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# Polycystic Kidney Disease, Autosomal Dominant

Synonym: ADPKD

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## Summary

### Clinical characteristics

Autosomal dominant polycystic kidney disease (ADPKD) is generally a late-onset multisystem disorder characterized by bilateral kidney cysts, liver cysts, and an increased risk of intracranial aneurysms. Other manifestations include: cysts in the pancreas, seminal vesicles, and arachnoid membrane; dilatation of the aortic root and dissection of the thoracic aorta; mitral valve prolapse; and abdominal wall hernias. Kidney manifestations include early-onset hypertension, kidney pain, and kidney insufficiency. Approximately 50% of individuals with ADPKD have end-stage kidney disease (ESKD) by age 60 years. The prevalence of liver cysts increases with age and occasionally results in clinically significant severe polycystic liver disease (PLD), most often in females. Overall, the prevalence of intracranial aneurysms is fivefold higher than in the general population and further increased in those with a positive family history of aneurysms or subarachnoid hemorrhage. There is substantial variability in the severity of kidney disease and other extra-kidney manifestations.

### Diagnosis/testing

The diagnosis of ADPKD is established in a proband with age-specific kidney imaging criteria and either an affected first-degree relative with ADPKD or a heterozygous pathogenic variant in *PKD1*, *PKD2*, or one of the less common associated genes (*ALG5*, *ALG9*, *DNAJB11*, *GANAB*, *IFT140*) identified by molecular genetic testing.

### Management

*Treatment of manifestations:* Treatment with vasopressin V2 receptor antagonists (e.g., tolvaptan) to slow disease progression is approved for individuals with rapidly progressive disease. Treatment for hypertension may include ACE inhibitors or angiotensin II receptor blockers and diet modification. Delayed onset of ESKD has been suggested with lipid control; low osmolar intake (e.g., moderate sodium and protein); increased hydration by moderate water intake; maintenance of sodium bicarbonate ≥22 mEq/L; moderation of dietary phosphorus

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intake; moderation of caloric intake; and low-impact exercise to maintain normal body mass index. 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, kidney denervation, and nephrectomy. Cyst hemorrhage and/or gross hematuria usually responds to bed rest, analgesics, and adequate hydration. Severe bleeding may require transfusion, segmental arterial embolization, or surgery. Treatment of nephrolithiasis is standard. Treatment of cyst infections is difficult, with a high failure rate. Therapeutic agents of choice include trimethoprim-sulfamethoxazole, fluoroquinolones, clindamycin, vancomycin, and metronidazole. ESKD is treated with dialysis and transplantation. Symptomatic liver cysts may improve with avoidance of estrogens and the use of H2 blockers or proton pump inhibitors. Severe symptoms may require percutaneous aspiration and sclerosis, laparoscopic fenestration, combined hepatic resection and cyst fenestration, liver transplantation, or selective hepatic artery embolization. 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 reaches 55-60 mm.

*Surveillance:* CT or MRI examination of the abdomen with and without contrast enhancement every one to five years in adults depending on disease stage; blood pressure monitoring every three years beginning at age five years in those with normal blood pressure; urine studies for microalbuminuria or proteinuria every one to five years in adults depending on disease stage; echocardiography or chest MRI every two to three years in adults with a first-degree relative with thoracic aortic dissection; MRA examination for intracranial aneurysms in adults determined to be at high risk.

*Agents/circumstances to avoid:* Long-term administration of nephrotoxic agents, high levels of caffeine, high-salt diet, smoking, and obesity, and in individuals with severe PLD, use of estrogens and possibly progestogens.

*Evaluation of relatives at risk:* Testing of adult relatives at risk permits early diagnosis, initiation of treatment, and treatment of associated complications.

*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, oligohydramnios, and fetal kidney anomalies including cysts, enlarged size, and atypical echogenicity.

## Genetic counseling

In most affected families, ADPKD is caused by a heterozygous *PKD1* or *PKD2* pathogenic variant and inherited in an autosomal dominant manner. More rarely, ADPKD is caused by a heterozygous pathogenic variant in *ALG5*, *ALG9*, *DNAJB11*, *GANAB*, or *IFT140.* Complex inheritance (biallelic *PKD1*- or *PKD2*-related ADPKD or digenic ADPKD) may play a role in a minority of families and is important when considering the risk to other family members. Most individuals diagnosed with ADPKD have an affected parent; 10%-20% of affected individuals have the disorder as the result of a *de novo* pathogenic variant. Each child of an individual who is heterozygous for an ADPKD-causing pathogenic variant has a 50% chance of inheriting the pathogenic variant. Once the ADPKD-causing pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

# Diagnosis

Diagnostic criteria for autosomal dominant polycystic kidney disease (ADPKD) are discussed in the executive summary of the KDIGO Controversies Conference [Chapman et al 2015, Bergmann et al 2018].

## Suggestive Findings

ADPKD **should be suspected** in individuals with the following:

- Multiple bilateral kidney cysts and absence of manifestations suggestive of a different cystic kidney disease
- Cysts in other organs, especially the liver, but also seminal vesicles, pancreas, and arachnoid membrane
- Enlargement of the kidneys or liver on physical examination
- Hypertension in an individual younger than age 35 years
- An intracranial aneurysm
- Family history consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

## Establishing the Diagnosis

The diagnosis of ADPKD **is established** in a proband with ANY of the following:

- Age-specific ultrasound criteria and an affected first-degree relative with ADPKD
- Age-specific MRI criteria and an affected first-degree relative with ADPKD
- Identification of a heterozygous pathogenic variant in one of the genes listed in Table 3

### Age-Specific Ultrasound Criteria

Age-specific ultrasound criteria in an individual with an affected first-degree relative [Pei et al 2009]:

- The presence of three or more (unilateral or bilateral) kidney 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

Note: (1) The positive predictive value of these criteria is described as 100%, if (a) the disorder is *PKD1*- or *PKD2*-related ADPKD and (b) the individual is age 15-59 years at the time of evaluation (see Table 1). Note that there are other genetic causes of kidney cysts in addition to fully penetrant pathogenic variants in *PKD1* or *PKD2* (see Tables 3, 5a, and 5b). (2) The sensitivity of ultrasound criteria is decreased in families with a pathogenic variant in *PKD2*, families with incompletely penetrant nontruncating *PKD1* pathogenic variants, and families with pathogenic variants in less commonly associated genes. In these situations, a significant number of affected individuals may not be diagnosed using these criteria, which may pose a problem when exclusion of the diagnosis is necessary to identify potential related kidney donors (see Excluding the Diagnosis).

**Table 1.** Ultrasound Criteria for Diagnosis of ADPKD in Individuals at 50% Risk for ADPKD Based on Family History

| Age | PKD1 | PKD2 | Unknown ADPKD Genotype |
|---|---|---|---|
| **15-30 yrs** | ≥3 cysts [1]<br>PPV = 100%<br>SEN = 94.3% | ≥3 cysts [1]<br>PPV = 100%<br>SEN = 69.5% | ≥3 cysts [1]<br>PPV = 100%<br>SEN = 81.7% |
| **30-39 yrs** | ≥3 cysts [1]<br>PPV = 100%<br>SEN = 96.6% | ≥3 cysts [1]<br>PPV = 100%<br>SEN = 94.9% | ≥3 cysts [1]<br>PPV = 100%<br>SEN = 95.5% |
| **40-59 yrs** | ≥2 cysts in each kidney<br>PPV = 100%<br>SEN = 92.6% | ≥2 cysts in each kidney<br>PPV = 100%<br>SEN = 88.8% | ≥2 cysts in each kidney<br>PPV = 100%<br>SEN = 90% |

Derived from Pei et al [2009]. All values presented are mean estimates.
ADPKD = autosomal dominant polycystic kidney disease; PKD = polycystic kidney disease; PPV = positive predictive value; SEN = sensitivity
*1.* Unilateral or bilateral

## Age-Specific MRI Criteria

Age-specific MRI criteria are particularly useful when ultrasound results are equivocal [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 more than ten cysts is sufficient for a diagnosis of ADPKD.

Note: These MRI 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.

## Excluding the Diagnosis

The absence of kidney cysts by ultrasound examination virtually excludes a diagnosis of ADPKD caused by a truncating *PKD1* pathogenic variant in an at-risk person age 15-30 years (negative predictive value [NPV] = 99.1%) or older than 30 years (NPV = 100%). However, absence of kidney cysts does not exclude the diagnosis in persons younger than age 40 years who are at risk for ADPKD caused by incompletely penetrant, nontruncating *PKD1* variants or pathogenic variants in the other ADPKD-related genes associated with milder disease. Ultrasound criteria used to exclude an at-risk relative as a potential living-related kidney donor are shown in Table 2.

MRI or contrast-enhanced CT examination, which has much higher sensitivity than ultrasound to detect cysts and is routinely used in most transplantation centers to assess potential donor kidney anatomy, provides further assurance for the exclusion of the diagnosis if cysts are absent.

