SUPPLEMENTAL APPENDIX

Autosomal Dominant Polycystic Kidney Disease (ADPKD): Report from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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ABSTRACT

Autosomal Dominant Polycystic Kidney Disease (ADPKD) affects up to 12 million individuals and is the 4th 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 report.

INTRODUCTION

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 for 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 (QOL).[2-4] Despite continuous destruction of renal parenchyma, compensatory hyperfiltration of the surviving glomeruli maintains renal function within the normal range for decades.[5,6] Only when the majority of nephrons have been destroyed, renal function declines, 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 two genes (i.e., *PKD1* and *PKD2*) account for the overwhelming majority of ADPKD cases.[7,8] There is no convincing evidence for the existence of a third PKD gene.[9,10] Disease severity is highly variable, in part due to a strong genic effect.[11,12] Compared to *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.[11,13] More recent studies have delineated a significant allelic effect in *PKD1* with milder disease associated with non-truncating compared to truncating mutations.[14-17] A previous gene linkage analysis of European families suggested that ~85% and ~15% of the cases were due to *PKD1* and *PKD2* mutations, respectively.[18] However, population-based studies from Canada and United States have documented a higher *PKD2* prevalence of 26% and 36%, respectively.[19,20]

Since polycystic kidney disease (PKD) has been known for over 300 years, it has been considered a rare and incurable disease.[21] With the medical advances of the last century, ADPKD is now diagnosed more frequently and there are several strategies through which QOL 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 (CKD)-related complications and renal replacement therapy (RRT). However, approaches to the diagnosis, evaluation, prevention and treatment of ADPKD vary substantially 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* and *PKD2* genes in 1994 and 1996,[22] respectively. Molecular genetic diagnosis in government approved labs is now available. Many therapeutic targets have been identified and tested in animal models and several clinical trials demonstrate 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, to identify knowledge gaps, and to propose a research agenda to resolve controversial issues. The following sections summarize the areas of consensus and controversy discussed by a global interdisciplinary expert panel on diagnosis; monitoring of kidney disease progression; management of hypertension, renal function decline and renal complications; management of ESRD including transplantation and dialysis; management of extrarenal complications; and practical integrated patient support. Additional information about the conference can also be found online at: http://kdigo.org/home/conferences/adpkd/.

1. DIAGNOSIS OF ADPKD

Pre-symptomatic screening of patients at risk for ADPKD.

ADPKD is a Mendelian autosomal dominant disorder where at-risk individuals have a 50% chance of inheriting the disease. Throughout this report, we define at-risk individuals as first-degree relatives of individuals diagnosed or suspected to have

ADPKD. Pre-symptomatic diagnosis of adults at risk for ADPKD is most commonly performed by ultrasonography (US) which is inexpensive and widely available.[8] Pre-symptomatic screening of at-risk children is not currently recommended based on the potential for adverse psychological consequences, denial of future insurance coverage, and the lack of evidence that such screening would improve outcomes. The possible implications of a positive diagnosis should be discussed beforehand and results clearly explained to the patient and to their parents in the case of minors.

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,*[23] and have been subsequently refined for *PKD2* and for at-risk adults of unknown gene type. "Unified Criteria" (Table 1) have been established for both diagnosis and exclusion of ADPKD.[24] Specifically, the presence of "a total of three or more renal cysts" for at-risk subjects aged 15-39 years and "two cysts or more in each kidney" for at-risk subjects aged 40-59 years are sufficient for a diagnosis of ADPKD. Conversely, the "absence of any renal cyst" is sufficient for disease exclusion only in at-risk subjects aged 40 years or older. These criteria were derived from a large cohort of at-risk subjects from *PKD1* and *PKD2* families by comparing their molecular genetic results and US findings using scanners with the capability of detecting cysts 1 cm or more in diameter.[24] High-resolution US using modern scanners which have imaging resolution enabling routine detection of renal cysts down to 2-3 mm will most likely result in a revision of the cyst number required for a diagnosis of ADPKD.

Subjects at risk for ADPKD are often evaluated as potential living kidney donors. Ultrasonography is a reasonable first test for excluding affected subjects. However, the "absence of any renal cyst" by conventional US is not sufficient for disease exclusion in at-risk subjects younger than 40 years of age without genetic information. As part of living donor evaluations, transplant centers include magnetic resonance imaging (MRI) or contrast-enhanced computerized tomography (CT). In this setting, the finding of a total of less than of 5 renal cysts by magnetic resonance imaging (MRI) is sufficient for disease exclusion.[25]

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

Diagnostic confirmation			
Age (years)	***PKD1***	***PKD2***	**Unknown gene type**
15-29	A total of ≥3 cysts*: PPV=100%; SEN=94.3%	PPV=100%; SEN=69.5%	PPV=100%; SEN=81.7%
30-39	A total of ≥3 cysts*: 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			
Age (years)	***PKD1***	***PKD2***	**Unknown gene type**
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.
*Unilateral or bilateral.

Testing of symptomatic subjects at risk for ADPKD

Imaging with US, CT or MRI, depending on the clinical setting, is indicated in at-risk subjects who present with medical complications (e.g., abdominal/flank pain, hypertension, hematuria, proteinuria, or increased serum creatinine). The implications of a positive diagnosis should be discussed beforehand and results clearly explained to the patients and their parents in the case of minors. When US-based testing is performed, the Unified Criteria can be used for diagnosis and exclusion of ADPKD.[24] Whether these criteria can be extrapolated to CT (contrast-enhanced) or MRI for evaluation of at-risk subjects using the number of cysts measuring 1 cm or more in size is unknown.

A positive family history is absent in 10-15% of patients with ADPKD. A family history may be absent due to *de novo* mutations, mosaicism, mild disease from *PKD2* and non-truncating *PKD1* mutations, or unavailability of parental medical records.[26] Reviewing the medical records and US screening of parents and older relatives may be useful. 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). However, kidney size can be close to normal with low cyst number in ADPKD and therefore mutation-based diagnostic workup may be required. There is no consensus on a diagnostic algorithm that integrates clinical findings with renal imaging and molecular genetic testing.

Newborns or children with renal cysts comprise a heterogeneous diagnostic group of common and rare cystic disorders.[8] US is commonly used in this setting due to its non-invasiveness and may provide specific diagnostic clues (e.g., dysplastic kidneys, glomerulocystic disease, and tuberous sclerosis complex). Thorough clinical assessment for extrarenal manifestations (for syndromic forms of PKD or ARPKD) and careful review for family history of renal cystic disease are the most important first steps. US screening of the parents and/or grandparents should be considered in the setting of a negative family history. Consultation with a specialist with expertise in hereditary renal disease is strongly encouraged as genetic testing is often required.

Table 2. Differential diagnosis of other renal cystic diseases

Disorder	Inheritance	Family history	Clinical features
Autosomal recessive polycystic kidney disease (ARPKD)	AR	Siblings (25%)	~ 1 in 20,000. Neonatal deaths in 30%; Potter's phenotype; biliary dysgenesis (congenital hepatic fibrosis, intrahepatic bile duct dilatation), resulting in portal hypertension and cholangitis.
Renal cysts and diabetes syndrome (RCDA/ MODY5 / HNF-1B[a])	AD	*De novo* mutations (often deletions) in 50%	Renal cysts or malformation in 90%, diabetes mellitus in 45%, hypomagnesemia in 40%, genital tract abnormalities in 20%, hyperuricemia in 20%, elevated liver enzymes in 15%
Tuberous sclerosis complex (TSC)	AD	Absent in two thirds of families	~1 in 10,000 live births. Skin lesions (facial angiofibromas, periungual fibroma, hypomelanotic macules, shagreen patch), >90%; cerebral pathology (cortical tuber, subependymal giant cell astrocytoma), 90%; renal (polycystic kidneys, angiomyolipomas), 50-70%; retinal hamartomas,50%; lymphangioleiomyomatosis.
PKD1-TSC contiguous gene syndrome	AD	Spontaneous presentation frequent	Presentation of severe ADPKD at an early age, with polycystic kidneys with renal angiomyolipomas frequently present after the first year of age.
von Hippel-Lindau disease	AD	*De novo* mutations in 20%	~1 in 36,000. Cerebellar and spinal hemangioblastoma; retinal angiomas; serous cystadenomas and neuroendocrine tumors of pancreas; pheochromocytoma; renal cell carcinoma.
Medullary cystic kidney disease (MCKD[b])	AD	rare	Slowly progressive kidney disease; medullary cysts (but uncommon in families with type 2 MCKD [now known as ADTKD-*UMOD*]); hyperuricemia and gout in type 2 MCKD (now known as ADTKD-*UMOD*); small- to normal-sized kidneys.
Medullary sponge kidney (MSK)	Unclear	Familial clustering reported	~1 in 5000. Medullary nephrocalcinosis; kidney stones; "brush" or linear striations on intravenous pyelogram.
Simple renal cysts	Acquired	None	Common; increase in number and size with age; normal renal function; normal-sized kidneys.
Acquired cystic kidney disease (ACKD)	Acquired	None	Common in patients with chronic renal failure or ESRD; multiple cysts associated with normal- or small-sized kidneys.

Abbreviations: AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; ADTKD, autosomal dominant tubulointerstitial kidney disease; AR; autosomal recessive; ESRD, end-stage renal failure; MODY5, maturity onset diabetes mellitus of the young type 5

[a]Current designation is ADTKD-*HNF1B*

[b]Use of the term MCKD is discouraged; formerly MCKD type 1 should now be referred as ADTKD-*MUC1* and formerly MCKD type 2 should now be referred as ADTKD-*UMOD*.

Molecular diagnosis of ADPKD

Historically, linkage analysis of polymorphic markers flanking the two disease genes has been used for a molecular diagnosis of ADPKD, but requires multiple (preferably 4 or more) affected family members to be informative.[8] Moreover, the test results are indirect and can be confounded by *de novo* mutations, mosaicism, and bilineal disease[9,10] Presently, mutation-based screening by Sanger sequencing of all exons and splice junctions of the *PKD1* and *PKD2* genes is the method of choice for molecular diagnosis of ADPKD.[20] Linkage analysis is rarely performed except for screening embryos in pre-implantation genetic diagnostics (PGD) where genotyping several markers associated with the familial mutation can provide assurance against problems associated with screening a very small amount of DNA, such as allele dropout. *PKD1* is a large complex gene with its first 33 exons duplicated in six pseudogenes (*PKD1P1-PKD1P6*) with high sequence identity, making mutation screening highly challenging.[7] By contrast, *PKD2* is a single copy gene which is highly amenable to conventional mutation screening. Comprehensive screening for *PKD1* mutations is now possible using protocols that exploit rare mismatches between the duplicated region and the *PKD1P1-P6* loci for *PKD1*-specific PCR (polymerase chain reaction).[20] This approach, however, is labor-intensive and costly.[7] In sequencing-negative cases, multiplex ligation-dependent probe amplification (MLPA) can be used as a follow-up test to detect large gene re-arrangements in less than 5% of cases.[27]

To date, more than 1270 and 200 pathogenic mutations have been reported for *PKD1* and *PKD2,* respectively (http://pkdb.mayo.edu). These results indicate extensive allelic heterogeneity, especially for *PKD1*, with no apparent mutation “hot-spots” or common recurrent mutations. Up to 15% of patients with suspected ADPKD are mutation-negative despite a comprehensive screen. Some of these patients with very mild or asymmetric PKD of *de novo* onset may have somatic mosaicism resulting from a disease-causing mutation affecting an oligopotent progenitor cell during early embryogenesis.[28] The hallmark of mosaicism is the presence of more than one genetically distinct cell line in an individual.[28] The difference between somatic and germline mosaicism is based on the findings of genetically distinct populations of cells in

the somatic and germline tissues, respectively.[29] Mosaicism is a well-recognized cause of variable disease expressivity in more than 30 Mendelian disorders but one that is very difficult to diagnose by Sanger sequencing. However, Sanger sequencing of an affected offspring of the mosaic individual may uncover the pathogenic mutation. Recent advances in resequencing (i.e., Next-Generation Sequencing [NGS]) technologies have enabled high-throughput mutation screening of both *PKD1* and *PKD2* with a recent "proof-of-principle" study showing promising results.[30] The adaptation of this new technology to molecular diagnostics in ADPKD is expected to facilitate mutation screening while reducing the costs at the same time.[31]

Marked discordant renal disease severity among affected family members has been well documented suggesting a role for both genetic and environmental modifiers.[32-35] In several of these families, two (homozygous or compound heterozygous) non-truncating mutations on different copies of *PKD1* have been found in affected subjects with atypical or severe renal disease while other family members with one non-truncating mutation have mild disease.[14] In other families, a truncating and a non-truncating mutation on different copies of *PKD1* or a non-truncating *PKD1* mutation in combination with a mutation in another cystogene (e.g., *HNF-1β* or *PKHD1*) has been found in patients diagnosed *in utero* or with severe renal disease.[16,36] Comprehensive mutation screening of *PKD1* and *PKD2* as well as other cystogenes has the potential to account for some of the within-family variability of disease severity, refine genotype-phenotype correlations and provide useful clinical prognostic information.[11-17,36]

Current approach and indications of genetic testing

Most patients with ADPKD do not need molecular genetic testing. When indicated, gene-based mutation screening of *PKD1* and *PKD2* by Sanger sequencing followed by MLPA to detect gene rearrangement in sequencing-negative cases is the method of choice but is laborious and expensive.[8] Molecular genetic testing is not required for most patients but may be considered in cases of equivocal or atypical renal imaging findings (e.g., markedly asymmetric PKD, renal failure without significant kidney enlargement); marked discordant disease within family; very mild PKD; sporadic PKD

with no family history; early and severe PKD or PKD with syndromic features; and reproductive counseling.

