KDOQI US Commentary on the KDIGO 2025 Clinical Practice Guideline for the Evaluation, Management, and Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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The Kidney Disease Outcomes Quality Initiative (KDOQI) convened a work group to review the 2025 KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guideline for the evaluation, management, and treatment of autosomal dominant polycystic kidney disease (ADPKD). The KDOQI work group reviewed the KDIGO guideline statements and practice points and provided perspective for implementation within the context of clinical practice in the United States. In general, the KDOQI work group concurs with several recommendations and practice points proposed by the KDIGO guidelines regarding the diagnosis, kidney manifestations of ADPKD, chronic kidney disease management and progression, and therapies to delay the progression of disease, along with management of extrarenal manifestations. The KDOQI work group acknowledges the growing evidence base to support a change in the nomenclature for ADPKD. In this commentary, the work group has also assessed and discussed various barriers and potential opportunities for implementing the recommendations put forth in the 2025 KDIGO guidelines while the scientific community continues to focus on prospective high-quality evidence to support specific recommendations for this systemic condition.

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Am J Kidney Dis. 87(4):447-507.

doi: 10.1053/j.ajkd.2025.11.006

Because they are designed to reflect the views and recommendations of the responsible KDOQI Commentary work group and they are reviewed and approved by KDOQI and NKF leadership, KDOQI Commentaries are not peer reviewed by AJKD. This article was prepared by a KDOQI Commentary work group composed of the authors. It was reviewed and approved by the NKF Scientific Advisory Board and the KDOQI.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) has a genetic prevalence of 9.3 per 10,000 individuals,[1] is the most common monogenic kidney disease and the fourth leading cause of kidney failure in the United States (US). ADPKD is a systemic, lifelong condition. Hypertension is one of the earliest manifestations, affecting 70% to 80% of individuals with 50%

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developing kidney failure by the age of 62. Kidney disease manifestations include upper and lower urinary tract infection (UTI) and cyst infection, cyst rupture or cyst hemorrhage, and an increased incidence of kidney stones. Extrarenal manifestations include liver and pancreatic cysts; intracranial aneurysms (ICA) and other vascular aneurysms; aortic root dilatation, pericardial effusion, or cardiac valvular abnormalities; abdominal hernias; diverticulosis; and male infertility.

In the last decade, advances in ADPKD have included improved diagnosis with both genetic testing and abdominal imaging contributing to improved diagnosis and risk stratification. At least 7 genes in addition to *PKD1* and *PKD2* contribute to the clinical spectrum of ADPKD. In general, these minor genes have a slower disease course than *PKD1*- or *PKD2*-mediated disease. A prognostic tool incorporating either a *PKD1* or *PKD2* genotype has been developed (the Predicting Renal Outcome in Polycystic Kidney Disease [PROPKD] score). Imaging advances include the development of age- and height-adjusted total kidney volume (htTKV)—known as the Mayo imaging classification—as an important prognostic tool in determining which patients are at higher risk of early loss of kidney function.

Treatment specific for ADPKD includes a stricter blood pressure (BP) target of 110/75 for high-risk patients with an estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73 m^2 and age < 50 years and use of tolvaptan both for high-risk patients and for patients showing an eGFR decline of >3 mL/min/year. Dietary and lifestyle guidelines are also important as both sodium intake and overweight/obesity impact total kidney volume (TKV) growth and kidney function decline. Somatostatin analogs may be considered for patients with symptomatic polycystic liver disease who are not surgical candidates.

The KDIGO guidelines[2] underscore the many clinical challenges that remain in optimizing the care of patients with

ADPKD. Many practice points are based on expert opinion rather than robust clinical data, reflecting gaps in the existing evidence base. For example, screening and management of extrarenal manifestations such as ICA and polycystic liver disease are based on expert opinion, in part because of our limited ability to predict which individuals with ADPKD are at the greatest risk. Other areas highlighted for further development include optimizing pediatric diagnosis and treatment, pregnancy, maternal, and fetal outcomes, and reproductive issues. Also highlighted is the importance of multidisciplinary patient-centered care and the value of education, advocacy, and research by community-based organizations and scientific societies whose work supports people with polycystic kidney disease (PKD) and their families.

Review and Approval Process for This Commentary

The Kidney Disease Outcomes Quality Initiative (KDOQI) Steering Committee selected co-chairs and members of the Commentary work group based on their clinical and research expertise as well as their interest in the guideline process or familiarity with ADPKD quality metrics. During the selection process, particular emphasis was placed on identifying individuals with diverse perspectives and with experience in taking care of adult and pediatric patients with ADPKD.

KDOQI work group members reviewed recent literature and provided commentary on the Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommendations. This commentary is the product of the KDOQI work group and presents the recommendations and practice points from the KDIGO guideline. The work group discussed the guideline via teleconference, and all work group members and KDOQI leadership reviewed and approved the commentary. This review and commentary follow the same order and numbering scheme used in the KDIGO guideline. All KDIGO guideline practice points and recommendations are reproduced, although commentary is not provided for each. The KDOQI committee agrees with the practice points and recommendations for which they provide no commentary. For those guideline recommendations that may have implications for clinical care in the US, we present comments and discuss their clinical utility and implementation. All material is reproduced with permission of KDIGO.

Chapter 1. Nomenclature, Diagnosis, Prognosis, and Prevalence

1.1. Definitions and Nomenclature

Practice Point 1.1.1: In people with autosomal dominant polycystic kidney disease (ADPKD) or autosomal dominant polycystic liver disease (ADPLD) with a known genetic cause, a common nomenclature should include the disease name followed by the gene name.

Commentary and Clinical Utility

The KDOQI work group supports efforts to establish consistent and interpretable nomenclature for ADPKD, considering the expanding list of minor disease genes associated with clinically diagnosed ADPKD, autosomal dominant polycystic liver disease (ADPLD), or ADPKD and ADPLD. We agree that adding the gene name to the standardized nomenclature will improve clarity for patients, physicians, and researchers. However, we note that adopting nomenclature that includes minor (less common) disease genes alters the traditional concept of "ADPKD." Historically this term has meant a disease caused by variants in *PKD1* or *PKD2*, with a significant likelihood of progressing to kidney failure within a normal human life span. Expanding the nomenclature for ADPKD or ADPLD to include other genes that result in autosomal dominantly inherited polycystic kidneys, or a polycystic liver, broadens the definition for both disease mechanisms and their expected outcomes.

Implementation and Challenges

Minor gene cases of ADPKD appear to be comparatively rare, but they are critical to identify because they often carry a very different renal prognosis. Given the broadened definition that results from including minor gene cases of ADPKD, guidelines and educational materials that are only applicable to ADPKD-*PKD1* and ADPKD-*PKD2* will need to be revised. We emphasize that the information provided in the KDIGO guideline tables regarding minor disease genes for ADPKD and ADPLD is based on limited experience with small patient populations. Gene lists and gene-based expectations and management recommendations will need ongoing updates as more affected individuals are genetically and phenotypically characterized.

Practice Point 1.1.2: People who have an ADPKD or ADPLD spectrum phenotype but have not been genetically tested will continue to be termed as having ADPKD or ADPLD.

Practice Point 1.1.3: People with clinical ADPKD or ADPLD who have been genetically tested but in whom a genetic diagnosis was not established will continue to be termed as having ADPKD or ADPLD.

Commentary

ADPKD and ADPLD are primarily diagnosed based on clinical findings. Because genetic testing is still uncommon for most affected patients within the US, many will continue to be classified by the older nomenclature. Conversely, some patients who undergo genetic testing may not receive a definitive genetic diagnosis. This may be because a disease-causing variant was missed (false negative) or because only a variant of uncertain significance (VUS) was identified. Per the American College of Medical Genetics and Genomics (ACMG) guidelines, a VUS is not sufficient to make a genetic diagnosis; therefore, when a VUS is found as the only possible explanation for ADPKD

or ADPLD, no gene name should be used in the nomenclature.[3] In some situations, a variant reported as a VUS may be reclassified based on additional information such as segregation within a family of several affected members, functional data, or the addition of other unique families to public databases. Upgrading the variant to "likely pathogenic" (which would then allow for inclusion of the gene into the nomenclature) or downgrading to "likely benign" must be based on ACMG criteria. Variant reclassification is discussed in KDIGO guideline Table 7.

Practice Point 1.1.4: For people who are genetically tested, ADPKD will be employed as the name of the disease resulting from a pathogenic variant to the major ADPKD genes, *PKD1* or *PKD2*, and the minor genes when pathogenicity is well supported.

Practice Point 1.1.5: For people who are genetically tested, ADPLD will be employed as the disease name for the major ADPLD genes, *PRKCSH* and *SEC63*, and the minor gene when pathogenicity is well supported.

Commentary

The KDOQI work group emphasizes that a genetic diagnosis of ADPKD or ADPLD should require confirmation of age-appropriate cyst burden. We highlight this because for some minor disease genes a person can carry a disease-causing variant but not actually show signs of the disease—a phenomenon known as incomplete penetrance.[1,4–8] Indeed, the KDIGO guidelines state in Practice Point 1.3.10, "In the rare case where a pathogenic allele for an ADPKD or ADPLD gene is incidentally identified in an individual undergoing genetic testing for reasons other than a cystic kidney or liver, clinical imaging is necessary to confirm the presence of cysts consistent with ADPKD or ADPLD before assigning these diagnoses." Characterization of cyst burden on imaging will also be necessary to specify ADPKD or ADPLD for genetic diagnoses of minor genes such as *GANAB* which can manifest as either clinical distinction.

Practice Point 1.1.6: Designation of *PKD1* pathogenic variants as truncating (T) or nontruncating (NT) should be noted, but not incorporated into the nomenclature.

Practice Point 1.1.7: People with ADPKD, families, healthcare providers, insurance companies, and others dealing with the welfare of the person with ADPKD need to be educated about the significance of the ADPKD and ADPLD nomenclature.

Commentary

Including polycystic kidney and liver disease cases caused by minor disease genes in the ADPKD nomenclature aims to streamline terminology but may also have unintended effects. Labeling individuals with an ADPKD diagnosis when their disease course may be subclinical for some of the minor genes could lead to undue anxiety and may impact insurance eligibility. It is crucial that patients and insurance companies be educated about this major distinction to prevent misunderstanding and limit harm.

1.2. Prevalence

1.2.1. Prevalence of ADPKD in kidney failure populations

No recommendations or practice points.

Commentary

The KDIGO Guideline's discussion of ADPKD prevalence integrates data from multiple countries and cohorts and includes estimates based on clinical diagnoses and genetic analyses. A key report by Lanktree et al[1] provides a comparison of frequency of pathogenic variants in both major and minor genes associated with both ADPKD and ADPLD. These authors show that many individuals who carry truncating variants in minor disease genes do not develop enough cysts to come to clinical attention. Cases of a middle-aged carrier of a pathogenic variant showing no cysts—referred to as incomplete or nonpenetrance—have been proposed or documented for several of the minor genes.[1,4–8] By contrast, genetic studies and expert consensus indicate that truly pathogenic variants in the major ADPKD genes (*PKD1* and *PKD2*) are nearly 100% penetrant, meaning that carriers would be expected to develop at least mild cyst burden by middle age.[4] Additional data from the Geisinger Health system suggest that use of *International Classification of Diseases* (ICD) codes to determine presence or absence of ADPKD for the purpose of prevalence calculations may lack both sensitivity and specificity in major gene and particularly in minor gene cases.[4] ADPLD does not have a distinct ICD code, further complicating efforts to capture its true prevalence.

1.3. Diagnosis

Practice Point 1.3.1: The values and preferences of the person with ADPKD should be central when discussing issues related to diagnosing ADPKD in individual people and families.

Practice Point 1.3.2: A multidisciplinary team may be helpful when discussing issues related to diagnosing people with ADPKD and families with complex disease.

Implementation and Challenges

Though a multidisciplinary team, including a nephrologist, geneticist, and genetic counselor, would be ideal in this regard, such a team is rarely available in clinical settings. Thus, an individual practitioner familiar with ADPKD and the potential benefits/harms associated with presymptomatic disease screening and possible diagnosis may be the only available individual to discuss these issues.

When a team is not available, referral to a Center of Excellence[9] for PKD care or a clinician experienced with ADPKD should be encouraged. Notably, in individuals whose personal values and preferences lead to ambivalence about undergoing screening, the lifestyle modifications discussed in Chapter 7 are generic and can be safely recommended to any individual regardless of ADPKD diagnosis.

Practice Point 1.3.3: Appropriate counseling about the possible value and complications before scheduling of imaging or genetic screening should be provided to people at risk. Additional counseling should be provided after screening to help interpret the results and plan next steps.

Recommendation 1.3.1: For screening adults at risk of ADPKD, we recommend first using abdominal imaging by ultrasound, in the context of the family history, kidney function, and comorbidities (1B).

Practice Point 1.3.4: Follow-up magnetic resonance imaging (MRI), computed tomography (CT) imaging, and/or genetic testing may clarify the diagnosis and further characterize the disease.

Commentary

The KDOQI work group agrees with the content of KDIGO guideline Figure 1 and Recommendation 1.3.1 (see Fig 1). It is important to emphasize that Figure 1 applies to individuals *with* a family history of ADPKD while KDIGO guideline Figure 2 (see Fig 2) applies to individuals *without* such a history. In both scenarios, the diagnostic algorithm is based on the detection of cysts on imaging. A higher cyst burden is required for diagnosis in those without an established family history of ADPKD. Although there may be a time when genetic testing becomes routine, for now abdominal imaging remains the first diagnostic test for ADPKD. Genetic testing is recommended when the diagnosis is uncertain, if requested by the patient. In the future, clinical trial eligibility may depend on genetic results. We are increasingly ordering genetic testing after appropriate counseling for interested patients with cystic disease to aid in prognostication and to determine future clinical trial eligibility. It is important to recognize, however, that genetic testing may result in inconclusive or unexpected findings (Practice Point 1.3.17, KDIGO guideline Table 7). To set realistic expectations, the potential outcomes of genetic testing should be discussed with patients in advance. The role of genetic testing—including its impact on diagnosis, treatment, prognosis, cost, and eligibility for life or disability insurance—should be evaluated on a case-by-case basis. Because genetic testing is likely to be ordered by the nephrology clinic, multidisciplinary support to provide additional counseling or help interpret complex genetic findings is of high value.

Practice Point 1.3.5: For people with a positive family history of ADPKD, age-specific numbers of cysts seen on ultrasound have been described to diagnose or exclude ADPKD (KDIGO guideline Figure 3 [see Table 1[10]] and Figure 4).

Practice Point 1.3.6: For people with a positive family history of ADPKD aged 16-40 years, the number of cysts seen on MRI to diagnose or exclude ADPKD have been described (KDIGO guideline Figure 5).

Commentary

The key implication of these practice points is that an ADPKD diagnosis is clinical and based on imaging characteristics. For patients without a family history, diagnosis is often based on imaging obtained for other reasons. A finding of more than 10 cysts per kidney in a patient with typical imaging of bilaterally enlarged kidneys is sufficient for a de novo diagnosis of ADPKD.[11]

Implementation and Challenges

Imaging may also be used to exclude the diagnosis of ADPKD in an at-risk family member. This is particularly important in the case of young individuals from ADPKD families seeking to donate a kidney to an affected family member who has reached end-stage kidney disease (ESKD). To clarify the criteria for excluding a diagnosis of ADPKD, Table 2 combines content from KDIGO guidelines Figures 4 and 5. One can exclude ADPKD by ultrasound with certainty if one finds no cysts after age 30 years in individuals from *PKD1* families or after age 40 years in those from *PKD2* families or if the family's disease gene is unknown. Thus, the KDOQI work group recommends that ultrasound not be used to exclude a diagnosis of ADPKD in individuals younger than 30 years of age. It should be recognized that these data are based on a single cohort with relatively modest numbers, particularly for *PKD2*.[12] At-risk individuals younger than 40 years may benefit from magnetic resonance imaging (MRI), which can exclude ADPKD as early as age 16 years.[12]

It should be noted that cyst criteria for "minor gene" diagnosis or exclusion are not currently defined. Having ≥4 cysts in kidney or liver is rare in the general population at any age, so this has been used in some literature to support consideration of possible genetic etiology.[3,13,14] The burden of kidney cysts in the general population is also outlined in the KDIGO guideline text following Practice Point 1.3.7.

For ADPLD, previously termed "isolated polycystic liver disease," an ultrasound-based diagnostic criteria for at-risk

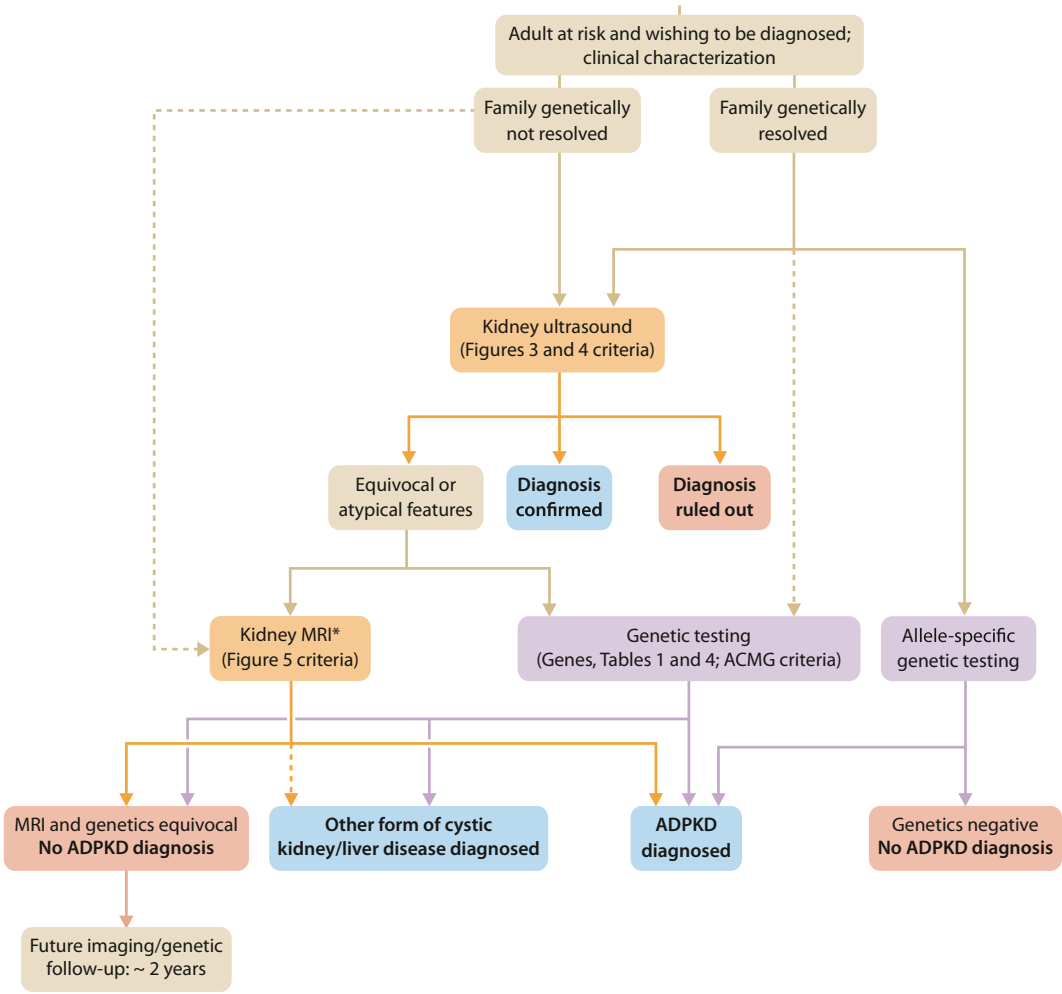


Figure 1. Diagnosis algorithm in at-risk adults (positive family history) for autosomal dominant polycystic kidney disease. Abdominal ultrasound is suggested as the first imaging analysis, with follow-up MRI analysis and/or genetic testing recommended in people with equivocal imaging or atypical extrarenal features. In genetically resolved families, simple testing of the family variant usually provides a diagnosis. Occasionally, if the disease presentation is very different from the family disease, broader genetic testing may be helpful. Solid lines indicate tests that are suggested, and dashed lines indicate tests to consider. *Computed tomography, either with or without contrast, can also be used. Abbreviations: ACMG, American College of Medical Genetics and Genomics; ADPKD, autosomal dominant polycystic kidney disease; ACMG, American College of Medical Genetics and Genomics; MRI, magnetic resonance imaging.

family members has been defined based on cyst numbers seen in the 2 largest ADPLD families studied.[14,15] In families with known ADPLD, an at-risk family member having at least 4 liver cysts after age 40 or any liver cysts before age 40 is considered to be affected. At-risk individuals older than age 40 with 1-3 cysts or younger than 40 without cysts are classified as having an "indeterminate" status. Family members without cysts after age 40 can be clinically excluded for APLD. Because liver cysts often occur late, ADPLD cannot be excluded before age 40.[16] As in the case of ADPKD, a negative genetic test for the family's specific pathogenic variant can exclude the inheritance of ADPLD at any age.

Practice Point 1.3.7: For people with no known family history of ADPKD but incidentally detected kidney cysts, kidney imaging can help to make a diagnosis.

Practice Point 1.3.8: Genetic testing can diagnose ADPKD in people with or without a known family history and provide prognostic information. However, genetic testing is not required to make an initial diagnosis of ADPKD in a person with a typical presentation (KDIGO guideline Figure 1).

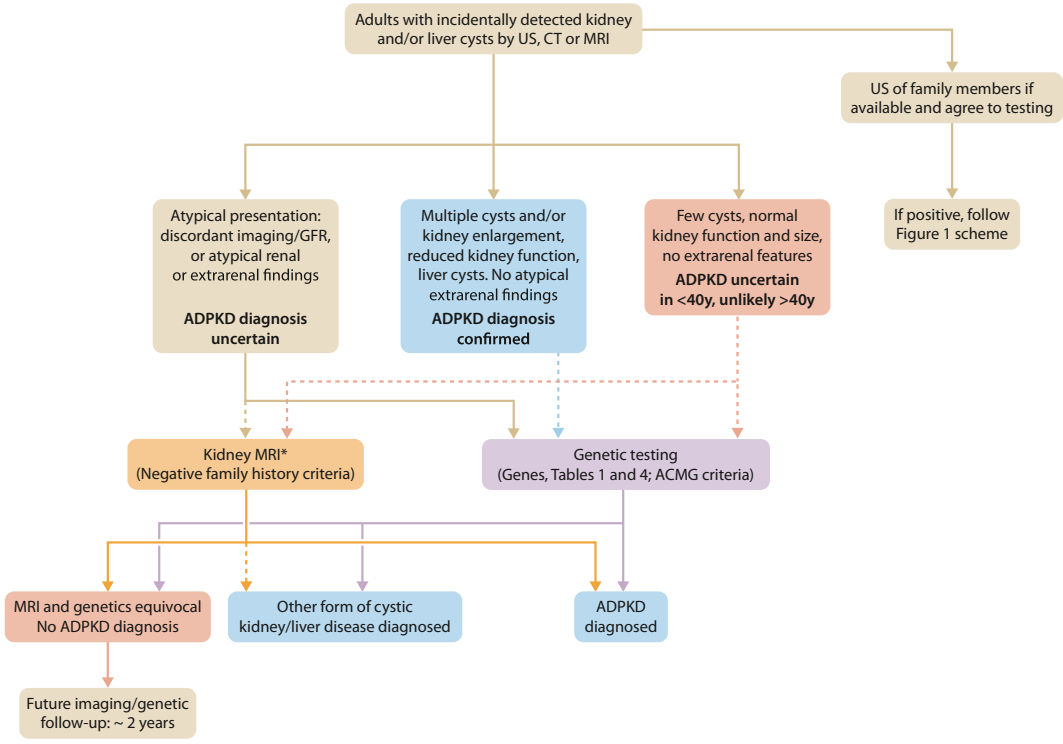


Figure 2. Diagnosis algorithm in adults with incidentally detected kidney and/or liver cysts in absence of known family history of autosomal dominant polycystic kidney disease. Solid lines indicate tests that are suggested, and dashed lines indicate tests to consider. *CT with or without contrast also can be used. Abbreviations: ACMG, American College of Medical Genetics and Genomics; ADPKD, autosomal dominant polycystic kidney disease; CT, computed tomography; GFR, glomerular filtration rate; MRI, magnetic resonance imaging; US, ultrasound.

Commentary

Figure 2 illustrates the options for diagnosis in the setting of an incidental finding of cysts without a known family history. Imaging studies of family members (with agreement and consent) can provide guidance on which algorithm to follow. If the clinical phenotype, including cyst burden, is highly suggestive of ADPKD or ADPLD, the diagnosis can be made based on imaging without additional genetic testing (see Fig 2, central blue box). However, any atypical presentation with discordant eGFR, extrarenal findings, or atypical imaging such as kidney cysts that are unilateral, segmental, asymmetric, lopsided, or segmental sparing, or kidney cysts with a bilateral presentation with unilateral or bilateral atrophy (Mayo class 2)[17] warrants genetic testing plus consideration of an MRI (if not previously performed) for further clarification of cyst burden in the kidney and other abdominal organs. These studies may clarify the diagnosis and/or provide a genetic diagnosis that can inform prognosis, as stated in Practice Point 1.3.8.

Table 1. Ultrasound Criteria by Age Group to Diagnose Autosomal Dominant Polycystic Kidney Disease in People With a Positive Family History Based on a Positive Predictive Value of the Test

		ADPKD-PKD1		ADPKD-PKD2		Unknown Gene Type	
Age, y	No. of Cysts (Test Criterion Based on No. of Cysts)	Predictive Value Based on a Positive Test	Sn	Predictive Value Based on a Positive Test	Sn	Predictive Value Based on a Positive Test	Sn
15-29	≥3 total	100%	94%	100%	70%	100%	82%
30-39	>3 total	100%	97%	100%	95%	100%	96%
40-59	≥ in each kidney	100%	93%	100%	89%	100%	90%
60+	≥4 in each kidney	100%	100%	100%	100%	ND	ND

Pei Y, Obaji J, Dupuis A, et al (2009).[10] The sensitivity of a test is its ability to designate an individual with the disease as positive.
Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ND, not determined; PKD, polycystic kidney disease; Sn, sensitivity.

Table 2. Criteria for Exclusion of ADPKD When There Is Positive Family History

Age, y	Test Criteria	Predictive Value for ADPKD Exclusion		
		PKD1	*PKD2*	Unknown Genotype
15-29	0 cysts on US	99	84	91
30-39	0 cysts on US	100	97	98
40-59	≤1 cyst on US	100	100	100
16-40	<5 cysts on MRI	100		
Any age	Genetic test negative for specific known family variant	100		

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; MRI, magnetic resonance imaging; PKD, polycystic kidney disease; US, ultrasound.

Although additional experience is needed to fully define the range of phenotypes associated with minor disease genes due to the limited number of published cases, current evidence suggests that patients with an ADPKD minor gene diagnosis or with atypical imaging findings generally have a better prognosis than those with ADPKD caused by *PKD1* or *PKD2* variants. The algorithm in Figure 2 suggests that cyst burden in patients with an uncertain diagnosis should be reassessed after approximately 2 years. Follow-up MRI may show progression or informative development of cysts or extrarenal manifestations. Results of genetic testing could also be re-evaluated following the identification of new disease genes or to determine if there has been recharacterization of VUS in public databases.

Practice Point 1.3.9: In a family with a known pathogenic variant, targeted screening for the specific variant (Sanger sequencing) is usually sufficient to diagnose or exclude ADPKD.

Practice Point 1.3.10: Genetic testing is particularly informative for people with an equivocal diagnosis based on kidney imaging and in those with a negative or unknown family history (KDIGO guideline Table 4).

Practice Point 1.3.11: Genetic testing is often useful for the selection of a living related donor for transplantation, especially if imaging results are equivocal.

Commentary

The KDOQI work group agrees with Practice Points 1.3.9, 1.3.10, and 1.3.11, but notes that, particularly in cases of an equivocal clinical diagnosis, genetic testing for ADPKD or ADPLD is frequently inconclusive. This may lead to confusion and anxiety for patients, highlighting the need for providers to be comfortable with framing the results in the appropriate clinical context.

The need to exclude ADPKD in potential kidney donors from ADPKD families is challenging in either young individuals (< age 30 for *PKD1* or < age 40 for *PKD2* or unknown genotype) or in those with equivocal imaging (see Table 1). If imaging-based exclusion of disease is not possible, genetic testing is indicated, especially if the family's pathogenic variant has been defined. In cases where the variant is unknown, we agree that the familial variant should first be identified in the affected member (in this case the recipient). Once a pathogenic variant is identified, the candidate donor with unknown affected status can be tested for the specific variant with Sanger sequencing (Practice Point 1.3.9).[18] This strategy reduces the risk of disqualifying a donor based on the identification of a VUS. In cases where a definitive pathogenic variant is not found in the affected family member, typical gene panel testing cannot be used to determine affected/unaffected status. If genetic determination of affected status is essential, referral to a geneticist for consideration of additional approaches for genetic evaluation—such as linkage analysis if multiple affected family members are available—or further testing of the affected member would be indicated.