When the family-specific pathogenic variant has not been identified:

- Ultrasound examination showing normal kidneys in an individual age 30-39 years or no more than one kidney cyst in an individual age 40 years or older has a negative predictive value of 100%.
- The family history of kidney disease severity can be used as a rough guide to predict the severity of disease in other affected family members, although there is significant intrafamilial variability (see Genotype-Phenotype Correlations).

**Table 2.** Ultrasound Criteria That Exclude an Individual at 50% Risk for ADPKD from Being a Kidney Donor

| Age | PKD1 | PKD2 | Unknown ADPKD Genotype |
|---|---|---|---|
| **15-30 yrs** | ≥1 cyst<br>NPV = 99.1%<br>SPEC = 97.6% | ≥1 cyst<br>NPV = 83.5%<br>SPEC = 96.6% | ≥1 cyst<br>NPV = 90.8%<br>SPEC = 97% |
| **30-39 yrs** | ≥1 cyst<br>NPV = 100%<br>SPEC = 96% | ≥1 cyst<br>NPV = 96.8%<br>SPEC = 93.8% | ≥1 cyst<br>NPV = 98.3%<br>SPEC = 94.8% |
| **40-59 yrs** | ≥2 cysts<br>NPV = 100%<br>SPEC = 98.4% | ≥2 cysts<br>NPV = 100%<br>SPEC = 97.8% | ≥2 cysts<br>NPV = 100%<br>SPEC = 98.2% |

Derived from Pei et al [2009]. All values presented are mean estimates.
ADPKD = autosomal dominant polycystic kidney disease; NPV = negative predictive value; PKD = polycystic kidney disease; SPEC = specificity

## Molecular Genetic Testing

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

- **A multigene panel** that includes *PKD1*, *PKD2*, *ALG5, ALG9*, *DNAJB11*, *GANAB*, *IFT140*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while

limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) Multigene panels using next-generation sequencing should be carefully designed to maximize identification of a *PKD1* pathogenic variant, which is complicated by several highly homologous pseudogenes [Trujillano et al 2014, Eisenberger et al 2015]. (2) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (3) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (4) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (5) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

- When the phenotype is indistinguishable from many other inherited disorders characterized by PKD, **comprehensive genomic testing** (which does not require the clinician to determine which gene is likely involved) is an option. A **multigene panel** or **exome sequencing** are most commonly used; **genome sequencing** is also possible. Note: (1) Exome sequencing may not detect all pathogenic variants in *PKD1* [Ali et al 2019]. (2) Methods to identify deletions and duplications should be included.

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

**Table 3.** Molecular Genetic Testing Used in ADPKD

| Gene [1] | Proportion of ADPKD Attributed to Pathogenic Variants in Gene | Proportion of Probands with a Pathogenic Variant [2] Detectable by Method | |
|---|---|---|---|
| | | Sequence analysis [3] | Gene-targeted deletion/ duplication analysis [4] |
| *PKD1* | ~78% | ~97% [5] | ~3% |
| *PKD2* | ~15% | ~97% [5] | ~3% |
| *ALG5* | <0.5% | >95% | None reported [6] |
| *ALG9* | <0.5% | >95% | None reported [6] |
| *DNAJB11* | <0.5% | >95% | None reported [6] |
| *GANAB* | <0.5% | >95% | See footnote 7. |
| *IFT140* | 1%-2% | >95% | None reported [6] |
| Unknown | ~5% | NA | |

NA = not applicable

*1.* See Table A. Genes and Databases for chromosome locus and protein.

*2.* See Molecular Genetics for information on variants detected in this gene.

*3.* Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants. Specific analysis is required to detect exon or whole-gene deletions/duplications. For issues to consider in interpretation of sequence analysis results, click here.

*4.* Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Due to the segmental duplication of *PKD1*, such analysis may require specific methods that detect large rearrangements, such as multiplex ligation-dependent probe amplification (MLPA) [Consugar et al 2008, Cornec-Le Gall et al 2013] or chromosomal microarray (CMA) that includes this gene/chromosome segment.

*5.* Rossetti et al [2007], Audrézet et al [2012], Cornec-Le Gall et al [2016], Heyer et al [2016], Lavu et al [2020]

*6.* Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

*7.* A deletion including *GANAB* was found in an individual with ADPKD and multiple liver cysts [Wilson et al 2020].

# Clinical Characteristics

## Clinical Description

### Kidney Manifestations

Although all individuals with autosomal dominant polycystic kidney disease (ADPKD) develop cysts within the kidneys, there is substantial variability in the severity of kidney disease and other manifestations of the disease. Less variability is observed between affected individuals from the same family, but significant intrafamilial variability still exists.

**Poor prognostic factors** include: diagnosis before age 30 years [Gabow 1996]; first episode of hematuria before age 30 years; onset of hypertension before age 35 years [Cornec-Le Gall et al 2016]; hyperlipidemia and high body mass index [Nowak et al 2018]; high urine sodium excretion [Torres et al 2017a]; lower kidney blood flow; lower serum high-density lipoprotein cholesterol [Torres et al 2011]; large total kidney volume (TKV) [Chapman et al 2012, Irazabal et al 2015, Lavu et al 2020]; and the presence of a truncating *PKD1* variant [Cornec-Le Gall et al 2013, Heyer et al 2016, Lavu et al 2020].

The lower incidence of end-stage kidney disease (ESKD) in affected females compared to males suggests that ADPKD is a more severe disease in males. Analysis of individuals with *PKD1*-related ADPKD showed earlier-onset ESKD in males than females; mean age at onset of ESKD was 58.1 years for males and 59.5 years for females [Cornec-Le Gall et al 2013]. In a study of individuals with *PKD1*- and *PKD2*-ADPKD, ages at ESKD were 58.2 years for males and 63.9 years for females [Lavu et al 2020]. Heyer et al [2016] showed lower estimated glomerular filtration rate (eGFR) and larger height-adjusted TKV (htTKV) in males compared to females in the Consortium of Imaging Studies to Assess the Progression of Polycystic Kidney Disease (CRISP) and HALT PKD study populations and in individuals with *PKD1*-related ADPKD. Males with *PKD2*-related ADPKD also had lower eGFR. Males with truncating *PKD1* variants, onset of hypertension before age 35 years, and/or a urologic event before age 35 years were the most severely affected [Cornec-Le Gall et al 2016].

**Cyst development and growth.** The kidney manifestations of ADPKD include kidney function abnormalities, hypertension, kidney pain, and kidney insufficiency. These manifestations are directly related to the development and enlargement of kidney cysts. A CRISP study of 241 non-azotemic affected individuals followed prospectively with annual MRI examinations showed that TKV and cyst volumes increased exponentially. At baseline, TKV was 1,060 ± 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 kidney volume, meaning that the larger the kidney, the faster the rate of kidney enlargement over time. Declining GFR was observed in persons with baseline TKV above 1,500 mL [Grantham et al 2006].

Kidney size has been shown to be a strong predictor of subsequent decline in kidney function, with an htTKV of ≥600 mL/m showing a high predictive value for the individual to develop kidney insufficiency within eight years [Chapman et al 2012]. Compartmentalizing age-adjusted htTKV into five classes based on htTKV/age has also shown that this strongly predicts decline in kidney function and ESKD. A model including htTKV (which can be estimated using kidney dimensions and the ellipsoid equation), age, and eGFR (available via an online app) has good predictive value in estimating future eGFR [Irazabal et al 2015]. Further studies have confirmed the relationship between htTKV and future decline in kidney function and age at ESKD [Yu et al 2018, Lavu et al 2020].

Individuals with *PKD1*-related ADPKD often have significantly larger kidneys with more cysts than individuals with *PKD2*-related ADPKD. However, the rates of cystic growth are not different, indicating that *PKD1*-related ADPKD is more severe because more cysts develop earlier, not because they grow faster [Harris et al 2006].

Occasionally, enlarged and echogenic kidneys with or without kidney cysts are detected prenatally in a fetus at risk for ADPKD [Zerres et al 1993]. The prognosis in these individuals is often more favorable than expected given the large kidney size, with a decrease in volume and no decline in kidney function commonly seen, at least during childhood. However, ESKD develops earlier than is typically seen in adult-onset disease [Fick et al 1993, Zerres et al 1993]. Biallelic *PKD1* or *PKD2* pathogenic variants have been reported in individuals with very early-onset ADPKD (see Genotype-Phenotype Correlations) [Cornec-Le Gall et al 2018b].

**Kidney function abnormalities.** Reduction in urinary concentrating capacity and excretion of ammonia occur early in individuals with ADPKD. 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 individuals with ADPKD. In turn, crystal deposition may accelerate the rate of cystogenesis [Torres et al 2019].

Studies suggest that the urinary concentrating defect and elevated serum concentration of vasopressin may contribute to cystogenesis [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 kidney 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 TKV during follow up in the CRISP study [Boertien et al 2013].

