<td>≥1 cyst NPV = 100% SPEC = 96%</td>
<td>≥1 cyst NPV = 96.8% SPEC = 93.8%</td>
<td>≥1 cyst NPV = 98.3% SPEC = 94.8%</td>
</tr>
<tr>
<td>40-59 years</td>
<td>≥2 cysts NPV = 100% SPEC = 98.4%</td>
<td>≥2 cysts NPV = 100% SPEC = 97.8%</td>
<td>≥2 cysts NPV = 100% SPEC = 98.2%</td>
</tr>
</tbody>
</table>

Derived from Pei et al [2009]. All values presented are mean estimates.

NPV = negative predictive value

SPEC = specificity

Genetically Related (Allelic) Disorders

Early-onset PKD. Rarely, early-onset PKD with an apparent negative family history (similar to the typical presentation in autosomal recessive PKD [ARPKD]) or early-onset PKD (renal cysts detected in utero and occasional perinatal demise) in a family with otherwise typical ADPKD has been described. These presentations have been associated (respectively) with the presence of two hypomorphic *PKD1* pathogenic variants inherited in *trans*
configuration or with inheritance of a typical pathogenic variant and a hypomorphic pathogenic variant in trans configuration [Rossetti et al 2009, Vujic et al 2010, Hopp et al 2012]. Coinheritance of a PKD1 and an HNF1B pathogenic variant can also result in early-onset PKD [Bergmann et al 2011].

**PKD with tuberous sclerosis complex.** A contiguous gene deletion syndrome in which PKD1 and the adjacent tuberous sclerosis complex gene TSC2 are disrupted by deletion has been described [Brook-Carter et al 1994, Sampson et al 1997, Consugar et al 2008]. 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; individuals with mosaicism may have milder disease.

**Clinical Characteristics**

**Clinical Description**

**Renal Manifestations**

Although all individuals with autosomal dominant polycystic kidney disease (ADPKD) develop cysts within the kidneys, there is substantial variability in severity of renal disease and other manifestations of the disease, even within the same family. Poor prognostic factors include: diagnosis before age 30 years; first episode of hematuria before age 30 years; onset of hypertension before age 35 years; hyperlipidemia; presence of sickle cell trait [Gabow 1996]; higher urine sodium excretion, lower renal blood flow and lower serum HDL cholesterol [Torres et al 2011a], large total kidney volume [Chapman et al 2012, Irazabal et al 2015], and presence of a PKD1 pathogenic truncating variant [Cornec-Le Gall et al 2013].

**Cyst development and growth.** The renal manifestations of ADPKD include renal function abnormalities, hypertension, renal pain, and renal insufficiency. These manifestations are directly related to the development and enlargement of renal cysts. A study by the Consortium of Imaging Studies to Assess the Progression of Polycystic Kidney Disease (CRISP) of 241 non-azotemic affected individuals followed prospectively with yearly MR examinations showed that total kidney volume (TKV) and cyst volumes increase exponentially [Grantham et al 2006]. At baseline, total kidney volume was 1060 ± 642 mL; the mean increase over three years was 204 mL or 5.3% per year. The baseline TKV predicted the subsequent rate of increase in renal volume, meaning that the larger the kidney, the faster the rate of renal enlargement over time. Declining glomerular filtration rate (GFR) was observed in persons with baseline TKV above 1500 mL [Grantham et al 2006].

More recently, kidney size has been shown to be a strong predictor of subsequent decline in renal function with a height-adjusted (ht)TKV of ≥600 mL/m showing a high predictive value for the individual to develop renal insufficiency within eight years [Chapman et al 2012].

Compartmentalizing age-adjusted htTKV into five classes based on rate of expansion has also shown that kidney size strongly predicts decline in renal function and ESRD. A model including htTKV (that can be estimated using renal dimensions and the ellipsoid equation), age, and eGFR (available via an on-line app) has good predictive value to estimate future eGFR [Irazabal et al 2015].

The kidneys in persons with a PKD1 pathogenic variant (so called PKD1 phenotype) are generally significantly larger and have a higher number of cysts than the kidneys of persons with the PKD2 phenotype; however, the rates of cystic growth are not different, indicating that PKD1 is more severe than PKD2 because more cysts develop earlier, not because they grow faster [Harris et al 2006].
Occasionally, enlarged and echogenic kidneys with or without renal cysts are detected prenatally in a fetus at risk for ADPKD [Zerres et al 1993]. The prognosis in these early onset cases is often favorable with a decrease in kidney size and no decline in renal function, at least during childhood, although ESRD is earlier than is typically seen in adult-onset disease [Fick et al 1993, Zerres et al 1993].

**Renal function abnormalities.** Reduction in urinary concentrating capacity and excretion of ammonia occur early and may be caused by disruption of the renal architecture by 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 the overlap between affected and unaffected individuals is significant. The reduction of urinary excretion of ammonia in the presence of metabolic stresses (e.g., 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 ADPKD.

More recent studies suggest that the urinary concentrating defect and elevated serum concentration of vasopressin may contribute to cystogenesis [Gattone et al 1999, Gattone et al 2003, Torres et al 2004, Nagao et al 2006]. They may also contribute to the glomerular hyperfiltration seen in children and young adults, development of hypertension, and progression of chronic kidney disease [Torres 2005].

Plasma copeptin concentration (a marker of endogenous vasopressin levels) has been associated with various markers of disease severity (positively with TKV and albuminuria and negatively with GFR and effective renal blood flow) in a cross-sectional analysis of people with ADPKD [Meijer et al 2011]. Plasma copeptin concentration has also been associated with the change in total kidney volume during follow-up in the CRISP study [Boertien et al 2013].

**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 [Torres et al 2007b].

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 ADPKD is often diagnosed late in the disease course. Twenty-four hour monitoring of ambulatory blood pressure of children or young adults without hypertension may reveal elevated blood pressure, attenuated decrease in nocturnal blood pressure, and exaggerated blood pressure response during exercise, which may be accompanied by left ventricular hypertrophy and diastolic dysfunction [Seeman et al 2003].

Early detection and treatment of hypertension in ADPKD is important because cardiovascular disease is the main cause of death. Uncontrolled high blood pressure increases the risk for:
- Proteinuria, hematuria, and a faster decline of renal function;
- Morbidity and mortality from valvular heart disease and aneurysms;
- Fetal and maternal complications during pregnancy.

**Renal pain.** Pain is a common manifestation of ADPKD [Bajwa et al 2004]. 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 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. 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 that 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 [Torres et al 2007a]. Postulated factors predisposing to the development of renal stone disease in ADPKD include: decreased ammonia excretion, low urinary pH, and low urinary citrate concentration. However, these factors occur with the same frequency in individuals with ADPKD with and without a history of nephrolithiasis [Nishiura et al 2009].

**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 infections more frequently than males; the majority of infections are caused by *E. coli* and other enterobacteriaceae. Retrograde infection from the bladder may lead to pyelonephritis or cyst infection. Renal cyst infections account for approximately 9% of hospitalizations in individuals with ADPKD [Sallée et al 2009].

**Renal cell carcinoma (RCC)** does not occur more frequently in individuals with ADPKD than in the general population. However, 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 and females with ADPKD are equally likely to develop RCC. A solid mass on ultrasound; speckled calcifications on CT; and contrast enhancement, tumor thrombus, and regional lymphadenopathies on CT or MRI should raise suspicion for a carcinoma.

An increased risk for RCC in individuals with ADPKD who are on dialysis for end-stage renal disease (ESRD) can be explained by the increased incidence of RCC with advanced kidney disease (rather than by an increased risk for RCC in individuals with ADPKD) [Hajj et al 2009, Nishimura et al 2009]. A retrospective study of 40,821 Medicare primary renal transplant recipients transplanted from January 1, 2000 to July 31, 2005 (excluding those with pre-transplant nephrectomy), demonstrated that acquired renal cystic disease pre-transplant, but not ADPKD, was associated with post-transplant RCC.