Practice Point 1.3.12: Genetic testing is helpful in families with marked phenotypic variability, including very early onset (VEO)-ADPKD or a suspected *de novo* mutational event.

Practice Point 1.3.13: Some proven and suspected ADPKD genes are also associated with recessive disorders, with significance for variant carriers. For these genes, people with a detected pathogenic variant should be counseled about the risk, and carrier testing should be offered to partners if they are considering having a family.

Practice Point 1.3.14: Several inherited diseases can clinically mimic ADPKD or ADPLD with kidney and/or liver cysts as part of their phenotype (KDIGO guideline Table 5).

Commentary

The KDOQI workgroup finds the KDIGO guideline Table 5 most useful for consideration in patients with atypical cystic kidney phenotypes. The KDIGO guideline Table 5 provides a broad differential for kidney cysts, and few of these genetic diagnoses would be expected to produce enlarged cystic kidneys characteristic of typical ADPKD. As such, we suggest careful consideration of the clinical phenotype and KDIGO Practice Point 1.3.18 before adjusting a clinical diagnosis away from ADPKD based on a genetic diagnosis in a gene from KDIGO guideline Table 5. The carrier frequency for some genes in this table—for example, *PKHD1*[19] or the *COL4*[20] collagen genes collectively—is close to 1:100, so these genotypes will occasionally co-occur with ADPKD as opposed to providing an alternative explanation for cysts. In some cases where the presentation is atypical or discrepant within families, biallelic/recessive genotypes should also be considered (Practice Points 1.3.12 and 1.3.13).

ADPLD is diagnosed by the presence of numerous (>10-20) large (>1-2 cm) liver cysts without fibrosis or signs of

malignancy or infection (eg, clustered cysts with echinococcus infection).[14] However, variants in known disease genes will be found in only approximately 25% to 50% of ADPLD cases, suggesting that there are as yet unidentified causative genes (KDIGO guideline Table 2).[21,22] Smaller liver cysts and microhamartomas, or mild liver cyst burden accompanied by fibrosis, can be seen in autosomal recessive polycystic kidney disease (ARPKD) or ciliopathies/nephronophthisis, but these cystic liver phenotypes with fibrosis do not have autosomal dominant inheritance and thus are not ADPLD.

Practice Point 1.3.15: A targeted next-generation sequencing (tNGS) panel or other clinically accredited genetic or genomic test should be employed when performing genetic testing for ADPKD.

Practice Point 1.3.16: Clinical genetic testing results should be classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

Commentary

All genetic testing should occur with appropriate pre- and post-test genetic counseling by a trained genetic counselor.[18] In clinical practice, an accredited gene panel, on a targeted next-generation sequencing or whole-exome backbone, is likely to be the first testing strategy.[18] The commercially available tests may vary in testing and analysis parameters and the number of genes tested; some may not yet include all the ADPKD or ADPLD genes defined in the guideline.

Implementation and Challenges

This section of the KDIGO guideline and guideline Table 6 nicely outline the challenges of sequencing and interpreting ADPKD genes and variants. These challenges include 6 pseudogenes for *PKD1*[17]; very high guanine–cytosine content in exon 1 of both *PKD1* and *PKD2*, which makes sequencing challenging[23]; the possibility of mosaicism[24] (in cases with negative family history); and high allelic heterogeneity such that many pathogenic variants have never been reported. In addition, *PKD1* hypomorphic alleles, which cause PKD only in homozygosity or in *trans* with another *PKD1* variant, have been reported, but there is no ACMG nomenclature for such alleles. The KDOQI work group recommends that commercially available genetic testing services should optimize their assessment for ADPKD and clearly report the limitations of the test. We suggest that the research community can help by collecting and disseminating clinical, biological, and bioinformatic assessments of variant interpretation and testing quality.

Practice Point 1.3.17: Genetic testing is not always definitive in ADPKD. Disease-causing variants in *PKD1* or *PKD2* are not always detected, because of the testing method employed, and some variants are not classified in a pathogenic category using the ACMG guidelines.

Practice Point 1.3.18: In a person with a typical clinical presentation of ADPKD, negative or uncertain genetic results do not exclude an inherited form of ADPKD.

Practice Point 1.3.19: In a person with cystic kidneys and imaging or another unusual presentation not typical for ADPKD, negative or uncertain genetic results do not exclude an inherited form of PKD.

Commentary

The KDOQI work group agrees that inconclusive genetic testing for ADPKD is not uncommon. As such, even in cases of diagnostic uncertainty, genetic testing should be considered on a case-by-case basis, considering patient values, setting appropriate expectations (Practice Points 1.3.1 and 1.3.2), and ideally involving communication from a provider with appropriate expertise (Practice Point 1.3.3). In situations where genetic testing is pursued, a conclusive result may be clinically useful. For example, a genetic test confirming a minor *PKD* gene pathogenic variant predicts a milder disease course and hence can reassure affected individuals. A molecular diagnosis of a truncating *PKD1* variant in the setting of severe cystic disease may impact a patient's willingness to begin treatment with tolvaptan. Finally, we anticipate that the role of genetic testing may evolve if variant-specific therapies become available.

1.4. Prognostics

1.4.1. Factors Associated With the Severity of Kidney Disease in ADPKD

Practice Point 1.4.1.1: The disease-causing gene influences the severity of kidney disease in ADPKD.

Practice Point 1.4.1.2: In ADPKD-*PKD1*, the type of *PKD1* pathogenic variant influences the severity of kidney disease.

Practice Point 1.4.1.3: The severity of kidney disease progression in the family can provide a guide to likely outcomes in other affected family members.

Practice Point 1.4.1.4: Male sex is a possible prognostic factor of more severe disease in ADPKD.

Practice Point 1.4.1.5: Overweight and obesity are likely risk factors for faster progression of kidney disease in ADPKD.

Practice Point 1.4.1.6: A higher salt-intake level is associated with faster progression of ADPKD.

1.4.2. Ways to Assess the Severity of Kidney Disease Progression

Practice Point 1.4.2.1: Height-adjusted total kidney volume (htTKV) for prognostics is most accurately measured by MRI or CT scan, calculated using an automated tool or semi-automated tool, but the ellipsoid equation is also an option to estimate htTKV.

Practice Point 1.4.2.2: htTKV predicts future decline in kidney function.

Practice Point 1.4.2.3: Ultrasound-determined TKV and kidney-length measurements also have prognostic value, but they are less precise than measurements using MRI or CT

Recommendation 1.4.2.1: We recommend employing the Mayo Imaging Classification (MIC) to predict future decline in kidney function and the timing of kidney failure (*1B*).

Practice Point 1.4.2.4: When using the MIC for prognostics, exclude people with atypical imaging patterns (subclass 2A and 2B), as htTKV does not predict kidney outcomes in these people.

Practice Point 1.4.2.5: When using the MIC for prognostics, exclude people who have pathogenic variants in genes other than *PKD1* or *PKD2* (if genetic information is available), as the predictions are likely unreliable in these people.

Practice Point 1.4.2.6: The Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score can aid in the identification of people with rapidly progressive disease.

Practice Point 1.4.2.7: Advanced MRI-based biomarkers may provide additional prognostic value.

Practice Point 1.4.2.8: Assessment of kidney function as eGFR in relation to age and/or longitudinal eGFR slope data can aid in the identification of people with rapidly progressive ADPKD.

Commentary. In ADPKD, TKV increases exponentially throughout life[25] whereas eGFR is preserved or even increased for many decades and does not begin to decline until later in adulthood.[26] Thus, TKV, or height-adjusted TKV (htTKV), is a useful prognostic biomarker of declining kidney function. The Mayo Imaging Classification (MIC) categorizes people with typical ADPKD into classes 1A to 1E based on their htTKV at 1 point in time, accounting for their age (and height) at the time of imaging, in effect extrapolating the rate of kidney growth.[27]

The KDOQI work group agrees with the KDIGO recommendation to use MIC to predict decline in kidney function. This recommendation is supported by multiple longitudinal observational studies conducted in over 5,000 individuals, including 3 studies published after the KDIGO guidelines were drafted, that show an association between MIC and eGFR, eGFR slope, chronic kidney disease (CKD) outcome, or kidney failure over a period of up to 13 years.[27-37] This is a particularly important point because patients at high risk of rapid progression are most likely to benefit from disease-modifying therapy (see "Chapter 4: Therapies to Delay the Progression of Kidney Disease").[28,29]

The affected gene (*PKD1* vs *PKD2* or minor ADPKD genes) and variant (truncating vs nontruncating with high or low penetrance) also impact the rate of kidney function decline.[31,38,39] However, in multivariable prognostic models, MIC explains most of the variance in outcome whereas genotype only slightly improves the model's performance.[30,31] This seems to be because the influence of genotype on kidney function is mediated by its effect on kidney size.[30] We therefore agree with the approach of KDIGO, which included practice points to consider the affected gene and variant as prognostic factors but did not make any specific recommendations for their use. Because eGFR decline is delayed, KDIGO warns against using eGFR alone to identify rapid progression, particularly in younger people. Nevertheless, the use of age-adjusted eGFR cutoffs or longitudinal eGFR slope data can be a useful adjunctive tool in determining disease severity.[30,40]

Clinical Utility. MIC is a practical clinical biomarker because it can be determined from a one-time imaging study, either an MRI or computed tomography (CT) scan. Although KDIGO Practice Point 1.4.2.1 indicates that calculation of htTKV with an automated or semi-automated tool is preferred for accuracy, most clinicians in the US currently do not have access to these tools. It should be noted that the MIC was originally developed and validated using htTKV calculated from simple measurements of the kidney dimensions by the ellipsoid equation.[27] Thus, the KDOQI work group considers the ellipsoid equation to be a valid approach to determine MIC, and it has the advantage that it can be performed quickly and easily using online tools with no additional software by either a radiologist or the treating physician.

Related to this, Practice Points 1.4.2.1 and 1.4.2.5 deserve emphasis. The MIC is only useful for prognostication in people with typical findings on imaging and is not valid in those with atypical findings, such as unilateral, segmental, or asymmetric cystic disease (MIC 2A) or renal atrophy (MIC 2B) (see Fig 3). Similarly, because MIC was developed and validated in a population with ADPKD predominantly due to *PKD1* and *PKD2* variants, the prognostic utility of MIC in individuals with minor gene variants is unknown and should not be used. Kidney failure without kidney enlargement in patients with variants in ADPKD-*DNAJB11* provides an instructive example of where kidney function and size are unrelated.

Recent analyses of longitudinal studies suggest that the observed rate of htTKV growth in ADPKD is, on average, greater than that predicted from the MIC at baseline, which means that in general patients are more likely to move up to a higher risk class.[37,41,42] Despite this, MIC class tends to remain stable over time. In the original publication by Irazabal et al,[25] only about 11% of people changed MIC class. In another study with serial imaging of 618 individuals,[37] MIC class remained stable in 82% of individuals. Those who changed classes were typically near the boundary between 2 categories and progressed to a

higher risk class. The optimal frequency for repeat imaging—and whether routine follow-up imaging offers clinical benefit outside a research setting—is unknown. However, it may be reasonable to repeat imaging for those individuals at the threshold between classes, for example, 1B and 1C, because reclassification could impact treatment decisions.

Implementation and Challenges. MRI is expensive, and not all patients have access to this imaging modality. Fortunately, in the US most insurance companies will cover MRI for ADPKD. For individuals who do not have access to MRI, two-dimensional ultrasound is less costly and widely available. Although ultrasound is much less accurate than MRI for assessing kidney size,[43] a kidney length of >16.5 cm is predictive of progression to CKD stage 3[44] and predictive of MIC 1C-1E in patients aged ≤45 years.[45] For this reason, Practice Point 1.4.2.3 is included to indicate ultrasound as an alternative, albeit suboptimal, test when MRI or CT are not available.

Genetic testing is not widely performed in ADPKD patients in the US due to the cost and uneven insurance coverage. However, this is rapidly changing with the advent of low-cost whole exome sequencing panels for renal disease genes. If genetic testing becomes more widespread, the PROPKD score[46] could be more widely implemented, though it is limited to use in patients over 35 years of age.

One important gap in knowledge is the performance of prognostic models for Black or Hispanic patients. To date, most of the available studies have been conducted in the US, Europe, or Asia, and patients from racial and ethnic minorities are underrepresented or absent. Thus, the current prognostication tools may not be fully accurate in these populations.

Practice Point 1.4.2.9: Urine and serum measured biomarkers are potentially useful to assess prognosis and monitor treatments in ADPKD.

Class, subclass, and term	Description
1. Typical ADPKD	Bilateral and diffuse distribution, with mild, moderate, or severe replacement of kidney tissue by cysts, where all cysts contribute similarly to TKV
2. Atypical ADPKD	
A	
Unilateral	Diffuse cystic involvement of one kidney causing marked kidney enlargement with a normal contralateral kidney defined by a normal kidney volume (<275 ml in men; <244 ml in women) and having no or only 1–2 cysts
Segmental	Cystic disease involving only one pole of one or both kidneys and sparing the remaining kidney tissue
Asymmetric	Diffuse cystic involvement of one kidney causing marked kidney enlargement with mild segmental or minimal diffuse involvement of the contralateral kidney defined by a small number of cysts (>2 but <10) and volume accounting for <30% of TKV
Lopsided	Bilateral distribution of kidney cysts with mild replacement of kidney tissue with atypical cysts where ≤5 cysts account for ≥50% TKV (the largest cyst diameter is used to estimate individual cyst volume)
B	
Bilateral presentation with acquired unilateral atrophy	Diffuse cystic involvement of one kidney causing moderate to severe kidney enlargement with contralateral acquired atrophy
Bilateral presentation with bilateral kidney atrophy	Impaired kidney function (serum creatinine ≥1.5 mg/dl [133 μmol/l]) without significant enlargement of the kidneys, defined by an average length <14.5 cm, and replacement of kidney tissue by cysts with atrophy of the parenchyma

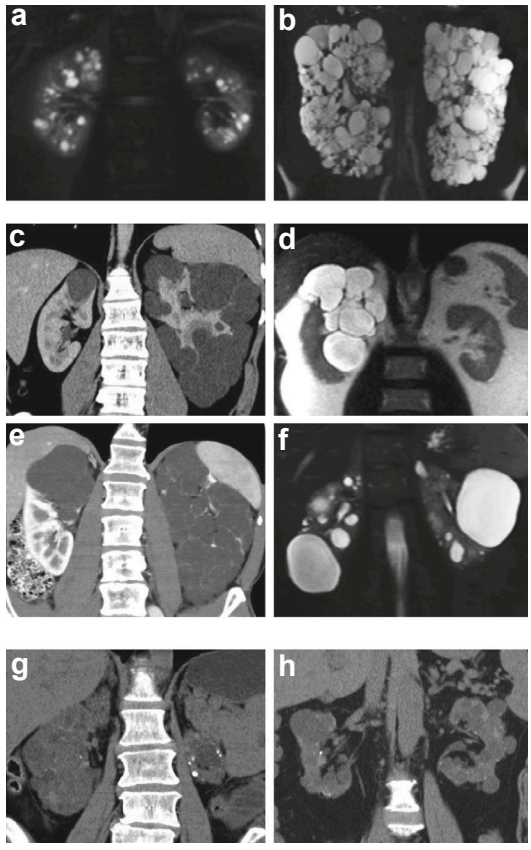


Figure 3. The Mayo Imaging Classification of autosomal dominant polycystic kidney disease (left panel) with examples (right panel) of (a,b) MIC subclass 1A and 1E, (c-f) MIC subclass 2A, and (g,h) MIC subclass 2B. Only the classification of typical ADPKD (class 1) has prognostic value. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; MIC, Mayo Imaging Classification; TKV, total kidney volume. Reproduced in part from Irazabal et al[27] with permission of the copyright holders.

Chapter 2. Kidney Manifestations

2.1. High Blood Pressure

Practice Point 2.1.1: Management of high blood pressure (BP) in people with ADPKD should include regular BP-monitoring, preferably with home BP measurements (HBPM), dietary and lifestyle modifications, and pharmacotherapy, if indicated (KDIGO guideline Figure 14).

Recommendation 2.1.1: We recommend standardized office BP measurement in preference to routine office BP measurement for the management of high BP in adults (*1B*).

Practice Point 2.1.2: An oscillometric BP device may be preferable to a manual BP device for standardized office BP measurement; however, standardization emphasizes adequate patient preparation for BP measurement, not the type of equipment.

Recommendation 2.1.2: We suggest that out-of-office BP measurements with home BP monitoring (HBPM) or ambulatory BP monitoring (ABPM) be used to complement standardized office BP readings for the management of high BP (*2B*).

Commentary

Hypertension, one of the most common associated features of ADPKD, occurs early and is easy to control in most cases. Hypertension is associated with the rate of TKV growth and is inversely associated with the rate of decline of kidney function and cardiovascular outcomes in ADPKD.[47] Therefore, BP monitoring and control are of utmost importance in ADPKD. The KDOQI work group endorses Recommendations 2.1.1 and 2.1.2, and Practice Point 2.1.2 which are adapted from the KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD as applicable to individuals with ADPKD.[48,49]

The KDOQI work group supports the use of standardized office BP measurement protocols, which require adequate patient preparation. High initial clinic BP readings should be confirmed using validated and regularly calibrated automated devices. The patient should be seated in a quiet room for at least 5 minutes with feet flat on the floor, back supported, and arm supported at the heart level. The patient should avoid caffeine, exercise, or smoking for at least 30 minutes before measurements. The cuff should be placed directly on the patient's arm with no clothing underneath. Systolic and diastolic BP should be measured in both arms and subsequent readings should be based on the arm with the higher initial reading. It is recommended to take at least 2 readings 1-2 minutes apart and use the average.[50]

Clinical Utility

Standardized, automated office BP measurements more accurately reflect true BP compared with routine measurements and can help detect white coat hypertension. Ambulatory blood pressure monitoring (ABPM) should be considered if BP is difficult to control, or if there is evidence of end-organ damage such as proteinuria or rapid kidney function decline, or if there is a discordance between home and office readings suggesting masked hypertension or white coat hypertension.

Implementation and Challenges

In the US, implementing standardized office BP protocols may be limited by time and space constraints and the need for training clinic staff. In addition, the limited availability and cost of ABPM may restrict its widespread use. Therefore, home blood pressure monitoring (HBPM) is a practical alternative. The American Medical Association provides a publicly accessible list of validated BP devices (https://www.validatebp.org). Patients should also be educated on proper measurement techniques, which are the same as those used in the office.

Practice Point 2.1.3: Healthy dietary and lifestyle interventions should be incorporated in the management of BP in all people with ADPKD.

Commentary

The KDOQI work group supports the use of non-pharmacologic interventions for management of BP, including dietary changes (DASH-type diet with low salt, high fiber, fruit and vegetables, whole grains, limited added sugar, limited saturated fat, and lean protein), optimal weight control, routine exercise, reduced alcohol consumption, and avoidance of nephrotoxins and drugs that may negatively affect BP (nonsteroidal anti-inflammatory drugs, cocaine, amphetamines, and other stimulant agents), as explained in more detail in sections 2.1 and 7.1 of the KDIGO guideline.

Clinical Utility

We recommend incorporation of these dietary and lifestyle modifications in all persons with ADPKD. A low-sodium diet (DASH-type, less than 2,000 mg daily) is particularly important in salt-sensitive hypertension and in patients with CKD.

Implementation and Challenges

The challenge of implementing these lifestyle modifications is not unique to ADPKD. In the US, these interventions are particularly challenging due to the high sodium and carbohydrate content of commercially available foods such as restaurant meals and prepackaged products. Healthier options including fresh fruits and vegetables are often more expensive and may be inaccessible to socioeconomically disadvantaged groups. Moreover, it is well recognized that maintaining these dietary changes over long periods is difficult.

Recommendation 2.1.3: For people with ADPKD aged 18-49 years with chronic kidney disease (CKD) G1-G2 and high BP (>130/85 mm Hg), we recommend a target BP ≤110/75 mm Hg as measured by HBPM, if tolerated (*1D*).

Commentary

The KDOQI work group supports a BP target of <110/75 mm Hg (if tolerated) based on HBPM, as demonstrated in the HALT-PKD trials–Study A (*1D*).[51] This study showed that a lower BP target of <110/75 versus <130/80 was associated with slower TKV growth, reduced microalbuminuria, and lower left ventricular mass index. Although the HALT-PKD trials represent the largest BP studies conducted in ADPKD, we concur with the grade 1D recommendation, reflecting a lower level of certainty. This rating acknowledges the limitations, including reliance on a single, randomized controlled trial (RCT), limited race and ethnicity diversity among the participants, a low number of hard renal end points, and no statistically significant difference in the slope of eGFR decline.[51] Long-term follow-up from the post-trial phase of the HALT-PKD study (covering approximately 70% of the original cohort across 5 of the 7 HALT-PKD centers, supplemented with US Renal Data System (USRDS) and National Death Index data from 2014 to 2020) did not show a clear benefit for mortality or ESKD-related outcomes. However, it remains unclear whether the participants consistently maintained assigned BP targets during the post-trial period.[52]

Clinical Utility

As noted previously, the beneficial effects of the low BP target included lower left ventricular mass index, which may ultimately lead to additional cardiovascular benefits.

Implementation and Challenges

As described in the HALT-PKD trials, achieving the lower BP target of <110/75 mm Hg in early ADPKD was limited by hypotension and orthostatic symptoms. Additionally, maintaining lower BP targets typically requires a higher number of antihypertensive agents, which can pose challenges for adherence as well as increasing costs. For some individuals, even modest increases in cost may be unaffordable or unacceptable. To help alleviate the financial burden, options such as using the generic version of antihypertensive agents, safety network systems (county or charity-based health care systems), cheaper online pharmacies, bulk purchasing (90-day supplies instead of 30-day supplies), or discounts through loyalty programs should be explored.

Practice Point 2.1.4: For people with ADPKD aged 18-49 years with CKD G1-G2 and BP <130/85 mm Hg and >110/75 mm Hg, use an individualized approach to BP control, incorporating shared decision-making between individual patients and their healthcare providers.

Recommendation 2.1.4: For people with ADPKD ≥50 years of age with any stage of CKD (CKD G1-G5), we suggest a target mean systolic blood pressure (SBP) <120 mm Hg, if tolerated, as assessed using standardized office blood pressure BP measurement (*2C*).

Commentary

Patients with a BP between 110/75 and 130/85 mm Hg may benefit from BP-lowering therapy. The decision of when to start therapy depends on an assessment of the risk of progression to kidney failure and the patient's willingness to consider initiating treatment. The KDOQI work group agrees with the recommendation of target systolic BP of <120 in patients with ADPKD who are older than 50 years in any stage of CKD. The recommendation is an extrapolation of the results of the SPRINT trial in essential hypertension in which nondiabetic patients with and without CKD were enrolled and randomized to low versus standard BP targets.[53] Patients with ADPKD were excluded from the SPRINT trial.

Clinical Utility

The lower systolic BP target of <120 is primarily to reduce cardiovascular mortality, as suggested in the SPRINT trials. However, the effect of this BP goal on kidney function outcomes in ADPKD has not been demonstrated.

Implementation and Challenges

BP control remains a major challenge in the US, with most hypertensive patients having suboptimally controlled hypertension. Interventions such as HBPM with automated reminders to check BP, more frequent office or nursing visits, and personally tailored antihypertensive regimens can be useful in achieving BP targets.

Recommendation 2.1.5: For people with ADPKD and high BP, we recommend using renin-angiotensin system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) as first-line treatment to achieve the recommended target BP (*1C*).

Recommendation 2.1.6: We recommend avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with ADPKD, with or without diabetes (*1B*).

Commentary and Clinical Utility

The KDOQI work group agrees with the use of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) as the first-line antihypertensive therapy. This recommendation relies on studies suggesting that the intrarenal renin-angiotensin-aldosterone system (RAAS) is activated in early ADPKD. There are several studies comparing the efficacy of renin-angiotensin system (RAS) inhibitors with other antihypertensive agents (diuretics, β-blockers, and calcium channel blockers) in ADPKD, showing superior results in renal outcomes, but these were mostly small, underpowered trials.

Implementation and Challenges

In the US, many ACE inhibitors and ARBs are generic and affordable. Hyperkalemia has been a limiting factor in the use of RAAS blockers in advanced CKD (typically CKD stages 4 and 5). Over the past several years, however, novel potassium-binding resins (such as patiromer and sodium zirconium cyclosilicate) have become available. These agents are useful adjuncts in controlling serum potassium, allowing RAS inhibitors to be continued. However, their affordability is often a limiting factor.

The KDIGO guideline did not suggest second-line BP agents, leaving this to the discretion of the provider based on the individual risks and benefits of each class of medication. The KDOQI workgroup notes that the evidence for comparative effectiveness of these agents on renal and cardiovascular outcomes is based on small studies with limited statistical power and methodological flaws.[54-58] Given the lack of evidence-based algorithms, a stepwise approach was used in the largest BP studies in ADPKD, the HALT-PKD trials.[51,59] In the HALT-PKD protocol, RAAS blockers (ACE inhibitors and ARBs) were followed by diuretics and β-blockers (metoprolol).[60] In cases of suboptimal control, additional agents such as hydralazine, clonidine, minoxidil, and non-dihydropyridine calcium channel blockers were considered.

Diuretics are not recommended as first-line agents based on concerns that they may cause volume depletion that results in increased vasopressin, which could result in epithelial cell proliferation and fluid secretion into the cysts, leading to larger TKV and worsened kidney function outcomes.[61] Furthermore, diuretics also activate the RAAS and may worsen urinary protein excretion in the absence of RAAS blockade.[61] Their use is acceptable as a second-line agent[54] but should be avoided in individuals being treated with tolvaptan. There have been concerns about the use of calcium channel blockers in ADPKD since a study in a nonorthologous rodent model of ADPKD demonstrated that they promote cyst growth.[55] However, there have been conflicting results in human studies.[56-58] Therefore, calcium channel blockers can be considered after ACE inhibitors/ARB as second- or third-line agents.

We note that the use of mineralocorticoid antagonists with or without ACE inhibitors or ARB has not been studied in ADPKD. However, because there is increasing use of these agents to treat proteinuric kidney disease, resistant hypertension, and heart failure, we anticipate more use in ADPKD. In summary, we concur with choosing ACE inhibitors and ARBs as first-line agents for the treatment of hypertension in ADPKD, but the choice of second- and third-line agents can be individualized.

Practice Point 2.1.5: Resistant high BP requiring ≥3 drugs should be investigated for causes of hypertension other than ADPKD.

Commentary

As demonstrated in the HALT-PKD trials,[51,59] most ADPKD patients require fewer than 2 antihypertensive agents to achieve a target BP. The KDOQI work group agrees with the statement that individuals requiring 3 or more antihypertensive agents for BP control should be investigated for secondary causes of hypertension because cases of primary hyperaldosteronism, renal artery stenosis, and Cushing disease have been reported in ADPKD.[62-66]

Implementation and Challenges

A complete workup for secondary causes of hypertension, which can include imaging studies, sophisticated hormone measurements, and occasionally renal vein sampling, is costly in the US. A stepwise individualized approach to evaluate the most likely secondary causes of hypertension may limit the cost burden.[50,67]

Practice Point 2.1.6: High-grade proteinuria in people with ADPKD should be investigated for a coexisting kidney disease.

Clinical Utility

Various glomerular diseases such as membranous nephropathy, mesangioproliferative glomerulonephritis, IgA nephropathy, lupus nephritis, focal and segmental glomerulosclerosis, and minimal change disease have been reported in ADPKD.[68-73]

Implementation and Challenges

ADPKD is a relative contraindication to percutaneous renal biopsy because the presence of diffuse cystic disease can make it challenging to obtain an adequate tissue sample. In addition, biopsy carries a higher risk of bleeding and cyst rupture. Therefore, the impact of a tissue diagnosis on management should be carefully weighed against the risks of an invasive procedure, especially in the setting of advanced ADPKD. In situations where a biopsy is deemed necessary, an open surgical biopsy or a laparoscopic biopsy may mitigate the risk. Conventional noninvasive evaluation of potential coexisting primary glomerular disease, such as anti-PLA2R (phospholipase A_2 receptor 1) antibodies for evaluation of membranous glomerulonephritis, may also be diagnostic.

2.2. Chronic Kidney Pain

Practice Point 2.2.1. Chronic flank, abdominal, or lumbar pain in people with ADPKD should be investigated to rule out causes other than ADPKD (e.g., mechanical or spinal back pain or malignancy in older people) or complications from ADPKD (e.g., chronic low-grade infection or stones).

