Diagnosis and Screening of Autosomal Dominant Polycystic Kidney Disease

York Pei and Terry Watnick*

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cause of kidney failure and accounts for ~5% of ESRD population in the United States. The disorder is characterized by the focal and sporadic development of renal cysts, which increase in size and number with age. Mutations of PKD1 and PKD2 account for most of the cases. Although the clinical manifestations of both gene types overlap completely, PKD1 is associated with more severe disease than PKD2, with larger kidneys and earlier onset of ESRD. In general, renal ultrasonography is commonly used for the diagnosis of ADPKD, and age-dependent criteria have been defined for subjects at risk of PKD1. However, the utility of the PKD1 ultrasound criteria in the clinic setting is unclear because their performance characteristics have not been defined for the milder PKD2 and the gene type for most test subjects is unknown. Recently, highly predictive ultrasound diagnostic criteria have been derived for at-risk subjects of unknown gene type. Additionally, both DNA linkage or gene-based direct sequencing are now available for the diagnosis of ADPKD, especially in subjects with equivocal imaging results, subjects with a negative or indeterminate family history, or in younger at-risk individuals being evaluated as potential living-related kidney donors. Here, we review the clinical utilities and limitations of both imaging- and molecular-based diagnostic tests and outline our approach for the evaluation of individuals suspected to have ADPKD.

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Key Words: Autosomal dominant polycystic kidney disease, Autosomal dominant polycystic kidney disease, Diagnosis, Screening, Genetic testing

Autosomal dominant polycystic kidney disease (ADPKD [MIM #173900]) is the most common form of monogenic, inherited kidney disease worldwide and affects 1 in 500 to 1,000 births.1-3 The disorder is characterized by age-dependent development and progressive enlargement of renal cysts resulting in chronic renal failure typically in mid to late adulthood. Early in life, individuals with ADPKD may not have detectable renal cysts by conventional imaging techniques. Later in life, however, the diagnosis is usually straightforward. In the setting of a positive family history, the hallmark radiographic findings of ADPKD are bilaterally enlarged kidneys with numerous cysts, which are frequently accompanied by liver cysts. There are, however, emerging indications for the early identification of individuals affected by ADPKD. This review explores strategies for presymptomatic diagnosis and their application in the care and management of individuals at risk for ADPKD.

Genetics of ADPKD: PKD1 Versus PKD2

Genetic studies have indicated that most if not all cases of ADPKD are caused by mutations in 2 genes. It is estimated that about 85% of affected individuals from linkage-characterized European families have mutations in the PKD1 gene (on chromosome 16p13.3), whereas 15% have PKD2 gene mutations (on chromosome 4q21).4-6 Two recent studies from Toronto, Canada, and Rochester,
MN, have documented a higher prevalence for PKD2 of 26% and 36%, respectively, suggesting that it may have been underdetected before the age of widespread imaging. A small fraction (~1%) of all ADPKD families is not linked to either of the known gene loci, suggesting that there may be at least 1 more disease gene. However, confirmation of a disease locus in these families has been lacking, and the disease in 1 such family was found to result from 2 independently segregating PKD1 and PKD2 mutations. Thus, the existence of a third gene for ADPKD is questionable at the present time.

As the name implies, ADPKD is inherited in an autosomal dominant fashion. Practically, this means that each affected individual carries only 1 copy of a mutant PKD gene, and the risk of passing that gene on to an offspring at birth is on average 50%. Although every cell in the body of an affected individual carries a PKD mutation, cyst formation is a focal process involving a small subset of cells. In a large proportion of cysts, there is evidence that somatic mutation results in loss of the wild-type PKD gene. This suggests that the decline of effective polycystin signaling below a critical threshold may lead to a series of cellular derangements that promote cyst formation.

As discussed in more detail elsewhere in this issue, the PKD1 protein product, polycystin-1 (PC1), is a large protein of unknown function that physically interacts with the PKD2 protein, polycystin-2 (PC2), which functions as a nonspecific cation channel. Recent studies suggest that the polycystin complex resides in the primary cilium of renal tubular cells in which it is thought to regulate intracellular calcium levels in response to external stimuli. Not surprisingly, mutations of either PKD1 or PKD2 result in an identical clinical profile including extrarenal cysts (eg, liver, pancreas, and spleen), hernias, cardiac valvular abnormalities, and intracranial aneurysms.