It has long been thought that a decline in kidney function, detected as a rise in serum creatinine, is generally seen only later in the course of disease, typically about a dozen years before ESKD. Once kidney function starts to deteriorate, GFR has been observed to decline rapidly (~4-6 mL/min/yr) [Klahr et al 1995]. However, more recent studies have shown the trajectory of eGFR decline to be close to linear from early adulthood in individuals with the largest kidneys, while the traditional curvilinear trajectory with later decline is observed in individuals with smaller kidneys [Yu et al 2019, Lavu et al 2020]. Genotype is also associated with the trajectory of eGFR loss, with a steeper earlier decline associated with inactivating *PKD1* pathogenic variants [Lavu et al 2020].

Another early functional abnormality is a reduction in kidney 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** often develops in young adults, and even in childhood, and usually before any decline in GFR. It is characterized by the following:

- Increase in kidney 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 kidney hemodynamics and sodium handling by converting enzyme inhibition

Hypertension is often diagnosed much later than when it first occurs in individuals with ADPKD; 24-hour monitoring of ambulatory blood pressure of children or young adults 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].

Monitoring of blood pressure in children at risk for ADPKD is recommended [Massella et al 2018, Gimpel et al 2019].

Early detection and treatment of hypertension in ADPKD is important because cardiovascular disease is the main cause of death. Uncontrolled high blood pressure also increases the risk for:

- Proteinuria, hematuria, and a faster decline of kidney function;
- Morbidity and mortality from valvular heart disease and aneurysms;
- Fetal and maternal complications during pregnancy.

**Kidney 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 kidney 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 kidney 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 kidney anatomy and metabolic factors plays a role in the pathogenesis [Torres et al 2007a]. Postulated factors predisposing to the development of kidney 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 [Suwabe 2020]. Retrograde infection from the bladder may lead to pyelonephritis or cyst infection. Kidney cyst infections account for approximately 9% of hospitalizations in individuals with ADPKD [Sallée et al 2009].

**Kidney cell carcinoma (KCC).** Whether KCC occurs more frequently in ADPKD than in other kidney diseases remains controversial [Wetmore et al 2014, Yu et al 2016]. However, when KCC develops in individuals with ADPKD, it has different biological behavior, including: earlier age of presentation; frequent constitutional symptoms; and a higher proportion of sarcomatoid, bilateral, multicentric, and metastatic tumors [Keith et al 1994]. Males and females with ADPKD are equally likely to develop KCC. A solid mass on ultrasound, speckled calcifications on CT examination, and contrast enhancement, tumor thrombus, and regional lymphadenopathies on CT or MRI examination should raise suspicion for a carcinoma.

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

When age and other covariants were taken into consideration, the rate of all cancers in individuals with ADPKD after kidney transplantation was reported to be lower than in kidney transplant recipients who did not have ADPKD [Wetmore et al 2014].

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

**Kidney failure.** Approximately 50% of individuals with ADPKD have ESKD by age 60 years [Lavu et al 2020]. Mechanisms accounting for the decline in kidney function include: compression of the normal kidney parenchyma by expanding cysts, vascular sclerosis, interstitial inflammation and fibrosis, and apoptosis of the tubular epithelial cells. The CRISP study [Grantham et al 2006] confirmed a strong relationship with kidney enlargement and showed that kidney and cyst volumes are the strongest predictors of kidney functional decline.

CRISP also found that kidney blood flow (or vascular resistance) is an independent predictor of kidney function decline [Torres et al 2007b]. This points to the importance of vascular remodeling in the progression of the disease and may account for reports in which the decline of kidney function appears to be out of proportion to the severity of the cystic disease [Shukoor et al 2020]. Angiotensin II, transforming growth factor beta, 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.

## Extra-Kidney Manifestations

**Polycystic liver disease (PLD)** is the most common extra-kidney manifestation of ADPKD.

Liver cysts are rare in children. The frequency of liver 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 of 15-24 years, 85% in those 25-34 years, and 94% in those 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 liver cysts increased in women who received estrogen replacement therapy, suggesting that estrogens have an important effect on the progression of PLD [Everson & Taylor 2005]. 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]. Analysis of individuals with severe PLD, defined as a height-adjusted total liver volume of 1.8 liters, showed that more than 80% were women, but no difference in frequency among those with truncating or nontruncating *PKD1* or *PKD2* pathogenic variants, suggesting that other factors are primarily responsible for the severity of PLD [Chebib et al 2016b]. This study also showed that severe PLD often regressed in females after menopause.

Liver cysts are usually asymptomatic and rarely 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, hepatic veins, or bile ducts [Torres 2007].

Liver cyst epithelia produce and secrete the 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 PLD 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 and MRI examination are helpful in the diagnosis of cyst infection but have low specificity. On CT examination, the following have been associated with infection: fluid-debris levels within cysts, cyst wall thickening, intracystic gas bubbles, and heterogeneous or increased density. Indium-labeled white blood cell scans are more specific but not always conclusive. $^{18}$F-fluorodeoxyglucose positron emission tomography examination is the most sensitive technique for diagnosis of infected cysts [Bleeker-Rovers et al 2003]. The rupture of a liver 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**

- A recent study found pancreatic cysts occur in 19% of individuals with ADPKD, and papillary mucinous neoplasia in 1% [McNicholas et al 2019]. The cysts are usually less prominent than those observed in von Hippel-Lindau syndrome (see Table 5). They are almost always asymptomatic, and rarely associated with recurrent pancreatitis [Başar et al 2006].
- An association between ADPKD and pancreatic carcinomas was reported [Sakurai et al 2001]; however, this may represent a chance association of two common disorders.

**Cysts in other organs**

- Seminal vesicle cysts, present in 40% of males, rarely result in infertility. Defective sperm motility is another cause of male infertility in ADPKD [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 individuals may 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, Krittanawong et al 2019].

Intracranial aneurysms occur in approximately 10% of individuals with ADPKD [Pirson et al 2002]. The prevalence is higher in individuals with a positive family history of intracranial or subarachnoid hemorrhage (22%) than in those without such a family history (6%). Recent data from the Genkyst study found that 4.7% of participants had a diagnosis of an intracranial aneurysm, 47% of whom had a family history of intracranial aneurysms. The level rose to 8.1% by age 70 years, with a higher prevalence in females at age 70 years (10.8% females, 5.4% males) [Lefèvre et al 2022]. 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 as follows:

- For aneurysms <10 mm in diameter: 0.05% per year
- For aneurysms 10-24 mm: ~1% per year
- For aneurysms ≥25 mm: 6% within one year

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

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

Intracranial aneurysm rupture confers a 35% to 55% risk for combined severe morbidity and mortality at three months [Inagawa 2001]. At the time of rupture of an aneurysm, most individuals have normal kidney 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, Sanchis et al 2019].

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].

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. Evidence of familial clustering of thoracic aortic dissections in ADPKD also exists [Nunes et al 2022].

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

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 kidney 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 $m^2$, 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].

Individuals with ADPKD may be predisposed to idiopathic dilated and hypertrophic obstructed cardiomyopathy and left ventricular noncompaction [Paavola et al 2013, Chebib et al 2017]. Congenital heart disease, categorized as left-to-right shunt, obstructive, or complex lesions, may also be more common in individuals with ADPKD (1.4% compared to 0.4% in the general population) [Chedid et al 2022].

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

## Phenotype Correlations by Gene

***PKD1* and *PKD2*.** Pathogenic variants in *PKD1* are associated with more severe disease with an earlier age at diagnosis and mean age of onset of ESKD * than in *PKD2*-related ADPKD (* 58.0 years for *PKD1*; 74.8 years for *PKD2*) [Hateboer et al 1999, Cornec-Le Gall et al 2013, Lavu et al 2020]. Most individuals with fully penetrant pathogenic variants in *PKD1* experience kidney failure by age 70 years; more than 50% of individuals with pathogenic variants in *PKD2* have adequate kidney function at that age.

***ALG5*.** Heterozygous pathogenic variants in *ALG5* have been associated with an ADPKD spectrum phenotype in 19 individuals in three families, and four additional individuals from two families in the Genome England project [Lemoine et al 2022]. The typical phenotype is non-enlarged cystic kidneys and interstitial fibrosis with few liver cysts leading to ESKD in older individuals.

***ALG9*.** Heterozygous loss-of-function *ALG9* variants have been associated with a mild-to-moderate ADPKD phenotype, with some evidence of reduced penetrance [Besse et al 2019]. Polycystic liver disease can also be present.

***DNAJB11*.** The phenotype is quite consistent and results in the development of small, bilateral kidney cysts, usually without kidney enlargement [Cornec-Le Gall et al 2018b]. In older individuals the kidneys become fibrotic and kidney insufficiency often develops. In a study of 77 individuals from 27 families, ESKD was noted in 32 individuals between ages 55 and 89 years (median age 75 years) [Huynh et al 2020]. The kidney insufficiency without kidney enlargement shows some characteristics of autosomal dominant tubulointerstitial kidney disease. Liver cysts are sometimes present, and vascular phenotypes may also be seen.

***GANAB*.** Pathogenic variants cause mild cystic kidney disease, usually without a decline in kidney function, with the majority of affected individuals having liver cysts [Porath et al 2016]. However, some affected individuals have a phenotype of autosomal dominant polycystic liver disease with severe liver cystic disease and few kidney cysts [Porath et al 2016, Besse et al 2017, Besse et al 2018].