Practice Point 2.2.2: Refractory chronic kidney pain in people with ADPKD is best managed by a multidisciplinary team as indicated, including nephrology, radiology, algology, psychology or psychiatry, physiotherapy, urology, and hepatology.

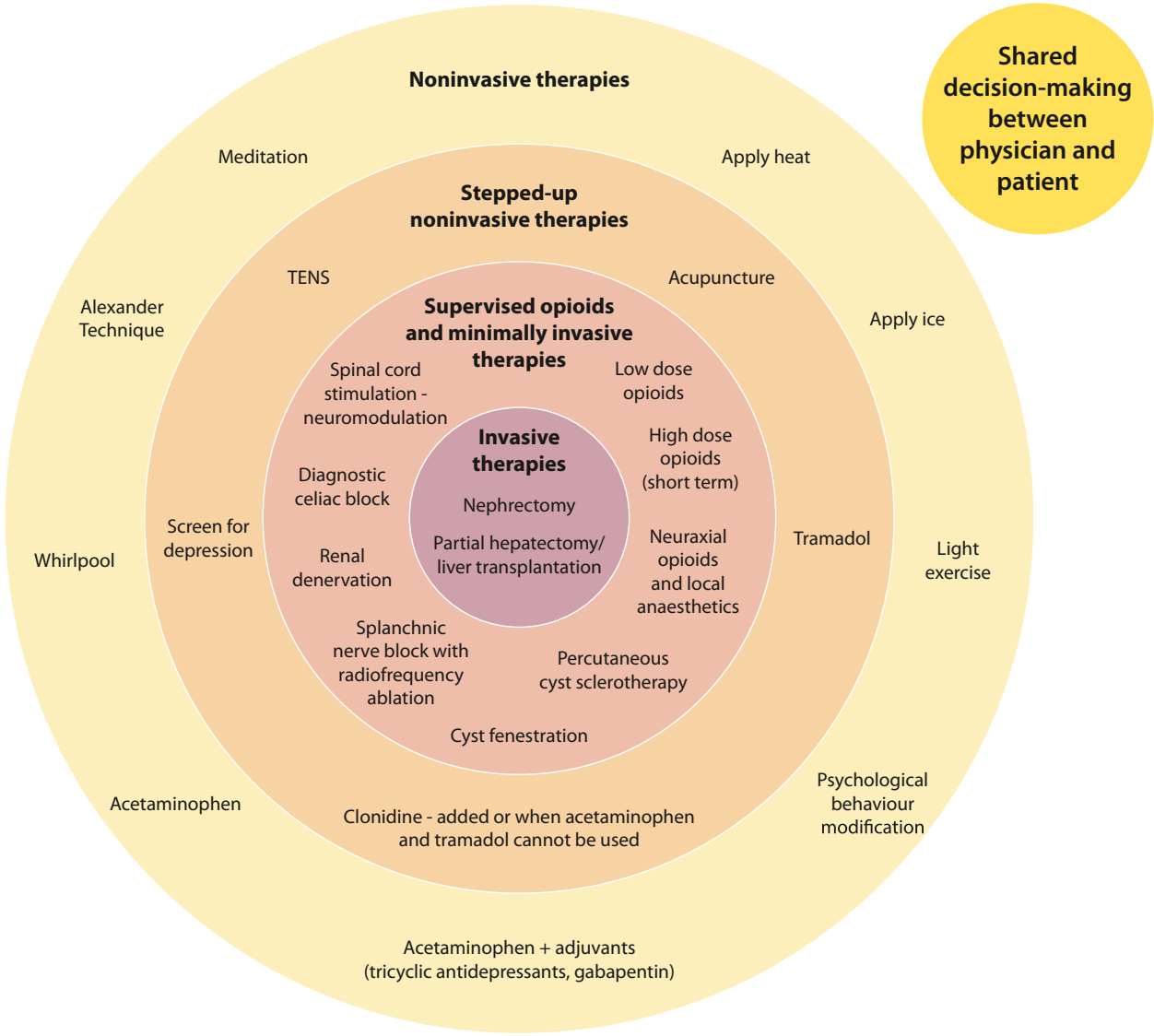


Figure 4. Shared decision making in management of chronic kidney pain in autosomal dominant polycystic kidney disease. The size of each concentric circle denotes how widely the treatment or maneuver may be used (ie, treatments within the largest circle should be widely used, whereas those within the smallest circle should be used rarely). Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; TENS, transcutaneous electrical nerve stimulation.

Commentary

The KDOQI work group strongly endorses a multidisciplinary approach to chronic refractory pain. We emphasize the importance of obtaining past medical history to identify other contributors to chronic pain. These include employment history, the presence of morbid obesity, history of psychiatric conditions (more specifically anxiety, depression, or sleep disorders), early emotional deprivation and childhood abuse, violent injuries of interpersonal violence, posttraumatic stress disorder (PTSD), surgical intervention (especially if the indication and outcomes were equivocal), fibromyalgia, irritable bowel syndrome, psychosomatic conditions, Munchausen syndrome, multiple unnecessary surgeries that did not improve the original pain symptoms, smoking, alcohol, or substance abuse, and a family history of chronic pain.[74] The presence of these issues should raise concerns about factors that affect pain perception. In these cases, invasive procedures should be carefully considered because they may not improve pain management and could even exacerbate symptoms.

Implementation and Challenges

The main limitation to the multidisciplinary approach in the US is the large proportion of uninsured or underinsured patients who may have limited access to costly

services (eg, interventional radiology, pain specialist). In addition, coverage for psychiatric care is often challenging in the US due to insurance restrictions for many providers (eg, out of network, nonacceptance of insurance plans).

Practice Point 2.2.3: Shared decision-making between the healthcare provider and the person with ADPKD or their caregiver should guide pain management strategies in ADPKD.

Commentary, Implementation, and Challenges

The KDOQI work group agrees with the comprehensive Figure 15 in the KDIGO guideline (see Fig 4) on shared decision making for pain management. Due to mandatory ethical and legal requirements in the US, extensive processes for informed consent precede pain management procedures.

Practice Point 2.2.4: Nonpharmacologic, noninvasive interventions generally should be considered as the initial treatment of chronic kidney pain in people with ADPKD.

Practice Point 2.2.5: Stepwise pharmacologic treatment for chronic kidney pain in people with ADPKD should be implemented when nonpharmacologic, noninvasive interventions do not adequately relieve pain.

Practice Point 2.2.6: The sequential approach and best choice of invasive intervention for chronic kidney pain in people with ADPKD depend on cyst characteristics and on the local expertise of the surgeon/interventional radiologist. Referral to a center of expertise should be made whenever possible.

Practice Point 2.2.7: Minimally invasive interventions to relieve chronic kidney pain may be considered for people in whom noninvasive management was ineffective and whose pain can be attributed to a single or to multiple dominant cysts, depending on the expertise of individual centers.

Commentary, Clinical Utility, Implementation, and Challenges

The KDOQI work group agrees with the KDIGO guideline's approach to invasive interventions. A review of CT or MRI images during the patient examination to correlate imaging findings with areas of reported pain may be helpful in selecting the appropriate cyst(s) for intervention.

Practice Point 2.2.8: Celiac plexus block, isolated or followed by major splanchnic nerve block, and percutaneous renal denervation may be effective in the treatment of selected people with refractory chronic visceral pain caused by cyst enlargement.

Commentary

The KDOQI work group agrees with KDIGO Practice Point 2.2.8 regarding these novel interventions. The long-term safety and efficacy of these interventions are poorly understood and should be assessed in future research studies.

Practice Point 2.2.9: Spinal-cord stimulation may provide significant pain relief in specific cases of moderate-to-severe refractory mechanical or visceral pain.

Commentary

The KDOQI work group agrees that consideration should be given to spinal cord stimulation. In certain circumstances, however, such as in the posttransplant patient with chronic pain, the surgical insertion of an external device for pain control may increase the infection risks. Native nephrectomy may be an alternative in these cases.

Practice Point 2.2.10: Nephrectomy is a treatment option reserved for severe intractable chronic kidney pain in selected people, typically with advanced kidney disease or after kidney failure, who have failed to respond to other modalities.

Commentary and Clinical Utility

The KDOQI work group agrees that nephrectomy is a treatment option of last resort that should primarily be considered for those individuals who are nearing the need for kidney replacement or who have already reached kidney failure. In some centers native kidneys can be removed at the time of kidney transplant (see Section 3) Patients should be warned that nephrectomy may occasionally be surgically impractical—for example, in cases of extremely large kidneys with extensive adhesions to the intestinal tract. This situation may result in the need for concomitant partial colectomy/intestinal resection.

2.3. Nephrolithiasis

Practice Point 2.3.1: People with ADPKD should be asked about their prior history of kidney stones, and their medical records should be reviewed.

Practice Point 2.3.2: Screening for kidney stones in people with ADPKD who have no history of kidney stones should be individualized.

Commentary

The KDOQI work group agrees with KDIGO Practice Point 2.3.2 which recommends an individualized approach to screening for stones.

Clinical Utility, Implementation, and Challenges

The KDOQI work group emphasizes that calcifications are commonly found in ADPKD. However, it is often difficult to differentiate cyst calcifications from true kidney stones, especially based on noncontrast CT.

A retrospective review of 84 ADPKD patients with non–contrast-enhanced CT scan imaging reported the frequency of nephrolithiasis at 36% and cyst calcification at 25%.[75] The presence of severe and acute flank pain and hematuria was associated with higher chances of nephrolithiasis (68% vs 35%).[75] The cumulative risk of exposure to ionizing radiation should also be weighed; each CT scan delivers 10 mSv of radiation, which is 100-fold higher than the exposure from a chest x-ray.[76] It is also important to note that abdominal MRIs are not sensitive in detecting kidney stones.

Practice Point 2.3.3: People with ADPKD and known kidney stones should undergo 24-hour urinary testing for lithogenic risk factors, serial kidney imaging studies to assess their stone burden, and analysis of their kidney stones if feasible.

Practice Point 2.3.4: Medical treatment of recurrent kidney stones in people with ADPKD should be the same as in the general population.

Practice Point 2.3.5: Because obstructing kidney stones are more challenging to treat in people with ADPKD, they should be managed by centers of expertise.

Commentary and Clinical Utility

The KDOQI work group agrees that the "Canadian Urological Association Guideline: Evaluation and Medical Management of Kidney Stones," reproduced in the KDIGO guidelines and intended for the general population, is applicable to individuals with ADPKD. However, we recognize a significant knowledge gap because these recommendations are based on relatively small case series.[77-80] To address this gap, we recommend collaborative research studies in large ADPKD cohorts to better define the epidemiology and pathophysiology of nephrolithiasis in this population, including genetic risk factors and the comparative safety, efficacy, and complication rates of treatment modalities.

Key recommendations from the existing guidelines include increasing fluid intake to achieve a urine output of 2.5 L per day, evaluation of other risk factors such as obesity, diabetes, and metabolic syndrome, and providing individualized dietary counseling.[81] Uric acid stones appear to be more common in ADPKD compared with the general population.[82] First-line dietary strategies to increase urine pH include moderation of animal protein intake and the use of alkalinizing agents such as potassium citrate. Uric acid–lowering agents (allopurinol, febuxostat) may be considered for individuals with recurrent uric acid stones.

2.4. Gout

Practice Point 2.4.1: People with ADPKD should not be treated pharmacologically for asymptomatic hyperuricemia. However, lifestyle and dietary modification may be beneficial (see *2020 American College of Rheumatology Guideline for the Management of Gout*[83]).

Practice Point 2.4.2: People with ADPKD and gout should be evaluated and treated in a manner accounting for their level of kidney function.

Commentary

The KDOQI work group agrees that the 2020 *American College of Rheumatology Guideline for the Management of Gout*, reproduced in the KDIGO guideline, and intended for the general population, applies to ADPKD.[83] Agreement with the management recommendations of the American College of Rheumatology (ACR) does not imply formal endorsement of the ACR guideline.

The work group agrees with Practice Point 2.4.2, noting that treatment of gout with allopurinol or febuxostat (as mentioned in ACR Recommendations 2.4.5) should favor the use of allopurinol. It is important to note that there is an increased risk of cardiovascular events with febuxostat compared with allopurinol (15 vs 11 per 1,000 patient/years) resulting in a US Food and Drug Administration (FDA) black box warning in 2019.[84] This risk should be carefully considered and communicated to patients, particularly because febuxostat has not demonstrated superiority in gout control over allopurinol.[84,85]

Practice Point 2.4.3: People with onset of hyperuricemia and gout in childhood or adolescence should be tested for autosomal dominant tubulointerstitial kidney disease (ADTKD).

Commentary

It is sometimes difficult to distinguish between atypical ADPKD and autosomal dominant tubulointerstitial kidney disease (ADTKD) because both may present with cystic kidneys and a bland urinalysis. In addition to early onset hyperuricemia and gout, suspicion for ADTKD should be raised when patients exhibit a discordance between cyst burden and kidney function. Specifically, individuals with ADTKD usually present with reduced kidney function despite having small or normal-size kidneys, and they typically lack the extrarenal features of ADPKD such as liver cystic disease.

2.5. Hematuria

Practice Point 2.5.1: Healthcare providers should be aware of the causes and natural history of hematuria in people with ADPKD to provide proper guidance and, if appropriate, reassurance.

Practice Point 2.5.2: Healthcare providers should discuss the possibility of gross hematuria with patients at the time of diagnosis of ADPKD to avoid unnecessary worry if it happens.

Commentary, Implementation, and Challenges

The differential diagnosis of hematuria includes cyst rupture, UTI, nephrolithiasis, IgA nephropathy or another glomerulonephritis, or cancers of the kidneys, bladder, or prostate. Gross hematuria is not uncommon in ADPKD, so an initial episode in an otherwise healthy young person may not require further evaluation for a genitourinary cancer or obstructing stone if the episode resolves without intervention and the patient is asymptomatic.

2.6. Urinary Tract Infections

Recommendations from the American Urological Association (AUA)/Canadian Urological Association (CUA)/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU)

Recommendation 2.6.1: Clinicians should not treat asymptomatic bacteriuria (ASB) in patients (1B).

Recommendation 2.6.2: Clinicians should use first-line therapy (i.e., nitrofurantoin, trimethoprim-sulfamethoxazole [TMP-SMX], fosfomycin) dependent on the local antibiogram for the treatment of symptomatic urinary tract infections (UTIs) in women (1B).

Recommendation 2.6.3: Clinicians should treat recurrent UTI (rUTI) patients experiencing acute cystitis episodes with as short a duration of antibiotics as reasonable, generally no longer than seven days (2B).

Recommendation 2.6.4: Following discussion of risks, benefits, and alternatives, clinicians may prescribe antibiotic prophylaxis to decrease the risk of future UTIs in women of all ages previously diagnosed with UTIs (2B).

Commentary

The KDOQI work group agrees that the statements from the American Urological Association (AUA)/Canadian Urological Association (CUA)/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU), reproduced in the KDIGO guideline, and intended for the general population, apply to people with ADPKD.[86] Agreement with the statements does not imply formal endorsement of the AUA/CUA/SUFU guideline. Further validation efforts are needed.

Practice Point 2.6.1: Recurrent UTIs in people with ADPKD should be investigated for a possible underlying predisposition.

Practice Point 2.6.2: A urine culture should be obtained before antibiotics are started for UTI, especially for upper UTI and/or suspected kidney cyst infection. Blood cultures should be obtained if an upper UTI or kidney cyst infection is suspected.

Commentary and Clinical Utility

The KDOQI work group agrees with the recommendation that urine and blood cultures should be obtained before antibiotics are started for a complicated UTI, suspected pyelonephritis, or cyst infection, especially if patients are in the hospital or emergency department.

Implementation and Challenges

In the US, obtaining a urine sample may be challenging. As a result, many providers, concerned about the risks of an untreated, potentially life-threatening UTI, opt to start empirical antibiotics without obtaining a urine specimen. In such cases, providers obtain a urine culture and then use that result to adjust antibiotic therapy if there is no clinical improvement within 48 to 72 hours. Although this approach is pragmatic, it lacks evidenced-based support.

Practice Point 2.6.3: UTIs in people with ADPKD need to be differentiated from noninfectious processes such as cyst hemorrhage or kidney stone.

Practice Point 2.6.4: People with ADPKD who present with fever, acute abdominal or flank pain, and increased white blood cells and/or C-reactive protein (CRP) should be worked up for kidney cyst infection (KDIGO guideline Figure 16).

Commentary

The algorithm presented in Figure 16 of the KDIGO guideline was developed by the Delphi survey of nephrologists and hepatologists, but it lacks formal validation in clinical studies. The algorithm presents arbitrary cutoffs for diagnostic features of cyst infection, requiring the presence of ≥2 items in ≥2 categories, giving equal importance to positive fluid cultures and some of the commonly observed imaging findings (eg, thickened cyst wall). We recommend that this diagnostic algorithm should be formally validated with a clear definition of features and outcome measures.

Recommendation 2.6.5: In people with ADPKD and kidney cyst infection, we suggest treatment with 4-6 weeks of antibiotic therapy rather than a shorter course (2D).

Practice Point 2.6.5: A lipid-soluble antibiotic (e.g., fluoroquinolones, trimethoprim-sulfamethoxazole) should be used to treat kidney cyst infection in people with ADPKD, if possible.

Commentary

The KDOQI work group agrees that antibiotics that have good tissue penetration should be used to treat kidney cyst infection. We would like to highlight a potential side effect of fluoroquinolones that may be particularly relevant for ADPKD. Fluoroquinolones have been associated with aortic aneurysms and dissections, as reported in several observational studies.[87] In response to these findings, the FDA issued a warning in 2018[88] recommending that fluoroquinolones be avoided in patients with existing aortic aneurysm or in those who are at risk for aortic aneurysm, including those with genetic conditions (eg, Marfan syndrome and Ehlers-Danlos syndromes), the elderly, and individuals with hypertension. It is important to note, however, that these reports have generated controversy because the observed association may be influenced by multiple confounders.[89] Additionally, a causal relationship has yet to be established. There are no studies to date demonstrating a positive association between fluoroquinolones and ICA, which is more prevalent in ADPKD.[90] The only case-time-control study did not show an increased risk of rupturing an ICA or developing a new one within 180 days of exposure to fluroquinolones versus amoxicillin.[91] Additionally the use of fluoroquinolones in ADPKD has not been specifically studied. Given these uncertainties we recommend that clinicians carefully weigh the risks and benefits on an individual basis when considering the use of fluoroquinolones in patients with ADPKD, but we agree with the overall use of these drugs to treat cyst infections in ADPKD. Similarly, use of trimethoprim-sulfamethoxazole may not be appropriate for those with advanced CKD or those taking other potassium-sparing medications.

2.7. Renal Cell Carcinoma

Practice Point 2.7.1: There is no clear association between ADPKD and an increased risk of renal cell carcinoma (RCC).

Practice Point 2.7.2: Healthcare providers should be aware of atypical presentation of RCC in people with ADPKD.

Commentary and Clinical Utility

The KDOQI work group agrees with the special considerations regarding renal cell carcinomas (RCCs) in ADPKD. Compared with the general population, RCCs in ADPKD are more often bilateral, multifocal, and sarcomatoid.[92] Sarcomatoid RCCs tend to be highly aggressive and have a high propensity to metastasize.[93] Contrast-enhanced imaging studies (CT or MRI) should be considered in cases of recurrent unprovoked gross hematuria. See Practice Point 3.2.10 for commentary on imaging considerations for individuals with ADPKD who have ESKD or advanced CKD.

Chapter 3. Chronic Kidney Disease (CKD) Management and Progression, Kidney Failure, and Kidney Replacement Therapy (KRT)

3.1. CKD Management and Progression

Practice Point 3.1.1: In general, management of CKD in ADPKD is similar to management of other kidney diseases.

Practice Point 3.1.2: People with ADPKD should receive optimal management of their anemia to avoid transfusions that may result in sensitization and may limit access to kidney transplantation.

Practice Point 3.1.3: Hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) should not be used to manage anemia in people with ADPKD who are not receiving dialysis.

Practice Point 3.1.4: Management of diabetes in people with ADPKD should be the same as that for people with other forms of CKD, with the possible exception that sodium-glucose cotransporter-2 inhibitors (SGLT2i) are not recommended at this time for people with ADPKD.

Commentary

The KDOQI work group agrees with the recommendation that diabetes mellitus management should be similar in ADPKD as for people with other forms of CKD. Two independent small clinical trials in adults with ADPKD found that 12 or 24 months of metformin was safe and tolerable, but these studies were not powered to detect efficacy. There is currently another Australian-led phase 3 RCT underway (IMPEDE-PKD, NCT04939935) designed to test the effect of metformin in early stage ADPKD. However, due to the lack of available clinical trial data, metformin, sodium/glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists cannot be recommended to treat ADPKD, but these agents can be used for the management of diabetes mellitus as they would in the non-ADPKD population. The KDOQI workgroup notes that there are also planned studies in the US and in Europe that are or will be testing the effects of SGLT2 inhibitors and GLP-1 receptor agonists in nondiabetic ADPKD patients.

Clinical Utility

The management of diabetes mellitus with SGLT2 inhibitors and GLP-1 receptor agonists has demonstrated improved outcomes, including a decreased number of cardiovascular events, all-cause mortality, and hospitalizations in both the general population and in patients with advanced CKD.[94] However, surprisingly little is known regarding the safety, tolerability, and efficacy of SGLT2 inhibitors and GLP-1 receptor agonists in adult patients with ADPKD and normal to mildly reduced kidney function.[95] Hence, the institution of lifestyle changes including modifications in exercise and diet should be pursued until

SGLT2 inhibitors and/or GLP-1 receptor agonists are shown to be safe and efficacious in patients with ADPKD.

Implementation and Challenges

SGLT2 inhibitors might have a potential benefit in ADPKD by directly affecting cell proliferation and subsequent fluid secretion with a resultant attenuation of cyst growth.[96] However, studies testing the effects of SGLT2 inhibitors in animal models of PKD have yielded conflicting results and failed to slow cyst growth in some studies,[97] and have unexpectedly enhanced cyst volume in the PCK rat model of ADPKD.[98] An important safety consideration in human ADPKD is that SGLT2 inhibitors, by causing glycosuria, natriuresis, and glucose-driven osmotic diuresis, could increase vasopressin,[95] which is known to stimulate cyst growth. Hence, recommendations regarding the use of SGLT2 inhibitors in ADPKD will require completion of well-designed clinical trials demonstrating the safety of these compounds in ADPKD patients.[99]

These challenges highlight the potential of interventions like GLP-1 receptor agonists for the management of diabetes or obesity in patients with ADPKD. GLP-1 receptor agonists were initially approved for the treatment of type 2 diabetes mellitus and have demonstrated effectiveness in significantly decreasing adiposity, improving insulin sensitivity, and providing renoprotection in various patient populations.[100] The FDA recently approved GLP-1 receptor agonists for the treatment of obesity in patients without diabetes. GLP-1 receptor agonists could represent an innovative therapeutic option in ADPKD patients, with the potential to revolutionize the treatment landscape of obese, overweight, and dysregulated metabolism in ADPKD patients. This will require clinical trials that test the efficacy of these agents in slowing kidney growth in diabetic or obese ADPKD patients.

Table 3. Posttransplant Complications That Are More Common With AKPKD Than They Are in People With Other Forms of Chronic Kidney Disease

Posttransplant Complication	Values
New-onset diabetes	Pooled RR, 1.92 (95% CI, 1.36-2.70)[a]
Erythrocytosis	Recipients with posttransplant erythrocytosis were more likely to have PKD than other kidney diseases (17% vs 6%; $P < 0.001$)[b]
Valvular heart disease	Greater risk for worsening of tricuspid, mitral, and aortic valve regurgitation[c]
Aortic root dilatation	Greater risk for dilation of sinus of Valsalva and ascending thoracic aorta[d]
Subarachnoid hemorrhage	3.8/1,000 hospital admission in kidney transplant recipients with ADPKD compared to 0.9/1,000 in kidney transplant recipients without ADPKD[d]
Thromboembolic events (DVT, PE)	8.6% of 534 patients with ADPKD vs 5.8% of 4,779 patients without ADPKD after kidney transplantation ($P = 0.009$)[e]
Skin cancers: SCC, BCC, melanoma	Adjusted ORs 1.22, 1.30, 1.21, respectively[f]
Urinary tract infections	Weak evidence only
Cyst infection	Cumulative IR 3%, 6%, and 12% (63% kidney, 37% liver) at 1, 5, and 10 years after transplantation (1.6 episodes per 100 person-years). Increased risk with history of cyst infection before transplantation (HR, 3.47 [95% CI, 1.29-9.31])[g]
Colon diverticulitis	Prevalence (2006-2013) in kidney transplant recipients with ADPKD compared to recipients without ADPKD (2.6% vs 0.8%)[h]

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; BCC, basal cell carcinoma; CI, confidence interval; DVT, deep vein thrombosis; IR, incidence rate; HR, hazard ratio; OR, odds ratio; PE, pulmonary embolism; PKD, polycystic kidney disease; RR, relative risk; SCC, squamous cell carcinoma.
[a]Cheungpasitporn et al (2016).[106]
[b]Alasfar et al (2021),[107] Alzoubi et al (2021),[108] Jacquet et al (2011),[104] Mekraksakit et al (2021),[109] and Ronsin et al (2022).[110]
[c]Chedid et al (2022).[111]
[d]Cheungpasitporn et al (2019).[112]
[e]Jacquet et al (2011).[104]
[f]Hao et al (2022).[113]
[g]Ronsin et al (2022).[110]
[h]Duarte-Chavez et al (2020).[114]

Practice Point 3.1.5: For the primary prevention of cardiovascular disease (CVD) in adults with ADPKD not treated with chronic dialysis or kidney transplantation, lipid lowering therapy should be initiated in line with the *KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease*.[101]

Practice Point 3.1.6: Voluntary participation in clinical trials of interventions to slow progression of ADPKD should be offered to all eligible people with ADPKD.

3.2. Kidney Transplantation

Practice Point 3.2.1: Kidney transplantation is the preferred treatment for kidney failure in people with ADPKD.

Commentary

This practice point highlights kidney transplantation as the preferred management option for people with ADPKD and kidney failure, offering better quality and quantity of life in the majority of patients. The KDOQI work group agrees that patients with ADPKD do well after transplantation. The evaluation of potential transplant candidates with ADPKD and the decision-making process is affected not only by the unique and challenging issues related to ADPKD but also by the transplant centers' approach along with national policies and practices.

According to the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) 2022 Annual Data Report, at the end of 2022, 8.8% of adults on the kidney transplant waiting list had cystic kidney disease, as opposed to 39% with diabetes and 20.3% with hypertension.[102] Among adult deceased donor kidney transplant (DDKT) recipients (from 2015-2017), 5-year patient and graft survival were

lower among recipients with diabetes as the cause of kidney failure versus other causes, including cystic kidney disease.[102] In a retrospective cohort study of 961 renal transplant recipients from the United Kingdom, Garland et al[103] demonstrated no significant differences in recipient survival between ADPKD and the various other primary renal disease categories, although they observed a significantly elevated risk of cardiovascular disease in recipients with ADPKD. Patients with an ADPKD diagnosis had the least and slowest posttransplant decline in eGFR over time compared with patients with diabetic kidney disease. Together these data points support the advantage of kidney transplant in ADPKD.

Clinical Utility

Patients with ADPKD present unique issues to consider during transplant evaluation, such as the possible need for native nephrectomy (see below), screening for ICA (see Section 6.1), and assessment of polycystic liver (see Section 5.1) and cardiovascular disease (see Section 3.1). Due to the increased risk of certain posttransplant complications (see Table 3)—such as valvular disease, erythrocytosis, thromboembolic events, diabetes, and hypertension, some which are common to other posttransplant patients—we agree with the importance of close posttransplant monitoring including regular clinic visits, laboratory tests, and health maintenance surveillance with colonoscopy, pap smears, mammograms, and regular dermatology visits.[104,105]

Implementation and Challenges

Like other patient populations, individuals with ADPKD require timely referral for transplant evaluation to optimize outcomes. Challenges to this process include appropriate management of chronic health issues, prompt completion of pretransplant studies, and gaps in social support and health disparities[115,116] that may hinder wait-listing or transplantation. Additional barriers include a lack of culturally targeted education, psychosocial issues, inability to complete multistep evaluation processes and multiple diagnostic tests, and insufficient or absent insurance.[117] Multidisciplinary interventions are needed to overcome these barriers.

Despite the clear survival advantage of kidney transplant over dialysis, patients can face waiting times of up to 10 years on the DDKT waiting list. Patients with ADPKD should be counseled about the benefits of kidney transplantation to facilitate timely referral. Completing the pretransplant evaluation promptly is essential, particularly for those without potential living donors, because it allows them to begin accruing time on the waiting list. Effective communication between the transplant center, referring physicians, and dialysis centers is key to facilitating this process.