The main distinction between individuals with PKD1 versus PKD2 mutations is that the latter is associated with less severe disease. Studies comparing the 2 groups of patients have shown that as a group individuals with PKD2 mutations have a milder phenotype by every criterion including later age at diagnosis, decreased prevalence of hypertension, and delayed onset of ESRD (median age: ~54 vs ~74). This reflects a lower cyst burden in PKD2 as shown by the Consortium of Radiological Imaging Study of PKD, which provided serial observations of total renal and cystic volumes by magnetic resonance imaging (MRI) in 156 PKD1 and 27 PKD2 patients over a 3-year period. At any given age, both the cyst number and the total kidney volume were significantly lower in the PKD2 cohort when compared with their PKD1 counterparts.

These marked differences in disease severity between PKD1 and PKD2 have practical implications for diagnosis because imaging modalities may have a higher rate of false-negative results in younger individuals from PKD2 families. Conversely, patients with PKD1 have a higher probability of being clinically diagnosed after 20 years of age. As a result, the differences in pretest probability of disease between the 2 gene types need to be adjusted accordingly to ensure proper evaluation of the performance characteristics of any imaging-based diagnostic test for ADPKD (Fig 1).

One question that is frequently asked is whether a family history of renal disease severity can be used to predict the ADPKD gene type (PKD1 vs PKD2). Barua and colleagues addressed this issue in a cohort of 481 affected individuals from 67 PKD1 and 23 PKD2 families. Despite significant variability in disease severity within individual families, the authors were able to devise predictive guidelines by focusing on cases in which ESRD developed very late or very early. They found that the presence of “at least 1 family member who developed ESRD at or before 55 years of age” was highly predictive of PKD1 (positive predictive value [PPV] = 100%, sensitivity [SEN] = 72%). Similarly, having “at least 1 family member with ESRD at or after 70 years of age” was highly predictive of PKD2 (positive predictive value = 100%, sensitivity = 72%). Thus, a detailed family history of renal disease severity in ADPKD may yield important prognostic information in over 70% of cases.

Distinguishing ADPKD From Other Cystic Diseases

In a majority of cases, establishing a diagnosis of ADPKD is uncomplicated. The typical
Patient presents with enlarged cystic kidneys in the setting of a positive family history. Accompanying clinical manifestations may include extrarenal cysts in organs such as the liver, pancreas or spleen, inguinal hernias, or intracranial aneurysms. In some cases, however, confounding aspects of a case may prompt the clinician to consider alternate diagnoses. In general, renal cysts can be a manifestation of both hereditary and acquired disorders other than ADPKD (Table 1). A careful review of the history, clinical, and radiologic investigations may reveal clinical features of these disorders that are atypical of ADPKD. We discuss several of these scenarios later.

Although ADPKD is primarily a disease of adulthood, there are rare instances of severe disease presenting in infancy or early childhood.\textsuperscript{13,24} In some cases, this may be caused by a contiguous gene syndrome involving a chromosomal deletion of both PKD1 and TSC2 (tuberous sclerosis) genes, which are located in close proximity on chromosome 16p13.3.\textsuperscript{25,26} Patients with this syndrome may present during infancy with rapid progression to ESRD. The absence of a family history is common in individuals with this type of mutation because their parents are somatic mosaics, whereas other cases represent de novo mutations. Clinical features suggestive of tuberous sclerosis complex (MIM #19100) such as angiomyolipomas or characteristic skin lesions may be absent in 30% of cases, however, leading to a misdiagnosis of this syndrome as ADPKD.\textsuperscript{26,27} In other instances, especially when an early-onset case occurs in the context of a family with typical ADPKD, adverse genetic and/or environmental modifiers are presumed to underpin the renal disease severity.

Isolated autosomal dominant polycystic liver disease (PCLD [MIM174050]), which is discussed in another article in this issue, may also be mistaken for mild ADPKD.\textsuperscript{28,29} PCLD is caused by mutations in a set of genes that are distinct from PKD1 and PKD2.\textsuperscript{30-32} In its classic form, one can distinguish PCLD by liver cysts in the absence of cystic kidney disease. However, on occasion, these patients may have a few renal cysts prompting the clinician to consider a diagnosis of ADPKD, but as a general rule these individuals have predominantly polycystic liver disease and do not develop ESRD.