Recent data suggest that the rate of all cancers in individuals with ADPKD after kidney transplantation is actually lower than in kidney transplant recipients who did not have ADPKD when age and other co-variants are taken into consideration [Wetmore et al 2014].

**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 ESRD by age 60 years. Once renal insufficiency has begun, the average yearly rate of decline in glomerular filtration rate (GFR) is approximately 5 mL/min [Klahr et al 1995]. Several mechanisms account for decline in renal function. 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. The CRISP study [Grantham et al 2006] confirmed previous studies suggesting a strong relationship with renal enlargement [King et al 2000, Fick-Brosnahan et al 2002] and showed that kidney and cyst volumes are the strongest predictors of renal functional decline [Chapman et al 2012, Irazabal et al 2015].

CRISP also found that renal blood flow (or vascular resistance) is an independent predictor of renal function decline [Torres et al 2007b]. This points to the importance of vascular remodeling in the progression of the disease and may account for cases in which the decline of renal function appears to be out of proportion to the severity of the cystic disease. Angiotensin II, transforming growth factor-β, and reactive oxygen species may contribute to the vascular lesions and interstitial fibrosis by stimulating the synthesis of chemokines, extracellular matrix, and metalloproteinase inhibitors.

Other factors including heavy use of analgesics may contribute to kidney disease progression in some individuals.

**Extrarenal Manifestations**

**Polycystic liver disease (PLD)** 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.

Hepatic cysts are rare in children. The frequency of hepatic cysts increases with age and may have been underestimated by ultrasound and CT studies. Their prevalence by MRI in the CRISP study is 58% in participants age 15-24 years, 85% in those age 25-34 years, and 94% in those age 35-46 years [Bae et al 2006]. PLD develops at a younger age in women than men 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 PLD [Everson & Taylor 2005]. Recent analysis of liver volumes and liver cyst volumes in 534 individuals with ADPKD in the HALT PKD study showed an increase in parenchymal volume and a correlation between the severity of PLD and biochemical and hematologic features, in addition to reduced quality of life [Hogan et al 2015].

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 2007].

The liver cyst epithelia produce and secrete carbohydrate antigen 19-9 (CA19-9), a tumor marker for gastrointestinal cancers. The concentration of CA19-9 is increased in the serum of individuals with polycystic liver disease and markedly elevated in hepatic cyst fluid. Serum CA19-9 levels correlate with polycystic liver volume [Waanders et al 2009, Kanaan et al 2010].

Complications of PLD include: cyst hemorrhage, infection, or rupture. Hemorrhagic cysts may cause fever and masquerade as cholecystitis or cyst infection. Usually cyst infections are monomicrobial, are caused by
enterobacteriaceae, and present with localized pain or tenderness, fever, leukocytosis, elevated erythrocyte sedimentation rate, and high serum concentration of alkaline phosphatase and CA19-9. Elevations of CA19-9, however, can also be observed in other conditions causing abdominal pain and fever, such as acute cholangitis or diverticulitis. CT scan and MRI are helpful in the diagnosis of cyst infection but have low specificity. On CT scanning, the following have been associated with infection: fluid-debris levels within cysts, cyst wall thickening, intracystic gas bubbles, and heterogeneous or increased density. White blood cell scans are more specific but not always conclusive. Radionuclide imaging and more recently $^{18}$F-fluorodeoxyglucose positron emission tomography scanning have been used for diagnosis [Bleeker-Rovers et al 2003]. 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 rarely seen in individuals with ADPKD.
- Cholangiocarcinoma is infrequently associated with ADPKD.
- Adenomas of the ampulla of Vater have been rarely reported.

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. They are almost always asymptomatic, with very rare occurrences of recurrent pancreatitis [Başar et al 2006].
- Intraductal papillary mucinous tumors (IPMN) have been reported with increased frequency, but their prevalence and prognosis in ADPKD are uncertain [Naitoh et al 2005].
- Some authors have reported an association between ADPKD and pancreatic carcinomas [Sakurai et al 2001]; however, these cases may represent chance associations of two common disorders.

Cysts in other organs

- Seminal vesicle cysts, present in 40% of males [Danaci et al 1998], rarely result in infertility. Defective sperm motility is another cause of male infertility in ADPKD [Li Vecchi et al 2003, Torra et al 2008].
- Arachnoid membrane cysts, present in 8% of affected individuals [Danaci et al 1998], are usually asymptomatic, but may increase the risk for subdural hematomas [Wijdicks et al 2000].
- Spinal meningeal diverticula may occur with increased frequency and in rare cases present with intracranial hypotension secondary to cerebrospinal fluid leak [Schievink & Torres 1997].
- Ovarian cysts are not associated with ADPKD [Stamm et al 1999, Heinonen et al 2002].

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 of familial clustering of thoracic aortic dissections in ADPKD also exists.

Intracranial aneurysms occur in approximately 10% of individuals with ADPKD [Pirson et al 2002]. The prevalence
is higher in those individuals with a positive family history of intracranial or subarachnoid hemorrhage (22%) than in those without such a family history (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 (39 years vs. 51 years). The risk of rupture of asymptomatic intracranial aneurysms depends on the history of rupture from a different site [International Study of Unruptured Intracranial Aneurysms Investigators 1998].

In the absence of a history of rupture from a different site, the risk for rupture is:

- 0.05% per year for aneurysms <10 mm in diameter;
- Approximately 1% per year for aneurysms 10-24 mm in diameter;
- 6% within one year for aneurysms ≥25 mm.

In the presence of a history of rupture from a different site, the risk of rupture is 0.5% to 1% per year regardless of size.

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

Intracranial aneurysm rupture has a 35% to 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, Irazabal et al 2011].

Individuals with ADPKD may be at increased risk for vasospasm and transient ischemic complications following cerebral angiography. They may also be at increased risk for central retinal arterial and venous occlusions, possibly as a result of enhanced vasoconstriction to adrenergic stimulation and arterial wall remodeling [Qian et al 2007b].

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

Aortic insufficiency may occur in association with dilatation of the aortic root. Although these lesions may progress with time, they rarely require valve replacement. Screening echocardiography is not indicated unless a murmur is detected on examination.

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. A study of 543 affected individuals with GFR >60 mL/min per 1.73 m², short duration of hypertension, and prior use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers who underwent cardiac MRI found a very low prevalence of left ventricular hypertrophy, possibly due to early blood pressure
intervention [Perrone et al 2011].

Pericardial effusion occurs with an increased frequency in individuals with ADPKD, possibly because of increased compliance of the parietal pericardium. These effusions are generally well tolerated and clinically inconsequential. In the absence of known predisposing factors, extensive investigative and/or therapeutic interventions for silent pericardial effusion in persons with ADPKD are not indicated [Qian et al 2007a].

**Diverticular disease.** Colonic diverticulosis and diverticulitis are more common in individuals with ESRD associated with ADPKD than in those with other renal diseases [Sharp et al 1999, Lederman et al 2000]. Whether this increased risk extends to persons with ADPKD prior to development of ESRD is uncertain.

Extracolonic diverticular disease may also occur with increased frequency and become clinically significant in a minority of affected individuals [Kumar et al 2006].

