Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Autosomal-dominant polycystic kidney disease (ADPKD) affects up to 12 million individuals and is the fourth most common cause for renal replacement therapy worldwide. There have been many recent advances in the understanding of its molecular genetics and biology, and in the diagnosis and management of its manifestations. Yet, diagnosis, evaluation, prevention, and treatment vary widely and there are no broadly accepted practice guidelines. Barriers to translation of basic science breakthroughs to clinical care exist, with considerable heterogeneity across countries. The Kidney Disease: Improving Global Outcomes Controversies Conference on ADPKD brought together a panel of multidisciplinary clinical expertise and engaged patients to identify areas of consensus, gaps in knowledge, and research and health-care priorities related to diagnosis; monitoring of kidney disease progression; management of hypertension, renal function decline and complications; end-stage renal disease; extrarenal complications; and practical integrated patient support. These are summarized in this review.

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Autosomal-dominant polycystic kidney disease (ADPKD), an inherited kidney disease that affects 12.5 million people worldwide in all ethnic groups, is responsible for up to 10% of patients in end-stage renal disease (ESRD) and is a major burden on public health.[1] It is characterized by relentless development and growth of cysts causing progressive kidney enlargement associated with hypertension, abdominal fullness and pain, episodes of cyst hemorrhage, gross hematuria, nephrolithiasis, cyst infections, and reduced quality of life.[2–4] Despite continuous destruction of renal parenchyma, compensatory hyperfiltration in surviving glomeruli maintains renal function within the normal range for decades.[5] Only when the majority of nephrons have been destroyed does renal function decline, typically after the fourth decade of life, and ESRD eventually ensues. ADPKD is a systemic disorder affecting other organs with potentially serious complications such as massive hepatomegaly and intracranial aneurysm (ICA) rupture.[2]

Mutations in the *PKD1* and *PKD2* genes account for the overwhelming majority of ADPKD cases. There is no convincing evidence for the existence of a third PKD gene.[6] Compared with *PKD1*, subjects affected with *PKD2* mutations have milder renal disease with fewer renal cysts, delayed onset of hypertension, and ESRD by almost two decades, and longer patient survival.[7,8] More recent studies have delineated a significant allelic effect in *PKD1* with milder disease associated with non-truncating compared with truncating mutations.[9–12] Gene linkage analysis of European families suggested that ~85 and ~15% of cases were due to *PKD1* and *PKD2* mutations, respectively. However, two recent studies from Canada and the United States have documented a higher *PKD2* prevalence of 26 and 36%, respectively.[13]

Table 1 | Performance of ultrasound-based unified criteria for diagnosis or exclusion of ADPKD

Age (years)	*PKD1*	*PKD2*	Unknown gene type
Diagnostic confirmation			
15–29	A total of ⩾3 cysts[a]: PPV = 100%; SEN = 94.3%	PPV = 100%; SEN = 69.5%	PPV = 100%; SEN = 81.7%
30–39	A total of ⩾3 cysts[a]: PPV = 100%; SEN = 96.6%	PPV = 100%; SEN = 94.9%	PPV = 100%; SEN = 95.5%
40–59	⩾2 cysts in each kidney: PPV = 100%; SEN = 92.6%	PPV = 100%; SEN = 88.8%	PPV = 100%; SEN = 90%
Disease exclusion			
15–29	No renal cyst: NPV = 99.1%; SPEC = 97.6%	NPV = 83.5%; SPEC = 96.6%	NPV = 90.8%; SPEC = 97.1%
30–39	No renal cyst: NPV = 100%; SPEC = 96%	NPV = 96.8%; SPEC = 93.8%	NPV = 98.3%; SPEC = 94.8%
40–59	No renal cyst: NPV = 100%; SPEC = 93.9%	NPV = 100%; SPEC = 93.7%	NPV = 100%; SPEC = 93.9%

Abbreviations: ADPKD, autosomal-dominant polycystic kidney disease; NPV, negative predictive value; PPV, positive predictive value; SEN, sensitivity; SPEC, specificity.
[a]Unilateral or bilateral.