Occasionally, ADPKD can be confused with autosomal recessive polycystic kidney disease (ARPKD [MIM263200]), which is caused by mutations in the fibrocystin/polyductin gene on chromosome 6.\textsuperscript{33,34} Individuals with ARPKD usually present in the neonatal period with enlarged, echogenic kidneys. With the advent of molecular diagnosis, however, adult

![Figure 1](Image)

**Figure 1.** The pretest probability of disease decreases with age in subjects born with a 50% risk of ADPKD and differs between PKD1 and PKD2. (A) The prevalence of PKD1 (solid color) and PKD2 (strip color) is assumed to be 85% and 15%, respectively. At birth, the proportion of affected but clinically undiagnosed subjects (green color) is equal to that of at-risk but unaffected subjects (blue color). With increasing age, the proportion of affected but clinically undiagnosed subjects (green color) diminishes as an increasing proportion of the affected subjects are clinically diagnosed (yellow color). However, a higher proportion of the more severely affected PKD1 subjects will be clinically diagnosed (solid yellow color) compared with affected PKD2 subjects (strip yellow color). (B) The pretest probability of disease among subjects born with 50% risk for PKD1 (circle) and PKD2 (diamond) diverges with increasing age (adapted with permission from Pei Y\textsuperscript{50}).
Table 1. Differential Diagnosis of ADPKD

<table>
<thead>
<tr>
<th>Cystic Disorder</th>
<th>Prevalence</th>
<th>Inheritance</th>
<th>Distinguishing Renal Findings</th>
<th>Distinguishing Extrarenal Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycystic liver disease</td>
<td>Unknown</td>
<td>AD</td>
<td>Small number of renal cysts</td>
<td>Predominantly liver cystic disease</td>
</tr>
<tr>
<td>Autosomal recessive polycystic kidney</td>
<td>~1:20,000-</td>
<td>AR</td>
<td>Early in life kidneys cystic, enlarged, and echogenic. With increasing age, kidneys are smaller with macroscopic cysts, nephrocalcinosis, and/or small medullary calcifications common.</td>
<td>Oligohydramnios and pulmonary hypoplasia in utero, congenital hepatic fibrosis, Caroli disease</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>~1:10,000</td>
<td>AD</td>
<td>Angiomyolipoma, contiguous deletion of PKD1/TSC2 results in severe early onset PKD with ESRD typically occurring in the first 2 decades of life</td>
<td>Skin lesions (facial angiofibromas, perungal fibroma, hypomelanotic macules, and Shagreen patch), retinal hamartomas, seizures, mental retardation, cortical tuber, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis</td>
</tr>
<tr>
<td>Von Hippel-Lindau</td>
<td>~1:50,000</td>
<td>AD</td>
<td>High risk of renal cell carcinomas</td>
<td>Central nervous system and retinal hemangioblastomas, pancreatic cysts, pancreatic endocrine tumors, pheochromocytoma</td>
</tr>
<tr>
<td>Orofaciodigital syndrome I</td>
<td>Very rare</td>
<td>X-linked, dominant</td>
<td></td>
<td>Embryonic male lethal, cleft palate, bifid tongue, hyperplastic frenula, hypertelorism, broadened nasal ridge, digital abnormalities including syndactyly, central nervous system malformations</td>
</tr>
<tr>
<td>Glomerulocystic disease</td>
<td>Rare</td>
<td>AD</td>
<td>Heterogeneous phenotypes: ultrasound may show hyperechogenic kidneys, renal hypoplasia/dysplasia, oligomeganephronia, multiple renal cysts, or glomerulocystic disease.</td>
<td>Mutations in the gene encoding HNF1-β, maturity-onset diabetes of the young; genital tract abnormalities such as epididymal cysts, atresia of vas deferens, and bicornuate uterus</td>
</tr>
<tr>
<td>Medullary cystic kidney disease</td>
<td>Unknown</td>
<td>AD</td>
<td>Interstitial fibrosis on renal biopsy. Rarely cysts in the corticomedullary junction; slowly progressive renal failure; small to normal size kidneys.</td>
<td>Hyperuricemia, gout</td>
</tr>
<tr>
<td>Simple renal cysts</td>
<td>Common</td>
<td>None acquired</td>
<td>Number increases with age. Normal renal function; normal sized kidneys with smooth contour.</td>
<td>None</td>
</tr>
<tr>
<td>Acquired renal cystic disease</td>
<td>Common</td>
<td>None acquired</td>
<td>Associated with chronic renal insufficiency or ESRD. Multiple renal cysts associated with small to normal sized kidneys.</td>
<td>None</td>
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AD, autosomal dominant; AR, autosomal recessive.
forms of ARPKD have been described. These cases may be confused with ADPKD by virtue of their demographic characteristics (ie, onset in adulthood). In addition to the absence of a family history, distinguishing features of older individuals with ARPKD include small kidneys with a few macrocysts and prominent hepatic disease characterized by congenital hepatic fibrosis and/or Caroli disease rather than liver cystic disease.