***IFT140*.** Heterozygous pathogenic variants in *IFT140* have been identified in 66 individuals from 38 families, with a mild PKD phenotype usually consisting of a few, larger cysts that can result in kidney enlargement and limited kidney insufficiency [Senum et al 2022]. Liver cysts are rarely seen.

## Genotype-Phenotype Correlations

### *PKD1*

As many as one half of in-frame pathogenic variants are hypomorphic and associated with milder kidney disease [Cornec-Le Gall et al 2013, Heyer et al 2016, Hwang et al 2016, Lavu et al 2020]. The average age at onset of ESKD in affected individuals with truncating *PKD1* variants is 55.6 years compared to 67.9 years for those with nontruncating *PKD1* variants.

More detailed bioinformatic analysis divided nontruncating *PKD1* pathogenic variants into two mutation strength groups (MSG; also called *PKD1* nontruncating groups, or NT1 and NT2) with nonconservative substitutions at well-conserved sites in orthologs and domains (MSG2; NT1) found to have similar severity to truncating *PKD1* pathogenic variants in terms of eGFR and htTKV [Heyer et al 2016]. Therefore, it is likely that approximately 50% of missense and other in-frame variants are fully penetrant pathogenic variants. However, a group of variants with more conservative substitutions at less well-conserved sites (MSG3; NT2) was found to be hypomorphic by analysis of eGFR, htTKV, and age at ESKD [Lavu et al 2020].

Family studies have identified incompletely penetrant nontruncating *PKD1* variants that are associated with much less severe disease [Rossetti et al 2009, Pei et al 2012]. One such well-studied *PKD1* variant, p.Arg3277Cys, causes just a few cysts or no evidence of disease in heterozygotes [Rossetti et al 2009]. These hypomorphic alleles often result in a reduced level of functional protein. Thus, the phenotype depends on whether a hypomorphic allele occurs in isolation or in combination with other *PKD1* and/or *PKD2* pathogenic variants (see Biallelic *PKD1*- and *PKD2*-Related ADPKD).

### *PKD2*

Truncating *PKD2* pathogenic variants have been associated with more severe disease with lower eGFR than nontruncating *PKD2* pathogenic variants [Cornec-Le Gall et al 2017]. Only one example of a clearly hypomorphic allele in *PKD2* has been described [Losekoot et al 2012].

### Biallelic *PKD1*- or *PKD2*-Related ADPKD

Fully penetrant (i.e., nonhypomorphic) 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]. However, biallelic pathogenic variants including at least one hypomorphic variant can be compatible with life. Rossetti et al [2009] reported two families with individuals homozygous for *PKD1* pathogenic variants, including p.Arg3277Cys. A hypomorphic allele *in trans* with a fully penetrant pathogenic variant has been identified in infants with prenatal-onset ADPKD [Zerres et al 1993, Rossetti et al 2009, Bergmann et al 2011, Audrézet et al 2016, Durkie et al 2021]. Biallelic hypomorphic variants can also result in early-onset disease with an apparently negative family history, and therefore can be mistaken for autosomal recessive PKD (ARPKD) [Vujic et al 2010].

Neonatal-onset ADPKD has also been associated with homozygosity of a hypomorphic *PKD2* variant that arose by uniparental disomy [Losekoot et al 2012].

### Digenic ADPKD

Individuals with pathogenic variants in both *PKD1* and *PKD2* have been described. Two individuals in one family were double heterozygotes for a pathogenic variant in both *PKD1* and *PKD2* and developed more severe kidney disease than was reported in heterozygous relatives [Pei et al 2001].

It has been suggested that early-onset PKD may be caused by a heterozygous pathogenic variant in both *PKD1* and *HNF1B* (digenic inheritance) [Bergmann et al 2011]. Variants in *HNF1B* are associated with *HNF1B*-related kidney disease (see Table 5). Additional evidence of digenic inheritance altering the *PKD1* or *PKD2* phenotype in humans and/or model systems has been documented with *COL4A1* (causing hereditary angiopathy w/ nephropathy, aneurysms, & muscle cramps), *PKHD1* (causing ARPKD), and the autosomal dominant polycystic liver disease genes, *PRKCSH* and *SEC63* [Bergmann et al 2011, Fedeles et al 2011, Cornec-Le Gall et al 2018a, Olson et al 2019].

## Penetrance

Penetrance in ADPKD is age and genotype dependent. The penetrance of multiple bilateral kidney cysts in older adults is close to 100%. However, because the disease is progressive, few cysts may be evident during childhood or young adulthood, especially in individuals with nontruncating *PKD1* pathogenic variants, pathogenic variants in *PKD2*, or a pathogenic variant in another ADPKD-related gene.

## Mosaicism

Variable disease presentation in a family and apparent *de novo* disease can be due to mosaicism. The disease phenotype in mosaic individuals ranges from typical ADPKD to much milder disease. A recent study

characterized mosaicism in 20 ADPKD families; the pathogenic variant was transmitted to the next generation in five families and was sporadic in 15 [Hopp et al 2020]. Analysis of kidney size and function showed that individuals with mosaicism had milder disease than a control *PKD1*-ADPKD population, but only a few had clearly asymmetric disease. It is estimated that at least 1% of individuals with ADPKD are mosaic.

## Nomenclature

The term "adult polycystic kidney disease" (APKD) is no longer in use.

## Prevalence

ADPKD is the most common potentially lethal single-gene disorder. Its prevalence at birth is approximately 1:1,000, and it affects approximately 300,000 persons in the United States.

# Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with intragenic germline pathogenic variants in *ALG5*, *PKD1*, *or PKD2*.

Other phenotypes associated with germline pathogenic variants in *ALG9*, *DNAJB11*, *GANAB*, and *IFT140* are summarized in Table 4.

**Table 4.** Allelic Disorders

| Gene | Disorder | MOI | Comment / Reference |
|---|---|---|---|
| *ALG9* | ALG9-CDG (*CDG-IL*) | AR | Congenital Disorders of N-Linked Glycosylation and Multiple Pathway Overview |
| | Gillessen-Kaesbach-Nishimura syndrome | AR | ARPKD w/microbrachycephaly, hypertelorism, & brachymelia (OMIM 263210) |
| *DNAJB11* | Kidney-hepatic-pancreatic cystic disease | AR | ARPKD w/dilatation & proliferation of pancreatic ducts & liver ductal plate malformations [Ateş et al 2021, Jordan et al 2021] |
| *GANAB* | ADPLD | AD | Some persons w/a heterozygous *GANAB* pathogenic variant have PLD w/severe liver cystic disease & few kidney cysts [Porath et al 2016, Besse et al 2017, Besse et al 2018]. |
| *IFT140* | Cranioectodermal dysplasia | AR | Cranioectodermal Dysplasia |
| | Short-rib thoracic dysplasia 9 w/ polydactyly | AR | OMIM 266920 |
| | Retinitis pigmentosa | AR | Nonsyndromic Retinitis Pigmentosa Overview |
| | Leber congenital amaurosis | AR | Nephronophthisis w/subsequent ESKD can be seen w/*IFT140*-assoc LCA (see Leber Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy Overview). |

AD = autosomal dominant; ADPLD = autosomal dominant polycystic liver disease; AR = autosomal recessive; ARPKD = autosomal recessive polycystic kidney disease; CDG = congenital disorder of glycosylation; ESKD = end-stage kidney disease; LCA = Leber congenital amaurosis; MOI = mode of inheritance; PLD = polycystic liver disease

***PKD1-TSC2* contiguous gene deletion syndrome.** Contiguous gene deletions involving both *PKD1* and the adjacent *TSC2* have been described [Brook-Carter et al 1994, Sampson et al 1997, Consugar et al 2008]. In individuals with this contiguous gene deletion, the phenotype of tuberous sclerosis and severe polycystic kidney

disease is usually evident in utero or is diagnosed in infancy; individuals with mosaicism can have milder disease.

## Differential Diagnosis

In the absence of a family history of polycystic kidney disease and/or in the presence of atypical presentations, benign simple cysts and other cystic diseases should be considered in the differential diagnosis. 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, respectively [Rule et al 2012].

Genetic disorders in the differential diagnosis of autosomal dominant polycystic kidney disease (ADPKD) are summarized in Table 5a; acquired conditions in the differential diagnosis are summarized in Table 5b.