Molecular genetic testing plays a greater role in childhood where PKD can be due to autosomal recessive polycystic kidney disease (ARPKD), ADPKD or a number of rare genetic diseases. Genetic testing of childhood PKD may be considered in cases of early and severe PKD and in PKD with syndromic features. Genetic testing in this setting requires consideration of diseases beyond ADPKD and should be performed by physicians/geneticists in centers with appropriate experience and expertise.

Future role of molecular diagnostics in ADPKD

The role of molecular diagnostics in clinical medicine is rapidly evolving. Recent advances in NGS which provides high-throughput and comprehensive diagnostic screening at low cost compared to Sanger sequencing can be readily applied to ADPKD.[30,31] Recent studies that employed comprehensive mutation screening of *PKD1*, *PKD2* and other cystogenes (e.g., *PKHD1*, *HNF1β*) have identified allelic and genic interactions that can modulate renal disease severity in ADPKD.[13-17] Targeted or whole exome sequencing will likely play an important role in the molecular diagnostics of childhood PKD in the future. Standardized and informative reporting as well as physician education is needed.

Pre-Implantation genetic diagnosis

PGD has been successfully applied in more than 300 genetic disorders for selecting healthy embryos created by in-vitro fertilization for implantation. Currently, PGD is most commonly used in severe genetic diseases with early manifestations such as cystic fibrosis, ARPKD, among many others.[37-39] PGD should be included in the discussion of reproductive choices with patients with ADPKD, but it is only available in certain countries and the acceptance of this technique is influenced by personal values as well as the severity of the disease.[40-42]

Identification of embryos harboring a pathogenic mutation requires a biopsy. The most

common approach is the biopsy of cleavage-stage embryos in which one blastomere is removed from the embryo on day 3 of development. PCR amplification of DNA from a single cell is subject to two major pitfalls: (i) amplification failure and (ii) amplification of only one of the two alleles present in the cell, so called 'allele drop-out' which can lead to misdiagnosis.[38,39] A haplotype-based screening using flanking and intragenic microsatellite markers and multiplex PCR can be used to provide assurance against this complication and has been successfully applied to ADPKD.[43] An alternative biopsy method (blastocyst biopsy) targets the trophectoderm on day 5 of development.[44,45] This approach removes multiple cells for analysis without sacrificing any part of the embryo proper. The larger DNA yield compared to the single blastomere method facilitates the molecular diagnosis. It is usually combined with cryopreservation and thawed embryo transfer to allow more time for the genetic testing.

2. MONITORING KIDNEY DISEASE PROGRESSION IN ADPKD

Clinical trials

Treatments proven to extend kidney survival in ADPKD do not currently exist. Ideally, treatment should start early, when the kidney parenchyma is relatively preserved.[46] At later stages, other pathologic mechanisms independent of ADPKD likely become dominant. Nevertheless, treatments in later stage disease are also important to preserve kidney function and their efficacy and safety should also be determined. Randomized clinical trials (RCTs) should ideally include patients with a high likelihood of disease progression. At early stages of ADPKD and for several decades, glomerular filtration rate (GFR) is normal and therefore not informative. However, kidney volume in relation to age[3,4,47,48] can identify patients with progressive disease.

Adopting GFR as an outcome in trials that include patients at early stages would require long periods of follow-up and are unrealistic. Conversely, change in total kidney volume (TKV) or change in volume of specific kidney compartments may be a valid primary or secondary outcome. TKV is an accurate estimate of kidney cyst burden and associates

with many renal manifestations of ADPKD including pain, hypertension, gross hematuria, and proteinuria or albuminuria. While there is broad consensus for the value of TKV as a prognostic biomarker, most regulatory agencies do not currently accept TKV as a primary endpoint in clinical trials for ADPKD.

Total kidney volume

TKV increases exponentially in virtually every ADPKD patient. The rate of increase is highly variable and unique for each individual. Average rates of increase of TKV in adults are 5-6%/year.[3,49,50] Elevated TKV, particularly when used together with age and kidney function, identifies individuals who are at highest risk for progression to advanced stage CKD and ESRD and conversely, those who will most likely never lose kidney function or progress to ESRD.[47,48]

TKV can be measured using a variety of imaging modalities (US, MRI and CT). Precise measurements of TKV necessary in clinical trials to assess the impact of therapeutic interventions over short periods of time[51] can be obtained by planimetry or stereology analysis of MR or CT images.[52,53] MRI and CT are equivalent with regard to precision and reproducibility,[48] but CT imaging is associated with radiation exposure. MRI measurements can be done using either T1 or T2 weighted images; however, T2 weighted images provide information regarding total cyst volume and do not require gadolinium, eliminating the risk for nephrogenic systemic fibrosis.

Although less expensive, US measurements of TKV are operator-dependent, less reproducible and less precise, and can overestimate TKV compared to MRI and CT.[54,55] US measurement of TKV typically is calculated utilizing the ellipsoid equation ($\pi/6 \times L \times W \times D$), by measuring maximum orthogonal length, width and depth of the kidney.[56] Although less precise, US has been used successfully to measure disease progression in studies with long periods of follow-up.[57] The ellipsoid equation can also be applied to kidney dimensions obtained from MRI or CT images for rapid calculations of TKV that can be used to select study populations in clinical trials or to help clinically in the determination of prognosis.[48]

In clinical practice, imaging of the kidneys should be obtained as an initial evaluation of a patient with ADPKD. Radiology reports should be standardized for all imaging modalities and include a maximum kidney length, width and depth, and an estimate of TKV. Given that there is no currently approved medical therapy to slow disease progression, repeated measurements of TKV in asymptomatic patients are not currently indicated. When approved disease-modifying therapies become available or if lifestyle modifications are shown to alter disease progression, repeated imaging may become an informative tool.

Other imaging parameters

Standardized reporting of imaging findings should also include the exact number of cysts when there are less than 10 in each kidney and the liver; minimal and maximal size of cysts in both organs; presence of complex cyst(s) and exophytic cyst(s); and the dominant pattern (i.e., cortical, medullary, or diffuse) for each kidney. However, the prognostic value of these data has not been adequately studied.

Other studies have underlined the importance of the non-cystic tissue as an indicator of disease severity. One group has taken advantage of advanced image processing techniques to subdivide non-cystic tissue on contrast-enhanced CT into two separate components, fully enhanced parenchyma and hypoenhanced ("intermediate") compartment. The latter is thought to represent fibrotic tissue.[58,59] The ratio of intermediate volume relative to parenchymal volume significantly correlates with baseline and longitudinal changes in GFR. Several MRI technologies such as diffusion weighted and diffusion tensor MRI and MR elastography have been used to assess the state of the parenchyma in various renal conditions[60,61] but have not yet been evaluated in ADPKD.

Although the potential of MRI as a non-invasive method for measuring blood flow *in vivo* is well-established, measurement of renal blood flow (RBF) by MRI is challenging. Several technological innovations have made it possible to measure RBF accurately and reproducibly.[62] At present, the methodology to measure RBF is not widely available.

In the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) study, reduction in RBF measured by MRI paralleled the increase in TKV, preceded the decline in GFR and predicted disease progression.[63,64]

Glomerular filtration rate

Estimation of GFR using equations including CKD-EPI and the MDRD equation (eGFR) is acceptable for clinical care of ADPKD patients. In specific circumstances, measurement of GFR (mGFR) using the clearance of inulin, iothalamate, diethylenetriaminepentaacetic acid (DTPA) or iohexol is warranted. A case in point is the timing of a potential living kidney donation procedure in an ADPKD patient with an abnormal muscle mass for age and gender in whom eGFR may be unreliable. In this instance, it may be necessary to assess mGFR using one of the aforementioned "gold-standard" techniques.

Whether estimation of GFR by equations is adequate for use in clinical trials of ADPKD has been debated. One report questioned the reliability of eGFR using the MDRD and CKD-EPI equations to reflect actual GFR values and suggested that use of eGFR may fail to detect changes in kidney function over time.[65] This concern is based on the theoretical rationale that ADPKD is a tubular disease and that tubular secretion of creatinine may be different in this disease when compared to non-ADPKD individuals. Another study reported that tubular creatinine secretion was indeed increased in ADPKD patients when compared to healthy controls at similar mGFR level (measured by a "gold standard" method, in this case iothalamate).[66] However, this effect was limited to those with a high-normal mGFR. Consequently, in this study the CKD-EPI and MDRD Study equations performed relatively well in estimating GFR and change in eGFR. These conclusions are corroborated by a third study, which added that using cystatin C in combination with creatinine to determine eGFR might even be better.[67] In addition, the relationship between mGFR and eGFR in the MDRD Study where patients had established renal insufficiency was not different in ADPKD as compared to other kidney disease populations. Therefore, eGFR is in general acceptable for clinical trials. When feasible, however, mGFR is preferable. Methods for mGFR are more

cumbersome, associated with considerable costs, and impractical in clinical trials with a large number of participating centers. Whether a limited number of mGFRs outperforms a larger number of eGFRs to assess change in kidney function over time in clinical trials is an unanswered question. Importantly, when developing novel medical treatments, it should be investigated whether such treatments interfere with tubular creatinine secretion. When this is the case, baseline pretreatment eGFR should be compared with off-treatment eGFR after study completion, or mGFR should be used.

Proteinuria

Proteinuria (greater than 300 mg/day), occurs in approximately 25% of adults diagnosed with ADPKD,[68] but typically does not exceed 1 gm/day. Its origin and glomerular versus tubular pattern have not been thoroughly ascertained.[69] Presence and level of proteinuria are associated with larger TKV, faster decline of renal function and earlier onset of ESRD, and therefore have prognostic value. Maximum reduction in proteinuria in ADPKD is the treatment goal. Strategies to reach these goals include appropriate blood pressure control and use of inhibitors of the renin-angiotensin system including ACE inhibitors and angiotensin receptor blockers as in other chronic kidney diseases.[70] In patients with nephrotic range proteinuria, the presence of a second kidney disorder and a renal biopsy should be considered if access to renal parenchyma is feasible.

Patient reported outcomes and QOL

Instruments such as patient-reported outcome measures (PROM) are useful as end-points for clinical trials.[51] They can also be used to improve patient care but there are gaps in knowledge about their usefulness.[71] There is no current validated PROM for ADPKD. The physical and psychological burdens to ADPKD patients are significant, yet they are incompletely characterized and difficult to quantify. Patients with ADPKD have not been found to score differently from the general population in standardized questionnaires (SF36) evaluating QOL.[71] Since the SF36 questionnaire was developed to evaluate individuals with more immediate life threatening disorders, it may not be sufficiently sensitive to characterize the domains of suffering in a chronic slowly progressive disease such as ADPKD. A large cohort (n = 1,043) of hypertensive ADPKD

individuals enrolled in the Polycystic Kidney Disease Treatment Network HALT clinical trials who completed SF36 questionnaire and the Wisconsin pain survey prior to randomization revealed no reduction in mental or physical SF 36 scores compared to the general population.[72] In patients with early disease (eGFR >60mL/min/1.73 m^2), there was no association between pain and height adjusted TKV (htTKV), except in patients with large kidneys (htTKV>1,000mL/m). Comparing across eGFR levels patients with eGFRs of 20-44mL/min/1.73m^2 were significantly more likely to report that pain impacted on their daily lives and had lower SF-36 scores than patients with eGFRs of 45-60 and ≥60mL/min/1.73 m^2.