**Genetic modifiers and demographics.** Significant intrafamilial phenotypic variability is seen in the severity of renal disease and the number and type of extrarenal manifestations, indicating that genetic modifiers and the environment significantly influence the disease presentation and course. Analysis of the variability in renal function between monozygotic twins and sibs supports the role of genetic modifying factors [Persu et al 2004]. Quantitative studies estimate that 18% to 59% of the variance in age at which ESRD occurs may result from as-yet unidentified heritable modifying factors [Fain et al 2005, Paterson et al 2005]. An association study with 173 candidate genes in 794 affected individuals highlighted the DKK3 locus as associated with eGFR levels [Liu et al 2010].

Lower incidence rates of ESRD in affected females compared to affected males suggest that ADPKD is a more severe disease in males. Recent analysis of a population of individuals with PKD1 from the French Genkyst cohort showed poorer renal survival in males than females (mean age at onset of ESRD was 58.1 years for males and 59.5 years for females) [Cornec-Le Gall et al 2013]. There was no significant difference in the smaller population of individuals with PKD2.

**Genotype-Phenotype Correlations**

Genetic heterogeneity, pathogenic variant type in PKD1, modifier genes, and environmental factors are presumed to account for the substantial variability in severity of renal disease and other manifestations that are observed in individuals with ADPKD [Rossetti & Harris 2007, Cornec-Le Gall et al 2014].

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

- Pathogenic variants in PKD1 are associated with more severe disease with an earlier age at diagnosis and mean age of onset of ESRD (58.1 years for PKD1; 79.7 years for PKD2) [Hateboer et al 1999, Cornec-Le Gall et al 2013].

- Therefore, while most individuals with fully penetrant pathogenic variants in PKD1 experience renal failure by age 70 years, more than 50% of individuals with pathogenic variants in PKD2 have adequate renal function at that age.

- The difference in severity between the PKD1 phenotype and the PKD2 phenotype may be related to the rate of cyst development (especially early in the disease) rather than to differences in the rate of cyst expansion [Harris et al 2006].
Pathogenic variant type and location in PKD1. The type of pathogenic variant in PKD1 has recently been shown to correlate with the severity of the disease [Cornec-Le Gall et al 2013].

- The average age at onset of ESRD in affected individuals with truncating PKD1 pathogenic variants was 55.6 years compared to 67.9 years for those with non-truncating variants, indicating that a significant proportion of in-frame changes are hypomorphic.

- Hypomorphic alleles cause partial loss of gene function, which is manifested as a reduced level of functional protein.
  - The one well-studied hypomorphic PKD1 allele, p.Arg3277Cys, appears to cause disease by slightly reducing the efficiency of the cleavage of the PKD1 protein, polycystin-1 (PC1), and by a folding/trafficking defect of PC1 [Hopp et al 2012].
  - Despite this, it is still likely that approximately 50% of missense and other in-frame changes are fully penetrant pathogenic variants [Harris & Hopp 2013].

- A study by Cornec-Le Gall et al [2013] did not find a correlation between pathogenic variant position in PKD1 and severity of renal disease.

Pathogenic variant type and location in PKD2. No clear correlations with pathogenic variant type or position were found in PKD2 [Magistroni et al 2003].

The extrarenal manifestations of ADPKD, including severe polycystic liver disease and an increased risk for intracranial aneurysm, are associated with mutation of either gene [Rossetti et al 2003].

- An influence of PKD1 pathogenic variant position has been suggested for the development of intracranial aneurysms, which were found more often in affected individuals with pathogenic variants in the 5' half of PKD1 compared to 3' changes [Rossetti et al 2003].

Homozgyous or compound heterozygous pathogenic variants

- Non-hypomorphic (fully penetrant) biallelic pathogenic variants in either PKD1 or PKD2 in humans are predicted to be incompatible with live birth, consistent with Pkd1 or Pkd2 knockout mice that develop fetal cystic kidneys and are embryonic lethal [Lu et al 1997, Wu et al 2000]. Consistent with this, a consanguineous family in which both parents were affected with PKD1 had two spontaneous miscarriages at four and six months' gestation; however, fetal tissue for histologic analysis was not available [Paterson et al 2002].

- Biallelic pathogenic variants where at least one pathogenic variant is hypomorphic can be compatible with life. Rossetti et al [2009] reported two families in which living individuals with PKD were found to be homozygous for PKD1 pathogenic variants. Heterozygosity for a hypomorphic allele can be associated with mild cystic disease, ranging from PKD2-like disease to just a few renal cysts [Rossetti et al 2009, Cornec-Le Gall et al 2013]. A hypomorphic allele in trans configuration with a typical disease-causing allele can also explain some cases of in utero-onset ADPKD [Zerres et al 1993, Rossetti et al 2009, Bergmann et al 2011]. Biallelic pathogenic variants in which both are hypomorphic alleles can also result in early onset disease with an apparently negative family history, and therefore can be mistaken for ARPKD [Vujic et al 2010]. A knock-in mouse model mimicking the PKD1 p.Arg3277Cys allele has proven the hypomorphic nature of this allele,
with homozygotes having slowly progressive disease. This allele in combination with a null allele in trans configuration results in early onset disease [Hopp et al 2012]. These studies have led to the notion that ADPKD is a disease where the dosage of the disease protein below a particular threshold is correlated with disease severity [Gallagher et al 2010, Hopp et al 2012, Cornec-Le Gall et al 2014].

- Neonatal-onset ADPKD has also been associated with homozygosity of a hypomorphic PKD2 allele, where the disease arose by uniparental disomy [Losekoot et al 2012].

**Mosaicism.** Variable disease presentation in a family and apparent de novo disease can be due to mosaicism. Four families with ADPKD in which an individual has been found to have a somatic and/or germline PKD1 pathogenic variant have been described [Connor et al 2008, Consugar et al 2008, Reiterová et al 2013, Tan et al 2015]. The disease phenotype in these families is variable, ranging from similar to other non-mosaic affected family members, to much milder disease, presumably reflecting the level of the pathogenic variant in the kidneys.

**Modifier genes/digenic disease**

- It has been suggested that an early-onset PKD phenotype can be caused by a combination of a heterozygous PKD1 pathogenic variant and a heterozygous pathogenic variant in HNF1B [Bergmann et al 2011], which alone is associated with the renal cysts and diabetes syndrome (RCAD).

- An example of digenic disease has been described: two individuals in one family were heterozygotes for both a PKD1 and a PKD2 pathogenic variant [Pei et al 2001]. The family history was complicated; the PKD1 pathogenic variant was predicted to be of the hypomorphic type, with a PKD2-like presentation, and so affected individuals with a heterozygous pathogenic variant in either PKD1 or PKD2 had a similar phenotype [Pei et al 2012]. However, more severe renal disease with ESRD in the early sixth decade was seen in the individuals who had both pathogenic variants, at least ten years earlier than any family member with either a PKD1 or PKD2 pathogenic variant alone. This enhanced phenotype with a combination of a PKD1 and a PKD2 pathogenic variant has recently been echoed in digenic studies of appropriate Pkd1 and Pkd2 mouse models [Gainullin et al 2015].

**Penetrance**

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

**End-stage renal disease (ESRD).** Penetrance is reduced for ESRD. While the majority of individuals with PKD1, especially with pathogenic truncating variants, experience ESRD during their lifetimes, many individuals with PKD2 have adequate renal function into old age.

In recent years there have been reports of an increase in age when affected individuals start renal replacement therapy (RRT), suggesting that better management of associated complications, especially hypertension, may be delaying the onset of ESRD [Schrier et al 2003, Orskov et al 2010]. However, another study concluded that this increase was due to older individuals with ADPKD receiving RRT rather than to improved renal survival, since there was no change in the incidence of RRT in the younger group (<50 years) [Spithoven et al 2014].