Practice Point 3.2.2: A kidney transplant from a living donor provides lower risk of rejection and longer allograft survival.

Practice Point 3.2.3: Preemptive living donor kidney transplantation is the optimal therapy for people with ADPKD.

Practice Point 3.2.4: Transplantation between blood type or human leukocyte antigen (HLA)-incompatible donors may be facilitated by kidney exchange.

Practice Point 3.2.5: People with ADPKD should be treated with the same immunosuppressive protocols as other transplant recipients.

Practice Point 3.2.6: Excluding the diagnosis of ADPKD in potential living-related kidney donors is an important consideration.

Commentary

The KDOQI work group agrees that pre-emptive living donor kidney transplant (LDKT) is the optimal choice for patients with ADPKD because of improved graft survival and a lower risk of primary graft nonfunction (Practice Points 3.2.2 and 3.2.3). According to the 2022 annual data report of the OPTN/SRTR, for patients transplanted between 2015 and 2017, LDKT recipients had better eGFR and better graft survival compared with DDKT recipients. LDKT recipients 65 years and older had a 5-year graft survival of 80.8% compared with 67.8% for DDKT recipients. Similarly, LDKT recipients between 18 and 34 years old had a 5-year graft survival of 90% compared with 81.4% for DDKT recipients.[102] Compared with DDKT recipients, LDKT recipients had better patient survival and were less likely to have been on dialysis before transplantation. Both graft survival and patient survival were lower among recipients with diabetes as the cause of kidney disease compared with other causes of kidney disease, including ADPKD. Given the significant advantages of LDKT, in the case of blood type or human leukocyte antigen (HLA) incompatibility, donors should be offered the option of donation through paired kidney donation/kidney exchange (Practice Point 3.2.4).

The KDOQI work group agrees that a potential donor at risk for ADPKD must be evaluated carefully to exclude a personal diagnosis of ADPKD (Practice Point 3.2.6). We agree that, especially when the familial variant is undefined, imaging should be the first step—see Chapter 1, Table 1 in the KDIGO guideline summarizing the imaging criteria for disease exclusion; also see the KDOQI work group commentary on Practice Points 1.3.9, 1.3.10, and 1.3.11 dealing with genetic testing in the transplant setting. We note that when evaluating a potential kidney donor from an ADPKD family, a presymptomatic and unexpected diagnosis could be made. Therefore, pretest counseling by an experienced provider should precede either imaging or genetic testing.

Preemptive living donor kidney transplant is the preferred treatment option in ADPKD. The KDIGO

guideline suggests that potential transplant candidates be referred for evaluation at least 12 months before dialysis initiation. However, in the US, transplant candidates cannot accrue waiting time for a deceased donor transplant until their eGFR is less than 20 mL/min/1.73 m^2. In many centers, evaluation begins once this threshold is reached. The KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation, published in 2020,[118] recommends all patients with eGFR < 30 mL/min/1.73 m^2 be informed of, educated about, and considered for kidney transplantation (Grade 1D, very low quality of evidence).

Implementation and Challenges

Although we agree that timely referral and early identification of living donors are essential for possible preemptive transplantation, the timing of referral for transplant evaluation might be different in different countries. Many challenges remain to implement the KGIDO recommendations. The evaluation of a living donor is complex and can take weeks to months to complete; it also requires a multidisciplinary team. For donors from an ADPKD family, genetic counseling and testing might not be available or covered by the recipient's insurance. In some cases, imaging and/or familial gene variant analysis could be indeterminate for ascertaining ADPKD status.

Practice Point 3.2.7: During the pretransplantation work-up for candidates with ADPKD, the total kidney and liver weight derived from total kidney and liver volumes should be calculated and subtracted from the patient's total body weight for a more accurate assessment of weight and body mass index (BMI).

Recommendation 3.2.1: We suggest that native nephrectomy in people with ADPKD receiving a kidney transplant should be performed only for specific indications when the benefit outweighs the risk (KDIGO guideline Figure 21) (*2C*).

Practice Point 3.2.8: Shared decision-making with patients pretransplant and multidisciplinary case conferencing should contribute to the decision regarding performing and timing of nephrectomy.

Recommendation 3.2.2: We suggest unilateral rather than bilateral native nephrectomy in people with ADPKD, when appropriate, based on clinical judgment and availability of local expertise (*2D*).

Recommendation 3.2.3: We suggest that kidney transplant candidates with ADPKD who require native nephrectomy undergo the procedure at the time of or after, but not before, transplantation, whenever possible (*2C*).

Practice Point 3.2.9: Shared decision-making regarding native nephrectomy should involve a multidisciplinary team to discuss timing, surgeon and center expertise, patient preferences, and whether the transplant will be from a living versus a deceased donor.

Recommendation 3.2.4: When feasible, we suggest the use of hand-operated laparoscopic nephrectomy rather than open nephrectomy in people with ADPKD (*2D*).

Commentary

KDOQI suggests that native nephrectomy for patients with ADPKD (pretransplant, at the time of transplant, or post-transplant) should be performed in specific situations where the benefits outweigh the risks (potential indications for native nephrectomy are listed in KDIGO guidelines Figure 21).[119] We want to emphasize that in the small number of retrospective studies and case series cited by KDIGO there was no clear benefit of native nephrectomy on either patient or graft survival. Although there was no "clear excess" of surgical complications, in cases where native nephrectomy is performed at the time of transplant, the potential exists for longer surgery times and increased bleeding.[120,121] Preemptive nephrectomy should not be performed routinely in patients with ADPKD who undergo evaluation for kidney transplantation, and patients should be counseled about the potential for kidney volume regression of native polycystic kidneys after transplantation.

There are relatively few studies directly comparing the timing of native nephrectomy in the peritransplant period. In a recent retrospective cohort of 391 patients with ADPKD, 29.2% of the patients underwent nephrectomy before kidney transplantation and 7.7% after transplantation.[122] There were no differences in 10-year patient survival and 10-year death-censored graft survival between the patients who had a nephrectomy before versus after transplantation. A key disadvantage of pretransplant nephrectomy, however, is the requirement for a period of dialysis before the transplant can take place. Several single-center studies, including one by Darius et al,[123] demonstrated that simultaneous ipsilateral native nephrectomy during kidney transplant surgery does not adversely impact surgical morbidity or graft survival. Nonetheless, removal of only 1 native kidney may introduce additional challenges such as increased technical difficulty during future abdominal surgeries due to adhesions (including a potential need for subsequent contralateral nephrectomy), abdominal asymmetry, and posture-related pain. When nephrectomy is performed simultaneously with kidney transplantation, the procedure is prolonged and involves a larger operative field and a bigger incision. We endorse shared decision making between patients and the care team when considering native nephrectomy.

The KDOQI work group finds Recommendation 3.2.2, which advises unilateral rather than bilateral native nephrectomy, to be relatively weak because it is based on

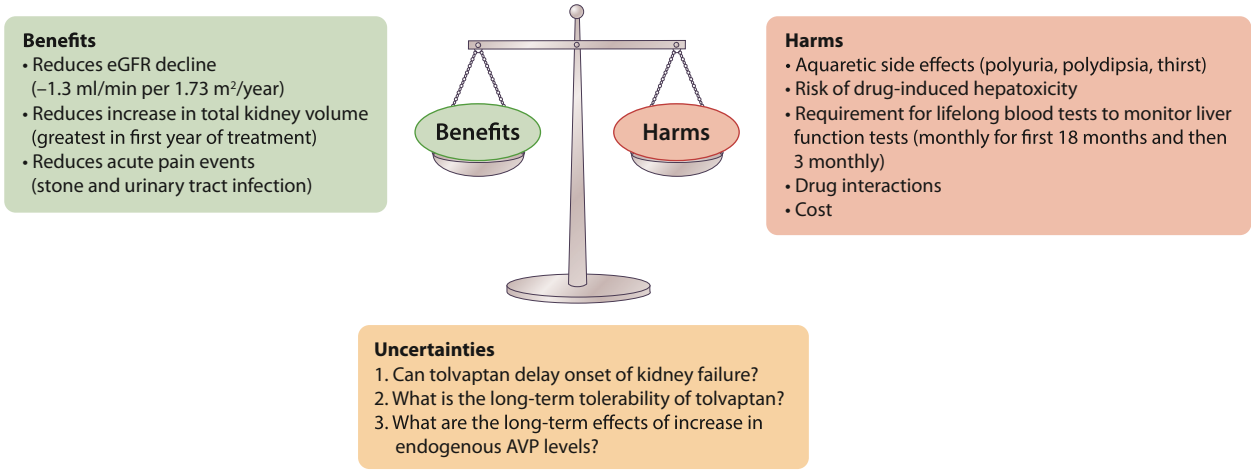


Figure 5. Schematic diagram summarizing the harms, benefits, and uncertainties regarding long-term treatment with tolvaptan in people with rapidly progressing autosomal dominant polycystic kidney disease. Abbreviations: AVP, arginine vasopressin; eGFR, estimated glomerular filtration rate. Reproduced from Chebib et al[129] with permission of the copyright holder (Wolters Kluwer Health, Inc).

only 1 study that in fact did not show excess complications in the group undergoing bilateral nephrectomy.[124] KDIGO based their recommendation on the assumption that unilateral nephrectomy would pose a lower surgical risk. Given the lack of robust data, we recommend an individualized approach that weighs anatomy and symptoms with potential risks and benefits.

The KDOQI workgroup disagrees with Recommendation 3.2.4, which suggests the use of hand-operated laparoscopic nephrectomy rather than open nephrectomy. Instead, we recommend that the surgical approach to nephrectomy be discussed and left to the surgical team evaluating the potential candidate. We note that intraoperative cyst rupture can result in the release of potentially infected cyst fluid into the peritoneal cavity, which can cause an inflammatory response or systemic inflammatory response syndrome. Additionally, there could be dissemination of undiagnosed kidney cancer. The risk of these events is likely greater with the laparoscopic nephrectomy of large polycystic kidneys. Due to these concerns, and without established clear benefits of hand-assisted laparoscopic nephrectomy in ADPKD patients, many surgeons prefer the open nephrectomy approach.

Clinical Utility

Unfortunately, there are no well-designed randomized controlled studies comparing different approaches regarding native kidney nephrectomy. Currently, the consensus is to remove the native kidneys—unilateral versus bilateral—when patients are symptomatic (pretransplant or posttransplant), and/or when there is no room for the graft (pretransplant or at the time or transplant), or when there is a history of recurrent kidney infection or bleeding (pretransplant), depending on the individual center's preference and expertise. Nephrectomy should not be performed routinely.

Implementation and Challenges

The indications and timing of native nephrectomy for transplant candidates and recipients with ADPKD should be carefully evaluated. This issue remains complex and requires careful risk–benefit assessment involving both nephrology and surgical teams at the time of transplant evaluation. Hence, the KDOQI work group believes that decisions regarding nephrectomy in patients with ADPKD will need to be individualized and should be reserved for patients with symptomatic cyst-related complications or with significantly enlarged kidneys that could make transplant surgery challenging.

> Practice Point 3.2.10: Evaluation for renal cell carcinoma prior to transplant in people with ADPKD should be individualized and imaging of the kidneys (e.g., abdominal MRI) within 1 year prior to anticipated timing of transplantation should be considered.

Commentary

The KDOQI work group concurs with the recommendation that evaluation for RCC before kidney transplantation can be considered in select individuals. As outlined in Practice Point 2.7.1, there is no clear evidence that ADPKD increases the risk of RCC. However, chronic immunosuppression may heighten the risk, and screening may be appropriate in individuals with recurrent gross hematuria or other concerning features. In addition to the studies cited by KDIGO, Drake et al[125] conducted a systematic review of studies reporting RCC occurrence in ADPKD patients through July 2023. They

identified nephrectomy specimens from 1,147 ADPKD patients, among whom 75 had RCC, corresponding to a per-person prevalence of 5.7%. Seven patients (9.9%) had bilateral RCC, a rate higher than that observed in the general population. Additionally, this might be an underestimate because not all studies reported bilateral nephrectomies. Most tumors were of the papillary RCC subtype, suggesting a distinct pattern of RCC development within native ADPKD kidneys.

KDOQI also agrees that noncontrast abdominal MRI (without gadolinium) is the preferred initial screening method, especially in those individuals with advanced kidney failure or who are on dialysis. If a suspicious solid lesion is detected, then it is reasonable to proceed with a contrast-enhanced study, either MRI or CT. The choice of contrast-enhanced CT versus MRI should be guided by shared decision making, considering the risks of contrast-induced nephropathy with iodinated contrast versus the rare but serious risk of nephrogenic systemic fibrosis (NSF) with gadolinium. NSF has been linked to group I gadolinium-based contrast agents (branded under the names Omniscan, Magnevist, and OptiMARK), which are contraindicated for use by the FDA in the US in advanced CKD stages 4 and 5, ESKD, and acute kidney injury. By contrast, the risk of NSF is almost nonexistent with group II agents such as gadobenate dimeglumine (branded under Multihance in the US). For clinically indicated imaging, the potential benefits of group II gadolinium-based contrast agents may exceed the minimal risk of NSF.[126]

Clinical Utility

Early detection and treatment of RCC is important in patients with ADPKD, so this recommendation is of high clinical utility.

Implementation and Challenges

KDIGO advises using abdominal MRI to screen for solid kidney lesions within 1 year before transplantation. This recommendation may be more feasible in ADPKD patients with potential living donors; however, given the long waiting times for DDKT and the unpredictable timing of surgery, it may be challenging to implement in patients on the DDKT waiting list. There are currently no standard guidelines for RCC screening in ADPKD. The KDOQI work group endorses the need for prospective registry studies to more accurately define the prevalence of RCC in individuals with ADPKD before and after transplant and to establish optimal screening and surveillance strategies.

3.3. Kidney Replacement Therapy

Practice Point 3.3.1: Choice of dialysis modality should be determined based on shared decision-making between physician and patient.

Recommendation 3.3.1: We suggest that in people with ADPKD, selection of dialysis modality (hemodialysis [HD] or peritoneal dialysis [PD]) for treatment of kidney failure should be determined by patient-related factors, patient choice, and availability of facilities (*2C*).

Practice Point 3.3.2: Peritoneal dialysis should be considered as a viable kidney replacement therapy (KRT) for people with ADPKD complicated by kidney failure, with caution indicated only when massive kidney and/or liver enlargement or other standard PD contraindications are present.

Practice Point 3.3.3: The prescription of HD and supportive therapies, such as anticoagulation, should be the same as that for people without ADPKD.

Chapter 4. Therapies to Delay the Progression of Kidney Disease

4.1. Tolvaptan

4.1.1. Indications for Tolvaptan in ADPKD

Recommendation 4.1.1.1: We recommend initiating tolvaptan treatment in adults with ADPKD with an estimated glomerular filtration rate (eGFR) ≥25 ml/min per 1.73 m² who are at risk for rapidly progressive disease (KDIGO guideline Figure 25) *(1B)*.

Practice Point 4.1.1.1: Shared and individualized decision-making should be undertaken when determining whether to initiate tolvaptan in people aged >55 years with rapid progression.

Practice Point 4.1.1.2: The MIC, ideally based on MRI, should be used as the primary imaging method for risk prediction and consideration of tolvaptan in routine clinical care. Low-dose or ultra-low-dose CT is an alternative imaging method to determine MIC. When MRI and CT are not available or are contraindicated, it is acceptable to use ultrasound to assess kidney volume with the ellipsoid formula.

Practice Point 4.1.1.3: A PROPKD score >6 may provide additional evidence for risk for rapid progression in ADPKD when the historical rate of eGFR decline or MIC is indeterminate.

Practice Point 4.1.1.4: Before concluding that a person has rapid progression and initiating tolvaptan treatment, other acute or chronic causes of eGFR decline should be assessed.

Commentary. Kidney failure is the most common severe complication of ADPKD. The KDOQI work group agrees that delaying the progression of kidney disease should be the primary goal of medical treatment in ADPKD. Supported by evidence from preclinical studies and RCTs, the cornerstone of current therapy for ADPKD involves inhibiting the effects of circulating vasopressin on kidney cyst growth using a vasopressin receptor 2 (V2R) antagonist; tolvaptan is currently the only V2R antagonist available for treatment of patients with ADPKD. The

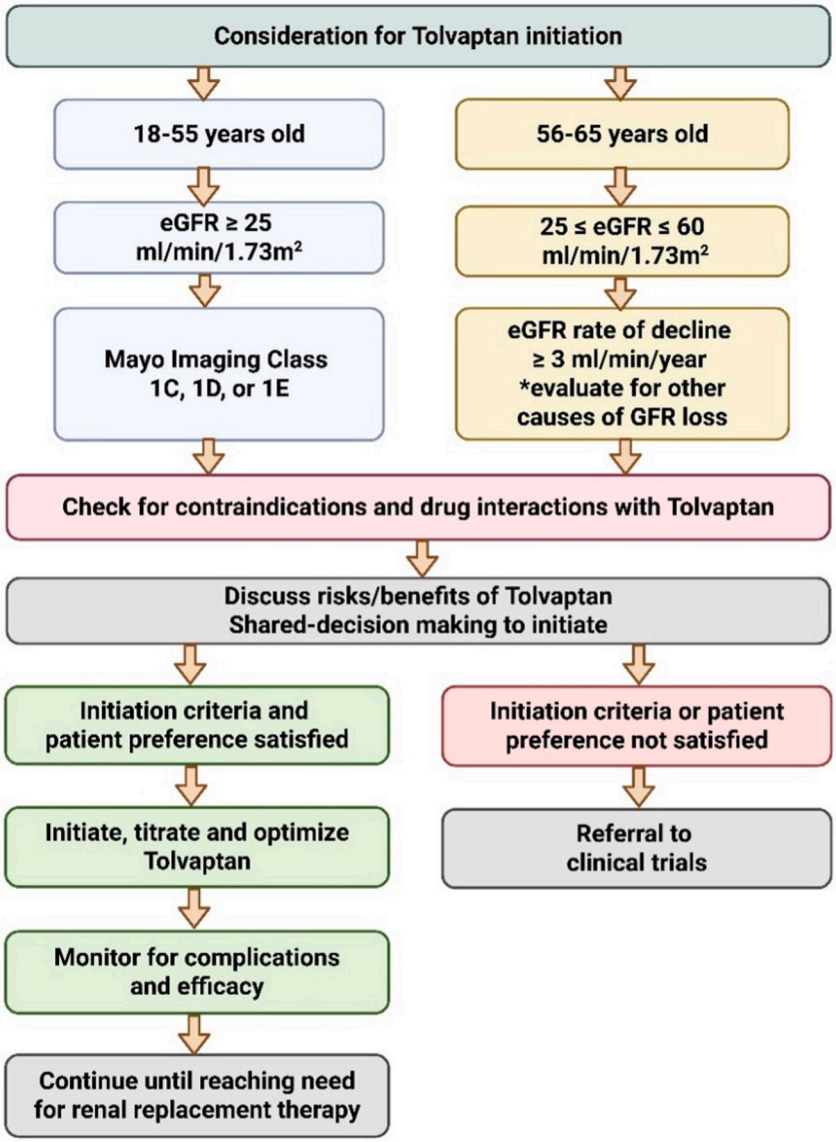


Figure 6. Workflow in shared decision making when considering tolvaptan in the treatment of ADPKD.

KDIGO guideline reviews the data demonstrating the nephroprotective benefits of tolvaptan for ADPKD including 2 pivotal RCTs (TEMPO 3:4 and REPRISE).[117,118] Overall, the net difference in eGFR was 1.3 mL/min per 1.73 m^2 per year (95% CI, 1.0-1.7) and in TKV was −2.7% per year (95% CI, −3.3 to −2.1), both favoring tolvaptan.

The KDOQI work group concurs with the recommendation to initiate tolvaptan treatment in adults with ADPKD and eGFR ≥ 25 mL/min/1.73 m^2 who are at risk of rapid progressive disease. However, as noted by the KDIGO work group, there remains a lack of global consensus on the definition of this risk. The KDOQI work group agrees with defining the risk of rapid progression in ADPKD as patients with Mayo Imaging Class (MIC 1C, 1D, or 1E) or with historical decline in eGFR (≥3 mL/min/year in the absence of another explanation such as uncontrolled hypertension, diabetic nephropathy, heart failure, nephrotoxic drugs, or a disease-causing variant in a non-PKD1/2 gene). We concur that for patients with ADPKD aged 18 to 55 years who are at risk of rapid progression and have eGFR ≥ 25 mL/min/1.73 m^2, the benefits of tolvaptan, which include a 33% relative reduction in GFR decline compared with placebo, outweigh the disadvantages, which include aquaresis and risk of hepatoxicity.[127-129] Given these side effects, however, careful patient selection is essential and the benefits, harms, and uncertainties should be thoughtfully and thoroughly discussed with patients (see Fig 5).

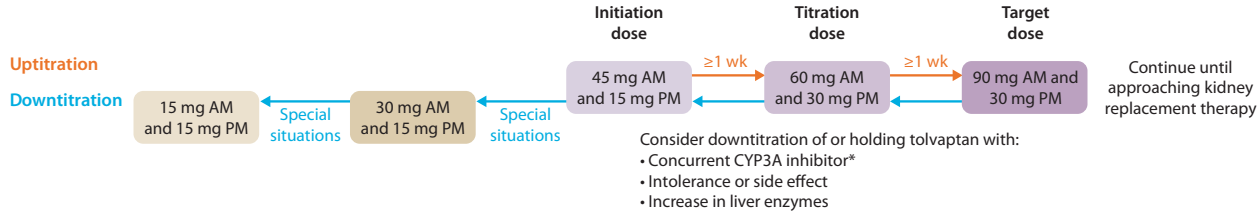


Figure 7. Commencement of and titration approach to tolvaptan use in autosomal dominant polycystic kidney disease. *Examples of strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitors (reduce clearance by >80%) are as follows: antifungals (itraconazole, ketoconazole), antibiotics (clarithromycin), and protease inhibitors (saquinavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir). Examples of moderate CYP3A inhibitors (reduce clearance by 50% to 80%) are as follows: antiarrhythmics (amiodarone), antifungals (fluconazole), antibiotics (erythromycin), calcium-channel blockers (diltiazem, verapamil), protease inhibitors (amprenavir, fosamprenavir), and complementary and/or dietary agents: grapefruit juice (240 mL coadministration).

Among participants older than 55 years in the REPRISE study, there was no statistically significant benefit of tolvaptan treatment on eGFR decline, but this subgroup included only 190 individuals (96 in the tolvaptan arm). Additional evidence is provided by an observational analysis combining data from REPRISE and other PKD clinical trials where 95 participants treated with tolvaptan (aged 55-67 years; CKD stages G3-G4) were matched to untreated individuals receiving the standard of care based on age, sex, baseline eGFR, and CKD stage. Over a 3-year follow-up period, the patients treated with tolvaptan experienced a significantly slower annual decline in eGFR compared with those receiving standard care.[130] As noted in the KDIGO clinical guidelines, there are inherent limitations in such observational studies, including the potential for unmeasured and residual confounding factors. Therefore, we agree with KDIGO that, given the more limited evidence presently available for adults older than 55, individualized, shared decision making with a discussion of risks and benefits is indicated, as outlined in the workflow shown in Figure 6.

Clinical Utility. Evidence supports, and KDOQI endorses, the additional practice points outlined by the KDIGO guideline, which include (1) using an MRI-based imaging classification as the primary method for risk prediction and consideration of tolvaptan treatment, (2) using the PROPKD score to provide additional evidence for risk of rapid progression where historical rate in eGFR or imaging classification are indeterminate, and (3) assessing other causes of acute or chronic eGFR decline before concluding that a person has rapid progression based on historical eGFR trends. Although not all ADPKD patients are candidates for tolvaptan treatment, the KDOQI work group emphasizes the importance of assessing disease progression in all patients and engaging in personalized discussions regarding the risks and benefits of tolvaptan. For TKV measurement, abdominal MRI is preferred over CT to avoid radiation exposure. Both MRI and CT are favored over ultrasound given ultrasound's tendency to underestimate TKV in up to 22% of cases.[45] The PROPKD score, which incorporates clinical and genetic factors, is considered an indicator of rapid progression when the score exceeds 6.[46] Furthermore, because eGFR decline is typically a late event in ADPKD—occurring after substantial kidney damage—best practice involves correlating the cystic burden and age with eGFR and its rate of decline to ensure alignment with the expected disease trajectory.

Implementation and Challenges. The primary challenge in implementing the recommended use of tolvaptan is its limited adoption. In the first 3 years following FDA approval, only a modest number of eligible patients (6,711 patients in the US) received prescriptions.[131] This uptake reflects a range of complex and multifaceted barriers, including insufficient awareness among physicians and patients, the difficulties associated with disease risk stratification, and challenges associated with obtaining MRI-based TKV measurements. Additional barriers are the need for frequent drug monitoring and significant time commitment on the part of both physicians and patients. Patient concerns about aquaresis, quality of life, and the risk of hepatotoxicity further influence decision making. Real-world data show declining adherence over time, with approximately 75% of people continuing the treatment after 1 to 3 years.[132,133] Addressing these challenges necessitates intentional, multidisciplinary efforts at local, regional, and national levels. Strategies to improve the use of tolvaptan include increasing awareness among providers and patients, enhancing comfort and familiarity through educational sessions and national forums, reducing barriers to obtaining MRI and TKV measurements, and improving resources and support for required monitoring. Optimizing patient care demands coordinated efforts between nephrologists and radiologists to accurately classify patients into typical versus atypical imaging categories to ensure precise TKV measurements, particularly in younger

patients where small differences can impact risk stratification, and to advocate for insurance coverage of imaging and tolvaptan use.

4.1.2. Precautions for Tolvaptan in ADPKD

Practice Point 4.1.2.1: Contraindications to tolvaptan should be reviewed in all eligible people with ADPKD before treatment is initiated.

Practice Point 4.1.2.2: Tolvaptan may raise uric acid level and should be used with caution in people with preexisting gout.

4.1.3. Dosage of Tolvaptan

Practice Point 4.1.3.1: Tolvaptan should be initiated at the lowest recommended split-dosage regimen and titrated gradually at an interval determined by the treating physician to permit adequate adaptation to aquaretic adverse events.

Practice Point 4.1.3.2: Tolvaptan should be initiated with a daily dose of 45 mg upon waking and 15 mg 8 hours later (KDIGO guideline Figure 28).

Practice Point 4.1.3.3: Uptitrating to a target daily dose of 90 mg upon waking and 30 mg 8 hours later should generally be the goal of therapy in all people with ADPKD unless this becomes intolerable or is contraindicated by drug interactions (KDIGO guideline Figure 28).

Practice Point 4.1.3.4: Tolvaptan use should be discontinued prior to pregnancy, during lactation, and prior to the commencement of KRT.

Practice Point 4.1.3.5: In people who have already commenced tolvaptan, treatment can be continued when they reach an age >55 years or if their eGFR falls below 25 ml/min per 1.73 m^2.

Commentary. The KDIGO Practice Points 4.1.3.2 and 4.1.3.3 specify an approach to dosing tolvaptan. The KDOQI work group acknowledges the importance of assessing both relative and absolute contraindications for tolvaptan, particularly when there is concurrent use of CYP3A inhibitors or P-glycoprotein inhibitors, which can increase tolvaptan exposure. The KDIGO work group has incorporated into the practice points the dosage regimens for tolvaptan that have been explored in clinical trials, starting with an initial dose of 45 mg/15 mg and adjusting up or down by 15 mg increments based on tolerability (see Figure 7). The goal is to maintain the highest tolerated dose for as long as possible until kidney replacement therapy (KRT) commences. The KDOQI work group concurs with these practice points, adding consideration for an initial dose of 15 mg/15 mg when increased tolvaptan exposure is anticipated due to the previously mentioned concomitant medications. Practice Point 4.1.3.3 recommends titrating up to the highest tolerated dose in accordance with the protocols used in pivotal trials[127,128] rather than dosing to target (a predose morning urine osmolality [Uosm] of ≤280 mOsm/kg), as suggested by US PKD experts in the 2018 practical guide[129] based on dose-finding studies.[134] The KDOQI work group concurs that titrating up to the highest tolerated dose of tolvaptan is the preferred approach because implementing predose morning Uosm measurements has proven to be error-prone and challenging for patients in real-life settings. However, a trough (predose morning) Uosm can be a useful adjunct in assessing whether there is adequate suppression of antidiuretic hormone, especially when tolerability is an issue.