3. MANAGEMENT of HYPERTENSION, RENAL FUNCTION DECLINE and RENAL COMPLICATIONS

Treatment of hypertension in the adult ADPKD population

Patients with ADPKD are at increased risk for hypertension, cardiovascular events and cardiovascular mortality when compared to the general population.[73,74] The increase in blood pressure (BP) in this patient group has been attributed to several causes, including increased activity of the renin-angiotensin-aldosterone system (RAAS), and increase in sympathetic tone and primary vascular dysfunction.[75-79]

At present, there is no consensus on whether disease-specific BP targets apply to ADPKD. At least, the general advice of the 2012 KDIGO Clinical Practice Guideline for the Management of BP in CKD should be followed, suggesting a BP target ≤140/90 mmHg.[80,81] In accordance with this guideline, blood pressure targets should be individualized taking comorbidities into account. In conditions such as left ventricular dysfunction, ICA, diabetes or proteinuria, lower BP targets are advised (≤130/80 mmHg).[80,81] A RCT in 79 adult hypertensive patients with left ventricular hypertrophy indicated that strict BP control (≤120/80 mmHg) versus regular BP control (≤140/90 mmHg) was more effective in reducing left ventricular mass.[82] The recently published

results of the HALT PKD clinical trials suggest that blood pressure targets below those recommended by current guidelines may be advantageous in young hypertensive ADPKD patients with CKD stages 1 or 2 and without diabetes mellitus or significant cardiovascular comorbidities (see below).

Home BP monitoring is relatively easy to accomplish, cost-effective and expected to result in better treatment adherence and BP control than BP measurement during clinic visits only.[83] 24h ambulatory BP measurement (ABPM) can identify subjects who do not show a normal BP decrease during night time (non-dippers) and thus may benefit from more intensive antihypertensive drug treatment, or drug dosing during evening hours; this issue warrants further study.[84]

BP control can be achieved by lifestyle modification and medical treatment. Although not formally studied in ADPKD patients, it is expected that achieving or maintaining a "healthy" weight (i.e., body mass index (BMI) 20-25 kg/m^2), undertaking an exercise program (aiming for at least 30 minutes 5 times per week), and lowering salt intake (≤90 mmol/day of sodium, corresponding to ≤5 g/day of sodium chloride and ≤2 g/day of sodium) will lower BP and consequently improve long-term cardiovascular outcome. The case for a salt-restricted diet is strengthened by observations that ADPKD patients have been shown to be sodium overloaded, have sodium-sensitive hypertension,[76,85] and the association between higher sodium intake and increased TKV in the CRISP study.[86]

It is generally accepted that agents that interfere with the RAAS should be first-line BP-lowering agents based on evidence of a hyperactive RAAS in ADPKD patients, the observation that these agents lower albuminuria and left ventricular mass more than other BP-lowering agents, and limited clinical evidence suggesting more renoprotection.[82,87-89] Angiotensin-converting enzyme inhibitor (ACEi) and angiotensin-receptor blocker (ARB) are regarded equivalent, although formal evidence is limited, and either can be used at the discretion of the treating physician. A small study (n=20) suggests that the ARB telmisartan is equivalent to enalapril in lowering BP, but has

more potent antiproteinuric, anti-inflammatory and antioxidative effects in ADPKD hypertensive patients with microalbuminuria.[90] RAAS blockade should be combined with a sodium-restricted diet to enhance the BP lowering, cardioprotective and potential renoprotective effects.[88] In the HALT PKD clinical trial, the administration of an ACE inhibitor alone was sufficient to achieve blood pressure control in the majority of patients, supporting the utilization of this class of antihypertensive agents as first-line blood pressure lowering agent. The utilization of an ACEi and ARB combination did not confer any additional benefit compared to an ACEi alone.[50] The place of mineralocorticoid receptor antagonists in ADPKD has not been ascertained and is worthy of study because they may exert anti-fibrotic effects[89] and interstitial fibrosis is an essential part of later stage ADPKD.[47]

There is controversy as to which second-line BP-lowering agents should be used. Large RCTs in non-ADPKD populations suggested that calcium channel blockers and diuretics may be preferred over beta-blockers for cardiovascular protection.[88] On the other hand, there are theoretical concerns that argue against using these agents in ADPKD. Calcium channel blockers may lower intracellular calcium concentration in collecting duct cells. This may result in an increase in tubular cell proliferation and fluid secretion, in turn leading to accelerated cyst growth and kidney function decline.[90] Diuretics increase plasma arginine vasopressin concentration (AVP), and there is experimental and clinical evidence suggesting that higher levels of AVP are also associated with more rapid kidney and cyst enlargement.[91,92] Furthermore, these agents may also increase uric acid and increase the activity of the RAAS in ADPKD, which in turn, could lead to accelerated disease progression. Comorbid conditions may influence the choice for a specific class. For instance, in patients with angina, beta-blockers may be preferred, and in subjects with prostate hypertrophy, alpha-blockers would be appropriate.

Diagnosis and management of hypertension in pediatric patients

Vascular abnormalities in ADPKD are evident from a young age. Epidemiological studies indicate an increased risk for hypertension as well as increased left ventricular mass index (LVMI), even in children with BPs in the prehypertensive or "borderline" range.[93,94] It is therefore recommended to screen children with a family history of ADPKD for hypertension, despite ethical implications of positive findings.

The approach to hypertension screening is dependent on country-specific circumstances. For instance, in some countries, all children undergo regular medical check-ups (including BP measurement) at school. In other countries, children routinely visit a pediatrician and BP may be checked as part of routine well childcare. In countries where children are not regularly seen by a physician and/or BP measurements are not standard practice, it is advised that children with a family history of ADPKD have their BP checked by a practitioner with experience in BP measurement in children. There is no consensus at what age such screening should be started, nor what the frequency should be. Screening from the age of 5 years onward, with an interval of 3 years in cases in which no hypertension is found, seems prudent. The diagnosis of hypertension is made when systolic or diastolic BP is $\geq$95th percentile for age, height and sex, in accordance with prevailing pediatric guidelines.[95]

When hypertension is diagnosed in children with a family history of ADPKD, ADPKD is the most likely underlying cause. Screening for other causes of secondary hypertension, therefore, will probably have limited utility and US will likely demonstrate polycystic kidneys. While establishing the diagnosis of ADPKD in a hypertensive child at risk for ADPKD may impact management (e.g., referral to specialist, choice of anti-hypertensive medication), it is important to recognize that the diagnosis may have significant psychological and economic consequences for the child and parents. Additional diagnostic testing, specifically US, should therefore be undertaken only after careful discussion of the possible consequences with the parents.

Treatment of hypertension in the pediatric population should follow prevailing pediatric guidelines. Based on data from the adult population (outlined above) and limited clinical evidence in the pediatric population,[96] RAAS blockade by either an ACEi or ARB is preferred as first-line treatment but should be used with caution in female adolescents at risk for teen-age pregnancies because of their teratogenic effects even in the first trimester of pregnancy.[97]

"Conventional" renoprotective treatments

Most ADPKD patients develop progressive renal insufficiency that eventually leads to ESRD between 40 to 70 years of age.[98] While several renoprotective strategies have been identified in non-ADPKD CKD (e.g., strict BP control, RAAS inhibition and low-protein diets), testing of such interventions in ADPKD has led to disappointing results.[82,99,100] However, many of these studies were underpowered, had short periods of follow-up or included patients in early disease stages at low risk for progression and with relatively stable renal function, in whom it is difficult to detect potential beneficial effects.

Recently, the results of the HALT PKD clinical trials have been published.[50,101] In study A, 558 hypertensive patients with ADPKD (15 to 49 years of age, with an eGFR >60 ml per minute per 1.73 m^2) were randomly assigned to either a standard blood-pressure target (120/70 to 130/80 mm Hg) or a low blood-pressure target (95/60 to 110/75 mm Hg) and to either lisinopril plus telmisartan or lisinopril plus placebo.[50] In study B, 486 patients hypertensive patients with ADPKD (18 to 64 years of age, with eGFR 25 to 60 ml per minute per 1.73 m^2) were randomly assigned to receive lisinopril plus telmisartan or lisinopril plus placebo, with the doses adjusted to achieve a blood pressure of 110/70 to 130/80 mm Hg.[101] Both studies showed that an ACE inhibitor alone can adequately control hypertension in most patients justifying its use as first-line treatment for hypertension in this disease. Study A showed that lowering blood pressure to levels below those recommended by current guidelines in young patients with good kidney function reduced the rate of increase in kidney volume (by 14%), the increase in renal vascular resistance, urine albumin excretion (all identified in CRISP as predictors of

renal function decline), left ventricular mass index, and marginally (after the first four months of treatment) the rate of decline in estimated glomerular filtration rate (eGFR). The overall effect of low blood pressure on eGFR, however, was not statistically significant, possibly because the reduction of blood pressure to low levels was associated with an acute reduction in eGFR within the first four months of treatment. Although these results may not be unanimously viewed as positive, they do underline the importance of early detection and treatment of hypertension in ADPKD. The addition of an ARB to an ACE inhibitor did not confer additional benefit.

Two observational studies have suggested that in ADPKD patients, the average age at start of RRT has increased considerably during the last two decades.[102,103] A recent study of ERA-EDTA Registry data on patients starting RRT between 1991 and 2010, spanning 12 European countries with 208 million inhabitants, also showed that mean age at onset of RRT among ADPKD patients (n=20,596) has increased, albeit considerably less than in the two aforementioned studies from 56.6 to 58.0 years.[1] While the RRT incidence did not change among ADPKD patients less than 50 years of age, it increased among older ADPKD patients (above the age of 70). These data suggest that the increased age of ADPKD patients at the onset of RRT may be explained by increased access of elderly to RRT, or by lower competing risk of mortality risk prior to the start of RRT, rather than the consequence of effective renoprotective therapies.[104] No changes in age or alterations in male to female ratio were observed among ADPKD patients who have started RRT in Catalonia between 1984 and 2009.[105]

Although a low-protein diet did not show an effect on the rate of renal function decline in ADPKD patients,[100] lowering protein intake to 0.8 g/kg/day is still recommended when eGFR is less than 30 ml/min/1.73 m^2 to avoid uremic complications in accordance with the 2012 KDIGO Guideline on CKD Evaluation and Management.[80] Prescribing a protein restricted diet should be done with appropriate patient education, preferably by a renal dietician, and patients on such a diet should be monitored for malnutrition, especially those patients with high total kidney and liver volumes, for whom dietary intake of nutrients may become insufficient.

“Novel” ADPKD specific renoprotective treatments

Based on better knowledge of pathophysiological processes, a large number of novel targets for lifestyle and medical interventions have been proposed.[106] In the past decades, experimental and epidemiological studies have suggested a detrimental role of the antidiuretic hormone AVP in ADPKD. V2 receptor activation by AVP *in vitro* increases intracellular cAMP levels, and consequently is believed to lead to cyst formation and cyst growth.[91,107-110] Serum levels of AVP and its surrogate copeptin are elevated in ADPKD patients and their levels have been associated with disease severity in cross-sectional studies[111] and disease progression in longitudinal studies.[92] These observations provided the rationale to study interventions that inhibit this cAMP-mediated pathway via increased water intake or use of vasopressin V2 receptor antagonists.

While beneficial effects of increased water intake in ADPKD have been suggested by animal studies,[112] confirming clinical data in humans are lacking. Given the theoretical background and the evidence from experimental data, we advise patients to increase their water intake. There is a controversy on how to identify ADPKD patients that may benefit from increased water intake, and the level to which water intake should be increased. Some have advised to increase the intake of water to achieve an average urine osmolality of 250 mOsm/kg.[113] Whether an increase in water intake can be sustained over long periods of time remains to be determined.[114] The risk of hyponatremia has to be considered, particularly in patients who have impaired kidney function and are also on a sodium restricted diet and receiving diuretics or drugs that can inappropriately stimulate the release of vasopressin or potentiate its action, such as serotonin reuptake inhibitors and tricyclic antidepressants.[113] It should also be noted that a recent study in 34 patients failed to demonstrate a beneficial effect of increased hydration in ADPKD.[115] Because the study was not randomized, lasted only one year, and the patients in the high water group had a higher salt intake (reflected by higher urine sodium excretion), it needs to be interpreted with caution. Long-term randomized studies of enhanced hydration in ADPKD are needed.

Given the importance of dietary interventions for the treatment of hypertension, as well as prevention of uremic symptoms and possibly to prevent renal function decline, we advise that dietary compliance be monitored with 24h urine collections to measure urine volume and excretions of sodium and urea nitrogen. Caffeine is a methylxanthine that increases intracellular cAMP levels in cultured ADPKD renal epithelial cells.[116] However, the clinical effects of caffeine restriction have been insufficiently investigated in ADPKD to support a firm recommendation on the limits of intake. A cross-sectional study of 102 ADPKD patients and healthy controls showed a low level of caffeine consumption by ADPKD patients likely due to awareness of the recommendation for caffeine restriction and no association between caffeine intake and kidney volume within the range of caffeine intake by ADPKD patients in this study (0-471 mg/day).[117] For now, avoiding high caffeine intake seems justified as a general principle.