**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 600,000 persons in the United States [Iglesias et al 1983].

In 2012, 2530 persons with ADPKD started renal replacement therapy (RRT) in the US with 29,881 of individuals receiving RRT (4.7%) having this ADPKD [US Renal Data System 2014]. While 2.6% of individuals on dialysis have ADPKD, 9.9% of persons receiving renal transplants have this disorder, indicating that transplant is the RRT of choice in those with ADPKD. Of individuals who received RRT from 1991-2010 in Europe, where levels of diabetic nephropathy are lower, 8.7% (35,164/437,496) had ADPKD [Spithoven et al 2014].

The prevalence of ADPKD-related ESRD has increased from 56.8 to 91.1 per million of the population comparing the periods 1991-1995 to 2006-2010, reflecting the increasing number of affected individuals accepted for RRT and their good survival.

Yearly incidence rates in men and women (respectively) for ESRD caused by ADPKD:

- 8.7 and 6.9 per million (1998-2001, US)
- 7.8 and 6.0 per million (1998-1999, Europe) [Stengel et al 2003]
- 5.6 and 4.0 per million (1999-2000, Japan) [Wakai et al 2004]

Age-adjusted sex ratios have approached unity (from 1.6 to 1.1) in recent years [US Renal Data System 2009, Spithoven et al 2014], although earlier-onset ESRD was found in males with PKD1 [Cornec-Le Gall et al 2013].

The percentage of ESRD attributable to ADPKD is lower among African Americans than among whites because of the higher incidence of other causes of ESRD among African Americans.

Differential Diagnosis

In the absence of a family history of PKD and/or in the presence of atypical presentations, benign simple cysts (see Table 4) and other cystic diseases should be considered in the differential diagnosis.

Table 4.

Prevalence of Simple Renal Cysts in Unaffected Individuals on Ultrasound Examination

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>Simple Renal Cysts 1</th>
<th>Bilateral Renal Cysts 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-29</td>
<td>0%</td>
<td>--</td>
</tr>
<tr>
<td>30-49</td>
<td>1.7%</td>
<td>1%</td>
</tr>
</tbody>
</table>
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 individuals with multiple cysts. More recent studies of potential kidney donors using contrast-enhanced CT, which detects smaller cysts (1-2 mm), showed that from age 19 to 49 years, 39%, 22%, 7.9%, and 1.6% had at least one cyst ≥2 mm, ≥5 mm, ≥10 mm, and ≥20 mm in diameter, respectively, while from age 50 to 75 years, 63%, 43%, 22%, and 7.8% had at least one cyst ≥2 mm, ≥5 mm, ≥10 mm, and ≥20 mm in diameter [Rule et al 2012].

The following conditions can be confused with ADPKD:

- **Renal cysts and diabetes (RCAD) syndrome** (OMIM 137920), also known as type 5 maturity-onset diabetes of the young (MODY5), is characterized by MODY, exocrine pancreatic failure and pancreatic atrophy, renal and genital malformations, and liver function abnormalities. Renal involvement ranges from urinary tract malformations and unilateral or bilateral renal hypoplasia/dysplasia to bilateral cystic renal disease mimicking ADPKD [Clissold et al 2015]. RCAD is caused by pathogenic variants in HNF1B, which encodes the transcription factor HNF1β [Faguer et al 2007, Heidet et al 2010].

- **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. The majority of individuals present in the neonatal period with enlarged echogenic kidneys. At initial presentation, approximately 45% of infants have liver abnormalities, including hepatomegaly, dilated intrahepatic (and occasionally extrahepatic) biliary ducts, and mildly increased echogenicity. Pulmonary hypoplasia resulting from oligohydramnios occurs in a number of affected infants. Approximately 30% of affected infants die in the neonatal period or within the first year of life primarily of respiratory insufficiency or superimposed pulmonary infections. More than 50% of affected children progress to end-stage renal disease (ESRD), usually in the first decade of life. With neonatal respiratory support and renal replacement therapies, the ten-year survival of those who live beyond the first year of life has improved to 82%. A minority present in older childhood or young adulthood with hepatosplenomegaly and evidence of portal hypertension, with focal cystic renal disease, similar to ADPKD [Adeva et al 2006].

The diagnosis of ARPKD is based on clinical findings in the proband and the absence of renal cysts in the proband’s parents, whereas individuals with ADPKD usually have an affected parent, although de novo cases occur often. PKHD1 is the only gene known to be associated with ARPKD. ARPKD is inherited in an autosomal recessive manner.

Rarely, a combination of PKD1 pathogenic variants can mimic the ARPKD phenotype, although congenital hepatic fibrosis may not be present [Vujic et al 2010]. See Genetically Related Disorders.

<table>
<thead>
<tr>
<th>50-69</th>
<th>11.5%</th>
<th>4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥70</td>
<td>22.1%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Ravine et al [1993]

1. ≥1 renal cyst
2. ≥1 cyst in each kidney
• **Polycystic liver disease (PCLD)** (OMIM 174050), without kidney involvement, is a dominantly inherited disorder distinct from ADPKD [Cnossen & Drenth 2014]. PCLD is genetically heterogeneous with three genes identified, **PRKCSH**, **SEC63**, and **LRP5** [Drenth et al 2003, Li et al 2003, Davila et al 2004, Cnossen et al 2014], but these are thought to account for only a minority of families, suggesting further genetic heterogeneity. Distinguishing between PCLD and ADPKD caused by a mild pathogenic variant may be difficult when PLD is present in conjunction with only a few renal cysts.

• **Tuberous sclerosis complex (TSC)** 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.

Individuals with the contiguous gene syndrome involving deletion of the adjacent genes **PKD1** and **TSC2** typically manifest clinical features of TSC and early onset PKD [Brook-Carter et al 1994, Sampson et al 1997, Consugar et al 2008]. See Genetically Related Disorders.

• **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 are often associated with multiple solid tumors. In the absence of solid tumors, the appearance of the kidneys in von Hippel-Lindau syndrome may mimic that of ADPKD.

• **Oral-facial-digital syndrome type 1 (OFD1)** is a rare X-linked disorder that is lethal in males. Affected females may have renal cysts that are indistinguishable from those seen in ADPKD. Liver cysts may also be present. The OFD1 diagnosis is suggested by the extrarenal manifestations, including oral abnormalities (e.g., hyperplastic frenula, cleft tongue, cleft palate or lip, malpositioned teeth), facial abnormalities (e.g., broad nasal root with hypoplasia of nasal alae and malar bone), and digital abnormalities.

• **Glomerulocystic kidney disease** is 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. Initially descriptions were of 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, but without linkage to **PKD1** or **PKD2** [Sharp et al 1997]. Glomerular cysts can also be found during the fetal period in ADPKD [Reeders et al 1986, Vujic et al 2010] and in some other cystic diseases [Bissler et al 2010].

• **Hajdu-Cheney syndrome** (OMIM 102500) can be associated with renal enlargement with cortical and medullary cysts with or without impairment of renal function [Kaplan et al 1995]. This rare autosomal dominant disorder, caused by pathogenic variants in **NOTCH2** [Simpson et al 2011], is also 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 is neither progressive nor
familial. This entity should be differentiated from asymmetric presentation of ADPKD as well as from other lesions including 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; occasional complications include hematuria, hemorrhage into cysts, cyst rupture with retroperitoneal hemorrhage, cyst infection, and development of adenomas or carcinomas.

**Management**

**Evaluations Following Initial Diagnosis**

To establish the extent of disease and needs of an individual diagnosed with autosomal dominant polycystic kidney disease (ADPKD), the following evaluations are recommended:

- **Renal ultrasound examination** (particularly when CT or MRI of the abdomen is unavailable) can be helpful to determine the severity of disease. Ultrasound can provide an estimate of size and distribution of cysts and of overall kidney size, but CT or MRI is more sensitive and allows for better quantification of the disease severity (see following).