**Table 5a.** Genetic Disorders in the Differential Diagnosis of ADPKD

| Gene(s) | Disorder | MOI | Features of Differential Diagnosis | |
|---|---|---|---|---|
| | | | Overlapping w/ADPKD | Distinguishing from ADPKD |
| *ALG8*<br>*GANAB*<br>*LRP5*<br>*PRKCSH*<br>*SEC63*<br>*SEC61B* | Polycystic liver disease [1] (OMIM PS174050) | AD | Liver cysts & occasional kidney cysts | • Predominant phenotype is liver disease w/very mild kidney disease (if present).<br>• Note: *GANAB* pathogenic variants can cause both ADPKD & ADPLD. |
| *COL4A1* | Hereditary angiopathy w/ nephropathy, aneurysms, & muscle cramps (See *COL4A1*-Related Disorders.) | AD | Kidney cysts | • Hematuria; muscle cramps or ↑ CPK; tortuosity of retinal artery; brain small-vessel disease<br>• Presentation w/mild PKD & few other phenotypes has been described. [2] |
| *COL4A3*<br>*COL4A4*<br>*COL4A5* | Alport syndrome | AD<br>AR<br>XL [3] | Kidney cysts | • Thinning of glomerular basement membrane, microhematuria<br>• Occasionally, kidney cysts are part of phenotype. [4] |
| *FLCN* | Birt-Hogg-Dubé syndrome | AD | Kidney cysts | • Hair follicle hamartomas, kidney tumors, spontaneous pneumothorax, lung cysts<br>• *FLCN* pathogenic variant was described in person w/"ADPKD" & lung cysts. [5] |
| *HNF1B* | *HNF1B*-related kidney disease | AD | Cystic kidney disease | • Maturity-onset diabetes of the young, pancreatic disease, ↑ liver enzymes, hypomagnesemia, congenital kidney & urinary tract anomalies<br>• Sometimes, presentation of isolated ADPKD-like phenotype |
| *MUC1* | ADTKD-*MUC1* | AD | Kidney cysts | • Kidney function ↓ w/o ↑ in TKV; no liver cysts<br>• Fibrosis rather than cysts is the major kidney phenotype. |
| *NOTCH2* | Hajdu-Cheney syndrome (OMIM 102500) | AD | Kidney enlargement w/ cortical & medullary cysts | Short stature, midfacial flattening w/proptosis, receding chin, hirsutism, acroosteolysis of terminal phalanges, basilar invagination of skull |

*Table 5a. continued from previous page.*

| Gene(s) | Disorder | MOI | Features of Differential Diagnosis | |
|---|---|---|---|---|
| | | | Overlapping w/ADPKD | Distinguishing from ADPKD |
| *OFD1* | Oral-facial-digital syndrome type 1 | XL | Kidney cysts in affected females | • Hyperplastic frenula, cleft tongue, cleft lip or palate, malpositioned teeth, broad nasal root w/ hypoplasia of nasal alae & malar bone, digital abnormalities<br>• Usually male lethal during gestation |
| *PKHD1* | ARPKD | AR | Bilateral kidney cystic disease | • Majority present in neonatal period.<br>• Pulmonary hypoplasia, early-onset kidney failure, liver fibrosis rather than cysts, TKV ↓ over time (rather than ↑) |
| | Monoallelic *PKHD1* | AD | Kidney &/or liver cysts | • Cyst development in kidney & liver, usually w/o kidney insufficiency or ESKD [6]<br>• Differentiating from the ADPKD spectrum may require genetic testing. |
| *REN* | ADTKD-*REN* | AD | Kidney cysts | Small echogenic kidneys w/interstitial fibrosis, early-onset anemia, & ↑ serum uric acid |
| *SEC61A1* | ADTKD-*SEC61A1* (OMIM 617056) | AD | Kidney cysts | Kidney function ↓ w/o ↑ in TKV; no liver cysts |
| *TSC1*<br>*TSC2* | Tuberous sclerosis complex | AD | Kidney cysts | Kidney angiomyolipomas, skin & brain manifestations, rhabdomyomas, lymphangioleiomyomatosis (See also *PKD1-TSC2* contiguous gene deletion syndrome in Genetically Related Disorders.) |
| *UMOD* | ADTKD-*UMOD* | AD | Kidney cysts | • Kidney function ↓ w/o ↑ in TKV; no liver cysts; gout<br>• Fibrosis rather than cysts is the major kidney phenotype. |
| *VHL* | Von Hippel-Lindau syndrome | AD | Kidney & pancreatic cysts | Hemangioblastomas, pheochromocytoma, neuroendocrine tumors |

AD = autosomal dominant; ADPLD = autosomal dominant polycystic liver disease; ADTKD = autosomal dominant tubulointerstitial kidney disease; AR = autosomal recessive; ARPKD = autosomal recessive polycystic kidney disease; CPK = creatinine phosphokinase; ESKD = end-stage kidney disease; MOI = mode of inheritance; TKV = total kidney volume; XL = X-linked

1. Porath et al [2016], Besse et al [2017], Besse et al [2018]
2. Cornec-Le Gall et al [2018a], Gulati et al [2018], Gulati et al [2019]
3. Alport syndrome caused by pathogenic variants in *COL4A5* is inherited in an X-linked manner; Alport syndrome caused by pathogenic variants in *COL4A3* or *COL4A4* can be inherited in an autosomal recessive or autosomal dominant manner.
4. Gulati et al [2019]
5. Schönauer et al [2020]
6. Gunay-Aygun et al [2011], Besse et al [2017]

**Table 5b.** Acquired Disorders in the Differential Diagnosis of ADPKD

| Disorder | Features Overlapping w/ADPKD | Distinguishing Features |
|---|---|---|
| Localized kidney cystic disease | Histologic appearance strongly resembling advanced ADPKD | Cystic degeneration of portion of 1 kidney, nonprogressive, nonfamilial |
| Acquired kidney cystic disease | Kidney cysts | Cysts develop after ESKD onset. |

ADPKD = autosomal dominant polycystic kidney disease; ESKD = end-stage kidney disease

# Management

Treatment guidelines formulated at the autosomal dominant polycystic kidney disease (ADPKD) KDIGO conference are summarized in Chapman et al [2015].

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with ADPKD, the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 6.** Recommended Evaluations Following Initial Diagnosis in Individuals with ADPKD

| System/Concern | Evaluation [1] | Comment |
|---|---|---|
| **Kidney** | • CT or MRI of abdomen w/ & w/o contrast enhancement<br>• Kidney ultrasound exam (if CT or MRI is unavailable) | To determine severity of disease & provide an estimate of size & distribution of cysts & kidney size<br>• CT & MRI are more sensitive to determine extent of cystic disease in kidneys & liver & estimate prognosis.<br>• CT (but not MRI) can detect stones & parenchymal calcifications.<br>• CT or MRA if visualization of kidney arteries is necessary<br>• MRI suggested when iodinated contrast material is contraindicated |
| | Blood pressure exam to detect hypertension beginning at age 5 yrs | When "white coat" hypertension [2] is suspected, ambulatory blood pressure monitoring is appropriate. |
| | Urine studies for microalbuminuria or proteinuria | In presence of severe cystic kidney disease, microalbuminuria or proteinuria may indicate disease progression & strict blood pressure control is needed. |
| **Hyperlipidemia** | Measurement of blood lipid concentrations | Hyperlipidemia is a correctable risk factor for progressive kidney disease, incl ADPKD. |
| **Cardiac** | Echocardiography | In persons w/murmur or systolic click to assess for valvular heart disease, mitral valve prolapse, or congenital cardiac abnormalities |
| | Echocardiography or cardiac MRI | In persons w/family history of thoracic aortic dissection to assess for aortic dilatation |
| **Intracranial aneurysms** | Head MRA or CT angiography [3] | • In persons w/family history of intracranial aneurysms<br>• Note: Screening for intracranial aneurysms in persons w/o family history of intracranial aneurysms is usually not recommended. [4] |

*Table 6. continued from previous page.*

| System/Concern | Evaluation [1] | Comment |
|---|---|---|
| **Genetic counseling** | By genetics professionals [5] | To inform affected persons & their families re nature, MOI, & implications of ADPKD to facilitate medical & personal decision making |

ADPKD = autosomal dominant polycystic kidney disease; MOI = mode of inheritance; MRA = MR angiography
*1.* Unless otherwise indicated, evaluation should be done at diagnosis in adulthood.
*2.* Blood pressure that is elevated when measured in the clinic, but normal when measured outside of the clinic
*3.* MRA is the diagnostic imaging modality of choice for presymptomatic screening because it is noninvasive and does not require intravenous contrast material. Most intracranial aneurysms found in asymptomatic individuals are small, have a low risk of rupture, and require no treatment [Irazabal et al 2011, Chapman et al 2015, Sanchis et al 2019], although dissenting opinions have been published [Rozenfeld et al 2014].
*4.* Sanchis et al [2019]
*5.* Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

Treatment guidelines formulated at the ADPKD KDIGO conference are summarized in Chapman et al [2015].

Current therapy for ADPKD is aimed at slowing the progression of declining kidney function and reducing morbidity and mortality from the kidney and extra-kidney complications.

### Vasopressin V2 Receptor Antagonists

Studies have shown that a vasopressin V2 receptor antagonist (tolvaptan) can slow the increase in kidney volume, delay decline in kidney function, and preserve estimated glomerular filtration rate (eGFR) [Torres et al 2012, Torres et al 2017b]. Tolvaptan causes elevations in liver enzyme levels in approximately 5% of individuals, which reversed on withdrawal from the medication. Tolvaptan has been approved for clinical use in persons with ADPKD in many parts of the world, including Japan, Canada, Europe, and the US. Various guidelines for administration of tolvaptan have been developed, focusing on selecting individuals with rapidly progressive disease that is likely to result in ESKD [Gansevoort et al 2016, Soroka et al 2017, Chebib et al 2018]. Factors considered for identifying rapidly progressive ADPKD are total kidney volume (TKV)/age, rate of change of TKV, eGFR/age, rate of decline of eGFR, genotype, and family history.