There are exciting developments with respect to medical treatments to manage renal disease progression in ADPKD.[118] There is overwhelming evidence for enhanced mTORC1 signaling in PKD cystic tissues, and preclinical trials of mTOR-inhibiting rapalogs (sirolimus and everolimus) in rodent models have been mostly encouraging. At doses and blood levels achievable in humans, sirolimus and everolimus were effective in a rat model of PKD affecting proximal tubules[119,120] but not in a model of ARPKD affecting the distal nephron and collecting duct.[121] Mice tolerate much higher doses and blood levels than rats and humans, and these high doses of rapalogs were consistently effective in orthologous and nonorthologous mouse models.[122,123] However, the results of clinical trials in ADPKD stages with early, as well as later stage CKD have been discouraging,[124-126] likely because blood levels capable of inhibiting mTOR in peripheral blood mononuclear cells do not inhibit mTOR in the kidney.[127] Several strategies to overcome the systemic toxicity and limited renal bioavailability of rapalogs deserve further study.[128-130]

The TEMPO 3:4 trial studied the effects of the vasopressin V2 receptor antagonist tolvaptan in 1445 ADPKD patients with an estimated creatinine clearance ≥60 mL/min and a TKV of ≥750 mL.[49] This RCT demonstrated a significant beneficial effect on the

rate of growth of TKV (-48%) and rate of eGFR decline (-26%) in patients with ADPKD. Tolvaptan was approved in March 2014 by the regulatory authorities in Japan for the suppression of progression of ADPKD in patients with increased and rapid rate of increase in TKV.[131] In the United States the FDA requested the manufacturer of tolvaptan to provide additional data to further evaluate the efficacy and safety of this drug in patients with ADPKD.[132] Concerns raised during the initial review process included: 1) not accepting TKV as an established surrogate; 2) uncertainty introduced by missing data and a post-treatment baseline for the key secondary endpoint; 3) potential risk for hepatotoxicity; and 4) the "small" 1 mL/min/1.73 m^2/year (26%) improvement in renal function decline. Applications for approval of tolvaptan for the treatment of ADPKD are currently under review by the European Medicines Agency (EMA) and Health Canada.

Somatostatin analogues, such as lanreotide and octreotide, have been studied for their effects on liver volume in ADPKD patients with symptomatic polycystic livers. Three placebo controlled RCTs all indicated a favorable effect on this outcome, and also suggested beneficial kidney volume growth reducing effects and preservation of kidney function.[133-136] These trials were of short duration and included a relatively small number of patients. Therefore, they do not allow firm conclusions. The recently published ALADIN study[137] included 79 ADPKD patients with an eGFR ≥40 mL/min/1.73 m^2 randomized to intramuscular injections of octreotide-LAR or placebo. The primary outcome variable, a mean increase in TKV at three years of follow-up, showed numerically smaller growth in the octreotide-LAR group than in the placebo group (220 versus 454 mL). The difference, however, was not statistically significant. A favorable effect was noted on the secondary outcome of kidney function, but this endpoint also did not reach statistical significance. These findings provide support for larger RCTs to test the protective effect of somatostatin analogues against renal function loss. At least one of such trials that includes 300 ADPKD patients with CKD stages 3a and 3b is ongoing.[138] Until the results of larger trials become available, somatostatin analogues should not be prescribed for renoprotection outside of a research study.

Lastly, an RCT of HMG-CoA reductase inhibition with pravastatin in ADPKD children with an estimated creatinine clearance ≥ 80 ml/min/1.73m^2 showed slower kidney volume growth and reduced loss of kidney function.[139] These promising data need confirmation also in the adult ADPKD population. A two-year, randomized open-label clinical trial of pravastatin in 49 adult ADPKD patients with all levels of renal function showed no significant differences in the rate of GFR decline or level of proteinuria between the active treatment and placebo arms despite a significant fall in total serum cholesterol in the pravastatin-treated patients.[140] Larger, longer duration studies are needed.

Hematuria and cyst hemorrhage

Cyst hemorrhage or gross hematuria occur in approximately 60% of patients. Cyst hemorrhage can be associated with fever and differentiation from cyst infection may be difficult. Gross hematuria can result from cyst hemorrhage, nephrolithiasis, infection and rarely renal cell or urothelial carcinoma, but often no specific cause can be identified. In young individuals with ADPKD, gross hematuria is commonly seen following impact trauma associated with sports and physical activity. Hematuria is positively associated with increased kidney volume and cyst wall calcifications. Microscopic hematuria also occurs in ADPKD but its frequency has not been well defined.

Hematuria can be asymptomatic or painless, or it can associate with acute pain syndromes necessitating medical attention and narcotic analgesics. Episodes of cyst hemorrhage or gross hematuria are usually self-limited and resolve within 2 to 7 days. If symptoms last longer than 1 week or if the initial episode of hematuria occurs after age 50 years, investigation to exclude neoplasm should be undertaken. Rarely, bleeding can be persistent or severe, sometimes with extensive subcapsular or retroperitoneal hematomas, requiring hospitalization. Temporary discontinuation of RAAS inhibitors and diuretics to avoid acute kidney injury during an episode of acute cyst hemorrhage has been suggested.[141] The antifibrinolytic agent tranexamic acid has been used successfully to treat the hemorrhagic complications of ADPKD, but no controlled studies have been performed.[142]

Nephrolithiasis

Nephrolithiasis and cyst wall calcifications are common in ADPKD. Increased urinary stasis and metabolic factors (reduced urine pH, ammonium excretion and urinary citrate) account for the increased frequency of stones.[143-146] Whether nephrolithiasis associates with an increased risk for renal insufficiency, as it has been reported in the general population, is uncertain.[147] CT is the best imaging technique for the detection and evaluation of kidney stones. Dual energy CT can differentiate uric acid from calcium containing stones.[148,149] Medical treatment of nephrolithiasis in patients with ADPKD is the same as in patients without ADPKD. Potassium citrate is the treatment of choice in the three stone-forming conditions associated with ADPKD: uric acid nephrolithiasis, hypocitraturic calcium oxalate nephrolithiasis, and distal acidification defects. Information on indications and results of surgical interventions for nephrolithiasis are limited to reports of center experiences and therefore subjected to substantial bias. Nevertheless these reports suggest that extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy can be used in most patients with ADPKD without increased complications compared to patients without ADPKD.[150] Flexible ureterorenoscopy with laser fragmentation has also been used safely and effectively with less risk for traumatic nephron loss.[151,152]

Management of renal cyst infection

Recent meta-analyses highlight the course and successful management of both renal and liver cyst infections.[153] The presence of fever, abdominal pain, and high sedimentation rate or level of C-reactive protein (CRP) should raise the suspicion of a cyst infection, but the differential diagnosis is broad and a definitive diagnosis is hindered by the lack of specificity of conventional imaging studies.[154,155] Blood and urine cultures may be negative and cyst aspiration for culture should be considered if a complex cyst in the right setting is identified. By some reports 18 F-fluorodeoxyglucose-positron emission tomography (FDG-PET) is particularly helpful in identifying infected cysts,[153] but it is not widely available or reimbursed for this indication in some countries and there is no consensus on whether it provides additional information that changes medical decision making.[156,157] Lipid-permeable anti-microbial agents such as

fluoroquinolones and trimethoprim-sulfamethoxazole, depending on sensitivity (if available), remain the standard treatment for cyst infections.[158] Once antibiotic therapy has been initiated, there is wide variability regarding duration of treatment and indications and timing of percutaneous or surgical draining; however extended antibiotic therapy is often warranted. Efficacy of antibiotic treatment and infection eradication are defined by the disappearance of fever, normalization of CRP levels, and at least two negative blood and/or urine cultures. Cyst infection may recur even after adequate periods of antibiotic therapy.

Management of chronic pain

Kidney pain is common in patients with ADPKD and it can be severe and disabling.[159-161] It may develop after an episode of acute pain and is likely maintained by aberrant activity of sensory and autonomic neurons innervating the kidney, renal pelvis and ureter. It has a negative impact on sleep, activity, mental status, and social relationships. Health care providers often fail to discuss pain during encounters with patients, leading to suboptimal management. Ongoing support to patients is essential for the management of chronic pain. Careful history taking and physical exam (location and characterization of the pain) are the initial steps.[160,161] Differential diagnosis should be sought by a multidisciplinary workup with radiologists, physical therapists, and pain specialists. Pre-medication therapy needs to be initiated with consultation of the patient and physical therapist. If needed, a sequential medication approach should be based on the WHO's pain relief ladder.[160,161] Percutaneous cyst aspiration is helpful as a diagnostic procedure to determine whether a more permanent intervention such as cyst sclerosis or laparoscopic cyst fenestration is worth pursuing.[162,163] Celiac plexus blockade, radiofrequency ablation, and spinal cord stimulation have also been used.[164] Thoracoscopic sympathosplanchnicectomy may be helpful in some patients with disabling pain but it is invasive and has potential complications such as pneumothorax and orthostatic hypotension.[165] Laparoscopic renal denervation has been helpful in a small series of patients.[166] Recently, percutaneous transluminal catheter-based denervation has also been shown to be effective for the treatment of kidney pain in single case reports and deserves further evaluation in ADPKD.[167,168]

Reproductive issues

All women of reproductive potential should receive counseling on potential aggravation of polycystic liver disease (PLD) with exogenous estrogen or progesterone exposure. Counseling for both parents should also discuss the risk of passing on the disease to their offspring, and the risks to both the baby and mother should pregnancy take place. Preemptive discontinuation of RAAS inhibitors is necessary due to the potential teratogenicity and increased risk of acute renal failure in the developing fetus. Utilization of appropriate antihypertensive medications documented to be safe in pregnancy is important.

Most of the available information on maternal and fetal outcomes during pregnancy in ADPKD was collected retrospectively in the 1980's and 1990's.[169,170] In general, ADPKD women with normal BP and kidney function have a favorable course during pregnancy. Nevertheless, pregnancy induced hypertension and preeclampsia occur more frequently. These rates increase when hypertension is present prior to the pregnancy. Recent data indicate that preeclampsia is a risk factor for future development of ESRD in the general population, but its contribution to disease progression in ADPKD has not been studied.[171] Multiple pregnancies (> 3) have been reported to be associated with a greater risk for decline in kidney function in ADPKD.[172]

Similar to general CKD, ADPKD women with established renal insufficiency are at increased risk for early fetal loss, difficulty in controlling hypertension and accelerated loss of kidney function.[173] Because of ADPKD pregnancies are associated with a higher frequency of new onset hypertension, pre-eclampsia, intrauterine growth retardation and premature delivery, referral to a high-risk obstetrician is recommended especially in patients with hypertension or elevated creatinine level.

New fetal US technology and improved imaging, specifically with regard to fetal kidneys and liver, presents an opportunity for prenatal screening for ADPKD. Currently this is not recommended due to ethical concerns of assigning a diagnosis when no proven therapy is available; lack of data regarding the application of prognosis and diagnosis to

abnormal kidney or liver fetal US findings; and limitations of semi-quantitative measures of amniotic fluid levels with regard to renal prognosis. Given the importance of the intra-uterine environment on terminal nephron differentiation and birth weight, a known risk factor for the development of CKD, further research into the role of intra-uterine environment in contributing to disease severity in ADPKD should be conducted.

4. MANAGEMENT of ESRD

ADPKD leads to renal failure in most affected individuals. While several aspects of ESRD management can be inferred from data in non-ADPKD patient populations, there are some issues which are specifically relevant for ADPKD patients.

Optimal choice of RRT

Kidney transplantation is the optimal choice of RRT in appropriate patients with ADPKD. This recommendation is based on the presumed applicability of data in the general ESRD population to ADPKD patients and on observational data in single centers and national or regional registries in France,[174] Denmark,[103] the US,[175] Italy,[176] and Catalonia.[105] Furthermore, the degree of comorbidity is generally lower in ADPKD than in other types of ESRD patients, and thus a higher percentage of the former is likely to benefit from renal transplantation. As for patients with other kidney disease etiologies, a direct comparison of the prognosis of transplanted and non-transplanted patients is difficult, due to strong selection bias. A comparison of the prognosis of transplanted patients with patients who are equally qualified for transplantation but still on the waiting list, has shown a benefit of transplantation in the general ESRD population.[177]

As in the general ESRD population, living kidney donation, ideally performed as preemptive transplantation is likely to be associated with best outcomes in ADPKD patients.[178] However, a direct comparison between the results of preemptive and later transplantation has not been performed in ADPKD patients and the time on dialysis associated with a worsening of prognosis is unknown. The long course of ADPKD, the

high level of family awareness and the predictable rate of loss of renal function facilitate arrangements for preemptive or at least early transplantation from a living donor. The limited number of potential donors in some affected families raises the question about donation priorities, in particular when children already have reduced kidney function at the time when one of their parents develops ESRD. Appropriate individual and family counseling is required to support decision making in such situations.

When transplantation is not an option, or for those waiting for transplantation, either hemodialysis (HD) or peritoneal dialysis (PD) are suitable treatment modalities. Although intra-abdominal space restrictions, increased risk for abdominal wall hernias and increased prevalence of colonic diverticula may pose challenges, ADPKD is not a contraindication for PD. The most convincing evidence supporting this conclusion comes from Hong Kong, where a general policy for starting ESRD therapy with PD is being implemented for all ESRD patients: ADPKD patients were not found to experience an increased risk of treatment failure.[179] Others have also reported the feasibility of PD in ADPKD.[180,181] Nevertheless determining risk factors for PD failure and complications based on patient history and measurements of total kidney and liver size and abdominal cavity volume are desirable to support rational decision making.