- **CT or MRI of the abdomen with and without contrast enhancement** to help determine the extent of cystic disease in the kidneys and liver, as well as to estimate the prognosis. CT, but not MRI, can detect stones and parenchymal calcifications. CT or MR angiography (MRA) 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, 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 an increased likelihood of disease progression 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. Note: Screening for intracranial aneurysms in individuals without a family history of intracranial aneurysms is not recommended [Irazabal et al 2011].
Treatment of Manifestations

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

Hypertension. The antihypertensive agent(s) of choice in ADPKD have not been clearly established. However, 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 [Eceder & Schrier 2001].
- In an 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 [Eceder & Schrier 2001].
- Another study found no renal protective effect of an ACE inhibitor over a β-blocker [van Dijk et al 2003]; another study found that although more rigorous blood pressure control did not preserve renal function, 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 (mean arterial pressure [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].
- The recent HALT PKD trial did not show a benefit of the addition of an angiotensin II-receptor blocker (ARB) to an ACE inhibitor in terms of preserving renal function [Torres et al 2014]. In the same trial, a lower blood pressure target (95-110/60-75 mm Hg) compared to the standard target (120-130/70-80 mm Hg) in younger affected individuals with preserved renal function was associated with a slower increase in kidney volume but no overall change in the decline in renal function, as measured by eGFR.

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 psychological dependence.
- Splanchnic nerve blockade with local anesthetics or steroids can result in pain relief beyond the duration of the local anesthetic.

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. Cyst aspiration can help to establish causality between a cyst and the presence of pain, but seldom provides long-lasting relief because of fluid reaccumulation.

- **Sclerosing agents**, such as 95% ethanol or acidic solutions of minocycline, are commonly used to prevent the reaccumulation of cyst fluid. Good 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.

In individuals with many cysts contributing to pain, laparoscopic or surgical cyst fenestration through lumbotomy or flank incision, renal denervation, and (in those who have reached ESRD) nephrectomy may be of benefit:

- **Surgical decompression** was effective in 80% to 90% of individuals for one year; 62% to 77% had sustained pain relief for longer than two years. Surgical intervention neither accelerates the decline in renal function nor preserves remaining 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 than open surgery.

- **Renal denervation** via a thoracoscopic approach was successful in one affected individual [Chapuis et al 2004]. Recently, percutaneous transluminal catheter-based denervation was shown to be effective for the treatment of kidney pain in single case reports [Shetty et al 2013, Casteleijn et al 2014].

- **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 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 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. Dual absorption CT now facilitates the differentiation of uric acid stones from calcium-containing stones.

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:

- High fluid intake and potassium citrate are the treatment of choice in uric acid lithiasis, hypocitrative calcium oxalate nephrolithiasis, and distal acidification defects.
- Medical dissolution of uric acid stones can usually be achieved by a program of high fluid intake, urine alkalization (to maintain a pH of 6-6.5), and administration of allopurinol.
- Extracorporeal shock-wave lithotripsy and percutaneous nephrostolithotomy can be successful in individuals with ADPKD without excessive complications [Umbreit et al 2010].

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

- CT and 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.
- $^{18}$F-fluorodeoxyglucose positron emission tomography scanning is the most sensitive method to detect an infected cyst, but it is expensive, not readily available and may not be reimbursed by insurance companies [Sallée et al 2009].

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, particularly if blood and urine cultures are negative [Torres et al 2007a].

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 cyst. 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. Clindamycin, vancomycin, and metronidazole are also able to penetrate cysts well. 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; 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. 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 or ureteroscopy.

**End-stage renal disease (ESRD).** Therapeutic interventions aimed at slowing the progression of ESRD 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. Because these interventions were introduced at a late state of the disease (GFR 13-55 mL/min per 1.73 m²), the 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 ESRD 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.

There is no difference in patient or graft survival between individuals with ADPKD and those with ESRD caused by other conditions. Living donor transplantation for ADPKD, which requires exclusion of ADPKD in the donor (see Testing Strategy), has increased in the last two decades. Nephrectomy of the native kidneys is reserved for affected individuals with a history of infected cysts, frequent bleeding, severe hypertension, or massive renal enlargement. There is no consensus on the optimal timing of nephrectomy; whether nephrectomy is performed before, at, or following transplantation depends to some extent on the indication for the nephrectomy and other patient-specific considerations [Lucas et al 2010, Kirkman et al 2011]. Hand-assisted laparoscopic nephrectomy is increasingly being used [Lee & Clayman 2004]. Complications after transplantation are no greater than in the general population. Complications directly related to ADPKD are rare. One study has suggested an increased risk for thromboembolic complications [Jacquet et al 2011]. Whether individuals with ADPKD are at increased risk for new-onset diabetes mellitus after transplantation (NODAT) is questionable [Ruderman et al 2012].

**Polycystic liver disease.** Most individuals with polycystic liver disease have no symptoms and require no treatment.

The treatment of symptomatic disease includes the avoidance of estrogens and caffeine 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, liver transplantation, or selective hepatic artery embolization. Any of these interventions should be tailored to the individual [Torres 2007, Drenth et al 2010].

- 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 evaluate for 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 [Schnelldorfer et al 2009]. 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 individuals for whom liver resection is not feasible or for those individuals in whom liver function is impaired.

- Because individuals with severe polycystic liver disease have mostly normal liver function, their MELD (model for end-stage liver disease) scores are low, placing them at a disadvantage for organ allocation. For highly selected individuals in this group, caval sparing hepatectomy and subsequent living donor liver transplantation could provide a potential alternative [Mekeel et al 2008].

- Selective hepatic artery embolization can be considered for highly symptomatic patients who are not surgical candidates [Takei et al 2007].

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

Asymptomatic aneurysms

- Those aneurysms measuring 5.0 mm or smaller in diameter and 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 aneurysms 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

**Early detection of hypertension.** Children with a family history of ADPKD should have their blood pressure (BP) monitored by a practitioner with experience in measurement of BP in children [Chapman et al 2015]. Screening from age five years onward, with an interval of three years in cases in which no hypertension is found, seems prudent. The diagnosis of hypertension is made when systolic or diastolic BP is ≥95th percentile for age, height, and sex, in accordance with prevailing pediatric guidelines.

**Renal cell carcinoma.** There is currently insufficient evidence for recommending screening in asymptomatic individuals with ADPKD.

**Intracranial aneurysms.** Widespread screening is usually not recommended since most intracranial aneurysms found by screening asymptomatic individuals are small, have a low risk of rupture, and require no treatment [Gibbs et al 2004, Irazabal et al 2011, Chapman et al 2015], although dissenting opinions have been published [Rozenfeld et al 2014].

Indications for screening in affected individuals with a good life expectancy include a family history of intracranial aneurysms or subarachnoid hemorrhage, previous rupture of an aneurysm, preparation for elective surgery with potential hemodynamic instability, high-risk occupations such as airplane pilots, and significant anxiety on the part of the individual despite adequate risk information.

Magnetic resonance angiography (MRA) is the diagnostic imaging modality of choice for presymptomatic screening because 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, rescreening after an interval of ten years has been suggested as a reasonable approach [Schrier et al 2004].

**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.

**Cardiac valvular abnormalities.** Screening echocardiography is not recommended unless a murmur is detected or there are other cardiovascular signs or symptoms [Chapman et al 2015].

**Colon diverticulosis.** Routine screening for diverticulosis is not recommended, but physicians should be aware of a possible increased occurrence of diverticulosis or diverticulitis in individuals with ADPKD who have reached ESRD [Chapman et al 2015].