Autosomal dominant medullary cystic kidney disease (MCKD, [MIM #603860]) is another disorder that may present in adulthood with renal dysfunction and occasionally renal cysts. MCKD is caused by mutations in the uroromodulin gene (encoding Tamm-Horsfall protein) on chromosome 16. A second locus for MCKD on chromosome 1 has also been reported. In contrast to ADPKD, MCKD is characterized by tubular interstitial fibrosis with normal- to small-sized kidneys usually accompanied by early hyperuricemia and gout. Medullary cysts may be detected in some individuals late in the course of disease but are frequently absent.

There are several additional syndromic inherited disorders that may present with renal cystic disease including Von Hippel-Lindau (MIM #19330) syndrome, orofaciiodigital syndrome I (MIM #311200), and glomerulocystic disease (MIM #137920) (Table 1). In each case, however, the spectrum of associated clinical findings is unique and distinguishes the disorder from ADPKD.

Although ADPKD is an inherited disease, it is not uncommon for individuals with the classic clinical findings of this disorder to report that they know of no other affected family members. Although one might consider alternative diagnoses, several series have suggested that a significant percentage of affected individuals in fact lack a family history. This may be because of the presence of a de novo mutation (estimated to occur in <10% of cases) or alternatively a failure to diagnose cystic kidney disease in mildly affected family members. This is probably more common in the case of PKD2 families who tend to exhibit a milder disease process. A review of parental imaging studies or autopsy reports, if available, may be helpful in establishing a family history.

Simple renal cysts and acquired renal cystic disease are noninherited forms of cystic kidney disease that may also be seen in adults. Simple renal cysts increase in frequency with age and are detected quite commonly with sensitive imaging methods such as computed tomography (CT) scans or MRI. For example, in 1 MRI-based series, ~11% of individuals 18 to 29 years of age, ~51% subjects 30 to 44 years of age, and ~93% of subjects 45 to 59 years of age had at least 1 renal cyst. This supports the assumption that the extrapolation of ultrasound-based criteria (see later) to MRI is likely to result in false-positive diagnoses. Acquired renal cystic disease is typically detected in individuals with longstanding kidney disease and can be found in up to 20% of patients with ESRD. Although patients with acquired cystic disease have multiple and bilateral renal cysts, kidney size is usually normal or small. This is in contrast to individuals with ESRD in the setting of ADPKD whose kidneys tend to be large.

Can ADPKD Be Detected Using Standard Imaging Techniques?

Ultrasound is the most commonly used imaging modality for screening individuals at risk for ADPKD. This is based on its safety and modest cost in comparison with CT scans and MRI. In most moderate to advanced cases, ultrasound easily detects the classic finding of ADPKD including multiple, bilateral renal cysts and liver cysts. In younger patients with early-stage PKD, however, the diagnosis may not be obvious because smaller cysts are more likely to escape sonographic detection, especially for patients with milder PKD2 (Fig 2).

Studies published in the 1990s by Ravine and colleagues established age-graded ultrasound criteria for PKD1. The basic principle, given that sporadic cysts occur more frequently with age, was that more cysts were required to make a diagnosis of ADPKD in older individuals. Thus, the presence of “2 unilateral or bilateral cysts” was sufficient to confirm the diagnosis in at-risk subjects between 15 and 29 years old, but at least “2 cysts per kidney” and “4 cysts per kidney” were required for diagnosis of at-risk subjects aged
30 to 59 years and 60 years of age or older, respectively. Although these criteria were designed to be used in individuals at risk for PKD1, in practice many clinicians have extrapolated them to all at-risk subjects, regardless of their underlying gene type. The concern here is that because PKD2 is typically less severe these criteria might not perform as well. Thus, there is a need for highly predictive criteria that can be applied to either ADPKD gene type.