Preparation for transplantation, nephrectomy prior to kidney transplantation

In preparing ADPKD patients for kidney transplantation, the removal of one kidney is frequently considered. However, nephrectomy in ADPKD patients, even when performed as elective surgery, is associated with significant morbidity, potential need for blood transfusions, and procedure-related mortality.[158,182-185] Therefore the indication should be based on a risk-benefit analysis and kidneys should not be routinely removed prior to transplantation. Hand assisted laparoscopic nephrectomy may be better tolerated, although conversion to open nephrectomy may be necessary for very large cystic kidneys.[186-188] Possible indications include recurrent and/or severe infection, symptomatic nephrolithiasis, recurrent and/or severe bleeding, intractable pain, and suspicion of renal cancer. Insufficient space for insertion of a kidney graft may represent an indication for native nephrectomy, but establishing this need is difficult and practices

vary widely, with pre-transplant nephrectomy rates between 3% and 100%.[174,182,184,189] While no direct comparisons of different strategies are available, on average less than one third of patients in published series undergo pre-transplant nephrectomy,[174,189,190] a figure that may serve as a benchmark for transplant programs. The decision for or against nephrectomy should also take into account that native kidney size typically declines after transplantation.[191] Space considerations are usually an indication for unilateral rather than bilateral nephrectomy. Experience with both, prior and simultaneous nephrectomy has been reported[189,192] but both practices have not been directly compared in a prospective and randomized fashion. Transcatheter artery embolization has been suggested as an alternative to nephrectomy to obtain sufficient volume reduction for graft implantation.[193]

Apart from the consideration of nephrectomy and, in very rare cases, combined liver/kidney transplantation, the evaluation of ADPKD patients prior to transplantation is the same as for non-ADPKD candidates. Some centers screen patients for ICA prior to transplantation, but the risk-benefit relationship of this approach remains unknown. Practice varies also with respect to screening for diverticular disease. Evaluation of BMI needs to take into account the weight of severely enlarged organs.

Post-transplant complications in ADPKD patients

There is no evidence to suggest that ADPKD patients should be treated with different immunosuppressive protocols as compared to other transplant recipients.

Overall, post-transplant morbidity appears not to be increased in ADPKD patients as compared to other, non-diabetic transplant recipients. However, specific complications have been reported to be more frequent, including new onset diabetes,[174] gastrointestinal (GI) complications,[194,195] erythrocytosis,[174] urinary tract infections,[174,196] thromboembolic complications,[174] and hemorrhagic stroke.[197]

Use of kidneys from ADPKD patients for transplantation

Occasionally the question arises whether kidneys from a deceased ADPKD patient can be offered for transplantation. Under specific circumstances the use of ADPKD kidneys with acceptable kidney function and size is an option, provided there is fully informed consent of the recipient. The success of such an approach has been reported.[198] However, the optimal donor, organ, and recipient characteristics needed to make this an acceptable strategy have not been defined.

Risk for renal cancer in ADPKD with renal failure

The incidence of clinically significant renal cell carcinoma (RCC) in ADPKD patients on dialysis or after transplantation is not known to be increased as compared to patients with other kidney disease etiology.[199,200] A recent study from the Scientific Registry of Transplant Recipients of 10,166 and 107,339 kidney recipients with and without ADPKD, respectively, found no increased risk of RCC associated with this diagnosis.[201] However, examination of ADPKD kidneys after nephrectomy of dialysis patients revealed a 5% to 8% incidence of RCC, most measuring ≤2 cm in diameter.[202,203] Although this observation raises concerns about the potential for malignant transformation in ADPKD kidneys, there is currently insufficient evidence for systematic screening in asymptomatic patients. Furthermore, the diagnostic value of non-invasive US is limited in ADPKD kidneys and the appropriate screening methodology (i.e., contrast-enhanced CT) is associated with costs and potential harm. Given the increased risk of nephrectomy in ADPKD patients, the optimal management of suspicious lesions (i.e., observation vs. intervention) remains unknown and as such decisions should be taken individually. In any case, visible hematuria requires evaluation of the entire urinary tract for cause.

Hemoglobin, BP, and lipid targets in ADPKD patients on dialysis

There is no evidence that therapeutic targets for BP, lipids or hemoglobin should be different in ADPKD compared to other patients on dialysis. Due to better preserved erythropoietin production, anemia is on average less severe in ADPKD patients than in

other CKD patients [180] and some patients spontaneously maintain hemoglobin levels above current treatment targets without receiving ESAs.[204] In general such patients do not appear to be at increased risk for thromboembolic complications. The threshold for intervention by phlebotomy can therefore be higher than the hemoglobin target range of patients treated with ESAs.

Anticoagulation

There is insufficient evidence to recommend a specific management of anticoagulation in ADPKD patients with ESRD. The history of bleeding and/or macrohematuria episodes should influence treatment decisions and trigger work-up in individual patients. Whether and to what extent the risk and/or severity of bleeding from ICA are increased by systemic anticoagulation is unknown.

5. MANAGEMENT of EXTRARENAL COMPLICATIONS

ADPKD is a systemic disorder, associated with numerous extrarenal manifestations that can be a significant cause of morbidity and mortality.[205] ICA and PLD are among the most common and debilitating of these manifestations.

Intracranial aneurysms

ICA rupture is one of the most serious complications of ADPKD, resulting in combined morbidity and mortality rates of 35-50%.[206-208] Given the safety and accuracy of current imaging methods for screening along with the availability of less invasive treatment modalities, early pre-symptomatic detection is desirable. However, major questions include: Is widespread screening for ICA of all patients with ADPKD justified? If not, which patients should be screened? If screening is negative, should patients be screened again and if so, at what time interval? When an unruptured ICA (UIA) is detected, what are the indications to intervene? If an UIA is recommended for conservative management, what are the recommendations for follow-up to reduce the risk of rupture?

There is limited information with respect to the natural history of ICA in ADPKD and most of our knowledge comes from small, single center observational studies. These studies suggest that the prevalence of asymptomatic ICA detected by magnetic resonance angiography (MRA) among patients with ADPKD is ~9-12%, compared with ~2-3% in the general population.[209-214208-213] The prevalence rates of ICA vary between ~20-27% in ADPKD patients with a positive family history vs. ~6% in those lacking a family history.[209-213,215]

There are no clear risk factors for ICA rupture in patients with ADPKD, other than family history of an ICA. The average age at ICA rupture is ~40 years, approximately 10 years earlier than in the general population.[206,207,216-218] Overall there appears to be no difference in the rate or size of ICA rupture between ADPKD and the general population.[216] One large international study of UIA (the ISUIA study) found that the rate of ICA rupture correlated with increasing size, location in the posterior vs. anterior circulation and prior history of subarachnoid hemorrhage.[208] Pre-symptomatic screening for ICA in the ADPKD population shows that 80-90% of ICA are in the anterior circulation of the circle of Willis, nearly all <7mm. If the findings from the ISUIA study are extrapolated to ADPKD, then most ICAs that are detected by pre-symptomatic screening would fall into a low risk category for rupture. However, there are reports of ICA rupturing at small sizes in ADPKD.[206,215,216,218] It has been suggested that small ICAs that form rapidly may be at the greatest risk for rupture soon after they develop.[208] Whether this process evolves differently in ADPKD is unknown.

It is often assumed that patients with ADPKD are not at increased risk of intracranial hemorrhage once they are on RRT. A retrospective analysis of the US Renal Data Service database, however, revealed that ADPKD is a significant predictor of this complication in ESRD, with an adjusted hazard ratio of 1.63 vs. non-ADPKD.[219] The authors observed that the increased risk did not manifest until approximately 3 years after starting dialysis and they surmised that the risk was mitigated after kidney transplantation.

ICA can be associated with mutations in both *PKD1* and *PKD2*.[220] Some series, but not others, have also reported that the median *PKD1* mutation position is more 5' (N-

terminal) in individuals with a vascular phenotype compared with controls.[220,221] Additional analyses in larger cohorts would be needed to determine whether mutation class could be used reliably for risk stratification.

A decision making analysis based on the ICA prevalence and risk of rupture[209] revealed that screening the ADPKD population at age 30 would result in a gain of quality-adjusted life years only if the 5-year rupture rate exceeds 8.5%, a figure that is far higher than the actual rate reported in ADPKD.[197]

Based on the data summarized above, ADPKD patients with a family history of ICA or a personal history of ICA rupture should be screened for asymptomatic ICA. Patients with no or unknown family history should be counseled about the risks of ICA that are associated with ADPKD as well as the pros and cons of pre-symptomatic screening. Those individuals who remain anxious about their risk should be offered screening. Screening should also be considered in individuals with high-risk professions (e.g., pilots) where ICA rupture might place lives of others at risk. Routine, long-standing headaches are not an indication for screening. However, the sudden occurrence of atypical, suddenly intense headache (often described as a thunder clap headache) possibly coupled with other neurologic symptoms, should be considered a neurologic emergency and requires urgent evaluation.[207]

Traditionally, angiographic methods have been the gold standard for diagnosis of ICA. However recent advances in technology and the desire to avoid iodinated contrast media in patients with renal disease have made MRI the screening method of choice. A recent study showed that 3D time-of-flight (TOF) MRA with a 3T magnet had a screening sensitivity of 67% for ICAs <3mm, 87% for those 3-5mm and 95% for those >5mm.[222] This was equivalent to the sensitivity of CT angiography where patients experience both radiation and contrast exposure. Therefore, TOF MRA without gadolinium enhancement, preferably with a 3T-imaging platform, should be used for pre-symptomatic screening.[223]

There is only one study that followed individuals with negative initial screening MRAs. Schrier et al. found that 2 out of 76 patients (one patient having a family history of ICA

rupture) with a negative MRA developed an ICA on re-screening after 10 years.[224] Based on this limited evidence, it appears prudent that individuals with a positive family history and a negative screening MRA should be re-screened at 5-10 year intervals while there is no need to re-screen those with a negative family history. Larger studies are needed to support this recommendation.

Management of UIA should be discussed with a multidisciplinary team including the treating nephrologist, neurosurgeon and interventional neuroradiologist. The size and location of the ICA, the general health and age of the affected individual, and the risk for rupture should determine the therapeutic approach.[210,223] Overall endovascular procedures appear to have lower associated morbidity and mortality in comparison with surgical approaches.[223,225,226] Nevertheless there remains concern with respect to the durability of coil embolization. Treatment is best performed in expert centers with large procedure volumes.

The natural history of UIA in ADPKD has been evaluated in a limited number of small studies,[210,224,227] suggesting that the risk of growth or rupture of small ICAs detected by pre-symptomatic screening in ADPKD patients is quite low. It is therefore reasonable to re-evaluate individuals with small untreated UIAs at intervals that are determined with neurosurgical consultation but usually ranging from 6 months (initially) to every two to three years (after stability has been established). Additional modifiable risk factors including smoking cessation, BP control, limited heavy alcohol use and control of cardiovascular risk factors such as hyperlipidemia should also be addressed. It is recognized that these risk factors for ICA have not been specifically evaluated in the ADPKD population.[228]

Despite the consensus of this panel that widespread screening for ICA is not indicated, other opinions are published,[223] and different attitudes exist across centers. Some centers screen ADPKD patients with either a *de novo* ADPKD (i.e., no family history) or an incomplete family history as well as those undergoing major elective surgery (e.g., cardiac surgery, hepatic resection and kidney/liver transplantation) or before transplantation.

Diagnosis of PLD and implications for contraception

Liver cysts are the most common extrarenal manifestation of ADPKD, with a prevalence >80% by the age of 30.[229] Liver cyst burden increases with age and is greater in women compared with men. Approximately 20% of patients with ADPKD go on to develop symptomatic PLD.[230]

The use of liver imaging to determine the extent of PLD should be part of the initial assessment of all patients with ADPKD. Most patients with PLD are asymptomatic and can be managed conservatively.[230,231] Typically, liver involvement does not cause hepatic dysfunction. However, massive liver enlargement can result in compression of surrounding organs. Compressive symptoms include abdominal pain and distension, back pain, early satiety potentially causing malnutrition, gastroesophageal reflux, compromised lung function with dyspnea or recurrent pneumonia, and hepatic venous-outflow obstruction.[230,232,233] Additional complications include infections, cyst rupture, and hemorrhage.