Additionally, we concur with the KDIGO practice point recommending that tolvaptan therapy can be continued in patients after age 55 or when their eGFR falls below 25 mL/min/1.73 m^2. We also agree that treatment can be maintained until the initiation of KRT (Fig 6). These recommendations are based on an observational, post hoc analysis demonstrating the beneficial effects of tolvaptan in patients with an eGFR of 15-29 mL/min per 1.73 m^2.[135] As emphasized by KDIGO, the evidence supporting these recommendations is limited. Therefore, shared decision making aimed at maximizing benefit and minimizing risks is indicated.

Clinical Utility. The practice points outlined by the KDIGO work group, drawing on evidence from RCTs, offer a practical framework to standardize dosing and titration, which may significantly improve adherence and optimize therapeutic benefits. The guidance permitting continuation of tolvaptan beyond certain age limits or eGFR thresholds and until KRT begins allows flexibility in guiding clinical decision making. Ultimately, we hope to see that tolvaptan use is delaying the onset of KRT.

Implementation and Challenges. Financial barriers, particularly insurance-related constraints on access to tolvaptan, present a significant implementation challenge. Improved reimbursement strategies for therapies that require frequent and complex monitoring would help expand patient access to tolvaptan for ADPKD. Beyond insurance, workplace inflexibility for frequent restroom breaks prohibits tolvaptan use for some patients. Although many larger PKD centers may have well-established programs for monitoring liver function tests (LFT) as required by the Risk Evaluation and Mitigation Strategy (REMS), practices with fewer ADPKD patients may have difficulty following and counseling patients who require frequent laboratory monitoring.

4.1.4. Counseling People With ADPKD Who Are Receiving Tolvaptan

Practice Point 4.1.4.1: Physicians should be aware of and educated on adverse effects, contraindications, and drug interactions of tolvaptan. People with ADPKD should be educated on the benefits and harms of tolvaptan and receive information about drug-drug interactions.

Practice Point 4.1.4.2: Education should be provided to people with ADPKD regarding the effect of tolvaptan to

increase urinary water loss (such as thirst, polyuria, nocturia, and pollakiuria), the need to drink enough water to replace urinary losses, as well as strategies to minimize and manage anticipated aquaretic effects to ensure long-term tolerability.

Practice Point 4.1.4.3: People with ADPKD and their physicians should be advised that tolvaptan treatment should be immediately interrupted in clinical situations causing volume depletion, inability to compensate for the aquaresis, or inability to properly monitor liver function tests.

Practice Point 4.1.4.4: People with ADPKD should have a "sick-day plan" and be advised to skip doses of their tolvaptan in situations associated with risk of volume depletion and acute kidney injury (AKI), such as limited access to water (including hiking or traveling), increased fluid losses (e.g., diarrhea, vomiting, fever), and when activities in warm weather increase insensible water loss. In addition, in some situational circumstances, a temporary short-term "drug holiday" may be appropriate (e.g., on a long car journey or airline flight).

Commentary. The KDOQI work group agrees with the practice points delineating safe practices for prescribing tolvaptan, which would entail educating both physicians and patients about the adverse effects, primarily aquaresis and strategies to mitigate the risk of volume depletion by implementing a "sick day plan" or "drug holiday" in certain situations.

Clinical Utility. The KDIGO guidelines offer a framework for prescribing physicians to follow, ensuring a safe treatment program that, in turn, enhances long-term adherence to medication. This approach aims to preserve quality of life without compromising the long-term benefits of treatment. As KDIGO notes, particular consideration should be given when treating younger individuals with ADPKD who are in the earlier stages of disease progression because they may be more sensitive to aquaretic symptoms.[136]

Implementation and Challenges. We have found that early, regular engagement with patients after treatment initiation, with frequent checks on tolerability, helps ensure long-term success with tolvaptan therapy. We warn patients that creatinine may rise on treatment initiation and discuss strategies to mitigate aquaretic effects. We also encourage patients to report all new medications to avoid adverse drug-drug interactions. This approach is effective but labor intensive.

4.1.5. Management and Risk Mitigation of Adverse Effects: Hepatotoxicity

Practice Point 4.1.5.1: Frequent monitoring of liver function tests is mandatory in people receiving treatment with tolvaptan for ADPKD, a process that should follow the instructions depicted in Figure 29 (KDIGO guideline).

4.1.6. Management and Risk Mitigation of Aquaretic Side Effects

Practice Point 4.1.6.1: People with ADPKD should be instructed to respond to thirst, ideally with ingestion of water, during treatment with tolvaptan.

Practice Point 4.1.6.2: Individual adjustments to the treatment may include adapting the schedule, timing, and doses of tolvaptan to the person's activities.

Practice Point 4.1.6.3: People with ADPKD should be counseled that healthy eating (especially lower sodium intake) may modestly reduce tolvaptan-induced polyuria.

Practice Point 4.1.6.4: There is insufficient evidence for using thiazide diuretics to mitigate aquaresis associated with tolvaptan.

Practice Point 4.1.6.5: Treatment with tolvaptan can be maintained close to the initiation of KRT, and the timing of withdrawal depends on individual patient circumstances. The withdrawal of tolvaptan may be associated with an ~5%-10% increase in eGFR.

Commentary. The KDOQI work group concurs with these practice points, which are designed to enhance patient comfort and adherence to treatment by managing primary adverse effects, which include hepatotoxicity and aquaresis. Tolvaptan carries an increased risk of idiosyncratic drug-induced liver injury. Clinical trials have shown that approximately 5% of ADPKD patients treated with tolvaptan experience elevations in transaminase levels to more than 3 times the upper limit of normal. However, serious or potentially fatal liver events are rare, with an estimated incidence of 0.06% in a US postmarketing REMS database analysis.[127,128,131] Given the increased risk, the FDA mandates regular monitoring of LFTs at 2 weeks, 4 weeks, monthly for 18 months, and every 3 months thereafter; note the mandate for more frequent testing in month 1 compared with that shown in KDIGO guideline Figure 29. The KDOQI work group agrees with frequent monitoring of liver enzymes and timely mitigation when an increase occurs. The other major side effect is polyuria, which is expected in almost all people treated with tolvaptan, often exceeding 5 L/day.

The KDIGO work group offers practical advice that includes initiating treatment on a nonworking day, educating patients that tolvaptan tolerability may increase days to weeks after initiation, advising the ingestion of water before feeling thirsty, regularly monitoring body weight to check for dehydration, adjusting the timing and dosing as needed, and reducing dietary sodium intake. The KDIGO work group advises against using thiazide diuretics to mitigate the nephrogenic diabetes insipidus effect of tolvaptan due to insufficient evidence supporting this practice.

Clinical Utility. These practice points provide clear guidance on the safe and effective use of tolvaptan in real-world clinical practice. The KDIGO recommendations and particularly LFT monitoring protocols can be incorporated into electronic health record templates to reduce the risk of missed laboratory checks. This is important because early detection and timely management of LFT abnormalities are crucial to avoiding more serious liver events. The practice points encourage physicians to set patient expectations and to adjust and individualize tolvaptan prescriptions to improve tolerability and support long-term adherence. The practice points address continuation of tolvaptan close to the initiation of KRT, where evidence is limited and individualized management is important.

Implementation and Challenges. Implementing these KDIGO practice points requires substantial effort and resources from prescribing physicians and their practices. The need for frequent laboratory monitoring entails consistent scheduling, tracking, and follow-up as well as staff to provide patient education. These demands can burden practices with limited infrastructure and especially those in rural settings without an integrated electronic health record system. The resources needed to manage and optimize tolvaptan treatment are often more accessible in specialized PKD clinics such as those designated as PKD Centers of Excellence or Partner Clinics by the PKD Foundation.

4.2. Water Intake in the Absence of Tolvaptan

4.2.1. General Advice Regarding Water Intake

Recommendation 4.2.1.1: We suggest adapting water intake, spread throughout the day, to achieve at least 2-3 liters of water intake per day in people with ADPKD and an eGFR ≥30 ml/min per 1.73 m² without contraindications to excreting a solute load (*2D*).

Practice Point 4.2.1.1: People with ADPKD should be provided individualized advice and education on how to maintain hydration, what behaviors achieve this, what fluids to drink, and how to recognize signs of dehydration.

4.2.2. Precautions Regarding Increasing Water Intake

Practice Point 4.2.2.1: A clinical assessment should be performed to identify risk factors for fluid retention and/or dilutional hyponatremia prior to advising people with ADPKD to increase water intake.

Practice Point 4.2.2.2: People with CKD G4-G5 (eGFR <30 ml/min per 1.73 m²) or who have a clinical contraindication to high water intake should drink to thirst and/or follow individualized clinical advice.

4.2.3. Counseling Regarding Increased Water Intake

Practice Point 4.2.3.1: Screen people with ADPKD to estimate habitual daily fluid intake during their initial evaluation and to enhance counseling and education.

Commentary. The KDOQI work group agrees that promoting adequate water intake is an important adjunct in the clinical management of ADPKD. The underlying rationale is that chronically elevated vasopressin levels contribute to cyst growth and disease progression and that increased water intake may suppress vasopressin secretion.[137] Maintaining a dilute urine through increased water intake is considered to be safe with the exception of those individuals with advanced CKD (eg, eGFR < 30 mL/min/1.73 m²) or other risk factors for hyponatremia. However, as noted by the KDIGO work group, there is limited empirical evidence supporting a clinical benefit of increased water intake in slowing ADPKD progression. The largest randomized trial to date, the PREVENT-ADPKD trial,[138] did not find a beneficial effect of a structured behavioral intervention to increase water intake on the rate of eGFR decline, htTKV increase, or pain. Notably, only half the participants in the active treatment arm achieved the target urine osmolality, and water intake remained high (approximately 2.5 L/day) in the control group, limiting the trial's ability to detect a treatment effect.

Clinical Utility and Implementation Challenges. The negative findings of the PREVENT-ADPKD trial do not disprove the hypothesis that suppression of vasopressin through increased water intake can slow disease progression in ADPKD. This hypothesis is supported by a small pilot study by Amro et al[139] and Dev et al[140] in which a low osmolar diet combined with targeted water intake reduced vasopressin levels and urine osmolality in a cohort of highly motivated participants. However, the PREVENT-ADPKD trial highlights the challenge of implementing this approach more broadly. Even a relatively intensive individualized behavioral intervention to increase water intake was not sufficient to achieve vasopressin suppression in the intervention arm, and only half of these participants achieved the target urine osmolality. Moreover, such intensive interventions may not be feasible in routine ambulatory care settings. Nevertheless, the intervention was safe, with only rare episodes of hyponatremia in patients selected for low risk of this complication.

In practice, relatively few additional resources would be required to provide periodic individualized counseling to promote optimal hydration, with a target of maintaining at least 2-3 L of daily urine output. Increased water intake should be considered only after a careful assessment of risk factors for fluid overload and hyponatremia, such as heart

failure, liver disease, or the use of medications that impair free water excretion.

4.3. Mammalian Target of Rapamycin (mTOR) Inhibitors

Recommendation 4.3.1: We recommend not using mammalian target of rapamycin (mTOR) inhibitors to slow kidney disease progression in people with ADPKD (*1C*).

4.4. Statins

Recommendation 4.4.1: We suggest not using statins specifically to slow kidney disease progression in people with ADPKD (*2D*).

4.5. Metformin

Recommendation 4.5.1: We recommend not using metformin specifically to slow the rate of disease progression in people with ADPKD who do not have diabetes (*1B*).

Commentary

The KDOQI work group agrees that mTOR inhibitors, statins, and metformin should not be used specifically to slow ADPKD disease progression. Although preclinical studies suggested that mTOR inhibitors might have beneficial effects on cyst growth, 4 RCTs of sirolimus and everolimus failed to demonstrate efficacy in slowing eGFR decline. These studies also showed conflicting effects on TKV and treatment was associated with significant dose-limiting adverse effects such as oral mucositis and diarrhea.[141-144] Pravastatin was shown to slow kidney growth in a small study of children (aged 8-22 years) with ADPKD, but only 91 participants completed the trial.[145] However, among 150 adult patients with ADPKD and preserved kidney function, pravastatin did not slow the increase in htTKV and had no effect on slowing the decline in renal blood flow and kidney function compared to placebo.[146] A large multicenter, international placebo-controlled clinical trial (IMPEDE-PKD trial) is currently underway to evaluate metformin's effect on ADPKD progression.[147]

The KDOQI work group emphasizes that these recommendations do not pertain to the use of statins for lipid management in patients with hyperlipidemia or metformin use for glycemic control in those with type 2 diabetes. Use of these medications for these specific indications in patients with ADPKD are addressed in other KDIGO CKD guidelines.[148]

4.6. Somatostatin Analogues

Recommendation 4.6.1: We suggest that somatostatin analogues should not be prescribed for the sole purpose of decreasing eGFR decline in people with ADPKD (*2B*).

Practice Point 4.6.1: Somatostatin analogues can be considered in people with ADPKD with severe symptoms due to massively enlarged kidneys to lower the growth rate of kidney cysts when no better options are available

Commentary

Somatostatin analogues have been examined in multiple clinical trials in ADPKD.[149-152] These studies have used different formulations of somatostatin analogues, and many of the trials have enrolled small numbers of participants. In the largest trial (DIPAK-1 trial), 309 individuals with ADPKD were randomized to lanreotide versus placebo for 2.5 years.[151] There was no effect on the rate of eGFR decline in the active treatment arm compared with placebo. The growth of htTKV was slowed modestly (by 1.3%/year) in the lanreotide group versus placebo. Gastrointestinal side effects (nausea, vomiting, abnormal stools) were common in the lanreotide group, and serious adverse events were more than twice as common in the treatment arm compared with placebo. Hyperglycemia and diabetes were side effects identified in some clinical trials.[150,151]

Because of the lack of clear efficacy in slowing eGFR decline and the side-effect profile of somatostatin analogues, the KDOQI work group agrees that they should not be used at this time as first-line agents in individuals with ADPKD for the purpose of slowing renal function decline. However, the KDOQI work group agrees that this class can be considered in selected patients where relief from massively enlarged kidneys is needed and there are "no better options are available."

Clinical Utility and Implementation and Challenges

Somatostatin analogues are indicated in select patients who have limited therapeutic options. Practical implementation challenges include the need for long-term monthly injections and the difficulty of obtaining insurance coverage for off-label use. Given these complexities, treatment should be managed by or in consultation with clinicians experienced in both ADPKD and somatostatin analogue therapy. Treatment will require careful monitoring of side effects, including gastrointestinal symptoms and hyperglycemia, along with serial assessment of kidney volume to ensure that the clinical benefits of continued treatment outweigh the risks.

4.7. Sodium/Glucose Cotransporter 2 (SGLT2) Inhibitors

Practice Point 4.7.1: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) should not be used to slow eGFR decline in people with ADPKD.

Commentary

The KDOQI work group agrees that using SGLT2 inhibitors to slow progression of ADPKD is not currently justified. Although large randomized controlled clinical trials have demonstrated that SGLT2 inhibitors slow the progression of diabetic and nondiabetic CKD, especially among those with albuminuria, these trials specifically excluded patients with ADPKD.[153,154] The FDA-regulated prescribing instructions for SGLT2 inhibitors that are approved for treatment of CKD do not recommend their use in patients with ADPKD.

Prior preclinical studies in rodent models of ADPKD have found variously that SGLT2 inhibitors slow cyst enlargement, have a neutral effect on renal function decline, or may increase cyst progression.[93-95] SGLT2 inhibitors may increase vasopressin levels, a driver of cyst progression in ADPKD.[155] In a small uncontrolled case series of 22 ADPKD patients treated with dapagliflozin (of whom half were on concomitant tolvaptan treatment), htTKV increased and eGFR decline was faster after dapagliflozin was initiated.[156] Therefore, at this time it is reasonable to avoid using SGLT2 inhibitors in ADPKD patients specifically to slow eGFR decline or cyst progression.

Randomized, placebo-controlled trials of empagliflozin in nondiabetic ADPKD patients (NCT05510115 and NCT06391450) are currently underway. The US trial will assess the safety and tolerability of this treatment and will provide preliminary estimates of its effects on eGFR and htTKV, with results anticipated in early 2026.[157]

Implementation and Challenges

The use of SGLT2 inhibitors is encouraged for slowing the progression of CKD in combination with RAAS inhibitors and is recommended by KDIGO for treatment of nondiabetic and diabetic CKD in those with an eGFR of at least 20 min/min/1.73 m^2. Therefore, treating nephrologists and referring primary care physicians may be considering their use for their CKD patients with ADPKD. However, considering the absence of high-quality data in patients with ADPKD, it remains reasonable and appropriate to avoid using these medications for the purpose of slowing ADPKD progression.

SGLT2 inhibitors are also approved for treatment of heart failure with reduced ejection fraction and for lowering of glucose in type 2 diabetes. The safety and efficacy of SGLT2 inhibitors in these patients who also have ADPKD remains uncertain. However, a recent retrospective review of US Veterans Affairs data suggests a benefit of SGLT2 inhibitors for older patients with both diabetes mellitus and ADPKD.[158] These findings highlight the need for prospective clinical trials to rigorously assess the role of SGLT2 inhibitors in ADPKD.

4.8. Ketogenic Interventions

Practice Point 4.8.1: Ketogenic interventions should not be implemented in people with ADPKD without further evidence from controlled clinical trials.

Commentary

Considering the paucity of clinical trials testing ketogenic interventions, the KDOQI work group agrees that providers should not recommend a ketogenic diet specifically for slowing ADPKD progression. Although preclinical studies in rodent models of ADPKD have suggested that a ketosis-promoting diet (or supplementation with ketoacids) can slow kidney cyst enlargement, the long-term feasibility, safety, and efficacy of this approach in human ADPKD remains uncertain.[159,160] A recent short-term feasibility study in participants with an eGFR of at least 30 mL/min/1.73 m^2 found that 3 months of a ketogenic diet was feasible and safe, with roughly 40% of patients reporting mild symptoms related to a ketotic state.[161] The ketogenic diet induced greater weight loss, but there was no difference in htTKV detected over the short period of the study. Among the unresolved questions are the potential long-term effects on nephrolithiasis due to hypercalciuria and on the development of dyslipidemia.

Implementation and Challenges

Longer term trials of ketogenic dietary interventions are needed, with appropriate statistical power to detect the potential effects on ADPKD progression and any potential risk of nephrolithiasis due to lithogenic changes in urinary electrolyte excretion. There are multiple potential challenges to long-term adherence to a ketogenic diet, and research is needed to determine the most effective methods to promote long-term dietary adherence if the diet is found to be clinically beneficial.

4.9. Complementary Medicines

Practice Point 4.9.1: Complementary medicines or supplements should not replace standard medical treatments in people with ADPKD.

Commentary

Due to the relatively high use of complementary and alternative medicines in the US,[162] it is essential for clinicians to routinely obtain a thorough medication history. The KDOQI work group agrees with KDIGO (Chapter 4) that such alternative therapies should not replace standard medical treatments for ADPKD. Although some alternative medications and supplements have been studied in preclinical models of ADPKD or in small, short-term clinical trials, there is insufficient evidence to support their use for slowing ADPKD progression or preventing major complications. Additionally concerns remain regarding the potential for contamination of supplements with pharmaceuticals or heavy metals, some of which may be nephrotoxic.

Implementation and Challenges

Assessment of complementary and alternative medicine use is already a standard component of medical history-taking in ambulatory care settings. A key challenge is ensuring that discussion around this issue is conducted in a nonjudgmental manner to encourage full disclosure. Additional research is needed to evaluate the safety and efficacy of commonly used complementary and alternative therapies in ADPKD, including those used to manage pain and hypertension. A further challenge is addressing the substitution of complementary medicines and supplements for evidence-based treatments, which may compromise clinical outcomes.

Chapter 5. Polycystic Liver Disease

5.1. Diagnosis and Staging of PLD

Practice Point 5.1.1: When CT scan or MRI is performed for patients with ADPKD, liver images should be evaluated to characterize the severity of PLD.

Practice Point 5.1.2: When people with ADPKD are informed about the presence of liver cysts found on imaging, they should be advised of the likely outcomes and possible symptoms.

Practice Point 5.1.3: People with ADPKD who are symptomatic due to possible hepatomegaly should have abdominal imaging performed to evaluate both liver and kidney volume.

Practice Point 5.1.4: Symptoms of PLD should be captured with the disease-specific symptom questionnaires Polycystic Liver Disease Questionnaire (PLD-Q) and Polycystic Liver Disease Complaint-specific Assessment (POLCA).

Commentary

Polycystic liver disease (PLD) may occur in the context of mild or severe ADPKD and may be due to genes associated with ADPLD. In this commentary we use PLD to mean both disease states because the liver disease is managed similarly.

The KDOQI work group agrees that the evaluation of ADPKD should include not only kidney but liver imaging to assess organ involvement. Significant progress has been made in using imaging techniques to stage PLD. High-quality cross-sectional CT and MRI imaging permits discussion of disease severity and treatment options with patients. Ultrasound can be useful as an initial imaging tool to assess the etiology of abdominal symptoms, but it may not be optimal for assessing PLD severity or reassessment following various interventions. We agree that further evaluation of liver status by measuring total liver volume (TLV) should be pursued in those individuals who are symptomatic. These measurements, when coupled with TKV, are important for assessing the contribution of liver versus kidney to cyst burden, thereby informing therapeutic options.

Clinical Utility, Implementation, and Challenges

One major implementation challenge of these practice points is that many nephrologists obtain a dedicated renal ultrasound rather than choosing an imaging study that will adequately gauge PLD status. The choice of imaging modality may be influenced by insurance coverage for more costly MRIs, for example. Additionally, many radiology reports fail to adequately describe liver cyst burden. It is important to note that the location and size of cysts may be valuable in evaluating pain and determining whether there is a cyst that might be amenable to percutaneous cyst aspiration and sclerotherapy. For those individuals who are symptomatic, the guidelines recommend measurement of liver volume, which is rarely routinely performed. Because there is no easy formula like the kidney ellipsoid formula, the time involved in manually measuring TLV or liver cyst volume (which may be an even more sensitive biomarker) is likely to be prohibitive. Ultimately these measurements may only be possible at a few designated Centers of Excellence. We note, however, that this landscape could change with rapid advances in the application of artificial intelligence to image analysis which could make routine TLV measurements feasible and could be used to automate PLD assessments such as cyst size, vascular compression, and cyst distribution. This information could inform which patients might benefit from surgery or percutaneous cyst drainage.

In the short term, we recommend educating nephrologists and radiologists regarding PLD assessments. For nephrologists, we recommend personal review of imaging studies so that cyst burden can be correlated with patient symptoms. To facilitate this, many states now have health information exchanges that allow physicians and patients to directly access imaging studies, and artificial intelligence can now generate understandable patient-facing reports with images on Health Insurance Portability and Accountability Act (HIPAA)-compliant patient portals. We

recommend developing a structured radiology report that more completely describes liver findings including TLV, if available.

5.2. Risk Factors

5.2.1. Female Sex Hormones

Practice Point 5.2.1.1: Women with ADPKD, particularly those with PLD, should be counseled about the benefits and potential harms of sex hormone therapy.

Commentary. Informing women about the potential impact of hormone therapy on PLD is essential because this issue is relevant at many stages of life. Women consistently experience more severe PLD compared with men, and they are more likely to seek care for PLD-related complications.[163] Observational studies indicate that liver growth appears to be accelerated in premenopausal women but slows after menopause,[164] suggesting that estrogen exposure might play a role in promoting liver growth. However, no large, well-controlled, prospective studies have specifically investigated hormone impact on liver growth.

Two studies highlighted by KDIGO provide relevant but limited insights. In one cross-sectional study of 287 women, self-reported annual exposure to hormone-containing contraceptives was linked to a small (1.45% greater) but significant increase in TLV in premenopausal women.[165] However, most of the women used combined progestin/estrogen-containing contraceptives, and due to the self-reported nature of the data no definitive conclusion could be drawn with respect to low- versus high-dose estrogen exposure. In this study, there was no association between estrogen exposure and TLV in post menopausal women. By contrast, another case-control study of 19 women reported that postmenopausal use of conjugated estrogens resulted in a modest increase in TLV over 1 year.[166] There are no data looking at the impact on PLD of transdermal estrogen patches or topical formulations, which theoretically avoid first-pass metabolism through the liver. Additionally, the impact of pregnancy on PLD has not been consistent across studies. In summary, the available data underscore the importance of defining the influence of hormones on PLD. However, the current evidence is insufficient to provide comprehensive guidance.

Clinical Utility, Implementation, and Challenges. Given the current state of evidence, we recommend individualized treatment approaches. For premenopausal women, hormonal contraception remains an important method for family planning. Physicians should discuss the use of these therapies in the context of a patient's liver cyst burden and the possible risks of pregnancy. We encourage nephrologists to familiarize themselves with the wide range of family planning options, including combination pills (estrogen and progestins), low-dose estrogen pills, progestins with antiandrogenic activity (drospirenone), intrauterine devices, and both hormonal and nonhormonal and progesterone-only contraceptives. For postmenopausal women, the practice of prescribing estrogen for menopause symptom management continues to evolve.[167]

Beyond the potential impact on PLD, other general considerations are the risk of thromboembolism, cardiovascular disease, and endometrial cancer. These factors must be evaluated individually for each woman, and consideration must be given to therapies available for managing menopause-associated vasomotor symptoms, insomnia, and vulvovaginal and genitourinary symptoms.[167-169] Except for 1 case report showing a favorable effect for tamoxifen,[170] the evidence for the efficacy of selective estrogen receptor modulators on PLD progression is lacking. A clinical trial is in progress with the gonadotropin-releasing hormone agonist leuprorelin to stop production of estrogen, progesterone, and other female hormones in PLD and thereby induce medical menopause.[171]

For both premenopausal and postmenopausal women, we recommend nephrologists communicate and collaborate with prescribing gynecologists or family medicine practitioners regarding the unique considerations related to PLD and hormone therapies.

5.2.2. Nutrition and Lifestyle

Practice Point 5.2.2.1: People should be advised that no specific diets are available to treat PLD, and that they should follow the dietary recommendations and lifestyle advice for people with ADPKD and CKD G1-G5.

Practice Point 5.2.2.2: People with symptomatic PLD should be assessed for sarcopenia and malnutrition (KDIGO guideline Table 13).

Practice Point 5.2.2.3: People with PLD and sarcopenia or malnutrition should be provided with intensive nutrition counseling and exercise rehabilitation.

Commentary and Clinical Utility. Malnutrition and sarcopenia are usually limited to individuals with severe PLD, sometimes concomitant with anorexia, early satiety, and vomiting due to compression of the upper gastrointestinal tract from enlarging cysts. Individuals with sarcopenia and malnutrition should have disease staging to determine the best management option. Prompt referral for liver transplantation may be required to avoid worsening functional status due to malnutrition.

Implementation and Challenges. Sarcopenia and malnutrition are often evaluated subjectively. Objective measures of sarcopenia such as skeletal muscle index via CT scan, muscle ultrasound, and bioelectrical impedance analysis have not been validated in PLD and may not be routinely available. Although such assessments have been evaluated in cirrhosis, there is limited evidence that quantifying sarcopenia improves outcomes in PLD.[172,173] In addition, implementation of exercise-based

rehabilitation may be challenging in individuals with severe PLD due to restricted mobility from massive polycystic liver size, which leads to dyspnea and pain with exertion. Intensive nutrition support may also be limited by anorexia and vomiting.

5.2.3. Management

Practice Point 5.2.3.1: Treatment for PLD should be performed in centers of expertise.

Practice Point 5.2.3.2: People with ADPKD and PLD should receive treatment (i.e., medical and/or surgical including minimally invasive treatments) if they experience cyst-related symptoms or complications that negatively impact their quality of life (QoL). Determination of treatment type should be based on symptoms, liver cyst characteristics, total liver volume (TLV), and treatment availability.

Commentary and Clinical Utility. The KDOQI work group agrees that individuals with moderate to severe PLD symptom burden should be referred to Centers of Excellence with specialized teams experienced in cyst aspiration and sclerotherapy, cyst fenestration, liver resection, and expertise in liver transplant surgery for PLD.

Implementation and Challenges. In the US, few centers with expertise in PKD have large enough case numbers with moderate to severe PLD to be able to provide the recommended treatment options for patients with cyst-related symptoms or complications. Symptomatic individuals may need to travel to centers where interventional radiologists, hepatologists, and liver surgeons experienced in managing individuals with highly symptomatic PLD are available.

Recommendation 5.2.3.1: We recommend prescribing long-acting somatostatin analogues in people with ADPKD and markedly enlarged polycystic livers with severe volume-related symptoms (*1B*).

Practice Point 5.2.3.3: The administration of long-acting somatostatin analogues is usually well tolerated. Prescribing physicians should be aware of possible side effects (gastrointestinal symptoms, gallstones, hyperglycemia, bradycardia).

Practice Point 5.2.3.4: When long-acting somatostatin analogues are prescribed, the effect on symptom burden and/or volume of polycystic livers and kidneys should be evaluated after 6-12 months. If beneficial effects of therapy are not observed, somatostatin analogues should be discontinued.