To address this issue, Pei and colleagues recently completed a multicenter study of 577 individuals from 58 PKD1 families and 371 individuals from 39 PKD2 families who underwent ultrasound screening. In addition, the authors used either DNA linkage or mutation analysis to determine the gene type and disease status of each study subject. The performance characteristics of various criteria were re-examined for individuals from both PKD1 and PKD2 families (Table 2). As expected, the Ravine criteria resulted in a higher rate of false-negative results when applied to individuals at risk for PKD2. Surprisingly, even though incidental simple renal cysts were thought to be vanishingly rare in young individuals, they found that 2.1% of the genetically unaffected population younger than 30 years of age had 1 to 2 renal cysts. These latter findings suggested that a more stringent criterion might be advantageous in this group of patients.

The authors also analyzed the performance characteristics of different ultrasound criteria in at-risk individuals of unknown gene type using a statistical resampling method termed “bootstrapping” to simulate the PKD1 and PKD2 case mix (ie, PKD1:PKD2 = 85:15). The recommended criteria are summarized in Table 2. Specifically, for at-risk individuals 15 to 39 years of age, the presence of “3 or more unilateral or bilateral renal cysts” was associated with a PPV of 100% but an SEN of 81.7% and 95.5% for the 15- to 29- and 30- to 39-age groups, respectively. For at-risk individuals aged 40 to 59 years, the presence of “at least 2 cysts in each kidney” was associated with a PPV of 100% and an SEN of 90%. Finally, for at-risk individuals 60 years or older, the presence of “at least 4 cysts in each kidney” had a PPV and an SEN of 100%.

Similarly, the investigators examined ultrasound diagnostic criteria for disease exclusion, an issue of importance for evaluating potential living-related kidney donors who are at risk for ADPKD (Table 3). Their study confirmed the limited ability of ultrasound to rule out disease in at-risk subjects less than 30 years of age with an unknown gene type.
in whom the negative predictive value (NPV) associated with no renal cysts was 90.8% (in other words, 10% of at-risk subjects with a negative ultrasound in this age group have ADPKD). The utility of ultrasound for disease exclusion improved with age such that the NPV associated with no renal cysts increased to 98.3% in at-risk subjects of unknown gene type aged 30 to 39 years. The NPVs varied between the 2 gene types but were higher in subjects at risk for PKD1 versus PKD2.

In those younger individuals in whom ultrasound might yield equivocal or indeterminate results, a negative CT scan or MRI may provide further assurance that they are unaffected, but it must be noted that this approach has not been validated by any systematic study. It would be inappropriate to extrapolate ultrasound criteria to CT scans or MRI because more simple cysts may be detected by these modalities as a result of their enhanced detection sensitivity. Future studies are needed to validate the use of these more sensitive imaging modalities in the younger subjects at risk of ADPKD.

**DNA Testing in ADPKD**

One take-home message is that there will always be equivocal cases in which a clinical diagnosis of ADPKD cannot be established with certainty on the basis of imaging. In these cases, DNA-based diagnostic strategies can be considered depending on the clinical situation.49-51

There are 2 methods for ADPKD DNA testing, which are both available on a fee-for-service basis: linkage analysis and direct mutation screening. In both cases, blood is collected and sent to a clinical laboratory where DNA is extracted from peripheral white blood cells for analysis. The most up-to-date information about which laboratories are currently providing DNA diagnosis for ADPKD can be obtained from GeneTests (www.genetests.org), a valuable Web-based resource that is

<table>
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<tr>
<th>Table 2. Ultrasound Criteria for the Diagnosis of ADPKD</th>
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<td>Age</td>
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<td>15-30</td>
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<td>40-59</td>
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For 95% confident intervals, please refer to the text.
Data from Pei et al.48

*Unilateral or bilateral.

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<tr>
<th>Table 3. Ultrasound Criteria for the Exclusion of ADPKD</th>
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<td>Age</td>
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<td>15-30</td>
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<td>40-59</td>
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For 95% confident intervals, please refer to the text.
Abbreviation: SPEC, specificity.
Data from Pei et al.48
funded by the National Institutes of Health. The Web site provides a comprehensive list of academic and commercial facilities in the United States and abroad that offer testing on either a clinical or research basis. The 2 methods of DNA analysis are reviewed and the limitations discussed.

