Unified Ultrasonographic Diagnostic Criteria for Polycystic Kidney Disease

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening hereditary disease in the United States, occurring in approximately one in every 400 to 1000 live births. ADPKD accounts for approximately 5 to 10% of end-stage renal failure in the United States requiring dialysis and renal transplantation. ADPKD is characterized by progressive enlargement of cyst-filled kidneys, severely affecting those who inherit one of the known genes that cause the disease. Mutations in PKD1, located on chromosome 16, are associated with a higher prevalence (85% of cases), earlier clinical presentation, and higher morbidity and mortality. Less profoundly affected individuals with mutations in PKD2, located on chromosome 4, account for the remaining 15% of cases. In patients with PKD2 mutations, end-stage kidney disease occurs on average 20 yr later than with PKD1 mutations (mean age 74 years versus 54 yr). In a study previously reported in JASN, PKD1 kidneys were significantly larger and had more cysts than PKD2 kidneys, although the rate of cyst growth was not different between PKD1 and PKD2 kidneys.

On the basis of effectiveness, cost, and safety, ultrasound is the most commonly used imaging modality to make the diagnosis of ADPKD. Magnetic resonance imaging and computed tomography scanning are used for research purposes, and no reported studies have compared ultrasound with computed tomography scanning are used for research purposes, and no reported studies have compared ultrasound with computed tomography scanning are used for research purposes, and no reported studies have compared ultrasound with computed tomography scanning are used for research purposes, and no reported studies have compared ultrasound with computed tomography scanning are used for research purposes, and no reported studies have compared ultrasound with computed tomography scanning are used for research purposes, and no reported studies have compared ultrasound with computed tomography scanning are used for research purposes, and no reported studies have compared ultrasound with computed tomography scanning are used for research purposes, and no reported studies have compared ultrasound with computed tomography scanning.

For patients from families with ADPKD of unknown genotype, the following is sufficient for making the diagnosis: in individuals between 15 and 39 yr of age, the presence of more than 10 cysts in each kidney and there are no renal or extrarenal findings suggesting another disease that causes renal cyst formation, such as tuberous sclerosis complex, von Hippel-Lindau disease, and acquired cystic kidney disease. Screening for ADPKD is controversial, because the consequences of a positive diagnosis (emotional and insurance issues) need to be weighed against the benefits because effective therapies for humans are not yet proved. Linkage analysis and direct DNA analytic techniques are available for genetic testing for PKD1 and PKD2 genes; however, genetic testing is not routinely performed. Genetic testing is not a useful screening tool because it can identify only approximately 70% of the hundreds of different PKD1 and PKD2 mutations. Genetic testing is mainly used for research purposes and to make a definite diagnosis in a potential living-related kidney donor who is younger than 30 yr and does not yet have kidney cysts on ultrasound. Thus, in clinical practice, ultrasound is the major screening and diagnostic tool.

Ravine et al. established age-dependent ultrasound diagnostic criteria for PKD1. Specifically, in at-risk individuals between 15 and 30 yr of age, at least two unilateral or bilateral kidney cysts; in individuals between 15 and 39 yr of age, two cysts in each kidney; and in individuals older than 60 yr, at least four cysts in each kidney. Because PKD2 mutations result in a milder form of ADPKD, false-negative ultrasound diagnostic results are more likely when screening young patients with PKD2 mutations. When at-risk patients with family histories and renal cysts are seen at the clinic, molecular genotyping is seldom performed and it is not known whether the patients have PKD1 or PKD2 mutations. Thus, the Ravine criteria established for PKD1 that are commonly used to diagnose PKD in patients with a family history but of unknown genotype may be inaccurate. Age-dependent ultrasound diagnostic criteria are needed for evaluating at-risk individuals from families with ADPKD of unknown genotype.

More than a decade after the establishment of ultrasound diagnostic criteria for PKD1 by Ravine et al., the article by Pei et al. in this issue of JASN evaluates the performance of ultrasound diagnostic criteria in 948 at-risk individuals from families who have PKD1 and PKD2 mutations and underwent molecular genotyping. They found the diagnostic criteria currently used for PKD1 in at-risk patients from 15 to 59 yr of age did not do as well when applied to patients with PKD2 because of a higher risk for false-negative results, which reduced test sensitivity. Thus, new standard diagnostic criteria for patients with ADPKD of unknown genotype are proposed.

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three or more unilateral or bilateral kidney cysts; in individuals between 40 and 59 yr of age, two or more cysts in each kidney; and in individuals ≥60 yr of age, at least four cysts in each kidney. In addition, the study by Pei et al.7 found that fewer than two renal cysts in at-risk individuals aged ≥40 yr is sufficient to exclude the disease.

The investigators used sensitivity data derived from genetically affected individuals (52.3% of the study participants) and specificity data derived from genetically unaffected individuals. Moreover, the authors created data sets that simulate the ratio of PKD1 to PKD2 as well as affected to unaffected individuals seen in clinic to evaluate at-risk individuals from families with unknown genotype.

The authors in this study used a statistical method called “bootstrapping” to estimate the confidence intervals for ultrasound criteria and genotype in different age groups of at-risk patients.8 Bootstrapping is a computer-intensive approach that randomly resamples a subset of the original cohort as an approximation of the underlying target population; when one subset is sampled, it is immediately replaced and resampled multiple (thousands) times from the complete cohort, and statistical conclusions regarding confidence intervals are drawn from an integrated assessment of resampled data.8 An alternative approach is another computer-intensive method called permutation test, which is a resampling method but without subset replacement. The bootstrapping method, using weights to control for variables, has been used for decades. In this study, the authors astutely assigned weights to each individual to control for the increasing probability of previous clinical diagnosis with increasing age and to ensure a constant ratio of unaffected PKD1 to unaffected PKD2 of 85:15.

The merit of this study is in the use of an elegant resampling method to establish ultrasonographic criteria in patients who have unknown genotype and are at risk for ADPKD. Moreover, the results demonstrate that the diagnostic criteria currently in use for PKD1 may be inaccurate when applied to PKD2 because of higher risks for false-negative results yielding a reduced sensitivity for individuals aged 15 to 59.

In summary, the authors propose new ultrasound diagnostic criteria for screening patients for ADPKD from families of unknown genotype. Because the majority of patients seen in clinical practice have unknown genotype, the proposed diagnostic criteria will be useful in screening patients who are at risk for ADPKD in the clinical setting in which the genotype is seldom known. According to the Ravine criteria for patients with PKD1,6 the finding of fewer than two cysts in each kidney is enough for disease exclusion in at-risk individuals aged ≥30 yr. In contrast, the study by Pei et al.7 of both patients with PKD1 and with PKD2 suggests the utility of ultrasound may be limited for at-risk individuals who are younger than 30 yr and have a negative or indeterminate scan and unknown genotype. For these individuals, repeat ultrasound scanning or even magnetic resonance imaging scanning may be useful to detect new cysts. According to the new unified criteria presented by Pei et al.,7 the presence of fewer than two renal cysts has a negative predictive value of 100% and is enough to exclude the disease in at-risk individuals who are aged ≥40 yr.

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DISCLOSURES

None.

REFERENCES


See related article, “Unified Criteria for the Ultrasound Diagnosis of ADPKD,” on pages 000–000.