### Hypertension

The blood pressure goal is ≤110/75 mm Hg in those age 18-50 years and eGFR >60 mL/min; otherwise ≤130/85 mm Hg.

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 kidney function. ACE inhibitors and angiotensin II receptor blockers increase kidney blood flow, have a low side effect profile, and may reduce vascular smooth muscle proliferation and development of atherosclerosis.

- The administration of ACE inhibitors, but not the administration of calcium channel blockers, has been shown to reduce microalbuminuria in individuals with ADPKD [Ecder & Schrier 2001].
- In a nonrandomized study, the administration of ACE inhibitors without diuretics resulted in a lower rate of decline in GFR and less proteinuria than the administration of a diuretic without an ACE inhibitor for similar control of blood pressure [Ecder & Schrier 2001]. However, another study found no kidney protective effect of an ACE inhibitor over a beta-blocker [van Dijk et al 2003]; another study found that although more rigorous blood pressure control did not preserve kidney 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 Kidney Disease (MDRD) study that involved protein restriction and low blood pressure targets showed that individuals with ADPKD randomized to the low blood pressure target (mean arterial pressure [MAP] <92 mm Hg) experienced significantly less ESKD and combined ESKD/death than those randomized to the usual blood pressure target (MAP <107 mm Hg) [Sarnak et al 2005].
- The HALT PKD trial did not show a benefit of the addition of an angiotensin II receptor blocker (ARB) to an ACE inhibitor in preservation of kidney function [Torres et al 2014]. However, 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 kidney function was associated with a slower increase in kidney volume but no overall change in the decline in kidney function, as measured by eGFR [Schrier et al 2014].The lower blood pressure target was associated with slower decline of eGFR in the subset of individuals with the most severe ADPKD [Irazabal et al 2017].

## Delaying ESKD

Additional measures to delay ESKD include the following:

- Lipid control to prevent hyperlipidemia with a low threshold to start statin therapy (aim for LDL ≤100 mg/dL)
- Low osmolar intake with moderate sodium (2-3 g/day) and dietary protein restriction (0.8-1 g/kg of ideal body weight). The MDRD trial showed only a slight (borderline significant) beneficial effect of a very low protein diet when introduced at a late stage of kidney disease (GFR: 13-55 mL/min per 1.73 $m^2$).
- Maintenance of urine osmolality at ≤280 mOsm/kg by moderately enhancing hydration spread out over 24 hours (during the day, at bedtime, and at night if waking up)
- Control of acidosis with maintenance of serum bicarbonate at ≥22 mEq/L
- Prevention of hyperphosphatemia by maintaining moderate dietary phosphorus intake (800 mg/day).
- Moderation of caloric intake and low-impact exercise to maintain normal body mass index (BMI). In the CRISP study BMI ≥30 kg/$m^2$ was associated with faster increase in kidney volume and decline in glomerular filtration rate [Nowak et al 2018].

## 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 recommended.

- **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 (NSAIDs).
- **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 kidney 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. Foam sclerotherapy is a safe and effective procedure for kidney volume reduction and amelioration of compressive symptoms in select individuals with ADPKD [Iliuta et al 2019].

In individuals with many cysts contributing to pain, laparoscopic or surgical cyst fenestration through lumbotomy or flank incision, kidney denervation, and (in those who have reached ESKD) 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 kidney function nor preserves remaining kidney 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.
- **Kidney denervation** via a thoracoscopic approach was successful in one affected individual [Chapuis et al 2004], and percutaneous transluminal catheter-based denervation was effective in a small number of individuals [Shetty et al 2013, Casteleijn et al 2014].
- **Laparoscopic and retroperitoneoscopic nephrectomy and arterial embolization** have been used in individuals with ADPKD who have ESKD [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. Simultaneous laparoscopic nephrectomy and kidney transplantation is now possible [Abrol et al 2021].

## Cyst Hemorrhage and Gross Hematuria

Cyst hemorrhage and 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. These individuals require hospitalization, transfusion, and investigation by CT or angiography. In individuals with unusually severe or persistent hemorrhage, segmental arterial embolization can be successful. If not, surgery may be required to control bleeding. Some reports suggest a role for tranexamic acid in the treatment of life-threatening hematuria [Hulme & Wylie 2015].

Gross hematuria persisting for 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 their location 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 for individuals without ADPKD:

- High fluid intake and potassium citrate are the treatment of choice in uric acid lithiasis, hypocitric 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 alkalinization (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 of detecting 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. Nongradient cysts, which are more common, allow solute access via diffusion. However, kinetic studies indicate that water-soluble agents penetrate nongradient cysts slowly and irregularly, resulting in unreliable drug concentrations within the cysts. Lipophilic agents have been shown to penetrate both gradient and nongradient cysts equally and reliably.

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.

## ESKD

Actuarial data indicate that individuals with ADPKD do better on dialysis than individuals with ESKD 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 kidney cyst. Despite kidney 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.

Following transplantation, there is no difference in patient or graft survival between individuals with ADPKD and those with ESKD caused by other conditions, and complications 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 is questionable [Ruderman et al 2012].

Nephrectomy of the native kidneys is reserved for affected individuals with a history of infected cysts, frequent bleeding, severe hypertension, or massive kidney 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 considerations [Lucas et al 2010, Kirkman et al 2011]. Hand-assisted laparoscopic nephrectomy is increasingly being used simultaneously with transplantation [Abrol et al 2021].

## Polycystic Liver Disease

Most individuals with polycystic liver disease (PLD) have no symptoms and require no treatment.

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

Severe symptoms may require percutaneous aspiration and sclerosis, laparoscopic fenestration, combined hepatic resection and cyst fenestration, 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 PLD and is often preferable to liver transplantation, which is reserved for individuals for whom liver resection is not feasible or in whom liver function is impaired [Chebib et al 2016a].
- Because individuals with severe PLD have mostly normal liver function, their MELD (*m*odel for *e*nd-stage *l*iver *d*isease) 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 individuals who are not candidates for surgery [Takei et al 2007].

## Intracranial Aneurysm

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

**Asymptomatic.** Aneurysms measuring ≤5.0 mm 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 >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 appears 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 55-60 mm, replacement of the aorta is indicated. Guidelines for management of thoracic aortic disease have been published [Hiratzka et al 2010]. Management of aortic dissection requires coordinated input from a multidisciplinary team including a cardiologist and cardiothoracic and vascular surgeons.

## Surveillance

Guidance on surveillance is available in Chapman et al [2015].

**Table 7.** Recommended Surveillance for Individuals with ADPKD

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Kidney** | • CT or MRI of abdomen w/ & w/o contrast enhancement<br>• Kidney ultrasound exam (if CT or MRI is unavailable) | Every 1-5 yrs beginning in adulthood, depending on disease stage |
| | Blood pressure exam to detect hypertension | Every 3 yrs beginning at age 5 yrs, in persons w/normal blood pressure |
| | Urine studies for microalbuminuria or proteinuria | Every 1-5 yrs beginning in adulthood, depending on disease stage |
| **Aortic dissection** | Echocardiography or chest MRI | • Every 2-3 yrs in 1st-degree adult relatives of persons w/thoracic aortic dissection<br>• Note: If aortic root dilatation is found, refer to cardiologist. |
| **Cardiac valvular abnormalities** | No surveillance recommended in persons w/o signs/symptoms | |
| **Intracranial aneurysms** | Consider MRA in those w/: [1]<br>• Family history of intracranial aneurysms or subarachnoid hemorrhage;<br>• Previous rupture of aneurysm;<br>• Preparation for elective surgery w/potential hemodynamic instability;<br>• High-risk occupation (e.g., airline pilot);<br>• Significant anxiety despite adequate risk info. | Consider every 10 yrs beginning in adulthood. [2] |
| **Kidney cell carcinoma** | No surveillance recommended in persons w/o concerning signs/symptoms | |

*Table 7. continued from previous page.*

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Colon diverticulosis** | No surveillance recommended in persons w/o concerning signs/symptoms | |

*1.* MRA is the diagnostic imaging modality of choice for presymptomatic screening because it is noninvasive and does not require intravenous contrast material. Most intracranial aneurysms found in asymptomatic individuals are small, have a low risk of rupture, and require no treatment [Irazabal et al 2011, Chapman et al 2015, Sanchis et al 2019], although dissenting opinions have been published [Rozenfeld et al 2014].
*2.* One of 76 individuals with an initial normal MRA study had a new intracranial aneurysm after a mean follow up of 9.8 years [Schrier et al 2004].