Polycystic kidney disease (PKD) has been known for over 300 years and was considered a rare and incurable disease. With medical advances, ADPKD is now diagnosed more frequently and there are several strategies through which quality of life and life span have improved. These include early detection and treatment of hypertension, lifestyle modifications, treatment of renal and extrarenal complications, management of chronic kidney disease-related complications, and renal replacement therapy. However, approaches to the diagnosis, evaluation, prevention, and treatment of ADPKD vary substantially between and within countries, and at present there are no widely accepted practice guidelines. Basic and translational research on PKD has increased exponentially in the last three decades, particularly after the discovery of the *PKD1* (1994) and *PKD2* (1996) genes. Molecular genetic diagnosis is now available. Many therapeutic targets have been identified and tested in animal models, with clinical trials yielding encouraging results. The relatively low frequency of *de novo* mutations, dominant pattern of inheritance, accurate measurement of cyst burden through renal imaging, and slow disease progression make ADPKD an ideal candidate for nephroprevention.

The objective of this KDIGO conference was to assess the current state of knowledge related to the evaluation, management, and treatment of ADPKD, to pave the way to harmonize and standardize the care of ADPKD patients, identify knowledge gaps, and propose a research agenda. The following sections summarize the areas of consensus and controversy discussed by a global interdisciplinary expert panel. The complete conference report is available in the Supplementary Appendix online and supplementary meeting materials (e.g., slides) can also be found at the conference website: http://kdigo.org/home/conferences/adpkd/.

DIAGNOSIS OF ADPKD

Presymptomatic screening of ADPKD is not currently recommended for at-risk children. For at-risk adults the potential benefits of presymptomatic diagnosis usually outweigh the risks, and it is most commonly performed by ultrasonography (US), which is inexpensive and widely available. The implications of a positive diagnosis vary from country to country and should be discussed beforehand with the test subject. Throughout this report, we define at-risk individuals as first-degree relatives of individuals diagnosed or suspected to have ADPKD.

Simple cysts occur more frequently with increasing age in the general population. Age-dependent US criteria for diagnosis and disease exclusion were initially established for *PKD1* and have been subsequently refined for *PKD2* and for at-risk adults of unknown gene type (Table 1).[14] Conventional US is suboptimal for disease exclusion in subjects at-risk for ADPKD who are younger than 40 years, often evaluated as potential living kidney donors. In this setting, the finding of fewer than five renal cysts by magnetic resonance imaging (MRI) is sufficient for disease exclusion.[15]

A positive family history is absent in 10–15% of patients with ADPKD because of *de novo* mutations, mosaicism, mild disease from *PKD2*, and non-truncating *PKD1* mutations, or because of unavailability of parental medical records.[16] In the absence of other findings to suggest a different cystic disease, a patient with bilaterally enlarged kidneys and innumerable cysts most likely has ADPKD. Otherwise, the differential diagnosis needs to be broadened to include other cystic kidney diseases (see Table 2).

Newborns or children with renal cysts comprise a heterogenous diagnostic group of cystic disorders. Although family history, imaging, and clinical assessment for extrarenal manifestations may provide specific diagnostic clues, specialized consultation is strongly encouraged as genetic testing is often required.

Linkage-based diagnosis of ADPKD using polymorphic markers flanking the two disease genes, which requires multiple affected family members and can be confounded by *de novo* mutations, mosaicism, and bilineal disease,[6,17] is now rarely performed. Presently, direct mutation screening by Sanger sequencing of the *PKD1* and *PKD2* genes is the method of choice for molecular diagnosis of ADPKD. However, mutation screening for *PKD1* is technically challenging, labor intensive, and costly because of its large size and complexity (i.e., duplication of its first 33 exons in 6 pseudogenes with high DNA sequence identity).[18,19] In sequencing-negative cases, multiplex ligation–dependent probe amplification can be used as a follow-up test to detect large gene rearrangements in $<5\%$ of cases.[20] Up to 15% of patients with suspected ADPKD are