A number of studies have shown that PLD tends to be more severe in women.[229,234-237] Risk factors for severe PLD include multiple pregnancies and use of exogenous estrogens. In one small prospective non-randomized study, polycystic liver volumes increased over one year in post-menopausal women taking estrogens.[237] There was consensus that exogenous hormones or hormone-containing contraceptives should be avoided in women who have symptomatic or severe PLD. Progesterone, like estrogens, stimulates the proliferation of cholangiocytes, therefore, contraceptives containing only progestogens may not be safer than those containing estrogens.[238]

What are the indications and modalities for intervention in PLD?

Treatment options for PLD include conservative management, surgical intervention, or medical therapy. The indications for intervention include symptomatic PLD with significantly diminished QOL. Several types of surgical approaches can be used to decrease cyst burden. The choice of a specific intervention should be tailored to the

individual patient depending on liver anatomy, stage of PLD, concomitant renal disease and expertise of the medical center.

The surgical options that can be considered for PLD have been reviewed in detail.[239] Aspiration and sclerotherapy involve percutaneous drainage of a cyst with subsequent instillation of an agent such as ethanol that destroys cyst lining cells so that fluid is no longer produced. The main indication for aspiration and sclerotherapy is a large dominant cyst that is causing symptoms. Fenestration involves drainage and surgical/laparoscopic deroofing of cysts. Multiple cysts can be drained at the same time using this procedure, although certain areas of the liver are not amenable to laparoscopic visualization. Partial or segmental liver resection can also be considered in severe, symptomatic PLD when one lobe is relatively spared and the vascular anatomy of the preserved liver is deemed suitable. This procedure can result in substantial morbidity. In one large series (N=124 cases) the perioperative morbidity and mortality were 63% and 3%, respectively.[240] Nonetheless liver resection can provide considerable and sustained symptomatic relief. In the same study, performance status had normalized or improved in ~75% of patients after a mean follow-up of 9 years. Given the complexity and risk of this surgery, partial hepatic resection should only be performed in centers that have extensive experience with this procedure.

Liver transplantation is a last option for selected patients with severe PLD who are not candidates for partial liver resection. This may be a particularly relevant option for ESRD patients who are candidates for renal transplantation. In some countries allocation of liver grafts is based strictly on the MELD (Model for End Stage Liver Disease) score, which doesn't accurately reflect liver disease severity in PLD. Since patients with severe PLD have intact liver synthetic function, they lack markers of liver dysfunction (e.g., international normalized ratio and serum albumin) that contribute to the MELD score, and thus priority on the liver transplant list is usually low. Data from the European Transplant Registry suggests that liver transplant outcomes in PLD patients are comparable to those of non-PLD liver recipients.[241] It must be noted that liver explantation can be challenging in patients with PLD if they develop adhesions as the result of prior liver procedures. Many transplant surgeons are reluctant to transplant

patients who have previously had liver resection due to the potential for serious complications.

Transcatheter arterial embolization of hepatic artery branches that supply major liver cysts has been reported to decrease total liver volume in small series.[242,243] There is limited experience with this procedure at most centers and therefore larger, controlled studies are needed before this therapy can be recommended.

Somatostatin analogues are a promising new avenue to reduce liver cyst volume in PLD.[234] These agents bind to somatostatin receptors and are thought to act by decreasing cAMP levels in biliary epithelial cells. Two long-acting somatostatin analogues, octreotide and lanreotide have been tested in clinical trials and yield a small but reproducible and clinically significant decrement in liver volume over 1-2 years of treatment (~ –4% - –6%) compared with ~ 0% - +1.6% in placebo groups.[135,136,244-247]

These agents have been relatively well tolerated, but with side effects including diarrhea, nausea, hyperglycemia and cholelithiasis. Several studies have suggested that most of the benefit is seen over the first year of treatment and that liver cyst volume begins to increase again once the drug is stopped.[245] The response to somatostatin analogues is quite variable but a pooled analysis suggests that women under the age of 48 exhibit the most benefit.[248] Although a small retrospective study suggested that sirolimus used in the post-kidney transplant setting might slow PLD,[249] adding everolimus in a prospective fashion to octreotide did not confer any additional benefit.[250] Thus far, somatostatin analogues have not been approved by regulatory agencies for treatment of PLD and therefore can only be recommended for use in a clinical trial setting. If compassionate, off-label use is contemplated in highly symptomatic cases, then liver volume should be followed using MRI or CT to document efficacy.

How to diagnose and treat liver cyst infections?

Liver cyst infections are a common complication of PLD that can pose diagnostic and therapeutic challenges.[155] Clinical features are non-specific and include fever, right upper quadrant tenderness and laboratory data consistent with inflammation.[251,252]

Serum and cyst fluid CA19-9 levels have been reported to be elevated in liver cyst infection but the levels are variable and diagnostic cut-off values have not been established.[155,253] Based on retrospective data, optimal treatment includes drainage of the infected cyst(s) and appropriate antimicrobial therapy.[254] Sampling and culture of infected cyst fluid is important for guiding antimicrobial therapy. MRI and CT are not sufficiently specific for identifying infected cysts since chronic parenchymal injury is usually present at baseline.[154,155] There are reports showing that FDG-PET may be a sensitive alternative for determining which cyst among many is infected.[254-256] The rationale for this approach is that metabolically active inflammatory cells take up high amounts of glucose. Patients with liver cyst infections may require a prolonged course of antibiotics to treat recurrent or persistent infections.[154] In general the choice of an antimicrobial agent will be guided by the culture results but antibiotics that have good cyst penetration such as fluoroquinolones are strongly advised.[251]

Additional extrarenal manifestations

Extrarenal complications from ADPKD such as cardiac and vascular abnormalities and development of cysts in other organs have also been reported. These are discussed in greater detail below and summarized in Table 3.

Cardiac valvular abnormalities. Mitral valve prolapse is found in up to 25% of ADPKD patients.[257,258] Aortic insufficiency may be found in association with dilatation of the aortic root. Although these lesions can progress with time, they rarely require valve replacement.[2] Pericardial effusion can be detected in up to 35% of ADPKD patients, but it is well tolerated and usually clinically insignificant.[259] We do not recommend screening echocardiography in ADPKD unless a murmur is detected or there are other cardiovascular signs or symptoms.

Extracranial aneurysms. Dissections and aneurysms of many large arteries including ascending aorta,[34,260] popliteal,[261] coronary,[262,263] and splenic arteries[264] have been reported in ADPKD. Abdominal aortic aneurysms, however, do not appear to be

increased in patients with ADPKD.[265] Clinicians should be aware that there may be a predisposition to a vascular phenotype in some ADPKD patients.

Arachnoid membrane cysts are found in 8 to 12% of ADPKD patients.[266,267] Arachnoid cysts are typically asymptomatic. In rare circumstances, arachnoid cysts have been associated with an increased risk for subdural hematoma.[268-270] Chronic subdural hematoma may present with headaches and focal neurologic deficits requiring surgical drainage.[268]

Spinal meningeal cysts are observed in 1.7% of ADPKD patients.[271] They rarely present with features of intracranial hypotension (orthostatic headache, diplopia, hearing loss, ataxia) that is caused by cerebrospinal fluid loss.

Pancreatic cysts are found in about 10% of patients with ADPKD.[272] They are usually asymptomatic but cystic compression of the pancreatic duct may rarely cause chronic pancreatitis.[273]

Diverticular disease. The prevalence of colonic diverticulosis in ADPKD may depend on renal status. In one series of ADPKD patients that had not reached ESRD, there was no increase in diverticulosis compared with controls.[274] However, in a smaller series of patients who had reached ESRD, diverticulosis was found in 50% (7 of 14) of ADPKD patients vs. 15% (13 of 86) of non-ADPKD controls.[275] In another retrospective study of ADPKD patients with ESRD, diverticulitis was found in 20% (12 of 59) of ADPKD patients versus 3% (4 of 125) in non-ADPKD controls.[276] There are case reports of diverticular disease in other regions of the GI tract as well.[277] We do not recommend routine screening for diverticulosis but one should be aware of a possible increased occurrence of diverticulosis in ADPKD patients who have reached ESRD.

Abdominal hernias. A retrospective study identified abdominal wall hernias (inguinal, incisional or para-umbilical) in 38 of 85 (45%) ADPKD patients on RRT vs. 8% in a matched non-ADPKD ESRD cohort.[278] This should be kept in mind when PD is contemplated in an ADPKD patient.

Seminal vesicle cysts are found in about 40% of male ADPKD patients but are not correlated with semen abnormalities.[279] Seminal vesicle cysts are rarely symptomatic and we do not recommend routine screening.

Infertility. A few studies have associated male infertility and sperm abnormalities (asthenozoospermia, defect in flagella) with ADPKD.[279,280] Whether infertility is more common in males with ADPKD remains unknown. Female infertility has not been associated with ADPKD.

Bronchiectasis. In one retrospective analysis of 95 ADPKD patients, CT scan revealed radiographic bronchiectasis in 37% of the ADPKD group versus 13% of the CKD control group.[281] Bronchiectasis was generally mild with no clinical consequences. Therefore, we do not recommend routine screening and imaging should be guided by symptoms.

Congenital hepatic fibrosis. Congenital hepatic fibrosis complicated by portal hypertension, a constant association of ARPKD, is a rare but potentially life-threatening complication of ADPKD.[282] Increased liver echogenicity on US, decreased platelet count, enlarged left lobe of liver, or enlarged spleen should alert physicians to this possibility. While in these families liver cysts occur in multiple generations, the association with congenital hepatic fibrosis is restricted to single individuals or siblings, suggesting the importance of modifier genes. Upon diagnosis of an index case, siblings should be evaluated for this association.

Table 3. Other extrarenal manifestations of ADPKD

Manifestation	Associated	% Affected	Screen	Comment
Cardiac valve abnormalities[244,245]	Yes	Mitral valve prolapse 25%	No	Screen only if cardiovascular signs/symptoms
Pericardial effusion[246]	Yes	Up to 35%	No	Screen only if cardiovascular signs/symptoms
Extracranial aneurysms[247-251]	Yes, case reports	Unknown	No	Clinicians should be aware of vascular phenotype in some patients
Arachnoid cysts[253-257]	Yes	8-12%	No	Possible increased risk for subdural hematoma
Spinal meningeal cysts[258]	Yes	1.7%	No	Rare cause of spontaneous intracranial hypotension
Pancreatic cysts[259,260]	Yes	10%	No	Usually asymptomatic
Diverticular disease[261-265]	Possibly in association with ESRD	~20-50% in ESRD	No	Increased incidence in patients who have reached ESRD
Abdominal hernias[265]	Yes	Unknown	No	
Seminal vesicle cysts[266]	Yes	~40%	No	Does not correlate with abnormal semen parameters
Male infertility[266,267]	Unknown	Unknown	No	Abnormal semen parameters reported
Bronchiectasis[268]	Possibly	37% in one series vs. 13% controls	No	Mild, no clinical consequence
Congenital hepatic fibrosis (CHF)[282]	Yes, case reports, usually affecting only one generation within a family with ADPKD	Rare	No	Rare but potentially life-threatening; early diagnosis in siblings with ADPKD can be lifesaving with appropriate monitoring and treatment. By comparison, CHF is a constant feature in ARPKD.

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ESRD, end-stage renal disease

6. PRACTICAL INTEGRATED PATIENT SUPPORT

Despite ADPKD being the most common inherited kidney disease encountered by every nephrologist worldwide, there is a lack of knowledge about the needs of and care for patients outside the clinic environment and routine care.

What should a doctor tell or give a patient at first diagnosis?

The first diagnosis contact between the patient and physician has major importance. Studies in cancer patients show that anxiety and distress can be lessened if the physician can recognize the patient's psychosocial needs and convey reassurance and support in that first consultation.[283] However, there are no studies about the ways to communicate about ADPKD to the newly diagnosed and how the latter react to the diagnosis. There is ample evidence to suggest that primary care providers (PCPs) do not have adequate training and knowledge about ADPKD and not all newly-diagnosed patients are referred automatically to a nephrologist. Furthermore, many nephrologists lack time and ability to explain the diagnosis and all its complex implications (e.g., medical, personal, insurance, genetics, etc.).[284] Patient education programs and tools for patients with CKD are available,[285] but there is little research about their implementation and effectiveness, and their relevance for ADPKD patients.

Evidence from one-to-one conversations or online community forums suggests that 'shock' is a common reaction of the newly-diagnosed. A patient may feel 'sad' and sometimes 'angry' at not being told previously by a parent.[286] Individual patient responses will also vary widely according to personality and age, ranging from determination to learn everything about ADPKD to willingness to 'put it away' and forget.

There is consensus that all patients need simple, disease-specific information initially, including a printed material that could be read later or at home. Practical implications such as potential impact on work, insurance, lifestyle and family planning should be included. Where possible, patients should be automatically referred to local or national support groups, online references and be encouraged to find someone to talk to. Each consultation should be individualized, reassuring and tailored to the patient's literacy

level and culture/language. Throughout the consultation, the physician should focus on the possibilities, not the problems, and retain a positive attitude.