## Agents/Circumstances to Avoid

Avoid the following:

- Long-term administration of nephrotoxic agents (e.g., combination analgesics, NSAIDs)
- Caffeine in large amounts. There is no evidence that low or moderate use of caffeinated beverages accelerates the progression of ADPKD.
- High-salt diet, smoking, and obesity
- Use of estrogens and possibly progestogens in individuals with severe polycystic liver disease

## Evaluation of Relatives at Risk

**For early diagnosis and treatment**

- **Asymptomatic at-risk adult relatives.** It is appropriate to clarify the clinical/genetic status of apparently asymptomatic at-risk adult (age ≥18 years) relatives of an affected individual in order to: allow those who are affected to be educated about ADPKD; identify those individuals who would benefit from surveillance and awareness of agents/circumstances to avoid; permit early detection; allow prompt initiation of specific therapy and treatment of associated complications; allow enrollment into clinical trials.

  Evaluations of at-risk relatives include the following:

  - Imaging with abdominal ultrasound, CT, or MRI examination
  - Molecular genetic testing if the ADPKD-causing pathogenic variant in the family is known. (For families with biallelic *PKD1*- or *PKD2*-related ADPKD and families with digenic ADPKD, molecular genetic testing for both familial variants is indicated.)

    Note: For families with a known pathogenic variant, molecular genetic testing may provide clarification if findings on imaging are equivocal.

- **Asymptomatic at-risk relatives younger than age 18 years.** At present, there is no indication for testing of asymptomatic children. This may change in the future, if and when effective therapies for children are developed.

**For kidney donation.** At-risk relatives being considered as kidney donors need to be evaluated to determine if they have ADPKD (see Excluding the Diagnosis):

- Comprehensive kidney image analysis by ultrasound, contrast-enhanced CT, and/or MRI examination (routine imaging for any kidney donor regardless of disease indication). See Table 2.
- If the ADPKD-causing pathogenic variant has been identified in an affected family member, any relative who is a potential kidney donor should undergo molecular genetic testing to clarify the relative's genetic

status so that only those who do not have the familial pathogenic variant are evaluated further. (For families with biallelic *PKD1*- or *PKD2*-related ADPKD and families with digenic ADPKD, molecular genetic testing for both familial variants is indicated.)

Note: If the family-specific ADPKD-causing pathogenic variant is not known, a "negative" molecular genetic test result in a potential donor is uninformative (i.e., the result does not prove that a potential donor does not have ADPKD).

- If the ADPKD-causing pathogenic variant has *not* been identified in an affected family member, evaluation consists of comprehensive kidney image analysis as described above.
- In potential donors with a small number of cysts, comprehensive genetic analysis with a PKD panel may be helpful to exclude pathogenic variants in known PKD-related genes – apart from the familial variant.

Note: Appropriate counseling prior to imaging or molecular testing, including a discussion of possible effects on insurability and employability, is critical.

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. In one study, ADPKD was associated with increased maternal complications during pregnancy but only a slight potential for increased fetal complications [Wu et al 2016].
- Pregnant women who develop hypertension during pregnancy or who have impaired kidney 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 additional likely targets for therapeutic intervention.

**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]. 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 vs the untreated group, but the difference was no longer statistically significant for either organ. A larger (261 affected individuals completed the trial) and longer (2.5 years) randomized study, DIPAK 1, found that although the rate of TKV growth was lower in the lanreotide vs control group, no difference in the annual rate of eGFR decline between the groups was seen [Meijer et al 2018]. Similarly, the ALADIN 2 study (100 affected individuals) showed a reduction in the amount of TKV growth but not a slower decline in GFR in the

octreotide-LAR treated group [Perico et al 2019]. 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]. Studies are ongoing with octreotide in individuals with symptomatic PLD.

**mTOR inhibitors.** The results of clinical trials of mTOR inhibitors for ADPKD have been mostly disappointing. These studies have shown either no effect on TKV or eGFR [Serra et al 2010], an association with a slower rate of increase in TKV but a faster rate of decline in eGFR [Walz et al 2010], or a faster decline in GFR and increase in TKV [Ruggenenti et al 2016]. Clinical trials of mTOR inhibitors have also been accompanied by significant drug toxicity [Serra et al 2010, Walz et al 2010, Ruggenenti et al 2016]. Because the intended dosage was limited by toxicity of the drug, the blood levels achieved may not have been enough to effectively inhibit mTOR activity in the kidney [Canaud et al 2010].

**Tyrosine kinase inhibitors.** A Phase II clinical trial of the Src inhibitor bosutinib showed a slower rate of increase in TKV and no difference in decline in eGFR in the treated group [Tesar et al 2017]. However, there was a high level of dropout from the study with significant adverse events, especially with a higher dose of the compound.

**Nuclear factor erythroid 2-related factor 2 (Nrf2) activator**. A Phase III clinical trial is under way with bardoxolone methyl (BARD), an activator of Nrf2. Activation of Nrf2 decreases oxidative stress and has been shown to be of value in CKD.

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

# Genetic Counseling

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

## Mode of Inheritance

In most affected families, autosomal dominant polycystic kidney disease (ADPKD) is caused by a heterozygous *PKD1* or *PKD2* pathogenic variant and inherited in an autosomal dominant manner. More rarely, ADPKD is caused by a heterozygous pathogenic variant in *ALG5*, *ALG9*, *DNAJB11*, *GANAB*, or *IFT140*.

Complex inheritance may play a role in a minority of individuals [Rossetti et al 2009, Cornec-Le Gall et al 2018b, Hopp et al 2020] and is important when considering the risk to other family members (see Genotype-Phenotype Correlations).

- **Biallelic *PKD1*- or *PKD2*-related ADPKD.** Rarely, ADPKD caused by biallelic *PKD1* or *PKD2* pathogenic variants – with at least one or both of the causative variants being hypomorphic – has been reported. In these families, the risk to individuals of inheriting the polycystic kidney disease phenotype depends on the specific variants segregating in the families.
- **Digenic ADPKD** has been observed in individuals with pathogenic variants in both *PKD1* and *PKD2* [Pei et al 2001], suggested in individuals with early-onset polycystic kidney disease and a heterozygous pathogenic variant in *PKD1* or *PKD2* and another gene, and demonstrated in animal models [Bergmann et al 2011, Fedeles et al 2011, Cornec-Le Gall et al 2018a, Olson et al 2019].

## Risk to Family Members (Autosomal Dominant Inheritance)

**Parents of a proband**

- Most individuals diagnosed with ADPKD have an affected parent.
- 10%-20% of individuals diagnosed with ADPKD have the disorder as the result of a *de novo* pathogenic variant [Iliuta et al 2017].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant (i.e., the proband is the only family member known to have ADPKD) include screening by imaging methods (especially by MRI or CT examination in families where the kidney manifestations are mild) and/or molecular genetic testing of both parents if the pathogenic variant in the proband is known.
- If the proband has a known pathogenic variant that is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant.
    - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism.* Parental mosaicism is thought to occur in approximately 0.25% of families with ADPKD [Hopp et al 2020]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

      * A parent with somatic and germline mosaicism for an ADPKD-causing pathogenic variant may be mildly/minimally affected (see Clinical Description, Mosaicism).
- 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 if the family-specific pathogenic variant is known) have been performed on the parents of the proband.

**Sibs of a proband.** The risk to sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to sibs of inheriting the pathogenic variant is 50%. Substantial variability in severity of kidney disease and other manifestations may be observed between family members with the same pathogenic variant (see Penetrance).
- If the proband has a known ADPKD-causing pathogenic variant that is not detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental mosaicism [Hopp et al 2020].
- If the genetic status of the parents is unknown but kidney image analysis suggests that the parents are unaffected, the recurrence risk to sibs is greater than that of the general population because of the possibility of later onset of disease in a heterozygous parent or parental mosaicism. Parental mosaicism has been reported (see Clinical Description, Mosaicism).

**Offspring of a proband.** Each child of an individual who is heterozygous for an ADPKD-causing pathogenic variant has a 50% chance of inheriting the pathogenic variant.

**Other family members.** The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected and/or has an ADPKD-causing pathogenic variant, the parent's family members may be at risk.

## Related Genetic Counseling Issues

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

**Predictive testing (i.e., testing of asymptomatic at-risk individuals)**

- **Predictive genetic testing** for at-risk asymptomatic family members requires prior identification of the ADPKD-causing pathogenic variant in the family. Such testing is helpful in predicting the future development of kidney disease and should be performed if the family member is considering becoming a kidney donor.

  Note: If the family-specific ADPKD-causing pathogenic variant is not known, a "negative" molecular genetic test result in an asymptomatic family member is uninformative (i.e., the result does exclude the possibility that the family member has ADPKD).

- Predictive testing of at-risk asymptomatic family members can also be performed by kidney imaging via ultrasound, CT, or MRI. This is usually informative in older family members or by age 18 years if the disease is severe but may not be informative in families with milder disease, especially in younger individuals (see Excluding the Diagnosis).

- Potential consequences of such testing (including, but not limited to, socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

**Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals age <18 years)**

- For asymptomatic minors at risk for adult-onset conditions for which early treatment is not available, predictive genetic testing is considered inappropriate, 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 for discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see 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.