In linkage analysis, the segregation of chromosomal markers flanking the disease gene is examined and compared within a family in whom the clinical status (ie, affected or unaffected) of each individual is known. By examining several markers, a haplotype (or a pattern of marker genotypes on the same chromosome) that segregates with the disease can be determined. This haplotype is then compared with that of the individual seeking testing, and the probability of having the disease is assessed. The calculated genetic risk is weighted by the prior probability that his/her disease is linked to the locus being examined (eg, 85% for PKD1 or 15% for PKD2). Linkage to both PKD1 and PKD2 must be assayed to fully understand the test results. The major advantage of this approach is that when a large family with multiple affected members (preferably 4 or more) is available, it is almost always possible to determine if the at-risk subject is an obligate carrier without the need to identify the pathogenic mutation (Fig 3).

There are several limitations to linkage testing; the most important is that no information can be obtained from testing the proband alone. A rough rule of thumb is that a minimum of 3 affected family members in 2 generations are required, but additional affected and unaffected family members can strengthen the accuracy with which the disease-related haplotype is ascertained. Linkage testing cannot be used if a family is small, if family members refuse to participate, or if the proband is suspected to have a de novo mutation. In addition, a definitive clinical diagnosis must be established in those individuals who agree to participate. Practically, the clinician should review the imaging studies for each family member participating in the analysis to make sure that the clinical diagnosis is correct. As of this writing, there is only 1 laboratory in the United States offering linkage testing for ADPKD. The cost (regardless of the number of samples sent) is ~$2,500, with results returning in about 3 weeks.

Direct mutation analysis is another option for molecular diagnosis in ADPKD. The commercially available test (in the United States, it is offered by Athena Diagnostics) involves direct DNA sequencing of the entire coding regions of both PKD1 and PKD2, including intron/exon boundaries. The cost is dependent on the entity being billed and varies between $3,650 and $4,880 with a minimum turnaround time of about 6 to 8 weeks. Theoretically, the advantage of direct mutation analysis is that one only needs a blood sample from a single patient. This is indeed the case if one identifies a mutation that is predicted to disrupt either PC-1 or PC-2. This class of mutation consists of those alterations such as (1) deletions or insertions that shift the reading frame of the message, (2) nucleotide substitutions that result in stop codons and therefore premature truncation of the protein, and (3) nucleotide substitutions that directly alter a consensus splice site that would likely result in the creation of a new message. The test result form typically refers to these mutations as “previously reported disease-associated mutations” or “predicted disease-associated mutations.” The major limitation of direct DNA testing, however, is that definitive disease-associated mutations are found in only about 40% to 60% of cases. Likely, disease-associated mutations may be detected in an additional 26% to 37% of patients. This category is comprised largely of nonsynonymous mis-sense variants that typically result in a single amino acid alteration (referred to as unknown amino acid change in the results report form). Although the pathogenicity of some mis-sense mutations has been established (ADPKD mutation database: http://pkdb.mayo.edu/), the disease-causing potential of other variants is uncertain. A variety of algorithms (such as Polyphen, available at http://genetics.bwh.harvard.edu/pph/) can be used to assess the likelihood that an amino acid substitution is deleterious to the protein function, but this may not provide sufficient certainty for clinical decision making. Therefore, in the absence of a valid functional assay, the clinical utility of this category of mutations remains uncertain.
Finally, up to 4% of the patients with ADPKD may have gross gene rearrangements that are missed by direct sequencing strategies. High-throughput screening methods for this type of mutation using a multiplex ligation-dependent probe amplification assay have been developed but are not yet commercially available. In general, for gene-based mutation screening, we recommend testing a definitively affected family member first to identify any potentially disease-causing variants to be tested in the at-risk subject of interest.

Why Establish a Diagnosis of ADPKD?
One might reasonably ask “why establish a presymptomatic diagnosis of ADPKD?” At the present time, there are no therapies proven...
to delay cyst progression and complications such as hypertension are treated as they arise irrespective of the underlying cause. Moreover, establishing a diagnosis may have negative implications such as restricting access to insurance. However, we believe that there are emerging indications for presymptomatic diagnosis of ADPKD in at-risk individuals.