Commentary and Clinical Utility. KDOQI agrees that long-acting somatostatin analogues should be reserved for individuals with ADPKD and markedly enlarged polycystic livers who are severely symptomatic. Three somatostatin analogs (SSAs)—octreotide, lanreotide, and pasireotide—are currently FDA-approved in the US for other indications, including acromegaly, carcinoid, and neuroendocrine tumors and variceal bleeding. Although the use of SSAs for symptomatic PLD is off-label, clinical trials are ongoing to support FDA approval of a subcutaneous formulation of octreotide for PLD.[174]

Among the available agents, octreotide and lanreotide have been most extensively studied in PLD. Small, randomized trials have demonstrated their efficacy in reducing liver growth and cyst expansion.[175,176] A pooled analysis of 3 RCTs suggested that women younger than 48 years who have rapidly progressive PLD derive the most benefit from treatment with SSAs. SSAs are generally well tolerated. The most common adverse effects are gastrointestinal symptoms early in the course of treatment, which typically improve over time. Less frequent side effects include cholelithiasis, hyperglycemia, and diabetes—the latter is more commonly associated with pasireotide. KDOQI concurs that patients who are treated with SSAs should be assessed for response to therapy after 6 to 12 months.[177-179] If there is no benefit in terms of liver growth or symptom improvement then the therapy should be discontinued. However, if treatment is deemed beneficial, SSAs can be continued beyond 12 months.

Implementation and Challenges. There are several challenges to implementing treatment with SSAs. First, these medications are costly and currently are used off label for PLD, requiring prior authorization to ensure insurance coverage. If approval for long-acting intramuscular formulations is denied, short-acting subcutaneous octreotide (administered twice daily) may be considered as an alternative. Second, long-acting SSAs are administered by intramuscular injection, which requires that they be delivered by trained providers (usually nurses) because patients can experience injection site bruising, pain, or other site reactions. Administration in an infusion center may increase the likelihood of insurance coverage.

To assess treatment response and guide management, we recommend regular monitoring of symptom burden and liver growth. Symptom assessment can be standardized using tools such as the PLD-Q questionnaire for patient-reported symptoms,[180] and liver growth can be evaluated annually by MRI or CT. We recommend obtaining baseline and follow-up electrocardiograms, particularly during the first year, to assess for bradycardia as well as regular monitoring of glucose and LFTs (Box 1). Patients should be counseled about potential side effects including gastrointestinal symptoms such as steatorrhea and loose stools and an increased risk of gall stones. Additionally, they should be advised to avoid medications that cause prolonged QT interval (eg, some commonly used antibiotics).[181]

Practice Point 5.2.3.5: Ursodeoxycholic acid, mTOR inhibitors, and vasopressin-2 (V_2) receptor antagonists should not be used to slow liver growth in people with PLD.

Practice Point 5.2.3.6: People with PLD should be referred for liver transplantation in the event of massive PLD in the absence of contraindications or alternative treatment options.

Practice Point 5.2.3.7: People with PLD should be referred for combined kidney–liver transplantation when an indication for liver transplantation is present and the person has severely impaired kidney function (eGFR of <30 ml/min per 1.73 m^2).

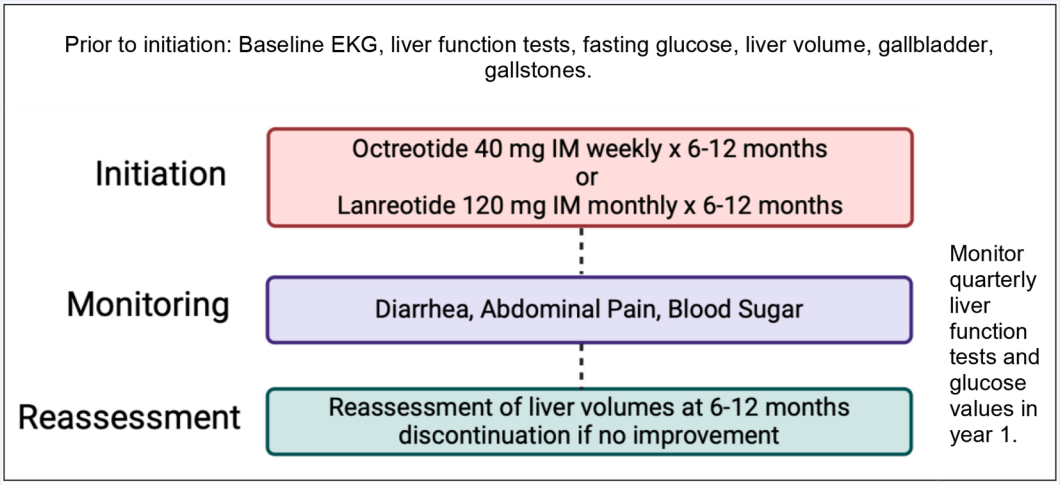
An approach to using somatostatin analogs that incorporates the KIDGO guideline with additional information regarding safety monitoring. Abbreviations: EKG, electrocardiogram; IM, intramuscular.

Commentary and Clinical Utility. Massive PLD can be debilitating, so liver transplant is an important therapeutic option that should be considered. Other rare indications for liver transplant in patients with ADPKD include variceal hemorrhage, ascites, obstruction of hepatic venous outflow (Budd-Chiari equivalent), and biliary tract obstruction by extensive cystic disease not amenable to other interventions.

In the US, liver transplantation candidacy is based on Model for End-Stage Liver Disease (MELD) score.[182] Despite the tremendous physical burden of disease, the MELD score for individuals with PLD often does not rise to levels qualifying for transplant. Fortunately, in this situation individuals with PLD may qualify for exception points. In the US, OPTN recommends MELD exception points for individuals with severe symptoms and any of the following:[183]

- Hepatic decompensation or severe portal hypertensive complications
- Concurrent hemodialysis
- GFR less than 20 mL/min
- Prior kidney transplant
- Moderate to severe protein calorie malnutrition as documented by a registered dietician using any of the following:
  - o Modified Global Leadership Initiative on Malnutrition (GLIM) Phenotypic criteria: The GLIM approach is based on the assessment of 3 phenotypic (weight loss, low body mass index, and low skeletal muscle mass) and 2 etiologic criteria (low food intake and presence of disease with systemic inflammation), with diagnosis confirmed by any combination of 1 phenotypic and 1 etiologic criterion fulfilled.[184]
  - o American Society for Enteral and Parenteral Nutrition (ASPEN) criteria: The ASPEN Criteria require the confirmation of any 2 of the following criteria: insufficient energy intake, weight loss, loss of subcutaneous fat, loss of muscle mass, fluid accumulation, and reduced hand-grip strength.[185]
  - o Nutrition Focused Physical Exam (NFPE): The NFPE approach is to perform a thorough examination to assess nutritional status and evaluate for malnutrition including assessment of muscle and subcutaneous fat wasting, oral health, hair, skin and nails, evaluating for edema, determining ability to suck, swallow, and breathe, ascertaining appetite, and evaluating affect.
  - o Subjective Global Assessment (SGA-C score): The SGA-C score incorporates 7 components including weight/weight change, dietary intake, gastrointestinal symptoms, functional capacity, disease state/comorbidities if related to nutritional needs, and physical

Box 1. Somatostatin Analogs: Baseline Assessment and Patient Education



An approach to using somatostatin analogs that incorporates the KIDGO guideline with additional information regarding safety monitoring. Abbreviations: EKG, electrocardiogram; IM, intramuscular.

examination (focusing on loss of subcutaneous fat, muscle wasting, and edema). The score inversely correlates with nutritional status.[186]
- Severe sarcopenia as documented with skeletal muscle index (<39 cm^2/m^2 in women and <50 cm^2/m^2 in men) or equivalent receive consideration for MELD exception points.[183]

Implementation and Challenges. There are 2 major implementation challenges in the US. First, individuals with PLD are not referred to hepatology because liver synthetic function is typically preserved. Nephrologists should be aware of the unique transplant criteria for PLD, which notably lacks an objective definition of "severe symptoms." This underscores the need to recognize the full spectrum of disease burden and incorporate standardized assessment of PLD severity into routine care of individuals with PKD. Ongoing education is necessary regarding ongoing adjustments to the MELD exception criteria such as the recent incorporation of protein malnutrition and sarcopenia.

Second, there are significant resource limitations in assessing protein-calorie malnutrition. Many smaller or rural centers may not have access to trained dieticians, and currently proposed nutritional assessment tools are not yet validated or accepted by the Academy of Nutrition and Dietetics, limiting their incorporation into clinical practice.

5.3. Liver Cyst Infections

5.3.1. Diagnosis

Practice Point 5.3.1.1: Diagnosis of liver cyst infections should utilize culture data, advanced imaging, and clinical signs and symptoms (KDIGO guideline Figure 33).

Practice Point 5.3.1.2: Imaging studies should be performed to determine the severity and location of a liver cyst infection.

Practice Point 5.3.1.3: Empirical antibiotics should not be used to treat people with localized liver pain without fever who have normal white blood cell counts and CRP levels. Other causes such as cyst hemorrhage should be considered.

Commentary and Clinical Utility. The diagnosis of liver cyst infection can be challenging and relies on a combination of factors, including clinical signs and symptoms, blood cultures (positive in >60% of liver cyst infections[187]), imaging, and response to empiric antibiotic treatment. Conventional imaging such as ultrasound, CT, or MRI can be useful in localizing an infected cyst, but positron emission tomography with ^{18}F-FDG (fluorodeoxyglucose) positron emission tomography (PET) CT has a positive predictive value of 84% and a negative predictive value of 82% and is recommended when confirmation is required.[188] In some instances, a cyst aspirate may be performed, with a finding of neutrophils or bacteria definitive for infection. The KDOQI work group agrees with the proposed KDIGO algorithm for diagnosing liver cyst infection (KDIGO guideline Figure 33). This algorithm considers other sources of infection or inflammation. Potential risks factors for infection such as recent bile duct sphincterotomy should also be considered.

Implementation and Challenges. Confirmatory imaging remains a challenge in diagnosing both kidney and liver cyst infections. Fortunately, PET-CT is now recognized by the US Centers for Medicare & Medicaid Services (CMS) as an appropriate diagnostic modality for fever of unknown origin. In addition, the 111-indium white blood cell scan is widely available and approved for clinical use. However, access to these imaging modalities may be limited in smaller or rural health care settings, requiring referral to larger hospitals or specialized imaging facilities.

5.3.2. Management

Practice Point 5.3.2.1: Empirical antibiotic treatment of liver cyst infections should target gram-negative bacteria in the *Enterobacteriaceae* family.

Practice Point 5.3.2.2: Empirical antibiotic treatment of liver cyst infections should be initiated with a third-generation intravenous (i.v.) cephalosporin with or without a fluoroquinolone. After clinical stabilization, i.v. therapy can be switched to an oral fluoroquinolone, with adjustment according to culture results when available.

Practice Point 5.3.2.3: Duration of antibiotic therapy should be ≥4 weeks for liver cyst infection. Longer treatment periods may be required based on the response to therapy.

Practice Point 5.3.2.4: Percutaneous drainage of infected liver cysts <48 hours after initiation of antibiotics may be reasonable in the presence of the following:
- Isolation of pathogens that are unresponsive to antibiotic therapy from a cyst aspirate;
- Immunocompromise in the patient;
- Large infected hepatic cysts (>8 cm); or
- Hemodynamic instability and/or signs of sepsis.

Practice Point 5.3.2.5: Infected liver cysts that do not respond to 48-72 hours of antibiotic treatment should be evaluated further. Placement of a percutaneous drain should be considered for failure to improve, worsening symptoms, or presence of the risk factors listed, and the drain should be kept in place until drainage stops. In the case of deep cysts for which percutaneous drainage is not feasible, surgical drainage may be necessary.

Commentary and Clinical Utility. It is generally thought that liver cyst infections arise from transmigration of intestinal pathogens. However, studies conclusively proving this mechanism are lacking. KDIGO Practice Points 5.2.3.1-5.2.3.3 provide general guidance regarding the therapy of cyst infections, including the choice of empiric antibiotics that should cover enteric Gram-negative bacteria and treatment for a minimum of 4 weeks. The specific antibiotic choice may need to be tailored according to local resistance patterns but should always include lipid-soluble antibiotics with good tissue penetration. Additional practice points (Practice Points 5.2.3.4 and 5.2.3.5) provide

recommendations for further refining therapy when liver cysts recur or fail to respond to initial therapy. The treatment of liver cyst infections should involve an infectious disease specialist who is aware of the patient's medical history, including prior liver cyst infections/procedures.

Implementation and Challenges. In the US, the recommended antibiotics and interventional approaches are readily obtainable in well-populated areas. However, the availability and expertise required to evaluate the need for drainage and/or surgery may be limited in rural or underserved areas. In situations where a patient fails to respond to empiric treatment, it may be reasonable to consider referral to or consultation with experts at a tertiary care center.

Chapter 6. Intracranial Aneurysms and Other Extrarenal Manifestations

6.1. Intracranial Aneurysms

Recommendation 6.1.1: We recommend informing adults with ADPKD about increased risk for intracranial aneurysms (ICAs) and subarachnoid hemorrhage (SAH) (KDIGO guideline Figure 35) (*1C*).

Commentary

Retrospective studies suggest that ADPKD is associated with approximately a 4-fold risk for development of an ICA compared with the general population (~10% to 12% vs ~3.2%).[189] In addition, the incidence of ICA/subarachnoid hemorrhage (SAH) is about 3- to 4-fold higher for those with a family history compared with those with ADPKD and no family history. Based on these observations, a positive family history is a well-established risk factor for ADPKD-associated ICA/SAH.[189] The KDOQI work group agrees with informing individuals with ADPKD of these risks as a part of shared decision making.

Clinical Utility

Rupture of an ICA is associated with high morbidity and mortality. The median age at aneurysm rupture in ADPKD is 41 years, compared with 52 years in the general population,[190] thereby increasing the impact of this potentially catastrophic event. Despite ICAs being one of the most consequential extrarenal manifestations of ADPKD, the KDIGO authors point out that there is a dearth of high-quality evidence supporting the recommendations and practice points due to inconsistencies in cohort recruitment, the small size of many study populations, screening practices, and the retrospective nature of most studies.

Implementation and Challenges

Defining those at high risk may be difficult (discussed more fully under Practice Point 6.1.2). In addition, 50% to 60% of ADPKD patients with ICAs have no family history of ICA or SAH,[191,192] making pre-emptive identification of these patients more difficult in the absence of systematic screening.

Practice Point 6.1.1. All people with ADPKD should be educated to recognize thunderclap headache, characterized by a severe sudden-onset headache that reaches its maximum intensity within seconds to a minute (KDIGO guideline Figure 38). Recognition of such symptoms should prompt immediate medical attention.

Practice Point 6.1.2: A detailed personal history of SAH and a family history of ICA, SAH, and unexplained sudden death should be obtained to identify people with ADPKD who are at higher risk for ICA.

Practice Point 6.1.3: Because smoking is a strong modifiable factor for ICA development and rupture, healthcare providers should ask all people with ADPKD about their tobacco use, advise them to stop using tobacco, and provide behavioral interventions and approved pharmacotherapy for cessation, if needed (Chapter 7).

Practice Point 6.1.4: Because uncontrolled hypertension is a moderate modifiable factor for ICA development and rupture, early diagnosis and adequate treatment of hypertension is indicated in people at risk of or diagnosed with ADPKD, particularly those at an increased risk for ICA (Chapter 2).

Practice Point 6.1.5. People with ADPKD should be informed of the implications of ICA screening as highlighted in (KDIGO guideline) Table 16 [Table 4].

Recommendation 6.1.2. We recommend screening for ICA in people with ADPKD and a personal history of SAH or a positive family history of ICA, SAH, or unexplained sudden death in those eligible for treatment and who have reasonable life expectancy (*1D*).

Commentary

Although KDIGO does not propose a universal screening protocol, they encourage shared decision making, thereby allowing flexibility in terms of who is ultimately screened. Therefore, the KDOQI workgroup supports the careful consideration of ICA screening issues shown in the KDIGO guideline Table 16 (see Table 4). In addition, the KDIGO authors highlight several clinical situations that merit special consideration. These guidelines are in keeping with the more general American Heart Association/American Stroke Association recommendations for ICA screening of anyone with ADPKD, particularly those with a family history.[193]

The strongest and most consistent risk factor for prevalent ICA or ICA rupture in ADPKD is a positive family history of ICA or SAH. Individuals with ADPKD who have such a family history are 4 times more likely to develop an ICA compared with those lacking a family history.[191,194] Risk factors showing a strong association with ICA or ICA rupture in the ADPKD population include a personal history of ICA or SAH and tobacco use. Other risk factors such

Table 4. Advantages and Limitations of Screening for Unruptured Intracranial Aneurysms

Advantages	Limitations
May allow intervention if an ICA at risk of rupture is identified, allowing prevention of death or significant comorbidity	May lead to the identification of ICA with very low risk of rupture (≤5 mm/anterior circulation) that do not require intervention but require long-term follow-up
May allow adequate imaging follow-up if an ICA with low risk of rupture is identified	Does not exclude the risk of *de novo* ICA development and rupture after screening
May reduce anxiety and provide reassurance when no ICA is detected	May lead to procedures with possible treatment failure or complications, including death or significant morbidity
	May cause anxiety when an ICA is identified
	May limit access to life insurance, loans, or driver's licenses
	May limit work opportunities

Abbreviation: ICA, intracranial aneurysm.

as female sex, uncontrolled hypertension, location, and size of the aneurysm are either supported only by moderately strong data or extrapolated from the general population without ADPKD. Within the PKD population, female sex, hypertension, age, a *PKD1* variant, and smoking were associated with an increased risk of ICA in some studies but not others.[192]

Clinical Utility

The clinical utility of screening is greatest when a high-risk aneurysm is found prior to rupture. However, most detected aneurysms are small and at low risk of rupture.[191] Thus, many patients will have small aneurysms detected, necessitating a clear workflow for continued monitoring of these low-risk aneurysms.

Implementation and Challenges

In clinical practice a family history may be difficult to obtain, either due to personal estrangement, adoption, in vitro fertilization with a donor egg or sperm, or presence of a de novo pathogenic PKD gene variant. Therefore, family history is helpful and should be obtained but should not be the only factor in shared decision making for asymptomatic screening. Similarly, genetic test results (*PKD1* or *PKD2* versus a minor ADPKD gene) should not be used to help determine the need for screening because most studies did not include genetic data, and further analysis is needed to fully characterize genotype-phenotype correlations with respect to the incidence or rupture of ICAs.

Practice Point 6.1.6. Screening for unruptured ICA also should be discussed for people with *de novo* ADPKD, those with unknown familial history or a small number of ADPKD-affected relatives, and those with personal or familial history of extracerebral vascular phenotype.

Commentary

The KDIGO work group judged that most patients would want to be informed about a potential risk of an aneurysm with shared decision making regarding the risks and benefits of screening. ICAs are found in up to 25% of those with a family history and 10% of all ADPKD patients.[195] Patients with a de novo ADPKD diagnosis, unknown family history, or only a few affected relatives do not know whether they are truly in a high-risk or low-risk group, so they may benefit from screening.

Clinical Utility

Screening in this group allows for a better capture of potentially high-risk patients.

Implementation and Challenges

A widespread screening strategy creates a burden of frequent imaging for those with small aneurysms that do not require treatment but may nevertheless increase patient anxiety. Other findings such as arachnoid cysts or anatomic arterial variants are also more common in ADPKD,[196] which may also increase the need for additional evaluation including computed tomography angiography, angiogram, or neurosurgical consultation. Some of these studies require the use of iodinated contrast dyes, which have the potential to cause acute kidney injury in some patients. In addition, some insurance carriers may decline to cover screening magnetic resonance angiography.

Practice Point 6.1.7. Screening for unruptured ICA also can be discussed in specific clinical settings, such as in the context of evaluation for kidney and/or liver transplantation or before major elective surgery.

Practice Point 6.1.8. People with ADPKD who are not considered at increased risk for ICA and who, after comprehensive information, prefer being screened for ICA should be given access to screening.

Practice Point 6.1.9. In women with ADPKD and either a family history of ICA, SAH, or unexplained sudden death; *de novo* ADPKD; unknown familial history; or a small number of ADPKD-affected relatives, screening for unruptured ICA should precede pregnancy planning (see Chapter 8).

Practice Point 6.1.10: Time-of-flight magnetic resonance angiography (MRA) without gadolinium enhancement should be the method of imaging when screening is to be pursued for ICA in people with ADPKD. High-resolution computed tomography angiography (CTA) can be used as an alternative.

Practice Point 6.1.11: If the screening is negative in people with a high risk of ICA, timing of rescreening should be individualized, possibly every 5-10 years, based on risk factors, age, and life expectancy.

Commentary

Practice Point 6.1.11 is based on expert opinion because there are few studies that have rigorously examined this question. In 1 prospective study of 76 individuals with ADPKD and an initial negative magnetic resonance angiography, 1 individual was found to have a new ICA on rescreening after approximately 10 years.[197] This individual had a family history of ICA rupture in at least 1 family member. Similarly, in another retrospective study[191] there was a low rate of de novo ICA on rescreening, and these occurred in individuals with risk factors—primarily a family history of ICA. Therefore, the KDOQI work group agrees with expert opinion suggesting rescreening every 5 to 10 years for those at high risk (those with a positive family history, tobacco exposure, and uncontrolled hypertension) with individualized discussion for those without a family history of ICA or SAH.

Clinical Utility

There is likely to be continued benefit of periodic rescreening in individuals with ADPKD who fall into high-risk groups.

Implementation and Challenges

The barriers to implementation are similar to those discussed previously for screening and include the burden of incidental findings that may not result in treatment but nonetheless require additional evaluation and can increase patient anxiety. In addition, systematic follow-up of high-risk patients may be difficult, particularly as patients transition from a primary nephrologist to receiving general posttransplant care. The cost and insurance coverage of rescreening may also be a challenge in some situations.

Practice Point 6.1.12: When one or several ICAs are identified, treatment options, such as conservative management and microvascular or endovascular repair, should be assessed within a multidisciplinary setting at centers of expertise with high ICA case volumes.

Commentary and Clinical Utility

There have been continued advances in both microvascular surgical clipping[198] and endovascular technologies for the treatment of ICA.[193,199] In addition, data suggest that clinical outcomes for patients with nontraumatic SAH are improved in centers with higher procedure volumes.[200] The KDOQI work group agrees that the treatment options for ruptured or unruptured ICAs are best assessed and implemented at centers with multidisciplinary expertise in neurovascular therapeutic approaches and with higher case volumes.

Implementation and Challenges

Expertise in the treatment of ICA is mostly restricted to tertiary care centers in densely populated areas of the US. Some patients with ADPKD and a diagnosed ICA or SAH may not have access to an experienced neurosurgeon or interventional neuroradiologist. Patients who need emergent treatment of a ruptured ICA will require transfer to a tertiary care center.

6.2. Other Vascular Associations

Practice Point 6.2.1: Routine screening of vascular abnormalities of non-intracranial large arteries has no role in people with ADPKD and no familial history of vascular aneurysms or dissections.

Commentary

There are numerous reports in the literature of patients with ADPKD with aneurysms or vascular dissections in extracranial arteries including coronary,[201] popliteal,[202] and splenic,[203] among others. These case reports, coupled with data showing that polycystins are expressed in both endothelial cells and vascular smooth muscle cells, point to the possibility of an increased risk for vascular complications in patients with ADPKD and suggest a biological role for polycystin proteins in vascular tissues. For the most part, however, these clinical events are sporadic, and therefore the KDOQI work group agrees that there is no role for systematic screening.

Clinical Utility

As the methods for predicting elevated risk of systemic aneurysms improve, the value of screening may improve.

Implementation and Challenges

Although no screening is being recommended, it is still important to follow any detected aneurysms to ensure timely treatment, as needed.

Practice Point 6.2.2: People with ADPKD and their first-degree relatives who have a family history of aortic root or thoracic aortic aneurysms should be screened for aortic aneurysms.

Commentary

In the case of aortic root and thoracic aortic aneurysms (TAA) there may be a stronger case for targeted screening based on family history. For example, a population-based cohort study using data from the Taiwan National Health Insurance Research Database reported a 5-fold increased risk of aortic aneurysm/dissection in ADPKD driven by an increased occurrence of TAA.[204] In addition, familial clustering of TAA has been reported.[205] Interestingly, this is the site of aneurysm formation in other inherited aortic diseases.[206] Therefore, the KDOQI work group agrees that in cases where there is a family history of TAA, screening should be performed.

Clinical Utility

As previously discussed, a patient's family history may be unknown or unobtainable, thus making it impossible to assign risk for aortic aneurysm based on family history. In practice, however, most patients reaching ESKD who are referred for transplant will have a screening echocardiogram as part of a pretransplant work-up which would detect an unsuspected aortic root aneurysm. In addition, some individuals may have an echocardiogram because of an incidentally noted cardiac murmur which could result in detection of aortic root dilation.

Implementation and Challenges

The lack of availability of comprehensive family histories is the largest challenge for following this practice point. Although cardiac assessment is required before kidney transplant,[118] not all centers have ADPKD-specific guidelines. It may be of value to develop such guidelines in the future, particularly given the high rates of pre-emptive kidney transplantation in the ADPKD population.

Practice Point 6.2.3. In people with ADPKD and dilatation of the aortic root or thoracic aortic aneurysm, therapeutic measures to limit aortic expansion should be offered; these include smoking cessation, statin therapy, and antihypertensive therapy including a beta-blocker and an ACEi or ARB.

6.3. Cardiac Associations

Practice Point 6.3.1: Echocardiography at baseline with occasional repeat echocardiograms should be offered in people with ADPKD who have a history of severe or uncontrolled hypertension, a heart murmur, signs or symptoms of cardiac dysfunction, other cardiovascular manifestations, or a familial history of thoracic aortic aneurysm (TAA) or nonischemic cardiomyopathy.

6.4. Abdominal Wall Hernia

Practice Point 6.4.1: In people with ADPKD and asymptomatic abdominal wall hernias, nonsurgical management should be discussed because of the increased risk for complications and hernia recurrence after surgical repair, especially in people with kidney and/or liver enlargement.

Practice Point 6.4.2: People with ADPKD who are managed expectantly for abdominal wall hernia should be educated to recognize symptoms of hernia incarceration or strangulation (e.g., acute pain, nausea, vomiting), which should lead to prompt surgical evaluation.

Practice Point 6.4.3: Surgical repair of abdominal wall hernias should be discussed in people with ADPKD who elect PD as a mode of KRT, as increased abdominal pressure is a known risk factor for enlargement and complications of hernias.

6.5. Other Extrarenal Manifestations

No recommendations or practice points.

Chapter 7. Lifestyle and Psychosocial Aspects

7.1. Nutrition Intake

Practice Point 7.1.1: People with ADPKD should follow general recommendations for a healthy diet, consistent with World Health Organization (WHO) and CKD guidelines (KDIGO guideline Table 18).

Practice Point 7.1.2: Healthcare providers should work with accredited nutrition providers or registered dietitians to provide individualized nutrition counseling to people with ADPKD, particularly people with CKD G4-G5 and those with or at high risk of urinary stones.

Practice Point 7.1.3: People with ADPKD who either have or have an increased risk of developing urinary stones should make dietary adjustments to prevent stone formation. The dietary strategy will depend on the composition of the stones or the concentration of lithogenic molecules in the urine.

Practice Point 7.1.4: People with ADPKD should maintain a healthy body weight, taking into account the additional weight due to enlarged kidneys and liver.

Practice Point 7.1.5: Total kidney and liver weight derived from total kidney and liver volumes should be calculated and subtracted from the patient's total body weight for a more accurate assessment of weight and BMI (see KDIGO guideline Figure 20).

Practice Point 7.1.6: Healthcare providers should work with accredited nutrition providers or registered dietitians to help people with ADPKD who are overweight (adjusted BMI 25-29.9 kg/m^2) or obese (adjusted BMI >30 kg/m^2) lose weight.

Practice Point 7.1.7: People with ADPKD with poor oral intake due to organomegaly or advanced CKD (CKD G4-G5) should be evaluated for malnutrition or sarcopenia.

Commentary

The KDOQI work group agrees that, given the slowly progressive, lifelong nature of ADPKD, consideration of nutritional intake should be an important aspect of multifaceted care. We agree that there is currently a lack of large interventional trials in individuals with ADPKD and that, in the absence of such data, following healthy diet guidance developed for the general population and recommendations for management of CKD is appropriate. We agree with Practice Points 7.1.1 to 7.1.7 and the overall approach to lifestyle and psychosocial care shown in Figure 40 of the KDIGO guideline (see Fig 8). We highlight the following additional considerations.