Agents/Circumstances to Avoid

The following should be avoided:

- Long-term administration of nephrotoxic agents such as combination analgesics and NSAIDs
- Caffeine in large amounts because it interferes with the breakdown of cAMP and hence may promote renal cyst growth
- Use of estrogens and possibly progestogens in individuals with severe polycystic liver disease [Alvaro et al 2006, Glaser et al 2008]
- Smoking
**Evaluation of Relatives at Risk**

The initial evaluation of at-risk relatives over age 18 years should be imaging with abdominal ultrasound examination, CT, or MRI. When the findings on imaging are equivocal or if the pathogenic variant in the family is known, molecular genetic testing may be appropriate.

Presymptomatic diagnosis:

- Allows those found to be affected to become better educated about the disease;
- Permits early detection and treatment of complications and associated disorders;
- Reassures those found to be unaffected.

A molecular diagnosis provides information for family planning choices, including PGD.

Note: (1) Appropriate counseling prior to imaging or molecular testing, including a discussion of the possible impact on insurability and employability, is most important. (2) At present, there is no indication for testing of asymptomatic children. This may change in the future, if and when effective therapies are developed.

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

**Pregnancy Management**

The literature on pregnancy and PKD is limited.

- Pregnant women with ADPKD should be monitored closely for the development of hypertension and urinary tract infections.
- Pregnant women who develop hypertension during pregnancy or who have impaired renal function are at increased risk and should be monitored closely for the development of preeclampsia, intrauterine fetal growth restriction, and oligohydramnios.
- A second-trimester prenatal sonographic examination is indicated if either parent has ADPKD to assess fetal kidney size and echogenicity, presence of fetal kidney cysts, and amniotic fluid volume [Vora et al 2008].

**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.

**Vasopressin V2 receptor antagonists.** 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 nephrinopathisis, ARPKD, and ADPKD [Gattone et al 2003, Torres et al 2004, Wang et al 2005, Wang et al 2008]. A phase II open-label clinical trial [Higashihara et al 2011] and a phase III global, randomized, double-blind, placebo-controlled trial with a vasopressin V2 receptor antagonist (tolvaptan) were completed [Torres 2008, Torres et al 2011b, Torres et al 2012]. The phase III trial, which extended over three years, included 1445 affected individuals with preserved renal function but large kidney volumes. The increase in kidney volume in the treated group was 2.8% per year compared to 5.5% in the untreated group. Use of tolvaptan was also associated with a slower decline in kidney function. There were fewer kidney related adverse events in the treated group but more aquareasis, and elevations in liver enzyme levels occurred in some affected individuals on tolvaptan. Tolvaptan was approved for
clinical use in persons with ADPKD and rapidly enlarging kidneys in Japan in 2014 and in Canada in 2015; it has not been approved for use in the US or Europe at the time of this update.

**Somatostatin analogs.** Octreotide, a long-acting form of somatostatin, has been shown to slow the enlargement of polycystic kidneys and livers in an animal model of PKD [Masyuk et al 2007] and of polycystic kidneys and liver in a small randomized, placebo-controlled, crossover study [Ruggenenti et al 2005, Caroli et al 2010]. Two randomized, placebo controlled trials of octreotide and lanreotide for polycystic kidney and liver disease have shown that the administration of these somatostatin analogs causes a moderate but significant reduction in liver volume and decreases the growth velocity of polycystic kidneys compared to placebo [van Keimpema et al 2009, Hogan et al 2010]. Recently, a randomized, three-year, single-blind, placebo-controlled trial of octreotide long-acting release (LAR) in 75 affected individuals (38 of whom received octreotide-LAR and 37 of whom received placebo) was completed in Italy [Caroli et al 2013]. The numeric increase in kidney and liver size was significantly smaller in the treated group after one year; after three years, the size of the organs was smaller in the treated group versus the untreated group, but the difference was no longer statistically significant for either organ. Larger and longer randomized studies are needed to determine whether these drugs can be administered safely to persons with ADPKD and/or polycystic liver disease and whether they are efficacious. Studies of tolvaptan and the somatostatin analog pasireotide in a *Pkd1* mouse model showed an additive effect of the combined treatment [Hopp et al 2015].

**mTOR inhibitors** modulate the enlargement of polycystic kidneys in animal models of PKD. Their effectiveness, however, depends on the blood levels that can be achieved in different models. They are consistently effective in mouse models but not rat models because mice tolerate higher doses and blood levels compared to rats [Shillingford et al 2010, Spirli et al 2010, Zafar et al 2010]. mTOR inhibitors are effective in a paradigm in which cysts develop from the proximal tubules [Tao et al 2005, Shillingford et al 2006, Wahl et al 2006], but not in one in which cysts derive from the distal nephron and collecting duct [Renken et al 2011], as is the case in human ADPKD.

The results of clinical trials of mTOR inhibitors for ADPKD have been mostly disappointing.

- A randomized, open-label, placebo controlled study of 100 affected individuals with an estimated creatinine clearance of >70 mL/min and a mean kidney volume of 907 mL (treated group) and 1003 mL (placebo group) showed no significant effect of treatment with *sirolimus* for 18 months on either kidney volume or GFR [Serra et al 2010], possibly because intended dosage was limited by toxicity of the drug and blood levels achieved may not have been enough to inhibit mTOR activity in the kidney [Canaud et al 2010].

A randomized, crossover study of 15 individuals with ADPKD who had an eGFR ≥40 mL/min/1.73 m² demonstrated that treatment with sirolimus for six months was associated with a smaller increase in total kidney volume compared to placebo [Perico et al 2010].

- A randomized, double-blind, placebo controlled study of *everolimus* (another mTOR inhibitor) in 431 affected individuals with an estimated glomerular filtration rate (eGFR) of >30 mL/min/1.73 m² and a mean kidney volume of 2028 mL (treated group) and 1911 mL (placebo group) demonstrated that the administration of everolimus for 24 months was associated with a slower rate of increase in total kidney volume and a faster rate of decline in eGFR [Walz et al 2010]. Limitations of this study include the advanced stage of renal insufficiency in many study individuals (6.2% with an eGFR at enrollment below the inclusion limit of 30 mL/min) and the high dropout rate among study participants, particularly in the study group (33%).
An open-label pilot study of 30 adults with ADPKD randomly assigned to low-dose or standard-dose rapamycin or to standard care showed a significant increase in GFR measured by iothalamate clearance in the low dose rapamycin compared with the standard care group, without a significant effect on kidney volume or eGFR after 12 months [Braun et al 2014].

These clinical trials of mTOR inhibitors [Perico et al 2010, Serra et al 2010, Walz et al 2010 Braun et al 2014] have been accompanied by significant drug toxicity.

**Antagonists of the epidermal growth factor receptor** [Sweeney et al 2000] and other agents targeting cell proliferation or fluid secretion have been effective in animal models of polycystic kidney disease, but are not yet in clinical trials [Torres et al 2007c]. A clinical trial of the Src inhibitor bosutinib is underway.

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.* —ED.

**Mode of Inheritance**

Autosomal dominant polycystic kidney disease (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* mutation is significant, occurring in at least 10% of families.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, two possible explanations are germline mosaicism in a parent or *de novo* mutation in the proband. Although the *de novo* mutation rate is high, germline mosaicism should also be considered in individuals with a negative family history.
  
  Note: If the parent is the individual in whom the pathogenic variant first occurred, s/he may have somatic mosaicism for the variant and may be mildly/minimally affected.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include screening by imaging methods, especially in families where the renal manifestations are mild; and/or molecular genetic testing of both parents if the pathogenic variant in the proband is known.
- The family history of some individuals diagnosed with ADPKD may 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. Therefore, an apparently negative family history cannot be confirmed unless appropriate evaluations (e.g., imaging and/or molecular genetic testing) have been
performed on the parents of the proband.