It is appropriate to consider testing of symptomatic individuals with PKD, including suspected ADPKD, regardless of age or family history.

**Family planning**

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

**DNA banking.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from

probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). Banking of DNA from individuals with atypical presentation (e.g., lethal in utero onset) is particularly valuable for understanding the disease etiology and offering family planning options. For more information, see Huang et al [2022].

## Prenatal Testing and Preimplantation Genetic Testing

Once the ADPKD-causing pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful. For more information, see the National Society of Genetic Counselors position statement on prenatal testing in adult-onset conditions.

# 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.*

- **MedlinePlus**
  Polycystic kidney disease
- **PKD Foundation**
  **Phone:** 816-931-2600
  **Email:** pkdcure@pkdcure.org
  www.pkdcure.org
- **Polycystic Kidney Disease Charity**
  United Kingdom
  **Phone:** 0300 111 1234
  **Email:** info@pkdcharity.org.uk
  www.pkdcharity.org.uk
- **Ciliopathy Alliance**
  United Kingdom
  ciliopathyalliance.org
- **ERKNet: The European Rare Kidney Disease Reference Network**
  **Phone:** 49 0 6221 56-34191
  **Email:** contact@erknet.org
  erknet.org
- **Kidney Foundation of Canada**
  Canada
  **Phone:** 514-369-4806
  **Email:** info@kidney.ca
  kidney.ca
- **National Kidney Foundation**
  **Phone:** 855-NKF-CARES; 855-653-2273
  **Email:** nkfcares@kidney.org

kidney.org

# Molecular Genetics

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

**Table A.** Polycystic Kidney Disease, Autosomal Dominant: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *ALG5* | 13q13.3 | Dolichyl-phosphate beta-glucosyltransferase | | ALG5 | ALG5 |
| *ALG9* | 11q23.1 | Alpha-1,2-mannosyltransferase ALG9 | ALG9 database | ALG9 | ALG9 |
| *DNAJB11* | 3q27.3 | DnaJ homolog subfamily B member 11 | | DNAJB11 | DNAJB11 |
| *GANAB* | 11q12.3 | Neutral alpha-glucosidase AB | | GANAB | GANAB |
| *IFT140* | 16p13.3 | Intraflagellar transport protein 140 homolog | IFT140 @ LOVD | IFT140 | IFT140 |
| *PKD1* | 16p13.3 | Polycystin-1 | ADPKD Mutation Database (PKD1) | PKD1 | PKD1 |
| *PKD2* | 4q22.1 | Polycystin-2 | ADPKD Mutation Database (PKD2) | PKD2 | PKD2 |

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

**Table B.** OMIM Entries for Polycystic Kidney Disease, Autosomal Dominant (View All in OMIM)

| | |
|---|---|
| 104160 | GLUCOSIDASE, ALPHA, NEUTRAL AB; GANAB |
| 173900 | POLYCYSTIC KIDNEY DISEASE 1 WITH OR WITHOUT POLYCYSTIC LIVER DISEASE; PKD1 |
| 173910 | POLYCYSTIN 2; PKD2 |
| 600666 | POLYCYSTIC KIDNEY DISEASE 3 WITH OR WITHOUT POLYCYSTIC LIVER DISEASE; PKD3 |
| 601313 | POLYCYSTIN 1; PKD1 |
| 604565 | ALG5 DOLICHYL-PHOSPHATE BETA-GLUCOSYLTRANSFERASE; ALG5 |
| 606941 | ALG9 ALPHA-1,2-MANNOSYLTRANSFERASE; ALG9 |
| 611341 | DNAJ/HSP40 HOMOLOG, SUBFAMILY B, MEMBER 11; DNAJB11 |
| 613095 | POLYCYSTIC KIDNEY DISEASE 2 WITH OR WITHOUT POLYCYSTIC LIVER DISEASE; PKD2 |
| 614620 | INTRAFLAGELLAR TRANSPORT 140; IFT140 |
| 618061 | POLYCYSTIC KIDNEY DISEASE 6 WITH OR WITHOUT POLYCYSTIC LIVER DISEASE; PKD6 |
| 620056 | POLYCYSTIC KIDNEY DISEASE 7; PKD7 |

## Molecular Pathogenesis

There is good evidence that polycystin-1 (PC1) and polycystin-2 (PC2) interact to form a functional polycystin complex with a cryo-EM structure consisting of 3x PC2 and 1x PC1 now available [Su et al 2018]. 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 polycystic

kidney disease (PKD), PC1 and PC2 are localized to primary cilia [Pazour et al 2002, Yoder et al 2002, Liu et al 2018]; PKD is a ciliopathy [Hildebrandt et al 2011], with loss of cilia associated with PKD [Lin et al 2003].

The cilium is known to be essential for a number of signaling pathways (e.g., sonic hedgehog and possibly planar cell polarity) that likely play a role in some ciliopathy phenotypes. Proteins causative of syndromic forms of PKD (e.g., Meckel syndrome, Joubert syndrome), 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, Yang et al 2015].

However, the precise role of the polycystin complex with respect to the cilium is controversial. It is likely that polycystins have a sensory/mechano-sensory/receptor role [Ong & Harris 2015], with changes in fluid flow within the tubule [Nauli et al 2003], binding of Wnt ligands [Kim et al 2016], or activation via the N-terminal region of PC1 [Ha et al 2020] possibly regulating the complex. Evidence that inactivation of polycystins in combination with loss of cilia results in a milder cystic phenotype than polycystin loss alone has been interpreted as the polycystin complex regulating a ciliary pathway that promotes cystogenesis [Ma et al 2013]. Key downstream signaling from the polycystin complex is also controversial, with $Ca^{2+}$, cAMP, and G-protein signaling all considered important [Torres & Harris 2014, Chebib et al 2015, Hama & Park 2016, Lemos & Ehrlich 2018]. Recent data have shown that reexpressing *Pkd1* or *Pkd2* from a transgene after the endogenous locus has been inactivated and cytogenesis has begun can reverse the cystic disease [Dong et al 2021].

Another location of polycystins and ARPKD protein (fibrocystin) is in urinary vesicles [Hogan et al 2009, Bakeberg et al 2011], where the secreted protein may play a signaling role in the nephron. The localization of polycystins to other phenotypic sites (e.g., the vascular system) indicates that reductions in the level of these proteins underlie disease complications such as intracranial aneurysms [Kim et al 2000].

*GANAB* encodes glucosidase II alpha, a protein that plays a role in trimming the glycans of glycosylated proteins, and as part of the calnexin/calreticulin cycle, contributes to quality control of membrane and secreted proteins [Xu & Ng 2015]. *DNAJB11* encodes the DNAJ/HSP40 homolog, subfamily B, member 11 (DNAJB11). It is a soluble ER protein that is a co-chaperone with binding immunoglobulin protein, which is required for the efficient folding of membrane and secreted proteins [Shen et al 2002, Shen & Hendershot 2005]. ALG9 is an alpha-1,2-mannosyltransferase and is involved in the glycosylation, folding, and trafficking of membrane and secreted proteins. ALG5 is a dolichyl phosphate glucosyltransferase; reduction of ALG5 disrupts N-glycosylation and affects PC1 maturation and localization. The development of liver and kidney cysts is a common phenotype associated with disruptions in the biogenesis pathway of membrane proteins and is likely perpetrated through disrupted PC1 trafficking [Fedeles et al 2011]. Studies of PC1 have shown that its maturation and trafficking are particularly sensitive to loss of DNAJB11, glucosidase II alpha, alpha-1,2-mannosyltransferase, and dolichyl phosphate glucosyltransferase [Porath et al 2016, Besse et al 2017, Cornec-Le Gall et al 2018b, Besse et al 2019, Lemoine et al 2022].

**Mechanism of disease causation.** Truncating variants likely cause autosomal dominant polycystic kidney disease through loss of function. However, there is increasing evidence that some hypomorphic nontruncating *PKD1* pathogenic variants have a folding/trafficking defect of PC1 [Hopp et al 2012, Cai et al 2014, Gainullin et al 2015].

**Gene-specific laboratory technical considerations.** The genomic region encoding *PKD1* has undergone a complex segmental duplication; six copies of the 5' three quarters of the gene are present as pseudogenes elsewhere on chromosome 16 [Symmons et al 2008].

**Table 9.** Notable *PKD1* Pathogenic Variants

| Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | Comment |
|---|---|---|---|
| NM_001009944.3<br>NP_001009944.3 | c.9829C>T | p.Arg3277Cys | Hypomorphic allele (See Genotype-Phenotype Correlations.) |

ADPKD = autosomal dominant polycystic kidney disease
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

# Chapter Notes

## Author Notes

Peter C Harris's web page

Vicente E Torres's web page

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- 29 September 2022 (sw) Comprehensive update posted live
- 19 July 2018 (sw) Comprehensive update posted live
- 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
- 6 June 2006 (me) Comprehensive update posted live
- 5 March 2004 (me) Comprehensive update posted live
- 10 January 2002 (me) Review posted live
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