Clinical Utility

The KDOQI work group notes slight differences between the US Dietary Guidelines for adults[207] and the World

Health Organization (WHO) guidelines referenced by KDIGO.[208] The WHO recommendation to restrict sodium intake to <2.0 g/day aligns with KDIGO guidance for patients with CKD and hypertension while the Dietary Guidelines for Americans recommend a slightly higher threshold of <2.3 g/day. A less stringent sodium restriction may be appropriate in individuals with early stage disease.

We further note that limiting protein intake to 0.8-1.0 g/kg/day may be more appropriate for those with ADPKD and reduced kidney function. We recommend avoiding high protein intake (≥1.3 g/kg/day) intake in those with an eGFR ≥ 30 mL/min/1.73 m^2.[209] Monitoring urine osmolality (eg, morning goal of <280 mOsm/kg) may provide an alternate method to ensure appropriately high water intake, but this approach may be difficult to implement consistently outside a clinical trial.[209] At present we do not recommend dietary supplements intended specifically to slow ADPKD progression because they have not been adequately tested in clinical trials.

The KDOQI work group concurs with the importance of maintaining a healthy body weight. Additionally, we note the importance of considering body composition and distinguishing between fat mass and lean mass. Visceral fat is a particularly strong adverse prognostic factor in ADPKD and may even attenuate the efficacy of tolvaptan therapy.[210] Visceral fat can be quantified by CT or MRI, but we note that these tools are primarily used in clinical research and are not standard in routine clinical practice. We agree that kidney and liver weight should be considered when calculating body mass index (BMI).[211] Clinicians should be educated on the potential for significant abdominal distension due to enlarged organs in patients with ADPKD, which should be distinguished from visceral adiposity.

Implementation and Challenges

Obesity continues to rise in the US, with a prevalence of 42%, and nearly three-quarters of adults aged 20 or older classified as either overweight or obese.[212,213] Similar to trends in the general population, BMI has been increasing in patients with ADPKD over recent decades,[214,215] with nearly 70% of adults with ADPKD being overweight or obese.[51,59,215] Higher BMI is a strong independent predictor of more rapid kidney growth in nondiabetic adults with early stage ADPKD.[216] More recently, it has been demonstrated that abdominal adiposity, quantified using MRI in the TEMPO 3:4 trial, is an independent predictor of kidney growth,[210] and that insulin sensitivity (via the gold standard of hyperinsulinemic-euglycemic clamp) and kidney oxidative metabolism (via ^{11}C-acetate positron emission tomography [PET]) are impaired in young adults with ADPKD and preserved kidney function compared with healthy controls.[217] These findings align with earlier observations that individuals with ADPKD and type 2 diabetes, have significantly larger kidney volumes,[218] suggesting that insulin resistance may contribute to disease progression. Additional mechanistic studies are needed to clarify the role of impaired insulin sensitivity in ADPKD patients without diabetes and to determine whether improving insulin sensitivity, enhancing kidney oxidative metabolism, or reducing visceral adiposity slows kidney growth or eGFR decline in ADPKD.

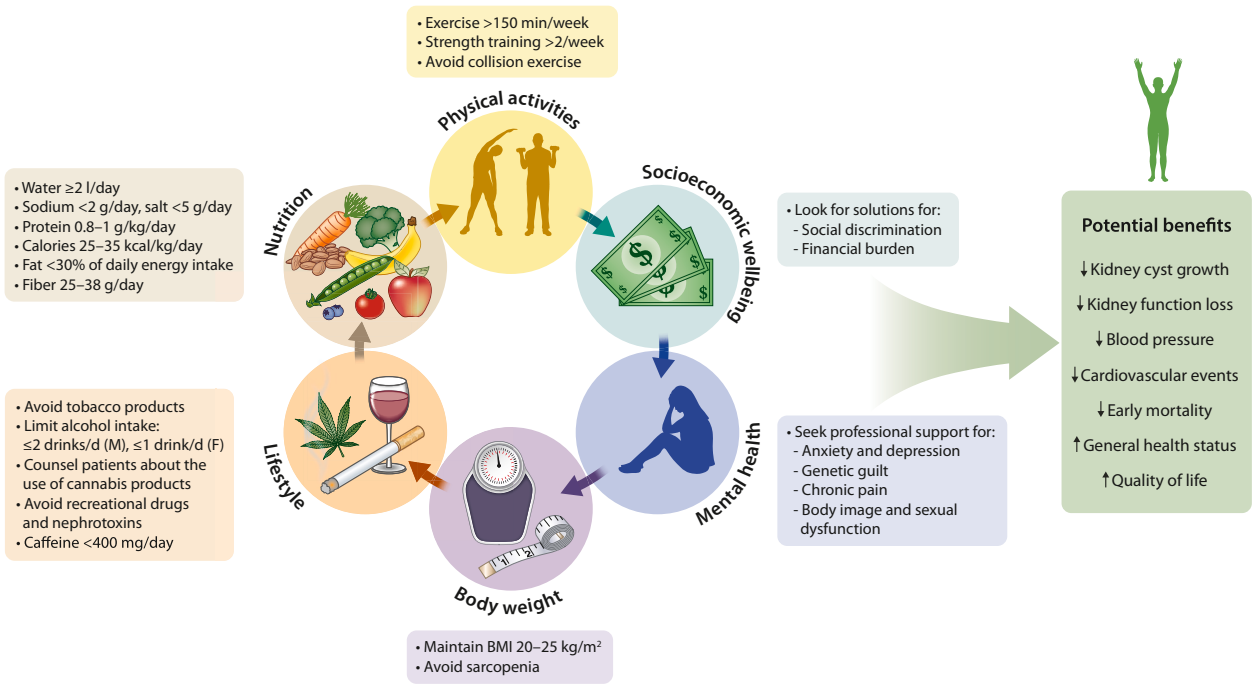


Figure 8. Lifestyle and psychosocial care for improved outcomes in people with autosomal dominant polycystic kidney disease (ADPKD). Abbreviations: BMI, body mass index; F, female; M, male.

The Healthy Eating Index (HEI) measures alignment with the Dietary Guidelines for Americans; on a 100-point scale, US adults aged 19-59 have an average score of 57.[219] These staggering statistics underscore the significant challenges of implementing and sustaining dietary interventions. The KDOQI work group emphasizes that individualized nutrition counseling is ideal; however, implementation is often limited by a shortage of trained providers, restricted access, and inconsistent insurance coverage. Promoting healthy eating and lifestyle early in life is essential for preventing overweight and obesity.

Sodium restriction remains difficult to implement in the US due to the widespread availability of processed, high-calorie foods and snacks. As a result, sodium intake remains high in the US despite national recommendations.[220] The PREVENT-ADPKD trials demonstrated that even with structured behavioral interventions, achieving high water intake is challenging in practice.[221]

The KDOQI work group emphasizes the need for clinical trials focused on dietary interventions and weight loss to inform evidence-based recommendations. A clinical trial of daily caloric restriction on kidney growth in overweight and obese adults with ADPKD is currently underway (NCT04907799). Only pilot studies of ketogenic diets have been conducted to date[161]; a trial of pharmacologic agents to induce weight loss, including GLP-1 receptor agonists, in ADPKD is ongoing (NCT06582875).

7.2. Physical Activity

Practice Point 7.2.1: Adults with ADPKD should be encouraged to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week or to a level compatible with their cardiovascular and physical tolerance. In addition, strength training should be undertaken for at least 1 hour, twice per week.

Practice Point 7.2.2: People with large kidneys and/or liver should be advised of the possibility of incurring direct injury to these organs during physical activity and exercise.

Practice Point 7.2.3: Consultation from specialists, such as an exercise therapist where available, is advisable in prescribing exercise for people with ADPKD with a high risk of adverse events, such as those with CVD, frailty, bone disease, or risk of falling, and those on dialysis or those who are post-transplantation.

Commentary

The KDOQI work group agrees with Practice Points 7.2.1-7.2.3 and underscores the paucity of data on exercise in patients with ADPKD. In particular, it is unclear whether patients with ADPKD meet current physical activity guidelines and how their activity levels compare with those in the general population and other CKD populations. These data are needed to inform clinical practice and identify future research priorities.

Clinical Utility

The KDOQI work group emphasizes that beyond the recognized health benefits of regular physical activity, combining moderate caloric restriction with exercise is a well-established approach for weight loss in individuals with obesity outside the context of ADPKD.[222] High levels of physical activity are among the strongest predictors of sustained weight loss in those who successfully lose weight.[223]

Implementation and Challenges

While the KDIGO guidelines highlight the need for further epidemiological research on exercise in ADPKD, the KDOQI work group notes additional areas where evidence is needed to support implementation. These include qualitative studies, such as focus groups, to better understand the perceived barriers and benefits of exercise in this population. Both quantitative and qualitative data will be essential to guide clinical practice. Prospective clinical trials to evaluate the safety and efficacy of specific regimens in ADPKD are also warranted. Further research is also needed to guide evidence-based recommendations for physical activity and sports participation in children with ADPKD.

7.3. Lifestyle Management

7.3.1. Tobacco

Practice Point 7.3.1.1: All people with ADPKD should be asked about their use of tobacco products and should avoid use of all tobacco products.

7.3.2. Alcohol

Practice Point 7.3.2.1: All people with ADPKD should be asked about their use of alcohol and should consume ≤1 alcoholic drink per day if female or ≤2 drinks per day if male.

7.3.3. Caffeine

No recommendations or practice points.

7.3.4. Cannabis Products

Practice Point 7.3.4.1: All people with ADPKD should be asked about their use of cannabis products and should be counseled about potential dangers of AKI related to product contamination and synthetic versions.

7.3.5. Nephrotoxins

Practice Point 7.3.5.1: All people with ADPKD should be asked about their use of recreational drugs and anabolic steroids and should refrain from using these drugs.

Commentary. The KDOQI work group agrees with Practice Points 7.3.1.1 to 7.3.5.1 and endorses the routine screening of individuals with ADPKD for tobacco, alcohol, cannabis, and other substance use. Although the direct evidence linking tobacco use to ADPKD progression is limited, we agree that it is reasonable to infer potential harm in ADPKD progression based on studies that have indicated a greater kidney function decline in the general population.[224,225] Cigarette smoking has been associated with a greater risk of ICA[191,192] and vascular dysfunction[226] in ADPKD, further supporting the recommendation to avoid the use of all tobacco products.

Given the growing use of recreational cannabis in the US, we emphasize the need for evaluating both the harms and therapeutic benefits in the ADPKD population. We agree that the contamination of unregulated cannabis products and the nephrotoxic potential of synthetic cannabinoids is a cause for concern.

We note that there are no specific recommendations regarding the use of caffeine because high-quality data on this issue in humans is lacking, which is a change from prior clinical practice.[227-229] We agree that ADPKD patients should follow the guidance for the general population, which includes limiting caffeine during pregnancy.

Clinical Utility. Given that substance use disorders, including tobacco, alcohol, and other illicit drug use, are common in the US, screening for these disorders in ADPKD patients has high clinical utility. Patients should be informed that active smoking, excessive alcohol use, or a positive urine drug screen for cannabinoids or other substances may negatively impact their candidacy for organ transplantation.

Implementation and Challenges. Screening for tobacco, alcohol, and illicit drug use is routinely incorporated into ambulatory nephrology care visits, so implementation is feasible. However, access to smoking cessation resources or other treatment programs may be limited by region or insurance coverage.

7.4. Psychosocial Care

Practice Point 7.4.1: Healthcare providers should monitor a patient's psychological health and social needs during consultations (KDIGO guideline Figure 42). Healthcare providers should screen and conduct periodic assessment of psychosocial issues in people with ADPKD (KDIGO guideline Figure 43).

Practice Point 7.4.2: Education programs to promote self-management should be implemented to provide comprehensive and practical information to people with ADPKD and their families.

Practice Point 7.4.3: People should be informed about patient organizations dealing with PKD or kidney disease in general, and other support and advice services.

Practice Point 7.4.4: The healthcare team should discuss with patients and their caregivers the financial impacts of having ADPKD and try to help them avoid incurring unnecessary medical expenses.

Commentary

The KDOQI work group agrees that assessing and supporting psychosocial health is central to multidisciplinary, holistic, patient-centered care for individuals with ADPKD. Prior studies have highlighted the importance of "genetic guilt" in contributing to psychological distress in ADPKD patients.[230,231] Additional research is needed to characterize the most common psychological symptoms in ADPKD patients, identifying the contributing factors and understanding their impact on health-related quality of life and functional outcomes—especially in early stage disease when intervention may be most effective. The KDOQI work group also supports the increased use of educational programs and self-management interventions to empower patients and caregivers. In addition, the financial burden of ADPKD on patients and families remains a source of psychological stress that deserves further study.

Clinical Utility

Given the relatively high prevalence of depressive symptoms and psychological distress in individuals with ADPKD, routine screening and assessment of psychosocial health have high clinical utility. Supporting disease self-management through education-based interventions is a key element of multidisciplinary care.

Implementation and Challenges

Implementing routine screening for depression in individuals with ADPKD presents several challenges. Although there are limited data specific to ADPKD, studies in the CKD population have identified validated screening instruments and optimal cut points for diagnosing major depressive disorder. These findings can be reasonably extrapolated to ADPKD.[232] However, most nephrologists have limited familiarity with mental health screening tools and time constraints during routine ambulatory care visits may hinder implementation. Access to psychosocial support and patient education may vary according to regional availability and socioeconomic status.

To address these challenges in the US, there are several resources available. The Polycystic Kidney Disease Foundation and the National Kidney Foundation (NKF) provide patient-facing educational materials, and they sponsor local/regional patient support groups. The NKF has a peer-mentoring program for patients with CKD. Furthermore, PKD Centers of Excellence[233]—as recognized and certified by the PKD Foundation—provide specialized resources,

including education and care navigation, that may alleviate financial strain and improve engagement in self-management.

Chapter 8. Pregnancy and Reproductive Issues

8.1. Management of Women With ADPKD

Practice Point 8.1.1: Healthcare for women with ADPKD of childbearing age includes management of hormonal therapies including contraception, preconception counseling, and pregnancy management (KDIGO guideline Figure 45).

Commentary

The KDOQI work group agrees with KDIGO guideline Figure 45 but recommends that preconception counseling also includes discussion of the increased risk of UTI and worsening kidney function (especially in women with reduced eGFR and hypertension at baseline).

Practice Point 8.1.2 Women with ADPKD and liver cysts should be educated regarding their contraceptive choices, given that estrogen and possibly progesterone exposure may be associated with an increased risk of PLD progression (see Chapter 5).

Practice Point 8.1.3: Contraception in adolescents and young adults with or at risk of ADPKD should not be restricted.

Commentary

The KDOQI work group agrees with KDIGO that contraception should be actively discussed and not restricted in adolescents and young adults with ADPKD. In women with moderate to severe PLD, nonhormonal methods are preferred, followed by progestin-only (non–estrogen-containing agents). For women with mild or no PLD, combined hormonal contraception may be considered with a preference for formulations containing lower doses of estrogen. Consultation with a gynecologist is recommended to guide individualized contraceptive planning.

In women with ADPKD and PLD who are undergoing in vitro fertilization (IVF), there is concern that the administration of high-dose estrogen for ovarian stimulation may be associated with liver cyst growth. Although the data are limited, there may be an increased risk of ovarian hyperstimulation syndrome in women with chronic liver disease though not necessarily PLD who are undergoing IVF.[234] Additionally, estrogen use is associated with an increased risk of deep venous thrombosis, which should be considered when deciding on the risks and benefits of contraceptive methods and estrogen dosing.[235,236]

Practice Point 8.1.4: When considering hormone therapy in women with ADPKD, liver imaging, ideally with MRI and/or CT and volumetry, should be made available to inform discussion about options for contraception, hormonal replacement, and other indications (Chapter 5).

8.2. Preconception Counseling

Practice Point 8.2.1: Preconception counseling should be offered to both men and women with ADPKD who are of reproductive age, and should be provided by a multidisciplinary team in an ADPKD referral center when possible (KDIGO guideline Figure 46).

Practice Point 8.2.2: Men and women of reproductive age with ADPKD should be offered appropriate counseling and all available reproductive options (KDIGO guideline Figure 47).

Commentary and Clinical Utility

The KDOQI work group agrees with the KDIGO guideline outlined in KDIGO guideline Figures 46 and 47, which recommend a multidisciplinary approach to preconception counseling for individuals with ADPKD. Early discussion of reproductive options allows for informed family planning, ideally before a significant decline in kidney function. This is particularly important for individuals with a family history of severe disease manifestations such as early onset of kidney failure or ICA.[237] Figure 9 includes a wide range of reproductive options to be considered, including adoption, accepting the risk of transmitting ADPKD, prenatal testing, and assisted reproductive technologies such as preimplantation diagnosis (PGD) and egg or sperm donation. Many individuals with ADPKD experience anxiety about the risk of passing the disease to their children, making reproductive counseling a valuable component of routine care at ADPKD centers.

The KDOQI committee emphasizes that full consideration of all options respects patient autonomy and enables patients to make reproductive choices that align with their personal beliefs. Given the complexities of these decisions, a multidisciplinary team—including a genetic counselor, nephrologist, reproductive endocrinologist, and maternal fetal medicine specialist—may be necessary to guide patients through this process.

Implementation and Challenges

With the increasing availability of genetic testing for cystic kidney diseases, there is a growing literature demonstrating the feasibility of PGD for ADPKD.[237-239] However, successful implementation requires advance planning, which underscores the importance of early reproductive counseling. The

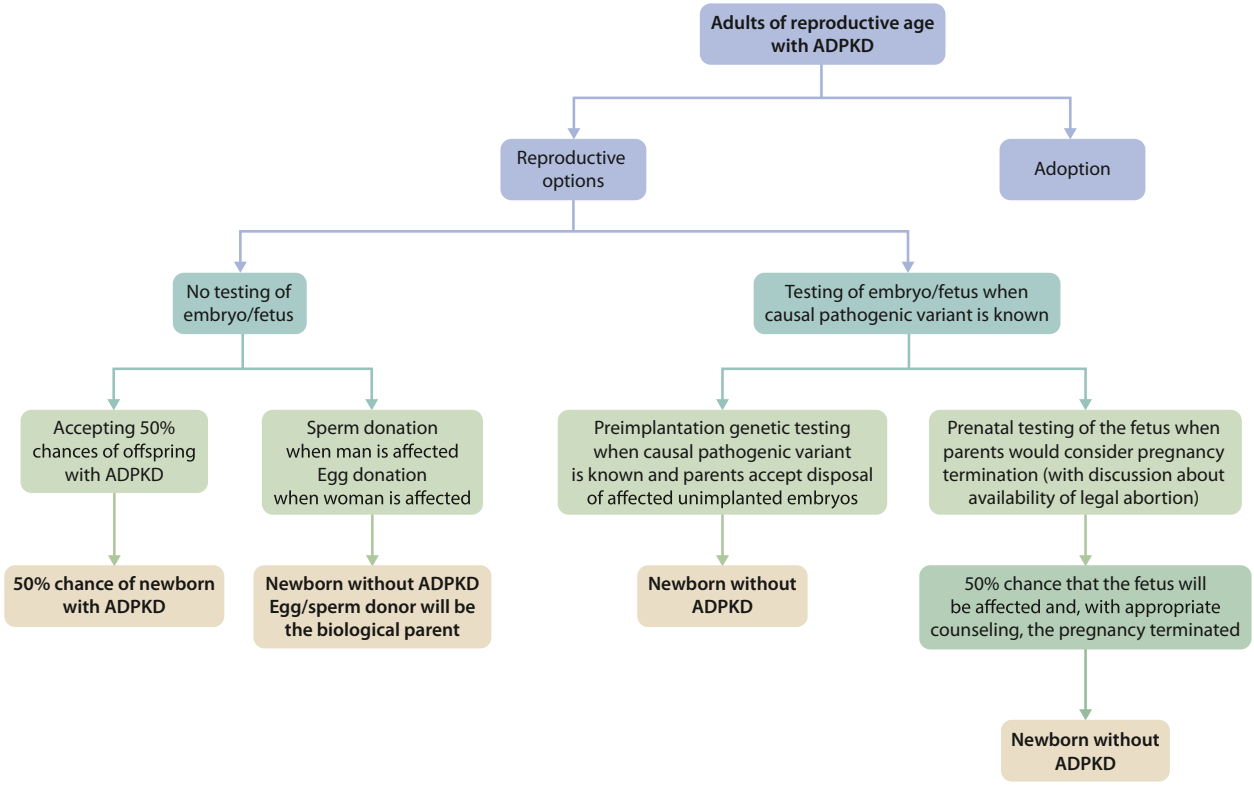


Figure 9. Reproductive options for men and women with autosomal dominant polycystic kidney disease. Abbrevation: ADPKD, autosomal dominant polycystic kidney disease.

pathogenic variant responsible for ADPKD must first be identified, a test that typically takes 6 to 8 weeks. Missense variants, which are common in the *PKD1* gene, present a particular challenge because some of these may be benign. In approximately 8% to 10% of cases, no pathogenic variant is identified, despite clinically evident ADPKD.[23,240,241] In these situations, PGD cannot be performed because the procedure relies on targeting a known, disease-causing variant. In cases involving a missense variant, linkage analysis is generally recommended and should include at least 2 affected family members with a definitive PKD phenotype from different generations.[238,242] In addition, there is increasing recognition that modifier alleles—either in *PKD1* or *PKD2* or other ciliopathy genes—may contribute to disease severity, complicating the efforts to define a single causative variant.[243,244,245]

Another significant barrier to implementation is cost. IVF and PGD are expensive and may not be fully covered by insurance, which poses financial obstacles for many families. From a research perspective, systematic studies are needed to determine the actual success rates of having a newborn without PKD after PGD in ADPKD. Although the general pregnancy success rate with IVF and PGD is estimated to be approximately 30% per embryo transfer, the disease-specific success rate for ADPKD has not been established.[246]

Finally, KDIGO recognizes the emerging legal and ethical concerns regarding PGD and IVF. The disposal of unimplanted embryos has come under scrutiny in certain US states, following recent legislative changes. The evolving legal landscape could impact access to PGD and IVF, and a discussion of local legislation may need to be factored into reproductive counseling.[247]

Practice Point 8.2.3: Use of tolvaptan and other teratogenic drugs should be stopped prior to pregnancy and not restarted until the mother has completed breastfeeding. Use of RASi (i.e., ACEi or ARBs) should be stopped prior to pregnancy and can be restarted during periods when breastfeeding is taking place, if other agents are not controlling BP adequately.

Practice Point 8.2.4: Although men with ADPKD demonstrate an increased prevalence of seminal tract cysts and sperm abnormalities, these do not appear to impact fertility; therefore, systematic screening is not indicated.

Practice Point 8.2.5: Before pregnancy, screening for ICA should be considered in women with a family history of ICA, women with de novo ADPKD, those with unknown familial history or a small number of ADPKD-affected relatives, and those with a personal or familial history of extracerebral vascular phenotype.

8.3. Pregnant Women With ADPKD

Practice Point 8.3.1: Care for a pregnant woman with ADPKD should be provided by a multidisciplinary team in an expert center.

Practice Point 8.3.2: During pregnancy, BP, kidney function, soluble fms-like tyrosine kinase-1-to-placental growth factor ratio (sFlt-1/PlGF), and proteinuria should be monitored in women with ADPKD, as they should in women with CKD.

Commentary and Clinical Utility

The KDOQI work group agrees with a multidisciplinary approach to the care of pregnant people with ADPKD, similar to CKD, with a particular emphasis on kidney function, BP, and proteinuria monitoring. Based on data from studies in women with glomerular disease, young women with ADPKD and normal kidney function and normal BP generally have excellent pregnancy outcomes.[239,248,249] With advancing age, however, women with PKD are more likely to have hypertension and reduced GFR, which are significant risk factors for adverse pregnancy outcomes such as pre-eclampsia, fetal growth restriction, preterm birth, and deterioration in maternal kidney function.[248,249] We recommend that women with ADPKD and CKD be advised about their increased risk of complications in pregnancy, including pre-eclampsia, preterm birth, fetal growth restriction, and neonatal intensive care admission, and their increased likelihood of requiring a cesarean delivery. In women with CKD due to glomerulonephritis, the risk of adverse pregnancy outcomes is correlated with the degree of reduction in GFR and pre-existing hypertension; studies in women with ADPKD suggest that the same association exists.[248-250]

Although there is no specific evidence for how best to manage BP in women with ADPKD during pregnancy, data suggest that BP should be maintained at <135/85 mm Hg in women with pre-existing chronic hypertension (without CKD).[251] If it is feasible, we recommend that women with ADPKD and pre-existing hypertension, particularly those with reduced kidney function, be co-managed by specialists in maternal-fetal medicine. However, the availability, insurance coverage, and cost of subspecialized services may be implementation obstacles.

The KDOQI work group agrees with the assessment of kidney function using serum creatinine (Scr) concentration because the eGFR equations have not been sufficiently validated for use in pregnancy. Cystatin C levels are also not recommended for monitoring GFR because these levels rise in the second trimester despite a fall in GFR.[252] However, cystatin C has been proposed as an early marker of pre-eclampsia with a sensitivity of 0.85 and specificity of 0.84.[253] In most women, Scr levels decrease during pregnancy and are approximately 84%, 77%, and 80% of nonpregnant mean values during the first, second, and third trimesters, respectively; usually Scr increases if pre-eclampsia develops.[254] Women with advanced stages of CKD may not demonstrate a decrease in Scr during pregnancy, possibly due to reduced renal reserve.[250] The absence of an early pregnancy decrease in Scr may be a poor prognostic marker indicating a greater risk of adverse outcomes.

Opinions vary regarding the best method for assessing proteinuria during pregnancy. The KDOQI work group agrees with the UK guidelines on pregnancy and renal disease and recommend quantification of proteinuria by protein-creatinine ratio or albumin-creatinine ratio,[255] although others suggest that measurement of 24-hour urine protein is the gold standard during pregnancy.[249]

Implementation and Challenges

KDIGO Practice Point 8.3.2 recommends monitoring soluble fms-like tyrosine kinase-1-to-placental growth factor ratio (sFlt-1/PlGF). While the KDOQI work group agrees with the importance of close monitoring during pregnancy in ADPKD, we note that there is no consensus on the use of sFlt1/PlGF biomarker monitoring in pregnancies at risk for pre-eclampsia.[256] One key barrier to implementation is that the test is not widely available and many hospital laboratories do not routinely perform it, making it impossible to order in many practices. In addition, laboratories use different assay platforms, yielding results for the same protein that may not be comparable, and reference ranges vary depending on gestational age, limiting interpretability. Moreover, the sFlt1/PlGF ratio has not been systematically validated for use in women with CKD, and its predictive value in ADPKD has not been extensively studied. In one recent study of 97 women with CKD (most with glomerulonephritis and 7 with ADPKD), the sFlt1/PlGF ratio was only predictive of pre-eclampsia in asymptomatic CKD patients when sampled in the third trimester. The authors noted that the baseline levels of these angiogenic proteins are higher in patients with CKD and therefore additional study was warranted to confirm the findings and define optimal cutoff values.[257] Given these limitations, we recommend that clinicians rely on standard monitoring of BP, proteinuria, and renal function in pregnant patients with ADPKD. The sFlt1/PlGF ratio should be considered, when available, and in consultation with maternal-fetal medicine specialists who are familiar with its applications and limitations.

Practice Point 8.3.3: Pregnant women with ADPKD should undergo monthly urinalyses to test for asymptomatic bacteriuria. If a patient has a confirmed positive urine culture, even when asymptomatic, she should be treated with appropriate antibiotics, as done in the general population.

Commentary and Clinical Utility

The KDOQI work group agrees with monthly urinalysis checks followed by urine cultures (as needed) in pregnant ADPKD patients for the screening and treatment of asymptomatic bacteriuria. Current American College of Obstetricians and Gynecologists (ACOG) guidelines suggest treating once in early pregnancy.[258] KDIGO suggests monthly screening and treatment. Although this may be reasonable given the higher risk of pyelonephritis/kidney cyst infection in ADPKD patients, data to support this approach are lacking.