Sibs of a proband

- The risk to sibs of the proband depends on 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 pathogenic variant found in the proband cannot be detected in the DNA of either parent, the disease in the proband is likely caused by de novo mutation and the risk to sibs is small. However, studies in four families have described the parent of an individual with ADPKD, or the individual him/herself, with mosaicism [Connor et al 2008, Consugar et al 2008, Reiterová et al 2013, Tan et al 2014]. Since mosaicism often goes unrecognized, the occurrence in ADPKD is likely higher than these few described cases suggest. These findings indicate that the risk to sibs of a proband with an apparent de novo pathogenic variant may still be significant.
- Complex inheritance may also play a role in a minority of patients [Rossetti et al 2009] and is important when considering the risk to other family members.

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

Other family members of the proband

- The risk to other family members depends on the genetic status of the proband's parents.
- If a parent is affected/has a pathogenic variant, his or her relatives are at risk.

Related kidney donor. At-risk relatives being considered as kidney donors need to be evaluated to determine if they have ADPKD. Evaluation consists of comprehensive renal image analysis by ultrasound, CT, and/or MRI, which is routine for any kidney donor regardless of disease indication. If the imaging is equivocal, if the potential donor is young (age <30 years), or in other cases where evidence of the disease status is considered unproven, molecular genetic testing can play a key role to establish the genetic status of the potential donor. If a known pathogenic variant has already been identified in an affected relative this analysis is straightforward. In genetically uncharacterized families, screening of an affected relative to identify the pathogenic variant must be performed before analysis of the potential donor. In cases where the pathogenic status of a detected variant(s) is not certain, molecular studies need to be interpreted with caution. If the pathogenic variant in an affected relative is not identified, or if the family has not had genetic testing, molecular testing of the potential donor is not appropriate; a ‘negative’ test does not prove that they do not have ADPKD.

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.

Testing of at-risk asymptomatic adults. Testing of at-risk asymptomatic adults for ADPKD should first involve renal image analysis. However, molecular genetic testing is increasingly playing a role in establishing the diagnosis and is possible after molecular genetic testing has identified the specific pathogenic variant in the family. Such testing should be performed in the context of formal genetic counseling. Since some generalizations can be made about the
phenotype expected in individuals with pathogenic truncating and non-truncating variants in \textit{PKD1} and of all pathogenic variant types in \textit{PKD2} (see Genotype Phenotype Correlations), knowledge of the involved gene and the specific causative pathogenic variant may provide some information on likely disease severity 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 be considered if the imaging results are equivocal or if a definite diagnosis in a young person (age <30 years) is required, as for a potential renal transplant donor.

\textbf{Molecular genetic testing of asymptomatic individuals younger than age 18 years} who are at risk for adult-onset disorders for which no treatment exists is not considered appropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause. However, the consensus holds that clinical monitoring for early disease presentations in individuals at risk for an adult-onset disorder is important.

Individuals who become symptomatic during childhood usually benefit from having a specific diagnosis established. See also the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

\textbf{Considerations in families with an apparent \textit{de novo} pathogenic variant.} When neither parent of a proband with an autosomal dominant condition has the pathogenic variant it is likely that the proband has a \textit{de novo} pathogenic variant. Possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

\textbf{Family planning}

- The optimal time for determination of genetic risk and discussion of the availability of prenatal 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 or at risk.

\textbf{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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. Banking DNA from individuals with atypical presentation (e.g., lethal \textit{in utero} onset) is particularly valuable to understanding the disease etiology and offering family planning choices to the family.

\textbf{Prenatal Testing}

\textbf{Molecular genetic testing.} If the \textit{PKD1} or \textit{PKD2} pathogenic variant has been identified in an affected family member, prenatal testing for pregnancies at increased risk may be available from a clinical laboratory that offers either testing of this gene or custom prenatal testing.

Requests for prenatal testing for adult-onset conditions which (like ADPKD) do not affect intellect are not common.
The possible exception is rare families with perinatal lethality as a result of severe renal disease or with infants with grossly enlarged kidneys. Since such families can be at high risk for a subsequent severely affected child, ultrasound monitoring for early evidence of renal enlargement is appropriate and prenatal molecular genetic testing may be considered if the pathogenic variant, and/or the modifying variant to early onset disease in the family, is known [Zerres et al 1993, Rossetti et al 2009].

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% to 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, discussion of these issues is appropriate.

**Preimplantation genetic diagnosis (PGD)** may be an option for some families in which the *PKD1* or *PKD2* pathogenic variant has been identified and is increasingly being employed by families at risk for ADPKD [De Rycke et al 2005, Zeevi et al 2013].

**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](http://www.ncbi.nlm.nih.gov/books/NBK1246/?report=printable).*

- **National Library of Medicine Genetics Home Reference**  
  Polycystic kidney disease
- **NCBI Genes and Disease**  
  ADPKD
- **PKD Foundation**  
  8330 Ward Parkway  
  Suite 510  
  Kansas City MO 64114-2000  
  **Phone:** 800-753-2873 (toll-free); 816-931-2600  
  **Fax:** 816-931-8655  
  **Email:** pkdcure@pkdcure.org  
  [www.pkdcure.org](http://www.pkdcure.org)
- **The PKD Charity (Polycystic Kidney Disease)**  
  91 Royal College  
  London W1 0SE  
  United Kingdom  
  **Phone:** 0300 111 1234  
  **Email:** info@pkdcharity.org.uk  
  [www.pkdcharity.org.uk](http://www.pkdcharity.org.uk)
- **Kidney Foundation of Canada**  
  310-5160 Decarie Blvd.
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.

Polycystic Kidney Disease, Autosomal Dominant: Genes and Databases

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome Locus</th>
<th>Protein</th>
<th>Locus Specific</th>
<th>HGMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKD1</td>
<td>16p13.3</td>
<td>Polycystin-1</td>
<td>ADPKD Mutation Database (PKD1)</td>
<td>PKD1</td>
</tr>
<tr>
<td>PKD2</td>
<td>4q22.1</td>
<td>Polycystin-2</td>
<td>ADPKD Mutation Database (PKD2)</td>
<td>PKD2</td>
</tr>
</tbody>
</table>

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

Table B.

OMIM Entries for Polycystic Kidney Disease, Autosomal Dominant (View All in OMIM)

<table>
<thead>
<tr>
<th>OMIM</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>173900</td>
<td>POLYCYSTIC KIDNEY DISEASE 1; PKD1</td>
</tr>
<tr>
<td>173910</td>
<td>POLYCYSTIN 2; PKD2</td>
</tr>
<tr>
<td>601313</td>
<td>POLYCYSTIN 1; PKD1</td>
</tr>
<tr>
<td>613095</td>
<td>POLYCYSTIC KIDNEY DISEASE 2; PKD2</td>
</tr>
</tbody>
</table>

Molecular Genetic Pathogenesis

There is good evidence that polycystin-1 and polycystin-2 interact to form a functional complex and recent data shows that this interaction is central for the maturation and localization of these proteins [Kim et al 2014, Gainullin et
al 2015]. Strong evidence indicates that, in common with the proteins associated with syndromic forms of PKD, such as Meckel syndrome, polycystin-1 and polycystin-2 are localized to primary cilia [Pazour et al 2002, Yoder et al 2002]; PKD is a ciliopathy [Hildebrandt et al 2011].