Over the past several years, much progress has been made in understanding the signaling pathways that are altered when polycystin signaling decreases below a critical threshold. Moreover, the results from several laboratories studying conditional murine models of \( Pkd1 \) inactivation support the notion that there may be a significant lag time between the disruption of these pathways and frank cyst formation.\(^ {56,59} \) This early phase, before fatal cystic distortion of renal architecture, may provide an optimal time for intervention and would conceivably require accurate presymptomatic diagnosis. There are several trials currently underway that are examining the efficacy of therapies such as tolvaptan, octreotide, and rapamycin in early to middle stages of disease, and so preventive therapies for ADPKD may not be too far off.\(^ {18} \)

Another relevant indication for early identification of ADPKD is clearing prospective kidney donors from affected families.\(^ {49,51} \) Many patients with ADPKD reach ESRD in mid adulthood with few comorbidities, and, therefore, they are good candidates for renal transplantation. Because deceased donor organs are in short supply, living-related donation should be considered if disease could be excluded in the prospective donor. The agenda in this scenario is a dual one: to exclude disease in younger individuals without cysts but also to ensure that older at-risk individuals are not disqualified from donating because of sporadic age-related renal cysts. Algorithms for screening donors from ADPKD families have been proposed. Because most transplant centers define donor anatomy via a CT scan or MRI, this is often the first step. DNA testing is usually pursued in those with equivocal imaging studies such as those prospective donors with a few renal cysts below age-specific diagnostic cutoffs.

There are other plausible reasons why individuals from ADPKD families might want to establish their disease status early on. Extrarenal complications such as intracranial aneurysms cluster in certain ADPKD families.
families, and the current recommendations are to screen individuals from these families via magnetic resonance angiography.\textsuperscript{54,60} In these families, it may be desirable to establish a diagnosis earlier rather than later in order to decide who might benefit from screening. Finally, the knowledge of disease status might impact family planning decisions for some individuals.

A Diagnostic Algorithm for ADPKD

Figure 4 shows our approach in the evaluation of a patient suspected to have ADPKD. As indicated in this algorithm, obtaining a detailed family history is a key step in the diagnosis not only to confirm the autosomal dominant pattern of inheritance but also to aid in determining underlying gene type. The knowledge of gene type helps in the selection of appropriate ultrasound criteria especially for the purpose of disease exclusion. In general, the presence of “3 unilateral or bilateral renal cysts” in at-risk subjects aged 15 to 39 years old or “2 cysts in each kidney” in at-risk subjects aged 40 to 59 years old can be considered sufficient for the diagnosis of ADPKD regardless of their underlying gene type (PPV = 100%) (Table 2). For older at-risk subjects aged 60 years or older, the presence of “at least four cysts in each kidney” is sufficient for diagnosis of ADPKD regardless of the gene type. The sensitivity (ie, the proportion of the affected subjects with the positive test result) of these criteria, however, will differ between the different gene types. On the other hand, individuals with an affected relative who developed ESRD at 55 years or younger are at risk of PKD1, and, therefore, PKD1-specific ultrasound criteria should be applied for earlier disease exclusion. In this case, the absence of any renal cyst by 30 years of age provides almost complete certainty for disease exclusion. By contrast, in the absence of such a family history indicative of PKD1, the ultrasound criteria for unknown genotype can be used and ADPKD cannot be excluded until 40 years of age.

When no family history of ADPKD is apparent, screening parents or review of their autopsy results if available may uncover occult disease, especially in small families with milder PKD2. Molecular genetic testing, however, is indicated in the evaluation of at-risk individuals with equivocal imaging results, younger at-risk individuals being evaluated for living kidney donation, and individuals with atypical or de novo renal cystic disease. In the not too distant future, the role of molecular genetic testing may expand if the ADPKD gene type influences the choice of effective disease-modifying treatments that are currently being tested.

There are a number of other disorders discussed previously that may mimic ADPKD (Table 1). In most cases, however, additional renal (eg, angiomyolipomas and renal cell carcinomas) and/or extrarenal (eg, facial and periungual fibromas and pancreatic cysts) findings may provide clues in identifying these syndromic disorders. Individuals with findings atypical for ADPKD should undergo further evaluation, including additional imaging, referral for medical genetics consultation, and molecular testing. On the other hand, the finding of small kidneys bilaterally should alert to the possibility of acquired cystic disease.

References


12. Paterson AD, Pei Y: PKD3-to be or not to be? Nephrol Dial Transplant 14:2965-2966, 1999