Nephrologists should be familiar with the extrarenal associations of ADPKD and appropriately educate their patients. These have been covered above and will not be discussed in detail here. Women should be advised about the increased prevalence of PLD in women and that multiple pregnancies or exposure to estrogens may increase the risk for complications in those with many liver cysts.[235] Physicians should disclose the potential risk for cysts in other organs to provide reassurance and avoid unnecessary investigations. Despite evidence about the low risk of ICA, patients remain fearful particularly when there is family history of ICA rupture. Patients should be advised that common headaches are not due to an ICA/UIA. Conversely, if the headache is a 'thunderclap' type, seeking emergency medical advice is essential. Screening should be offered if the patient requires reassurance or is highly stressed about ICA risk.

Physicians should show empathy towards patients who present with pain. Pain should be addressed quickly to prevent the body becoming sensitized to it. Strategies for pain management in ADPKD have also been covered above.

Family planning

Family planning issues fall broadly into three areas: contraception/family planning, genetic counseling, and PGD/in vitro fertilization (IVF). Considerations include ethical, moral, legal, financial, and religious perspectives. Nephrologists and genetic counselors should be objective in their communication of information and options. A patient (and partner when relevant) should feel sufficiently informed and empowered to make their own decisions. Information about contraception should be provided and individualized, particularly on the risk of PLD in women. Female patients should be referred for a scan to ascertain the severity of the PLD.

For genetic counseling, consistent with current clinical practice, kidney imaging is considered sufficient. Patients should receive precise information about the extent of the disease. With increasing availability of genetic testing and clinical relevance of such

testing for prognosis,[17] physicians and counselors will need to be trained to communicate the potential benefits and limitations of these analyses. Globally, there is a wide variation in awareness, provision and exclusion of reimbursement of genetic counseling services exists throughout the world.

The PGD/IVF subject is controversial but there was consensus that these services should be available to all patients. Cost should not be a consideration for refusal as the long-term cost to society of ADPKD is potentially significant. There is wide variation across countries (from tightly restricted to available and unregulated) in the licensing of PGD for ADPKD.

Talking to children about ADPKD and deciding when to screen

Parents with at-risk but undiagnosed children have three options: 1) screen the children as young as possible and disclose the results to the entire family; 2) screen and disclose results only to the parents; 3) do not screen. Parents have the right to choose. It is preferable to be open with children if parents choose to disclose that one parent has ADPKD,[287] rather than face potential adverse consequences of diagnosis later in life. Parents are advised to disclose the diagnosis to a child, strengthen their knowledge and set a good example by including the entire family in a healthy lifestyle program. Adolescents in particular may experience a range of difficulties (with friendships, relationships, talking about ADPKD, bullying, self-worth, their future, and exclusion from sports) and in need of special support.

What dietary and lifestyle modifications should be recommended?

Patients with ADPKD are advised to avoid high salt/sodium intake, not smoke,[288] eat a healthy diet, keep hydrated, moderate their alcohol intake and take exercise. Additionally, patients should be encouraged and supported to self-monitor their BP and weight. Physicians should explain the implications of blood test results and offer referral to a renal dietitian as necessary.

Despite general consensus on these recommendations, little is known about the effectiveness of these ADPKD-specific ‘healthy’ lifestyle modifications to delaying disease progression and about how to motivate patients to adhere to such a 'healthy' diet/lifestyle. The majority of ADPKD patients and families are confused about what they should, can and cannot eat or drink. It is recommended to have some measures of lifestyle change effectiveness studies, in order to encourage patient adherence. Although there are a few PKD-friendly cookbooks available for all stages of the disease, more are needed and they should be offered in all languages. Renal dietitians tend to care for patients on dialysis who often follow very strict dietary regimens and the tendency is for negative messages, e.g., 'Don't eat this and that'. More comprehensive patient education, with focus on positive messages about diet and lifestyle are required. An example would be “You can qualify for a transplant if you lose weight.” Patient socio-demographics play a role in adherence[289] and this should be factored into dietary/lifestyle guidance. Where possible, patients could be self-empowered through web-apps and research into these types of patient support programs is encouraged.

Similarly, there is controversy about soy in the diet. It is known that soy is a suitable substitute for animal protein in CKD[290] (and ADPKD by extrapolation) but nothing is known about its action on PLD. There is a general lack of patient lifestyle guidance for PLD.

Impact of hobbies and sports

There is a large void of evidence on the impact of exercise in ADPKD patients.[291] Exercise is generally recommended, but an individual risk assessment should be carried out for concerns related to enlarged kidneys and/or liver and a disposition to cyst rupture. Historically, patients have always been told to 'avoid contact sports' but no definitions are given of these. A large retrospective study of 4.4 million 'athlete-exposures' in high school athletes with a single (non-ADPKD) kidney showed very few kidney related injuries.[292] Patients should be cautious of 'hard' contact sports, e.g., American football or rugby, or other potentially problematic activities such as horseback riding, particularly when enlarged kidneys can be felt on physical examination. However, the final decision should be made by the patient or parents.

Do we need to provide doctors with psychological guidelines for the care of ADPKD patients?

Physicians should actively listen and have empathy for psychological and emotional concerns of ADPKD patients, including anxiety about the condition and its impact on normal life, body image/dysmorphic issues, and sexual dysfunction. It is known that anxiety and depression are highly prevalent in CKD patients and are related to lowered life expectancy.[293] Dialysis disfigurement can lead to insecurity and relationship stress. Many couples split during these difficult times, further increasing stress and poor outcomes. Physicians should be trained in asking psychosocial questions to ADPKD patients. A set of indirect questions for healthcare providers may be developed to circumvent the difficulties inherent in asking such questions. Similarly, a set of prompts for these difficult conversations could also be developed for patients to ask their physicians.

There is a lack of knowledge and evidence about the impact of these psychological factors on the QOL of ADPKD patients. Some studies have shown that anxiety is present even in the newly diagnosed, symptomless patients.[294] Another study found depression in over 60% of ADPKD patients.[295] There is no validated tool to measure these factors in ADPKD patients. One study using the SF-36 tool concluded that it lacked the sensitivity and specificity to detect QOL changes, in particular the growing burden of cystic kidneys.[71] Strategies for managing anxiety exist for other chronic conditions[296,297] and should be tested in ADPKD.

Financial impacts of ADPKD: careers, income, life and health insurance

Insurers' actuarial algorithms are out of date and do not take account of improvements in symptom management, especially hypertension.[298] There is inequitable access to insurance with international/regional variation. Diagnosed adults cannot purchase life insurance in many countries and positive diagnosis can impact ability to buy a house in some. Patients and physicians may not disclose it on forms but many insurers now explicitly ask about PKD or 'inherited conditions'. It is recommended that an up-to-date, standardized and endorsed statement about ADPKD be produced that patients could

use when dealing with banks, insurers, employees and health payers. This should be a global PKD community initiative.

Support for patients and families

Nephrologists and PCPs should know where to refer patients for reliable and unbiased sources of information (Table 4) and patient support groups should raise and sustain awareness among healthcare providers of their websites. Patient groups should promote patient empowering. Patients should be encouraged to become their own advocates for care and to ask for support and information from their nephrologists. Studies of medical information available on the internet have suggested recommendations for providing up-to-date authoritative information written for the particular audience.[299] There is a gap in knowledge about the best sources of information, as up-to-date content is not available in all languages. More collaboration between worldwide patient groups is encouraged such as the potential development of a global 'PKD Portal'.

Table 4. List of support information websites for ADPKD by country

Australia	http://pkdaustralia.org
Canada	http://www.endpkd.ca
France	http://www.polykystose.org
Germany	http://www.pkdcure.de
Italy	http://www.renepolicistico.it
Japan	http://www.pkdfcj.org
Netherlands	http://www.nvn.nl/nierziekten-en-behandeling/nierziekten/cystenieren
Spain	http://airg-e.onmedic.org
Switzerland	http://www.swisspkd.ch
UK	http://www.pkdcharity.org.uk
USA	http://www.pkdcure.org

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease

Benefit of recognized 'PKD Center or Clinic' vs. single nephrologist

There is consensus about the value of a multidisciplinary team approach to care, with all relevant specialties provided in one center or clinic to ADPKD patients. Benefits include: a) opportunities for patients to meet other patients; b) opportunities to publicize research studies and speed up recruitment to trials; c) potential for physicians to build up an expert network; d) potential for reduction in inefficiencies from multiple clinic appointments and fragmented care; e) potential for improved patient outcomes. There is evidence of integration benefits and impressive cost savings in the care of patients with rare diseases in general.[300]

There are challenges in the uneven geographical distribution of expertise and patients. Establishment of specialized services in centers of excellence would inevitably result in some patients having to travel long distances to attend. This difficulty could be addressed by the growth in telemedicine, which is implemented across a number of complex care specialties in the US and elsewhere.[301] A 'telenephrology' approach to care in CKD has been proposed and could be adapted for ADPKD.

CONCLUSION AND PERSPECTIVES

As a major genetic disorder affecting up to 12 million individuals worldwide and the 4th most common global cause for RRT, ADPKD is of critical importance for nephrology and society at large. Improvements in the diagnosis and management of the disease manifestations paralleled general advances in medicine during the last century. More recently, improved understanding of the molecular genetics and biology of ADPKD have raised the hope that slowing renal disease progression or even making it inconsequential is within reach. Yet, approaches to the diagnosis, evaluation, prevention and treatment of the renal and extrarenal manifestations of ADPKD vary widely and there are no broadly accepted practice guidelines. Like other types of inherited kidney disorders, challenges and barriers to the translation of breakthroughs in basic science to clinical care of patients with ADPKD exist, with considerable

heterogeneity across various countries.[302] Similarly, the perceptions of the disease are also widely divergent between physicians and patients worldwide.

The KDIGO controversy conference on ADPKD represents the first global initiative that brought together a panel of multi-disciplinary clinical expertise and engaged patients from 20 countries to perform a detailed analysis of the literature and to identify areas of consensus, gaps in knowledge, and research and healthcare priorities. To this end, this conference report has proposed an extensive research agenda with the goal to close up these said gaps and resolve outstanding controversies (Table 5). Current knowledge and the large volume of ongoing clinical trials and large collaborative studies warrant the development of practice guidelines/best practice policies for ADPKD. Facing the identification of priorities for clinical research, there is a need for a global, academic network to prioritize, facilitate, coordinate and avoid duplication of such trials. Patient support organizations play a key role in closing the gap between disease understanding and the development of effective education tools, new treatments, and improved health policies.

Table 5. Gaps in knowledge and research agenda in ADPKD

Topic areas	Gaps in knowledge or outstanding questions	Research agenda
DIAGNOSIS		
Presymptomatic diagnosis in individuals at 50% risk	Factors driving the decision process: Risks (variability of life and disability insurance in different countries) and uncertain benefits of early diagnosis (particularly in children and in different prognostic subgroups).	Studies to better define the natural history of ADPKD in childhood, including different prognostic subgroups (i.e., by mutation screen and/or TKV) and to evaluate the potential clinical benefits of early screening.
Symptomatic diagnosis in individuals at 50% risk	Impact of changing resolution of imaging technologies on diagnostic criteria.	Development of criteria based on number and size of cysts and image resolution.
Diagnosis in newborns and children, or in adults with multiple renal cysts without a family history of ADPKD	Lack of evidence-based algorithms integrating clinical findings with renal imaging and molecular genetic testing.	Development of a diagnostic algorithms based on large cohorts of newborns, children and adults.
Exclusion of diagnosis in living kidney donors at risk	Is the NPV of MRI or contrast-enhanced CT (obtained during the evaluation of kidney donors) higher than that of US?	Development of MRI- and CT-based diagnostic criteria for ADPKD.
Use of PGD in ADPKD	What are the barriers for access to PGD and the reliability of *PKD1* mutation detection in PGD?	Survey ADPKD patients and physicians on awareness and attitudes towards PGD, and identification of access barriers. Examine the performance of single (blastomere) and multiple (trophectoderm) cell biopsies to diagnose ADPKD.
MONITORING KIDNEY DISEASE PROGRESSION		
Total kidney volume and other volumetric parameters as prognostic biomarkers	Do specific volumes (cyst, parenchyma, intermediate) and cyst patterns (number, distribution, complexity, etc) add to the value of TKV?	Further evaluation of existing large imaging collections.
Functional MRI as an early prognostic biomarker	Is RBF measured by MRI useful to monitor disease progression?	Standardization of RBF measurements and further studies to ascertain their value.