The precise role that the polycystin complex normally plays on the cilium is controversial. The cilium is known to be essential for a number of signaling pathways, such as sonic hedgehog and possibly planar cell polarity (PCP) that likely play a role in some ciliopathy phenotypes. Proteins causative of syndromic forms of PKD (like Meckel or Joubert syndromes), with ciliopathy phenotypes in other organs, are involved in regulating the protein composition of the cilium [Fischer et al 2006, Hildebrandt et al 2011, Garcia-Gonzalo & Reiter 2012]. However, it is likely that the polycystins have a sensory/mechano-sensory role. One suggestion is that they play a role in the detection of fluid flow within the tubule [Nauli et al 2003]. Hence, 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, or lowering of the level of the polycystin complex below a pathogenic threshold as a result of pathogenic variants in PKD1 or PKD2 (possible plus somatic events), results in altered Ca$^{2+}$ homeostasis that may be associated with the multiple cellular changes (e.g., increased proliferation and apoptosis and altered polarity and secretory properties) that are characteristic of ADPKD cells [Harris & Torres 2009].

Alternative hypotheses note that the majority of polycystin-2 is in the endoplasmic reticulum (ER) and it is thought to play a role in regulating the level of intracellular calcium that in turn influences the level of cAMP that is elevated in PKD [Torres & Harris 2014]. Another location noted for the polycystins and the ARPKD protein, fibrocystin, is in urinary vesicles [Hogan et al 2009]. It is possible that this secreted protein is playing a signaling role in the nephron.

Common to the vascular and cardiac lesions in ADPKD 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 appears likely that PKD1 and PKD2 pathogenic variants are directly responsible for the vascular and cardiac manifestations of ADPKD because 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 [Torres et al 2001, Qian et al 2003]. Polycystin-1 is also thought to have a role as a pressure sensor on endothelial cells lining the vasculature [Sharif-Naeini et al 2009].

**PKD1**

**Gene structure.** PKD1 encodes an approximately 14-kb transcript with a 12909 nucleotide coding region and comprises 46 exons within 50 kb of genomic DNA [Hughes et al 1995]. The genomic region encoding PKD1 has undergone a complex segmental duplication such that six reiterated copies of the 5’ three-quarters of the gene are present as pseudogenes elsewhere on chromosome 16 [European Polycystic Kidney Disease Consortium 1994, Loftus et al 1999]. The high sequence homology among these pseudogenes and PKD1 has complicated molecular genetic testing. Sequence analysis requires appropriate primers to avoid a co-amplification of pseudogene(s) segments. Whole-exome sequencing does not accurately identify pathogenic variants in the duplicated region of PKD1 (see Testing Strategy). For a detailed summary of gene and protein information, see Table A, Gene.

**Pathogenic allelic variants.** PKD1 is characterized by extreme allelic variability, with 50%-70% of pathogenic variants unique to a single family [Rossetti et al 2007, Audrézet et al 2012]. The ADPKD Mutation Database (Table A) lists a total of approximately 1275 likely pathogenic PKD1 changes, accounting for about 1875 families with...
PKD1. The pathogenic variants are spread throughout the gene; an estimated 65% are predicted to truncate the protein product. The pattern of many different pathogenic variants of different types causing ADPKD is consistent with any pathogenic variant that inactivates a single allele resulting in ADPKD. Recent data also indicate that as many as one half of in-frame pathogenic variants are hypomorphic (alleles that cause partial loss of gene function through reduced RNA, protein, or protein function) and associated with milder kidney disease [Corneç-Le Gall et al 2013, Harris & Hopp 2013]. It has been suggested that somatic mutation disrupting the normal allele is required for cyst initiation [Qian et al 1996], and although somatic mutation likely plays a role in cyst development it is now clear that cysts can develop with some polycystin-1 present and so a polycystin-1 threshold hypothesis seems more appropriate [Gallagher et al 2010, Hopp et al 2012, Corneç-Le Gall et al 2014].

Table 5.

PKD1 Pathogenic Variants Discussed in This GeneReview

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Protein Amino Acid Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.9829C&gt;T</td>
<td>p.Arg3277Cys</td>
<td>NM_001009944.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NP_001009944.2</td>
</tr>
</tbody>
</table>

Note on variant classification: Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.

Note on nomenclature: GeneReviews follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The PKD1 product, polycystin-1, is a 4303 amino-acid protein with a calculated, unglycosylated 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. Cleavage of the protein occurs at the GPS domain but the protein products appear to stay attached [Ponting et al 1999, Qian et al 2002, Yu et al 2007]. 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 but it is thought to play a role in regulating the polycystin-2 channel as part of a polycystin complex [Ong & Harris 2005].

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

Abnormal gene product. The wide array of pathogenic truncating variants in PKD1 indicates that the mechanism of disease involves inactivation of an allele and that cysts develop when less or no functional protein is present. The threshold hypothesis holds that below a certain level of polycystin-1 cysts can develop and that this threshold can be reached by loss of the normal allele by somatic mutation [Qian et al 1996], or other non-genetic changes, and that cyst development and expansion is a complex process [Lantinga-van Leeuwen et al 2004, Jiang et al 2006, Gallagher et al 2010, Hopp et al 2012, Corneç-Le Gall et al 2014].

PKD2
**Gene structure.** *PKD2* has a transcript of approximately 5.5 kb and a 2904-nucleotide coding region; it comprises 15 exons in a genomic area of approximately 70 kb [Mochizuki et al 1996].

**Pathogenic allelic variants.** *PKD2* is characterized by extreme allelic variability, with approximately 50% of pathogenic variants unique to a single family [Rossetti et al 2007, Audrézet et al 2012]. According to the ADPKD Mutation Database (Table A), approximately 200 different *PKD2* pathogenic variants have been described, accounting for nearly 440 families. As in *PKD1*, the pathogenic variants are spread throughout the gene and the majority of them (~85%) are predicted to truncate the protein, consistent with inactivation of the allele. Only one example of a clearly hypomorphic allele has been described in *PKD2* [Losekoot et al 2012].

**Normal gene product.** Polycystin-2 is predicted to have six transmembrane domains with cytoplasmic N- and C-termini [Mochizuki et al 1996]. It shares a region of homology with polycystin-1 in the transmembrane region. It also has sequence similarity to TRP channels and is now considered to be a member of the TRP family of proteins (TRPP2). Polycystin-2 is widely expressed, similar to that of polycystin-1, but it continues at a more consistent level in the adult.

**Abnormal gene product.** As with *PKD1*, the mechanism of disease is associated with reduction or loss of functional protein below a particular threshold. 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, González-Perrett et al 2001, Vassilev et al 2001, Koulen et al 2002]. Cyst development may be associated with the role of polycystin-2 on the primary cilia and its function in the influx of Ca\(^{2+}\) associated with flow, although it is also probably associated with intracellular Ca\(^{2+}\) stores in the ER [Torres & Harris 2014].

**References**

**Published Guidelines/Consensus Statements**


**Literature Cited**


38. Gallagher AR, Germino GG, Somlo S. Molecular advances in autosomal dominant polycystic kidney


75. Irazabal MV, Huston J 3rd, Kubly V, Rossetti S, Sundsbak JL, Hogan MC, Harris PC, Brown RD Jr, Torres VE. Extended follow-up of unruptured intracranial aneurysms detected by presymptomatic screening in


Shillingford JM, Piontek KB, Germino GG, Weimbs T. Rapamycin ameliorates PKD resulting from


16221255


186. Umbreit EC, Childs MA, Patterson DE, Torres VE, LeRoy AJ, Gettman MT. Percutaneous nephrolithotomy


Suggested Reading


Chapter Notes

Revision History

- 11 June 2015 (me) Comprehensive update posted live
- 8 December 2011 (me) Comprehensive update posted live
- 2 June 2009 (cd) Revision: deletion/duplication analysis available clinically for PKD2
- 15 December 2008 (cd) Revision: FISH (deletion/duplication analysis) no longer listed in the GeneTests Laboratory Directory as being offered for PKD1
- 7 October 2008 (me) Comprehensive update posted live