Pyelonephritis should be suspected in the presence of fever of 38° C or higher, with suggestive urine studies and additional symptoms of upper tract infection such as flank or abdominal pain and nausea. Given the risk for sepsis and acute kidney injury, we recommend treatment of suspected pyelonephritis in the hospital with empiric antibiotic therapy that has adequate tissue penetration. Parenteral antibiotics should be continued until clinical improvement is demonstrated.[258] Abdominal imaging may be necessary to rule out cyst infections. The duration of antibiotic treatment is longer in cyst infections than in pyelonephritis and drainage may be necessary.[239] We recommend treatment for a minimum of 2 to 4 weeks for pyelonephritis and longer (up to 6 or 8 weeks) for cyst infections. The choice of antibiotics should consider maternal and fetal safety. In general, penicillins, cephalosporines, meropenem, aztreonam, nitrofurantoin, clindamycin, daptomycin, erythromycin, and azithromycin are considered safe. Aminoglycosides and tetracyclines are contraindicated in pregnancy, and quinolones should be avoided unless the benefits outweigh the risks.[259]

Implementation and Challenges

The widespread availability and low cost of urinalysis and oral antibiotics in the US make implementation of these recommendations feasible. However, monthly screening for asymptomatic bacteriuria may not be part of routine prenatal care and therefore would require education of care providers. Prolonged or recurrent treatment with antibiotics may increase the risk of gastrointestinal side effects such as diarrhea or *Clostridioides difficile* colitis. These risks might be mitigated by the prophylactic use of probiotics, which are recommended.

Practice Point 8.3.4: Women with ADPKD can perform vaginal delivery safely.

Practice Point 8.3.5: When a pregnant woman with ADPKD experiences acute abdominal pain, imaging can be performed safely with either ultrasound or MRI.

8.4. Hypertension in Pregnancy

Practice Point 8.4.1: More frequent BP-monitoring, preferably weekly HBPM, is advised in all women with ADPKD who become pregnant, and, most importantly, in those with preexisting hypertension or hypertension diagnosed during their pregnancy.

Commentary

The KDOQI work group agrees with more frequent HBPM (weekly) in pregnancy given that gestational or pregnancy-induced hypertension is more frequent in women with ADPKD.

Clinical Utility

This practice point is especially relevant for pregnant women with PKD who often have pre-existing chronic hypertension; this marker of more advanced disease is associated with increased htTKV and reduced GFR, which increase the risk for pre-eclampsia. In general, adverse pregnancy outcomes are proportional to baseline GFR and the presence of hypertension and proteinuria. Pre-eclampsia is also a recognized risk factor for future cardiovascular disease in the general population. Pregnant women with all forms of CKD who develop pre-eclampsia during pregnancy are at greater risk for worsening kidney function after delivery.[260] These considerations should be emphasized when counseling women with ADPKD about pregnancy planning and risk.

Implementation and Challenges

Health literacy and access to prenatal care is variable across the US. This may negatively impact the implementation of rigorous BP monitoring.

Practice Point 8.4.2: Antihypertensive medications to control BP during pregnancy have been studied extensively for efficacy and safety in the general population and can be used, when indicated, in women with ADPKD.

Commentary

The KDOQI work group suggests a BP target of <135/85 mm Hg and agrees with the choice of antihypertensive agents that have been recommended as safe for pregnant women in the general population. These include oral methyldopa, clonidine, β-blockers, and nifedipine. Hydralazine and prazosin can be used but are second- or third-line agents. We agree that RAS inhibitors are contraindicated in pregnancy.[261]

Implementation and Challenges

Oxprenolol (a β-blocker mentioned in the KDIGO guidelines) is not available in the US. Most β-blockers, except perhaps atenolol which has been associated with lower birthweight, are safe for use in pregnant women. Although diuretics have not been studied extensively in recent years, earlier studies suggest that if prescribed at lower doses they are not associated with adverse maternal or fetal effects. In women with reduced GFR and signs of volume overload, it may be necessary to use low doses of diuretics. Development of electrolyte abnormalities, particularly hypokalemia, should be closely monitored when prescribing diuretics in these patients.

8.5. Pre-eclampsia

Practice Point 8.5.1: Women with ADPKD are at an increased risk of preeclampsia and preterm delivery and should be

monitored carefully throughout their pregnancy and in the postpartum period. Assessment of the sFlt-1/PlGF ratio in plasma, from 24 weeks of gestation and every 4-6 weeks, should be done to rule out preeclampsia.

Commentary

The KDOQI work group agrees that there is increased risk of pre-eclampsia in ADPKD. We also agree with statements about pre-eclampsia increasing the risk of future kidney failure and cardiovascular risk across all forms of CKD, although these have not been studied specifically in ADPKD.[262] The KDOQI work group recommends using the 2020 ACOG criteria for diagnosis of pre-eclampsia.[263] This classification presents a comprehensive set of criteria that may be present in patients with pre-eclampsia.

Please refer to our previous comments on the use of sFlt-1/PlGF ratio in plasma under Practice Point 8.3.2.

Practice Point 8.5.2: Low-dose aspirin (75-150 mg daily) should be prescribed from week 12 to week 36 in pregnant women with ADPKD (KDIGO guideline Figure 45).

Commentary

The KDOQI work group agrees with the recommendation to use aspirin, 75-150 mg daily, for prevention of pre-eclampsia between the 12th and 36th weeks of gestation for all CKD patients, including patients with ADPKD. Although aspirin use is safe in pregnancy for the mother and the baby, there is no additional guidance on how to manage ADPKD patients with normal renal function without hypertension. These patients may be considered low risk for pre-eclampsia, particularly if they have had a prior uncomplicated full-term pregnancy.

Implementation and Challenges

The only aspirin preparations available in the US are the 81 mg and 325 mg doses. The American College of Obstetricians and Gynecologists recommends use of low-dose aspirin in women with kidney disease and/or hypertension but does not specify a dose.[263] Most clinical trials have utilized 81 mg daily.

The KDOQI work group recommends avoiding nonsteroidal anti-inflammatory drugs in the postpartum period in women with uncontrolled hypertension or increased Scr levels because they can cause worsening hypertension and acute kidney injury.

8.6. Fetal Evaluation for ADPKD

Practice Point 8.6.1: Mild radiographic abnormalities in the fetus, observed prenatally or during routine follow-up of pregnancy, do not necessarily predict severe ADPKD in the child. In this setting, shared decision making regarding the value and short- and long-term implications of confirmatory genetic testing is advised.

Practice Point 8.6.2: Severe fetal bilateral structural kidney cystic disease and/or oligohydramnios portend a higher risk of poor neonatal outcome or early-onset childhood kidney dysfunction.

Practice Point 8.6.3: Parents should be counseled that a normal fetal ultrasound does not exclude the diagnosis of ADPKD in an at-risk child.

8.7. Postpartum Care

Practice Point 8.7.1: Women with ADPKD should be seen by a nephrologist <6 months after delivery for a postpartum kidney review (see KDIGO guideline Figure 49). The precise timing will depend on the woman's eGFR and any pregnancy or delivery complications.

Practice Point 8.7.2: Women with ADPKD may have bladder instability or urinary incontinence after delivery and should be offered pelvic floor physical therapy, especially if tolvaptan will be prescribed.

Chapter 9. Pediatric Issues

9.1. Diagnosis of ADPKD in Children

Practice Point 9.1.1: ADPKD may begin in early childhood or antenatally, although clinical symptoms rarely are seen early in life. Very-early-onset (VEO)-ADPKD and early-onset (EO)-ADPKD forms of ADPKD are rare and distinct subentities of ADPKD (KDIGO guideline Table 21).

Commentary and Clinical Utility

Very-early-onset (VEO) ADPKD *with or without* oligohydramnios can be an important differential consideration for the recessive form of PKD that more typically presents in the perinatal period. Within the subgroups of VEO and early onset (EO) ADPKD, disease severity can range from oligo- or anhydramnios to normal amniotic fluid and poor to normal lung development.[264] When present, low amniotic fluid may impact the delivery method and predisposition individuals to early labor, necessitating a higher level of maternal-fetal medicine care.[265]

VEO-ADPKD most often involves a *trans* biallelic combination of a *PKD1* hypomorphic allele with a loss of function allele or another hypomorphic allele that results in decreased *PKD1* gene dosage.[266] Digenic patterns have been rarely described. Genetic testing may help clarify risk of progression and disease features. More typically in ADPKD, antenatal ultrasound for fetal development may show the presence of 1 or more cysts. Although these

children are at higher risk of early onset kidney disease from ADPKD, most will have a normal childhood, with perhaps early development of hypertension.

Implementation and Challenges

In ARPKD, low amniotic fluid volume is associated with poor postnatal outcomes with about one-third of infants requiring dialysis within 3 years of life.[267] Similar data are not available for ADPKD due to the lack of systematically studied cohorts. This limitation of evidence should be discussed in prenatal consultations, and the presence of low amniotic fluid in ADPKD families should not necessarily be equated with a severe prognosis.

Practice Point 9.1.2: Discussion of potential benefits and harms related to diagnosis in children who are at risk for ADPKD should employ a family-centered approach with shared decision-making, including the parents and/or legal guardians and mature child (Chapter 1; KDIGO guideline Figure 50).

Practice Point 9.1.3: Offer expert counseling about potential diagnostic options to the parents and/or legal guardians and the mature child by a multidisciplinary team including a pediatric nephrologist and a geneticist with expertise in ADPKD.

Commentary and Clinical Utility

The definition of the "mature child" is unclear in the diagnostic workflow shown in Figure 10; hence, we recommend use of the phrase "children above the legal age for assent."

An important gap in the field is the lack of evidence-based screening recommendations for children at risk for ADPKD due to a parental history of ADPKD. The general pediatrician is often the first contact for most at-risk children, most of whom will not be evaluated by a pediatric nephrologist or a geneticist with expertise in ADPKD. Clear guidance for primary care providers about indications for imaging, genetic testing, and referral to specialty programs needs to be developed.

Practice Point 9.1.4: Use ultrasound as the preferred imaging method when diagnosis of ADPKD in children is desired.

Practice Point 9.1.5: Inform people and families that the presence of a single kidney cyst in a child (aged <15 years) with a positive familial history of ADPKD is highly suspicious for the diagnosis of ADPKD (KDIGO guideline Figure 51).

Practice Point 9.1.6: Inform people at risk and their families that ultrasound examination without detection of cysts does not rule out ADPKD in at-risk children and adolescents (KDIGO guideline Figure 51).

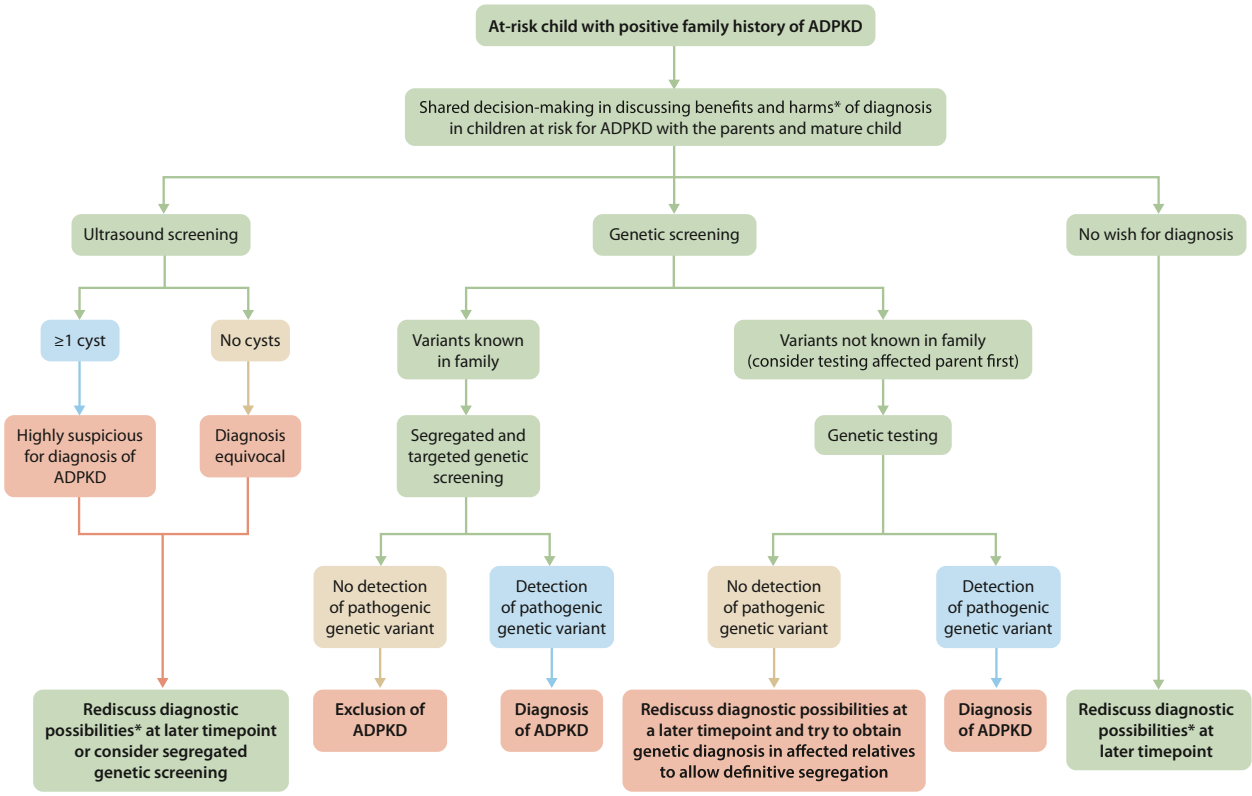


Figure 10. Diagnosis of children at risk of autosomal dominant polycystic kidney disease, which should be performed by a pediatrician with expertise in ADPKD. Abbreviation: ADPKD, autosomal dominant polycystic kidney disease.

Practice Point 9.1.7: Perform ultrasound of the parents (or grandparents if the parents are aged <40 years) to help clarify diagnosis in children with kidney cysts and negative family history for ADPKD who seek further diagnosis (KDIGO guideline Figure 51).

Practice Point 9.1.8: Benign simple cyst should be considered in the differential diagnosis of children with an isolated cyst, negative family history, and negative ultrasound workup of the parents (or grandparents, if the parents are aged <40 years).

Practice Point 9.1.9: Offer genetic testing for children with VEO-ADPKD or atypical presentation of ADPKD.

Practice Point 9.1.10: Offer genetic testing for children with cystic kidneys and a negative familial history of ADPKD.

9.2. BP Control in Children and Adolescents With ADPKD

Practice Point 9.2.1: Assess standardized office BP annually from birth, in children and adolescents with and at risk for ADPKD.

Practice Point 9.2.2: Perform annual 24-hour ABPM in accordance with recommendations on BP targets in pediatric CKD for children and adolescents (aged ≥5 years; height ≥120 cm) with ADPKD and office BP ≥75th percentile for age, sex, and height.

Practice Point 9.2.3: Perform annual 24-hour ABPM in children and adolescents (aged ≥5 years; height ≥120 cm) with VEO-ADPKD or EO-ADPKD.

Commentary

In the clinical context, ABPM is not routinely used for children ≤5 years old, and therefore it is not readily applicable for patients in this age group who have VEO-ADPKD and EO-ADPKD.

Practice Point 9.2.4: If ABPM is not available, routine in-office or HBPM are acceptable alternatives.

Practice Point 9.2.5: Evaluation of high BP in children and adolescents with or at risk for ADPKD should consider the possibility of primary or other secondary causes of high BP.

Practice Point 9.2.6: Perform echocardiography to exclude left ventricular hypertrophy (LVH) in children and adolescents with ADPKD and high BP.

Recommendation 9.2.1: We recommend targeting BP to ≤50th percentile for age, sex, and height or ≤110/70 mm Hg in adolescents in the setting of ADPKD and high BP (*1D*).

Commentary and Clinical Utility

Although the recommended BP target of <110/70 mm Hg for adolescents is supported by the HALT-PKD study,[51] the evidence for the recommended target BP ≤ 50th percentile for children <15 years old is primarily predicated on the ESCAPE study[268] and may not be fully applicable to children with ADPKD. A key finding in the ESCAPE study was that "intensified blood-pressure control effectively delayed the progression of renal disease among children with an underlying glomerulopathy or renal hypoplasia or dysplasia, but not among children with other congenital or hereditary nephropathies." This latter group comprised 18% of the study population (69 of 385), and it is not clear how many of these 69 children had ADPKD.

The European Society of Hypertension revised its pediatric guideline to a target BP below the 75th percentile in hypertensive children without proteinuria and below the 50th percentile in those with proteinuria.[269] Based on the available data, a recent international consensus statement on the diagnosis and management of children with ADPKD recommended a target BP below the 75th percentile for treatment of hypertensive children with ADPKD.[270]

Implementation and Challenges

Clinical implementation of the 75th percentile as the BP target is confounded by the fact that the normative BP tables in the 2016 European Society of Hypertension pediatric BP guideline include data for the 75th percentile[268] whereas the guideline issued by the American Academy of Pediatrics in 2017 does not include specific data for this percentile.[271,272]

Recommendation 9.2.2: We recommend use of RASi (i.e., ACEi or ARBs) as the first-line pharmacologic therapy for high BP in children and adolescents with ADPKD (*1D*).

Practice Point 9.2.7: High BP should be managed by a pediatric nephrologist or other local expert.

9.3. Follow-up Assessment in Children With ADPKD

Practice Point 9.3.1: Monitoring of kidney disease progression in children with ADPKD should be tailored based on clinical indications such as BP, kidney function, urine studies, and ultrasound (KDIGO guideline Figure 52).

Practice Point 9.3.2: Do not perform routine screening for extrarenal manifestations including liver, pancreas, or spleen cysts; cardiac valvular disease; or ICA in children and adolescents with ADPKD (KDIGO guideline Figure 52). Apply screening recommendations from adulthood (Chapter 6).

Commentary and Clinical Utility

Liver imaging may be indicated in the evaluation of atypical cases, including those without a family history, especially to exclude other hepatorenal fibrocystic disorders. It is important to avoid unnecessary imaging and

anxiety around the morbidity associated with ICAs, given the very low risk of clinically significant ICAs in children and adolescents with ADPKD.

Practice Point 9.3.3: Assess for extrarenal manifestations only when there are concerning symptoms or to differentiate the findings from other cystic kidney diseases (KDIGO guideline Figure 52). Apply assessment of extrarenal manifestations from adulthood (Chapter 6).

Practice Point 9.3.4: Manage UTI in children with ADPKD, according to local standards for children without ADPKD.

Practice Point 9.3.5: Perform diagnostic assessment with an ultrasound examination to rule out cyst infection in children with atypical courses of UTIs.

Practice Point 9.3.6: Evaluate abdominal pain in children with ADPKD, with consideration for kidney cyst complication in addition to other common causes of abdominal pain in childhood. Minimize the use of nonsteroidal anti-inflammatory drugs (NSAIDs) due to underlying kidney disease.

Practice Point 9.3.7: Manage nephrolithiasis in children with ADPKD the same as for children without ADPKD. Frequent use of NSAIDs should be avoided.

Practice Point 9.3.8: Evaluation and treatment of proteinuria in children with or at risk of ADPKD should be the same as those for children with other underlying kidney diseases.

Practice Point 9.3.9: Do not use vasopressin analogues to treat nocturnal enuresis in children with or at risk of ADPKD.

Practice Point 9.3.10: Wait and watch in children with a single kidney cyst with normal BP and urine findings, negative family history for ADPKD, and negative ultrasound findings in parents.

9.4. Diet and Lifestyle in Children With ADPKD

Practice Point 9.4.1: Encourage and implement healthy lifestyle measures in children with and at risk for ADPKD (KDIGO guideline Figures 52 and 53).

Practice Point 9.4.2: Children with ADPKD should follow general recommendations for a healthy diet, consistent with WHO guidelines, and should maintain a healthy body weight.

Practice Points 9.4.3: Children with ADPKD and hypertension or CKD should follow the same diets and physical activities recommended for all children with hypertension or CKD.

9.5. Optimal Models of Care for Children With ADPKD

Practice Point 9.5.1: As children enter young adulthood, a formal transition process should be developed for all children diagnosed with or at risk for ADPKD. Assessment for extrarenal manifestations should be recommended as stated in Chapter 6.

Commentary and Clinical Utility

The lack of evidence-based recommendations for the timely and effective transition of adolescents with ADPKD to adult care systems needs to be addressed.

Practice Point 9.5.2: Nephrologists can empower parents and grandparents affected by ADPKD to discuss the condition with affected or at-risk children and grandchildren.

Practice Point 9.5.3: There is currently insufficient evidence to support use of targeted or disease-modifying therapies for ADPKD in children beyond antihypertensive treatment.

Commentary

The KDOQI work group recommends that children who either do not meet imaging criteria for ADPKD or who fall into the category "no wish for diagnosis" should have annual BP and urinalyses to monitor for disease expression.

Chapter 10. Approaches to the Management of People With ADPKD

Practice Point 10.1: Shared decision-making should be the cornerstone of patient-centered management in people with ADPKD.

Practice Point 10.2: The lifelong management of people with ADPKD should follow a comprehensive, multidisciplinary, and holistic care pathway (KDIGO guideline Figure 56).

Commentary

The KDIGO guideline recommends shared decision making between provider and patient, along with a focus on comprehensive, multidisciplinary, and holistic care. Shared decision making is defined as a collaborative approach in which clinicians and patients share best available evidence for patients to consider their options and make informed decisions about preferences and choices for their care. The goal in providing this care is to address all elements of the ADPKD health experience, including mental health, and to take a holistic approach that tailors care according to the individual's needs and unique circumstances that may affect their ability to adhere to treatment(s) and/or lifestyle recommendations. Early diagnostic and prognostic assessment and longitudinal care should be led by a nephrologist, preferably at a center with expertise in ADPKD, with participation of the primary care physician, subspecialists (which will vary by individual needs), and the local nephrologist.

Clinical Utility

The benefits of shared decision making, a cornerstone of patient-centered care, are well established. Due to the burden of the only currently available treatment (specifically, polyuria associated with tolvaptan) and the many therapeutics for ADPKD in the pipeline, which could become available in the next few years, it will be particularly important for providers to be aware of clinical trial opportunities and to engage with patients in shared decision making regarding the ongoing standard of care versus experimental therapy. This will allow patients to weigh the risks and benefits of therapeutic options and to make the best individualized choices.

Implementation and Challenges

Although physicians often support the concept of shared decision making, lack of time is perceived as a barrier to its implementation. This is particularly relevant as physicians are increasingly being asked to see more patients with less time allotted per visit. Best practice methods of implementing shared decision making, using existing publicly available resources such as high-quality educational materials on YouTube or other websites, may maximize efficiency for both patients and clinicians.

Practice Point 10.3: People with ADPKD should be encouraged and enabled to participate in registries, cohort studies, and clinical trials testing novel diagnostic or therapeutic approaches (including novel agents, repurposed drugs, or combinations of agents).

Practice Point 10.4: Physicians caring for people with ADPKD should be educated about the benefits and harms of genetic testing in ADPKD and should have relevant literacy.

Commentary

Genetic testing is becoming more widely available at lower cost, and integration of genetic testing is an important and evolving component of contemporary ADPKD management (see Chapter 1). In the future, genotype-specific therapy may be available, which will also drive the use of genetic testing.

Clinical Utility

The use of genetic testing may have diagnostic and prognostic value, as discussed earlier in this commentary, but decision making about testing requires adequate training of providers, counseling of patients by these providers, and expertise in interpreting results (for example, VUS). The impact of genetic testing on mental health in ADPKD is also unknown.

Implementation and Challenges

Interpreting genetic testing results and counseling patients on their implications is a complex and evolving aspect of PKD care. Access to adequate genetics expertise may not be available in all centers, and the referral wait time to see a geneticist can be lengthy. In addition, many commercial genetic testing reports lack detail—such as whether a variant is truncating versus nontruncating—which has important prognostic value and is used in tools such as the PROPKD score.

Notably, variant classification remains challenging. VUS, which are especially common in *PKD1*, may require further interpretation. Publicly available databases, such as the Mayo Clinic's polycystin 1 and 2 variants database (https://pkdb.mayo.edu/welcome), can assist in evaluating the likelihood of disease causation of a VUS but are not sufficient to reclassify a variant. However, not all variants for *PKD1* and *PKD2* genes have been identified or resolved. Furthermore, databases for the minor ADPKD genes (some of which remain to be identified) do not exist. These data should continue to improve as genetic testing becomes more widespread and results are correlated with clinical phenotype information.

Practice Point 10.5: Healthcare systems should provide care coordination or patient navigation for people with ADPKD to ensure holistic care along their care pathways.

Practice Point 10.6: Healthcare systems should implement a structured self-management program for people with ADPKD, taking into consideration local context, variable cultures among their patients, and availability of resources.

Commentary

ADPKD is a chronic condition with broad impacts on overall health and quality of life. The care pathways in ADPKD are often complex, requiring multiple subspecialists and care providers. Care coordination or patient navigation, by team members who can complement nephrology expertise, may be beneficial. Furthermore, self-management by a patient with chronic disease can contribute to positive outcomes.

Clinical Utility

Self-management has been proven beneficial and cost-effective for health-related outcomes in conditions including diabetes and hypertension. There are several aspects of care for the ADPKD patient that require self-motivation, including avoiding overweight and obesity, eating a healthy diet, drinking sufficient water to counteract polyuria (due to decreased concentrating ability) and to avoid dehydration, practicing regular aerobic exercise, and observing mindfulness therapy to help with pain or anxiety. This is a motivated population; with adequate instruction, encouragement, and longitudinal monitoring by a multidisciplinary care team, it is likely that patients can be successful in instituting self-management practices that are likely to improve outcomes. Established methods to improve self-management include decision making, problem-solving, effective use of resources, taking action, and building partnerships with health care providers.[273] Educating individuals with ADPKD in these

approaches may strengthen their sense of agency and engagement in their own care.

Implementation and Challenges

A major barrier to widespread implementation is the lack of specific ADPKD self-management education programs along with a lack of information on their effectiveness and cost-effectiveness.

Practice Point 10.7: Healthcare systems should promote the participation of people with ADPKD in registries that gather outcome data using standardized data definitions.

Practice Point 10.8: ADPKD-focused patient organizations, national kidney federations, and patient support groups can help enhance the care of people with ADPKD and their families through provision of general information and peer support.

Commentary

Registries and organizations focused on ADPKD patients and families can facilitate collection of "real-world" clinical data. For example, data from the PKD Foundation registry was instrumental in characterizing the pain burden of ADPKD patients and correlating these findings with progression of kidney disease.[274] In addition, we anticipate that registries will support enrollment in future clinical trials by identifying individuals who might meet specific inclusion criteria.[274]

Implementation and Challenges

Some individuals may have privacy concerns about participation in registries outside the context of their usual health care systems, especially if they are asked to link self-reported data to an electronic medical record. Patient support groups should work to improve trust in registries and emphasize their importance for enhancing patient care.

Conclusions

ADPKD is a lifelong, systemic condition. Patients will have varying needs for health care utilization depending on family history, ADPKD genotype, and other comorbidities. The KDIGO guidelines are the first systematic review of care for ADPKD individuals at all stages of life. When the published data are insufficient, thoughtful and measured expert opinion is provided. We anticipate that overall care for ADPKD will improve as the KDIGO guidelines become the standard of care, with modifications for the US health care system as noted in this commentary. We also note that as a nephrology community we need to engage early with individuals with ADPKD, allowing discussion of appropriate therapies and ongoing clinical trial eligibility prior to significant loss of kidney function. The PKD Foundation Center of Excellence program[274] was created to address some of the gaps in care and knowledge described in this commentary.

Further evaluation of rare events in ADPKD, such as development of ICA or hepatomegaly, and rare genotypes contributing to the ADPKD spectrum of disease will require ongoing collaboration to create large data registries, ideally with participation of all individuals with ADPKD.

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Support: None.

Financial Disclosure: Dr Chebib has received research support from Otsuka Pharmaceutical, Regulus, and Natera Inc. Dr Cowley Jr is a consultant for Otsuka Pharmaceutical Development & Commercialization, Inc., and Sparrow Pharmaceuticals, Inc. Dr Dahl has received research support from Natera and Vertex and consulting fees from Vertex, Regulus, Renasant Bio, Estuary Bio, and Natera. Dr Goral has received research support from Otsuka Pharmaceutical, Reata, Kadmon, and Sanofi. Dr Hogan has received research support for somatostatin analog studies from Camurus Pharmaceuticals and Novartis, has received research support from Regulus, and has served as a consultant to Otsuka Pharmaceutical. Dr Nowak has received consulting fees from Otsuka Pharmaceutical Development & Commercialization. Dr Park has received consulting fees from Otsuka America Pharmaceutical Inc, Vertex, and Natera, and is a member of the board of directors of the PKD Foundation. The remaining authors declare that they have no relevant financial interests.

Acknowledgements: The authors gratefully acknowledge the expert support of National Kidney Foundation staff, Jessica Joseph, MBA and Genevieve Coorey, PhD. Guideline recommendations included in this article originally were published in Kidney International Supplements, are ©2025 KDIGO, and were reproduced with permission from KDIGO.

Peer Review: Received October 9, 2025, following review and approval by the National Kidney Foundation Scientific Advisory Board (membership listed at https://www.kidney.org/about/sab) and KDOQI Chair and Vice Chairs (listed at https://www.kidney.org/professionals/guidelines/leadership). Accepted November 16, 2025 after editorial review by a Deputy Editor.

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