Total kidney volume as a clinical trial endpoint	Is TKV an adequate endpoint for RCTs at early stages of the disease? Under what conditions?	Evaluation of RCTs to determine under what conditions TKV can be used as an adequate endpoint.
Total kidney volume in clinical practice	What should be included in a standard clinical report?	Assessment of available TKV rendering from clinically obtained renal images by CT, MRI and US.
Glomerular filtration rate	What is natural history of GFR during the course of ADPKD? Is there a phase of hyperfiltration? When does GFR start declining?	Large patient cohorts with many years of follow-up to define the pattern of change in GFR over time.
Estimated GFR versus measured GFR	Under which conditions is mGFR superior to eGFR in clinical trials for ADPKD? Is there an added value of eGFR equations using cystatin C?	Clinical trials comparing mGFR and eGFR when feasible. Validation of cystatin C measurements in ADPKD.
Functional nephron mass or renal reserve capacity	No validated method to measure functional nephron mass is currently available.	Develop and validate methods to measure functional nephron mass or renal reserve capacity to be used to assess renal outcome in RCTs especially in early stage disease.
Proteinuria and albuminuria	Source and pathogenesis of proteinuria and albuminuria in ADPKD. Does it add value to other prognostic indicators?	Inclusion of proteinuria and/or albuminuria to monitor response to therapy and their value as secondary outcomes in clinical trials.
Other biomarkers	What is the diagnostic and prognostic value of proteomic and metabolomics signatures in ADPKD?	Evaluate non-traditional urine and serum markers in ADPKD on a variety of platforms including metabolomics and proteomic assessments.
Quality of life	Appropriately sensitive QOL questionnaires that capture the physical and psychological stresses of patients with ADPKD do not exist.	Development and validation of methodologies and questionnaires.

MANAGEMENT OF HYPERTENSION AND RENAL MANIFESTATIONS		
Hypertension	Preference for ACEi or ARB as first-line treatment since excellent BP control can be achieved in majority of patients with ADPKD. No consensus on second-line antihypertensive agents. Inconclusive evidence for antihypertensive treatments extending renal survival.	Clinical trials of antihypertensive agents and strategies to define second-line agents and value of aldosterone antagonists. Do patients with early ADPKD or with left ventricular hypertrophy benefit from low blood pressure targets? Compare the value of home and 24hr versus office BP measurement.
Pediatric hypertension	No consensus on the age when formal screening for hypertension should be started or on what the frequency of screening should be.	Studies to ascertain the value of early detection and treatment of hypertension. Determine whether prehypertension (BP 90-95th or even 75-95th percentile) should be treated.
Dietary interventions	Unproven benefit from dietary interventions in ADPKD. Should 24hr urine collection and analysis be used to monitor compliance?	Epidemiologic studies and RCTs of dietary interventions. Is increased hydration renoprotective? How to identify patients who will benefit? What should the amount of water intake be? How to monitor whether water intake is sufficient? Feasibility of maintaining increased hydration long-term? What type of fluid to drink? How much caffeine is harmful?
Potential renoprotective therapies	When and how should hyperlipidemia or hyperuricemia be treated?	Determine whether statins slow kidney volume growth and reduce loss of kidney function in adults. Evaluate whether treating hyperuricemia slows disease progression.
Novel therapies	Disconnect between rates of progress in basic research and preclinical studies and their translation into clinical trials.	Clinical trial networks to facilitate the prioritization and implementation of RCTs.

Renal/cyst hemorrhage and hematuria	Lack of a standardized protocol for the evaluation of cyst hemorrhage and gross hematuria. Prevalence, significance and evaluation of microscopic hematuria. Role for tranexamic acid to treat hemorrhagic complications?	Prospective RCT of tranexamic acid to treat the hemorrhagic complications of ADPKD. Observational studies to define the prevalence and significance of microscopic hematuria.
Nephrolithiasis	Does it increase the risk for renal function decline?	Conduct epidemiological and registry studies to examine this potential association.
Renal cyst infection	Lack of evidence-based algorithms to guide evaluation and treatment. Differences in availability of or reimbursement for FDG-PET.	Multicenter, cooperative studies to ascertain the value of FDG-PET and biomarkers for diagnosis and management. Adequacy of different duration and routes of antibiotic administration. Indications for and added value of cyst drainage procedures.
Chronic pain	Pathogenesis is not well understood. Long-term efficacies of cyst decompression and renal denervation are not well defined.	Studies addressing pathogenesis and management. Clinical trial of catheter-based renal denervation.
Pregnancy: Maternal outcomes	Information on maternal outcomes mostly collected retrospectively from 1980s and 1990s.	Multicenter, cooperative, prospective study of ADPKD pregnancies: Maternal outcomes, effects on kidney and liver cyst burdens and on renal function. Effects of pre-eclampsia on renal outcomes.
Pregnancy: Fetal outcomes	Information on fetal outcomes mostly collected retrospectively from 1980s and 1990s.	Multicenter, cooperative, prospective study of ADPKD pregnancies: Fetal outcomes; effects of intrauterine environment on ADPKD severity.
MANAGEMENT OF ESRD		
Choice of RRT	Feasibility of PD in ADPKD patients.	Determine risk factors for PD failure and complications based on history and TKV/TLV size and abdominal cavity volume.

Preparation for transplantation: Indications for and timing of native nephrectomy	No objective criteria for nephrectomy before transplantation. No prospective randomized comparison of prior vs. simultaneous or post-nephrectomy. Effect on residual renal function is unknown.	Development of objective criteria for nephrectomy. RCT comparing prior against simultaneous or post-transplant nephrectomy for volume space restriction; alternative strategies for kidney size reduction (e.g., embolization, laparoscopy). Assess impact of unilateral nephrectomy on residual kidney function.
Post-transplantation complications	Isolated reports, specific complications reported.	Registry analysis on incidence of complications in ADPKD vs. non-ADPKD and impact on long-term outcomes.
Using ADPKD kidneys for transplantation	No definition of donor, organ and recipient criteria.	Defining criteria for using ADPKD kidneys for transplantation; follow-up after transplantation should be collected in a global registry.
Risk for renal cancer in ADPKD with renal failure	No evidence for systematic screening in asymptomatic patients. Optimal management of suspicious lesions is unknown.	Long-term registry studies on the development of clinically significant RCC in dialysis and transplant patients with ADPKD.
Anticoagulation	Whether and to what extent the risk/severity of bleeding from ICAs is increased by systemic anticoagulation is not known.	Determine incidence and severity of kidney-related bleeding complications in ADPKD patients receiving systemic anticoagulation on dialysis and transplantation.

MANAGEMENT OF EXTRARENAL COMPLICATIONS		
Intracranial aneurysm	Limited information on natural history of ICA in ADPKD. What factors trigger their formation and rupture? At what age should MRA screening be initiated in high-risk patients? What anti-hypertensive therapy is indicated in patients with ICA? Are the morbidity and mortality of newer therapeutic approaches (e.g., endovascular coiling) the same as in the ADPKD population?	Prospective multicenter/international observational studies of ADPKD individuals with ICA, coupled with PKD mutation analyses and GWAS. Decision analysis addressing cost, safety, and efficacy of MRA screening and therapeutic interventions. Prospective study of ICA screening in ADPKD patients undergoing pre-transplant evaluation or major surgery.
Polycystic liver disease	Lack of defined criteria for massive PLD, of data on how liver size correlates with symptoms and of a validated tool to measure QOL for use in clinical trials. Disagreement over how hormone-containing contraceptives should be utilized in young women and the effect of pregnancy on ADPKD. No genetic modifiers (aside from gender) or risk factors influencing PLD severity have been identified.	Studies to define the effects of hormonal therapies (including low-dose oral contraceptives, topical estrogens, and hormonal replacement therapy in postmenopausal women) on liver cyst growth. Studies to correlate liver size with symptoms and validation of a QOL instrument.
Polycystic liver disease: Cyst infection	Lack of rigorous diagnostic criteria and poor understanding of risk factors for liver cyst infection. Sensitivity and cost effectiveness of FDG/PET CT or CA19-9 for diagnosis of cyst infection. No data on liver cyst penetration of newer antibiotics. No prospective studies to define the best method to treat liver cyst infection including duration of antibiotic treatment.	Prospective studies to define diagnostic criteria, risk factors, optimal duration of antibiotic treatment, and risk of relapse/recurrence for liver cyst infection. Rigorous studies testing the sensitivity/specificity of various diagnostic tools (CA19-9, FDG/PET CT) for liver cyst infection. Studies of cyst penetration of newer antibiotics.

Polycystic liver disease: Treatment of symptomatic or severe disease	Need to individualize treatment. Barriers to liver transplantation for severe PLD in some countries.	Further development of objective criteria for individualization of treatment and evaluation of outcomes
Additional extrarenal manifestations	Often unrecognized	Further education of physicians and patients.
PRACTICAL INTEGRATED PATIENT SUPPORT		
Information for patients and proper diagnostic pathway	How to best inform patients about diagnosis? What about implementation, relevance and effectiveness of CKD education programs and tools for ADPKD?	Production of a standardized diagnostic care pathway with endorsement by an appropriate body; effectiveness of this pathway in improving outcomes should be ascertained.
Family planning	Heterogeneity and lack of knowledge in this area; need to integrate genetics, PGD/IVF options. What is the psychological impact of diagnosis at an earlier age?	Production of a comprehensive family planning guide, with research on outcomes. Role of peer-to-peer support networks and youth counselors for children and adolescents.
Talk to children about ADPKD	How to support adolescents? How to manage the undiagnosed, at-risk child?	Development of communication tools and observation studies to evaluate the effectiveness of such interventions.
Dietary and lifestyle	Effectiveness of lifestyle changes	Observational and intervention studies on lifestyle and dietary changes (e.g., water intake, long-term consequences, adequacy of monitoring).
Pain management	Efficacy of new techniques for pain relief (e.g., denervation)	Examine the efficacy of renal denervation.
Hobbies and sports	Impact of exercise in ADPKD patients.	Observational studies, registries.
Psychology of ADPKD patients	Impact of psychological factors in ADPKD. Lack of validated tools or strategies for managing anxiety and depression.	Develop specific tools to measure the psychological impact of ADPKD. Test efficacy of strategies to manage anxiety and depression.

Polycystic liver disease	Impact of oral contraception and hormone replacement therapy. Effect of non-estrogen based contraceptives. Impact of other lifestyle measures and diet.	Investigate impact of hormones on PLD.
Financial impact of ADPKD	Mortality data in ADPKD patients, long-term effects of improved care. Impact of social inequalities.	Cohort and registry studies to address the effect of changing care modalities on the survival of ADPKD patients. Development of a standardized and endorsed statement about ADPKD that patients could use it when dealing with banks, insurers, employees and health payers.
PKD centers	Lack of criteria and no study on potential benefit in terms of care and costs.	Defining criteria for expert centers; studies of the potential benefit in terms of patients and cost outcomes. Research on telenephrology approach to ADPKD.
Patient-reported outcome measures	Usefulness of PROM in care management; specific tools needed for ADPKD.	Global initiative to create a uniform ADPKD PROM.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ADPKD, autosomal dominant polycystic kidney disease; ARB, angiotensin-receptor blocker; BP, blood pressure; CKD, chronic kidney disease; CT, computerized tomography; eGFR, estimated glomerular filtration rate; FDG-PET, fluorodeoxyglucose-positron emission tomography; GFR, glomerular filtration rate; GWAS, genome-wide association studies; ICA, intracranial aneurysm; IVF, in vitro fertilization; mGFR, measured glomerular filtration rate; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NPV, negative predictive value; PD, peritoneal dialysis; PGD, preimplantation genetic diagnosis; PKD, polycystic kidney disease; PLD, polycystic liver disease; PROM, patient-reported outcome measures; QOL, quality of life; RBP, renal blood flow; RCC, renal cell carcinoma; RCT, randomized controlled trial; RRT, renal replacement therapy; TKV, total kidney volume; TLV, total liver volume; US, ultrasound

DISCLOSURE

ABC declared having served on the Otsuka Steering Committee and received grant support from CRISP, MODIFIER, and SPRINT. OD declared having served on Steering Committee for the TEMPO studies. RTG declared having received consultancy fees from Abbott/Abbvie, Bayer, Ipsen and Otsuka (all paid to employer UMCG); research support from the Dutch Kidney Foundation and Ipsen. TH declared having received honoraria from Otsuka Europe and Otsuka Japan. SH declared having received consultancy fees and speaker honorarium from Otsuka. BLK declared having received consultancy fees from Rockwell and speaker honoraria from Rockpoint and Sanofi; NIH grant for a study on Living Kidney Donors. Y Pei declared having received consultancy fees from Otsuka. RDP declared having received consultancy fees from Otsuka (all paid to employer Tufts Medical Center), Sanofi-Genzyme, and Vertex; research support from Otsuka. Y Pirson declared having received speaker honorarium from Otsuka. RWS declared having received consultancy fees from Otsuka and research support from NIH on slowing progression of ADPKD. VET declared having received grant support from NIH, NIDDK, and Otsuka. TW declared having received consultancy fees from PKD Foundation; research support from Otsuka; royalties from a joint licensing agreement with Athena Laboratories and Johns Hopkins on sales of PKD gene testing. DCW declared having received consultancy fees from Otsuka. KUE, DO, and RT reported no relevant disclosures.

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